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Phase I trial of SAR103168, a novel multi-kinase inhibitor, in patients with refractory/relapsed acute leukemias or high-risk myelodysplastic syndromes

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Introduction

There is no effective treatment for patients with relapsed/refractory acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and outcomes are dismal.^{1,2} Conventional chemotherapy regimens generally result in remission rates of less than 20% and there are few durable responses.³ A small, selected minority of patients with relapsed/refractory disease can achieve long-term disease-free survival after allogeneic stem cell transplantation, but novel therapies are desperately needed for the remaining majority.⁴ SAR103168 (1-[2-(2,1,3-benzothiazol-5-ylamino)-6-(2,6-dichlorophenyl)-pyridol[2,3-*d*]pyrimidin-7-yl]-3'-*tert*-butylurea) is a novel multi-targeted kinase inhibitor with preclinical activity in several in vitro and murine AML models. Nanomolar activity has been observed against the Src kinase family, the BCR-Abl kinase and several angiogenic receptor kinases, such as vascular endothelial growth factor receptor type 1 and type 2 (VEGFR1 and VEGFR2), Tie2, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and epidermal growth factor receptor (EGFR). SAR103168 demonstrated anti-leukemic effects in acute and chronic myeloid leukemic cells at nanomolar IC₅₀ via inhibition of proliferation and induction of apoptosis.⁵ Also, SAR103168 was noted to significantly reduce proliferation of leukemic progenitor cells from 29 patients with AML and over 85% of the AML patient samples were sensitive to the agent, including those with poor-prognosis chromosome abnormalities.⁵ Finally, administration of SAR 103168 resulted in tumor regression in animals implanted with human AML leukemic cells.⁵ Preclinical toxicology

studies suggested a favorable toxicity profile. Thus, there was a strong preclinical rationale to initiate a phase I study of SAR103168 in patients with relapsed/refractory AML or MDS. The primary objectives of the study were to determine the maximum tolerated dose (MTD) and dose-limiting toxicities of SAR103168 and to evaluate its pharmacokinetic profile. Secondary objectives were to evaluate the global safety profile, metabolites and preliminary anti-leukemic efficacy of this agent.

Materials and methods

This was an open label, phase I, dose escalation study of SAR103168 given as a single agent by intravenous infusion over one hour once daily for 5 consecutive days, repeated every 2 weeks (NCT00981240). The study was conducted in 3 centers in the United States. Each 5-day treatment with SAR103168 was considered a treatment course. The dose limiting toxicities were evaluated in a period of up to 21 days of the first course. The drug product was formulated as a concentrate for solution for infusion in vials containing 60 mg of SAR103168 in 3 mL of Solutol® HS15/Ethanol 75/25 (w/w) mixture. The starting dose was 1.2 mg/m²/day, based on GLP rat and dog studies. The primary objectives were to determine the maximum tolerated dose (MTD, see definition below) of SAR103168 and to characterize its dose limiting toxicities (DLT, see definition below) and pharmacokinetic (PK) profile. Secondary objectives included: 1) characterization of global safety profile, evaluation of preliminary anti-leukemic efficacy, investigation of the potential induction effect of SAR103168 on CYP3A4 and possible persistence of this effect by using oral midazolam as a probe substrate in patients enrolled into the expanded cohort at the MTD; 2) determination of the metabolic pathways of SAR103168 and identification of the chemical structures of metabolites; 3) determination of the potential impact of SAR103168 on the QTc interval in patients enrolled at the MTD. The study had a modified 3×3 dose escalation design in which 3–4 patients were enrolled to each cohort. The decision for dose escalation was made once all patients in the cohort had been observed for a minimum of 21 days and were evaluable for DLT. If there was no DLT in the first group of patients (n=3 or n=4), dose escalation was permitted. If DLT was observed in the first group of patients, the cohort was expanded to 6 patients and dose escalation was permitted only if there were no further episodes of DLT. Dose escalation to approximately 40 mg/m²/day was anticipated, based on non-clinical toxicology and pharmacology assessments. Hematological DLT was defined as severe pancytopenia (absolute neutrophil count $0.5 \times 10^9/L$, platelet count $20 \times 10^9/L$ and hemoglobin < 6.5 g/dL) associated with severe bone marrow hypoplasia, but without residual leukemia ($> 5\%$ blasts in a bone marrow biopsy with $> 5\%$ cellularity), and persisting for > 28 days after the initial dose of study drug. Non-hematological, non-cardiovascular DLT was defined as any drug-related grade 3 or 4 toxicity according to the NCT-CTC version 3.0, except for grade 3 nausea/vomiting, diarrhea or infection responsive to optimal treatment within 72 hours and asymptomatic, uncomplicated grade 3 laboratory abnormalities persisting for < 7 consecutive days. Cardiovascular DLT required review and confirmation by the investigator and/or a cardiologist and was defined as: 1) hypertension, i.e. systolic blood pressure > 180 mm Hg and/or diastolic blood pressure > 110 mm Hg or increase in blood pressure of more than 40 mm Hg from baseline for at least 2 successive measurements taken at 15 minute intervals; 2) hypotension, i.e. systolic blood pressure < 90

