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A first-in-human phase 1 study of the SHP2 inhibitor BBP-398 in patients with advanced solid tumors

Gerald Falchook[1,12], Camila Braganca Xavier[2,12], David Van Veenhuyzen[3], Jyoti Malhotra[4], Saeed Sadeghi[5], Arash Rezazadeh Kalebasty[6], Lauren Wood[3], Faisal Rahman[3], Elizabeth Li[7], Yvonne Pak[3], Maya Khalil[8], Alexander I. Spira[9], David Sommerhalder[10], Ignacio Garrido-Laguna[11] & David S. Hong[2]✉

[1]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA. [2]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [3]BridgeBio, Palo Alto, CA, USA. [4]City of Hope Comprehensive Cancer Center, Duarte, CA, USA. [5]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA. [6]University of California, Irvine, Irvine, CA, USA. [7]PharmaStat, Fremont, CA, USA. [8]The University of Alabama at Birmingham, O'Neal Comprehensive Cancer Center, Birmingham, AL, USA, [9]NEXT Oncology, Fairfax, VA, USA. [10]NEXT Oncology, San Antonio, TX, USA. [11]University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA. [12]Co-first authors.

✉Department of Investigational Cancer Therapeutics, Unit 455, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA,

e-mail: dshong@mdanderson.org

Abstract

BBP-398 is a selective allosteric SHP2 inhibitor designed to inhibit mitogen-activated protein kinase (MAPK) pathway–driven tumors. We performed the first-in-human phase 1 trial described herein to assess the safety, tolerability, pharmacokinetics, and preliminary efficacy of BBP-398 in patients with advanced solid tumors harboring MAPK pathway mutations. Once-daily BBP-398 was administered at 350-550 mg in the dose-escalation phase (1a; *n* = 35) followed by a dose-expansion phase (1b; *n* = 37). The study endpoints were dose-limiting toxicities, treatment-emergent adverse events, pharmacokinetics, target engagement, disease control rate, progression-free survival, and overall survival. In phase 1a, 26% of the 23 evaluable patients had stable disease, with a median progression-free survival duration of 1.8 months (range, 1.7-4.1 months). In phase 1b, 30% of the 27 evaluable patients had stable disease (31% at 350 mg, 27% at 450 mg), with median progression-free survival of 2.2 months and 1.9 months at 350 mg and 450 mg, respectively. We halted dose escalation at 550 mg owing to an increased rate of thrombocytopenia and edema. At daily doses of up to 450 mg, BBP-398 exhibited an acceptable safety profile and produced disease stabilization in nearly 30% of heavily pretreated patients.

Introduction

The *RAS* genes are the most frequently mutated oncogenes in patients with cancers [1], and the ubiquitous tyrosine phosphatase SHP2 (also known as PTPN11) has emerged as a major regulator of the RAS pathway and subsequently the downstream receptor tyrosine kinase–mediated mitogen-activated protein kinase (MAPK) signaling pathway [2]. The MAPK pathway in turn plays a key role in regulation of cell growth, proliferation, and differentiation and is frequently activated in patients with cancer [3]. Beyond the RAS/MAPK pathway, receptor tyrosine kinases also activate other downstream effector pathways, such as the phosphatidylinositol 3-kinase, protein kinase B (AKT), Janus kinase, signal transducer and activator of transcription, and phospholipase C gamma/protein kinase C signaling pathways [4].

Structurally, SHP2 comprises tandem N-SH2 and C-SH2 domains, a PTP domain, and a disordered C-terminal tail containing two tyrosine residues (Tyr542 and Tyr580) susceptible to conditional phosphorylation, both flanking a flexible proline-rich region. In its inactive state, SHP2 has a closed conformation in which the N-SH2 domain extensively interacts with the PTP domain, thereby occluding the phosphatase catalytic site [5]. Early efforts to develop small-molecule SHP2 inhibitors predominantly concentrated on identifying compounds targeting the catalytic site of the SHP2 molecule using conventional strategies commonly applied to the design of ATP-competitive protein kinase inhibitors [6]. Such SHP2 inhibitors exhibited suboptimal drug-like attributes, including nonselective inhibition of multiple kinases causing fatigue, diarrhea, nausea, skin rashes, among other side effects, which obscured their specific mechanisms of action. The use of ionizable phosphotyrosine bioisosteres to engage the active site yielded compounds with low membrane permeability and limited therapeutic efficacy [7,8]. Thus, clinical development of allosteric SHP2 inhibitors largely stalled.

Allosteric SHP2 inhibitors have been characterized as molecular glue owing to their mechanism of action, which stabilizes the inherently autoinhibited, closed conformation of SHP2 [9,10]. BBP-398 (formerly known as IACS-15509) is a potent, selective, orally active allosteric SHP2 inhibitor that induces simultaneous inhibition of multiple receptor tyrosine kinases. We performed the first-in-human phase 1 study described herein to evaluate the safety,

tolerability, and maximum tolerated dose (MTD) of BBP-398 and establish its recommended phase 2 dose in patients with advanced solid tumors harboring mutations in the MAPK signaling pathway, including *RAS* mutations. We hypothesize that BBP-398 will demonstrate an acceptable safety profile and may represent a viable therapeutic option for disease control in heavily pretreated patients.

Results

Patients

Thirty-five patients were enrolled and treated in the dose-escalation phase (1a). The population was 57% female and 74% White and had a median age of 63 years (range, 33-79 years). At baseline, most of the patients (91%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1, whereas the remainder had an ECOG PS of 0. The most common site of the primary tumor was the colon (37%), followed by the lung (17%), pancreas (14%), and rectum (14%). More than half of the patients (54%) received third-line therapy, and 26% received further line therapy. Twenty-one patients (60%) had to discontinue their most recent prior therapy because of progressive disease.

Thirty-seven patients were enrolled and treated in the dose-expansion phase (1b). The population was 57% female and 81% White and had a median age of 60 years (range, 38-82 years). At baseline, most of the patients (68%) had an ECOG PS of 1, with the remainder having an ECOG PS of 0. In this cohort, the most common site of the primary tumor was the pancreas (27%), followed by the colon (22%) and lung (16%). Third-line therapy was received by 38% of the patients, and 19% received further line therapy. Seventeen patients (46%) had to discontinue their most recent prior therapy because of progressive disease. Figure 1 displays the study consort diagram for patients' allocation. The patient characteristics are summarized in Table 1.

