CLINICAL STUDY REPORT

Genotype and phenotype guided supplementation of TAMoxifen standard therapy with ENDOXifen in breast cancer patients

Prospective, multi-center, interventional, blinded, three treatment arms, multi-dose, pharmacogenetic, pharmacokinetic study in Germany

EudraCT No: 2016-000418-31

Investigational Products:	Endoxifen
Indication:	Breast cancer
Study Protocol:	IKP275 / GBG 91 Protocol Version 2.0 – June 26, 2020
Phase:	2
Report Version:	1.0
First Patient First Visit:	10 September 2019
Last Patient Last Visit:	03 May 2021
Coordinating Investigator:	Prof. Dr. med. Matthias Schwab Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie Auerbachstraße 112 70376 Stuttgart, Germany
Sponsor:	Robert Bosch Gesellschaft für Medizinische Forschung mbH (RBMF) Auerbachstraße 112 70376 Stuttgart, Germany
Date of this report:	24 January 2025
Date of any previous reports:	N/A

1. SIGNATURES

STUDY TITLE: Genotype and phenotype guided supplementation of TAMoxifen standard therapy with ENDOXifen in breast cancer patients

STUDY NUMBER: IKP275 / GBG 91

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

SIGNATURE:  **DATE:** 28.01.2025

Prof. Dr. med. Matthias Schwab
Sponsor Representative /
Coordinating Investigator
Dr. Margarete Fischer-Bosch
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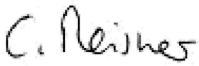
SIGNATURE:  **DATE:** 27.01.2025

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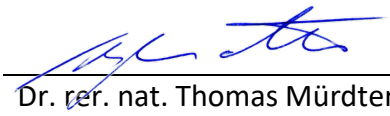
SIGNATURE:  **DATE:** 27.01.2025

Dr. rer. nat. Thomas Mürdter
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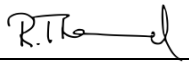
SIGNATURE: 

DATE: 27.01.2025

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2. SYNOPSIS

Name of Sponsor: RBMF	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: N/A	Volume:	
Name of active ingredient: (Z)-Endoxifen hydrochloride	Page:	

Title of Study:

Genotype and phenotype guided supplementation of TAMoxifen standard therapy with ENDOXifen in breast cancer patients

Investigators:

Coordinating Investigator

Prof. Dr. med. Matthias Schwab
Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie
Auerbachstraße 112, 70376 Stuttgart, Germany
(other PIs see "Study Center(s)"

Study Center(s):

This study was conducted in Germany. A total of 38 study sites were initiated.

1. Gemeinschaftspraxis Dres. Brudler/Heinrich/Bangerter, Halderstr. 29, 86150 Augsburg (PI: Dr. Bernhard Heinrich)
2. Sozialstiftung Bamberg und Medizinisches Versorgungszentrum am Bruderwald (MVZ), Buger Straße 80, 96049 Bamberg (PI: Dr. Denise Wrobel)
3. DRK Kliniken Köpenick, Brustzentrum, Salvador-Allende-Str. 2-8, 12559 Berlin (PI: Dr. med. Anke Kleine-Tebbe)
4. Marienhospital Bottrop gGmbH, Klinik für Gynäkologie u. Geburtshilfe, Josef-Albers-Str. 70, 46236 Bottrop (PI: Dr. Hans-Christian Kolberg)
5. Evangelisches Diakonie-Krankenhaus gGmbH, Frauenklinik, Gröpelinger Heerstr. 406-408, 28239 Bremen (PI: Dr. Karen Wimmer)
6. St. Johannes Hospital Dortmund, Johannesstr. 9-17, 44137 Dortmund (PI: PD Dr. Georg Kunz)
7. Onkozentrum Dresden, Leipziger Str. 118, 01127 Dresden (PI: Dr. Thomas Göhler)
8. Luisenkrankenhaus Düsseldorf, Brustzentrum Dr. Mehdi Rezai, Luise-Rainer-Straße 6- 10, 40235 Düsseldorf (PI: Dr. med. Maren Darsow)
9. MVZ Eggenfelden, Frauenärzte am Schellenbruckplatz, Schellenbruckstr. 15, 84307 Eggenfelden (PI: Dr. Jürgen Terhaag)
10. Klinikum Frankfurt Höchst GmbH, Gotenstr. 6-8, 65929 Frankfurt am Main (PI: Prof. Dr. med. Volker Möbus)
11. SRH Wald-Klinikum Gera GmbH, Klinik für Frauenheilkunde/Geburtsmedizin, Straße des Friedens 122, 07548 Gera (PI: Dr. Dirk-Michael Zahm)
12. Helios Klinikum Gifhorn, Frauenklinik, Campus 6, 38518 Gifhorn, 2. Standort: MVZ am Schlosssee GmbH, Zur Allerwelle 4, 38518 Gifhorn (PI: Dr. med. Thomas-H. Dewitz)
13. Gemeinschaftspraxis Gynäkologie Dres. Uleer/J.Y. Pourfard, Bahnhofsplatz 5, 31134 Hildesheim (PI: Dr. Christoph Uleer)
14. ViDiA Christliche Kliniken Karlsruhe, Vincentius-Diakonissen Kliniken gAG, Diakonissenkrankenhaus, Diakonissenstr. 28, 76199 Karlsruhe (PI: Dr. med. Gerhard Deutsch)

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15. Städtisches Klinikum Karlsruhe, Frauenklinik, Moltkestr. 90, 76133 Karlsruhe (PI: Dr. Gabriele Kaltenecker)
16. Elisabeth Krankenhaus Kassel gGmbH, Brustzentrum, Weinbergstrasse 7, 34117 Kassel (PI: Dr. Sabine Schmatloch)
17. Kliniken der Stadt Köln GmbH, Krankenhaus Holweide, Brustzentrum, Neufelder Str. 32, 51067 Köln (PI: Dr. med. Ilka Bernhöft)
18. Klinikum Ludwigsburg, Klinik für Frauenheilkunde und Geburtshilfe, Ambulantes Tumorzentrum, Posilipostr. 4, 71640 Ludwigsburg (PI: Dr. Claudia Hänle)
19. Klinikum Magdeburg gGmbH, Klinik für Hämatologie/Onkologie, Birkenallee 34, 39130 Magdebrug (PI: Prof. Dr. med. Christoph Kahl)
20. Klinikum Memmingen, Zentrales Studienbüro, Bismarckstr. 23, 87700 Memmingen (PI: Christina Bechtner)
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24. Diakonissen-Stiftungs-Krankenhaus Speyer, Brustzentrum, Gynäkologische Abteilung, Paul-Egell-Str. 33, 67346 Speyer (PI: Dr. med. Ute Baumstark)
25. Johanniter Frauenklinik Stendal, Bahnhofstr. 24-26, 39576 Stendal (PI: Dr. med Andrea Stefek)
26. Robert Bosch Gesellschaft fir Medizinische Forschung, Robert-Bosch-Krankenhaus, Gynäkologie und Geburtshilfe/Brustzentrum, Dr. Margarete Fischer-Bosch Institut für klinische Pharmakologie, Auerbachstr. 110, 70376 Stuttgart (PI: Prof. Dr. med. Matthias Schwab)
27. SRH Zentralklinikum Suhl GmbH, Klinik für Frauenheilkunde/Geburtsmedizin, Albert-Schweitzer-Str. 2, 98527 Suhl (PI: Dr. med. Uwe Rhein)
28. Universitätsklinikum Tübingen, Frauenklinik, Calwerstr. 7, 72076 Tübingen (PI: Prof. Dr. Andreas Hartkopf)
29. Harzklinikum Dorothea Christiane Erxleben GmbH, Abteilung Gynäkologie und Geburtshilfe, Ilsenburger Str. 15, 38855 Wernigerode, 2. Standort: Klinikum Quedlinburg, Frauenklinik, Ditfurter Weg 24, 06484 Quedlinburg (PI: Dr. Sven-Thomas Graßhoff)
30. Helios Dr. Horst Schmidt Kliniken Wiesbaden, Klinik für Gynäkologie und gynäkologische Onkologie, Ludwig-Erhard-Straße 100, 65199 Wiesbaden (PI: Prof. Dr. Michael Eichbaum)
31. Rems-Murr-Klinikum Winnenden, Brustzentrum Winnenden, Am Jakobsweg 1, 71364 Winnenden (PI: Prof. Dr. H.-J. Strittmatter)
32. Marienhospital Witten, Marienplatz 2, 58452 Witten (PI: Dr. John Hackmann)
33. Helios Universitätsklinikum Wuppertal, Landesfrauenklinik, Heusnerstr. 40, 42283 Wuppertal (PI: Prof. Dr. med. Vesna Bjelic-Radisic)
34. Helios Klinikum Krefeld, Zentrum für ambulante gynäkologische Onkologie (ZAGO), Lutherplatz 40, 47805 Krefeld (PI: Dr. med Gunther Rogmans)
35. medius Kliniken gGmbH, medius Klinik Ostfildern-Ruit, Brustzentrum, Hedelfinger Str. 166, 73760 Ostfildern (PI: Dr. med. Wilma Ehrle)

Name of Sponsor: RBMF	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
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36. medius Kliniken gGmbH, medius Klinik Nürtingen, Brustzentrum, Auf dem Säer 1, 72622 Nürtingen (PI: Dr. Elke Faust)
37. Klinikum Esslingen GmbH, Klinik für Frauenheilkunde und Geburtshilfe, Hirschlandstr.97, 73730 Esslingen (PI: Prof. Dr. med. Thorsten Kühn)
38. SRH Kliniken Landkreis Sigmaringen GmbH, Hohenzollernstr. 40, 72488 Sigmaringen (PI: Dr. Gabriele Stalzer)

Publication (reference):

N/A

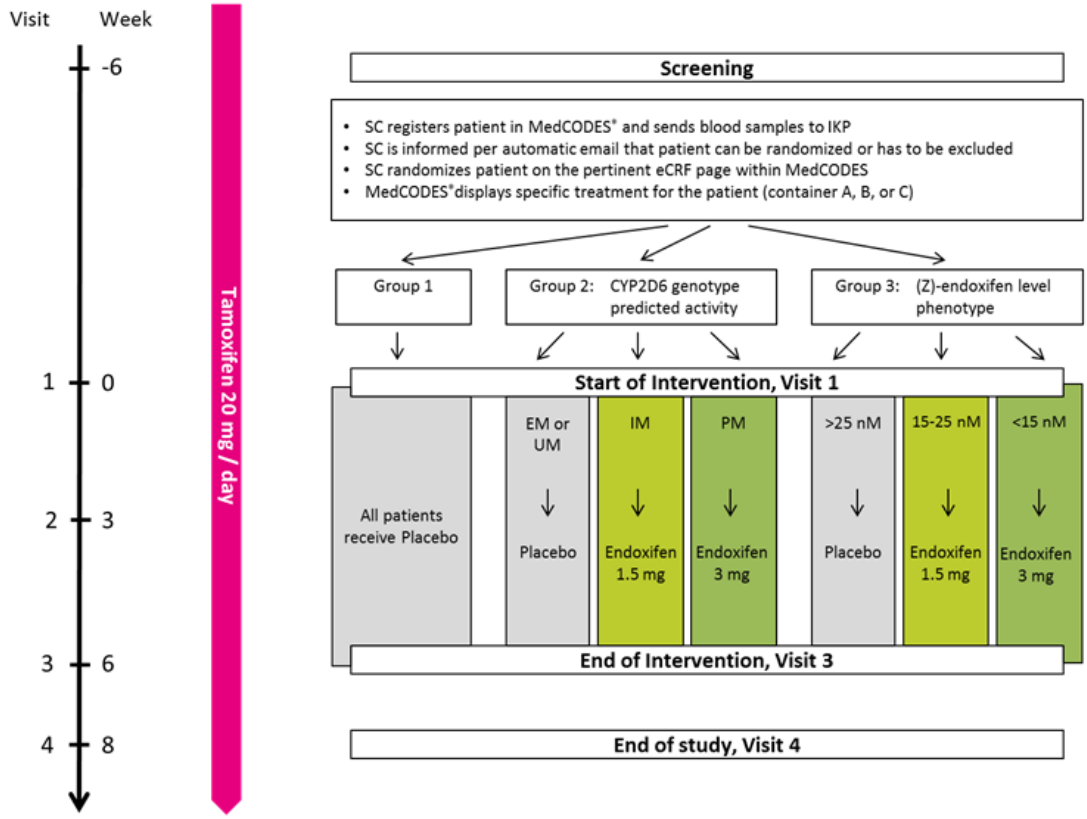
Studied Period (years):

Date of the First Patient First Visit: 10 September 2019
Date of the Last Patient Last Visit: 03 May 2021

Phase of Development:

Phase II

Study Design:



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Objectives:

Primary Objective:

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.

Secondary Objectives:

- To increase (Z)-endoxifen steady state concentrations in patients with CYP2D6 genotype predicted PM activity to levels observed in patients with full CYP2D6 activity by supplementation with 3 mg/day (Z)-endoxifen (> 32 nM)
- To increase (Z)-endoxifen steady state concentrations in patients with CYP2D6 genotype predicted IM activity to levels observed in patients with full CYP2D6 activity by supplementation with 1.5 mg/day (Z)-endoxifen (> 32 nM)
- To increase (Z)-endoxifen steady state concentrations in patients with basal (Z)-endoxifen plasma levels ≤ 15 nM to levels observed in patients with full CYP2D6 activity by supplementation with 3 mg/day (Z)-endoxifen (> 32 nM)
- To increase (Z)-endoxifen steady state concentrations in patients with basal (Z)-endoxifen plasma levels > 15 nM and ≤ 25 nM to levels observed in patients with full CYP2D6 activity by supplementation with 1.5 mg/day (Z)-endoxifen (> 32 nM)
- To assess safety of low dose (Z)-endoxifen supplementation
- To assess and compare steady state plasma levels of tamoxifen, desmethyltamoxifen, 4-hydroxtamoxifen, and possible other tamoxifen metabolites between the intervention groups and control group.

Methodology:

This is a prospective multi-center, interventional, single-blinded, three treatment arms, multi-dose, placebo-controlled, pharmacogenetics / pharmacokinetic study in pre- and postmenopausal female patients with ductal carcinoma in situ (DCIS) or locally advanced breast cancer including stage I, IIA, IIB and IIIA.

Number of patients (planned and analyzed):

Planned (according to clinical study protocol version 1.2, dated 10.07.2019): 504

Planned (according to clinical study protocol version 2.0, dated 26.06.2020): 129 in the first stage of adaptive design for interim analysis, approximately 133 to 375 in total after the second stage

Enrolled: 338, randomized: 246, analyzed (safety): 235, analyzed (efficacy): 235

Diagnosis and Main Criteria for Inclusion:

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.

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

Investigational product in this study were enteric-coated tablets containing 0 mg (Placebo), 1.5 mg or 3 mg (Z)-endoxifen.

Batch numbers provided: TAMENDOX/*201930 (Placebo); TAMENDOX/201929* (1.5 mg), TAMENDOX/201928 (3 mg)

Duration of Treatment:

The entire treatment period was 6 weeks.

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

See above for details on therapy and dose.

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Criteria for Evaluation:

Efficacy:

The primary endpoint was reached if in one or both intervention groups, the proportion of patients with steady state (Z)-endoxifen plasma concentration > 32 nM was greater or equal to the proportion of patients in the control group that reaches steady state (Z)-endoxifen plasma concentration of > 32 nM.

Secondary Endpoints:

- Increase in steady state (Z)-endoxifen concentration from baseline to end of intervention (Visit 3) in patients with or without supplementation of (Z)-endoxifen
- Steady state plasma concentrations of tamoxifen, desmethyltamoxifen, 4-hydroxytamoxifen, and other tamoxifen metabolites following (Z)-endoxifen supplementation for 6 weeks

Safety:

For all patients of the intervention groups adverse drug reactions are reported descriptively. Safety and tolerability are assessed by clinical review of all relevant parameters including adverse events, laboratory tests, vital signs, weight, and ECGs. No inferential testing for statistical significance is performed. AE are be classified using the MedDRA® classification system. All AEs will be summarized by system organ class, preferred term, severity, and relationship to IMP. AEs leading to death or to discontinuation from treatment and SAE will also be tabulated. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity. Laboratory, vital signs, weight, and ECG data will be summarized descriptively.

Statistical Methods:

- Primary endpoint: The proportion of patients in both intervention groups, which has a steady state (Z)-endoxifen concentration > 32 nM will be compared to the proportion of patients attaining > 32 nM in the control group. This will be statistically assessed by means of two Mantel-Haenszel $\chi 2$-tests (Group 2 vs. control and Group 3 vs control)
- Secondary endpoints: Comparison of other tamoxifen metabolite profiles in the intervention groups compared to the control group
- Safety: Adverse drug reactions will be reported descriptively

SUMMARY

Efficacy Results:

Primary efficacy measurement is the proportion of patients in the intervention groups, who reached (Z)-endoxifen plasma concentrations above 32 nM. In each of the intervention groups receiving (Z)-endoxifen doses either according to their CYP2D6 genotype or according to their basal (Z)-endoxifen plasma concentration 52/78 patients (66.7%) showed (Z)-endoxifen plasma concentrations >32 nM. In contrast, only 18/79 (22.8%) of patients in the control group had (Z)-endoxifen plasma concentrations >32 nM (one-sided Mantel-Haenszel $\chi 2$-test stratified by genotype or basal (Z)-endoxifen plasma concetrations, respectively: $p<0.0001$).

