CLINICAL STUDY REPORT

A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in patients pre-treated with anti-HER2- therapy with HER2-positive metastatic breast cancer

- E-VITA -

EudraCT no.: 2010-023237-37

Indication:	Metastatic breast cancer
Phase:	II
Study Protocol:	GBG 64 Protocol (September 9th, 2011) Amendment 1 (September 11th, 2013)
Investigational Products:	Eribulin (IMP), Lapatinib (Non-IMP)
Clinical Study Report Version:	Synopsis Version 2
First Patient Enrolled:	February 20th, 2012
Last Patient Completed:	March 31st, 2015
Data Cut-off Database:	February 29th, 2016
Co-ordinating Investigator:	Prof. Dr. Serban-Dan Costa Universitätsfrauenklinik Magdeburg Gerhart-Hauptmann-Straße 35, D-39108 Magdeburg Germany
Sponsor	GBG Forschungs GmbH Martin-Behaim-Straße 12, D-63263 Neu-Isenburg Germany
Date of this report:	March 23rd, 2016

1. SYNOPSIS

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) HALAVEN® (2) TYVERB®		
Name of active ingredient: (1) Eribulin (2) Lapatinib		

Title of Study:

A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in patients pre-treated with anti-HER2- therapy with HER2-positive metastatic breast cancer

(E-VITA).

Investigators:

Co-ordinating Investigator: Prof. Dr. Serban-Dan Costa (Universitätsfrauenklinik Magdeburg)

Principal Investigators: see Section "Study Center(s)"

Study Center(s):

The study was conducted at the following study centers in Germany:

- Universitätsklinikum Aachen, Frauenklinik für Gynäkologie und Geburtshilfe, Pauwelsstraße 30, 52074 Aachen (PI: Bauerschlag);
- Ostalb-Klinikum, ABC Brustzentrum, Frauenklinik, Im Kälblesrain 1, 73430 Aalen(PI: Gnauert);
- Gemeinschaftspraxis Dres. Heinrich / Bangerter , Halderstr. 29, 86150Augsburg (PI: Heinrich);
- MediOnko-Institut GbR, Praxisklinik Krebsheilkunde, Möllendorffstr. 52, 10367 Berlin (PI: Klare);
- DRK Kliniken Köpenick, Frauenklinik, Salvador Allende Str. 2-8, 12559, Berlin, (PI: Kleine-Tebbe);
- Klinikum Ludwigsburg-Bietigheim, KH Bietigheim, Gynäkologie, Riedstr. 12, 74321, Bietigheim-Bissingen, (PI: Sözgen);
- Gemeinschaftspraxis für Hämatologie und Onkologie, Kurt-Schumacher Platz 4, 44787 Bochum (PI: Bückner);
- Hämato-Onkologie im Medicum, Schwachhauser Heerstraße 50, 28209 Bremen (PI: Doering);
- Klinikum Chemnitz Frauenklinik, Flemmingstr. 4, 09116 Chemnitz (PI: Krabisch);
- Krankenhaus Cuxhaven GmbH, Frauenklinik, Altenwalder Chaussee 10-12, 27474 Cuxhaven (PI:Deichert);
- Städtisches Klinikum Dessau, Frauenklinik, Auenweg 38, 06847 Dessau (PI:Voß);
- Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Frauenklinik, Fetscherstr. 74, 01307 Dresden (PI: Kast);
- Sana Kliniken Düsseldorf GmbH Gerresheim, Senologie, Gräulinger Straße 120, 40625 Düsseldorf (PI: Nestle-Krämling);
- Kliniken Essen-Mitte Evang. Huyssens-Stiftung/Knappschaft GmbH, Klinik für Senologie / Brustzentrum, Henricistr. 92, 45136 Essen (PI: Kümmel);
- Universitätsklinikum Essen, Klinik für Frauenheilkunde und Geburtshilfe; Brustzentrum, Hufelandstrasse 55, 45147 Essen (PI: Aktas);
- Klinikum der J. W. Goethe Universität, Zentrum der Frauenheilkunde und Geburtshilfe, Med. Klinik 2 Hämatologie / Onkologie , Theodor-Stern-Kai 7, 60590 Frankfurt am Main, (PI: Ruckhäberle);
- MVZ Osthessen GmbH, Tumorklinik, Pacelliallee 4, 36043 Fulda (PI: Distelrath);
- Helios Klinikum Gifhorn, Interdisziplinäres Brustzentrum, Campus 6, 38518 Gifhorn (PI: Dewitz);
- Universitätsmedizin Greifswald , Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Ferdinand-Sauerbruch-Straße, 17475 Greifswald (PI: Belau);

