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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT01161836 Study code: BEX11505
Title of the study: An open-label study investigating the disposition and QT/QTc interval effects of 400 mg [^{14}C]-BSI-201 (3.7 MBq, 100 µCi) administered at Cycle 1 as a 60-minute intravenous infusion to patients with advanced solid tumors followed by extended treatment with BSI-201 with or without additional chemotherapy	
Study center(s): 1 study center in US for Segment 1 and 1 study center in US for Segment 2	
Study period: Date first patient enrolled (Segment): 30/Jul/2010 Date last patient completed (Segment 2): 30/Jun/2011	
Phase of development: Phase 1	

Objectives:

Primary:

Segment 1: The primary objectives of this segment of the study were:

- To determine the excretion balance and systemic exposure of radioactivity after intravenous (IV) administration of [14C]-iniparib to humans;
- To determine the pharmacokinetics (PK) of iniparib, 4-iodo-3-amino-benzamide (IABM), and 4-iodo-3-amino-benzoic acid (IABA) and their contribution to overall exposure of radioactivity;
- To evaluate the effects of iniparib on changes in the electrocardiogram (ECG) with special focus on the QTcF (Fridericia correction of QT interval) interval duration; and
- To collect samples in order to determine the metabolic pathways of iniparib and identify the chemical structures of the main metabolites.

Segment 2: The primary objectives of this segment of the study were to assess the safety and tolerability of iniparib with or without chemotherapy.

Secondary:

Segment 1: The secondary objective of the study was to assess the clinical and biological tolerability of iniparib.

Segment 2: None

Methodology: The main purpose of the study was to evaluate the disposition and QT/QTc interval effects of 400 mg [^{14}C]-iniparib (3.7 MBq, 100 µCi) administered at Cycle 1 as a 60-minute IV infusion to patients with advanced solid tumors (Segment 1). Patients were then offered to continue treatment with iniparib with or without additional chemotherapy (Segment 2). During Segment 1, which was open-label and nonrandomized, patients were administered a single IV dose of [^{14}C]-iniparib. Patients progressed to Segment 2 on Day 8 of the study, at physician discretion, even if the End of Segment 1 had not yet been reached. During Segment 2, which was also open-label and nonrandomized, patients were administered iniparib with or without additional chemotherapy. Acceptable chemotherapy regimens were limited to those for which previous experience with iniparib exists.

Number of patients:	Planned: Segment 1: 8 (at least 6 evaluable); Segment 2: those patients treated in Segment 1 Treated: Segment 1 and 2: 7
Evaluated:	
	Pharmacodynamic: Segment 1: 7
	Safety: Segment 1 and 2: 7
	Pharmacokinetics: 7

Diagnosis and criteria for inclusion:

- Male or female patients with advanced solid tumors that had become refractory to standard treatment or for which no standard treatment existed.
- Normal vital signs and electrocardiogram (ECG).
- 18 to 75 years of age inclusive.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
- Adequate hematological, hepatic, and renal functions.

Study treatments

Investigational medicinal product(s):

Segment 1: The [^{14}C]-iniparib 10 mg/mL drug product was supplied in clear glass vials (100 mg/10 mL; 0.25 µCi/mg) with a fluorotec-coated stopper crimp sealed with an aluminum cap.

Segment 2: The iniparib 10 mg/mL drug product for infusion was supplied in clear glass vials (100 mg/10 mL).

Dose:

Segment 1: A dose of 400 mg (40 mL) taken from 4 vials of [^{14}C]-iniparib (3.7 MBq/100 µCi) product solution was administered by IV infusion following dilution in 0.9% sodium chloride solution.

Segment 2: Each patient received a weight-based dose of 5.6 mg/kg administered by IV infusion following dilution with 0.9% sodium chloride solution. The study protocol indicated a dose of 5.6 mg/kg iniparib for all regimens except when used in combination with irinotecan where a dose of 8.0 mg/kg was specified in Appendix C of the study protocol (Appendix 14.1.1). The protocol also allowed for iniparib to be used alone.

Route of administration: Intravenous infusion (60 minutes)

Duration of treatment:

Segment 1: Single dose infusion of 400 mg/40 mL [^{14}C]-iniparib (3.7 MBq/100 µCi) over 60 minutes.

Segment 2: The dose regimen and treatment duration were based on the clinical indication, combination chemotherapy selected, and clinical judgment of the Investigator.