Safety Results:

During administration of study medication and follow up until visit 4 187/235 (79.6%) of patients reported any AE. 75/155 (48.4%), 40/155 (25.8%), and 8/155 (5.2%) patients receiving no (Z)-endoxifen reported AEs with CTC-Grade 1, 2, and 3, respectively. 18/46 (39.1%), 17/46 (37.0%), and 4/46 (8.7%) patients receiving a daily dose of 1.5 mg (Z)-endoxifen reported AEs with CTC-Grade 1, 2, and 3, respectively. 8/34 (23.5%), 15/34 (44.1%), and 2/34 (5.9%) patients receiving adaily dose of 3 mg (Z)-endoxifen reported AEs with CTC-Grade 1, 2, and 3, respectively. No CTC-Grade 4 AE occurred during administration of study medication and during 4 weeks of follow up time until visit 4.

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CONCLUSIONS:

Overall Conclusion: The supplementation of standard tamoxifen therapy (20 mg/day) with either CYP2D6 genotype or basal (Z)-endoxifen plasma concentration guided low dose of 1.5 or 3 mg (Z)-endoxifen was efficient to increase (Z)-endoxifen plasma concentrations. The AE profile was unremarkable.

Date of the Report:

24 January 2025

3. TABLE OF CONTENTS

3.1 LIST OF IN-TEXT TABLES

3.2 LIST OF IN-TEXT FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
AI	Aromatase inhibitor
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
BMI	Body mass index
CA	Competent Authority
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
C_{ss}	Steady state concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCIS	Ductal carcinoma in situ
EC	Ethics committee, Synonymous to Institutional Review Board and Independent Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
EudraCT	European clinical trials database
ECG	Electrocardiogram
EM	Extensive metabolizer (normal CYP2D6 genotype predicted activity)
e.g.	For example
FDA	Food and Drug Administration
GBG	German Breast Group Forschungs mbH
GCP	Good Clinical Practice
GMP	Good manufacturing practice
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.e.	That is
i.v.	Intravenous
IKP	Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology
IM	Intermediate metabolizer (decreased CYP2D6 genotype predicted activity)
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
IT	Information Technology
ITT	Intention-to-treat population
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute(s)
ml	Milliliter(s)
N/A	Not applicable
No.	Number(s)

Abbreviation or special term	Explanation
NYHA	New York Heart Association
PBPK	physiology-based pharmacokinetic
PGx	Pharmacogenomics
PI	Principal investigator; a person responsible for the conduct of a clinical study at a study site. Every study center has a principal investigator.
PK	Pharmacokinetics or pharmacokinetic
PM	Poor metabolizer (very low CYP2D6 genotype predicted activity)
PP	Per protocol population
PV	Pharmacovigilance
RBMF	Robert Bosch Gesellschaft für Medizinische Forschung mbH
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedures
SmPC = SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAM	Tamoxifen
UM	Ultrarapid metabolizer (increased CYP2D6 activity)
WMA	World medical association
WOCBP	women of child bearing potential
β-HCG	Human chorionic gonadotropin

5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

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.

Competent Ethics Committee: Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität, Gartenstraße 47, 72074 Tübingen

Competent Authority: Bundesinstitut für Arzmeimittel und Medizinprodukte, Kurt-Georg-Kiesinger-Allee 3. 53175 Bonn

The Competent EC and the CA were informed on 08 April 2020 that the patient recruitment was stopped due to the COVID-19 pandemic.

To restart the patient recruitment in August 2020, a substantial protocol amendment (substantial protocol amendment no. 1, version 1.0 dated 26.06.2020 – the only substantial protocol amendment) and the corresponding amended study protocol (version 2.0 dated 26.06.2020) were submitted and a favourable opinion from the Competent EC and an approval from the CA were obtained.

The substantial protocol amendment also describes the implementation of an interim analysis and other minor changes.

5.2 Ethical Conduct of the Study

The clinical study was conducted in accordance with the Declaration of Helsinki (Sommerset 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.

5.3 Patient Information and Consent

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.

Prior to the beginning of any specific protocol procedures such as screening activities, the patients were informed in writing (hand-out of the Patient Information Sheet and Informed Consent Form) and verbally by the investigator about the nature of the study drug, the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the patient was exposed were explained.

The Informed Consent Form was then read and signed by the patient, and, if required, a witness, and the investigator. The patient was provided with a copy of the signed Informed Consent Form. The patient could withdraw from the study at any time without this affecting

his future medical treatment. Verification of a signed Informed Consent Form was noted on the patient's Case Report Form.

The patients were informed that their data would be pseudonymised and stored electronically and / or on paper and that such data would not be revealed to any unauthorized third party.

The patients were also informed that their data were reviewed by the monitor and could potentially be reviewed by an independent auditor and / or by representatives of regulatory authorities.

The terms of the General Data Protection Regulation (GDPR) and local data protection legislation were applied as appropriate.

5.4 Patient Insurance

Patient insurance for the compensation of patients for possible study-related injury was provided by RBMF as the sponsor according to local law. The insurance was concluded with Barbican Syndicate 1955 at Lloyd’s, One Lime Street, London EC3M 7HA, United Kingdom (insurance policy number: BARCLT18223).

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigational Centre/Site

A total of 38 study sites were initiated in Germany. 33 of the 38 study sites recruited patients. 2 of the 38 study sites received a favourable opinion, recruited patients, but the recruited patients turned out to be screening failures (Helios Klinikum Krefeld, medius Klinik Ostfildern-Ruit). 3 of the 38 study sites received a favourable opinion but did not recruit patients (medius Klinik Nürtingen, Klinikum Esslingen GmbH, SRH Kliniken Landkreis Sigmaringen GmbH). Therefore, these 5 study sites were not included in the analysis.

6.2 Sponsor and Investigators

The following roles/functions and affiliations were involved in the clinical study:

Role/Function	Name	Affiliation
Sponsor	Robert Bosch Gesellschaft für medizinische Forschung mbH	Auerbachstr. 112 70376 Stuttgart
Sponsor Representative	Prof. Dr. med. Matthias Schwab	Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie, Auerbachstr. 112 70376 Stuttgart
Coordinating Investigator	Prof. Dr. med. Matthias Schwab	Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie, Auerbachstr. 112 70376 Stuttgart
Sponsor's Project Manager	Dr. rer. nat. Thomas Mürdter	Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie Auerbachstraße 112 70376 Stuttgart
Head of Core Facility Chemical Analytics and Synthesis	Dr. rer. nat. Thomas Mürdter	Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie Auerbachstraße 112 70376 Stuttgart
Research Group Leader Pharmacogenomics and Digital Health	Dr. rer. nat. Roman Tremmel	Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie Auerbachstraße 112 70376 Stuttgart

Role/Function	Name	Affiliation
Biostatistician	Dr. rer. nat. Christoph Meisner	Institut für Klinische Epidemiologie und angewandte Biometrie (IKEAB) Silcherstr. 5 72076 Tübingen
Biostatistician	Dr. rer. nat. Imma Fischer	Institut für Klinische Epidemiologie und angewandte Biometrie (IKEAB) Silcherstr. 5 72076 Tübingen
Academic Research Organisation (ARO)	GBG Forschungs GmbH (GBG)	Martin-Behaim-Str. 12 63263 Neu-Isenburg (new address since 18.07.2022: Dornhofstraße 10, 63263 Neu-Isenburg)
Pharmacovigilance	GBG Forschungs GmbH (GBG)	See above

All affiliations are located in Germany and are provided in the synopsis.

The investigators at the study sites were qualified by training and experience to investigate the study medication. At each site, the principal investigator was responsible for the study.

The study protocol was prepared by the Protocol Board of the sponsor in cooperation with the GBG.

The clinical study report (CSR) was written by the sponsor and the GBG.

6.3 Laboratory

Blood sampling at screening included safety laboratory parameters (EDTA, Li-Heparin) and a serum pregnancy test (β-HCG) in women of child-bearing potential. Serum triglycerides were measured; in case of a pathologic result, a fasting sample had to be obtained. Furthermore, a urine dipstick test and a resting ECG were obtained. Follow-up and treatment of pathologic laboratory or ancillary test results were in the responsibility of the investigator.

In addition, EDTA whole blood samples were drawn for genotyping and EDTA plasma for quantification of (Z)-endoxifen concentrations. As all eligible patients had taken tamoxifen for more than three months, tamoxifen levels were assumed to be in steady-state. Nevertheless, documentation of the time-point of last tamoxifen intake was mandatory. In order to allow a timely randomization, one of the blood samples for genotyping and one plasma aliquot for tamoxifen/(Z)-endoxifen quantification were sent together to IKP once weekly, (up to a maximum of 10 calendar days were tolerated) on dry ice.

Patients who had tamoxifen levels <150 nM were excluded from the study because levels of <150 nM result most likely from non-compliance for tamoxifen intake. Investigators were informed by email to exclude the patient.

Results from CYP2D6 genotyping and endoxifen phenotyping were entered into MedCODES® exclusively by IKP. These data determined the assignment of the patients within the group 2 and 3 to treatment with placebo, 1.5 mg or 3 mg (Z)-endoxifen. In case all inclusion/exclusion criteria are met, investigators were notified by email. Subsequently, patients were randomized via MedCODES® and were invited for visit 1, which should be scheduled within one week after randomization.

Patients who had already been screened but could not be randomized within 6 weeks, e.g. due to COVID-19 pandemic, and still were willing to participate have been assigned to a new patient-ID and were screened again. Patients who had already been randomized but did not receive study medication due to COVID-19 pandemic were also assigned to a new patient-ID and screened again. It was documented in the CRF that these patients had already been screened before.

6.4 Protocol Board

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6.5 Steering Committee

The Steering Committee of the TAMENDOX study was called the 'Protocol Board' and consisted of the following persons:

- Prof. Dr. med. Matthias Schwab, Institut für klinische Pharmakologie (IKP), Sponsor Representative
- Dr. med. Svitlana Igel, IKP
- Dr. med. Simon Jäger, IKP
- Dr. rer. nat. Imma Fischer, Institut für Klinische Epidemiologie und angewandte Biometrie (IKEAB), Eberhard Karl Universität Tübingen (UKT)
- Dr. med. Andreas Gerteis, Robert-Bosch-Krankenhaus (RBK) Stuttgart, Abteilung für Gynäkologie und Geburtshilfe

The tasks of the „Protocol Board" were as follows:

- Review the assessment of the pharmacovigilance (conducted by GBG Forschungs GmbH)
- Assessment of SAEs and SUSARs for plausibility and potential relationship to the study medication
- Assessment of the results from medical monitoring, compliance with the study protocol and study conduct
- Release of publications of the study
- Review of the manuscript to prevent forfeiture of patent rights to data not in the public domain
- Review and agree to any substantial amendments which may have an impact on the conduct of the study, on the potential benefit of the patient or may affect patient

safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects

- Review and agree to any non-substantial amendment, which means administrative changes of the protocol (minor corrections and/or clarifications that have no effect on the way the study is to be conducted)
- Consideration of an early termination of the trial based on the suggestion of the IDMC if less than 50 patients are recruited within 12 months.

6.6 Independent Data Monitoring Committee

In addition to the Protocol Board, the Independent Data Monitoring Committee (IDMC) of the GBG reviewed and monitored the conduct of the trial. The IDMC consisted of five members, three medical oncologists, one biometrician and a patients' advocate. The members were independent from the trial and familiar with the methodology of oncology trials. They were aware of the dangers of conclusions based on immature data and had agreed with the design and the goals of this protocol. IDMC meetings were held every six months. The mission of the IDMC was to ensure the ethical conduct of the trial and to protect patients' safety interests in this study.

After each meeting, the IDMC provided the Sponsor with a written recommendation to either modify or discontinue the study or to continue the study unchanged. The final decision to amend the protocol or to discontinue the clinical study could only be made by the Sponsor.

Early termination of the clinical study would have been considered by the Protocol Board based on the suggestion of the IDMC if less than 50 patients had been recruited within 12 months.

The IDMC consisted of the following 5 experts:

Anthony Howll, MD, Prof of Medical Oncology (Chair)

Dirk Hasenclever, Dr., Biometrics

Renate Haidinger, Journalist, Patient representative

Monica Castiglione, MD, Prof of Oncology

Dieter Hoelzer, MD Dr.h.c., Prof of Hematology and Oncology.

7. INTRODUCTION

Breast cancer is the most frequent female neoplasm. Up to 75% of tumors are estrogen receptor (ER)-positive and are therefore amenable to anti-hormonal treatment via an antiestrogen or the inhibition of estrogen synthesis. The selective estrogen receptor modulator tamoxifen, which was approved for the treatment of hormone-receptor positive breast cancer in the 1970s, is the mainstay of the treatment for premenopausal patients and is also used for postmenopausal patients with contraindications for an aromatase inhibitor. While adjuvant endocrine therapy with tamoxifen reduces recurrences risk by half, approximately one third of patients will suffer from disease relapse (Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2011).

Tamoxifen is extensively metabolized and (Z)-endoxifen (Z-4-hydroxy-N-desmethyl-tamoxifen) is its major active metabolite showing a approx. 100-fold higher efficacy at the ER. Of note, the formation of (Z)-endoxifen is mainly catalyzed by the highly polymorphic CYP2D6 enzyme and depends on genetic variation of the encoding gene. About 8% of the European population are CYP2D6 poor metabolizers (PM) due to the lack of functional alleles and up to 40% show reduced enzyme activity (Saladores et al. 2013; Zanger und Schwab 2013). Genetically determined compromised CYP2D6 activity leads to lower (Z)-endoxifen steady state plasma concentrations and tamoxifen efficacy (Schroth et al. 2009; Madlensky et al. 2011; Saladores et al. 2015; Helland et al. 2017).

Previous and ongoing studies with (Z)-endoxifen in patients with breast cancer and other solid tumors proofed the safety of daily (Z)-endoxifen doses of up to 160 mg/day. Moreover, (Z)-endoxifen has been approved for the acute treatment of manic episodes with or without mixed features of Bipolar I disorder by the Indian authorities. (List of new drugs approved in the year 2019 till date" (PDF). Central Drugs Standard Control Organisation. 1 October 2021. p. 4.).

The concept of the present TAMENDOX study pursues the supplementation of standard adjuvant tamoxifen (20 mg/d) with only low doses of endoxifen (up to 3 mg/d). In collaboration with Bayer, the doses used in this study have been calculated and validated by physiology-based pharmacokinetic (PBPK) modeling (Dickschen et al. 2012; Dickschen et al. 2014). (Z)-endoxifen concentrations as found in normal metabolizers (EM) can be attained by IM and PM patients in this way.

8. STUDY OBJECTIVES

Primary Objective

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.

Secondary Objectives

- To increase (Z)-endoxifen steady state concentrations in patients with CYP2D6 genotype predicted very low activity (PM genotype) to levels observed in patients with full CYP2D6 activity by supplementation with 3 mg/day (Z)-endoxifen (> 32 nM).
- To increase (Z)-endoxifen steady state concentrations in patients with CYP2D6 genotype predicted reduced activity (IM genotype) to levels observed in patients with full CYP2D6 activity by supplementation with 1.5 mg/day (Z)-endoxifen (> 32 nM).
- To increase (Z)-endoxifen steady state concentrations in patients with basal (Z)-endoxifen plasma levels ≤ 15 nM to levels observed in patients with full CYP2D6 activity by supplementation with 3 mg/day (Z)-endoxifen (> 32 nM).
- To increase (Z)-endoxifen steady state concentrations in patients with basal (Z)-endoxifen plasma levels > 15 nM and ≤ 25 nM to levels observed in patients with full CYP2D6 activity by supplementation with 1.5 mg/day (Z)-endoxifen (> 32 nM).
- To assess safety of low dose (Z)-endoxifen supplementation.
- To assess and compare steady state plasma levels of tamoxifen, N-desmethyltamoxifen, 4-hydroxytamoxifen, and possible other tamoxifen metabolites between the intervention groups and control group.

Explorative Objectives

Pharmacogenomic factors (e.g. gene variation, epigenetics) *other than* CYP2D6 that may explain the variability in pharmacokinetics of plasma levels of tamoxifen and its metabolites were assessed as explorative objectives. Biomaterial for part of these analyses was collected during the TAMENDOX trial. An independent additional informed consent had to be signed, called „Patienten-Information und Einwilligungserklärung: Etablierung einer Biomaterial-Bank im Rahmen der TAMENDOX-Studie“.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan Description

The clinical study was a prospective multi-center, interventional, single-blinded, three treatment arms, multi-dose, placebo-controlled, pharmacogenetics / pharmacokinetic study in pre- and postmenopausal female patients with ductal carcinoma in situ (DCIS) or locally advanced breast cancer including stage I, IIA, IIB and IIIA.

Tamoxifen treatment (20 mg/day) for at least three months in premenopausal and postmenopausal patients was mandatory prior to the start of the study, and was continued during intervention period without change of dosage. During the intervention, a daily oral dose of endoxifen or placebo was given according to CYP2D6 genotype or (Z)-endoxifen plasma concentrations (phenotype).

1. **Control group (Group 1):** Patients received placebo independent of *CYP2D6* genotype or (Z)-endoxifen plasma concentration.
2. **Group 2:** Patients received (Z)-endoxifen dosed according to *CYP2D6* "genotype" (i.e. genotype predicted IM or PM activity) or placebo (genotype predicted EM /UM).
3. **Group 3:** 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).

