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*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

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| **Sponsor / Company:** Sanofi<br>**Drug substance(s):** SAR245409 | **Study Identifiers:** NCT01410513, UTN U1111-1119-2906<br>**Study code:** TCD12012 |
| **Title of the study:** A Phase 1b, multicenter, open-label, dose-escalation study of SAR245409 to evaluate the safety, tolerability, and clinical activity of SAR245409 in combination with rituximab or bendamustine plus rituximab in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma, mantle cell lymphoma, or chronic lymphocytic leukemia | |
| **Study center(s):** 3 study centers | |
| **Study period:**<br>Date first patient enrolled: 07/Dec/2011<br>Date last patient completed: 28/May/2014 | |
| **Phase of development:** Phase 1b | |

**Objectives:**

Primary objective:

To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose for SAR245409 when administered in combination with bendamustine and/or rituximab.

Secondary objectives:

- To determine the safety and tolerability of SAR245409 in combination with bendamustine and/or rituximab in patients with indolent non-Hodgkin lymphoma (iNHL), mantle cell lymphoma (MCL), or chronic lymphocytic leukemia (CLL);
- To determine the pharmacokinetics (PK) of SAR245409, bendamustine, and rituximab when used in combination in patients with iNHL, MCL, or CLL;
- To determine the pharmacodynamic (PD) effects of SAR245409 in combination with bendamustine and/or rituximab in patients with iNHL, MCL, or CLL;
- To determine the antitumor activity of SAR245409 in combination with bendamustine and/or rituximab in patients with iNHL, MCL, or CLL.

Exploratory objective:

To explore correlations between preexisting molecular alterations directly or indirectly involved in PI3K/mTOR and other pathway(s) and response and/or resistance to SAR245409 in combination with bendamustine and/or rituximab in patients with iNHL, MCL, or CLL.

**Methodology:**

This was a phase 1b, 3-arm, dose-escalation, nonrandomized, open-label, multi-institutional study in patients with iNHL, MCL or CLL.

The study consisted of 2 phases: the dose escalation phase and the MTD expansion phase.

Dose escalation phase:

Arm A enrolled patients with relapsed/refractory iNHL, MCL, or CLL to receive a fixed dose of rituximab (375 mg/m$^2$) and increasing doses of SAR245409 (30 or 50 mg twice daily [BID]). Arm B1 enrolled patients with relapsed/refractory iNHL or MCL to receive fixed doses of bendamustine (90 mg/m$^2$) and rituximab (375 mg/m$^2$), and increasing doses of SAR245409 (30 or 50 mg BID). Arm B2 enrolled patients with relapsed/refractory CLL to receive fixed doses of bendamustine (70 mg/m$^2$) and rituximab (375 mg/m$^2$), and increasing doses of SAR245409 (30 or 50 mg BID).

Arms A, B1 and B2 enrolled simultaneously. Each arm and tumor-type cohort planned to enroll 3-6 patients at each dose level.

For each arm, the starting dose of SAR245409 was 30 mg BID with escalation to 50 mg BID (ie, MTD of SAR245409 administered as single agent). The dose escalation followed a 3+3 design. An intermediate SAR245409 dose level (ie, 40 mg BID) or a lower dose level (<30 mg bid) could have been tested based on dose-limiting toxicity (DLT) observation.

Maximum tolerated dose expansion phase:

In each arm and tumor-type cohort, a minimum of 6 additional patients were to be treated at the preliminary MTD to further evaluate the safety and tolerability of this dose in combination with rituximab or bendamustin plus rituximab. A maximum of 12 patients were to be treated at the MTD dose level per arm and per tumor type. In protocol amendment, it was decided to stop the enrollment of the MTD expansion cohort for Arm B2 (CLL, triplet combination).

The study was terminated early due to shifting of development priorities when Arm B1 expansion cohort had not started.

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| **Number of** patients**:** | Planned: Approximately 54 |
| | Treated: 37 |
| **Evaluated:** | |
| | Efficacy: 35 |
| | Safety: 37 |
| | Evaluable-for-DLT: 32 |
| | Pharmacokinetics: 37 |

**Diagnosis and criteria for inclusion:** Patients with histologically or cytologically and phenotypically confirmed diagnosis of iNHL, MCL or CLL who have relapsed or have been refractory to at least 1 standard therapy were enrolled in this study. Refractory disease was defined as unresponsive to a standard regimen or progressing within 6 months of completing a standard regimen.