Duration of observation:

- Screening: 2 to 28 days prior to inclusion.
- Treatment period: A total of 96 hours in the Clinical Unit (Day 1 to the morning of Day 5), including 60 minutes of infusion.
- Follow-up and End of Segment 1: a maximum of 5 weeks; if the release criterion was not met by Day 5, patients were to be discharged on Day 5 and required to return weekly to the Clinical Unit for 24-hour confinement for collection of excreta on Day 10, Day 14, and then weekly thereafter, up to Day 35.
- Total Segment 1 duration: From 1 to 9 weeks (including screening time).
- End of Segment 1 was determined by the definitive count of combined excretion of >90% of radioactivity which was assessed on Day 5 and could be reassessed up to Day 35 until this criterion was met.

Segment 2: Patients were permitted to continue treatment with the investigational drug iniparib, with or without the addition of a standard chemotherapy regimen. Patients could begin Segment 2 on Day 8 of the study, at the Investigator's discretion, even if the End of Segment 1 had not yet been reached. The maximum number of treatment cycles allowed during Segment 2 was based upon the standard of care for an individual solid tumor type. In general, patients were allowed to continue treatment at the Investigator's discretion until one of the following occurred: disease progression, unacceptable toxicity, or withdrawal of consent.

Criteria for evaluation:

Pharmacodynamics (Segment 1 only): Electrocardiograms were recorded at the site using ECG recorders provided by core ECG laboratory, eResearch Technology (ERT), Philadelphia, PA, USA. QTc (corrected QT interval) duration was evaluated by the Investigator during the trial. Digital ECGs were also transmitted from the site via modem to ERT for measurement of the cardiac intervals and morphological assessment by a central cardiologist.

Six (6) ECGs were recorded between 7 and 8 am (ie, starting 1 hour prior to the start of infusion of study drug) approximately 10 minutes apart. Three (3) ECGs were taken about 2 to 3 minutes apart after the end of the infusion of study drug and then again at 2, 4, 7, and 10 hours postinfusion, as well as on Day 2 and Day 3 at about 24 and 48 hours after the end of study drug administration. Electrocardiograms were taken before the pharmacokinetic (PK) blood sample at all postinfusion time points. The ECG parameters collected included heart rate; PR, QRS, QT, QTcB, and QTcF intervals; and ECG morphology. For safety evaluation only, as noted in the Safety section below, other ECGs evaluating the same parameters and handled in the same manner were recorded at single time points, but not included in the ECG pharmacodynamic (PD) analyses.

Safety: The following safety evaluations were performed and collected during Screening and Segment 1:

- Physical examination during screening (Day -28 to Day -2), the day prior to dosing (Day -1), prior to discharge at 96 hours (Day 5), and End of Segment 1.
- Temperature during screening (Day -28 to Day -2) and the day prior to dosing (Day -1).
- Performance status (ECOG) during screening (Day -28 to Day -2).
- Adverse events from screening (Day -28 to Day -2) through the End of Segment 1.
- Hematology, biochemistry, and urinalysis during screening (Day -28 to Day -2), the day prior to dosing (Day -1), Day 5 (96 hours), and End of Segment 1.
- Archival blood sample: Predose at 0 hours (Day 1) and only used if any unexpected safety issue were to occur to ensure a predrug baseline value would be available.
- Urine pregnancy test during screening (Day -28 to Day -2), the day prior to dosing (Day -1), and End of Segment 1
- Vital signs during screening (Day -28 to Day -2), the day prior to dosing (Day -1), predose at 0 hours (Day 1), every 24-hour period postinfusion on Days 2 to 5 (24, 48, 72, and 96 hours), and at the End of Segment 1.
- Single 12-lead ECG during screening (Day -28 to Day -2), the day prior to dosing (Day -1), at 72 hours postinfusion, on the day of discharge, and at the End of Segment 1 visit (if not the same as day of discharge). Note: Other ECGs for PD analyses were performed at the time points listed above in the PD section.
- Concomitant medications from screening (Day -28 to Day -2) to the End of Segment 1.

Segment 2: At beginning of each cycle: Adverse events, hematology, biochemistry, disease assessment, physical examination, body weight, body temperature (oral), vital signs, and concomitant medication. Adverse events were also reported throughout this segment.

Pharmacokinetics (Segment 1 only): Sampling times and bioanalytical methods were as follows:

- Blood samples were collected on Days 1 to 5. Day 1 samples were collected at predose (0 hours) and at the following times after the start of infusion: 30 minutes; 1 hour; 1 hour 10 minutes; 1 hour 20 minutes; 1 hour 40 minutes; 2, 4, 7, and 10 hours; and then every 24-hours on Days 2 to 5 (ie, at 24, 48, 72, and 96 hours).

