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Sponsor / Company: Sanofi **Drug substance(s):** SAR245409	**Study Identifiers:** NCT01240460 **Study code:** TED11605
Title of the study: An Exploratory Pharmacodynamic Study of SAR245409 (XL765) and SAR245408 (XL147) Administered as Single Agents to Subjects with Recurrent Glioblastoma Who are Candidates for Surgical Resection	
Study center(s): Four study centers in the United States (US)	
Study period: Date first patient enrolled: 20/Jan/2011 Date last patient completed: 20/Jun/2012	
Phase of development: Exploratory	

As of 28 February 2011, the sponsorship of the study transferred from Exelixis to Sanofi; therefore, all references to the investigational drug codes XL765 and XL147 (Exelixis) are fully applicable to SAR245409 and SAR245408 (Sanofi), respectively. As these designations refer to the same product, they are referred to as SAR245409 and SAR245408 for the purpose of this report.

Objectives:

Primary objective:

- To explore the biological effect of SAR245409 and SAR245408 measured by modulation of phosphatidyl-inositol-3-kinase (PI3K)/ mammalian target of rapamycin (mTOR) pathway readouts in glioblastoma multiforme (GBM) tumor tissue.

Secondary objectives:

- To examine the safety profile of daily oral administration of SAR245409 and SAR245408 in patients with recurrent GB;
- To determine the levels of SAR245409 and SAR245408 in plasma and GB tumor tissue;
- To assess the antiproliferative and pro-apoptotic effects of SAR245409 and SAR245408 on tumor cells;
- To measure changes in tumor after surgery in patients receiving SAR245409 and SAR245408 using a modified response criteria based on the recommendations from the Response Assessment for Neuro-Oncology (RANO) working group;
- To conduct analyses of gene expression, mutations, and copy number alterations, on tumor tissue removed during the on-study resection and compare, where feasible, with tissue removed during the initial surgical resection;
- To evaluate the pharmacodynamic effects of SAR245409 and SAR245408 in blood and/or blood cells for identification and characterization of surrogate biomarkers associated with the biological effects of SAR245409 and SAR245408;
- To explore the relationship between clinical response and genomic and proteomic biomarkers in the PI3K and epidermal growth factor receptor (EGFR) pathways.

Methodology: This was a multicenter exploratory study of SAR245409 and SAR245408 administered as single agents to patients with recurrent GB who were candidates for surgical resection.

Six to 10 patients were to be enrolled into each of 3 cohorts to receive either once-daily (qd) SAR245409, twice-daily (q12h) SAR245409, or qd SAR245408 for a minimum of 10 consecutive days (and for a maximum of 28 days, unless agreed upon by the sponsor) prior to surgery. Patients could resume treatment after recovering from surgery. The SAR245409 and SAR245408 starting dose levels were based on the on-going Phase 1 studies. The SAR245409 doses were the defined single-agent maximum tolerated doses (MTDs). The exposure at the 200 mg tablet dose for SAR245408 was in the range of that observed for the 400 or 600 mg capsule, the established MTD for the capsule formulation. If the surgical procedure was planned to occur outside the study site, sponsor approval was necessary prior to enrolling the patient.

Procedures to assess the safety, pharmacokinetics (PK), and exploratory effects (including pharmacodynamic correlates of clinical activity and radiographic tumor response) of SAR245409 and SAR245408 were performed at specified time points.

Number of patients**:**	Planned: Approximately 18 and up to approximately 40 patients were to be enrolled to ensure at least 6 evaluable patients in each of the treatment groups.
	Randomized: 21 patients (8, 6, and 7 in Cohorts 1, 2, and 3, respectively)
	Treated: 21 patients
Evaluated:	
	Pharmacodynamic: 19 patients (6, 6, and 7 in Cohorts 1, 2, and 3, respectively)
	Safety: 21 patients
	Pharmacokinetics: 21

Diagnosis and criteria for inclusion: Patient had histologically confirmed diagnosis of primary GB for which the patient had received prior treatment, including radiation and/or chemotherapy, and would be undergoing a subsequent resection. Note: Patients scheduled to have a fine-needle biopsy or procedure that was not anticipated to yield a minimum of 200 mg of GB tissue were not eligible.

Study treatments

Investigational medicinal product(s): SAR245409

Formulation: 10-mg, 30-mg, and 50-mg capsules, which were distinguishable by color

Route(s) of administration: Oral

Dose regimen: 90 mg once daily and 50 mg every 12 hours (twice daily)

Investigational medicinal product(s): SAR245408

Formulation: 100-mg, 150-mg, and 200-mg tablets, which were distinguishable by shape and/or size

Route(s) of administration: Oral

Dose regimen: 200 mg once daily

Duration of treatment: Patients received cohort-assigned study treatment for a minimum of 10 consecutive days (a maximum of 28 days, unless agreed upon by the sponsor) prior to surgery. Patients could resume their pre-surgical study treatment (including dose and schedule) once recovered from the effects of surgery (approximately 14 days after surgery) and upon sponsor approval until progressive disease (PD) or unacceptable toxicity.

