ERRATA

An International, Phase 3, Multicenter, Randomized, Open-Label Trial Comparing Balixafortide in Combination with Eribulin versus Eribulin Alone in Patients with HER2 Negative, Locally Recurrent or Metastatic Breast Cancer (FORTRESS)

PROTOCOL NUMBER
POL6326-009

ERRATA DATE: 10 January 2022

CONFIDENTIAL

1. Reason for the Errata

There is a discrepancy in the last patient last visit (LPLV) date in the synopsis versus the cover page of the CSR.

- The cover page of the CSR shows the correct LPLV date of 19 Oct 2021
- The synopsis has the LPLV date as 13 Sep 2021, which is incorrect. The date in the synopsis should be 19 Oct 2021.

2. Impact to the Clinical Study Report

The above discrepancy does not affect the interpretation of study results or overall study conclusions as presented in the clinical study report (CSR). The CSR was not corrected; the version number and date of the CSR did not change.

The CSR was approved by the Clinical Scientist and Chief Medical Officer of Polyphor, Ltd.; however, this errata document was written after the closing date of Polyphor's merger with EnBiotix on 30 Dec 2021 (the combined company name was changed to Spexis AG). Therefore the approval of this errata document was signed by a representative of Spexis AG.

3. Changes to the Appendices and the Clinical Study Report Table of Contents

This discrepancy does not affect the CSR appendices or table of contents.

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Signature of Preparer: DocuSigned by: Nicola Will Signer Name: Nicola Will Signing Reason: I am the author of this document Signing Time: 10-Jan-2022 | 6:18:58 PM GMT BAAC136AC1D54B3490F1EB7C5C07BAF3 Date: 10 January 2022

SPONSOR SIGNATURE FOR ERRATA

STUDY TITLE: An International, Phase 3, Multicenter, Randomized, Open-Label Trial Comparing Balixafortide in Combination with Eribulin versus Eribulin Alone in Patients with HER2 Negative, Locally Recurrent or Metastatic Breast Cancer (FORTRESS)

I have read this document and confirm that to the best of my knowledge it accurately describes the correct results of the study.

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DATE: 10 JANUARY 2022

Synopsis

Title of Study: An International, Phase 3, Multicenter, Randomized, Open-Label Trial Comparing Balixafortide in Combination with Eribulin versus Eribulin Alone in Patients with HER2 Negative, Locally Recurrent or Metastatic Breast Cancer (FORTRESS) – POL6326-009; EudraCT: 2018-004211-42

Publications: None

Study Period: 30 May 2019 (First subject first visit) to 13 Sep 2021 (Last subject last visit)

Drug Development Phase: 3

Objectives: Objectives are summarized below:

Primary Objective[a]	**Primary Endpoint**
3rd Line+ Population: • To evaluate the efficacy of balixafortide + eribulin versus eribulin monotherapy on ORR in and PFS. 2nd Line+ Population: • To evaluate the efficacy of balixafortide + eribulin versus eribulin monotherapy on the primary endpoint of PFS.	• ORR and PFS according to RECIST v1.1 guidelines as assessed by the IRC • PFS according to RECIST v1.1 guidelines, as assessed by the IRC.[b]
Secondary Objectives[a]	**Secondary Endpoints**
3rd Line+ and 2nd Line+ Populations	
• To compare the OS between patients in the balixafortide + eribulin treatment arm versus eribulin monotherapy treatment arm.	• OS[c]
• To compare measures of tumor response between patients in the balixafortide + eribulin treatment arm versus eribulin monotherapy treatment arm.	• PFS according to RECIST v1.1 guidelines, as assessed by the local Investigator's review. • ORR [confirmed CR + confirmed PR]) according to RECIST v1.1 guidelines, as assessed by the IRC in the Overall Population.[d] • ORR (confirmed CR + confirmed PR) according to RECIST v1.1 guidelines, as assessed by the local Investigator's review. • CBR (proportion of patients with confirmed CR, confirmed PR, or SD ≥6 months) according to RECIST v1.1 guidelines as assessed by the IRC and by the local Investigator's review. • DCR (number of patients with confirmed CR, confirmed PR, or SD) according to RECIST v1.1 guidelines as assessed by the IRC and by the local Investigator's review. • Time to response as assessed by the IRC

	and by the local Investigator's review.[e] • Duration of response as assessed by the IRC and by the local Investigator's review.
To evaluate the safety and tolerability of balixafortide + eribulin versus eribulin monotherapy[f]	• Type, frequency and severity of AEs (including SAEs, AESIs). • Laboratory abnormalities. • Vital signs.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CBR = clinical benefit rate; CR = complete response; CSR = clinical study report; DCR = disease control rate; eDISH = evaluation of drug-induced serious hepatotoxicity; IRC = Independent Review Committee; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease.