mm Hg and decrease by > 20 mmHg from the pre-infusion values, for at least two successive measurements at 10–15 minute intervals while awake; 3) cardiac troponin I levels equal to or greater than the cut-off values defined by the laboratory as diagnostic for cardiac ischemia and confirmed by a second assessment; 4) cardiac ischemia on a 12-lead ECG (ST segment elevation or depression > 1 mm in at least 2 contiguous leads, new T-wave inversion in at least 2 contiguous leads or presence of Q-waves); 5) grade 3 left ventricular systolic dysfunction (symptomatic congestive heart failure responsive to intervention, LVEF 39% to 20%); 6) atrio-ventricular block requiring cardiac pacing; 7) symptomatic and sustained ventricular tachycardia; 8) supra-ventricular arrhythmias requiring treatment/intervention. Any other toxicity, regardless of grade, was also considered DLT if deemed so by the sponsor, in discussion with the study investigators. MTD was defined as the highest dose at which no more than 1 of a maximum of 6 patients experienced DLT.

Adult patients with refractory/relapsed acute leukemias (including AML and acute lymphoblastic leukemia), chronic myeloid leukemia in accelerated or blast phase, or high-risk myelodysplastic syndromes with no curative option available were eligible for study participation. Patients with first relapse of AML were required to have had remission duration of less than 12 months. Patients over age 60 with previously untreated AML and poor-risk cytogenetics who were not eligible for or did not accept induction chemotherapy were eligible for inclusion in an expanded cohort at the MTD. The final study protocol and amendments were reviewed and approved by the Institutional Review Board at each participating site, in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients before study participation.

Patients were followed for 30 days after the last infusion of SAR103168 or until recovery or stabilization of any related adverse event. Safety was assessed through the collection of adverse events, vital signs (blood pressure and heart rate), laboratory tests, physical examination, Eastern Cooperative Oncology Group performance status, ophthalmologic exam, bone marrow aspiration, left ventricular ejection fraction, and cardiac troponin I. Laboratory abnormalities were graded according to NCI-CTCAE version 3.0.

Pharmacokinetics of SAR103168 were assessed using non-compartmental analysis (WinNonlin®, Pharsight, version 5.2) on Day 1 and Day 5 of the first course and on Day 5 of the 2nd and all subsequent courses. Blood samples were collected pre-dose and at time-points 30 minutes, 1 hour (just before end of infusion), 1.08, 1.25, 1.5, 2, 3, 4, 7, and 24 hours after the start of infusion. On Day 8, a sample was also collected 72 hours after the last treatment in Course 1. For subsequent courses, blood samples were collected on Day 5 at the end of the infusion. SAR103168 concentrations were determined in plasma using a validated bioanalytical liquid chromatography/tandem mass spectrometry method with a lower limit of quantification of 20 ng/mL. Under an optional procedure with separate informed consent, bone marrow aspirates or biopsies and blood samples were to be collected from patients who demonstrated a potential response to SAR103168. However, no pharmacodynamic analyses were conducted. Blood samples were collected at pre-dose on Day 1 to assess genetic variants of drug metabolizing enzymes.