The intervention period was 6 weeks to assure steady-state levels. The duration of the total study period from inclusion (screening visit) until end of study visit (visit 4) was up to 14 weeks per patient. Initially, patient recruitment was planned to last up to one year.

Primary endpoint was the number of patients obtaining (Z)-endoxifen plasma concentrations >32 nM following 6 weeks of daily intake of the respective study medication.

Due to the COVID-19 pandemic, the patient recruitment had to be stopped in March 2020. In the substantial protocol amendment no. 1, dated 26.06.2020, 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.

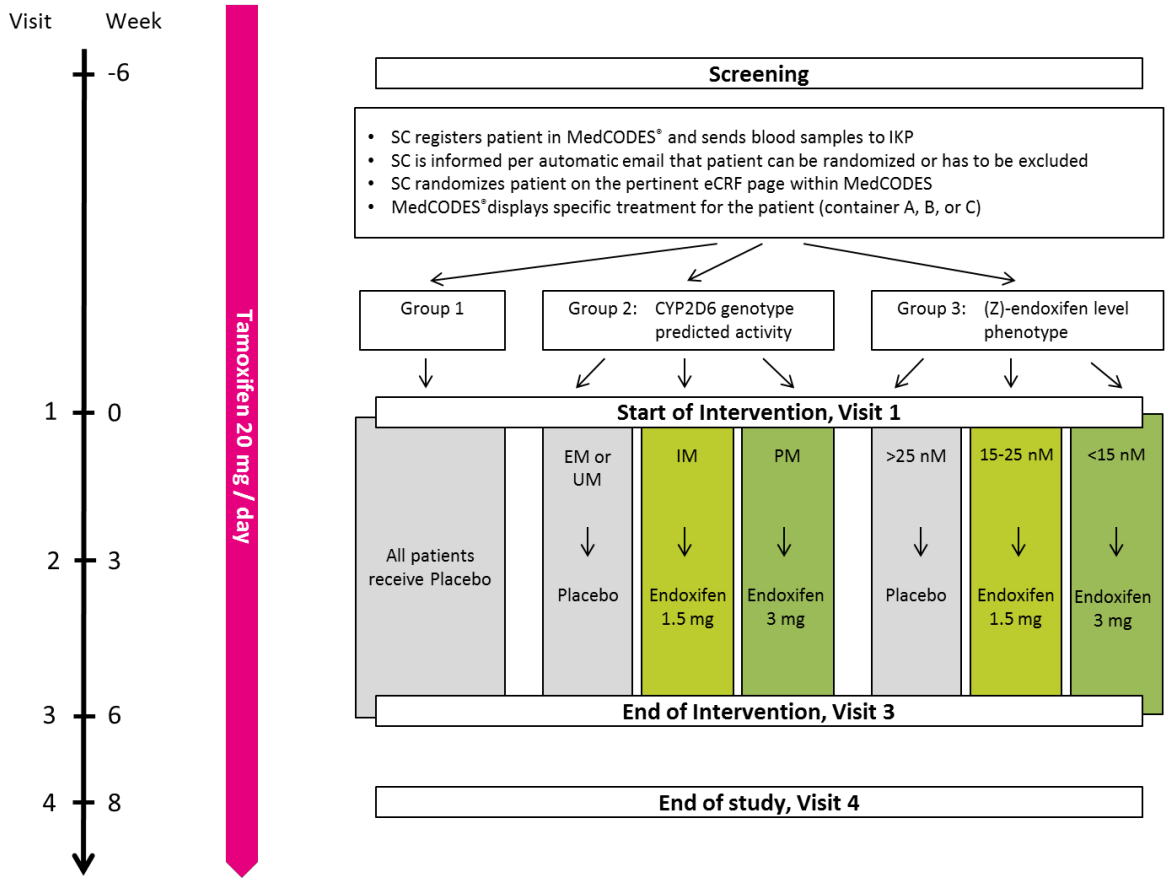


Figure 1 Study outline of TAMENDOX trial

PM = poor metabolizer, IM = intermediate metabolizer, EM = extensive metabolizer, UM = ultrarapid metabolizer

9.2 Discussion of Study Design, Including the Choice of Control Groups

The primary objective of the trial was to compare the proportion of patients reaching steady state (Z)-endoxifen levels > 32 nM in both interventions groups versus the proportion of patients reaching steady state (Z)-endoxifen levels > 32 nM in the control group. Supplementation will be based either on CYP2D6 genotype or (Z)-endoxifen plasma levels on screening, which will allow conclusions regarding the better strategy to reach (Z)-endoxifen levels > 32 nM. Details of the dose finding procedure are given below.

9.3 Selection of Study Population

The main eligibility criterion of the TAMENDOX trial was an established endocrine therapy in patients with a hormone receptor positive DCIS or stage I, II A, IIB or IIIA invasive cancer with 20 mg tamoxifen per day, for at least 3 months.

Number of patients

- To be analysed: 129 in the first stage of adaptive design, approximately 133 to 375 in total after the second stage.
- To be randomised to trial: n = 149 to 459 (estimated dropout rate: 20%).
- To be assessed for eligibility after signed informed consent: n = 181 to 643.

9.3.1 Inclusion Criteria

The study was initiated based on study protocol version 1.2, dated 10.07.2019. Following the recruitment stop due to COVID-19 pandemic in the substantial protocol amendment no. 1 to restart the recruitment, minor changes to inclusion criteria were made. According to the amended clinical study protocol, version 2.0, dated 26.06.2020, patients had to meet all of the following criteria (criteria from version 1.2 in brackets):

1. Written informed consent obtained prior to study entry. The patient must be accessible for scheduled visits and treatment.
2. Pre- and postmenopausal women with ductal carcinoma in situ (DCIS) or early stage breast cancer. This includes stage I, IIA, IIB, and IIIA breast cancers.
3. ER+/PR+, ER+/PR- or ER-/PR+ receptor status. Criteria for endocrine sensitivity is ≥1% ER-positive or PR-positive tumor cells on immune-histochemical staining
4. Patients on standard tamoxifen monotherapy (20 mg/d) for at least three months or patients who had switched from AI to tamoxifen who are on tamoxifen treatment for at least three months
5. Age ≥ 18 years
6. Body mass index of 18.5 to 35.0 kg/m2 *(previous version 1.2, dated 10.07.2019: 18.5 to 30.0 kg/m2)*
7. The Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
8. Absolute neutrophil count greater than or equal to 1 500/µL
9. Platelets greater than or equal to 100 000/µL
10. Total bilirubin within less than or equal to 1.5 times institutional upper limit of normal
11. AST/ALT less than or equal to 2.5 times institutional upper limit of normal
12. The subjects need to be either
    a. of non-childbearing potential (documented postmenopausal status, defined as no menses for 12 months without an alternative medical cause, or post hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or
    b. of childbearing potential (WOCBP) with negative serum pregnancy test (due to the known reproduction toxicity of tamoxifen found in preclinical studies, WOCBP need to use a highly effective non-hormonal contraception. These are copper IUDs, bilateral tubal ligation, a vasectomized partner (vasectomy at least three months prior to screening) or sexual abstinence. Male or female condoms with/ without spermicide or caps, diaphragms or sponges with spermicide are associated with a failure rate > 1% per year and are thus not sufficient during the intervention period.
13. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 5.0 Grade ≤ 2 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion)
14. Surgery and radiation therapy of the breast has to be completed upon study entry

9.3.2 Exclusion Criteria

The study was initiated based on study protocol version 1.2, dated 10.07.2019. Following the recruitment stop due to COVID-19 pandemic in the substantial protocol amendment no. 1 to restart the recruitment, minor changes to exclusion criteria were made. According to the amended clinical study protocol, version 2.0, dated 26.06.2020, patients had to meet all of the following criteria (criteria from version 1.2 in brackets):

1. Subjects who are unable to understand written and verbal instructions
2. Locally advanced (Stadium IIIB or IIIC) or metastatic (Stage IV) breast cancer at the time of surgery
3. Ongoing chemotherapy and/or treatment with trastuzumab within the last three months; participation in another trial with any investigational/not-marketed drug within 3 months prior to baseline visit
4. Other active second malignancy
5. Invalid result of genotyping
6. Pregnancy
7. Breast feeding/lactation
8. Oral contraceptives containing estrogens and/or progesterones
9. Pathologic vaginal bleeding in pre-menopausal women or vaginal bleeding in post-menopausal patients
10. Current severe acute somatic or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in judgement of the investigator, would make the patient inappropriate for entry into this study.
11. Severe chronic cardiac or pulmonary disease (heart failure NYHA class 3 and 4), COPD GOLD C or D
12. Chronic or acute renal disease with a glomerular filtration rate < 60 ml/min/1.73 m2, and any patient on peritoneal dialysis or hemodialysis
13. Medical history of thromboembolism (deep vein thrombosis or pulmonary embolism)
14. QTc interval >470 ms at screening ECG *(previous version 1.2, dated 10.07.2019: 14. QTc interval >0.45 sec at screening ECG)*
15. Concurrent treatment with strong to moderate inhibitors of CYP2D6 which may alter tamoxifen metabolism (Consortium on Breast Cancer Pharmacogenomics 2008):

    paroxetine, fluoxetine, bupropione, quinidine

    and

    duloxetine, diphenhydramine, thioridazine, amiodarone, cimetidine, sertraline
16. Known allergies against an ingredient of the investigational product (e.g. Mannitol, modified cellulose, magnesium stearate, polyvinylpyrrolidone, methacrylic acid and ethyl acrylate copolymer, talcum, titanium dioxide, triethyl citrate, glycerol triacetate, silica, sodium dodecyl sulfate, sodium bicarbonate) or tamoxifen

9.3.3 Removal of Patients from Therapy or Assessment

If a patient showed one of the following reasons the study treatment had to be discontinued:

- Discontinuation of tamoxifen therapy due to any reasons (e.g. relapse of breast cancer)
- Intolerable toxicity
- Withdrawal of consent or loss to follow-up (the subject did not receive any further investigational product or further study observation)
- Pregnancy or intent to become pregnant
- Initiation of alternative anticancer therapy including another investigational agent
- Patient's request or non-compliance

The reason and date of discontinuation for all patients was documented on the Case Report Form (e.g. progressive disease, death, adverse event, withdrawal of consent, lost to follow-up, etc.). The investigator attempted to complete all the procedures planned for Visit 4 at the time of discontinuation of systemic treatment.

9.4 Treatments

9.4.1 Treatments Administered

9.4.1.1 Treatment Plan

Non-investigational product:

Patient continued tamoxifen therapy with 20 mg per day throughout the study. Dosage or time point of intake should not be changed during the study period.

Investigational product:

Patients were randomized into a placebo group and two intervention groups. Patients in the intervention groups received (Z)-endoxifen or placebo according to their CYP2D6 genotype (Group 2) or according to their basal (Z)-endoxifen plasma concentration phenotype (Group 3).

Table 1 Treatment in different study groups

Patient groups	Medication	Dosage	Duration
Control group:			
All patients	placebo	1 tablet/d	42 days [(1)]
Group 2: CYP2D6 genotype			
PM	(Z)-endoxifen	3 mg/d	42 days [(1)]
IM	(Z)-endoxifen	1.5 mg/d	42 days [(1)]
EM / UM	placebo	1 tablet/d	42 days [(1)]

Group 3: (Z)-endoxifen plasma concentration phenotype			
≤ 15 nM	(Z)-endoxifen	3 mg/d	42 days [1]
> 15 to ≤ 25 nM	(Z)-endoxifen	1.5 mg/d	42 days [1]
> 25 nM	placebo	1 tablet/d	42 days [1]

[1] Patient received medication for 50 days. Per protocol treatment was 6 weeks = 42 days. In any case, the study medication had to be taken until the day before visit 3 (which was at the latest at day 50)

9.4.1.2 Dose Modification and/or Treatment Delay

(Z)-Endoxifen dosage was based either on CYP2D6 genotype or basal (Z)-endoxifen plasma concentration according to Table 1. No dose modification was foreseen. However, if a patient showed one of the following reasons the study treatment had to be discontinued:

- Discontinuation of tamoxifen therapy due to any reasons (e.g. relapse of breast cancer)
- Intolerable toxicity
- Withdrawal of consent or loss to follow-up (the subject will not receive any further investigational product or further study observation)
- Pregnancy or intent to become pregnant
- Initiation of alternative anticancer therapy including another investigational agent
- Patient's request or non-compliance

9.4.2 Identity of Investigational Product(s)

Table 2 Investigational Medicinal Product

	Enteric-coated tablets (Z)-endoxifen 1.5 mg	Enteric-coated tablets (Z)-endoxifen 3 mg	Placebo (enteric-coated tablets)
Active ingredient	(Z)-endoxifen	(Z)-endoxifen	N/A
Formulation:	Enteric coated tablet	Enteric coated tablet	Enteric coated tablet
Strength or concentration:	1.5 mg	3 mg	0 mg
Route/Mode of administration:	oral	oral	oral
Batch number	TAMENDOX/201929	TAMENDOX/201928	TAMENDOX/201930

9.4.3 Method(s) of Assigning Patients to Treatment Groups

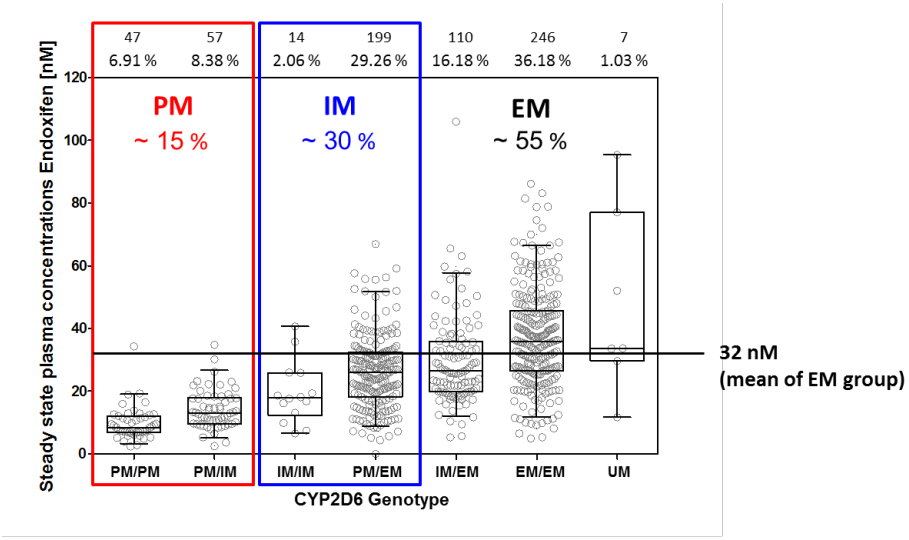
Baseline blood samples were obtained for genotyping of *CYP2D6* and quantification of tamoxifen and (Z)-endoxifen plasma concentrations, which was finished by IKP within a maximum of three weeks after reception of the blood samples. Patients were randomly assigned to one of the three groups:

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 (Institute for Clinical Epidemiology and Applied Biometry, Tübingen). The resulting randomization list was sent to the GBG and implemented in MedCODES®. During the study, the patient was not informed about the treatment allocation, the results of genotype and plasma concentration respectively and the dosage of the study medication (single blind).

9.4.4 Selection of Doses in the Study

Dose calculation was based on two independent complementary modelling approaches using data from 680 pre-/postmenopausal tamoxifen treated patients of prospective studies IKP211 (Mürdter et al. 2011) (DRKS00000605) and POSH (Saladores et al. 2015), see Figure A and B). No differences in (Z)-endoxifen plasma concentrations were observed between pre- and postmenopausal patients.

A



B

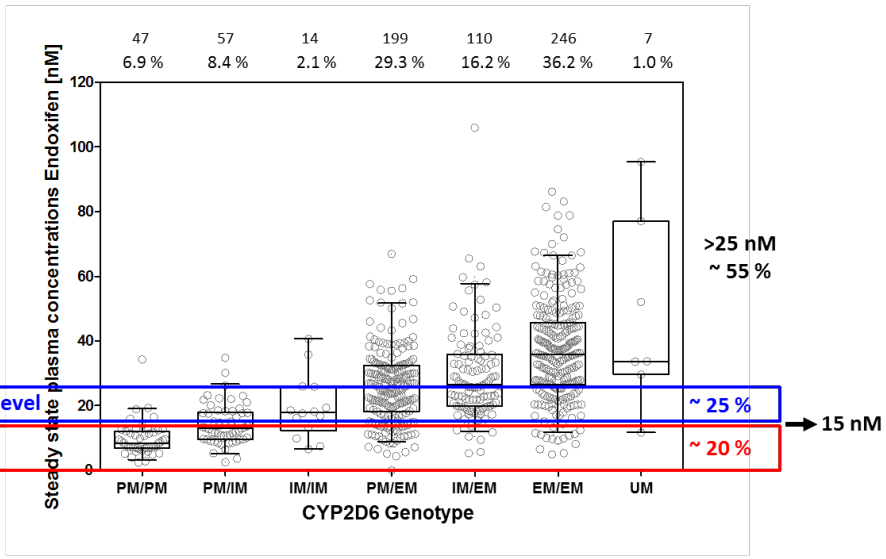


Figure 2 (Z)-endoxifen steady state plasma concentrations

680 European breast cancer patients under therapy with 20 mg tamoxifen were stratified according to *CYP2D6* genotype (for allele assignment see Table 8.3). A: Intervention group 2 by *CYP2D6* genotype. B: Intervention group 3 by (Z)-endoxifen plasma concentration phenotype.