In phase 1a, the overall median duration of BBP-398 exposure was 30 days (range, 1-212 days), with a lower median duration of exposure at 550 mg (15.0 days) than at 400 mg (42.0 days) and 450 mg (33.5 days). The most common reasons for treatment discontinuation were progressive disease (*n* = 24 [69%]) and adverse events

(AEs; *n* = 4 [11%]). The most common reasons for study termination were death (*n* = 16 [46%]) and progressive disease (*n* = 4 [11%]).

In phase 1b, the overall median duration of BBP-398 exposure was 51 days (range, 6-336 days), with similar median durations of exposure at 350 mg and 450 mg. The most common reasons for treatment discontinuation were progressive disease (*n* = 23 [62%]), withdrawal of consent (*n* = 5 [14%]), physician decision (*n* = 5 [14%]), and AEs (n = 4 [11%]). The most common reasons for study termination were progressive disease (*n* = 10 [27%]), withdrawal from the study (*n* = 9 [24%]), death (*n* = 8 [22%]), and the study sponsor's decision to discontinue long-term follow-up (*n* = 5 [14%]).

Efficacy

In the dose-escalation phase, the best response was stable disease, which occurred in 6 of 23 evaluable participants (26%). The median progression-free survival duration was 1.8 months (95% CI, 1.4-1.8) across all dose levels. The median overall survival duration was 5.9 months (95% CI, 3.2-13.7) across all dose levels combined.

In the dose-expansion phase, the best response was stable disease in 8 of 27 evaluable participants (30%) overall (5 of 16 [31%] in the 350-mg group and 3 of 11 [27%] in the 450-mg group). The median progression-free survival duration was 2.2 months (95% CI 1.7-4.7) in the 350-mg group and 1.9 months (95% CI 1.4-5.3) in the 450-mg group. Also, the median overall survival duration was 5.7 months (95% CI 4-NR) in the 350-mg group and 5.3 months (95% CI 1.7-NR) in the 450-mg group. Efficacy results were generally comparable for the two dose groups. The efficacy findings for BBP-398 are summarized in Table 2.

Safety

The overall median duration of BBP-398 exposure in phase 1a was 30 days (range, 1-212 days), with a lower median duration at 550 mg (15.0 days) than at 400 mg (42.0 days) and 450 mg (33.5 days). We stopped dose escalation at 550 mg because we observed an increase in the rate and grade of thrombocytopenia (5 patients, 38.5% versus 2 patients, 20% at 450 mg) and edema (2 patients, 23% versus 1 patient, 10% at 450 mg) at this dose. The MTD of BBP-398 was not reached. The most common treatment-emergent AEs (TEAEs) occurring in at least 20% of the patients were diarrhea (34%), nausea (26%), peripheral edema (26%), decreased platelet count (23%), abdominal

pain (20%), and vomiting (20%). Fourteen patients (40%) experienced at least one grade 3 TEAE, the most common of which were pulmonary embolism (11%), decreased platelet count (9%), anemia (6%), increased AST level (6%), and peripheral edema (3%). BBP-398–related TEAEs occurred in 27 patients (77%); those occurring in more than 10% of patients overall were diarrhea (26%), nausea (26%), peripheral edema (20%), decreased platelet count (20%), vomiting (17%), increased weight (17%), and generalized edema (11%). Ten patients (29%) had a total of 13 serious TEAEs, none of which occurred in more than one patient. We observed one BBP-398–related serious TEAE, which was pulmonary embolism. One patient died of a TEAE unrelated to the study drug (COVID-19 pneumonia). Three patients (9%) had TEAEs leading to treatment discontinuation: temperature intolerance (related), peripheral edema (related), and intracranial hemorrhage (unrelated).

In phase 1b, the overall median duration of BBP-398 exposure was 51 days (range, 6-336 days) and was consistent in the two dose groups. The most common TEAEs were peripheral edema (43%), increased weight (27%), dyspnea (24%), abdominal distension (22%), and hypocalcemia (22%). Twenty-two patients (59%) had at least one grade 3 TEAE, the most common of which were hypokalemia (11%); pulmonary embolism (11%); anemia (8%); decreased platelet count (8%); acute kidney injury, sepsis, small intestinal obstruction, thrombocytopenia, and increased weight (5% each); and peripheral edema (3%). BBP-398–related TEAEs occurred in 29 patients overall (78%); those occurring in more than 10% of patients overall were peripheral edema (35%), increased weight (26%), and dermatitis acneiform, diarrhea, fatigue, hypocalcemia, hypomagnesemia, and rash (14% each). Sixteen patients (43%) had a total of 23 serious TEAEs; those occurring in more than one patient were pulmonary embolism (four patients) and acute kidney injury (two patients). BBP-398–related serious TEAEs were pulmonary embolism, anemia, and acute kidney injury. One patient died of a TEAE (respiratory failure) deemed unrelated to the study drug. Four patients (11%) had TEAEs leading to treatment discontinuation: ischemic stroke (not related), anemia (related), peripheral edema (related), and fluid retention (related). The TEAE numbers were generally similar for the 350-mg and 450-mg dose groups. However, we observed differences in the incidence of some events, such as increased weight (40% in the 350-mg group vs. 12% in 450-mg group), anemia (30% vs. 6%), hypomagnesemia (30% vs. 6%), pulmonary embolism (25% vs. 12%), ascites (25% vs. 6%), vomiting (15% vs. 35%), and diarrhea (10% vs. 29%).

Clinical laboratory tests demonstrated grade 3-4 thrombocytopenia (grade 3 in two patients, grade 4 in one patient), grade 3 anemia (two patients), and grade 3 decreased neutrophil count (one patient) in phase 1a. In phase 1b, we observed grade 3 anemia (four patients), thrombocytopenia (five patients), leukocytosis (one patient), and leukopenia (one patient). Furthermore, we observed grade 3 increased AST level (two patients) and increased bilirubin level (one patient) in phase 1a. Finally, we observed grade 3 hyponatremia (one patient) in phase 1a and grade 3 hypokalemia (four patients) and hyperkalemia (one patient) in phase 1b. Most alterations in laboratory parameters were not dose-dependent.