For patients with acute leukemias and MDS, responses to SAR103168 were evaluated using IWG criteria.⁶ Responses to SAR103168 in patients with accelerated or blast phase chronic myeloid leukemia were evaluated using the European LeukemiaNet response definitions.⁷ Bone marrow aspiration/biopsy was performed at baseline and then on Day 11 to Day 14 of the second course and then, every 2 courses (eg, 4, 6, 8) and at end of Study (Day 28 to Day 35). Evaluation of the bone marrow was not required if the patient had clear evidence of disease progression based on peripheral blood assessment.

Descriptive analysis of safety parameters were performed on the whole treated population, defined as all patients exposed to at least 1 dose of SAR103168. To be evaluable for dose limiting toxicity, patients must have completed the dose evaluation period up to Day 21 of the first course. Patients who withdrew from the study before Day 21 and experienced a dose limiting toxicity were also considered evaluable for dose limiting toxicity. Patients were not considered evaluable if they met any criteria for replacement. Type (according to MedDRA version 14.1), frequency, seriousness, and relatedness of treatment emergent adverse events were analyzed. Descriptive statistics were used for plasma concentrations, pharmacokinetic parameters and anti-leukemic activity of SAR103168.

Results

The Sponsor decided to discontinue the study after enrollment of 30 patients and prior to reaching the MTD. During the dose escalation phase of the study, it became clear that it was impossible to draw conclusions on the dose proportionality of the investigational agent due to high pharmacokinetic variability in several dose cohorts (described in detail below). Thus, the decision to discontinue the study was due to the unpredictable relationship between drug dose and exposure, not safety concerns.

Thirty patients were enrolled in the study and of those, 29 were treated with SAR103168 (Table 1). All 29 treated patients completed at least 1 course of treatment and the mean number of courses was 2.1 (SD 0.9). All patients discontinued study treatment. The most common reasons for discontinuing study treatment were disease progression (48.3%), other (41.4%, primarily lack of response), and adverse events (10.3%). At last study contact, 44.8% of patients had died. No patients were lost to follow-up.

In the treated population, patient age ranged from 18 to 83 (mean age 59.4 SD 14.2 years). Demographics included 58.6% male, 62.1% Caucasian, 20.7% Black, 6.9% Asian, and 10.3% other. Serious adverse events are presented in Table 2. A total of 31 serious adverse events were reported in 20 patients. Twenty-eight patients reported at least 1 treatment-emergent adverse event. Grade 3–4 events, regardless of relationship to study drug, were observed in 22 patients (76%) overall, and within 3 weeks of the first study drug administration in 18 patients. The adverse events were as expected in the study population, including febrile neutropenia (24%), pneumonia (17%), disease progression (17%), and bacteremia (10%). Overall, there were 4 isolated grade 3 events assessed as related to study treatment, including: hypokalemia (1.2 mg/m² dose group, recovered in 24 hours); infusion reaction (1.7 mg/m² dose group, recovered same day); dizziness (9.6 mg/m² dose group, recovered in 24 hours); left ventricular dysfunction (14.4 mg/m² dose group, persistent, no

clinical sequelae). Two of these events, hypokalemia and dizziness, took place within 3 weeks of the first study drug administration and the event of dizziness, though without clinical consequence, met the protocol-specified definition of DLT. No Grade 4 events were deemed related to study drug. Three adverse events that led to investigator-initiated study discontinuation were reported in 1 patient each; grade 2 pleural effusion, grade 2 fatigue, and grade 2 abnormal echocardiogram. The latter finding took place in a patient with a history of coronary artery disease and was assessed as related to study drug. The patient died 95 days after the last dose of SAR103168 due to disease progression. A total of 13 deaths were reported in the study, all of which were assessed by the Investigator as due to disease progression.

