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Sponsor / Company: Sanofi **Drug substance(s):** SAR245408	**Study Identifiers:** NCT01082068 **Study code:** ARD11437
Title of the study: A Phase 1/2 Dose-Escalation Study of XL147 (SAR245408) or XL765 (SAR245409) in Combination with Letrozole in Subjects with Hormone Receptor-Positive and HER2-Negative Breast Cancer Refractory to a Nonsteroidal Aromatase Inhibitor	
Study center(s): 23 study centers in the USA, France, and Spain	
Study period: Date first patient enrolled: 22/Jun/2010 Date last patient completed: 15/Apr/2013	
Phase of development: Phase 1/2	
Objectives: • To determine the maximum tolerated dose (MTD) of the combination of SAR245408 with letrozole and the combination of SAR245409 with letrozole (Phase 1). • To evaluate the co-primary efficacy endpoints of objective response rate (ORR) (confirmed complete response [CR] or confirmed partial response [PR]) and progression free survival at 6 months (PFS6) in each arm (Phase 2). • To evaluate the safety and tolerability of the combination of SAR245408 with letrozole and the combination of SAR245409 with letrozole (Phase 1 and Phase 2).	
Methodology: Open-label, 2-arm, dose-escalation study in patients with hormone receptor-positive (ER+ and/or PGR+), HER2- breast cancer whose disease was refractory to a nonsteroidal aromatase inhibitor. Patients were alternately assigned to Arm 1 and Arm 2. Patients in Arm 1 received SAR245408 in combination with letrozole, and patients in Arm 2 received SAR245409 in combination with letrozole. There was no formal comparison between treatment arms. There was both a Phase 1 and a Phase 2 component. The enrollment of the Phase 2 component was not completed, as the sponsor made a decision to terminate the development of SAR245408 or SAR245409 as an investigational medicinal product in combination with letrozole for the treatment of HR+ advanced or metastatic breast cancer, after the results of the interim analysis of part one of each Phase 2 arm. As such, complete analysis of the secondary and exploratory objectives, including analysis of the pharmacodynamic and pharmacokinetic data, was not performed.	
Number of patients**:**	Planned: Up to 24 in Phase 1, up to 96 in Phase 2 Treated: 21 in Phase 1, 51 in Phase 2 Drug limiting toxicity (DLT) Evaluable (Phase 1):21 Efficacy Evaluable (Phase 2): 50 Safety: 21 in Phase 1, 51 in Phase 2
Diagnosis and criteria for inclusion: Patients with hormone receptor-positive (ER+ and/or PGR+), HER2- breast cancer whose disease was refractory to a nonsteroidal aromatase inhibitor.	

Study treatments

Investigational medicinal product(s): SAR245408; SAR245409

SAR245408 formulation: 100, 150, 200 mg tablets

SAR245409 formulation: 10, 30, 40, 50 mg capsules

Route(s) of administration: Oral

SAR245408 dose regimen: Starting dose of 200 mg daily in Phase 1; 400 mg daily in Phase 2

SAR245409 dose regimen: Starting dose of 30 mg twice daily in Phase 1; 50 mg twice daily in Phase 2

Noninvestigational medicinal product(s): Letrozole

Formulation: 2.5 mg tablet

Route(s) of administration: Oral

Dose regimen: 2.5 mg daily, 30 minutes after dose of SAR245408 or SAR245409 (morning dose)

Duration of treatment: Patients without radiographic progressive disease per RECIST (Response Evaluation Criteria in Solid Tumors) Version 1.1 and unacceptable toxicity may have received study treatment for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and Sponsor.

Duration of observation: Patients were to return to the study site 30-37 days after the last dose of study treatment for an End-of-Treatment Visit. Patients who discontinued study treatment before documentation of radiographic progressive disease were to continue to undergo tumor assessments until disease progression the initiation of subsequent anticancer therapy, or death.

