Science For A Better Life

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.

Date of report:	23 OCT 2017
Study title:	An open-label, non-randomized, multicenter Phase I study to characterize the safety, tolerability, pharmacokinetics, pharmacodynamics, and maximum tolerated dose of oral MKNK1 inhibitor BAY 1143269 given alone or in combination with intravenous docetaxel in subjects with advanced solid tumors.
Sponsor's study number:	17450
NCT number:	NCT02439346
EudraCT number:	2014-004810-27
Sponsor:	Bayer
Clinical phase:	I
Study objectives:	**Primary objectives** • Determine the safety, tolerability, and maximum tolerated dose (MTD) and / or recommended Phase 2 dose (RP2D) of oral BAY 1143269 given alone or in combination with intravenous (IV) docetaxel in subjects with advanced solid tumors. • Characterize the pharmacokinetics (PK) of oral BAY 1143269 and IV docetaxel when oral BAY 1143269 was given alone and when both agents were given in combination in subjects with advanced solid tumors. **Secondary objectives** • Assess the preliminary tumor response to oral BAY 1143269 given alone or in combination with IV docetaxel in subjects with advanced solid tumors. **Exploratory objectives** • Assess the pharmacodynamic (PD) effects of oral BAY 1143269 on biomarkers in plasma, peripheral blood mononuclear cells (PBMC) and tumor tissue when oral BAY 1143269 was given alone and when oral BAY 1143269 and IV docetaxel were combined in subjects with advanced solid tumors. • Evaluate further biomarkers related to BAY 1143269

	(i.e. mode-of-action-related effect and / or safety) and / or the pathomechanism of the disease. • Assess the PK / PD relationships between the exposure to BAY 1143269 in plasma and the effects on safety, tumor response rate, and changes from baseline in PD biomarkers when oral BAY 1143269 was given alone and when oral BAY 1143269 and IV docetaxel were combined in subjects with advanced solid tumors. • Optionally perform the exploratory profiling of human metabolites of oral BAY 1143269 in plasma.
Test drug:	BAY 1143269
Name of active ingredient(s):	(2R)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}propan-1-amine
Dose:	The starting dose of oral BAY 1143269 was 5 mg once daily (QD).
Route of administration:	Oral
Duration of treatment:	Until evidence of tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator.
Reference drug:	Not applicable
Indication:	Advanced solid tumors
Diagnosis and main criteria for inclusion:	**Inclusion criteria (selected):** • Subjects must be male or female aged >18 years • Subjects must have histologically or cytologically confirmed locally advanced or metastatic solid tumors and must be refractory to any standard therapy, or have no standard therapy available, or have actively refused any standard therapy or, in the investigator's opinion, experimental treatment in this study is clinically and ethically acceptable for the subject. • Subjects must have at least 1 measurable or evaluable tumor lesion according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors, version 1.1). • Subjects must have a life expectancy of at least 12 weeks • Subject must have adequate bone marrow, liver and renal function to be assessed within 14 days before the first dose of any study treatment. • Subjects must have Eastern Cooperative Oncology Group