Seventeen of 25 evaluated patients (68%) in the efficacy population received 2 courses of study treatment, 4 patients received 4 courses, 3 patients received 1 course, and 1 patient received 3 courses. The best overall hematological response seen in the 25 evaluated patients in the efficacy population was stable disease in 15 patients, and progressive disease in 10 patients. One patient experienced a transient decrease in peripheral blasts. The Sponsor decided to discontinue the study prior to reaching the MTD. Thus, no efficacy conclusions can be made regarding SAR103168.

A summary of pharmacokinetic parameters following treatment with SAR103168 (1.2 to 14.4 mg/m²) is presented in Table 3 and in Figures 1 and 2. Human protein binding was high (>99.3%) and similar to preclinical species. There was no saturation of protein binding over a clinically relevant concentration range. Peak plasma concentrations were reached close to the end of the infusion (1 hour) and then declined in a biphasic manner, with mean concentrations below the limit of detection by 24 hours in all dose groups. There was evidence for a longer terminal phase at the highest dose level (14.4 mg/m²) and, therefore, the elimination half-life estimate of 3.32 to 5.46 hours is likely to represent an intermediate phase, rather than the true terminal phase. Both the geometric mean C_{max} and AUC_{last} increased in a dose-related manner after a single dose (Day 1) and multiple dosing on Day 5. However, it was not possible to draw conclusions on dose proportionality due to high inter-patient variability. As a result, it was impossible to predict whether there would be an exposure benefit with increasing doses and, based on preclinical models, it appeared unlikely that the C_{max} or AUCs could reach an exposure target that would translate into a biological response. Based on the preclinical data, ~30 mg/m² (10 mg/kg in mouse) was a putative, partially active dose level. Although plasma exposure in study patients reached higher concentrations than those which showed activity in *in vitro* models (ex-vivo clonogenic assays), they were still considerably lower than the exposures (AUCs -16000 ng/h/mL) which demonstrated *in vivo* activity in xenograft models with SAR103168. An active dose in various tumor models was 16.7 mg/kg IV or 2 × 40 mg/kg PO in mice. No patient ever reached the exposure levels achieved in those animal models (C_{max} from 3600 ng/mL and AUCs from 16000 ng/h/mL). Considering that patient exposures at 14.4 mg/m² were only ~500 ng/mL and ~1000 ng/h/mL, the clinical doses were far off target. Assuming the models were predictive, it is unlikely that significant drug exposure would have been achieved given the dose increments allowed. Overall, there was limited accumulation in exposures (C_{max} or AUC_{last}) upon multiple daily dosings within the first course of treatment. The total variability of C_{max} and AUC_{last}, as measured by CV%, was low to

high (16.9 to 163%) reflecting a few high individual values within some dose groups (particularly at 2.4 mg/m² on Day 5), varied patient cohorts, and the sparse data over this dose range (tlast generally was ~7 hours).

Limited pharmacogenomic evaluations were conducted. There were only two poor metabolizers in the patient population, one of CYP2D6 and the other of CYP2C19. There was no obvious link to higher exposures of SAR103168 in these patients, one of whom had an AUClast of 56 ng.h/mL (group mean 228 ng.h/mL) and the other had AUClast 456 ng.h/mL (group mean of 577 ng.h/mL). This was not surprising, as CYP2D6 contributed to only ~20% of the compound's metabolism and other CYPs (except CYP3A4) played only a minor role in its metabolism. The secondary objectives of the protocol, i.e. assessments of the metabolic pathways of SAR103168 and its effect on induction of CYP3A4, were not investigated due to premature termination of the study.