9.4.5 Selection and Timing of Dose for Each Patient

The dose for a given patient was determined according to the study group into which the patient was randomized:

Group 1: Control

All patients randomized to control group received placebo.

Group 2: Dosage according to *CYP2D6* genotype

Patients with two non-functional alleles and patients with one non-functional allele and one allele encoding for a protein with reduced activity are defined as PM. Patients with two alleles of reduced activity and patients with one non-functional allele and one allele encoding for a fully functional allele are defined as IM. Patients with one reduced-activity allele and one functional allele, or with two functional alleles, or with duplicated functional alleles are defined as EM, including the ultra-rapid metabolizers (Table 3). The doses of endoxifen supplementation for the PM and IM group have been estimated by PBPK-modelling according to Dickschen et al. 2012 (Dickschen et al. 2014). In addition, population pharmacokinetics (pop-PK) analysis was performed using a refinement of the method published by Dahmane 2013 (Dahmane 2013). Both models led to comparable dosages with slightly lower doses in the pop-PK approach. Patients assigned to the EM group will not receive any (Z)-endoxifen supplementation but placebo (Table 4).

Table 3 Assignment of CYP2D6 alleles to CYP2D6 activity

CYP2D6 genotype predicted activity	CYP2D6 alleles tested
Poor metabolizer (PM)	*3, *4, *5, *6, *7, *8, *14
Intermediate metabolizer (IM)	*9, *10, *17, *41
Extensive metabolizer (EM)[(1)]	*1

[(1)] Including ultrarapid metabolizers (UM/EM) resulting from gene duplication

Table 4 Dosage of endoxifen tablets in Group 2 (“Genotype”)

CYP2D6 activity	Assigned according to CYP2D6 genotype	(Z)-Endoxifen (free base)
PM	PM/PM, PM/IM	3 mg
IM	IM/IM, PM/EM	1.5 mg
EM / UM	IM/EM, EM/EM, UM/EM	none

<u>Group 3:</u> Dosage according to (Z)-endoxifen steady state plasma concentrations under standard tamoxifen treatment

The cut-off between patients with low (Z)-endoxifen plasma concentrations (requiring the higher dose) and patients with medium (Z)-endoxifen plasma concentrations (requiring a lower dose) was set according to clinical outcome data at 15 nM (Madlensky et al. 2011; Saladores et al. 2015). Patients with (Z)-endoxifen plasma concentrations > 25 nM will not receive any (Z)-endoxifen supplementation but placebo. The dosage in this intervention group is based on the pop-PK analysis (Table 5).

Table 5 Dosage of endoxifen tablets in Group 3 ("Phenotype")

Assigned according to basal (Z)-endoxifen C_{ss}	**(Z)-Endoxifen (free base)**
≤ 15 nM	3 mg
> 15 nM ≤ 25 nM	1.5 mg
> 25 nM	none

9.4.6 Blinding

Blinding was performed for patients and for the person in charge and all laboratory staff of the measurement of (Z)-endoxifen plasma levels during the treatment phase of the study. Members of the laboratory only had access to eCRF-pages "BL07a and b "Biomaterials", BL08a and b "Backup Sample", BL09a and b "Central LAB (IKP)" (MedCODES role for central lab users). These pages included only the Patient No. and did not disclose any information on patients and medications.

9.4.7 Prior and Concomitant Therapy

All medications (prescription and non-prescription) taken by the subject from screening throughout their entire participation in the study, including those initiated prior to the start of the study, had to be recorded on the subject's source document and on the appropriate page of the eCRF. The active substance and its indication had to be recorded.

By definition, all patients received tamoxifen as standard treatment. Co-prescription of tamoxifen and medications that inhibit CYP2D6 has already been thoroughly investigated and recommendations were published, e.g. in (Consortium on Breast Cancer Pharmacogenomics 2008).

<u>Prohibited Medication</u>

Prohibited medications during the study are listed below.

- Oral contraceptives containing oestrogens and/or progesterone
- Concurrent chemotherapy and trastuzumab
- Concurrent treatment with strong to moderate inhibitors of CYP2D6 which may alter tamoxifen metabolism (Consortium on Breast Cancer Pharmacogenomics 2008):

  paroxetine, fluoxetine, bupropione, quinidine

  and

  duloxetine, diphenhydramine, thioridazine, amiodarone, cimetidine, sertraline

Antidepressants that are allowed as concomitant medication include venlafaxin, citalopram, and escitalopram. Premenopausal patients treated with an adjuvant endocrine therapy regimen that includes GnRH (gonadotropin-releasing hormone) analogues, e.g. leuprolide, buserelin, histrelin, and deslorelin, in order to achieve ovarial suppression are permitted to enter the study. No significant interactions between GnRH analogues and endoxifen are expected.

Other Restrictions

Surgery and radiation therapy had to be completed upon study entry, as outlined in the inclusion and exclusion criteria.

Grapefruit juice should be avoided during the intervention period (visit 1 to visit 3) due to its known inhibition of CYP3A4. Regular consumption (i.e. intake of grapefruit juice over more than three days) should be documented.

9.4.8 Treatment Compliance

Study personnel instructed the study patients about intake of the study medication prior to dispensing the IMP. Investigational product was dispensed as noted in the "Patient Drug Accountability Log".

The patients received a medication diary and were instructed to return the bottle with the unused IMP to the study site at visit 3 for tablet counts and disposal. Patients were asked whether they had taken their IMP as instructed at study visits 2 (3 weeks of intervention) and 3 (6 weeks of intervention) and the diary was reviewed and data were transferred to the eCRF.

Any problems with IMP compliance were discussed with the patient. Missing three or more consecutive days of dosing constituted a major protocol violation and had to be discussed with GBG and the Sponsor.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

9.5.1.1 Efficacy Assessments /Endpoints

Evaluation of primary endpoints

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. The analysis was stratified for genotype for a target significance level (α) of 0.05 and the decision for maintaining or rejecting the null hypothesis was made by applying one-sided tests. In order to take account of the multiple testing problem, a pre-defined hierarchical procedure was conducted in the interim analysis.

The observed effects will be described by applying means which include the relative risks and the appropriate 95 % confidence intervals. The confirmatory statistical analysis will be based on the intention-to-treat principle (ITT) using the results of the pharmacokinetic analysis of the blood samples at visit 4. In the final analysis (not in the interim analysis) a per-protocol (PP) analysis will be conducted in addition.

Evaluation of secondary endpoints

As secondary endpoints the increase of (Z)-endoxifen levels between Visit 1 and Visit 3 in patients without and with (Z)-endoxifen supplementation at different doses were calculated.

Furthermore, steady state plasma levels of tamoxifen, desmethyl-tamoxifen, 4-hydroxytamoxifen, and possibly other tamoxifen metabolites were compared between the intervention groups and the control group. These analyses were statistically assessed for descriptive purposes and not in a confirmatory manner. The aim was the receipt of an explorative data analysis, not hypothesis-testing or generation of evidence for efficacy.

Secondary endpoints were not analysed in the interim analysis.

Evaluation of explorative endpoints

To assess pharmacogenomic factors (e.g. gene variation, epigenetics) other than CYP2D6 which can explain the variability in pharmacokinetics of plasma levels of tamoxifen and its metabolites was a explorative objective of the TAMENDOX trial. All variables were evaluated using descriptive statistical analysis methods. Pharmacokinetic parameters (e.g. metabolite plasma levels) and other variables between groups (e.g. of genetic variants) were compared by t-tests, non-parametric tests (e.g. Wilcoxon-Mann-Whitney tests, Kruskal-Wallis tests) or Fisher's exact tests as appropriate. All statistical analyses were performed by statistical software packages in SAS Version 9.4. No evaluation of exploratory endpoints was planned for the interim analysis.

9.5.1.2 Safety Assessments /Endpoints

For all patients of the study groups adverse drug reactions were reported descriptively. Safety and tolerability were assessed by clinical review of all relevant parameters including adverse events, laboratory tests, vital signs, weight, and ECGs. No inferential testing for statistical significance was performed. Laboratory, vital signs, weight, and ECG data were summarized descriptively.

Adverse Events

All subjects were monitored for AEs during the study by the investigators. Patients were instructed by the investigator to report the occurrence of any adverse event.

AEs were classified using the MedDRA® classification system. All AEs were summarized by system organ class, preferred term, severity, and relationship to IMP. AEs leading to death or to discontinuation from treatment and SAE were also tabulated. In the by-subject analysis, a subject having the same event more than once was counted only once and by greatest severity.

Laboratory Evaluations

- Haematology: haematocrit, erythrocyte count, haemoglobin, white blood cell count with differential, platelets
- Chemistry: Glucose, creatinine, urea, sodium, potassium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyl transferase (GGT), albumin, bilirubin, INR. Triglycerides will only be

measured at screening and visit 3. Pathologic laboratory values in triglycerides levels have to be controlled with a fasting blood sample.

- Urinalysis: Standard urine dipstick: pH, specific gravity, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, erythrocytes. In case of clinically relevant findings, further evaluation should be performed and the findings documented.
- Pregnancy test: a serum pregnancy test needs to be obtained at the time points indicated in the Table of Assessments in women of child-bearing potential.

Vital Signs, ECG, Physical Examination and Other Safety Related Observations

Vital signs (blood pressure, heart rate and body temperature) were recorded at every visit indicated in the Table of Assessments.

Blood pressure and heart rate: Systolic and diastolic blood pressure as well as the heart rate (electronically and/or by palpation, count for 30 seconds) were measured after 5 min of rest in seated position.

Body temperature: Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid and reproducible results according to common clinical practice.

9.5.2 Appropriateness of Measurements

All measurements described in Section 8.5.1.2 of this report are recognized standard methods. Therefore, no further details concerning reliability or relevance will be discussed here.

9.5.3 Primary Efficacy Variable(s)

This study is a pharmacokinetic study without any efficacy parameters monitored. Therefore, as efficacy parameters only the steady state plasma concentrations of (Z)-endoxifen (primary endpoint) and tamoxifen, N-desmethyltamoxifen and (Z)-4-hydroxytamoxifen (secondary endpoints) were determined by a validated UPLC tandem mass spectrometric assay involving isotope labelled internal standards.

Pharmacokinetic efficacy was defined as the proportion of patients with steady state (Z)-endoxifen plasma levels above 32 nM (Z)-endoxifen (mean of EM group in Fig. 2A) following (Z)-endoxifen supplementation after 6 weeks.

9.5.4 Other Measurements

N/A

9.6 Data Quality Assurance

Data Management and Documentation

Data management was carried out by the GBG Forschungs GmbH using the proprietary GBG Forschungs web-based EDC system, “GBG MedCODES® – Medical CRF Online Documentation

& Evaluation System". Data management activities included CRF design, database creation, MedCODES® application hosting, Data Entry and Data Validation.

Monitoring

Monitoring was the responsibility of GBG Forschungs GmbH. On-site visits were made before the study began and, as far as possible due to COVID-19 pandemic reasons, at regular intervals during the study. In cases, monitors were not allowed to enter the study centre remote monitoring was conducted during the study. Source data verification was conducted on site.

In particular, the patient enrolment, the completeness, accuracy and plausibility of the data entered in the CRFs, verification against source data and occurrence of AEs were monitored. The confidentiality of study documents was maintained at all times.

Handling of missing data

All variables included in the CRF were mandatory. The monitoring assured quality of the assessments. According to the study protocol version 2.0 dated 26.06.2020, the pattern of missing data for the primary endpoint was analysed within a blinded review before the close of the data base and unblinding. The details of handling of missing data in the analysis of the primary endpoint are described in the SAP and the Statistical Report. All other missing data are given in the tables but excluded from the statistical tests.

Data Entry and Queries

All CRF data were entered by the study staff at the study site into the trial database using the MedCODES® application. These data were checked for plausibility and value ranges automatically or manually before the data were accepted.

Patient diary data were entered into MedCODES® by the study nurses. Laboratory values concerning endoxifen levels and genotyping were entered into MedCODES® eCRF by laboratory staff of IKP (MedCODES role for central lab users).

Other lab values assessed by IKP like i.e. desmethyltamoxifen, 4-hydroxytamoxifen, and possible other tamoxifen metabolites were not brought into the eCRF, but entered and stored in an IKP system.

All CRF data were reviewed by a data entry clerk, who created queries for data fields that do not match the trial guidelines. These queries were stored and forwarded (within MedCODES®) to the study site for resolution. The resolved queries were checked again by a data entry clerk and either closed or re-queried.

Data Validation

Visual and computerized methods of data validation were applied in order to ensure accurate, consistent and reliable data (for details, see “Data Validation Plan”, version 1.4 dated 26.02.2021).

Database Closure and Lock

At the end of recruitment, new patient randomization or registration functionality was stopped. After data base closure (soft lock), new data entry was not permitted, but data changes for cleaning were still allowed. After database lock (hard lock), all patient data was set to “Final Status” and no data changes were permitted any longer. The database was locked to any kind of manipulation and handed over to the biostatisticians at IKEAB.

Data Protection

The Informed Consent Form included data protection and privacy legislation. Pursuant to this wording, the patients authorized the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study by signing the Informed Consent Form. Confidentiality is maintained in accordance with the General Data Protection Regulation (GDPR) and respective national data protection laws.

In the Informed Consent Form it is also explained that for data verification purposes, monitors, auditors and/or inspectors from a regulatory authority may require direct access to the study records including patients’ medical history.

On request, investigators were provided with a written report of the patients CYP2D6 metabolic activity at Visit 4 (End of Study) (8.7.1.).

The sponsor will never provide individual genotype results to any insurance company, any employer, their family members, general practitioner or any other third party, unless required to do so by law.

Pseudonymisation and anonymisation

All patient data were pseudonymised and entered into the eCRF by the study staff at the study sites. The eCRF is the electronic study database, where the pseudonymised patient data were stored. Only pseudonymised data were communicated between the trial site and the GBG Forschungs GmbH as well as between the GBG Forschungs GmbH and the sponsor and the biostatisticians.

Pseudonymisation means that no names or initials were used, only a number and/or letter code. No one other than the study site could identify the name of the patient by this number.

Other third parties only received anonymized data, which could not anymore be assigned to a patient.

Data Transfer and Network Access

All Communication between the MedCODES® server and the client computers was conducted via 256 Bit encrypted HTTPS (Secure HTTP) connections.

User Access Control

Every user was provided with a personal username and password which defined their access rights as well. Access control was based on the Users Role in MedCODES®. Therefore users could only access and amend those datasets necessary for them to fulfil their tasks. Each activity in MedCODES® was tracked in an audit trail and could be analysed at each time point.

Record retention

Copies of all pertinent on-site information (investigator's file and source data) are retained by the investigator for a period of at least 10 years from the end of the trial. The Trial Master File and Trial Databases (representing the original Case Report Forms) are kept at the RBMF for the same period of time. Thereafter study documents will be destroyed.

Laboratory

All study centres were supplied with a laboratory manual describing the blood sampling procedures, processing, storage and shipment of samples to the central laboratory at IKP. All (Z)-Endoxifen plasma concentrations were determined by a validated analytical procedure according to GLP requirements at the central laboratory.

All clinical chemistry parameters were assessed by the local clinical laboratory according to the locally established and validated processes.

Auditing

Auditing was performed by different independent auditors according to their field of expertise:

cGMP production of the API at Alchem Laboratories Corporation (13305 Rachael Boulevard, Alachua, FL 3261, USA) was audited by Frederick M Lochner, (Intertek, Palm Harber, FL, USA) from 16. – 17.11.2017.

GMP-manufacturing process at Corden Pharma GmbH was audited by Dr. David Meyrath (Universitätsklinikum Heidelberg, Apotheke, Im Neuenheimer Feld 670, 69120 Heidelberg) based on the report created by Valeri L. Whipp, Supervisory Consumer Safety Officer, OPQO, Devision I, FDA, 10 Waterview Blvd, Parsippany, NJ, USA during her audit from 2. – 6.7.2018.

Labelling and release of IMP by the University Hospital Pharmacy Heidelberg (Universitätsklinikum Heidelberg, Apotheke, Im Neuenheimer Feld 670, 69120 Heidelberg) was audited by Melanie Zillig, Head of Quality Assurance (SocraTec R&D GmbH, Im Setzling 35, 61440 Oberursel, Germany) on 26.09.2018.

The subcontractor qualification audit of the German Breast Group Forschungs mbH (GBG), Martin-Behaim-Straße 12, 63263 Neu-Isenburg (new address since 18.07.2022: Dornhofstraße 10, 63263 Neu-Isenburg) was performed by Melanie Zillig, Head of Quality Assurance (SocraTec R&D GmbH) on 26.-27.02.2018 (except for data management, IT and PV)

Data Management and IT at GBG was audited by Roland Buchholz, QM Consulting and Audit Services on 18.-19.06.2018

Pharmacovigilance at GBG was audited by Dr. Andrey Molchanov, Fontane Pharma GmbH on 19.06.2018.