As an event of interest, breakdown from venous thromboembolism events is provided by subtype and grade. In Phase 1a, 5 patients (14.3%) experienced ≥1 VTE, including pulmonary embolism (PE; 5 patients, 14.3%; Grade 3 in 4 patients [11.4%]), deep vein thrombosis (DVT; 1 patient, 2.9%; Grade 3), and portal vein thrombosis (PVT; 1 patient, 2.9%; Grade 3). All VTEs in Phase 1a occurred in the higher-dose cohorts (400, 450, and 550 mg). In Phase 1b, 10 patients (27.0%) experienced ≥1 VTE, including PE (7 patients, 18.9%; Grade 3 in 4 patients [10.8%]), PVT (2 patients, 5.4%; both Grade 2), and DVT (1 patient, 2.7%; Grade 2). Overall VTE incidence was comparable between the two Phase 1b dose groups; however, PE was more frequent in the 350 mg cohort (5 patients, 30.0%) than in the 450 mg cohort (2 patients, 11.8%). Those events follow a reasonable temporal sequence from the time of study drug administration but could also be caused by other factors such as underlying concomitant diseases as active cancer itself, being therefore classified as potentially related to the study drug. The only finding of note regarding the patients' vital signs was increased body weight after the start of treatment, which was related to the occurrence of edema, a known class effect of SHP2 inhibitors. No electrocardiograms or echocardiograms indicated an effect of BBP-398 on cardiac function. The overall safety of BBP-398 is summarized in Table 3.

Pharmacokinetics

All patients in both phases of the study had plasma samples available for pharmacokinetic evaluations. We characterized the plasma BBP-398 profiles for individual patients following administration of a single oral dose (cycle 1 day 1 [C1D1]) and once-daily dosing (on C2D1) of 80-550 mg of BBP-398 under fasted conditions. On C1D1, we observed mean peak drug concentrations at median times ranging from 1.85 h to 3.88 h across the different BBP-398 doses. After repeat BBP-398 dosing, we observed mean peak drug concentrations at median times ranging from 1.07 h to 3.87 h on C2D1 across the different BBP-398 doses. BBP-398 concentrations were below the limit of quantitation for all C1D1 predose samples. Following single oral administration of 80-550 mg of BBP-398 (C1D1), mean exposure parameters (C_{max} and AUC0-τ) increased as the dose of BBP-398 increased. After once-daily oral administration of 80-450 mg of BBP-398 (C2D1), the C_{max} and AUC0-τ generally increased as the dose of BBP-398 increased under fasted conditions up to 350 mg. Although we tested 550 mg of BBP-398 given daily, no patients receiving this dose had evaluable pharmacokinetics on C2D1. Most patients (9 out of 10) receiving 550 mg BBP-398 attained plasma concentrations that were greater than 1 uM 24 hours post-dose on C1D1 and all evaluable patients attained trough concentrations on C1D8 that were at least 2-fold above 1 uM, the steady-state trough plasma concentration corresponding to at least 50% suppression of MAPK signaling and robust anti-tumor efficacy in nonclinical mouse models. We observed no more than twofold accumulation of BBP-398 after repeat dosing. Based on our comparison of evaluable mean predose concentrations of BBP-398, on average, steady-state appeared to be achieved by C1D8 following once-daily oral administration. Interpatient variability in the steady-state C_{max} and AUC0-τ of BBP-398 was generally low to moderate (<54%). Mean apparent terminal elimination half-life of BBP-398 ranged from 9.21 to 14.7 hours on C1D1 and 9.97 to 14.4 hours on C2D1 across the evaluable dose range of 80 to 450 mg QD BBP-398; however, these half-life values were almost half or greater than half of the sample collection interval and should be considered as estimates. The mean plasma concentrations of BBP-398 over time (semi-log scale) by dose group at C1D1 and C2D1 are summarized in Figure 2 and Figure 3, respectively.

Pharmacodynamics

Analysis was performed and reported in two parts: 1) with the gating strategy from the 8302 original panel including all monocytes population, and 2) including the viability marker 8302-mDL800 panel for monocytes selection. Overall, pharmacodynamic data were reported for 54 plasma samples analyzed with the 8302 original panel and for 456 samples analyzed with the 8302-mDL800 panel. Sixteen patients met the pharmacodynamic population definition of patients in the safety population with baseline and at least one post-treatment evaluable pharmacodynamic result. In these 16 patients, we found lower phosphorylated extra cellular signal-regulated kinase (pERK) expression at different time points after treatment with BBP-398 than at baseline (C1D1 predose) and other predose time points. Furthermore, at the C1D2 predose time point, the patients receiving at least 350 mg of BBP-398 tended to have lower pERK expression than at the C1D1 predose time point, suggesting that the reduction in pERK expression after initial treatment was better maintained in these patients than in those in the lower dose groups (80, 150, and 250 mg of BBP-398). At steady-state (C2D1) in the 350- and 450-mg dose groups, pERK expression levels decreased to 12.66% and 2.14% of baseline, respectively, by 4 h after treatment, indicating an average maximal pERK downregulation of greater than 85% at both doses. At the 450-mg dose, this level of pERK downregulation was maintained over the 24-h dosing interval. An overview of the pERK expression changes in all patients from the pharmacodynamic population from all dose levels at select time points is shown in Figure 4.

Discussion

In this study, treatment with oral BBP-398 at daily doses of up to 450 mg had an acceptable safety and tolerability profile among patients with advanced or metastatic solid tumors and MAPK pathway alterations. Of note, the MTD was not reached, as target engagement occurred at dose levels lower than predicted preclinically. Also, in this challenging scenario of heavily pretreated patients with limited standard treatment options, we found that nearly

30% of the patients had stable disease as the best response to treatment at all doses, with the remaining patients having progressive disease. This finding is slightly better than that of a previous first-in-human study evaluating the use of TNO155, a selective, allosteric, oral inhibitor of SHP2, in which stable disease was the best observed response in 20% of the patients [11]. A phase 1 trial evaluating daily dosing and intermittent dosing schedules with RMC-4630, another SHP2 inhibitor, demonstrated single-agent anticancer activity. Furthermore, preliminary efficacy results demonstrated that patients with non-small cell lung cancer harboring the KRAS G12C mutation, a much more selected population than that in our trial, had a disease control rate of 71%, with reductions in tumor volume reported in three patients (43%) [12].