- Urine and fecal samples were collected at predose on Day -1 (-12 to 0 hours before dosing) and then over the following intervals after the start of infusion; 0 to 24 hours, 24 to 48 hours, 48 to 72 hours, and 72 to 96 hours.
- If definitive counts showed that >90% of the administered dose had not been excreted by 96 hours (morning of Day 5), patients were to return to the Clinical Unit weekly on Days 10, 14, 21, 28, and 35 (ie, at 216, 312, 240, 648, and 816 hours) for 24-hour confinement for the collection of blood samples and excreta until the release criterion was met. Follow-up clinical visits could occur ±1 day to allow for scheduling.
- Blood sample for genotyping and deoxyribonucleic acid (DNA) banking were collected during screening (Day -28 to Day -2).

Plasma samples were analyzed for iniparib, IABM, and IABA by a validated liquid chromatography tandem mass spectrometry LC-MS/MS) method. Determination of radioactivity in whole blood, plasma, and excreta (urine and feces) was carried out using liquid scintillation counting, either directly (plasma and urine), or after combustion (whole blood and feces).

Statistical methods:

Pharmacodynamics (Segment 1 only): Electrocardiogram data were analyzed for central tendency, outliers, and morphology.

Safety: In both segments, descriptive statistics were used to summarize safety data. Selected data were listed.

Segment 1: Treatment-emergent adverse events (TEAEs) for Segment 1 were defined as any AE that developed or worsened in severity compared to baseline during the on-treatment period of Segment 1. The on-treatment period in Segment 1 was defined as the date of dosing of [^{14}C]-iniparib up to the earliest of (1) 30 days after [^{14}C]-iniparib dosing, or (2) the first date of iniparib administration in Segment 2. Concomitant medications were defined as medications taken after dosing of [^{14}C]-iniparib (including medications ongoing from before dosing that continued) up to the earliest of (1) 30 days after [^{14}C]-iniparib dosing or, (2) the first date of iniparib administration in Segment 2.

Segment 2: Treatment-emergent adverse events for Segment 2 were defined as any AE that occurred in the on-treatment period of Segment 2. The on-treatment period in Segment 2 was defined as the earliest of (1) 30 days after [^{14}C]-iniparib dosing, or (2) the first date of iniparib administration in Segment 2. In addition, any AE that occurred prior to Segment 2 and continued to the earliest of (1) 30 days after [^{14}C]-iniparib dosing, or (2) the first date of iniparib administration in Segment 2 was counted as an AE if it developed during this time period or worsened in severity compared to Segment 1. Concomitant medications were defined as medications taken after the first dosing of iniparib to the last dose of iniparib.

Pharmacokinetics (Segment 1 only): The following PK parameters were evaluated and summarized using descriptive statistics:

- Plasma iniparib, IABM, and IABA; plasma, and blood radioactivity: C_{max}, t_{max}, AUC_{last}, AUC, terminal $t_{1/2z}$;
- Blood/plasma radioactivity: blood-to-plasma radioactivity ratio at each time point;
- Urine and feces radioactivity: fractional, cumulative excretion.

An exploratory PK/PD analysis consisting of correlation of QTc change from baseline with iniparib plasma concentration was evaluated.

Summary: Seven patients were included in the study. All 7 patients were evaluable for PD (ECG), safety, and PK analyses. Five female patients between 43 and 68 years of age and 2 male patients between 31 and 68 years of age participated in this study. The type of cancers the patients in this study had were pancreatic (n=3), ovarian (n=2), breast (n=1), and esophageal (n=1).

Segment 1: All 7 patients received a complete infusion of [^{14}C]-iniparib.

Segment 2: All 7 patients treated in Segment 1 entered into Segment 2 of the study and received from 1 to 13 cycles of iniparib in combination with chemotherapy (gemcitabine [n=4], gemcitabine and carboplatin [n=2], and carboplatin and paclitaxel [n=1]).

Pharmacodynamic results (Segment 1 only): The mean change from baseline for heart rate was +5.1 beats per minute (bpm) with a time point analysis showing that this change began about 4 hours after dosing and lasted for 48 hours. The mean change from baseline for QRS duration was 0 ms and the time point assessment showed no clinical signal of change. The QTcF duration change from baseline was a -2.3 ms and the time point analysis also demonstrated no signal of any effect on the duration of this interval. In addition no outliers were identified in the 7 patients.

There were no bradycardic outliers, but there was 1 patient of the 7 who met the tachycardic outlier criteria with a baseline value of 99 bpm and a maximum heart rate value of 127 bpm at the 24-hour time point. There were no PR, QRS, QT, or QTc outliers. No new morphological changes on treatment were observed in the 7 patients.