The GCLP document audit of the central laboratory at the IKP was conducted by Roland Buchholz on 11.05. – 03.06.2020.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

9.7.1.1 Analysis Sets

Analyses were based on the following sets:

ITT Set

The intention-to-treat population (ITT) includes all randomized patients, with the exception of:

- Patients who are randomized in contradiction to one of the inclusion or exclusion criteria
- Patients who withdraw their informed consent for the analysis of their data during the study. As written in the informed consent for this trial the patients will be not able to withdraw their informed consent for the analysis of their collected data.
- Patients who were randomized but not treated. According to the blind review (data analysis for pre-defined variables with unknown group allocation) n = 11 patients were randomized but never treated. Due to the treatment blinding for patients and physicians within this study, this procedure will have no influence to the study results.
- The reasons for no treatment were:

  n = 2 COVID-19 infection (received no study medication)

  n = 7 patient's decision (n = 1 patient's wish, n = 1 did not want to start, 1 = booking holiday in Namibia for march, n = 1 dose reduction of Tamoxifen, n = 3 withdraw of informed consent)

  n = 2 investigator's decision (PatID 15: vaginal bleeding since screening; PatID 100: new unclear gynaecological finding Tamoxifen is likely to be discontinued).

Per Protocol Set

The per protocol population (PP) was based on the ITT, and additionally patients with major protocol violations (e.g. use of prohibited medications during the study) were excluded. The PP is the secondary analysis population.

Safety Set:

The safety population includes all randomized patients who received at least one tablet of study medication.

9.7.1.2 Demographic and Baseline Characteristics

The following variable groups were considered as demographic and baseline variables:

- Demographic characteristics (age, gender, race, smoking status)
- Anamnestic characteristics (BMI, ECOG performance status, reproductive status)
- Disease parameters (tumour site, diagnosis since, histopathological parameters: tumour type, tumour grading, UICC staging, ER, PR, HER-2, KI-67), signs and symptoms (with CTCAE grade) and cardiac monitoring
- Tamoxifen level, basal (Z)-endoxifen phenotype and CYP2D6 genotype.

9.7.1.3 Efficacy Analyses

9.7.1.3.1 Primary Endpoint

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.

For every patient the primary endpoint was defined as follows:

1) Patients who reach a steady state (Z)-endoxifen plasma levels above 32 nM were defined as success.

2) Patients with a steady state (Z)-endoxifen plasma levels ≤ 32 nM were defined as failures.

Statistical analysis of the primary outcome was a chi-square test stratified for genotype (Mantel Haenszel; one-sided).

H_o: The proportions of successes are equal in the supplementation groups (group 2) and in the control group (group 1).

H_1: The proportions of successes are higher in the genotype group (group 2) than in the control group (group 1).

The observed effects were described by applying means which include the relative risks and the appropriate 95 % asymptotic Wald confidence intervals. This analysis was performed for the ITT population and for the PP population as well. The analysis of the results was performed according to section 6.3 of the SAP dated 23.08.2021.

9.7.1.3.2 Secondary Endpoints

As secondary endpoints the increase of (Z)-endoxifen levels between Visit 1 and Visit 3 in patients without and with (Z)-endoxifen supplementation at different doses will be calculated.

Additionally, the secondary endpoints according to section 3.6.2 of the SAP dated 23.08.2021 were analysed.

Furthermore, steady state plasma levels of tamoxifen, N-desmethyltamoxifen, 4-hydroxytamoxifen, and possibly other tamoxifen metabolites were compared between the intervention groups and the control group. These analyses was statistically assessed for descriptive purposes and not in a confirmatory manner. The aim was the receipt of an explorative data analysis, not hypothesis-testing or generation of evidence for efficacy.

For every patient the secondary endpoints were defined as follows:

- Increase of (Z)-endoxifen level

  1) Patients with increased (Z)-endoxifen plasma level until visit 3 were defined as success.

  2) Patients with no increase of the (Z)-endoxifen plasma level until visit 3 were defined as failures.

Statistical analysis of the secondary outcomes was also performed via chi-square test stratified for genotype (Mantel Haenszel; one-sided).

- Increase of (Z)-endoxifen level:

  H_0: The proportions of successes are equal in the supplementation groups (group 2 and 3) and in the control group (group 1).

  H_1: The proportions of successes are higher in the genotype group (group 2) and phenotype group (group 3) than in the control group (group 1).

The observed effects were described by applying means which include the relative risks and the appropriate 95 % confidence intervals. This analysis was performed for the ITT population and for the PP population.

9.7.1.3.3 Exploratory Endpoints

It was planned to assess pharmacogenomic factors (e.g. gene variation, epigenetics) other than CYP2D6 which can explain the variability in pharmacokinetics of plasma levels of tamoxifen and its metabolites is an explorative objective of the TAMENDOX trial. All variables should have been evaluated using descriptive statistical analysis methods. Pharmacokinetic parameters (e.g. metabolite plasma levels) and other variables between groups (e.g. of genetic variants) should have been compared by t-tests, non-parametric tests (e.g. Wilcoxon-Mann-Whitney tests, Kruskal-Wallis tests) or Fisher's exact tests as appropriate.

These analysis were not performed due to lower number of patients available for these analysis. Due to COVID-19 pandemic the number of patients randomised was lower than originally planned. Furthermore, not all patients gave their informed consent to these additional analyses.

9.7.1.3.4 Additional Analyses to Assess Impact of COVID-19 Pandemic

For the patients with re-screening (n = 15) only the data of the second screening were used within the analyses. Due to the small number of patients with re-randomization (n = 2) no separate analysis was performed for this group, the data of second randomization were analysed within the planned descriptive and statistical analyses.

9.7.1.4 Safety Analyses

For all patients of the intervention groups adverse drug reactions were reported descriptively. Safety and tolerability were assessed by clinical review of all relevant parameters including adverse events, laboratory tests, vital signs, weight, and ECGs. No inferential testing for statistical significance was performed. AE were classified using the MedDRA® classification system, version 24, March 2021.

All AEs were summarized by system organ class, preferred term, severity, and relationship to IMP. AEs leading to death or to discontinuation from treatment and SAE were also tabulated. In the by-subject analysis, a subject having the same event more than once was counted only once and by greatest severity, and any repetition was ignored; the denominator was the total safety population size.

Laboratory, vital signs, weight, and ECG data were summarized descriptively.

9.7.1.5 Other Target Parameters

N/A

9.7.2 Determination of Sample Size

TAMENDOX is a superiority trial, designed to demonstrate superiority of (Z)-endoxifen supplementation in comparison to placebo. A fixed sample size was calculated to show a 42.9% relative increase (from 35% to 50%) in the primary outcome with an alpha (type 1 error) of 0.05 (one-tailed) and a power of 80%. This increase was considered clinically relevant as in a cohort under standard tamoxifen, which consisted of extensive metabolizers, 50% achieved the target value of 32 nM. A sample size of 134 in each group will have 80% power to detect the difference of 15% between intervention and control group (one-sided χ^2-test; nQuery Version 7.0). Assuming a drop-out rate of approximately 25%, a total of 504 patients need to be randomized to obtain 402 evaluable patients with complete data.

As the recruitment in the study was lower than half of expected (98 randomized, 252 expected, end of March, 2020); and, unfortunately the recruitment was stopped due to COVID-19 pandemic; it seems to be unrealistic to reach the planned sample size until end of 2020. Therefore, alternatively to the original planned fixed design for the TAMENDOX study, an adaptive design according to Bauer/Köhne (1994) was planned. Additional pre-defined rules for eventually stopping one of the two experimental arms were implemented in a hierarchical approach. With the hierarchical approach it should be possible to decide, which one of the two experimental arms should be stopped after the interim analysis with stopping preference for the phenotype arm. With the adaptive design it should be possible to

determine stopping rules (for futility or efficacy) for one or two of the experimental arms and/or to determine sample size for a final analysis in a two-armed study after the interim analysis.

The results concerning the primary in step 1 for the first 129 randomized patients who have reached the end of the treatment phase according to the intention-to-treat principle. Depending on the results of this first step a second step will be carried out.

Within the interim analysis the data of the first n = 129 randomized patients who successfully terminated the trial were analysed according to the SAP for the interim analysis dated 29.12.2020. As presented in the Statistical Report for the Interim Analysis, final dated 25.01.2021, 26.2% (n = 11) of n = 42 patients in the control group, 69.6% (n = 32) of n = 46 patients in the genotype group, and 78.0% (n = 32) of n = 41 patients in the phenotype group reached the primary endpoint (endoxifen plasma concentration > 32 nM after 6 weeks therapy). The comparison of success between the randomized groups results in $p < 0.001$ (one-sided Mantel-Haenszel χ^{2}-test stratified for genotype). This result was significant on the $\alpha_1 = 0.0045$ level.

Therefore, the trial was successful and needs no further sample size calculation. According to the study protocol Version 2.0 dated 26.06.2020 the trial was closed to recruitment at 15.02.2021 (IKP letter to IDMC, answer of IDMC 26.02.2021); last randomization date 01.03.2021).

9.8 Changes in the Conduct of the Study or Planned Analyses

Due to COVID-19 pandemic, the recruitment of patients had to be interrupted from March to August 2020. Moreover, the number of patients recruited until March 2020 was lower than expected. Therefore, in the substantial amendment no. 1, version 1.0 dated 26.07.2020, an interim analysis has been implemented and a corresponding Statistical Analysis Plan (SAP) for the Interim Analysis (version 2.0 dated 29.12.2020) was drawn up.

Alterations to the Statistical Analysis Plan

No changes of the finalised SAPs (Statistical Analysis Plan (SAP) of Interim Analysis, final version, signed by statistician on 05.01.2021 and Statistical Analysis Plan of the final analysis, final version dated 23.08.2021, were made.

10. STUDY PATIENTS

10.1 Disposition of Patients

Overall n = 338 patients were screened for study participation. Out of these patients 72.8 % (n = 246) fulfilled the inclusion criteria and did not violate against one of the exclusion criteria. 95.5 % (n = 235) of the patients will be included in the statistical analysis (ITT population), and 88.6 % (n = 218) were analysed as PP population (see Figure 3).

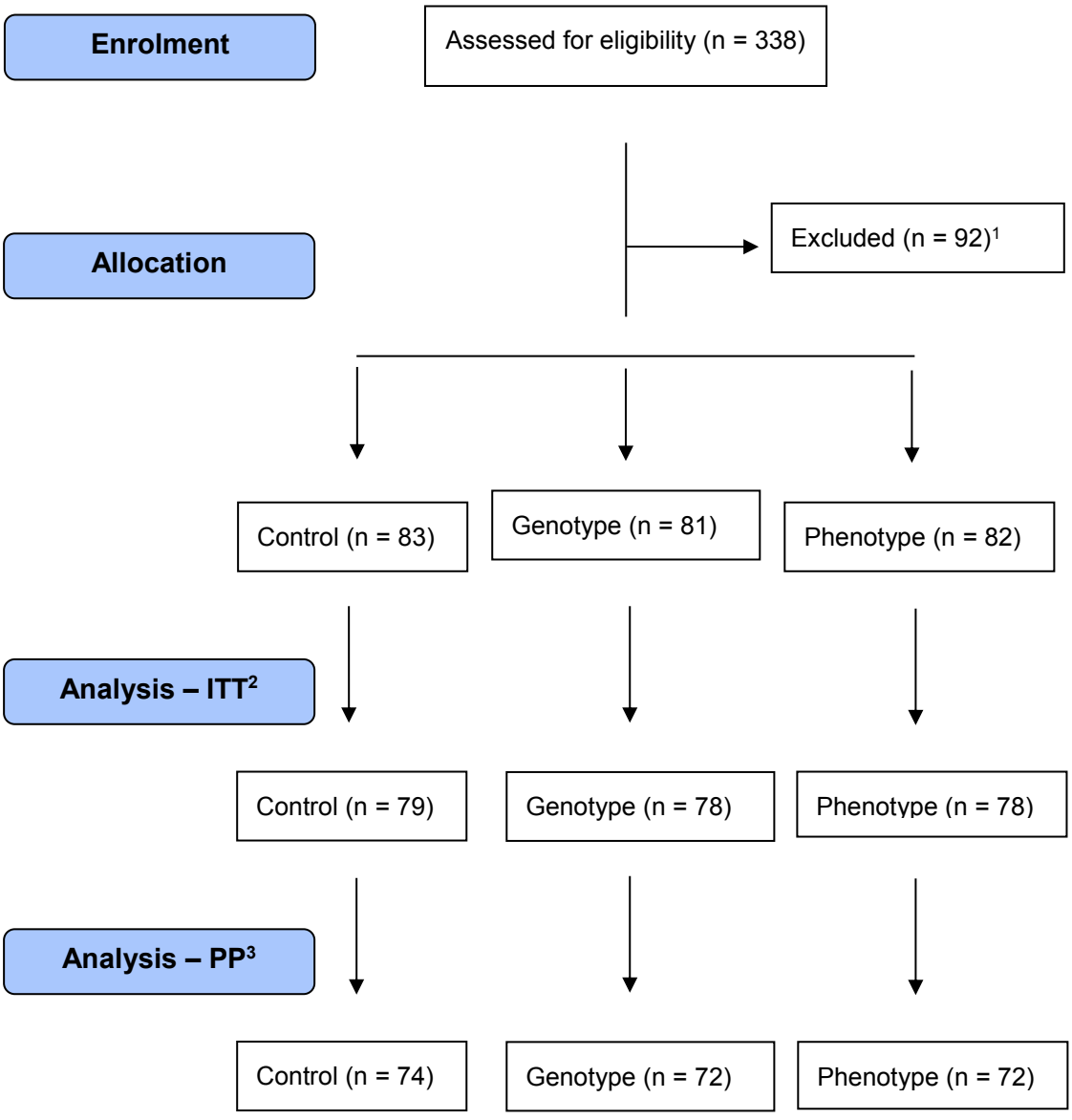


Figure 3 CONSORT 2010 Flow chart for analysis populations

[1] Reasons for exclusion of patients screened but not randomised (see table 1 in appendix 3 to the Statistical Report, dated 25.01.2023)

[2] Reasons for exclusion of patients allocated but not analysed:

- CoVID-19 infection (n = 2; Pat-ID 122 genotype group, Pat-ID 134 phenotype group)
- Investigator's decision (n = 2; Pat-ID 15 control group, Pat-ID 100 phenotype group)
- Patient's decision (n = 7; Pat-ID 21, Pat-ID 152, Pat-ID 352 control group, Pat-ID 99, Pat-ID 111 phenotype group, Pat-ID 306, Pat-ID 348 genotype group)

[3] Reasons for exclusion of patients from PP (see table 1.4.2 appendix 1 to the Statistical Report, dated 25.01.2023)

For the randomised patients (n = 246) the treatment termination was documented, whereby 7.7 % (n = 19) patients did not complete study treatment until week 6, reasons are given in table 1.2 in appendix 1. 57.9 % (n = 11) of these patients were not treated at all or without reliable data for treatment, and were excluded from the ITT population. Therefore, a number of n = 235 patients (95.5 % of the randomized patients) remained for the Intention-to-treat population (ITT).

Overall, 98.7 % (n = 232) of the ITT population performed all intended visits (table 1.3.1 in appendix 1), Pat-ID 221, Pat-ID 223 and Pat-ID 225 discontinued visit 3. The average study participation for the patients were 42.7 (± 4.6) days (see table 1.3.2 in appendix 1 to the Statistical Report, dated 25.01.2023).

Reasons for the end of treatment were documented in table 1.3.3 in appendix 1, where 3.4 % (n = 8) of the patients had no regular end of treatment (n = 3 AE (Pat-ID 93, Pat-ID 223, Pat-ID 225), n = 1 relapse (Pat-ID 341), n = 1 patient's decision (Pat-ID 221), and n = 3 investigator's decision (Pat-ID 239, Pat-ID 240, Pat-ID 243)). From the ITT 96.6 % (n = 227) of the patients had a regular end according to the study protocol.

10.2 Protocol Deviations

Within the ITT population for 7.2 % (n = 17) of the patients at least one of the major protocol violations, occurred. The violations as well as the number of violations per patient are shown in table 1.4 in appendix 1 to the Statistical Report (1.4.1 Table and 1.4.2 Listing).

Major protocol violation according to SAP "Interruption or ending or change of dosage of 20 mg tamoxifen therapy per day throughout the study" included the following:

- Interruption: > 2 consecutive days during V1 – V3 → n = 1 (Pat-ID 225, randomized for phenotype), whereby this patient terminate prematurely the IMP therapy (= major protocol violation)
- End of treatment: > 2 consecutive days immediately before V3 → n = 2 (Pat-ID 189 and Pat-ID 242, all randomized for phenotype)
- Change of dosage of tamoxifen → n = 0

Additional major protocol violations were:

- n = 1 patient (Pat-ID 28, randomized for phenotype): the documentation in the data base for the IMP dosage was faulty. Patient was documented to receive placebo but as IMP she received 3 mg (Z)-endoxifen.
- n = 1 patient (Pat-ID 316, randomized for genotype): CYP2D6-genotyping at the beginning of the study was IM/IM, PM/EM, leading to an IMP dosage of 1.5 mg (Z)-endoxifen during the study. The re-analyse of the CYP2D6-genotype delivered an CYP2D6 genotype of PM/PM, PM/IM for this patient. Correctly, this patient would have a dosage of 3 mg (Z)-endoxifen as IMP.

For both patient additional major protocol violations occurred (see listing to table 1.4.2 in appendix 1 to the Statistical Report, dated 25.01.2023), therefore in any case they were excluded from PP population.

According to the SAP (final version dated 23.08.2021) all patients with major protocol violations were exclude from the ITT population to build up the per-protocol population (PP, see 1.4.1 and 1.4.2 in the Appendix 1 to the Statistical Report, dated 25.01.2023).