Considering their limited activity in monotherapy for unselected tumor types, pairing SHP2 inhibitors with mutant-selective agents may be a more promising therapeutic strategy than monotherapy. In preclinical cellular models, BBP-398 produced robust inhibition of pERK, leading to decreased viability of multiple cell lines harboring activated MAPK pathway alterations, including those with epidermal growth factor receptor and KRAS G12C mutations. In vivo, BBP-398 has effectively attenuated RAS/ERK pathway activity in xenograft models of cancer driven by receptor tyrosine kinase or RAS alterations [13]. Also, researchers explored combinations of the SHP2 inhibitor TNO155 with epidermal growth factor receptor inhibitors, BRAF and MEK inhibitors, KRAS G12C inhibitors, and cyclin-dependent kinase 4 and 6 inhibitors in treatment of lung and colorectal cancer patient–derived xenografts, demonstrating preclinical benefit of this strategy in the xenograft models [14].

In the clinical scenario, researchers evaluated the SHP2 inhibitor PF-07284892 (ARRY-558) alone and in combination with different matched targeted therapies (lorlatinib for tumors with anaplastic lymphoma kinase/ROS proto-oncogene 1 fusions, encorafenib plus cetuximab for BRAF V600E–mutated colorectal cancers, and binimetinib for tumors harboring MAPK pathway mutations) in patients with oncogene-driven tumors. Using the RECIST v1.1 guidelines, they observed partial responses in three patients (two with lorlatinib and one with binimetinib), and stable disease in six patients [15]. In a different study, investigators evaluated the small-molecule inhibitor ERAS-601 administered as monotherapy and in combination with cetuximab in patients with advanced

or metastatic solid tumors. They observed a partial response in a patient with a BRAF class III mutation [16]. Of note, class III BRAF mutations exhibit functionally attenuated or absent kinase activity and therefore depend on receptor tyrosine kinase–driven RAS activation to sustain MAPK signaling. As a result, these variants are particularly vulnerable to SHP2 inhibition [17,18]. Unfortunately, phase 1 trials of BBP-398 in combination with sotorasib in patients with solid tumors and KRAS G12C mutations (NCT05480865) and in combination with osimertinib for patients with non-small cell lung cancer and epidermal growth factor receptor–sensitizing mutations (NCT06032936) were prematurely terminated for business reasons, with publication of data pending.

From the immune activation perspective, researchers showed that in the humanized mouse KYSE-450 esophageal cancer model, harboring an H179R mutation in the TP53 gene, the combination of BBP-398 with sintilimab (an anti-programmed cell death protein 1 antibody) or durvalumab (an anti-programmed death-ligand 1 antibody) had compelling synergistic antitumor activity that was better than the antitumor activity of the respective monotherapies. Also, a phase 1 clinical trial exploring the rationale for use of the combination of BBP-398 and nivolumab in patients with advanced non-small cell lung cancer and a KRAS mutation (NCT05375084) was terminated early in cohort 3 of escalation prior to expansion for business reasons, with safety and efficacy data yet to be published.

SHP2 mediates programmed cell death protein 1 signaling in T cells through numerous mechanisms, providing co-stimulatory signals for T-cell activation, which makes this a promising backdrop for examining potential combinations of SHP2 inhibitors and immune checkpoint inhibitors [19]. In vivo, experiments using colon cancer xenograft models demonstrated increased antitumor immunity and decreased tumor load with immunotherapy combined with SHP2 inhibition [20]. SHP2 is also a downstream regulator of colony-stimulating factor 1 receptor signaling, inducing macrophage proliferation and M2 macrophage polarization in the tumor microenvironment, suggesting another mechanism by which SHP2 inhibition enhances antitumor immunity [21]. Given these tumor-intrinsic and immune-mediated mechanisms of antitumor activity, SHP2 inhibitors also

represent a rational combination partner for immunotherapies such as treatment with immune checkpoint inhibitors.

Methods

Study design and patients

This was an open-label, sequential-cohort, nonrandomized, first-in-human phase 1 study. The study had two phases: dose escalation (phase 1a) and dose expansion (phase 1b; NCT04528836). The study was approved by the Institutional Review Board at the participants sites and carried out in accordance with the Declaration of Helsinki and local regulations regarding the conduct of clinical research. All patients provided written informed consent. The dose-escalation phase was conducted to determine the MTD and recommended dose for expansion of BBP-398. The dose-expansion phase was performed to evaluate the efficacy, safety, and tolerability of BBP-398 at two distinct doses as part of dose optimization. Eligible patients were at least 18 years of age, had advanced or metastatic solid tumors with MAPK pathway alterations (excluding known activating mutations of BRAF V600X, PTPN11 [SHP2], MEK, or RAS Q61X), and had no available standard-of-care or curative therapies. For the dose-expansion phase, patients were required to have an advanced or metastatic KRAS-mutant solid tumor, neurofibromatosis type 1 loss-of-function solid tumor, BRAF class II/III mutant solid tumor, or chordoma, with no available standard-of-care or curative therapies. All enrolled patients were required to have measurable disease according to the RECIST v1.1 guidelines, a stable ECOG PS of 0-1, and a life expectancy longer than 12 weeks. Patients were excluded if they previously received an SHP2 inhibitor (e.g., TNO155, RMC-4630, RLY-1971). In the dose-escalation phase, a Bayesian Optimal Interval (BOIN) design was used with planned BBP-398 doses of 80, 150, 250, 400, 550, and 700 mg given once daily. With exposures and target engagement exceeding what was preclinically predicted to translate into clinical efficacy, the 700-mg dose was not tested (dose escalation did not exceed 550 mg) even though the MTD was not identified, and an additional dose level of 450 mg was added. In the dose-expansion phase, the BBP-398 doses were 350 mg and 450 mg given once daily. Dosing was planned to

continue for 2 years unless the patient experienced disease progression and stopped taking BBP-398 or if the patient was withdrawn from the study.

Assessments

The primary objective of this phase 1 trial was to evaluate the safety, tolerability, and MTD of BBP-398 and establish its recommended phase 2 dose. AEs were coded using the Medical Dictionary for Regulatory Activities (v23.0). TEAEs were defined as 1) events with a start date on or after the start of the treatment period and up to at least 28 days after administration of the last dose during the study (end of the treatment period) or the date of the decision to permanently discontinue the study treatment or 2) events with a start date prior to treatment whose severity worsened on or after the start of treatment. The severity and intensity of the AEs were assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (v5.0). Secondary objectives were assessment of the preliminary antitumor activity of BBP-398 according to the objective response rate, duration of response, duration of progression-free survival, and pharmacokinetic and pharmacodynamic profiles of BBP-398. Tumor response was evaluated locally by the investigator according to RECIST v1.1. Assessments of response were performed at baseline and every 8 weeks after starting the study treatment until disease progression. Survival status was assessed at least every 3 months after discontinuation of the study treatment and for up to 3 years unless the patient was withdrawn from the study or until the end of the study, whichever occurred first.