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) HALAVEN® (2) TYVERB®		
Name of active ingredient: (1) Eribulin (2) Lapatinib		

- DIAKOVERE Henriettenstift Gynäkologie, Frauenklinik, Schwemannstr. 19, 30559 Hannover, (PI: Lübbe);
- Vinzenzkrankenhaus, Gynäkologie, Lange-Feld-Str. 31, 30559 Hannover, (PI: Deuker);
- Gynäkologisch onkologische Praxis am Pelikanplatz, Pelikanplatz 23, 30177 Hannover, (PI: Schrader);
- Universitätsklinikum Heidelberg NCT, Gynäkologische Onkologie, Im Neuenheimer Feld 460, 69120 Heidelberg, (PI: Marmé);
- Marienhospital Herne, Onkologische / Hämatologische Ambulanz, Hölkeskampring 40, 44625 Herne (PI: Strumberg);
- Elisabeth Krankenhaus, Brustzentrum, Weinbergstrasse 7, 34117, Kassel, (PI: Conrad);
- Universitätsklinikum Schleswig-Holstein, Klinik für Gynäkologie und Geburtshilfe SGO Kiel, Arnold-Heller-Str. 3, Haus C Station 516, 24105 Kiel, (PI: Mundhenke);
- Institut für Versorgungsforschung in der Onkologie, Praxisklinik für Hämatologie und Onkologie, Neversstraße 5, 56068 Koblenz am Rhein, (PI: Thomalla);
- St. Elisabeth-Krankenhaus, Brustzentrum Köln-Hohenlind, Werthmannstr. 1, 50935 Köln (PI: Schumacher);
- Caritas Krankenhaus Lebach, Abteilung für Hämatologie und internistische Onkologie, Heeresstr. 49, 66822 Lebach, (PI: Kremers);
- St. Elisabeth Krankenhaus, Senologie, Biedermannstr. 84, 04277 Leipzig, (PI: Langanke);
- Klinikum der Otto-v.-Guericke-Universität, Frauenklinik, Gerhart-Hauptmann-Str. 35, 39108 Magdeburg, (PI: Costa);
- Universitätsklinikum Mannheim GmbH, Frauenklinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, (PI: Gerhardt);
- Rotkreuzklinikum München, Frauenklinik, Taxisstr. 3, 80637 München, (PI: Hanusch);
- Klinikum rechts der Isar der Techn. Univ. München, Frauenklinik, Studienzentrale (Zi 1.31) Ismaninger Strasse 22, 81675 München, (PI: Ettl);
- Universitätsklinikum Münster, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Albert-Schweitzer-Campus 1, 48149 Münster, (PI: Radke);
- medius Kliniken gGmbH, medius Klinik Nürtingen, Brustzentrum, Auf dem Säer 1, 72622 Nürtingen, (PI: Faust);
- Sana Klinikum Offenbach GmbH, Frauenklinik, Studienambulanz AOZ, Starkenburgring 66, 63069 Offenbach am Main, (PI: Jackisch);
- Klinikum Oldenburg AöR, Universitätsklinik für Innere Medizin - Onkologie und Hämatologie, Rahel-Straus-Str. 10, 26133 Oldenburg, (PI: Köhne);
- Klinikum Quedlinburg, Frauenklinik, Ditfurter Weg 24, 06484 Quedlinburg, (PI: Graßhoff);
- Oncologianova GmbH, Onkologie, Am Stadion 9, 45659 Recklinghausen, (PI: Overkamp);
- Praxis Pihusch MVZ GbR, Stollstr. 6, 83022 Rosenheim, (PI: Pihusch);
- Klinikum Südstadt, Universitätsfrauenklinik, Südring 81, 18059 Rostock, (PI: Gerber);
- g.SUND Gynäkologie Kompetenzzentrum Stralsund, Studiensekretariat, Große Parower Straße 47-53, 18435 Stralsund, (PI: Ruhland);
- Mutterhaus der Borromäerinnen, Krankenanstalt, Med. Abteilung I, Feldstraße 16, 54290 Trier, (PI: Clemens);
- GOSPL - Gesellschaft für onkologische Studien, Hämatologie und Onkologie, Schloßstr. 18, 53840 Troisdorf, (PI: Forstbauer);
- Universitätsklinikum Tübingen, Frauenklinik, Calwerstr. 7, 72076, Tübingen, (PI: Grischke);