	(ECOG) performance status of 0 or 1
Study design:	This was a multicenter, open-label, non-randomized, Phase I, dose-escalation study.
Methodology	A treatment cycle in this study was defined as a period of 21 days. The dose escalation part for oral BAY 1143269 given alone was a first-in-human, open-label, non-randomized, multicenter, Phase I study to characterize the safety, PK, and PD and determine the MTD and preliminary clinical antitumor activity of oral BAY 1143269 given alone in subjects with advanced solid tumors. The maximum recommended safe starting human dose of oral BAY 1143269 in humans of 6 mg per day was determined in compliance with the applicable regulatory guidance based on the results from the nonclinical safety and PK studies with BAY 1143269. Based on this, the BAY 1143269 dose of 5 mg QD was acceptable as the starting dose in Study 17450. Dose escalation was be conducted in the appropriate number of sequential cohorts. The dose levels were planned as nominal doses for the respective cohorts. The dose-escalation part with oral BAY 1143269 given alone incorporated a PK go / no-go decision point, based on available data. The investigators and the sponsor evaluated the human PK and PD data from the first cycle to determine if the expected efficacious human exposure to BAY 1143269 in plasma could be reached with doses up to the maximum oral dose that is feasible to administer QD (2000 mg), or with the maximum dose below 2000 mg associated with an acceptable benefit-risk ratio. To ensure that enough subjects are available for the safety and PK analysis, 4 subjects were initially enrolled in each cohort. At least 3 subjects with complete Cycle 1 (21 days) safety data were needed to proceed to the next BAY 1143269 dose level. BAY 1143269 dose escalation decisions were assisted by the Bayesian adaptive dose selection model (modified continual reassessment measurement, mCRM) according to pre-specified rules based on actual observations of TEAEs that fulfill the criteria for a dose-limiting toxicity (DLT). Dose escalation of BAY 1143269 given alone was planned to stop if: • The MTD had been defined with good precision or

	• At any time when the selected dose level for the next cohort had already been given in 9 subjects or • Maximum possible dose was safe or • First dose tested (5mg) was toxic The final decision about the MTD was planned to be made at the investigators' discretion after consultation with the sponsor. After the MTD would have been declared for oral BAY 1143269 given alone in subjects with advanced solid tumors, the conduct of the study was planned to continue simultaneously in 3 directions: (1) Continued enrollment of a sufficient number of subjects with solid tumors in the dose-escalation MTD cohort for obtaining mandatory paired fresh tumor biopsies in at least 6 subjects treated with oral BAY 1143269 given alone at the MTD. (2) MTD expansion with oral BAY 1143269 given alone at the MTD in subjects with unresectable, locally advanced or metastatic recurrent NSCLC. (3) Dose escalation or de-escalation of oral BAY 1143269 in combination with IV docetaxel given Q3W in subjects with unresectable, locally advanced or metastatic recurrent NSCLC eligible for docetaxel therapy, and naïve to docetaxel.
Study center(s):	4 investigational centers enrolled subjects in 2 countries: 1 center in UK, 3 centers in USA.
Publication(s) based on the study (references):	None at the time of report creation
Study period:	First subject, first visit: 15 JUN 2015 Last subject, last visit: 27 MAR 2017 Study completion: 24 APR 2017
Early termination	Yes
Number of subjects:	Planned: Dose-escalation cohort: 48 subjects MTD expansion cohort: 20 subjects Dose-escalation/de-escalation cohort: 24 subjects Analyzed: 15 subjects were treated and valid for safety evaluation, all subjects were valid for PK evaluation

	in the dose escalation cohort.
Criteria for evaluation	
Pharmacokinetics:	The following parameters were to be derived from the plasma concentration-time profiles of BAY 1143269: • **Cycle 1 Day 1** (single dose PK without docetaxel): o C_{max}, t_{max}, AUC(0-24) • **Cycle 2 Day 1** (multiple dose PK without docetaxel): o C_{max}, t_{max}, AUC(0-24)
Safety:	Maximum tolerated dose (MTD) of oral BAY1143269 alone and MTD of oral BAY 1143269 in combination with IV docetaxel; Assessment of adverse events.
Efficacy:	Tumor response per RECIST 1.1
Statistical methods:	This was a descriptive Phase I study. No formal sample size calculation was performed. All subjects who received at least 1 dose of the study treatment were included in the safety evaluation. All subjects who had valid PK concentrations without major changes versus the protocol were included in the evaluation of PK for BAY 1143269. All data was listed and summary tables and figures were provided.
Substantial protocol changes:	**Amendment 1**, dated 30 MAR 2015, was a globally implemented amendment: • Incorporation of health authority feedback from Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA)

Early termination of the study / termination of the project

The subject recruitment in the study 17450 was stopped as of 11 JUL 2016, in light of strategic considerations and project prioritization within the product portfolio.