**Study treatments**

**Investigational medicinal product(s):** SAR245409

Formulation: SAR245409 is provided in capsule formulation at strengths of 10-, 30-, 40-, and 50-mg capsules

Route(s) of administration: oral

Dose regimen: 30 or 50 mg BID (in the morning and evening), with a preferred interval of 12 (±1) hours between doses.

**Investigational medicinal product(s):** rituximab

Route(s) of administration: Intravenous (IV) infusion

Dose regimen:

Arm A: Patients received rituximab 375 mg/m$^2$ IV weekly (Days 1, 8, 15, and 22 of a 28-day cycle) for 2 cycles. Continuation of rituximab on a monthly or bi-monthly regimen after completing Cycle 2 may be permitted at the discretion of the Investigator after discussion with the Sponsor.

Arm B1: Patients with MCL/iNHL received rituximab 375 mg/m$^2$ IV on Day 1 of each 28-day cycle for up to 8 cycles. Discontinuation of rituximab after completing Cycle 2 may be permitted at the discretion of the Investigator after discussion with the Sponsor.

Arm B2: Patients with CLL received rituximab 375 mg/m$^2$ on Cycle 1 Day 1 (C1D1), then 500 mg/m2 on Day 1 of Cycles 2 through 6. Discontinuation of rituximab after completing Cycle 2 may be permitted at the discretion of the Investigator after discussion with the Sponsor.

**Investigational medicinal product(s):** bendamustine

Dose regimen:

Arm B1:Patients with MCL/iNHL received bendamustine 90 mg/m$^2$ IV on Days 1 and 2 of each 28-day cycle for up to 8 cycles. In October 2012, the study committee recommended to lower the dose of bendamustine in Arm B1 (90 mg/m$^2$ to 70 mg/m$^2$).

Arm B2: Patients with CLL received bendamustine 70 mg/m$^2$ IV on Days 1 and 2 of each 28-day cycle up to 6 cycles.

**Duration of treatment:** Combination therapy with SAR245409 and rituximab as doublet therapy, or with bendamustine and rituximab as triplet therapy, was administered over a 28-day cycle. Patients may continue treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

**Duration of observation:** Observation period included a period for screening of up to 28 days, the on-treatment phase and a safety follow-up phase of a minimum of 30 days after the last administration of study treatment.

**Criteria for evaluation:**

Safety: The safety was assessed by evaluation of AEs, vital signs, electrocardiogram, 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 (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Dose-limiting toxicities (DLTs) included:

Hematologic toxicity:

- Grade 4 neutropenia (ANC <0.5 x $10^9$/L) lasting >7 days;
- Febrile neutropenia defined as an ANC of <1.0 x $10^9$/L with a single temperature >38.3°C or a sustained temperature ≥38°C for more than 1 hour;
- Grade 4 thrombocytopenia (platelet count <25.0 x $10^9$/L [CTCAE]; decrease in platelet from baseline ≥75% or platelet count <20.0 x $10^9$/L for CLL patients [IWCLL]) lasting >7 days or of any duration associated with Grade >3 hemorrhage.

CLL patients with compromised bone marrow function having baseline count values for ANC and/or platelets ≥grade 3 were evaluable for DLT referable to ANC and/ or platelets.

Nonhematologic toxicity:

- Any Grade ≥3 nonhematologic toxicity except diarrhea, nausea, or vomiting.
  - Nausea/vomiting or diarrhea was considered a DLT in patients who had Grade ≥3 toxicity for >2 days despite receiving optimal prophylaxis and/or treatment.
  - Grade 4 diarrhea of any duration was considered a DLT.
- Any Grade 3 rash in patients receiving SAR245409 in combination with bendamustine failing to recover to Grade ≤1 toxicity by Day 28.
- Any toxicity resulting in a treatment delay of >2 weeks.
- A TEAE that in the opinion of the study committee was of potential clinical significance such that further dose escalation would expose patients to unacceptable risk.

Adverse events of special interest (AESI) included study treatment related DLTs, elevated alanine aminotransferase/aspartate aminotransferase ≥Grade 2, pregnancy, and symptomatic overdose with study treatment, and were reported with immediate notification.

Efficacy: Indolent NHL and MCL assessment was based on the International Working Group (IWG) criteria for malignant lymphoma. Diagnostic studies used depended on the location and degree of disease, but had to include imaging using positron emission tomography (PET) and/or diagnostic computerized tomography (CT) scans. Chronic lymphocytic leukemia assessment was based on the IWG criteria for CLL.

Disease assessments were performed at screening and after completion of every 2 cycles of therapy following C1D1. If radiographic imaging was used for disease assessment, the imaging method used at screening had to be used throughout the entire study.