Blood samples for pharmacokinetic evaluation were collected from all treated patients in the study, with intense sampling for the first dose and at steady state (C2D1). For pharmacodynamic evaluation, the pERK1/2 levels in monocytes from whole blood samples was used as a surrogate marker for SHP2's on-target activity. Sample stimulation and flow cytometry methods (standard operating procedures TP-SP-014 and TP-OTH-209, respectively) transferred from the study sponsor and qualified at CellCarta (Montreal, Quebec, Canada) under study code 8301. This testing was performed from November 30, 2020, to November 28, 2024. The pharmacodynamic population was defined as patients included in the safety population with a baseline and at least one posttreatment evaluable pharmacodynamic test result. Also, each patient in this population must have

received a stable daily dose of BBP-398 in the 7 days leading up to the C2D1 visit to have steady-state concentrations of the drug, allowing for assessment of full target engagement.

Statistical analysis

The planned sample size was 35 patients for dose escalation (phase 1a) and up to 40 patients for dose expansion (phase 1b), with up to 20 patients enrolled per dose level. The objective response rate was defined as the proportion of patients who had a best overall response of a confirmed complete response or partial response according to RECIST v1.1, with the rates presented along with their corresponding 95% CIs. The Kaplan-Meier method was used to estimate the duration of response, progression-free survival, and overall survival. These time-to-event variables are summarized using medians.

Data availability

Anonymized individual participant data on completed studies and applicable supporting clinical study documents are available upon request in a secured access environment. Requests for access to data can be submitted to the corresponding author. Access will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement.

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Competing interests

G.F. has received royalties from Wolters Kluwer; been an advisor for AbbVie, Jubilant, BostonGene, Teon, Merck, Sanofi, BridgeBio, and Beijing Avistone (2024); received a speaker honorarium from Clinical Care Options; received travel funds from Sarah Cannon Research Institute, Amgen, Synthorx/Sanofi, GSK, and Cyteir; and received research funding from Abbisko, ABL Bio, Abbvie, ADC Therapeutics, Accutar, Agenus, Aileron, Alterome, Amgen, Arcus, ARMO/Eli Lilly, Artios, Astellas, AstraZeneca, Bayer, BeiGene, Beijing Avistone, Bioatla, Bioinvent, Biomea Fusion, Bicycle, Black Diamond, Boehringer Ingelheim, Boundless, Centessa, Conjupro, Cyteir, Cytomx, D3 Bio, Daiichi, Deciphera, Dynamicure, Eikon, Eli Lilly, Epizyme, Erasca, Exelixis, Freenome, Fujifilm, GSK, Harbour BioMed, Hutchison MediPharma, IGM Biosciences, IDEAYA, Ikena, Immuneering, Immunitas, ImmunoGen/MacroGenics, Incyte, Jacobio, Jazz, Jounce, Jubilant, Kineta, Kumquat, Kura, Loxo/Bayer, Medilink, Merck, Metabomed, Mirati, ModeX, Molecular Templates, Nammi, Navire/BridgeBio, NGM Bio, NiKang, Novartis, Nuvalent, Nuvectis, Oncorus, Oncusp, OnKure, Phanes, Poseida, Prelude, PureTech, Pyramid, Pyxis, Quanta, RasCal, Regeneron, Relay, Rgenix, Ribon, Roche, Samumed, Sapience, Sarah Cannon Development Innovations, Seagen, Silicon/Stingthera, Simcha, Sirnaomics, Synthorx/Sanofi, Tachyon, Takeda, Tallac, Tango, Tarus, Tarveda, Teneobio, Tesaro, TORL, Turning Point, Xencor, and Zhuhai Yufan. D.V.V. has been employed by Navire Pharma. J.M. has been an advisor for Astra Zeneca, Janssen, Abbvie, Jazz, Sanofi, Bristol Myers Squibb, Takeda, and Daiichi Sankyo; been a consultant for Regeneron and Bristol Myers Squibb; been a Data Safety and Monitoring Committee member for Bioatla; and received research funding from NCI/ARPA-H and Astra Zeneca. S.S. has been a consultant and/or served on the speaker bureau for Eisai and BMS. A.R.K. has received grants and/or personal fees from Pfizer, AstraZeneca, Bristol Myers Squibb, EMD Serono, Exelixis, Genentech, Gilead Sciences, Immunomedics, Novartis, Seattle Genetics/Astellas, Amgen, Astellas Medivation, AVEO, Eisai, Genentech/Roche, Janssen, Merck, Myovant Sciences, Sanofi, Bayer, Arvinas, Mirati Therapeutics, and POINT Biopharma and has stock and other ownership interests in ECOM Medical. L.W. has been employed by Navire Pharma. F.R. has received consulting fees from Eikon Therapeutics. E.L. has received consulting fees from Navire Pharma for performing the data analyses and summaries for the present study, which may be considered a potential conflict of interest with