Conclusions

The Sponsor decided to discontinue Study TED10416 of agent SAR103168 after enrollment of 30 patients and prior to reaching the MTD. During the dose escalation phase of the study, it became clear that it was impossible to draw conclusions on the dose proportionality of the investigational agent due to high pharmacokinetic variability in several dose cohorts. Thus, the decision to discontinue the study was due to the unpredictable relationship between drug dose and exposure, not safety concerns. The pharmacokinetics of SAR103168 after single or five daily intravenous infusions administered to acute myeloid leukemia patients were characterized by a plasma C_{max} at the end of the infusion, followed by a biphasic decline in the elimination profile. Mean half-life estimates were approximately 3 to 5 hours where they could be assessed, although the plasma profile suggested there may have been a longer terminal phase. Both the geometric mean C_{max} and AUC_{last} increased with dose on Day 1 and after multiple dosings on Day 5, but it was not possible to draw conclusions on dose proportionality due to high intersubject variability. There was limited accumulation in the systemic exposure after 5 days of dosing. The total variability of C_{max} and AUC_{last}, as measured by CV%, was low to high (16.9 to 163%), probably reflecting a few high individual patient values, small patient numbers, and limited detection of drug in plasma over the dose range.

The adverse event profile of SAR103168 was as expected for the patient population and did not demonstrate individual toxicities specific to the investigational drug. Febrile neutropenia was the most frequently reported grade 3–4 treatment-emergent adverse event, followed by pneumonia, disease progression and bacteremia. There were a few episodes of cystitis, anemia, deep vein thrombosis, bone pain, and fatigue and all other grade 3–4 treatment-emergent adverse events occurred in 1 patient each. No grade 4 events or deaths on study were assessed as related to study treatment. SAR103168 did not demonstrate a clear clinical benefit within the tested dose range, but preclinical *in vitro* and *in vivo* data using this agent suggest that the doses tested in patients may have been much too low. There are now many examples of both narrowly and more widely-targeted kinase inhibitors which have failed to live up to their promising preclinical potential when tested in patients with AML and MDS. It is possible that we should view these therapeutic failures as evidence that multi-kinase

inhibitors should not continue to be tested as single agents in these diseases. Certainly, it seems unlikely that a single-agent multi-kinase inhibitor will be effective in randomly selected AML or MDS patients with relapsed or refractory disease. Also of concern, however, is whether preclinical modeling of such agents will really help us to use them in AML and MDS patients, especially since a) these patients invariably require multiple concomitant medications which are likely to influence both pharmacokinetics and pharmacodynamics and b) multi-kinase inhibitors should almost certainly be used in combination with other anti-leukemic agents for maximal efficacy. Finally, it is clear that different, innovative and aggressive dose and schedule-defining clinical trial designs are needed for multi-kinase inhibitors to have a chance to demonstrate their efficacy in patients with acute leukemia and MDS.

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Small sample size rule applied to calculation of summary variable
 Source = PKS Study : TED10416; Scenario: P-D-A-IN-OD-E01, Version 36
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Figure 1.
 Mean SAR103168 plasma concentration-time profiles after a single IV infusion (semi-log plot)

Small sample size rule applied to calculation of summary variable

Source = PKS Study : TED10416; Scenario: P-D-B-IN-OD-E01, Version 4

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Figure 2.

Mean SAR103168 plasma concentration-time profiles after multiple IV infusions on Day 5 (semi-log plot)

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Table 1

Patient groups

	SAR103168 (mg/m ²)						
	1.2	1.7	2.4	4.8	9.6	14.4	All
Enrolled population	8	4	5	3	5	4	30
All treated population	8	4	5	3	5	4	29
DLT assessment population	6	3	4	3	5	3	24
Pharmacokinetic population	8	4	5	3	5	4	29
Activity/efficacy population	8	4	4	3	4	2	25