Patients with pretreatment bone marrow involvement (determined by biopsy, flow cytometry, or immunohistochemistry) were considered a PR unless CR was confirmed by bone marrow biopsy, including molecular analysis.

Disease assessments were performed at any time to confirm suspected progression of disease.

Imaging and bone marrow biopsies were assessed by the Investigator/site.

**Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:**

Pharmacokinetics

Pharmacokinetic parameters were to be calculated using plasma concentrations of SAR245409, bendamustine and its active metabolite M3, and serum concentrations of rituximab.

Sampling times:

SAR245409: Pre-dose on C1D1, C1D2, C1D8, C1D15, C1D22, C2D1, C2D2, and C3D1; 1, 2, 3, 4, 6, 8, 12 hours post-infusion on C1D1 and C2D1; and any time on C4D1 and C5D1.

Rituximab: Pre-screen before treatment; pre-dose on C1D1, C1D2, C1D8, C1D15, C1D22, C2D1, C2D2, C3D1, C4D1, and C5D1; end of infusion on C1D1 and C2D1; and 6 and 8 hours post-infusion on C1D1 and C2D1.

Bendamustine and M3: Pre-dose on C1D1, C1D2, and C2D1; middle and end of infusion on C1D1 and C2D1; and 1.25, 1.5, 2, 3, 5, and 7 hours post-infusion on C1D1 and C2D1.

Genotyping: Pre-dose.

Bioanalytical methods:

SAR245409 plasma samples were assayed 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. Serum samples of rituximab were assayed using validated enzyme-linked immunosorbent assays (ELISA) with an LLOQ of 100 ng/mL. Plasma samples of bendamustine/M3 were assayed using validated LC-MS/MS methods with LLOQs of 0.25 ng/mL and 0.100 ng/mL, respectively.

Pharmacogenetics: Deoxyribonucleic acid (DNA) was extracted from whole blood or saliva from genotyping samples and the genes allelic variants were assayed using the Affymetrix DMET Plus array method and analyzed using the Affymetrix DMET Console software.

Pharmacodynamics

Pre- and post-dose blood and tumor samples were collected from consented patients for analyses of a variety of established and exploratory biomarkers as specified in the Protocol. The analyses were intended to demonstrate pharmacodynamic impact of SAR245409 in patients with relapsed or refractory iNHL, MCL, or CLL by documenting changes in PI3K pathway components/modulators and circulating growth factors and cytokines functionally reflective of PI3K pathway modulation.

**Statistical methods:**

Analyses populations:

Safety population: The safety population was defined as all registered patients exposed to the IMP, regardless of the amount of treatment administered.

Evaluable-for-DLT population: The evaluable-for-DLT population was defined as all enrolled patients who had completed the assessments for DLT evaluation and received at least 80% of the dose of SAR245409 during the first cycle, or received a partial dose of study treatment and developed DLT during the first cycle.

Pharmacokinetic population: The PK analysis was to be performed on patients having received at least 1 cycle of drug administration and with valid PK samples.

Efficacy population: The efficacy population was defined as treated patients with baseline tumor assessment and at least 1 post-baseline tumor assessment or that was discontinued due to clinical progression or death from any cause.

Safety analyses:

The safety profile was based on the incidence, severity, and cumulative nature of TEAEs. Vital signs, electrocardiogram, and laboratory tests were also assessed. All safety analyses were essentially descriptive without systematic testing, performed for the safety population by actual dose level. The safety analysis focused on the TEAE period. For patients not included in the treatment extension study (TED12414), the on-treatment period was defined as the time from the first administration of SAR245409 up to 30 days after the last administration of SAR245409. For patients included in the treatment extension study, the on-treatment period was defined as the time from the first administration of SAR245409 up to the last administration of SAR245409 in the study or study discontinuation date, whichever is later.

Pharmacokinetics endpoints:

Descriptive statistics of plasma concentrations and PK parameters of SAR245409 and bendamustine/M3 and serum concentrations of rituximab were to be provided.

Efficacy analyses:

The efficacy endpoints are best overall response (CR, PR, nodular partial response [nPR], stable disease [SD] and progressive disease [PD]) and objective response rate (ORR) (CR or PR). Best overall response and ORR were summarized using frequency counts and percentages by treatment arm and overall combined groups within the efficacy population.

Progression-free survival (PFS) was also summarized by the number and percentage of subjects with PFS >24 weeks and median PFS.