Criteria for evaluation: Safety was assessed by evaluation of adverse events (AEs), vital signs, electrocardiogram (ECG), laboratory tests, and concomitant medications. Adverse event seriousness, severity grade, and relationship to study treatment were to be assessed by the Investigator. Severity grade was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0.

Tumor response was assessed in Phase 1 and Phase 2 using RECIST Version 1.1. Patients were to be assessed using an magnetic resonance imaging (MRI) or computed tomography (CT) scan at screening, 8 weeks after the first dose of study treatment (Week 9 Day 1), and every 8 weeks thereafter until documented radiographic progression, the initiation of other anticancer therapy, or death. Responses were to be confirmed by repeat assessments at least 4 weeks after the response criteria were met.

Pharmacokinetics (PK): SAR245408, SAR245409, and letrozole

Sampling: Plasma samples for the PK analysis of SAR245408, SAR245409, and letrozole were collected at pre-dose, and 2, 4, 8 10-12 hour post-dose on Week 1 Day1 and Week 5 Day 1; pre-dose and 4 hour post-dose on Week 9 Day 1; pre-dose on Week 1 Day 2, Week 3 Day 1, Week 5 Day 2, and Week 13 Day 1. After Week 13, pre-dose plasma samples for SAR245408 and SAR245409 were collected every 16 weeks.

Bioanalytical methods: Plasma concentrations of SAR245408 and SAR245409 were determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.00 ng/mL.

Plasma concentrations of letrozole were determined using a validated LC-MS/MS method with an LLOQ of 1.00 ng/mL and then a LLOQ of 0.500 ng/mL following a change in sponsor.

Pharmacogenomics: Blood samples were collected and genotyped. The analyses of pharmacogenomic data used to explore the association between the main enzyme systems for SAR245408 and SAR245409 metabolism and safety and other potential associations between genes variations and clinical outcomes will be presented in a separate report.

Statistical methods: Each arm is evaluated independently; no formal comparisons between arms were planned.

In Phase 1, no formal statistical tests were planned. Confidence intervals (CIs) may have been calculated for selected safety and exploratory variables.

For Phase 2, the co-primary efficacy endpoints for each arm are: 1) ORR, defined as the proportion of patients for whom the best response is a confirmed CR or confirmed PR, and 2) PFS6, defined as the proportion of patients who survive and are progression free at least 24 weeks after the date of the first dose of study drug. Determination of response and progression was based on evaluation per RECIST Version 1.1.

The study was designed to test the following hypotheses for each arm:

- H0: ORR is ≤ 5% and proportion with PFS6 is ≤10%.
- HA: ORR is ≥ 20% or proportion with PFS6 is ≥30%.

The sample size estimate of 48 patients evaluable per protocol in each arm was based on a two-stage design with a nominal alpha of 0.07 and power of 90%.

Summary:

Study patients:

In the SAR245408 arm, 12 patients were enrolled in Phase 1 (6 patients at 200 mg QD, and 6 patients at 400 mg QD) and 25 patients were enrolled in part one of Phase 2 (at 400 mg QD). In the SAR245409 arm, 9 patients were enrolled in Phase 1 (3 patients at 30 mg BID, and 6 patients at 50 mg BID) and 26 patients were enrolled in part one of Phase 2 (at 50 mg BID). The study population were women with a mean age of 56.4 years in the Phase 1 component (range: 37-68) and 63.5 years in the Phase 2 component (range: 33-87). All patients had breast cancer that was estrogen receptor positive (ER+), and most patients had ER+/progesterone receptor positive (PGR+) status (81.0% of patients in the Phase 1 component, and 72.5% of patients in the Phase 2 component). Infiltrating ductal carcinoma was the most commonly reported histology.