a. Only the objectives addressed in this abbreviated CSR are shown here. Refer to the protocol for a full description of all planned objectives and endpoints.
b. In the Overall Population intended for regulatory submissions in the European Union and jurisdictions in which the 2nd line + eribulin label applies.
c. OS presented in this CSR is interim and is referred to as iOS in the efficacy sections.
d. In this CSR, the Overall Population is referred to as the 2nd Line+ population
e. Time to response was initially planned but was not assessed for this CSR due to a low number of patients with events.
f. Additionally, signs and symptoms of anaphylaxis were captured and summarized in accordance with guidance provided by the second symposium on the definition and management of anaphylaxis (Sampson et al 2006). Evaluation of liver parameters were made according to the eDISH criteria (FDA 2009).

Methodology: This international, multicenter, open-label, randomized, parallel, two-arm, pivotal Phase 3 trial was designed to investigate the efficacy and safety of balixafortide in combination with an established, approved therapy (eribulin) relative to eribulin monotherapy in patients with human epidermal growth factor receptor 2 (HER2) negative, locally recurrent or metastatic breast cancer (BC) who have previously been treated with 1−4 chemotherapeutic regimens for locally recurrent or metastatic BC. Unless contra-indicated for safety reasons, patients had previously received an anthracycline and a taxane in either the adjuvant or metastatic setting. In this protocol, locally recurrent BC is defined as unresectable locoregionally recurrent BC.

Two populations of patients were studied:

- Overall Population (referred to as 2nd Line+ in this clinical study report), who received study treatment as 2nd to 5th line of therapy, which was to constitute the

primary population for regulatory submissions in the European Union and jurisdictions in which the 2nd line + eribulin label applies.

- 3rd Line+ Population, who received study treatment as 3rd to 5th line of therapy (3rd line +), which was to constitute the primary population for regulatory submissions in the United States (US) and jurisdictions in which the 3rd line + eribulin label applies.

The study included:

- Screening assessments to be obtained ≤21 days before randomization.
- Randomization within 21 days of starting screening and after having completed the required screening assessments. Patients were randomized either to the balixafortide+eribulin treatment arm or to the eribulin treatment arm. Patients were to start treatment within 3 days after randomization.
- Treatment Phase: Patients were to receive 21-day cycles of treatment. All patients were to receive eribulin on Days 2 and 9 of each cycle. Patients randomized to the balixafortide+eribulin arm received balixafortide on Days 1−3 and Days 8−10 of each cycle.

  From the date of randomization, patients were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

  Evaluations were based on computed tomography/magnetic resonance imaging (CT/MRI) scans performed every 6 weeks (±7 days) during the first year, then every 12 weeks (±7 days), thereafter, until PD was documented by RECIST v1.1. At the discretion of the Investigator, additional radiographic tumor assessments may have been done at any time if disease progression was suspected. The decision about the patient's disease status and progression during the study was taken based on the local radiologist's/Investigator's assessment.

  From the date of randomization, additional bone scans were performed at the discretion of the Investigator (e.g. to confirm CR, to follow up existing metastases, or if [based on signs and symptoms] new bone metastases were suspected).

After initial documentation of an objective response, a confirmatory CT/MRI scan was to be performed at least 4 weeks later.

Patients discontinued from treatment for reasons other than PD were to enter the PD Follow up (as described in PD Follow-up below) unless death occurred, the patient withdrew consent to efficacy follow-up, or the patient was lost to follow-up.

- End-of-Treatment (EOT) Evaluation: This was to occur as soon as possible, within 7 days after discontinuation of study treatment and before initiation of any new anticancer therapy, regardless of the reason for discontinuation.

- 30-Day Safety Follow-up: This occurred 30 days (and no later than 37 days) from the last dose of study drug. AEs were assessed and recorded for all patients at this visit. Concomitant medications were also recorded for patients with unresolved AEs.

- Long-term Follow-up:

    - PD Follow-up: Regardless of treatment arm, patients who discontinued study treatment for any reason in the absence of PD were to undergo repeat imaging and tumor response assessments (including CT/MRI scans) every 8 weeks ±7 days (every 12 weeks ±7 days if the patient had been on the study for ≥1 year) until:

        - PD was documented as per RECIST v1.1, or

        - death occurred, or

        - patient was lost to follow-up, or the patient withdrew consent (whichever occurred first).