Post treatment period: The patient returned to the study site 30 to 37 days after the last dose of study treatment for an end-of-treatment assessment. Additional follow-up occurred for AEs related to study treatment that led to treatment discontinuation and were not resolved by this visit and/or serious adverse events (SAEs) that occurred >30 days after the last dose of study treatment.

Criteria for evaluation:

Efficacy assessment: Tumor imaging at specified times using standard magnetic resonance imaging (MRI) protocols and assessed using modified RANO criteria.

Tumor assessments and vascular metabolic profiles: Tumor imaging was performed for all patients at specified times using standard MRI protocols and assessed using a modified response criteria based on the recommendations from the RANO working group. Tumor assessments were to continue until permanent study treatment discontinuation. A daily record of systemically administered glucocorticoids was to be collected from Week 1 Day 1 of the Pre-Surgery Treatment Period (T-W1D1) until study treatment was permanently discontinued.

In addition, the vascular and metabolic properties of the tumor were assessed with diffusion, perfusion, and spectroscopic imaging for all patients at screening and approximately 24 hours before the scheduled surgical resection.

Safety: Safety was assessed by the evaluation of adverse events (AEs), serious adverse events (SAEs), vital signs, electrocardiogram (ECG), clinical laboratory tests, and concomitant medications. Adverse event seriousness, severity grade, and relationship to study treatment were assessed by the investigator. Severity grade was defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

Pharmacodynamics: Archival tumor tissue of sufficient quantity and quality was collected to perform the pharmacodynamics analysis. Phospho-S6RP should be detected in the archival tumor tissue sample. Sufficient tissue was collected during the on-study surgical resection to perform the pharmacodynamic analyses.

Pharmacokinetics: Blood samples for measurement of SAR245409 and SAR245408 in plasma were taken at specified times.

On-study surgical resection samples: A portion of tumor tissue, if available, was used to assess the concentration of the study drugs in tumor tissue.

In order to correlate SAR245409 and SAR245408 exposure with clinical toxicity in patients, an additional PK blood sample was to be collected, if possible, at the time any clinically significant toxicity was identified by the site.

Pharmacodynamic biomarkers:

Blood sampling:

Blood samples were to be collected from all patients at specified time points for exploratory biomarker analysis, genotyping/single nucleotide polymorphism (SNP) analysis, and pharmacodynamic analyses.

Tumor tissue:

Archival samples: Patients were required to have a formalin-fixed paraffin-embedded tumor tissue block identified and designated for central laboratory analysis before enrollment for immunohistochemical (IHC) assessment of biomarkers of PI3K/mTOR activity, proliferation, and apoptosis. In addition, provided a sufficient amount of tumor tissue was available, frozen tumor samples from archived tissue collected before enrollment may have also been analyzed for 1 or more of the following: mutational and/or epigenetic status, gene expression profile, gene copy number, and additional IHC markers.

On-treatment biopsy samples: Tissue removed during the surgery was utilized for biomarkers of PI3K/mTOR activity, proliferation, and molecular correlative analyses. This tissue included representative samples of tumor tissue and any surrounding normal brain tissue that was sampled per the surgeon's discretion. The goal was to collect a minimum of 200 mg of tissue. Tissue samples were analyzed for biomarkers of cell-signaling pathway activity (eg, PI3K, mTOR, EGFR, and/or RAS pathway activation status), tumor proliferation, mutational and/or epigenetic status, additional IHC analysis, and gene expression and copy number (provided a sufficient amount of tumor tissue was available).

Statistical methods: The study evaluated 3 potential treatment regimens: SAR245408 once daily, SAR245409 once daily, or SAR245409 twice daily. For each regimen, the primary assessment of pharmacodynamic effect was based on exploratory comparison of the level of phosphorylated S6 ribosomal protein (pS6RP), determined by immunohistochemistry (IHC) staining, between tumor tissue collected after a minimum of 10 days of treatment on this study (S2) and the archival tumor tissue sample at diagnosis (S1), using descriptive statistics and pairwise *t* test. Similar summary statistics were performed to additional pharmacodynamic markers of interest.

Six patients were to be enrolled into each treatment regimen. Assuming the true rate of achieving a reduction of at least 75% in pS6RP after treatment with SAR245408 or SAR245409 was 75%, there was an 83% chance that at least 4 of 6 patients would be observed to meet this goal. If the true success rate were 40%, then there would be only an 18% chance that at least 4 of 6 patients would be observed to meet this goal.