In the SAR245408 arm, study treatment lasted for a mean of 25.2 weeks at the 200 mg QD dose (median of 17.5 weeks; range 6.7-70.0) and 19.4 weeks at the 400 mg QD dose (median of 13.1 weeks; range: 0.3-70.0). In the SAR245409 arm, the mean duration exposure at the 30 mg BID dose was 21.3 weeks (median of 12.1 weeks; range: 7.0-44.9), and 10.7 weeks (median of 8.0 weeks; range: 0.3-71.9) at the 50 mg BID dose. The most common reason for discontinuation of study treatment in both arms was disease progression.

Efficacy results: The primary efficacy analysis was based on Phase 2 patients only. In the SAR245408 arm, one patient had a PR, with a maximum reduction in tumor burden of 34.2% in the single target lesion being followed, a lymph node supraclavicular mass. This resulted in an ORR of 4.2% (90% CI of 0.2%-18.3%), and the PFS6 (patients with disease progression or death after 24 weeks, or censored at week 24 with standard disease) in this arm was 16.7% (4 of 24 patients; 90% CI of 5.9%-34.2%), reaching the efficacy endpoint to move to the part two of the Phase 2 component of this arm. The efficacy endpoint of the first part of Phase 2 of the SAR245409 arm was not reached as no patients in the SAR245409 arm had a response (CR or PR). In this arm, the PFS6 was 7.7% (2 of 26 patients; 90% CI of 1.4%-22.3%).

Safety results (SAR245408 arm):

There was 1 DLT (serious Grade 3 drug reaction with eosinophilia and systemic symptoms) reported in the 6 patients enrolled at the highest dose level studied in the Phase 1 component, 400 mg QD.

One patient in this arm died due to a serious adverse event (SAE) considered possibly related to study drug (pneumonitis), and 1 patient died due to disease progression a little more than 1 month after discontinuing study treatment due to the progressive disease.

Ten patients experienced SAEs (27.0%), with 6 of 10 patients having an SAE considered at least possibly related to study drug. At least one AE leading to discontinuation of study drug was experienced by 7 patients (18.9%), 6 of whom were treated at the 400 mg QD dose level.

The most common treatment emergent adverse events (TEAEs) were rash (in 43.2% of patients), diarrhea (37.8%), nausea (32.4%), vomiting (24.3%), and dizziness (21.6%). The majority of rash AEs, and approximately half of the diarrhea AEs, were assessed as related to study drug.

There were 4 patients (10.8%) who reported an alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin of ≥Grade 2. Lymphocytes decreased of Grade 3 were observed in 2 patients (5.4%), and gamma glutamyl transpeptidase (GGT) increased of Grade 3 was reported in 7 patients (18.9%). Most other observed hematology and chemistry abnormalities were of Grade 1 or 2.

Safety results (SAR245409 arm):

There was 1 DLT (Grade 3 skin rash that prevented the patient from taking at least 75% of the required doses in the first 28 days of study treatment) reported in the 6 patients enrolled at the highest dose level studied in the Phase 1 component, 50 mg twice a day (BID).

No deaths occurred within 30 days of study treatment, or in the post-treatment period.

Ten patients experienced SAEs (28.6%), with 6 of 10 patients having an SAE considered at least possibly related to study drug. There were 9 patients that had at least one AE leading to discontinuation of study drug (25.7%), all of whom were treated at the 50 mg BID dose level.

The most common TEAEs were nausea (60.0%), diarrhea (42.9%), vomiting (34.3%), fatigue (31.4%), cough (25.7%), dyspepsia (25.7%), and rash (25.7%). The majority of rash, diarrhea, fatigue, and dyspepsia AEs, and approximately half of the nausea AEs, were assessed as related to study drug.

There were 12 patients (34.3%) who reported an ALT, AST, alkaline phosphatase, or total bilirubin of ≥Grade 2. Lymphocytes decreased of Grade 3 were observed in 4 patients (11.4%), and GGT increased was reported at Grade 3 for 6 patients (17.1%) and at Grade 4 for 1 patient (2.9%). Most other observed hematology and chemistry abnormalities were of Grade 1 or 2.

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