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) HALAVEN® (2) TYVERB®		
Name of active ingredient: (1) Eribulin (2) Lapatinib		

- Kliniken Landkreis Tuttlingen, Gesundheitszentrum, Frauenklinik, Zeppelinstr. 21, 78532 Tuttlingen, (PI: Martin);
- HELIOS Dr. Horst Schmidt Kliniken Wiesbaden Klinik für Gynäkologie und gynäkologischen, Ludwig-Erhard-Straße 100, 65199 Wiesbaden, (PI: Neunhöffer);
- Onkologische Gemeinschaftspraxis, Hämatologie / Onkologie, Mauerfeldchen 72, 52146 Würselen, (PI: Maintz).

Publication (reference):
N.a.

Studied Period (years): 3
Date of the first patient enrolled: February 20th, 2012
Date of the last patient completed: March 31st, 2015

Phase of Development:
Phase II

Objectives:
Primary Objectives
1. To assess the time to progression (TTP) of eribulin at a dose of 1.23mg/m² i.v. days 1+8, q d21 and eribulin given at a dose of 1.76mg/m² i.v. day 1, q d21 both in combination with lapatinib.
2. To assess the safety and toxicity of both treatment arms.

Secondary Objectives
1. To determine the objective response rate of both treatment arms.
2. To determine the overall clinical benefit rate (CR + PR + SD > 24 weeks) of both treatment arms.
3. To determine overall survival in both treatment arms 3 years after first patient has been randomized.
4. To assess biomarkers like PI3K mutation, PTEN expression, c-myc on the primary tumor and correlate them with TTP in both treatment arms.

Methodology:
Randomised, open, multicenter study in parallel groups.

Number of patients (planned and analysed):
Planned: 80
Enrolled: 43
Randomised: 43
Analysed patients (efficacy and safety): 41

Diagnosis and Main Criteria for Inclusion:
Women with histologically confirmed carcinoma of the breast with HER2 overexpression and locally advanced or metastatic stage of disease not suitable for surgery or radiotherapy alone.

1. Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements.

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) HALAVEN® (2) TYVERB®		
Name of active ingredient: (1) Eribulin (2) Lapatinib		

2. Complete baseline documentation must be submitted via the web-based data collection system MedCODES to the GBG Forschungs GmbH.

3. Histological confirmed carcinoma of the breast with over-expression of HER2 (IHC3+ or FISH pos., according to current guidelines of AGO). Every effort should be made to make paraffin embedded tissue or slides from the original tumor and/or from metastatic tissue available for confirmation of diagnosis and additional translational research.

4. Locally advanced or metastatic stage of disease not suitable for surgery or radiotherapy alone.

5. Patients must have either measurable or non-measurable target lesions according to RECIST criteria. Complete staging work-up within 4 weeks prior to registration. All patients must have chest X-ray (PA and lateral), abdominal ultrasound or CT scan or MRI, and bone scan. In case of positive bone scan, bone X-ray is mandatory. Other tests may be performed as clinically indicated.

6. The following previous systemic treatments are eligible:

- • Previous treatment with anti HER2 therapy either as (neo)adjuvant treatment for early breast cancer
  and/or first, second and/or third line treatment for metastatic breast cancer,
- • adjuvant and up to 3 chemotherapy regimen for metastatic breast cancer,

• if previous chemotherapy regimen were anthracycline based, the maximum cumulative dose of prior anthracycline therapy must not exceed 360mg/m² for doxorubicin and 720mg/m² for epirubicin,
• adjuvant endocrine therapy,
• palliative endocrine treatments,
• treatment with bisphosphonates (adjuvant and/or palliative),

- • radiotherapy with full recovery from clinical relevant side effects. The measurable disease must be completely outside the radiation field or there must be pathologic proof of progressive disease.

7. Age > 18 years.

8. ECOG performance status 0-2.

9. Laboratory requirements:

• absolute neutrophil count ≥ 1500 cells/µl,
• hemoglobin ≥ 10.0g/dL (hemoglobin < 10.0g/dL is acceptable if it is corrected by growth factor or transfusion),
• platelet count ≥ 100,000 cells/µl,
• bilirubin ≤ 1.5x the upper limit of normal for the institution (ULN),
• elevation of transaminases and alkaline phosphatase < 2.5x ULN or < 5x ULN for patients with liver metastases,
• creatinine ≤ 1.5x ULN or creatinine-clearance > 40 ml/min (according to Cockroft-Gault),
• negative pregnancy test (urine or serum) within 14 days prior to registration for all women of childbearing potential.

