Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	BAY86-5044 / 91484	NCT00555919
Study Phase:	II	
Official Study Title:	Randomized phase II study to investigate the efficacy, safety and tolerability of ZK 230211 (25 mg vs. 100 mg) as second-line endocrine therapy for postmenopausal women with hormone receptor-positive metastatic breast cancer	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Lonaprisan, ZK 230211, BAY86-5044	
Name of Active Ingredient:	Lonaprisan (ZK 230211)	
Dose and Mode of Administration:	Group 1: 1 x 25 mg tablet once daily, Group 2: 2 x 50 mg tablet once daily; oral	
Reference Therapy/Placebo		
Reference Therapy:	None	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Subjects were to be treated until they had disease progression, became unable to tolerate therapy, had any intercurrent condition that precluded continuation of study treatment, were noncompliant with therapy, withdrew consent, or died.	
Studied period:	Date of first subjects' first visit:	10 Mar 2008
	Date of last subjects' last visit:	21 Mar 2011
	The study was terminated prematurely due to slow recruitment and expected futility due to the low response rate.	

Study Center(s):	28 study centers in 10 countries: Austria (4 centers), Finland (2 centers), France (6 centers), Germany (5 centers), Great Britain (1 center), Italy (1 center), Poland (4 centers), Spain (1 center), Sweden (3 centers), Switzerland (1 center)
Methodology:	Tumor lesions were evaluated according to RECIST 1.0 criteria. Randomization was performed with stratification for disease status (measurable/non-measurable disease) and previous chemotherapy (yes/no). RECIST Criteria were to be used to evaluate the primary efficacy endpoint 'clinical benefit' and the two secondary efficacy endpoints 'progression-free survival' and 'objective response rate' in the subset of subjects with measurable disease.
Indication/ Main Inclusion Criteria:	Hormone receptor-positive metastatic breast cancer - Postmenopausal women with progesterone receptor-positive metastatic breast cancer (Stage IV, UICC) - Disease progression after first-line endocrine therapy for advanced breast cancer (i.e. with tumor remission or stabilization lasting at least 3 months under endocrine therapy) - At least one measurable or non-measurable tumor lesion (according to Response Evaluation Criteria in Solid Tumors [RECIST]) - World Health Organization (WHO) performance status ≤ 1 Subjects with more than one prior endocrine treatment for advanced breast cancer and subjects with previous combination of endocrine treatment with any other type of treatment (except chemotherapy), or previous sequential endocrine treatments (if there was disease progression between treatments) were to be excluded.
Study Objectives:	<u>Primary:</u> The primary objective was to evaluate the efficacy (clinical benefit) of 2 doses of Lonaprisan (25 mg and 100 mg) when administered once daily per os <u>Secondary:</u> Secondary objectives were the evaluation of : - Safety and tolerability - Pharmacokinetics of Lonaprisan - Effect of Lonaprisan on Quality of Life - Biomarkers (exploratory analysis)
Evaluation Criteria:	<u>Efficacy (Primary):</u> The primary efficacy variable was clinical benefit, i.e. the proportion of subjects with: - Complete response (CR) or partial response (PR) at any time point up to Month 6 or

	- Stable disease (SD) for 6 months from the start of study treatment Efficacy (Secondary): Time-to-event variables: progression-free survival (PFS), objective response rate (ORR), duration of response, duration of clinical benefit, overall survival (OS) Safety AEs and SAEs (including CTCAE toxicity grading)
	Pharmacokinetics: Evaluation of the pharmacokinetics of Lonaprisan Other: Effect of Lonaprisan on quality of life Exploratory analysis of biomarkers
Statistical Methods:	Efficacy (Primary): The primary objective of this study was not an inferential comparison between the two groups, but hypothesis testing within each group (without an adjustment of the test level). The study was designed to demonstrate a positive effect of ZK PRA (within each group) compared with a threshold clinical benefit rate of 15% (p0=0.15). Within each treatment group, the primary efficacy variable was to be analyzed in a single-stage design. The study outcome was to be considered as successful if 9/36 assessable subjects in one treatment group (25 mg / 100 mg) showed clinical benefit. The null hypothesis was to be tested with an exact binomial test at a one-sided test level of α=10%. The main analysis of efficacy was to be performed after all subjects had been treated for 6 months or had dropped out before Month 6, whichever came earlier. Apart from p-values or confidence intervals, data was to be displayed by appropriate descriptive statistics (e.g. frequency tables, percentiles, means, standard deviations, and box-plots). Efficacy (Secondary): Descriptive statistics; Kaplan-Meier estimates if applicable Safety: Descriptive statistics Pharmacokinetics: Descriptive statistics Other: Quality of life: descriptive statistics