Safety results:

Segment 1: [^{14}C]-iniparib was well tolerated. Five patients had at least 1 TEAE and 1 patient experienced Grade 3 TEAEs. There were no deaths during Segment 1 of this study. Two patients experienced SAEs (abdominal pain, diarrhea, and emesis in 1 patient; and pleural effusion in another patient); all of these events were assessed as not related to [^{14}C]-iniparib. No patients withdrew from Segment 1 due to AEs. The most frequently reported TEAEs were headache and nausea in 2 patients each. The highest grade reported was Grade 3 for the SAEs of abdominal pain, diarrhea, and emesis in 1 patient. Although mean changes from baseline to Day 5 or End of Segment 1 were observed in some biochemistry and hematology parameters and some patients experienced out-of-range values, these changes were expected in this patient population.
There were no major abnormalities in mean heart rate or mean systolic or diastolic blood pressure. Mean changes from baseline for these parameters were not clinically important.
None of the 7 patients demonstrated any ECG changes from the single-time point ECG data that suggested a cardiac safety signal from the heart rate and interval data.

Segment 2:
Pretreatment adverse event data during Segment 2: Pretreatment AEs that began prior to the first dose in Segment 2 were reported on Segment 2 case report form pages. Two Grade 3 AEs that occurred within 30 days after [^{14}C]-iniparib administration were reported by the Segment 2 site, namely, an SAE of nausea in 1 patient and a nonserious AE of orthopnea in another patient; both AEs were assessed as treatment-related to [^{14}C]-iniparib; the nausea resolved and the orthopnea remained ongoing. Three other AEs that occurred within 30 days after [^{14}C]-iniparib administration were reported by the Segment 2 site: Grade 1 musculoskeletal discomfort in 1 patient and Grade 1 hypercholesterolemia and Grade 2 dyspnea in another patient (all 3 events were assessed as not related to [^{14}C]-iniparib and were not serious; musculoskeletal discomfort and hypercholesterolemia were ongoing; dyspnea changed in grade over the course of the study and also remained ongoing).

On-treatment safety data during Segment 2: All 7 patients had at least 1 TEAE and 3 patients experienced Grade 3 TEAEs during Segment 2 (Grade 3 was the highest grade reported). Out of the 7 total patients, the most frequent TEAEs were fatigue (n=6 patients); nausea (n=5 patients); anemia, headache, peripheral neuropathy, constipation, or vomiting (n=4 patients each). Two patients experienced serious TEAEs (fluid overload and abdominal pain in 1 patient and dyspnea in another patient; all of these events were Grade 3 in severity). Only the fluid overload was assessed as being related to iniparib and was ongoing; the abdominal pain resolved; dyspnea changed in grade over the course of the study and remained ongoing. Two patients withdrew from the study due to TEAEs; 1 patient experienced abdominal pain, diarrhea, nausea, and vomiting and another patient experienced peripheral edema and pleural effusion. All events for both patients were assessed as Grade 2 in severity, related to iniparib, and were ongoing.

Most laboratory values during treatment were Grade 1 or 2 and expected in this population. One patient experienced potentially clinically significant abnormalities in heart rate, which had also been experienced by the same patient during Segment 1.

Pharmacokinetic results (Segment 1 only):

Excretion balance of total radioactivity (% dose)

Matrix	Period	Mean (SD) n=7
Urine	0 - 96 h	72.6 (2.94)
Fecesa	0 - 96 h	15.9 (6.25)
Total	0 - 96 h	88.5 (5.24)

a: Two patients had radioactivity in feces at 240 hours after dosing that was less than 0.6% of the dose

The recovery of the radioactive dose was almost complete (mean: 88.5% of the dose) by 96 hours. Approximately 72.6% of the radioactivity was excreted in the urine and 15.9% in the feces. Iniparib, IABM, and IABA concentrations were cleared from plasma quickly after the end of infusion with mean (CV%) terminal elimination half-lives of 10.9 minutes (7.6%), 0.8 hours (20%), and 2.1 hours (19%), respectively. Mean (CV%) AUC values for iniparib, IABM, and IABA were 3,050 ng h/mL (44%), 13.3 ng h/mL (24%) and 58.6 ng h/mL (32%), respectively. IABM and IABA metabolite exposure (AUC) was 0.4% and 1.9% of the iniparib AUC value, respectively. Iniparib accounted for only 8.4% of the circulating radioactivity. Mean (CV%) terminal elimination half-life for radioactivity in blood and plasma was 15.8 hours (125%) and 18.5 hours (22%), respectively. The blood-to-plasma ratio of radioactivity ranged from 0.61 to 0.78 between 0.5 and 24 hours, suggesting that the distribution of iniparib and/or its metabolites into red blood cells was limited. No change in QTcF was apparent with an increase in iniparib plasma concentration in patients with solid tumors following a single 60 minute IV infusion of [^{14}C]-iniparib 400 mg.
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