Adverse events and SAEs were summarized by System Organ Class and Preferred Terms. Adverse events were summarized for CTCAE grade and causal relationship to study drug. Results from standard laboratory tests were summarized by change from baseline in CTCAE grade or other measures.

Summary:

Population characteristics: A total of 21 patients were enrolled and treated in the study. The mean patient age was 55.1 years with a range of 37 to 74 years. Fourteen patients (66.7%) were male and 7 patients (33.3%) were female. Twenty patients (95.2%) were white and 1 patient (4.8%) did not report race. The majority of patients (13 patients, 61.9%) had a baseline Karnofsky performance status (KPS) of ≥90. The remaining 8 patients (38.1%) had a baseline KPS between 60 and 80.

All patients had a relapse of GB. The brain site at relapse for which surgery in this study was indicated included:

- Temporal lobe in 7 patients (33.3%);
- Frontal lobe in 7 patients (33.3%);
- Parietal lobe in 5 patients (23.8%);
- Frontoparietal region in 1 patient (4.8%);
- Frontotemporal region in 1 patient (4.8%).

For the 21 patients with relapse, the median time from initial diagnosis to relapse for which surgery in this study was indicated was 13.93 months (range: 4.9 to 98.6 months). The median time from relapse for which surgery in the current study was indicated until first dose of study drug was 0.56 months (range: 0.3 to 3.0 months). Within treatment cohorts, the median time from relapse for which surgery in the current study was indicated until first dose of study drug was:

- 0.97 months (range: 0.3 to 2.2 months) for the SAR245409 twice daily cohort;
- 0.61 months (range: 0.3 to 0.9 months) for the SAR245408 once daily cohort;
- 0.49 months (range: 0.3 to 3.0 months) for the SAR245409 once daily cohort.

Pharmacodynamic results: A total of 19 patients (out of 21 enrolled) were determined to be evaluable for the pharmacodynamic population based on the criteria set in the protocol.

Two sets of pharmacodynamic assessments were performed to determine the impact on PI3K/mTOR pathway activities.

First set of pharmacodynamics analyses involved semi-quantitative measurement of the change in phosphorylation of PI3K/mTOR pathway readouts by immunohistochemistry (IHC) using intrasubject, matched pre-treatment (archival tissue at diagnosis, S1) and post-treatment (on-study surgery, S2) tumor tissues. Pharmacodynamic analyses by IHC revealed reductions in PI3K/mTOR signaling, assessed by p-S6RP$^{Ser235/236}$, p-S6K1^{Thr389}, p-4EBP1$^{Thr37/46}$, and p-PRAS40^{Thr246}, in greater than 50% of patients in each of the three treatment cohorts. For example, the median percentage change in p-S6RP$^{Ser235/236}$ post- vs. pre-treatment was

- -40.65% (range: -66.7% to 64.1%; n=6) for the SAR245409 twice daily cohort
- -21.41% (range: -57.3% to 38.1%; n=6) for the SAR245408 once daily cohort
- -14.90% (range: -61.1% to 41.5%; n=7) for the SAR245409 once daily cohort

Second set of pharmacodynamic analyses involved quantitative measurement of levels of p-Akt^{Ser473}, tAkt, and p-S6RP$^{Ser240/244}$ by electrochemiluminescence (Meso Scale immunoassay) in frozen tissue from the surgical resections and comparison with that in a control group of approximately 50 SAR245409/SAR245408-naïve but otherwise similar recurrent GB tissue samples. Median levels of p-Akt^{Ser473} normalized against tAkt in artificial unit was:

- 5.26 (range: 3.0 to 59.1; n=5) for the SAR245409 twice daily cohort;
- 6.77 (range: 2.8 to 28.1; n=4) for the SAR245408 once daily cohort;

- 2.08 (range: 0.5 to 10.1; n=5) for the SAR245409 once daily cohort;
- 5.28 (range: 0.8 to 144.6; n=48) for the SAR245409/SAR245408-naïve control GB cohort.

Safety results: A total of 15 patients were treated with SAR245409 (8 patients in the 50 mg twice daily regimen and 7 patients in the 90 mg once daily regimen) and 6 patients were treated with 200 mg SAR245408 once daily. All 21 patients experienced 1 or more treatment-emergent adverse event (TEAE), with Grade 3 or 4 TEAEs reported for 7 patients (87.5%) in the SAR245409 twice daily cohort, 2 patients (33.3%) in the SAR245408 once daily cohort, and 4 patients (57.1%) in the SAR245409 once daily cohort.