Number of Subjects:	Planned: 72 subjects (36 in each group) were needed for evaluation. Additional subjects were to be randomized as necessary to account for drop-outs. Analyzed: The efficacy analysis was based on the full analysis set (FAS) which consisted of 34 subjects in the 25 mg group and 34 subjects in the 100 mg group.

Study Results

Results Summary — Subject Disposition and Baseline

A total of 83 subjects were screened for inclusion in the study, leading to a total of 69 who were randomized (34 subjects to the 25 mg group and 35 to the 100 mg group). All but 1 subject in the 100 mg group took at least 1 dose of study medication. Eleven of 69 subjects (15.9%), thereof 6 (17.6%) in the 25 mg group and 5 (14.3%) in the 100 mg group, discontinued the study prematurely. AEs were the most frequent primary reason for premature discontinuation (6 subjects); 3 subjects were discontinued due to protocol deviations and 2 subjects died. In all but 1 subject the reasons for end of study and end of study medication were identical. In subject no. 101079 death was given as reason for end of study and AE as reason for end of study medication. One subject in each group was still being treated when the database was locked.

The 68 randomized and treated subjects were included in the full analysis set (FAS) and in the safety analysis set (SAF). Eight subjects with major protocol deviations were excluded from the per protocol set (PPS) which thus consisted of 60 subjects.

The mean age in the FAS was 65.1 ± 10.2 years (median: 66.0 years; range: 42 – 94 years) and except 1 Hispanic subject all subjects were of Caucasian origin. As required per protocol all subjects entered the study with UICC Stage IV breast cancer. Twenty-five subjects (36.8%) had initially been diagnosed with invasive ductal carcinoma and 9 subjects (13.2%) with invasive lobular carcinoma. Previous treatment included adjuvant/neoadjuvant hormone therapy (35 subjects; 51.5%), adjuvant/neoadjuvant chemotherapy (28 subjects; 41.2%), chemotherapy for advanced disease (4 subjects; 5.9%), chemotherapy as first-line therapy for metastases (14 subjects; 20.6%) and radiotherapy (44 subjects; 65.7%; N=67). The proportion of subjects with abnormal physical examination findings or ongoing symptoms or diseases at baseline was greater in the 100 mg group (33 subjects; 97.1%) than in the 25 mg group (27 subjects; 79.4%). Besides this imbalance the two treatment groups were comparable with respect to demographic and baseline characteristics.

Results Summary — Efficacy

Due to the low number of responders (8/58 subjects with SD for 6 months; based on evaluable subjects in the FAS), the primary efficacy variable 'clinical benefit' was not analyzed. Six subjects in the 25 mg group and 2 subjects in the 100 mg group showed SD at Month 6; 3 subjects in the 25 mg group and 1 subject in the 100 mg group showed SD at Month 12. One subject in the 25 mg group presented with disease stabilization for 19.5 months and discontinued treatment due to AE/SAE. No subjects achieved confirmed CR or PR. The best overall response in the 58 subjects with available data was SD in 18 subjects (31.0%) [9 subjects in each group] and PD in 40 subjects (69.0%) [20 subjects in each group].

The analysis of the time-to-event variables PFS, ORR, duration of response, duration of clinical benefit and OS were omitted due to lack of responders.

Results Summary — Safety

In total, 12 deaths were reported (4 in the 25 mg group and 8 in the 100 mg group). Progression of study disease was given as cause of death in the majority of cases (4/4 in the 25 mg group and 5/8 in the 100 mg group). One subject died of cardiorespiratory distress and one of hepatic failure due to disease progression; in one case the cause of death was documented as "other" and further specified with "reduced general condition; nausea, upper abdominal pain". No deaths were reported to be related to ZK 230211.

A total of 21 subjects (30.9%), 9 (26.5%) in the 25 mg group and 12 (35.3%) in the 100 mg group experienced at least one SAE. The highest incidence of SAEs by system organ class was seen for gastrointestinal disorders (5 subjects; 7.4%). SAEs (preferred term) reported in more than 1 subject were endometrial hypertrophy (3 subjects), and myocardial infarction, ascites, subileus and dyspnea (2 subjects each). One patient developed endometrial hyperplasia.