10. Normal cardiac ejection function as determined by cardiac ultrasound (LVEF above institutional normal range).

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) HALAVEN® (2) TYVERB®		
Name of active ingredient: (1) Eribulin (2) Lapatinib		

11. A female either of:
- Non-childbearing potential i.e., physiologically incapable of becoming pregnant because of history of hysterectomy, bilateral oophorectomy (ovarectomy), bilateral tubal ligation or postmenopausal status.
- Childbearing potential with a negative serum pregnancy test within 2 weeks prior to registration, preferably as close to the first dose as possible, and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:
  - an intrauterine device with a documented failure rate of less than 1% per year.
  - vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
  - complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
  - double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

12. Female patients who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

13. Patients must be available and compliant for treatment and follow-up. Patients registered on this trial must be treated and followed up at the participating or a cooperating center.

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

Patients will be randomized to receive in addition and simultaneously to lapatinib either
- eribulin 1.23mg/m² i.v. days 1+8, q d21
  - Batch Number provided: N1100578

or
- eribulin 1.76mg/m² i.v. day 1, q d21.
  - Batch Number provided: N1100578

Duration of Treatment:

Treatment will be given until disease progression or unacceptable toxicity of the study drug, or withdrawal of consent of the patient.

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

All patients will be treated with lapatinib 1000 mg/d orally as a standard treatment option for HER2 positive trastuzumab pretreated metastatic breast cancer.

Criteria for Evaluation:

Efficacy

Primary endpoint

Time to progression (TTP) is defined as the time period between randomization and documented disease progression or disease-related death.

Safety by toxicity grades is defined by the NCI-CTCAE version 4.0. Compliance will be assessed by the number and reasons of patients whose treatment had to be reduced, delayed or permanently stopped eribulin and/or lapatinib.

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) HALAVEN® (2) TYVERB®		
Name of active ingredient: (1) Eribulin (2) Lapatinib		

Secondary endpoints

Response of tumor lesions is based on investigator assessments and will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST). Missing data on response evaluation will be set to no response.

CBR is defined as all patients with a complete, partial and stable disease for at least 24 weeks.

Overall survival (OS) is defined as the time period between randomization and death due to any cause.

Statistical Methods:

An intention-to-treat (ITT) analysis for the primary endpoints will include all randomized patients.

Sample size determination:

It is planned to recruit 80 patients into this study. As this is a feasibility study, no formal sample size calculation was performed.

SUMMARY

Efficacy Results:

Lapatinib in combination with capecitabine has been approved for the treatment of women with HER2-positive advanced breast cancer that have progressed after anthracycline-, taxane-, and trastuzumab-containing therapies. The use of this combination is limited by overlapping toxicities such as diarrhea and cutaneous side effects. Therefore, other combinations of lapatinib with less toxic cytotoxic agents are needed. In the EMBRACE study, eribulin mesylate at a dose of 1.4 mg/m² given on day 1and 8 every 3 weeks has shown a superior overall survival by 2.5 months compared to treatment of physicians choice in patients with locally advanced or metastatic breast cancer who were previously treated for 2-5 lines with anthracyclines, taxanes, and capecitabine. In the E-VITA study two schedules of eribulin in association with lapatinib have been investigated.

The E-VITA study showed a median time to progression of 8.1 months (95% CI 4.8-9.4) for patients treated with lapatinib and eribulin 1.23mg/m^2 day 1, 8 q 21 compared to 6.5 months (95% CI 4.6-13.4) for patients treated with lapatinib and eribulin 1.76mg/m^2 day 1 q 21. No difference in OS as seen between the two arms (23.1 months [95% CI 12.5-35.0] vs. 23.2 months [95%CI 13.7-30.1]). The overall response rate were 52.4% (95% CI 31.0-73.7) and 45.0% (95% CI 23.2-66.8), respectively, with a preponderance of partial response. Only one complete response was observed with eribulin 1.23mg/m^2 day 1, 8 q21 compared with none with eribulin 1.76mg/m^2 day 1 q21. Overall, 2 and 1 cases of disease progression were seen respectively. The clinical benefit rate between the two arms was 71.4% (95% CI 52.1-90.8) and 75.0% (56.0-94.0) respectively.