    - Survival Follow-up: The Investigator monitored the patient for overall survival (OS) status every 6 months (or more frequently) until:

        - death,

        - the patient withdrew consent to follow-up for survival, or until the patient was lost to follow-up (whichever occurred first).

Number of Patients (Planned and Analyzed): In this study, 384 patients were planned to be enrolled (192 patients in the balixafortide+eribulin treatment arm, and 192 patients in the eribulin treatment arm) including 320 patients who received study treatment as 3rd line +.

Test Product, Dose and Mode of Administration: Patients were randomized to one of the following 2 treatment regimens:

- Balixafortide+eribulin treatment arm: Balixafortide was administered on Days 1-3 and Days 8-10 and eribulin was administered on Days 2 and 9 of each 21-day cycle.
- Eribulin monotherapy treatment arm: Eribulin was administered on Days 2 and 9 of each 21-day cycle.

Balixafortide was administered, at a dose of 5.5 mg/kg, intravenously (IV) over a minimum of 2 hours ±10 minutes; however, the infusion time of balixafortide could have been increased to a maximum of 3 hours at the discretion of the treating physician, for reasons of patient tolerability (i.e. to manage injection site reactions).

Eribulin was administered IV at a dose of 1.4 mg/m^2 over 2 to 5 minutes on Days 2 and 9 of each 21-day cycle. This dose is expressed as the salt, eribulin mesylate; however, in some countries this dose is expressed as the base, equivalent to eribulin 1.23 mg/m^2. In the balixafortide+eribulin treatment arm, eribulin was administered within 45 minutes after the end of the balixafortide infusion. The eribulin dose was to be modified in patients with hepatic and/or renal impairment as described in the regulatory label for eribulin in the country where the patient is being treated or as described in the protocol Table 4 for other countries.

Crossover was not allowed at any time after randomization.

Duration of Treatment: The mean number of cycles was 6.2 in the balixafortide+eribulin arm, and 5.9 in the eribulin monotherapy arm, and the mean duration of treatment was 126.9 days and 117.3 days in the balixafortide+eribulin and eribulin monotherapy arms, respectively.

Safety: Type, frequency and severity of adverse events (AEs; including SAEs, AEs of special interest [AESIs]), laboratory abnormalities, and vital signs. Additionally, signs and symptoms of anaphylaxis were to be captured and summarized in accordance with guidance provided

by the second symposium on the definition and management of anaphylaxis. Evaluation of liver parameters were made according to the evaluation of drug-induced serious hepatotoxicity (eDISH) criteria; this required log-log plots of alanine aminotransferase/aspartate aminotransferase (AST) vs total bilirubin to identify potential cases of concern, followed by time course plots of all the identified potential cases.

Statistical Methods: Two statistical analysis plans (SAPs) were written; one for the US submission (Food and Drug Administration). Both SAPs, located in an appendix, describe the statistical methods and planned analyses for this study.

Summary of Results:

Subject Disposition (3rd Line+ Population): A total of 26 patients were ongoing at the time of the soft lock. All patients were ultimately discontinued and completed safety follow-up before the hard database lock on 22 Oct 2021. Information provided below does not include the patients who were continuing on study after the database soft lock date of 26 Sep 2021.

In the 3rd Line+ population 175 and 173 patients were randomly assigned to the balixafortide+eribulin and eribulin monotherapy arms, respectively. Of these:

- **Balixafortide+eribulin arm:** 174 (99.4%) patients were treated, 172 (98.9%) discontinued study treatment, and 167 (95.4%) discontinued the study.

  Reasons for study discontinuation included: study closed (52 [29.7%]), death (105 [60.0%]), withdrew consent (7 [4.0%]), lost to follow-up (2 [1.1%]), and other (1 [0.6%]).

  Reasons for study treatment discontinuation included: disease progression (138 [79.3%]), AE (6 [3.4%]), withdrew consent (13 [7.5%]), study terminated by sponsor (7 [4.0%]), death (4 [2.3%]), and other (4 [2.3%]).

- **Eribulin monotherapy arm:** 166 (96.0%) patients were treated, 165 (99.4%) discontinued study treatment, and 162 (93.6%) discontinued the study.

  Reasons for study discontinuation: study closed (54 [31.2%]), death (93 [53.8%]), withdrew consent (11 [6.4%]), lost to follow-up (2 [1.2%]), and other (2 [1.2%]).