respect to the subject matter of this manuscript. A.I.S. has been a consultant or advisor for Incyte, Amgen, Novartis, Mirati Therapeutics, Jazz Pharmaceuticals, Takeda, Janssen Research & Development, Mersana, Gritstone bio, Daiichi Sankyo/AstraZeneca, Regeneron, Eli Lilly, Black Diamond Therapeutics, Sanofi, ArriVent Biopharma, Synthekine, GSK, Crispr Therapeutics, and Revolution Medicines and has received research funding from LAM Therapeutics, Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, Incyte, AbbVie, Ignyta, Takeda, Macrogenics, CytomX Therapeutics, Astex Pharmaceuticals, Bristol-Myers Squibb, Loxo, Gritstone bio, Plexxikon, Amgen, Daiichi Sankyo, ADC Therapeutics, Janssen Oncology, Rubius, Synthekine, Mersana, Blueprint Medicines, Regeneron, Alkermes, Revolution Medicines, Medikine, Black Diamond Therapeutics, BluPrint Oncology, Nalo Therapeutics, Scorpion Therapeutics, ArriVent Biopharma, Prelude Therapeutics, and Eli Lilly. D.S. has been an employee and shareholder of Texas Oncology, a shareholder of NEXT Oncology, received honoraria from Syneos, received consulting fees from Guidepoint, received advisory board payments from Revolution Medicines and Nimbus Therapeutics, and received ongoing or past institutional research funding for studies from Abbvie, Acrivon Therapeutics, ADC Therapeutics, Aprea Therapeutics, Ascentage Pharma Group, Astellas, Avenzo Therapeutics, Biomea Fusion, Boehringer Ingelheim, BJ Bioscience, BioNTech, Bristol Myers Squibb, Compugen, Day One Biopharma, Dicerna/Novo Nordisk, Dren Bio, Exelixis, Fate Therapeutics, Gilead Sciences, GSK, Haihe Pharmaceutical, Iconovir Bio, Ideaya Biosciences, Immuneering, Impact Therapeutics, Incendia, Kura Oncology, MediLink Therapeutics, Mirati Therapeutics, ModeX Therapeutics, Monopteros Therapeutics, Navire Pharma, Nimbus Therapeutics, NGM Biopharmaceuticals, OBI Pharma, OncoResponse, Pfizer, Revolution Medicines, Step Pharmaceuticals, Symphogen, Tachyon Therapeutics, Teon Therapeutics, Tyligand Bioscience, Vincerx Pharma, Vividion Therapeutics, ZielBio, and Zymeworks. I.G.-L. has been a consultant or advisor for SOTIO, AbbVie, Revolution Medicines, Eli Lilly, and Quanta Therapeutics and received research funding from EcoR1, Guidepoint, Novartis, Bayer, Bristol Myers Squibb, Pfizer, MedImmune, Eli Lilly, Incyte, GSK, Tolero Pharmaceuticals, BridgeBio Pharma, Jacobio, Repare Therapeutics, Sumitomo Dainippon Pharma Oncology, Revolution Medicines, Yingli Pharma, Quanta Therapeutics, 280 BIO, ABM Therapeutics, and

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Table 1 | Demographics and baseline characteristics of the study patients

	n (%)	
Characteristic	**Dose escalation: phase 1a (*n* = 35)**	**Dose expansion: phase 1b (*n* = 37)**
Median age, years **(range)**	63 (33-79)	60 (38-82)
Age group		
<65 years	20 (57)	21 (57)
≥65 to <75 years	10 (29)	14 (38)
≥75 years	5 (14)	2 (5)
Sex		
Female	20 (57)	21 (57)
Male	15 (43)	16 (43)
Race		
American Indian or Alaska Native	1 (3)	1 (3)
Asian	0	1 (3)
Black	3 (9)	3 (8)
Native Hawaiian or other Pacific Islander	1 (3)	0
White	26 (74)	30 (81)
Other	1 (3)	2 (5)
Unknown	3 (9)	0
Ethnicity		
Hispanic or Latino	7 (20)	6 (16)
Not Hispanic or Latino	25 (71)	30 (81)

Unknown	3 (9)	1 (3)
ECOG PS		
0	3 (9)	12 (32)
1	32 (91)	25 (68)
Most frequent tumor type		
	Colon 13 (37)	Pancreatic 10 (27)
	Lung 6 (17)	Colon 8 (22)
	Pancreatic and rectal 5 each (14)	Lung 6 (16)
Previous treatment lines		
<3	7 (20)	16 (43)
3	19 (54)	14 (38)
>3	9 (26)	7 (19)
Previous treatment drugs		
Chemotherapy	32 (91)	32 (86)
Targeted-therapy	23 (66)	16 (43)
MAPK pathway-target agent	6 (17)	0
Immunotherapy	12 (34)	11 (30)
Relevant Comorbidities		
Cardiac disorders	4 (11)	7 (19)
Hepatobiliary disorders	4 (11)	6 (16)

Table 2 | Summary of BBP-398 efficacy

Variable	Dose escalation: phase 1a (*n* = 35)	Dose expansion: phase 1b (*n* = 37)
Patients assessable for response, *n*	23	27
Response category, *n* (%)		
Complete response[a]	0	0
Partial response	0	0
Stable disease	6 (26)	8 (30)
Duration of stable disease, *median, mo*	*4 mo*	*4.6*
Tumor types with SD *(n)*	Ovarian (1), colorectal (3), GIST (1), NSCLC (1)	Pancreas (3), chordoma (4), cholangiocarcinoma (1)
Progressive disease	16 (70)	18 (67)
Unable to evaluate	0	0
Not assessed	1 (4)	1 (4)
Objective response rate[b]	0/23	0/27
95% CI (%)[c]	0-14.8	0-12.8

[a]Best overall response was defined as the best confirmed or unconfirmed response recorded during the study.

[b]Defined as the proportion of patients achieving a confirmed best response of complete or partial response.

[c]Ninety-five percent CIs were calculated using the Clopper-Pearson exact method.

Table 3 | Overall BBP-398 safety summary

	n (%)	
Variable	**Dose escalation: phase 1a (*n* = 35)**	**Dose expansion: phase 1b (*n* = 37)**
Median duration of BBP-398 exposure, days (range)	30 (1-212)	51 (6-336)
Patients with at least one TEAE	34 (97)	37 (100)
Number of TEAEs	268	414
Common TEAEs (≥10% of patients)		
Diarrhea	12 (34)	7 (19)
Nausea	9 (26)	6 (16)
Peripheral edema	9 (26)	16 (43)
Decreased platelet count	8 (23)	5 (14)
Abdominal pain	7 (20)	-
Vomiting	7 (20)	9 (24)
Abdominal distension	6 (17)	8 (22)
Dyspnea	6 (17)	9 (24)
Pyrexia	6 (17)	-
Increased weight	6 (17)	10 (27)
Increased ALT level	5 (14)	-
Increased AST level	5 (14)	6 (16)
Pulmonary embolism	5 (14)	7 (19)