**Summary:**

Safety results: In Arm A, 4 patients were first treated with SAR245409 30 mg BID in combination with rituximab (R/S30) with no DLT reported; 3 patients were then treated with SAR245409 50 mg BID in combination with rituximab (R/S50) with 1 fatal DLT (unrelated necrotizing fasciitis) and the cohort was expanded to include 3 additional patients with no other DLT reported. The MTD for Arm A was 50 mg BID. In Arm B1, 3 patients were treated with SAR245409 30 mg BID in combination with rituximab and bendamustine 90 mg/m$^2$ (R/B90/S30) and 2 reported DLTs (related tumor lysis syndrome and related rash macular). The dose level of bendamustine was adjusted to SAR245409 30 mg BID in combination with rituximab and bendamustine 70 mg/m$^2$ (R/B70/S30), and 3 patients were recruited with no DLT reported. Three additional patients were treated with SAR245409 50 mg BID in combination with rituximab and bendamustine 70 mg/m$^2$ (R/B70/S50) and no DLT was reported. No further dose escalation for SAR245409 was planned in the protocol. In Arm B2, 4 patients with CLL were treated with R/B70/S30 and 1 patient reported 2 DLTs (thrombocytopenia and rash maculo-papular). The cohort was expanded to include 2 additional patients with no DLT reported. Six more patients were treated with R/B70/S50 with no DLT reported. No further dose escalation was planned. A true MTD based on the occurrence of DLTs for Arms B1 and B2 was not defined.

All patients reported at least 1 TEAE, with 10.8% of patients (4 patients) reporting DLTs, and 73.0% of patients (27 patients) reporting a TEAE that was considered to be related to SAR245409.

Overall, 8 patients died during the observation period, with 4 of them due to disease progression. The other 4 cases of death were due to enterobacter sepsis, septic shock, necrotizing fasciitis, and dyspnea and small cell lung cancer. Only enterobacter sepsis was considered to be related to SAR245409 by the Investigator. Of the 8 deaths, 6 patients died during the on-treatment period (within 30 days from the last dose of study treatment).

The TEAEs reported by >20% of patients, regardless of relationship to SAR245409, were headache (12 patients, 32.4%), anemia (11 patients, 29.7%), thrombocytopenia (11 patients, 29.7%), neutropenia (10 patients, 27.0%), and decreased appetite (8 patients, 21.6%). The AEs reported by >20% of patients and assessed as related to SAR245409 were nausea (10 patients, 27.0%) and fatigue (8 patients, 21.6%).

Overall, 23 patients (62.2%) experienced treatment-emergent SAEs. Of these, 9 patients (24.3%) experienced at least 1 treatment-emergent SAE related to SAR245409. Most of the SAEs occurred in 2 patients or less. The SAEs occurred in ≥3 patients were febrile neutropenia (3 patients, 8.1%) and pyrexia (4 patients, 10.8%).

There were 12 patients (32.4%) who experienced AEs leading to discontinuation of study drug. The only PT reported as leading to discontinuation in more than 1 patient overall was vomiting, reported in 2 patients (5.4%).

Selected PTs in MedDRA were combined into liver toxicity and rash groups using the judgment of the clinical team. Adverse events in the rash grouping were reported in 17 patients (45.9%; of Grade ≥3 in 4 patients [10.8%]) and liver toxicities were reported in 6 patients (16.2%; none of Grade ≥3). Nine patients (24.3%) experienced rash AEs and 3 patients (8.1%) experienced liver toxicities that were assessed as related to SAR245409.

In assessment of laboratory parameters, most patients had hematology abnormalities during the on-treatment period: 97.3% of patients had anemia, 75.7% of patients had leukopenia, 64.9% of patients had lymphopenia, 75.7% of patients had neutropenia, and 86.5% of patients had thrombocytopenia. Approximately half of the patients experienced Grade 3-4 lymphopenia (56.8%) or neutropenia (48.6%). The majority of biochemistry abnormalities were of Grade 2 or less.

There were no safety issues identified in the data from vital signs or ECG assessments.

Pharmacokinetic results: Only listings of the plasma concentrations of SAR245409 and bendamustine, and serum concentrations of rituximab are provided.

Pharmacodynamic results: Due to the changes in conduct of the study, planned PD analyses were not performed.

Efficacy results: Limited anti-tumor activity was observed. There were 4 patients who had a CR and 13 patients who had a best response of PR. The ORR for all patients was 48.6%. A total of 17 patients (48.6%) were progression free at 6 month (PFS >24 weeks). The median PFS calculated by Kaplan-Meier analysis was 32.1 weeks for all patients.

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