Since the dose escalation was not completed, neither the planned maximum tolerated dose (MTD) expansion cohort with oral BAY 1143269 given alone, nor the dose escalation or de-escalation with oral BAY 1143269 in combination with IV docetaxel were initiated.

At the time the study was stopped, one last subject was under treatment in Cohort 4 of the dose escalation. The subject received study drug (MKNK1 inhibitor BAY 1143269 50 mg

once daily [QD]) until the treatment was permanently discontinued on 22 FEB 2017 due to disease progression.

No important or potential risks were identified with BAY 1143269 during the study.

Study subjects

This study was conducted at four centers across two countries. Seventeen subjects with advanced solid tumors were enrolled in the study. Two subjects did not complete screening (one screening failure and one withdrawal by subject). There were no major protocol deviations in this study.

Fifteen white subjects (7 female and 8 male) with an average age of 59.6 years (range: 44 to 72 years), a mean body mass index of 28.32 kg/m^2 (min: 21.5 kg/m^2, max: 40.7 kg/m^2), and advanced solid tumors were enrolled and treated in the study.

The fifteen subjects were assigned to treatment for the following dose levels:
Cohort 1 (5 mg BAY1143269 QD): N=3, Cohort 2 (10mg BAY1143269 QD): N=4, Cohort 3 (25mg BAY1143269 QD): N=4, Cohort 4 (50mg BAY1143269 QD): N=4.

Twelve subjects discontinued from the study due to progressive disease (all radiological progression), 1 due to adverse event (AE) not associated with clinical disease progression and 2 due to physician's decision. Nine subjects completed safety follow-up.

All 15 subjects who received at least 1 dose of study drug were included in the safety analysis set (SAF) and the PK analysis set.

Efficacy

The dose escalation was prematurely discontinued, before the predicted human efficacious dose range could be reached . The best overall response was stable disease, observed in one patient in the 50 mg QD cohort.

All patients who were administered BAY 1143269 at doses comprised between 5-50 mg QD underwent disease progression.

Pharmacokinetic evaluation

All 15 subjects that completed the study prior to its termination had complete PK concentration profiles in Cycle 1. In Cycle 2, all but two subjects provided PK samples and had complete PK concentration profiles. Therefore, data from 13 subjects with complete PK concentration profiles were used for the comparison of Cycle 1 and Cycle 2 to determine time-dependent PK of BAY 1143269. As expected, an increase in dose resulted in an increase in BAY 1143269 exposure. At the 5 mg dose cohort, plasma concentrations were below the LLOQ and could not be measured 12 hours post BAY 1143269 administration.

BAY 1143269 was rapidly absorbed with median t_{max} observed around 3 hours post dose. Inter-subject variability in exposure was generally low to moderate (Coefficient of variation [CV]: 16 – 54%) except at the 5 mg dose cohort where high variability (CV: 96 – 143%) was

observed. In the dose range 5 mg QD to 50 mg DQ, nearly dose proportional increase in single dose (Cycle 1 Day 1) BAY 1143269 exposure was observed. Comparable plasma concentrations and exposure of BAY 1143269 were observed in Cycle 1 and Cycle 2, suggesting no time-dependent (auto-induction) PK of BAY1143269.

Table 1 summarizes the PK parameters of BAY 1143269 as geometric mean and geometric coefficient of variation (CV).