Treatment-emergent SAEs were reported for 5 patients (62.5%) in the SAR245409 twice daily cohort, 1 patient (16.7%) in the SAR245408 once daily cohort, and 1 patient (14.3%) in the SAR245409 once daily cohort, with study drug-related treatment-emergent SAEs reported for 1 patient (12.5%) in the SAR245409 twice daily cohort, 0 patients in the SAR245408 once daily cohort, and 1 patient (14.3%) in the SAR245409 once daily cohort.

Two deaths in the SAR245409 twice daily cohort (25.0%) were attributed to a TEAE (respiratory failure, not related to study drug; subdural hematoma, not related to study drug). There were no deaths attributed to TEAEs in the other 2 treatment cohorts.

Treatment-emergent AEs led to permanent discontinuation of study drug for 3 patients (37.5%) in the SAR245409 twice daily cohort, 0 patients in the SAR245408 once daily cohort, and 2 patients (28.6%) in the SAR245409 once daily cohort and dose reduction or interruption for 6 patients (75.0%) in the SAR245409 twice daily cohort, 0 patients in the SAR245408 once daily cohort, and 2 patients (28.6%) in the SAR245409 once daily cohort.

The TEAEs at the PT level reported by the most patients (≥33.3% overall) were:

- Fatigue, reported for 7 patients (87.5%) in the SAR245409 twice daily cohort, 2 patients (33.3%) in the SAR245408 once daily cohort, and 6 patients (85.7%) in the SAR245409 once daily cohort;
- Headache, reported for 2 patients (25.0%) in the SAR245409 twice daily cohort, 3 patients (50.0%) in the SAR245408 once daily cohort, and 3 patients (42.9%) in the SAR245409 once daily cohort;
- Hypophosphatemia, reported for 4 patients (50.0%) in the SAR245409 twice daily cohort, 1 patient (16.7%) in the SAR245408 once daily cohort, and 3 patients (42.9%) in the SAR245409 once daily cohort;
- Nausea, reported for 4 patients (50.0%) in the SAR245409 twice daily cohort, 1 patient (16.7%) in the SAR245408 once daily cohort, and 3 patients (42.9%) in the SAR245409 once daily cohort;
- Constipation, reported for 4 patients (50.0%) in the SAR245409 twice daily cohort, 2 patients (33.3%) in the SAR245408 once daily cohort, and 1 patient (14.3%) in the SAR245409 once daily cohort;
- Convulsion, reported for 2 patients (25.0%) in the SAR245409 twice daily cohort, 3 patients (50.0%) in the SAR245408 once daily cohort, and 2 patients (28.6%) in the SAR245409 once daily cohort;
- Hemiparesis, reported for 3 patients (37.5%) in the SAR245409 twice daily cohort, 2 patients (33.3%) in the SAR245408 once daily cohort, and 2 patients (28.6%) in the SAR245409 once daily cohort.

There was some evidence for liver toxicity associated with SAR245409, with study drug-related TEAEs of:

- ALT increased, reported for 4 patients (50.0%, 2 patients with Grade 3 or 4) in the SAR245409 twice daily and 2 patients (28.6%, 1 with Grade 3 or Grade 4) in the SAR245409 once daily cohort;
- AST increased, reported for 1 patient (12.5%) in the SAR245409 twice daily cohort and 1 patient (14.3%) in the SAR245409 once daily cohort;

- Blood bilirubin increased, reported for 1 patient (12.5%) in the SAR245409 twice daily cohort;
- Gamma-glutamyltransferase increased, reported for 1 patient (14.3%) in the SAR245409 once daily cohort;
- ALT increased, leading to:
  - dose delays for 2 patients (25.0%) in the SAR245409 twice daily cohort and 1 patient (14.3%) in the SAR245409 once daily cohort;
  - dose reductions for 3 patients (37.5%) in the SAR245409 twice daily cohort;
  - discontinuation from study drug for 1 patient (12.5%) in the SAR245409 twice daily cohort and 1 patient (14.3%) in the SAR245409 once daily cohort.

However, no patients met the criteria for drug-induced liver injury (Hy's law: ALT >3 x ULN or AST >3 x ULN and total bilirubin >2 x ULN).

No TEAEs of ALT increased, AST increased, blood bilirubin increased, or gamma-glutamyltransferase increased were reported for the SAR245408 once daily cohort.

There was no evidence of cardiovascular toxicity with either study drug.

Pharmacokinetic results: From the tumor tissue concentration data, SAR245409 and SAR245408 distributed into the CNS, which resulted in a mean tumor to plasma ratio of 0.27 and 0.40 in cohorts 1 and 3 and 0.27 in cohort 2.

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