11. EFFICACY EVALUATION

11.1 Data Sets Analysed

Data analyses were performed using the ITT-population as defined Chapter 9.

11.2 Demographic and Other Baseline Characteristics

Table 6 Demographic Data (ITT- population, N = 235)

Characteristics	Control	Genotype [2]	Baseline Endoxifen [3]	All
n	79	78	78	235
Age [y] median (range)	51 (29 - 76)	51 (31 - 71)	51 (31 - 71)	51 (29-76)
ever smoker (min. 6 months)				
Yes	31 (39.2%)	24 (30.8%)	24 (30.8%)	79 (33.6%)
no	48 (60.8%)	54 (69.2%)	54 (69.2%)	156 (66.4%)
Menopausal status, n (percentage)				
Pre-/perimenopausal	36(45.6%)	41 (52.6%)	40 (51.3%)	117 (49.8%)
Documented postmenopausal	33(41.8%)	26 (33.3%)	31 (39.7%)	90 (38.3%)
Post hysterectomy/bilateral oophorectomy	10 (12.7%)	11 (14.1%)	7 (9.0%)	28 (11.9%)
Histological tumour type, n (percentage) [4]				
Invasive carcinoma of no special type	64 (78.0%)	56 (70.9%)	60 (75.9%)	180 (75.0%)
Invasive or mixed lobular carcinoma	11 (13.4%)	12 (15.2%)	9 (11.4%)	32 (13.3%)
DCIS	7 (8.5%)	11 (13.9%)	10 (12.7%)	28 (11.7%)
Histological grading, n (percentage) [4]				
Grade 1	17 (20.7%)	19 (24.1%)	17 (21.5%)	53 (22.1%)
Grade 2	47 (57.3%)	43 (54.4%)	45 (57.0%)	135 (56.3%)
Grade 3	18 (22.0%)	17 (21.5%)	17 (21.5%)	52 (21.7%)
UICC-Staging, n (percentage) [4]				
0	10 (12.2%)	9 (11.4%)	10 (12.7%)	29 (12.1%)
IA	38 (46.3%)	38 (48.1%)	35 (44.3%)	111 (46.3%)
IB	4 (4.9%)	2 (2.5%)	1 (1.3%)	7 (2.9%)
IIA	19 (23.2%)	10 (12.7%)	18 (22.8%)	47 (19.6%)
IIB	8 (9.8%)	15 (19.0%)	8 (10.1%)	31 (12.9%)
IIIA	3 (3.7%)	3 (3.8%)	5 (6.3%)	11 (4.6%)
Not applicable	0	2 (2.5%)	2 (2.5%)	4 (1.7%)
Receptor status				
ER+/PR+	78 (95.1%)	77 (97.5%)	71 (89.9%)	226 (94.2%)
ER+/PR-	4 (4.9%)	2 (2.5%)	6 (7.6%)	12 (5.0%)
ER-/PR+	0	0	2 (2.5%)	2 (0.8%)
CYP2D6 genotype				
PM/PM, PM/IM	9 (11.4%)	13 (16.7%)	16 (20.5%)	38 (16.2%)
IM/IM, PM/EM	31 (39.2%)	25 (32.1%)	30 (38.5%)	86 (36.6%)
IM/EM, EM/EM, UM	39 (49.4%)	40 (51.3%)	32 (41.0%)	111 (47.2%)
Basal (Z)-endoxifen				
≤ 15 nM	19 (24.1%)	12 (15.4%)	21 (26.9%)	52 (22.1%)
> 15 - 25 nM	18 (22.8%)	18 (23.1%)	20 (25.6%)	56 (23.8%)
> 25 nM	42 (53.2%)	48 (61.5%)	37 (47.4%)	127 (54.0%)

[1]: All patients included who received at least one tablet of study medication.

[2]: (Z)-Endoxifen supplementation according to genotype derived CYP2D6 metabolizer activity

[3]: (Z)-Endoxifen supplementation according to baseline (Z)-Endoxifen plasma concentration determined at initial visit

[4]: 5 patients had bilateral tumours (3 in control, 1 in genotype, 1 in basal endoxifen group)

Table 6 describes the baseline data (demographic characteristics, anamnestic parameters and central laboratory data) important to prove the absence of any bias between the three study groups. For all data see table 2.1.1.5 in the Appendix 1 to the Statistical Report, final version dated 25.01.2023.

11.3 Measurements of Treatment Compliance

From baseline (visit 1) until visit 3 (week 6) the amount of daily intake of study medication ((Z)-endoxifen or placebo) was documented in the eCRF document "TREAT01 (Z)-endoxifen/placebo". This intake was additionally controlled by pill counting. Furthermore, the daily intake of the original therapy tamoxifen was recorded in the eCRF document "TREAT02 tamoxifen treatment".

See table 1.4.1 and 1.4.2 in Appendix 1 to the Statistical Report, final version dated 25.01.2023.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of Efficacy

The aim of this clinical study was to assess pharmacokinetic data on the supplementation of the standard tamoxifen therapy with low dose (Z)-endoxifen in patients with compromised CYP2D6 enzyme activity. Therefore, primary data collected have been plasma concentrations of tamoxifen and its major metabolites N-desmethyl tamoxifen, 4-hydroxy tamoxifen and endoxifen. No pharmacodynamic data were obtained during this clinical study.

11.4.1.1 Primary Endpoint

According to the study protocol, version 2.0 as of 26.06.2020 statistical analysis of the primary outcome was a chi-square test stratified for Genotype (Mantel Haenszel) with type 1 error 0.025 (one-sided). This was done identical in stage 1 (interim analysis) and stage 2 (final analysis) of the adaptive design. Final analysis was done in the ITT-population.

Therefore, the primary endpoint - defined as the proportion of patients with steady state (Z)-endoxifen plasma level above 32 nM endoxifen following (Z)-endoxifen supplementation after 6 weeks - was compared between the genotype group (group 2) and the control group (group 1) by a stratified one-sided Mantel-Haenszel χ^2-test. As within the interim analysis the primary endpoint was additionally compared exploratively between the phenotype group (group 3) and the control group (group 1) by a stratified one-sided Mantel-Haenszel χ^2-test. Results are shown in table 3.

Table 7 Comparison of success ((Z)-endoxifen plasma level > 32 nM) between the randomized groups (ITT-population)

(Z)-endoxifen plasma level > 32 nM	Genotype (n = 78)	Control (n = 79)	Phenotype (n = 78)	Relative Risk (95%-CI)	p-value
Confirmatory analysis					
Yes	52 (66.7%)	18 (22.8%)		2.888 (1.822 – 4.577)	p < 0.0001*
No	26 (33.3%)	61 (77.2%)			
Exploratory analysis					
Yes		18 (22.8%)	52 (66.7%)	3.007 (1.836 – 4.924)	p < 0.0001**
No		61 (77.2%)	26 (33.3%)		

* Mantel-Haenszel χ^2-test stratified for genotype

** Mantel-Haenszel χ^2-test stratified for phenotype

The patients in the genotype group - with (Z)-endoxifen therapy according to their genotype - show 2.9 times more often (Z)-endoxifen plasma level > 32 nM after 6 weeks than the patients in the control group. According to the study protocol version 2.0, dated 26.06.2020, for the overall α the critical value of product p_1 (= p-value of the interim analysis) times p_2 (= p-value of the final analysis) is $c_\alpha = 0.0038$. The interim analysis results in $p_1 < 0.001$ (see Statistical Report for the Interim Analysis, dated 25.01.2021).

$p_1 * p_2 = 0.001 * 0.001 = 0.000001$.

So that the result of the final analysis is statistically significant at least on the overall α level (0.025, see section 6.3).

The patients in the phenotype group - with (Z)-endoxifen therapy according to their baseline (Z)-endoxifen plasma concentrations - show 3.0 times more often (Z)-endoxifen plasma level > 32 nM after 6 weeks than the patients in the control group. This result is also significant at least on the overall α level. Analysis of the PP-population came to a similar result (Table 8).

Table 8 Comparison of success ((Z)-endoxifen plasma level > 32 nM) between the randomized groups (PP-population)

(Z)-endoxifen plasma level >32 nM	*CYP2D6* Genotype (n = 72)	Control (n = 74)	baseline (Z)-endoxifen plasma concentration (n = 72)	Relative Risk (95%-CI)	p-value*
Yes	49 (68.1%)	16 (21.6%)		3.1 (1.9 – 5.0)	p < 0.001
No	23 (31.9%)	58 (78.4%)			
Yes		16 (21.6%)	51 (70.8%)	3.4 (2.0 – 5.8)	p < 0.001
No		58 (78.4%)	21 (29.2%)		

* Mantel-Haenszel χ^2-test

Additionally, the results of proportion of patients within the randomization groups as well as the results of the comparisons between Genotype and control within the genotype group are shown in table 9 for genotype and table 10 for phenotype.

Table 9 Proportion and comparison of success ((Z)-endoxifen plasma level > 32 nM) within the genotype groups (ITT-population)

	Genotype groups					
	PM/PM or PM/IM		IM/IM or PM/EM		IM/EM, EM/EM or UM	
(Z)-endoxifen plasma level increased at V3	Genotype (n = 13)	Control (n = 9)	Genotype (n = 25)	Control (n = 31)	Genotype (n = 40)	Control (n = 39)
Yes	12 (92.3%)	0 (0%)	22 (88.0%)	2 (6.5%)	18 (45.0%)	16 (41.0%)
No	1 (7.7%)	9 (100%)	3 (12.0%)	29 (93.5%)	22 (55.0%)	23 (59.0%)
Relative Risk (95%-CI)	10.000 (1.558 – 64.198)		9.778 (3.307 – 28.907)		1.083 (0.701– 1.674)	
p-value	< 0.0001*		< 0.0001*		0.721**	

* Fisher's Exact test, ** Chi-square test

Table 10 Proportion and comparison of success ((Z)-endoxifen plasma level > 32 nM) within the phenotype groups (ITT-population)

	Phenotype groups					
	≤ 15 nM		> 15 – 25 nM		≥ 25 nM	
(Z)-endoxifen plasma level increased at V3	Phenotype (n = 21)	Control (n = 19)	Phenotype (n = 20)	Control (n = 18)	Phenotype (n = 37)	Control (n = 42)
Yes	18 (85.7%)	0 (0%)	19 (95.0%)	1 (5.6%)	15 (40.5%)	17 (40.5%)
No	3 (14.3%)	19 (100%)	1 (5.0%)	17 (94.4%)	22 (59.5%)	25 (59.5%)
Relative Risk (95%-CI)	7.333 (2.562 – 20.990)		17.100 (2.539 – 115.177)		1.002 (0.621 – 1616)	
p-value	< 0.0001*		< 0.0001*		0.9954**	

* Fisher's Exact test, ** Chi-square test

11.4.1.2 Secondary Endpoints

10.4.1.2.1 Increase of (Z)-endoxifen level until visit 3

According to the study protocol version 2.0 as of 26 June 2020 the increase of (Z)-endoxifen level between visit 1 and visit 3 in patients without and with (Z)-endoxifen supplementation at different doses was calculated as secondary endpoints. As given in section 8.3 increase of (Z)-endoxifen until visit 3 level was defined as success, no increase was defined as failure.

For all patients the change of (Z)-endoxifen level between baseline and visit 3 (week 6) was calculated and compared between the genotype group (group 2) and the control group (group 1) by a stratified one-sided Mantel-Haenszel χ^2-test, and between the phenotype group (group 3) and the control group (group 1) by a stratified one-sided Mantel-Haenszel χ^2-test (see

section 8.2). Stratification was performed for genotype group and phenotype group resp., results are shown in table 11.

Table 11 Comparison of success (increase of (Z)-endoxifen until visit 3) between the randomized groups (ITT-population)

(Z)-endoxifen plasma level increased	Genotype (n = 78)	Control (n = 79)	Phenotype (n = 78)	Relative Risk (95%-CI)	p-value
Yes	50 (64.1%)	28 (35.4%)		1.794 (1.280 – 2.514)	p < 0.001*
No	28 (35.9%)	51 (64.6%)			
Yes		28 (35.4%)	53 (68.0%)	1.841 (1.330 – 2.548)	p < 0.001**
No		51 (64.6%)	25 (32.1%)		

* Mantel-Haenszel χ^2-test stratified for genotype

** Mantel-Haenszel χ^2-test stratified for phenotype

Additionally, the results of proportion of patients within the randomization groups as well as the results of the comparisons between Genotype and control within the genotype group are shown in table 12 for genotype and table 13 for phenotype.

Table 12 Proportion and comparison of success (increase of (Z)-endoxifen) within the genotype groups (ITT-population)

	Genotype groups					
	PM/PM or PM/IM		IM/IM or PM/EM		IM/EM, EM/EM or UM	
(Z)-endoxifen plasma level increased at V3	Genotype (n = 13)	Control (n = 9)	Genotype (n = 25)	Control (n = 31)	Genotype (n = 40)	Control (n = 39)
Yes	13 (100%)	4 (44.4%)	23 (92.0%)	10 (32.3%)	14 (35.0%)	14 (35.9%)
No	0 (0%)	5 (55.6%)	2 (8.0%)	21 (67.7%)	26 (65.0%)	25 (64.1%)
Relative Risk (95%-CI)	2.250 (1.034 – 4.671)		2.852 (1.690 – 4.812)		0.975 (0.538 – 1.768)	
p-value	0.0048*		< 0.0001*		0.9336**	

* Fisher's Exact test, ** Chi-square test

Table 13 Proportion and comparison of success (increase of (Z)-endoxifen) within the phenotype groups (ITT-population)

	Phenotype groups					
	≤ 15 nM		> 15 – 25 nM		≥ 25 nM	
(Z)-endoxifen plasma level increased at V3	Phenotype (n = 21)	Control (n = 19)	Phenotype (n = 20)	Control (n = 18)	Phenotype (n = 37)	Control (n = 42)
Yes	21 (100%)	9 (47.4%)	20 (100%)	7 (38.9%)	12 (32.4%)	12 (28.6%)
No	0 (0%)	10 (52.6%)	0 (0%)	11 (61.1%)	25 (67.6%)	30 (71.4%)
Relative Risk (95%-CI)	2.111 (1.314 – 3.391)		2.571 (1.441 – 4.589)		1.135 (0.583 – 2.212)	
p-value	< 0.0001*		< 0.0001*		0.7096**	

* Fisher's Exact test, ** Chi-square test

10.4.1.2.2 Comparison of tamoxifen and tamoxifen metabolites

According to the study protocol version 2.0, dated 26.06.2020, the steady state plasma levels at visit 3 (6 weeks) of tamoxifen, N-desmethyltamoxifen, 4-hydroxytamoxifen, between the intervention groups and control group were compared. The distribution of the values as well as the results of the comparisons are documented in table 14.

Table 14 Comparison of tamoxifen and its metabolites at V3 after 6 weeks of intervention (ITT-population)

Parameter	N						Percentile		
	Valid	Miss.	Mean	SD	Min.	Max.	25	Median	75
Tamoxifen									
All (n = 235)	230	5	311.3	108.9	95.5	774.1	230.2	300.8	370.9
Genotype (n = 78)	78	0	317.0	116.5	95.5	774.1	235.4	305.8	386.3
Phenotype (n = 78)	75	3	305.9	105.2	132.8	636.2	241.3	290.0	351.2
Control (n = 79)	77	2	310.8	105.6	108.7	578.9	218.9	318.4	372.6
Comparison of the 3 groups (ANOVA)					p = 0.8203				
Comparison Genotype vs. Control (post-hoc Scheffé test)					p = 0.9409				
Comparison Phenotype vs. Control (post-hoc Scheffé test)					p = 0.9615				
Comparison Genotype vs. Phenotype (post-hoc Scheffé test)					p = 0.8212				
Desmethytamoxifen									
All (n = 235)	230	5	613.2	215.2	223.6	1457.6	462.0	557.0	726.5
Genotype (n = 78)	78	0	629.2	229.0	223.6	1438.3	465.7	610.3	785.1
Phenotype (n = 78)	75	3	617.9	185.1	264.8	1303.5	499.0	578.0	719.2
Control (n = 79)	77	2	593.5	228.8	281.1	1457.6	429.5	540.9	660.5
Comparison of the 3 groups (ANOVA)					p = 0.5762				
Comparison Genotype vs. Control (post-hoc Scheffé test)					p = 0.5895				
Comparison Phenotype vs. Control (post-hoc Scheffé test)					p = 0.7839				
Comparison Genotype vs. Phenotype (post-hoc Scheffé test)					p = 0.9495				

Parameter	N		Mean	SD	Min.	Max.	Percentile		
	Valid	Miss.					25	Median	75
Tamoxifen									
4-Hydroxtamoxifen									
All (n = 235)	230	5	4.54	1.97	1.13	12.85	3.21	4.28	5.51
Genotype (n = 78)	78	0	4.85	2.22	1.13	12.85	3.42	4.43	5.84
Phenotype (n = 78)	75	3	4.29	1.94	1.43	11.68	2.88	4.15	5.15
Control (n = 79)	77	2	4.47	1.72	1.56	9.27	3.24	4.24	5.59
Comparison of the 3 groups (ANOVA)					p = 0.2073				
Comparison Genotype vs. Control (post-hoc Scheffé test)					p = 0.5005				
Comparison Phenotype vs. Control (post-hoc Scheffé test)					p = 0.8447				
Comparison Genotype vs. Phenotype (post-hoc Scheffé test)					p = 0.2172				

11.4.2 Statistical/Analytical Issues

Statistical analyses were performed as planned and described in Chapter 8.7.