Table 2

Listing of all serious adverse events, regardless of relationship to study drug

Planned dose level (mg/m ²)	SAE Preferred Term	Relationship to Study Drug
1.2	Multi-organ failure	No
1.2	Pneumonia	No
1.2	Bacteremia	No
1.2	Pneumonia fungal	No
1.2	Febrile neutropenia	No
1.2	Echocardiogram abnormal	Yes
1.7	Pulmonary embolism	No
1.7	Deep vein thrombosis	No
1.7	Febrile neutropenia	No
1.7	Staphylococcal sepsis	No
1.7	Disease progression	No
2.4	Perirectal abscess	No
2.4	Febrile neutropenia	No
2.4	Anemia	No
2.4	Disease progression	No
2.4	Septic shock	No
4.8	Bone pain	No
4.8	Febrile neutropenia	No
4.8	Disease progression	No
9.6	Pneumonia	No
9.6	Bacteremia	No
9.6	Asthenia	No
14.4	Disease progression	No
14.4	Sinusitis fungal	No
14.4	Sepsis	No

Table 3

SAR103168 plasma pharmacokinetics parameters (course 1).

		Plasma SAR103168, mean $\pm$ SD (geometric mean) [CV%]					
		1.2 mg/m ² <i>n</i> = 5	1.7 mg/m ² <i>n</i> = 4	2.4 mg/m ² <i>n</i> = 5	4.8 mg/m ² <i>n</i> = 3	9.6 mg/m ² <i>n</i> = 5	14.4 mg/m ² <i>n</i> = 4
Day 1							
<i>C</i> _{max} (ng/mL)		69.4 $\pm$ 29.4 (61.9) [42.4]	78.3 $\pm$ 15.6 (77.0) [19.9]	140 $\pm$ 70.4 (125) [50.2]	204 $\pm$ 83.2 (194) [40.7]	259 $\pm$ 43.8 (256) [16.9]	533 $\pm$ 198 (501) [37.2]
<i>t</i> _{max} [*] (h)		0.92 (0.50–7.00)	0.50 (0.50–0.83)	0.92 (0.50–0.92)	0.92 (0.50–0.92)	1.00 (0.67–1.42)	0.88 (0.50–0.92)
AUC _{last} (ng·h/mL)		109 $\pm$ 60.1 [†] (96.0) [55.1]	75.5 $\pm$ 21.6 (73.4) [28.7]	283 $\pm$ 340 (164) [120.3]	217 $\pm$ 66.3 (211) [30.6]	744 $\pm$ 800 (543) [107.5]	822 $\pm$ 265 (784) [32.3]
Day 5							
<i>C</i> _{max} (ng/mL)		63.9 $\pm$ 47.8 (51.9) [74.8]	170 $\pm$ 144 (138) [84.8]	350 $\pm$ 546 (156) [155.8]	238 $\pm$ 81.5 (228) [34.3]	291 $\pm$ 76.9 (282) [26.5]	467 $\pm$ 255 (420) [54.6]
<i>t</i> _{max} [*] (h)		0.92 (0.50–3.95)	0.96 (0.92–1.33)	1.08 (0.92–1.28)	0.92 (0.50–0.92)	0.92 (0.88–1.00)	0.90 (0.50–1.00)
AUC _{last} (ng·h/mL)		45.7 $\pm$ 40.2 (31.5) [87.9]	228 $\pm$ 171 (176) [74.8]	468 $\pm$ 761 (193) [162.7]	577 $\pm$ 179 (560) [31.0]	987 $\pm$ 1140 (681) [115.5]	992 $\pm$ 684 (3.49) [114.3]
<i>T</i> _{1/2z} (h)		NC $\pm$ NC (NC) [NC] [‡]	NC $\pm$ NC (NC) [NC] [§]	4.35 $\pm$ 5.13 (2.41) [117.8] [¶]	NC $\pm$ NC (NC) [NC] [‡]	3.32 $\pm$ 2.69 (2.62) [80.9] [†]	5.46 $\pm$ 6.24 (3.49) [114.3]

*C*_{max}, peak plasma concentration; *t*_{max}, time of peak plasma concentration; AUC_{last}, area under the curve up to last measurement; *t*_{1/2z}, terminal exponential half-life; SD, standard deviation; CV, coefficient of variation; NC, not calculated.

^{*} Median (min-max).

[†] *n* = 4.

[‡] *n* = 1.

[§] *n* = 0.

[¶] *n* = 2.