Anemia	4 (11)	7 (19)
Constipation	4 (11)	5 (14)
Generalized edema	4 (11)	-
Hypokalemia	4 (11)	6 (16)
Pleural effusion	4 (11)	-
Hypocalcemia	-	8 (22)
Decreased appetite	-	7 (19)
Fatigue	-	7 (19)
Hypomagnesaemia	-	7 (19)
Rash	-	7 (19)
Ascites	-	6 (16)
Acneiform dermatitis	-	6 (16)
Increased blood creatine phosphokinase level	-	5 (14)
Fall	-	5 (14)
Dysgeusia	-	4 (11)
Hypoalbuminemia	-	4 (11)
Grade ≥3 TEAEs		
Pulmonary embolism	4 (11)	4 (11)
Decreased platelet count	3 (9)	3 (8)
Anemia	2 (6)	3 (8)
Increased A**ST level**	2 (6)	-
Peripheral edema	1 (3)	1 (3)
Hypokalemia	-	4 (11)
Acute kidney injury	-	2 (5)

Sepsis	-	2 (5)
Small intestinal obstruction	-	2 (5)
Thrombocytopenia	-	2 (5)
Increased weight	-	2 (5)
Grade 4 TEAEs		
Intracranial hemorrhage	1 (3)	-
Decreased platelet count	1 (3)	-
Acute kidney injury	-	1 (3)
Grade 5 TEAEs (leading to death)		
Respiratory failure[a]	-	1 (3)
COVID-19 pneumonia[b]	1 (3)	-
TEAEs leading to study drug discontinuation		
Temperature intolerance (grade 1)	1 (3)	
Peripheral edema (grade 3)	1 (3)	1 (3)
Intracranial hemorrhage[a] (grade 4)	1 (3)	
Ischemic stroke[a] (grade 3)		1 (3)
Anemia (grade 3)		1 (3)
Fluid retention (grade 3)		1 (3)

[a]Not related to treatment.

[b]One patient died due to an unrelated TEAE of COVID-19 pneumonia.

Figures title and legends

Figure 1. Study Consort diagram

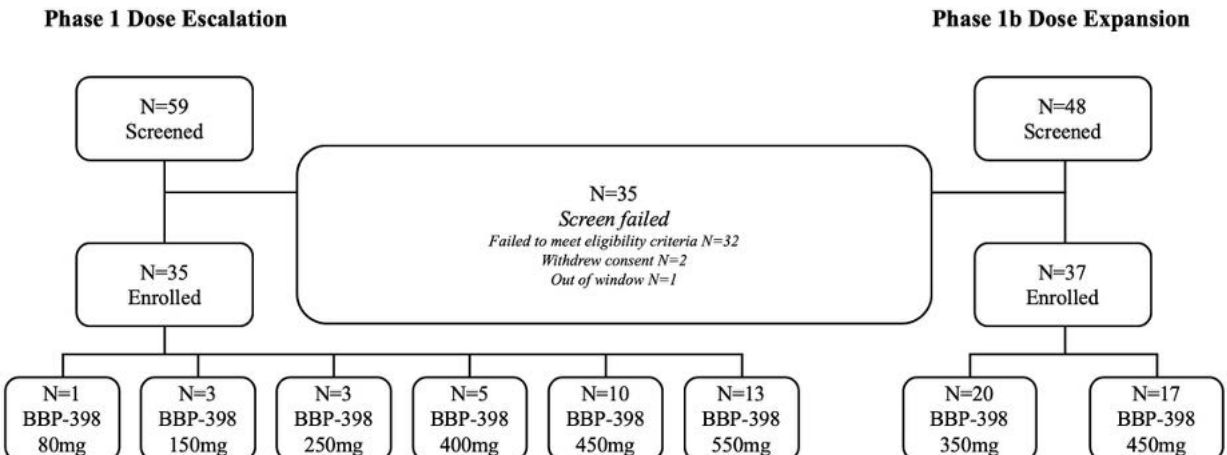
Figure 2. Plasma Concentration-Time Profiles (Mean±SD; Semi-log Scale) of BBP-398 by Dose Group at Cycle 1 Day 1 – Pharmacokinetic Population

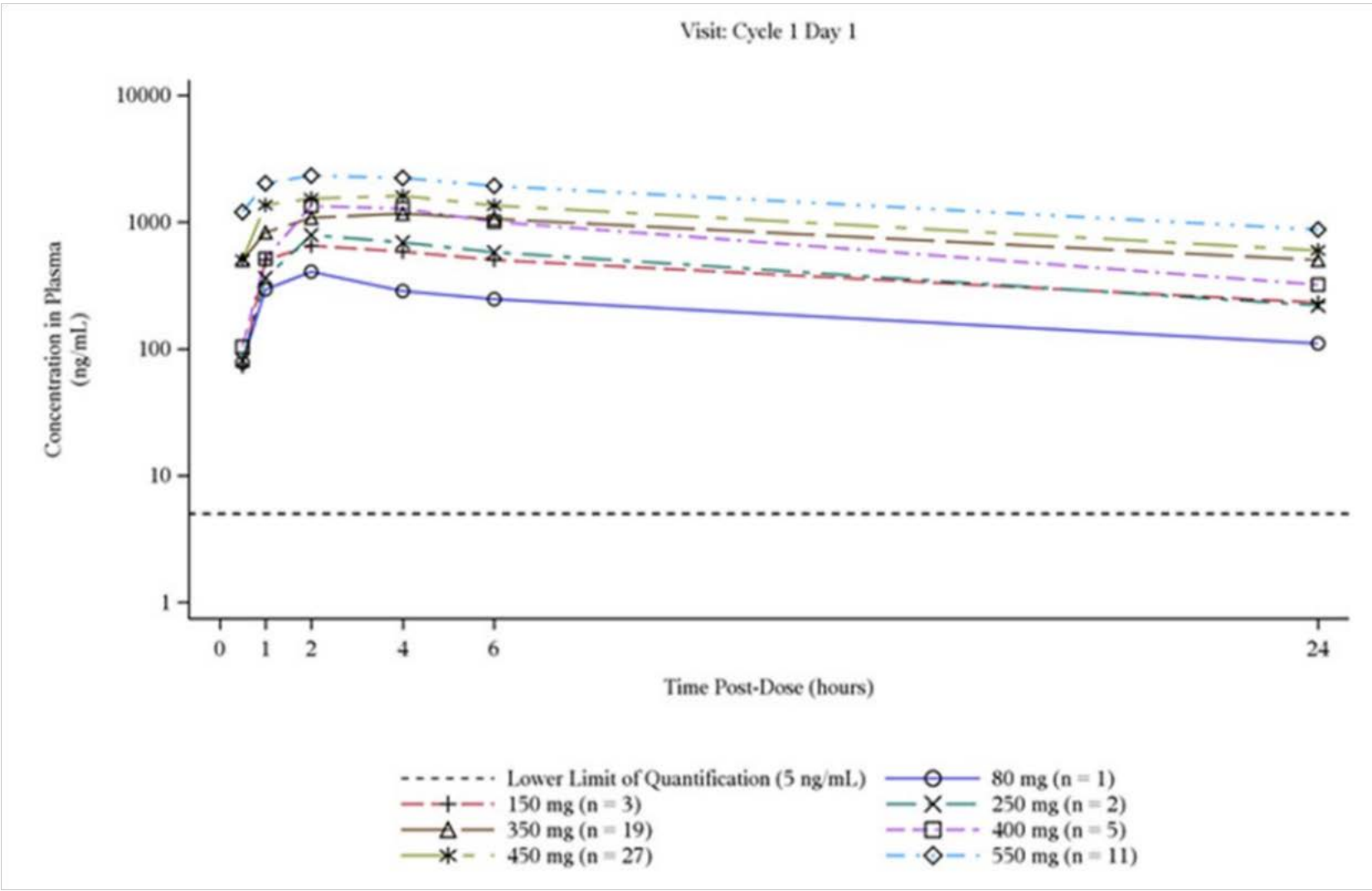
Figure 3. Plasma Concentration-Time Profiles (Mean±SD; Semi-log Scale) of BBP-398 by Dose Group at Cycle 2 Day 1 – Pharmacokinetic Population