Table 1: Geometric mean (%CV) pharmacokinetic parameters of BAY 1143269

		BAY 1143269 dose			
		5 mg (n = 3)[B]	**10 mg (n = 4)**	**25 mg (n = 4)**	**50 mg (n = 4)**
Cycle 1 Day 1	C_{max}, µg/L	4.3 (143 %)	12.7 (39 %)	45.0 (51 %)	63.7 (28%)
	t_{max}, h [A]	3 [3 – 6]	3 [2 – 4]	3 [2 – 6]	4 [3 – 6]
	AUC(0-24), µg.h/L	70.4, 96.7	169 (35%)	443 (27%)	801 (24%)
Cycle 2 Day 1	C_{max}, µg/L	5.1 (96 %)	15.8 (30%)	31.2 (33%)	76.2 (37%)
	t_{max}, h [A]	3 [2 – 3]	3 [2 – 6]	3 [2 – 4]	4 [3 – 4]
	AUC(0-24), µg.h/L	40.0 (112 %)	184 (24%)	284 (16%)	790 (54%)

[A] Median [range]; [B] N = 2

Abbreviations: CV=Coefficient of variation, C_{max}=Maximum drug concentration in plasma after single dose administration, t_{max}= Time to maximum plasma concentration, AUC(0-24)=AUC versus time curve from time 0 to 24 hours

Safety evaluation

All 15 subjects valid for the safety evaluation experienced at least 1 treatment emergent adverse event (TEAE) and 9 (60%) subjects experienced at least 1 drug-related TEAE. Five (33.3%) subjects experienced at least 1 Grade 3 TEAE. There was no Grade 4 or Grade 5 TEAEs in this study. One subject (6.7%) experienced at least 1 Grade 3 drug-related TEAE. TEAEs led to dose modification in 4 (26.7%) subjects. The events that resulted in dose modification were considered as drug-related in 2 subjects (13.3%). Study treatment was permanently discontinued due to TEAE in 1 (6.7%) subject.

The most common TEAEs (in ≥ 20% of subjects) were: decreased appetite in 5 subjects (33.3%), abdominal pain, nausea and cough in 4 subjects (26.7%) each and, fatigue, weight decreased, back pain and tumor pain in 3 subjects (20.0%) each. All other TEAEs occurred in 1 or 2 subjects only.

Worst Grade 3 intensity was assessed for the following TEAEs: anemia (25 mg cohort), atrial fibrillation (25 mg cohort), urosepsis (25 mg cohort), blood alkaline phosphatase increased (in two subjects, 5 mg cohort and 10 mg cohort), blood bilirubin increased (10 mg cohort), renal failure (25 mg cohort) and, hemoptysis (50 mg cohort).

The most frequently occurring drug-related TEAE was fatigue in 2 subjects (13.3%). All other drug-related TEAEs occurred in 1 subject each. One subject (12001-0003) in the BAY 1143269 25 mg cohort experienced atrial fibrillation with the intensity of Grade 3. The investigator assessed the event as causally related to study medication. This TEAE was considered a DLT.

No deaths occurred before/during treatment and after/within 30 days following the last dose of study drug.

Three subjects experienced at least 1 serious adverse event.

Overall conclusions

Patient recruitment was stopped as of 11 JUL 2016, in light of strategic considerations and project prioritization within the product portfolio.

The data collected and presented in this abbreviated CSR were obtained from the 15 patients enrolled until this date in the first 4 Cohorts

Mean maximum plasma concentration was observed around 3 hours post BAY 1143269 dose. At the BAY 1143269 dose range of 5 mg – 50 mg QD, nearly dose-proportional increase in exposure was observed. Mostly low to moderate inter-subject variability was observed for BAY 1143269. No time-dependent PK was observed following daily dosing of BAY 1143269.

Preliminary data suggests that the exposure levels reached with the maximal dose tested (50 mg QD) are ~ 34-fold lower than the exposure level estimated to be efficacious in humans (~1700 mg QD).

In conclusion, BAY 1143269 appeared to be safe and well tolerated within a dose range of 5-50 mg QD . The data collected were not sufficient to determine the MTD nor to define the anti-tumor activity of BAY 1143269, because, due to portfolio reprioritization, the dose escalation was prematurely discontinued before the MTD or the predicted human efficacious dose range could be reached .