Four subjects (1 in the 25 mg group and 3 in the 100 mg group) experienced SAEs that were considered by the investigators to be at least possibly related to ZK 230211. In the 25 mg group this was 1 case of endometrial hypertrophy; in the 100 mg group these were anemia and subileus in 1 subject, myocardial infarction and chest pain in 1 subject and 1 case of endometrial hypertrophy. All other SAEs were considered not related or unlikely to be related to ZK 230211.

The study drug was discontinued due to AEs in 3 subjects in the 25 mg group ('increase of alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) level', 'increase of endometrial thickness' and 'elevated liver enzymes') and in 3 subjects in the 100 mg group ('non-ST elevated myocardial infarction', 'fatigue, chills' and 'liver failure').

Twenty-nine subjects (85.3%) in the 25 mg group and 32 subjects (94.1%) in the 100 mg group experienced at least 1 AE. The proportion of subjects with more than 6 AEs was considerably higher in the 100 mg group (55.9%) than in the 25 mg group (29.4%). The highest incidences (≥ 10%) of AEs were observed for fatigue (25.0%), hot flush (19.1%), dyspnea (17.6%), nausea (17.6%), asthenia (16.2%), headache (11.8%), constipation (10.3%), vomiting (10.3%) and decreased appetite (10.3%) (Table 14.3.2/3). In 18 subjects (52.9%) in the 25 mg group and 24 subjects (70.6%) in the 100 mg group at least 1 AE was considered to be drug-related. Drug-related AEs most frequently referred to general disorders and administration site conditions (25.0%). Eight subjects (23.5%) in the 25 mg group and 12 subjects (35.3%) in the 100 mg group experienced AEs of CTCAE grade 3 or higher. CTCAE grade 3 events occurring in more than 1 subject were fatigue (3 subjects), ascites (2 subjects) and dyspnea (2 subjects). Three subjects suffered CTCAE grade 4 events (2 cases of myocardial infarction and 1 case of esophageal obstruction) and 4 subjects CTCAE grade 5 events (1 case each of cardiac arrest, cardiorespiratory distress, multi-organ failure and hepatic failure). Apart from 1 case of myocardial infarction, none of the CTCAE Grade 4/5 events were considered to be drug-related.

Results Summary — Pharmacokinetics

A pharmacokinetic evaluation was performed at 1 month and at 2 months of treatment. At the 1-month visit, blood samples for PK analysis were collected up to 8 hours post-dose, whereas at the 2-month visit only a pre-dose and 3-hour post-dose sample were collected. Samples were assayed for parent compound (BAY 86-5044/ZK 230211) and metabolites (BAY 86-1708, BAY 1029427, and BAY 1029434). Summary statistics of the plasma concentration data were presented for each of the analytes.

Individual patient data and summary statistics were presented for PK data. The data showed dose-related increases in exposure for drug and metabolites, when increasing the dose from 25 to 100 mg. At both doses, all metabolites had higher AUC(0-tn) and Cmax values compared to the parent compound (BAY 86-5044), with BAY 1029427 being the major metabolite. Geometric mean trough concentrations were calculated after 1 and 2 months of

treatment with the 100 mg dose, but insufficient data were available for the 25 mg dose. Week 8 trough levels tended to be slightly higher than the Week 4 values, suggesting that steady-state may not have been attained by Week 4. However, no notable accumulation was apparent from Week 4 to Week 8.

Results Summary — Other

Quality of life: The FACT-ES mean total score decreased slightly over the course of the study. The endocrine subscale score remained relatively unchanged. There were no relevant differences between the dose groups.

Exploratory biomarker analysis: Due to the low response rate seen in this study, it was decided not to pursue the biomarker analysis.

Conclusion(s)

Although disease stabilization was observed in some patients for a considerable period of time, the study did not meet its primary endpoint. No subject achieved complete or partial response. The most common AEs were fatigue, hot flush, dyspnea, nausea and asthenia. Adverse drug reactions were more frequent in the 100 mg dose group. In conclusion, this study indicated that ZK 230211 had limited activity as second-line endocrine therapy in metastatic breast cancer subjects.

Publication(s):	None
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