In November 2013, given that the study recruitment was behind the planned schedule, the study was amended in order to prolong the recruitment period. Despite that the study was stopped in July 2014 due to the persistent difficulty in accrual. Overall, only half of the planned patients entered the trial. Therefore, no definitive conclusion could be drawn on the better eribulin schedule to be used in association with lapatinib.

Safety Results:

Overall, the most frequently adverse events observed were anemia, leukopenia, neutropenia, alopecia, fatigue, diarrhea, sensory neuropathy, transaminases increase and nausea. Overall, only one patient discontinued the therapy due to hematological toxicities related to the study medication (eribulin 1.76 mg/m^2); 1 patient in the eribulin 1.23mg/m^2 arm and 2 patients in the eribulin 1.76mg/m^2 arm discontinued the treatment due to non-hematological toxicities related to the study medication. A total of 13 and 12 patients respectively discontinued treatment due to progression. The adverse events observed during the trial were in line with the known safety profile of eribulin and lapatinib. No new safety concerns emerged from the study.

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) HALAVEN® (2) TYVERB®		
Name of active ingredient: (1) Eribulin (2) Lapatinib		

CONCLUSIONS:

Lapatinib in combination with capecitabine has been approved for the treatment of women with HER2-positive advanced breast cancer that have progressed after anthracycline-, taxane-, and trastuzumab-containing therapies. The use of this combination is limited by overlapping toxicities such as diarrhea and cutaneous side effects. Therefore, other combinations of lapatinib with less toxic cytotoxic agents are needed. In the EMBRACE study eribulin mesylate at a dose of 1.4 mg/m² given on day 1, 8 every 3 weeks has shown a superior overall survival by 2.5 months compared to treatment of physicians choice in patients with locally advanced or metastatic breast cancer who were previously treated for 2-5 lines with anthracyclines, taxanes, and capecitabine. The better tolerated schedule of eribulin is still under investigation. Therefore, in the E-VITA study two schedules of eribulin in association with lapatinib have been investigated.

The E-VITA study showed a median time to progression of 8.1 months (95% CI 4.8-9.4) for patients treated with lapatinib and eribulin 1.23mg/m^2 day 1, 8 q21 compared to 6.5 months (95% CI 4.6-13.4) for patients treated with lapatinib and eribulin 1.76mg/m^2 day 1 q21. No difference in OS was seen between the two arms (23.1 months [95%CI 12.5-35.0] vs. 23.2 months [95%CI 13.7-30.1]). The overall response rate was 52.4% (95% CI 31.0-73.7) and 45.0% (95% CI 23.2-66.8), respectively, with a preponderance of partial response. Only one complete response was observed with eribulin 1.23mg/m^2 day 1, 8 q21 compared with none with eribulin 1.76mg/m^2 day 1 q21. Overall, 2 and 1 cases of disease progression were seen respectively. The clinical benefit rate between the two arms was 71.4% (95% CI 52.1-90.8) and 75.0% (56.0-94.0), respectively.

In November 2013, given that the study recruitment was behind the planned schedule, the study was amended in order to prolong the recruitment period. Despite that the study was stopped in July 2014 due to the persistent difficulty in accrual. Probably due to other treatment options which have become available in the meantime (e.g. T-DM1). Overall, only half of the planned patients entered the trial. Hematological adverse events as well as non-hematological adverse events were more frequently observed in patients treated with lapatinib and eribulin 1.76mg/m^2 day 1 q21. The most frequently reported hematological adverse events of any grade with lapatinib and eribulin 1.23mg/m^2 day 1, 8 q21 and lapatinib and eribulin 1.76mg/m^2 q21 were anemia (85.7% vs. 75.0%) and leukopenia (90.5% vs. 85.0%), whereas the most frequently grade 3-4 adverse event was neutropenia (47.6% vs. 70.0%). Leukopenia high grade was observed in 23.8% and 55.0% of cases respectively. The most frequently observed non-hematological adverse event of any grade was alopecia (95.2% vs. 90.0%), followed by fatigue (76.2% vs. 80.0%), increased ASAT (61.9% vs. 75.0%) and ALAT (71.4% vs. 60.0%), sensory neuropathy (61.9% vs. 70.0%), diarrhea (57.1% vs. 60.0%) and nausea (47.6% vs. 45.0%). The most frequently reported grade 3-4 adverse events were fatigue (19.0% vs. 0.0%) and diarrhea (9.5% vs. 5.0%). The observed adverse events were in concordance with those observed in study 301. Patients were randomized to receive either eribulin 1.4 mg/m^2 days 1 and 8, or capecitabine 1.25 g/m^2 orally twice per day on days 1 to 14, both in 21-day cycles. The most common adverse events for eribulin and capecitabine were neutropenia (54% vs. 16%), hand-foot syndrome (< 1% vs. 45%), alopecia (35% vs. 4%), leukopenia (31% vs. 10%), diarrhea (14% vs. 29%), and nausea (22% vs. 24%).