Reasons for study treatment discontinuation: disease progression (129 [77.7%]), AE (9 [5.4%]), withdrew consent (8 [4.8%]), study terminated by sponsor (8 [4.8%]), death (7 [4.2%]), other (3 [1.8%]), and lost to follow-up (1 [0.6%]).

Demography and Baseline Characteristics (3rd Line+ Population): The mean age of 3rd Line+ patients was similar between treatment arms (55 to 56 years), and in both groups most patients were under 65 years of age. Over 99% of the 3rd Line+ patients were women; 1 male patient was enrolled in each treatment arm. The majority of 3rd Line+ patients were White. Most 3rd Line+ patients' Eastern Cooperative Oncology Group performance status was "1", restricted physical activity, followed by "0", fully active.

Efficacy Results:

PFS by IRC assessment (RECIST version 1.1): In the 3rd Line+ population there was no statistically significant difference between the 2 treatment arms (hazard ratio [HR] and 96% CI = 1.07 [0.81, 1.41] with p=0.6158); thus, the primary endpoint for this study (PFS according to RECIST v1.1 guidelines) was not met. In addition, there was no statistically significant difference between the 2 treatment arms (HR and 96% CI = 1.10 [0.85, 1.41] with p=0.4450) in the 2nd Line+ population.

ORR by IRC assessment (RECIST version 1.1): In the 3rd Line+ population the distribution of best overall response (BOR) was similar between the 2 groups. There was no statistically significant difference between the treatment arms for ORR as assessed by the IRC (odds ratio [exact 99% CI] = 1.0 [0.3, 3.0] with p=1.0000); thus, the coprimary endpoint for this study (PFS according to RECIST v1.1 guidelines) was not met.

Interim Overall Survival (iOS) by IRC assessment (RECIST version 1.1): There was no statistically significant difference between the treatment arms for iOS as assessed by the IRC (p=0.6126).

Safety Results: Safety assessments were conducted on the 2nd Line+ population.

Number of Patients With	Balixafortide + Eribulin (N=218) n (%)	Eribulin Monotherapy (N=204) n (%)	Total (N=422) n (%)
Any TEAE	214 (98.2)	197 (96.6)	411 (97.4)
Any TEAE with CTCAE Grade 3 or above	149 (68.3)	128 (62.7)	277 (65.6)
Any serious TEAE	63 (28.9)	54 (26.5)	117 (27.7)
Any TEAE related to study treatment[a]	206 (94.5)	181 (88.7)	387 (91.7)
Any TEAE related to balixafortide	199 (91.3)	0	199 (47.2)
Any TEAE related to eribulin	174 (79.8)	181 (88.7)	355 (84.1)
Any serious TEAE related to study treatment[a]	22 (10.1)	19 (9.3)	41 (9.7)
Any serious TEAE related to balixafortide	15 (6.9)	0[c]	15 (3.6)
Any serious TEAE related to eribulin	17 (7.8)	19 (9.3)	36 (8.5)
Any TEAE leading to study treatment discontinuation[b]	22 (10.1)	18 (8.8)	40 (9.5)
Any TEAE leading to balixafortide discontinuation	21 (9.6)	2 (1.0)[c]	23 (5.5)
Any TEAE leading to eribulin discontinuation	21 (9.6)	17 (8.3)	38 (9.0)
Any TEAE leading to death	15 (6.9)	13 (6.4)	28 (6.6)
Any TE AESI	18 (8.3)	15 (7.4)	33 (7.8)
Any TE AEPI	91 (41.7)	31 (15.2)	122 (28.9)

Abbreviations: AE = adverse event; AEPI = adverse event of particular interest; AESI = adverse event of special interest; CTCAE = common terminology criteria for adverse events; TE = treatment-emergent; TEAE = treatment-emergent adverse event.

Note: Data presented in this table are unclean data and should be interpreted with caution.

TEAEs were defined as AEs that occurred at or after administration of the first dose of any study treatment and through 30 days after the last dose of any study treatment.

If the severity of an AE was missing, the AE was reported as “Grade 3”.

CTCAE version 5.0.

a. For patients in the balixafortide+eribulin treatment arm, an event was considered treatment-related if it was related to either study treatment. If the relationship was missing, the AE was considered as ‘related’.

b. For patients in the balixafortide+eribulin treatment arm, this was discontinuation from either study treatment, regardless of causality.

Conclusions:

- The primary efficacy endpoints (ORR and PFS in the 3rd Line+ population and PFS in the 2nd Line+ population) were not met.
- The observed safety profile was consistent with the safety profile expected in this study population after exposure to balixafortide and eribulin. No new safety signals were identified.

Date and Version of This Report: 09 Dec 2021 (Final)