11.4.2.1 Adjustment for Covariates

No covariate analyses nor prognostic factor analyses were performed.

11.4.2.2 Handling of Drop-outs or Missing Data

All variables included in the CRF were mandatory. The monitoring assured quality of the assessments. To handle patients with unknown status for the primary endpoint due to laboratory failures, drop out, AEs, organizational reasons etc. a detailed analysis of the drop out/missing data patterns was conducted.

According to the study protocol version 2.0, dated 26.06.2020, the pattern of missing data for the primary endpoint was analysed within a blinded review before the close of the data base and unblinding. Overall for 2.1 % (n = 5) patients of the ITT the (Z)-endoxifen level at visit 3 (day 28, primary endpoint) is missing.

One patient decided to withdraw from the blood sampling 6 weeks after start of study medication, three patients missed blood sampling due to adverse events (each one arthralgia grade 3, diarrhoea grade 3 and Covid-19 infection, for all cases no action was taken concerning study medication); for one patient the reason for missing blood sampling was unknown.

Due to the low proportion of patients with unknown status for the primary endpoint and the reasons for missing endpoint data these patients were handled as failures (defined as (Z)-endoxifen level < 32 mmol/l) in the analysis of the primary endpoint.

All other missing data will be given in the tables but excluded from the statistical tests.

11.4.2.3 Interim Analyses and Data Monitoring

Within the interim analysis the data of the first n = 129 randomized patients who successfully terminated the trial were analysed according to the SAP for the interim analysis dated 2021/12/29. As presented in the Statistical Report for the Interim Analysis, final dated 25.01.2021, 26.2% (n = 11) of n = 42 patients in the control group, 69.6% (n = 32) of n = 46 patients in the genotype group, and 78.0% (n = 32) of n = 41 patients in the phenotype group reached the primary endpoint (endoxifen plasma concentration > 32 nM after 6 weeks therapy). The comparison of success between the randomized groups results in $p < 0.001$ (one-sided Mantel-Haenszel χ^{2}-test stratified for genotype). This result was significant on the $\alpha_1 = 0.0045$ level.

Therefore, the trial was successful and needs no further sample size calculation. According to the study protocol Version 2.0 dated 26.06.2020 the trial was closed to recruitment at 15.02.2021. The sponsor informed the IDMC about the intention to close the recruitment and to terminate the clinical study. However, patients already recruited were followed to their individual end of study (last randomization date 01.03.2021). The IDMC agreed to this procedure in its answer dated 26.02.2021. For details on IDMC see chapter 6.6.

11.4.2.4 Multicentre Studies

The TAMENDOX trial was performed as a multi-centre study with 38 centres initiated, of which 35 centres included patients. The trial was not explicitly designed to detect centre effects.

According to the results of the blinded review overall n = 9 centres of the participating centres included 55.5 % (n = 131) of the whole ITT population. All of these centres included at least 10 patients. The remaining patients (n = 105) were treated within 24 centres. Therefore, stratification of the analysis to centres was not considered to be appropriate.

11.4.2.5 Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons were performed.

11.4.2.6 Use of an “Efficacy Subset” of Patients

All patients who received at least one daily dose of study medication were included into the data analysis of the ITT-population. This is the most stringent analysis and therefore no issues with dropping out patients exist.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

N/A

11.4.2.8 Examination of Subgroups

No subgroup analysis was implemented neither in the study protocol nor in the SAP.

11.4.3 Tabulation of Individual Response Data

Primary endpoint of this study were changes in (Z)-endoxifen plasma concentrations. Figure 4 compares individual (Z)-endoxifen plasma concentrations between baseline and end of intervention.

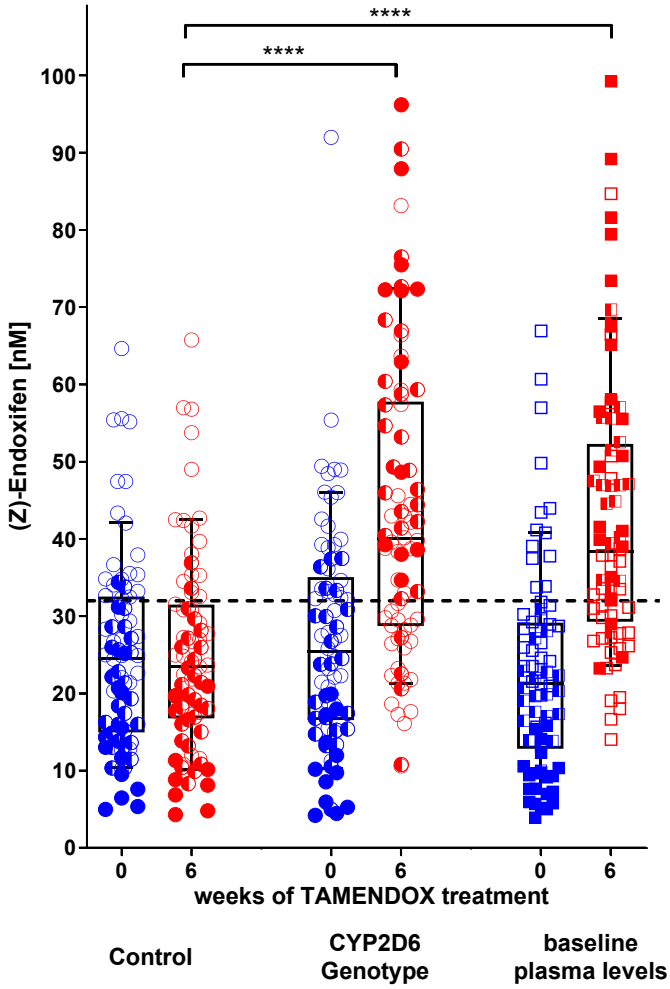


Figure 4: (Z)-Endoxifen plasma concentrations in the control group ((open circles, EM; half-filled circles, IM; filled circles, PM; all patients receiving placebo), in the intervention group according to CYP2D6 phenotype (open circles, EM, placebo; half-filled circles, IM, 1.5 mg (Z)-Endoxifen; filled circles, PM, 3 mg (Z)-endoxifen) and in the intervention group according to basal (Z)-endoxifen plasma concentrations (open quadrats, > 25 nM, placebo; half-filled quadrats, > 15 - 25 nM, 1.5 mg (Z)-endoxifen; ≤ 15 nM, 3 mg (Z)-endoxifen) before and after 6 weeks of intervention. ****: Student's t-test p<0.0001.

Individual data points see Appendix 3, section 8, to the Statistical Report, final version dated 25.01.2023.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

N/A

11.4.5 Drug-Drug and Drug-Disease Interactions

N/A

11.4.6 By-Patient Displays

N/A

11.4.7 Efficacy Conclusions

As primary and secondary endpoints were pharmacokinetic parameters the efficacy conclusions are limited to PK data and do not include any pharmacodynamic data. The data analysis showed that the supplementation of standard tamoxifen therapy (20 mg/day) with either CYP2D6 genotype or baseline (Z)-endoxifen plasma concentration guided low dose of 1.5 or 3 mg (Z)-endoxifen was efficient to increase (Z)-endoxifen plasma concentrations.

12. SAFETY EVALUATION

12.1 Extent of Exposure

All patients received a standard tamoxifen therapy (20 mg/day) at least for 3 months, which was required for inclusion (see inclusion criterion 4) and was not expected to be study medication.

Patients with CYP2D6 IM phenotype or baseline (Z)-endoxifen levels between 15 and ≤25 nM received 1.5 mg/d (Z)-endoxifen. Patients with CYP2D6 PM phenotype or baseline (Z)-endoxifen levels <15 nM received 3 mg/day (Z)-endoxifen. No further dose adjustment was permitted. All other patients received placebo.

In total, 155 patients received placebo, 46 patients received 1.5 mg (Z)-endoxifen and 34 patients received 3 mg (Z)-endoxifen. Per protocol treatment duration was 42±5 days. All patients, who received at least one dose of (Z)-endoxifen were included in efficacy and safety evaluation.

In this study no further subgroup analysis was reasonable.

12.2 Adverse Events (AES)

12.2.1 Brief Summary of Adverse Events

AEs were reported descriptively. For details see chapter 11.2.2.

No CTC Grade-4 AEs were observed during treatment and less than 8% (6/80) of the patients on (Z)-endoxifen study medication developed CTC Grade 3 AEs (1 myalgia, 1 intraductal proliferation breast lesion, 2 libido decreases, 2 hot flushes).

12.2.2 Display of Adverse Events

For all patients who receive at least one tablet (Z)-endoxifen the safety and tolerability were analysed. For AEs results first the greatest severity during the study course was given (table 1.1.1 in appendix 2 to the Statistical Report final version dated 25.01.2023), sorted by system organ class and preferred term. Overall 83.0 % (n = 195) of the patients had at least one AE, one of these AEs for a patient in the phenotype group was classified with grade 4 (table 1.1.2 in appendix 2), no SAE occurred. Second the relation of the AEs to treatment was given, which occurred for 40.4 % (n = 95) of the patients (table 1.1.3 in appendix 2). Additionally, listing of the patients with AEs leading to discontinuation from treatment were given (table 1.1.4 in appendix 2) with each n = 1 patient in the genotype group and control group, and n = 3 patients in the phenotype.

Within the eCRF laboratory parameters were classified with >/< as upper/lower limit and related to IMP, results are shown in table 1.2 (appendix 2 to the Statistical Report final version dated 25.01.2023). Overall, most frequently the parameters white blood cells (4.3 %, n = 10), lymphocytes (3.4 %, n = 8), glucose (3.0 %, n = 7), and monocytes (3.0 %, n = 7) were >/< as upper/lower limit.

According to the study protocol version 2.0, dated 26.06.2020, and the SAP final version dated 23.08.21, all AEs observed during the whole study period from screening visit to end of study visit (visit 4) are reported. Data were stratified by the 3 study groups: control, (Z)-endoxifen supplementation according to CYP2D6 genotype derived enzyme activity and according to the

basal (Z)-endoxifen plasma concentration under standard tamoxifen therapy. All patients, who received at least one tablet of study medication (ITT-populations) were included (Table 15).

Table 15 Number of Patients with Toxicity Grades 1-4 (ITT-population, N = 235)

	study group according to randomization			
System Organ Class CTC-Grade	**Control (N = 79) n (%)**	**Genotype (N = 78) n (%)**	**Phenotype (N = 78) n (%)**	**All (N = 235) n (%)**
Any event	67 (84.8%)	63 (80.8%)	65 (83.3%)	195 (83.0%)
CTC-Grade 1 - mild event	40 (50.6%)	35 (44.9%)	26 (33.3%)	101 (43.0%)
CTC-Grade 2 - moderate event	24 (30.4%)	23 (29.5%)	30 (38.5%)	77 (32.8%)
CTC-Grade 3 - severe event	3 (3.8%)	5 (6.4%)	8 (10.3%)	16 (6.8%)
CTC-Grade 4 - life-threatening or disabling event	-	-	1 (1.3%)	1 (0.4%)
Blood and lymphatic system disorders	3 (3.8%)	3 (3.8%)	-	6 (2.6%)
CTC-Grade 1 - mild event	1 (1.3%)	1 (1.3%)	-	2 (0.9%)
CTC-Grade 2 - moderate event	1 (1.3%)	2 (2.6%)	-	3 (1.3%)
CTC-Grade 3 - severe event	1 (1.3%)	-	-	1 (0.4%)
Cardiac disorders	-	4 (5.1%)	2 (2.6%)	6 (2.6%)
CTC-Grade 1 - mild event	-	3 (3.8%)	2 (2.6%)	5 (2.1%)
CTC-Grade 2 - moderate event	-	1 (1.3%)	-	1 (0.4%)
Ear and labyrinth disorders	1 (1.3%)	-	-	1 (0.4%)
CTC-Grade 3 - severe event	1 (1.3%)	-	-	1 (0.4%)
Eye disorders	4 (5.1%)	5 (6.4%)	7 (9.0%)	16 (6.8%)
CTC-Grade 1 - mild event	4 (5.1%)	4 (5.1%)	6 (7.7%)	14 (6.0%)
CTC-Grade 2 - moderate event	-	1 (1.3%)	1 (1.3%)	2 (0.9%)
Gastrointestinal disorders	18 (22.8%)	12 (15.4%)	15 (19.2%)	45 (19.1%)
CTC-Grade 1 - mild event	16 (20.3%)	11 (14.1%)	12 (15.4%)	39 (16.6%)
CTC-Grade 2 - moderate event	2 (2.5%)	1 (1.3%)	2 (2.6%)	5 (2.1%)
CTC-Grade 3 - severe event	-	-	1 (1.3%)	1 (0.4%)
General disorders and administration site conditions	23 (29.1%)	14 (17.9%)	20 (25.6%)	57 (24.3%)
CTC-Grade 1 - mild event	17 (21.5%)	12 (15.4%)	13 (16.7%)	42 (17.9%)
CTC-Grade 2 - moderate event	6 (7.6%)	2 (2.6%)	7 (9.0%)	15 (6.4%)
Immune system disorders	2 (2.5%)	1 (1.3%)	5 (6.4%)	8 (3.4%)
CTC-Grade 1 - mild event	2 (2.5%)	1 (1.3%)	3 (3.8%)	6 (2.6%)
CTC-Grade 2 - moderate event	-	-	2 (2.6%)	2 (0.9%)
Infections and infestations	10 (12.7%)	7 (9.0%)	13 (16.7%)	30 (12.8%)
CTC-Grade 1 - mild event	6 (7.6%)	2 (2.6%)	8 (10.3%)	16 (6.8%)
CTC-Grade 2 - moderate event	4 (5.1%)	5 (6.4%)	4 (5.1%)	13 (5.5%)
CTC-Grade 4 - life-threatening or disabling event	-	-	1 (1.3%)	1 (0.4%)
Injury, poisoning and procedural complications	1 (1.3%)	2 (2.6%)	3 (3.8%)	6 (2.6%)
CTC-Grade 1 - mild event	1 (1.3%)	2 (2.6%)	2 (2.6%)	5 (2.1%)
CTC-Grade 2 - moderate event	-	-	1 (1.3%)	1 (0.4%)
Investigations*	29 (36.7%)	31 (39.7%)	20 (25.6%)	80 (34.0%)
CTC-Grade 1 - mild event	28 (35.4%)	30 (38.5%)	18 (23.1%)	76 (32.3%)
CTC-Grade 2 - moderate event	1 (1.3%)	1 (1.3%)	2 (2.6%)	4 (1.7%)

study group according to randomization

System Organ Class CTC-Grade	Control (N = 79) n (%)	Genotype (N = 78) n (%)	Phenotype (N = 78) n (%)	All (N = 235) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	1 (1.3%)	1 (1.3%)	2 (0.9%)
CTC-Grade 3 - severe event	-	1 (1.3%)	1 (1.3%)	2 (0.9%)
Nervous system disorders	31 (39.2%)	22 (28.2%)	23 (29.5%)	76 (32.3%)
CTC-Grade 1 - mild event	25 (31.6%)	18 (23.1%)	15 (19.2%)	58 (24.7%)
CTC-Grade 2 - moderate event	6 (7.6%)	4 (5.1%)	7 (9.0%)	17 (7.2%)
CTC-Grade 3 - severe event	-	-	1 (1.3%)	1 (0.4%)
Psychiatric disorders	13 (16.5%)	9 (11.5%)	12 (15.4%)	34 (14.5%)
CTC-Grade 1 - mild event	8 (10.1%)	6 (7.7%)	8 (10.3%)	22 (9.4%)
CTC-Grade 2 - moderate event	5 (6.3%)	1 (1.3%)	4 (5.1%)	10 (4.3%)
CTC-Grade 3 - severe event	-	2 (2.6%)	-	2 (0.9%)
Renal and urinary disorders	1 (1.3%)	4 (5.1%)	2 (2.6%)	7 (3.0%)
CTC-Grade 1 - mild event	1 (1.3%)	3 (3.8%)	2 (2.6%)	6 (2.6%)
CTC-Grade 2 - moderate event	-	1 (1.3%)	-	1 (0.4%)
Reproductive system and breast disorders	10 (12.7%)	11 (14.1%)	11 (14.1%)	32 (13.6%)
CTC-Grade 1 - mild event	8 (10.1%)	9 (11.5%)	7 (9.0%)	24 (10.2%)
CTC-Grade 2 - moderate event	2 (2.5%)	2 (2.6%)	4 (5.1%)	8 (3.4%)
Respiratory, thoracic and mediastinal disorders	4 (5.1%)	8 (10.3%)	3 (3.8%)	15 (6.4%)
CTC-Grade 1 - mild event	4 (5.1%)	7 (9.0%)	2 (2.6%)	13 (5.5%)
CTC-Grade 2 - moderate event	-	1 (1.3%)	1 (1.3%)	2 (0.9%)
Skin and subcutaneous tissue disorders	14 (17.7%)	11 (14.1%)	14 (17.9%)	39 (16.6%)
CTC-Grade 1 - mild event	13 (16.5%)	9 (11.5%)	10 (12.8%)	32 (13.6%)
CTC-Grade 2 - moderate event	1 (1.3%)	2 (2.6%)	4 (5.1%)	7 (3.0%)
Surgical and medical procedures	-	1 (1.3%)	3 (3.8%)	4 (1.7%)
CTC-Grade 1 - mild event	-	1 (1.3%)	-	1 (0.4%)
CTC-Grade 2 - moderate event	-	-	3 (3.8%)	3 (1.3%)
Vascular disorders	26 (32.9%)	27 (34.6%)	28 (35.9%)	81 (34.5%)
CTC-Grade 1 - mild event	12 (15.2%)	18 (23.1%)	15 (19.2%)	45 (19.1%)
CTC-Grade 2 - moderate event	13 (16.5%)	8 (10.3%)	10 (12.8%)	31 (13.2%)
CTC-Grade 3 - severe event	1 (1.3%)	1 (1.3%)	3 (3.8%)	5 (2.1%)

* laboratory parameters

The only grade 4 adverse event was a tooth root inflammation in a patient randomized to the phenotype group who received placebo due to her baseline (Z)-endoxifen level. Moreover, this AE took place before the patient received any study medication and therefore was a non-treatment emerging event not related to study medication.