In E-VITA study, 2 SUSARs for the same patients were reported, both related to eribulin 1.23 mg/m^2: macular edema and retinal haemorrhage. Overall, only one patient discontinued therapy due to hematological toxicities related to study medication (eribulin 1.76 mg/m^2); 1 patients in the eribulin 1.23mg/m^2 arm and 2 patients in the eribulin 1.76mg/m^2 arm discontinued the treatment due to non-hematological toxicities related to the study medication. A total of 13 and 12 patients respectively discontinued treatment due to progression.

Two deaths were reported. Only one was related to the study medication (pneumonia) in eribulin 1.23mg/m^2 arm. The observed toxicities were in line with the expected toxicities of lapatinib and eribulin. No new safety concerns emerged from the study. The reported SUSARs and deaths do not affect the known safety-benefit

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) HALAVEN® (2) TYVERB®		
Name of active ingredient: (1) Eribulin (2) Lapatinib		

ratio of the two drugs. The combination of eribulin and lapatinib show an acceptable safety profile, with neutropenia being the most common high grade hematological toxicity and alopecia and fatigue the most common non-hematological toxicities. Overall, no definitive conclusion could be drawn on the better eribulin schedule to be used in association with lapatinib.

Date of the Report:
March 23th, 2016

Annex 1

Amendment to Protocol, early stopping of the trial:

There was one substantial Amendment to the protocol of E-Vita.

In November 2013, given that the study recruitment was behind the planned schedule, the study was amended in order to prolong the recruitment period, as well as to allow the use of new Anti-HER2 treatment options as T-DM1.

Despite that the study was stopped in July 2014 due to the persistent difficulty in accrual.

Amendment 1 protocol changes:

Protocol:
A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in trastuzumab pre-treated patients with HER2-positive metastatic breast cancer.
Amendment 1:
A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in patients pre-treated with anti-HER2- therapy with HER2-positive metastatic breast cancer.

Protocol:
Stratification factors for randomization will be:
• previous line of chemotherapy for metastatic disease (0-1 vs. 2).
Amendment 1:
Stratification factors for randomization will be:
• previous line of chemotherapy for metastatic disease (0-1 vs. 2-3).

Protocol:
Inclusion criterion no.6
The following previous systemic treatments are eligible:
• Previous treatment with trastuzumab either as (neo)adjuvant treatment for early breast cancer and/or first and/or second line treatment for metastatic breast cancer,
adjuvant and up to 2 chemotherapy regimen for metastatic breast cancer,
…
• at least 4 weeks since radiotherapy, with full recovery. The measurable disease must be completely outside the radiation field or there must be pathologic proof of progressive disease.
Amendment 1:
The following previous systemic treatments are eligible:
• Previous treatment with anti HER2 therapy either as (neo)adjuvant treatment for early breast cancer and/or first, second and/or third line treatment for metastatic breast cancer,
• adjuvant and up to 3 chemotherapy regimen for metastatic breast cancer,
…
• radiotherapy with full recovery from clinical relevant side effects. The measurable disease must be completely outside the radiation field or there must be pathologic proof of progressive disease.

Protocol:
Exclusion criterion no.2
Patients who have received eribulin or lapatinib before.
Amendment 1:
Patients who have received eribulin or who have received lapatinib as part of the last therapy before entering this trial.

Protocol:
Enrollment Period

24 months (Q-III 2011 – Q-II 2013).
Amendment 1:
36 months (Q-I 2012 – Q-I 2015).

Protocol:
Regular End of Study
The end of this study is defined as 3 years after the 1st patient entered the trial. Planned end of study is June 2014.
Amendment 1:
The end of this study is defined as 4 years after the 1st patient entered the trial. Planned end of study is Q-I 2016.