In addition AE-data were evaluated with respect to the (Z)-endoxifen dose administered as study medication (Table 16). For this analysis only the time period between visit 1 (start of study medication administration) and follow-up until visit 4 (end of study visit) was taken into account.

Table 16 Number of Patients with Toxicity Grades 1-4 during administration of study medication and follow up until visit 4 (ITT-population, N = 235)

	IMP as treated			
System Organ Class CTC-Grade	**None (N = 155) n (%)**	**1.5 mg (N = 46) n (%)**	**3 mg (N = 34) n (%)**	**All (N=235) n (%)**
Any event	123 (79.4%)	39 (84.8%)	25 (73.5%)	187 (79.6%)
CTC-Grade 1 - milde event	75 (48.4%)	18 (39.1%)	8 (23.5%)	101 (43.0%)
CTC-Grade 2 - moderate event	40 (25.8%)	17 (37.0%)	15 (44.1%)	72 (30.6%)
CTC-Grade 3 - severe event	8 (5.2%)	4 (8.7%)	2 (5.9%)	14 (6.0%)
Blood and lymphatic system disorders	4 (2.6%)	2 (4.3%)	-	6 (2.6%)
CTC-Grade 1 - milde event	2 (1.3%)	-	-	2 (0.9%)
CTC-Grade 2 - moderate event	1 (0.6%)	2 (4.3%)	-	3 (1.3%)
CTC-Grade 3 - severe event	1 (0.6%)	-	-	1 (0.4%)
Cardiac disorders	1 (0.6%)	1 (2.2%)	3 (8.8%)	5 (2.1%)
CTC-Grade 1 - milde event	1 (0.6%)	1 (2.2%)	3 (8.8%)	5 (2.1%)
Eye disorders	4 (2.6%)	4 (8.7%)	3 (8.8%)	11 (4.7%)
CTC-Grade 1 - milde event	4 (2.6%)	4 (8.7%)	1 (2.9%)	9 (3.8%)
CTC-Grade 2 - moderate event	-	-	2 (5.9%)	2 (0.9%)
Gastrointestinal disorders	28 (18.1%)	9 (19.6%)	4 (11.8%)	41 (17.4%)
CTC-Grade 1 - milde event	24 (15.5%)	8 (17.4%)	3 (8.8%)	35 (14.9%)
CTC-Grade 2 - moderate event	3 (1.9%)	1 (2.2%)	1 (2.9%)	5 (2.1%)
CTC-Grade 3 - severe event	1 (0.6%)	-	-	1 (0.4%)
General disorders and administration site conditions	35 (22.6%)	4 (8.7%)	9 (26.5%)	48 (20.4%)
CTC-Grade 1 - milde event	29 (18.7%)	2 (4.3%)	8 (23.5%)	39 (16.6%)
CTC-Grade 2 - moderate event	6 (3.9%)	2 (4.3%)	1 (2.9%)	9 (3.8%)
Immune system disorders	2 (1.3%)	3 (6.5%)	1 (2.9%)	6 (2.6%)
CTC-Grade 1 - milde event	2 (1.3%)	2 (4.3%)	-	4 (1.7%)
CTC-Grade 2 - moderate event	-	1 (2.2%)	1 (2.9%)	2 (0.9%)
Infections and infestations	17 (11.0%)	3 (6.5%)	5 (14.7%)	25 (10.6%)
CTC-Grade 1 - milde event	12 (7.7%)	1 (2.2%)	3 (8.8%)	16 (6.8%)
CTC-Grade 2 - moderate event	5 (3.2%)	2 (4.3%)	2 (5.9%)	9 (3.8%)
Injury, poisoning and procedural complications	3 (1.9%)	2 (4.3%)	-	5 (2.1%)
CTC-Grade 1 - milde event	2 (1.3%)	2 (4.3%)	-	4 (1.7%)
CTC-Grade 2 - moderate event	1 (0.6%)	-	-	1 (0.4%)
Investigations*	46 (29.7%)	17 (37.0%)	6 (17.6%)	69 (29.4%)
CTC-Grade 1 - milde event	44 (28.4%)	17 (37.0%)	5 (14.7%)	66 (28.1%)
CTC-Grade 2 - moderate event	2 (1.3%)	-	1 (2.9%)	3 (1.3%)
Metabolism and nutrition disorders	10 (6.5%)	1 (2.2%)	2 (5.9%)	13 (5.5%)
CTC-Grade 1 - milde event	9 (5.8%)	1 (2.2%)	2 (5.9%)	12 (5.1%)
CTC-Grade 2 - moderate event	1 (0.6%)	-	-	1 (0.4%)
Musculoskeletal and connective tissue disorders	39 (25.2%)	12 (26.1%)	10 (29.4%)	61 (26.0%)
CTC-Grade 1 - milde event	25 (16.1%)	7 (15.2%)	4 (11.8%)	36 (15.3%)
CTC-Grade 2 - moderate event	12 (7.7%)	4 (8.7%)	6 (17.6%)	22 (9.4%)
CTC-Grade 3 - severe event	2 (1.3%)	1 (2.2%)	-	3 (1.3%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.6%)	1 (2.2%)	-	2 (0.9%)

	IMP as treated			
System Organ Class CTC-Grade	**None (N = 155) n (%)**	**1.5 mg (N = 46) n (%)**	**3 mg (N = 34) n (%)**	**All (N=235) n (%)**
CTC-Grade 3 - severe event	1 (0.6%)	1 (2.2%)	-	2 (0.9%)
Nervous system disorders	52 (33.5%)	8 (17.4%)	9 (26.5%)	69 (29.4%)
CTC-Grade 1 - milde event	40 (25.8%)	6 (13.0%)	7 (20.6%)	53 (22.6%)
CTC-Grade 2 - moderate event	11 (7.1%)	2 (4.3%)	2 (5.9%)	15 (6.4%)
CTC-Grade 3 - severe event	1 (0.6%)	-	-	1 (0.4%)
Psychiatric disorders	19 (12.3%)	9 (19.6%)	4 (11.8%)	32 (13.6%)
CTC-Grade 1 - milde event	14 (9.0%)	4 (8.7%)	2 (5.9%)	20 (8.5%)
CTC-Grade 2 - moderate event	5 (3.2%)	4 (8.7%)	1 (2.9%)	10 (4.3%)
CTC-Grade 3 - severe event	-	1 (2.2%)	1 (2.9%)	2 (0.9%)
Renal and urinary disorders	3 (1.9%)	1 (2.2%)	2 (5.9%)	6 (2.6%)
CTC-Grade 1 - milde event	2 (1.3%)	1 (2.2%)	2 (5.9%)	5 (2.1%)
CTC-Grade 2 - moderate event	1 (0.6%)	-	-	1 (0.4%)
Reproductive system and breast disorders	19 (12.3%)	5 (10.9%)	4 (11.8%)	28 (11.9%)
CTC-Grade 1 - milde event	14 (9.0%)	4 (8.7%)	3 (8.8%)	21 (8.9%)
CTC-Grade 2 - moderate event	5 (3.2%)	1 (2.2%)	1 (2.9%)	7 (3.0%)
Respiratory, thoracic and mediastinal disorders	7 (4.5%)	3 (6.5%)	2 (5.9%)	12 (5.1%)
CTC-Grade 1 - milde event	7 (4.5%)	3 (6.5%)	-	10 (4.3%)
CTC-Grade 2 - moderate event	-	-	2 (5.9%)	2 (0.9%)
Skin and subcutaneous tissue disorders	18 (11.6%)	5 (10.9%)	8 (23.5%)	31 (13.2%)
CTC-Grade 1 - milde event	17 (11.0%)	3 (6.5%)	5 (14.7%)	25 (10.6%)
CTC-Grade 2 - moderate event	1 (0.6%)	2 (4.3%)	3 (8.8%)	6 (2.6%)
Surgical and medical procedures	3 (1.9%)	-	-	3 (1.3%)
CTC-Grade 1 - milde event	1 (0.6%)	-	-	1 (0.4%)
CTC-Grade 2 - moderate event	2 (1.3%)	-	-	2 (0.9%)
Vasculardisorders	43 (27.7%)	24 (52.2%)	10 (29.4%)	77 (32.8%)
CTC-Grade 1 - milde event	24 (15.5%)	16 (34.8%)	4 (11.8%)	44 (18.7%)
CTC-Grade 2 - moderate event	17 (11.0%)	7 (15.2%)	5 (14.7%)	29 (12.3%)
CTC-Grade 3 - severe event	2 (1.3%)	1 (2.2%)	1 (2.9%)	4 (1.7%)

*: laboratory

Note: Within the safety analysis the data of the patient with incorrect IMP (Pat-ID 28; randomised for placebo, received 3 mg (Z)-endoxifen)) were analyzed according to the really received IMP. Within the individual data listing patient was documented according to the eCRF documentation with the given label „none“ for the treatment arm.

In the previous Tables 15 and 16, AEs were summarized according to the Systems Organ Class (SOC). For detailed data regarding the “preferred terms” according to MedDRA, version 24.0, see appendix 2 to the Statistical Report, final version dated 25.01.2023. Table 17 references all listings of safety analysis data.

Table 17 Tables of the listings for the safety analysis (appendix 2 to the Statistical Report, final version dated 25.01.2023)

Safety analysis according to randomization		Chapter in appendix 2
	AEs by system organ class, preferred term and greatest severity per patient	1.1.1
	Listing CTC-grade 4 (life-threatening or disabling event)	1.1.2
	AE by system organ class, preferred term and maximum treatment relatedness per patient	1.1.3
	Listing of AEs leading to discontinuation form treatment	1.1.4
	Laboratory parameters classifying >/< as upper/lower limit related to IMP per patient	1.2
Safety analysis according to IMP		
	AEs by system organ class, preferred term and greatest severity per patient	2.1.1
	AE by system organ class, preferred term and maximum treatment relatedness per patient	2.1.2
	Laboratory parameters classifying >/< as upper/lower limit related to IMP per patient	2.2

12.2.3 Analysis of Adverse Events

Due to the unremarkable safety profile no further analysis was done.

12.2.4 Listing of Adverse Events by Patient

See appendix 2 to the Statistical Report, final version dated 25.01.2023.

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No deaths and SAEs occurred.

12.3.1.1 Deaths

N/A

12.3.1.2 Other Serious Adverse Events

N/A

12.3.1.3 Other Significant Adverse Events

N/A

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

N/A

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

N/A

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

No CTC-grade 3 to 5 AEs were observed in laboratory values (see SOC “Investigations” in Chapter 11.2.2 Table 16). As all patients received standard tamoxifen therapy, any relationship of mild and moderate AEs (CTC-grade 1 and 2) to tamoxifen or (Z)-endoxifen study medication cannot be differentiated.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Patients were monitored according the side effects mentioned in the prescribing information for tamoxifen. Transient anemia or thrombocytopenia as well as leukopenia are not uncommon, but severe cytopenias are rare. Consequently, a complete blood count was obtained at sceening and visits 1, 2 and 3. As changes in liver enzymes and the development of fatty liver are common and cases of serious liver disease (including fatalities) have been reported, liver enzymes were monitored during the study. Calcium was monitored because hypercalcemia has been described under Tamoxifen therapy, although this affects mainly patients with bone metastases, especially at the beginning of therapy. For other common and less common side effects (described in the Investigator’s Brochure) close clinical monitoring at the visits is sufficient.

The following laboratory parameters have been monitored:

- Hematology: Hematocrit, erythrocyte count, hemoglobin, white blood cell count with differential, platelets
- Chemistry: Glucose, creatinine, urea, sodium, potassium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyl transferase (GGT), albumin, bilirubin, INR. Triglycerides were only measured at screening and visit 3. Pathologic laboratory values in triglycerides levels were controlled with a fasting blood sample.
- Urinalysis: Standard urine dipstick: pH, specific gravity, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, erythrocytes.

- Pregnancy tests had to be obtained at the time points indicated in the Table of Assessments in women of child-bearing potential.

In case of clinically relevant findings, these were assigned to CTC-grades. Further evaluation was performed and the findings were documented.

Hematology

In 2 patients receiving (Z)-endoxifen CTC-grade 2 AEs occurred. No other AEs were observed. The treatment was not modified.

For more details including the "preferred term" according to MedDRA see appendix 3 to the Statistical Report final version dated 25.01.2023.

Chemistry

Only AEs with CTC-grades 1-2 occurred. In total 23 AEs with SOC "Investigations" were documented under treatment with (Z)-endoxifen, but only 1 with CTC-grade 2. The treatment was not modified.

For more details including the "preferred term" according to MedDRA see appendix 3 to the Statistical Report final version dated 25.01.2023.

Nephrology/Urology

In 3 patients receiving (Z)-endoxifen CTC-grade 1 AEs occurred. No other AEs were observed. The treatment was not modified.

For more details including the "preferred term" according to MedDRA see appendix 3 to the Statistical Report final version dated 25.01.2023.

Pregnancy

No patient became pregnant during the clinical study.

12.4.2.2 Individual Patient Changes

As no severe abnormalities in laboratory measurements have been observed, no individual patient changes are shown.

12.4.2.3 Individual Clinically Significant Abnormalities

No clinically significant abnormalities have been observed.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

No findings and observations were made.

12.6 Safety Conclusions

From a safety perspective, the (Z)-endoxifen supplementation concept takes advantage from the well-known safety and toxicity profile of tamoxifen in that the maximum achieved circulating plasma levels of (Z)-endoxifen do not exceed those observed in patients with normal CYP2D6 activity on standard tamoxifen. No Grade-4 AEs were observed and less than 8% of the patients on (Z)-endoxifen study medication developed severe AEs.

As these are known to be either disease related or are typically observed during tamoxifen therapy, we consider the low-dose (Z)-endoxifen application safe and consistent with the reported mild safety profile as shown in healthy human subjects and in high-dose (Z)-endoxifen treated cancer patients.

13. DISCUSSION AND OVERALL CONCLUSIONS

Efficacy

Both, supplementation of standard tamoxifen therapy with daily 20 mg of Tamoxifen according to CYP2D6 genotype and basal (Z)-endoxifen plasma concentrations under standard tamoxifen therapy, led to a significant and comparable increase in proportion of patients with (Z)-endoxifen plasma concentrations above 32 nM.

Safety

No difference in overall AE was observed between patients receiving only placebo or any of the two (Z)-endoxifen doses.

Overall Conclusion

The supplementation of standard tamoxifen therapy (20 mg/day) with either CYP2D6 genotype or basal (Z)-endoxifen plasma concentration guided low dose of 1.5 or 3 mg (Z)-endoxifen was efficient to increase (Z)-endoxifen plasma concentrations. The AE profile was unremarkable.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

All figures and tables referred to in the text are included in the respective chapters or as referred to in the statistical report.

14.1 Demographic Data

See Table 6 in chapter 11.2.

14.2 Efficacy Data

See Tables 7 to 14 in chapter 11.4.1.1.

14.3 Safety Data

14.3.1 Displays of Adverse Events

See Tables 15 and 16 in chapter 12.2.

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

N/A

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

N/A

14.3.4 Abnormal Laboratory Value Listing (each patient)

See appendix 3 to the Statistical Report final version dated 25.01.2023.

15. REFERENCE LIST

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16. APPENDICES

All documents in this section are available upon request.

16.1 Study Information

16.1.1. Protocol and Protocol Amendments

16.1.2. Sample Case Report Form (Unique Pages Only)

16.1.3. List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) – Representative written information for patient and sample consent forms

16.1.4. List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

16.1.5. Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

16.1.6. Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used – (N/A – only one batch was used)

16.1.7. Randomisation scheme and codes (patient identification and treatment assigned)

16.1.8. Audit certificates (if available)

16.1.9. Documentation of statistical methods (e.g. SAP)

16.1.10. Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

16.1.11. Publications based on the study

16.1.12. Important publications referenced in the report

16.2 Patient Data Listings

All listings are available in the Statistical Report.

16.2.1. Discontinued patients

16.2.2. Protocol deviations

16.2.3. Patients excluded from the efficacy analysis

16.2.4. Demographic data

16.2.5. Compliance and/or drug concentration data (if available)

16.2.6. Individual efficacy response data

16.2.7. Adverse event listings (each patient)

16.2.8. Listing of individual laboratory measurements by patient, when required by regulatory authorities

16.3 Case Report Forms

16.3.1. CRFs for deaths, other serious adverse events and withdrawals for AE – (N/A)

16.3.2. Other CRFs submitted – (N/A)

16.4 Individual Patient Data Listings (US Archival Listings) – (N/A)