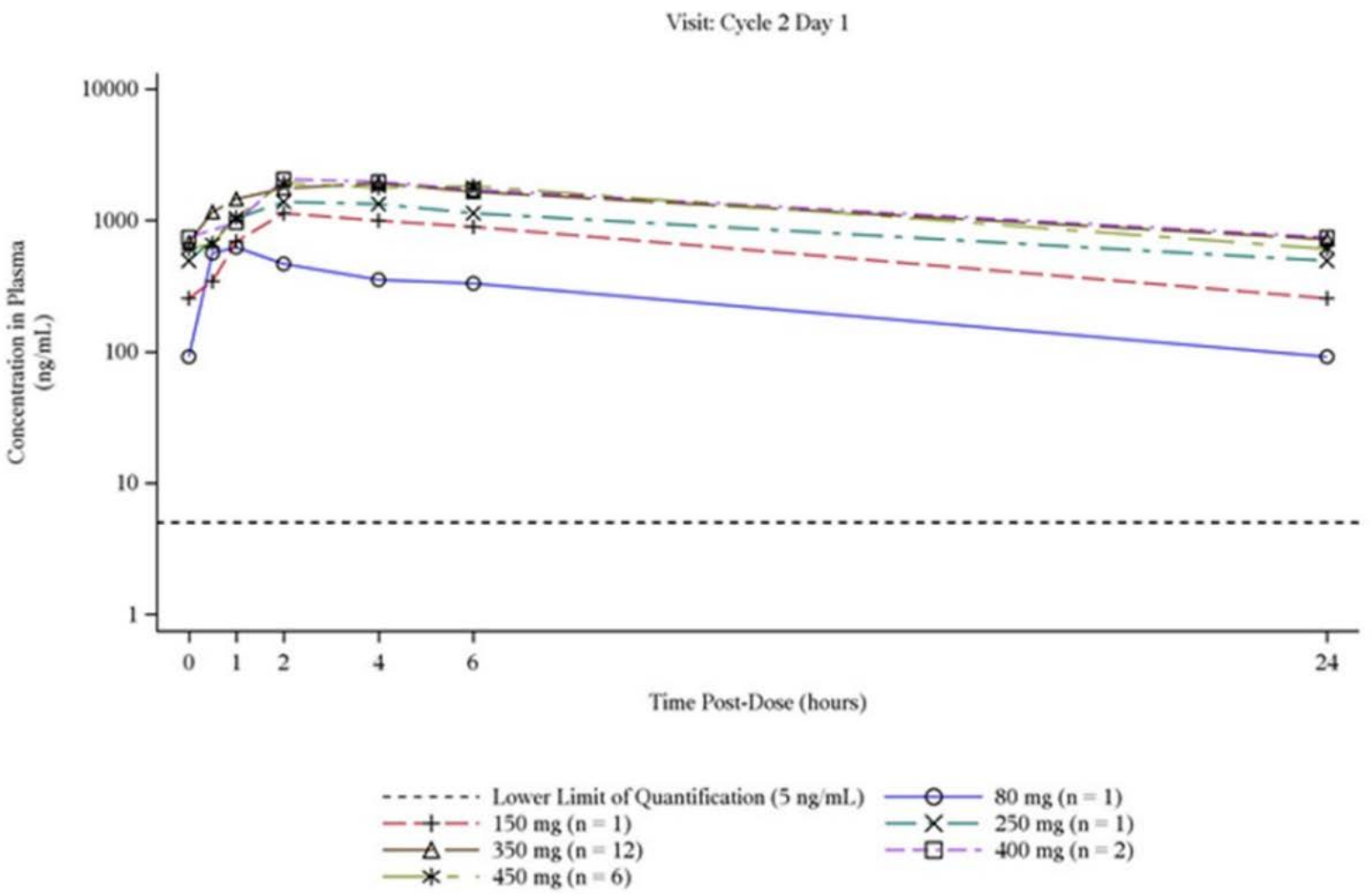
Figure 4. Overview of pERK Percent of Baseline (PD population Excluding Subjects with Dose Holds, Missing Doses and-or Dose Reductions).

Bars and error bars represent the average and standard deviation of pERK (% of Baseline) for all patients at the indicated timepoints for each group. The dotted line refers to 100% (or no decrease in pERK).

N, number; C, cycle; D, day; h, hours; pERK, phosphorylated extra cellular signal-regulated kinase.




Visit: Cycle 1 Day 1
Concentration in Plasma (ng/mL)
10000
1000
100
10
1
0
1
2
4
6
24
Time Post-Dose (hours)
Lower Limit of Quantification (5 ng/mL)
80 mg (n = 1)
150 mg (n = 3)
250 mg (n = 2)
350 mg (n = 19)
400 mg (n = 5)
450 mg (n = 27)
550 mg (n = 11)


Visit: Cycle 2 Day 1
Concentration in Plasma (ng/mL)
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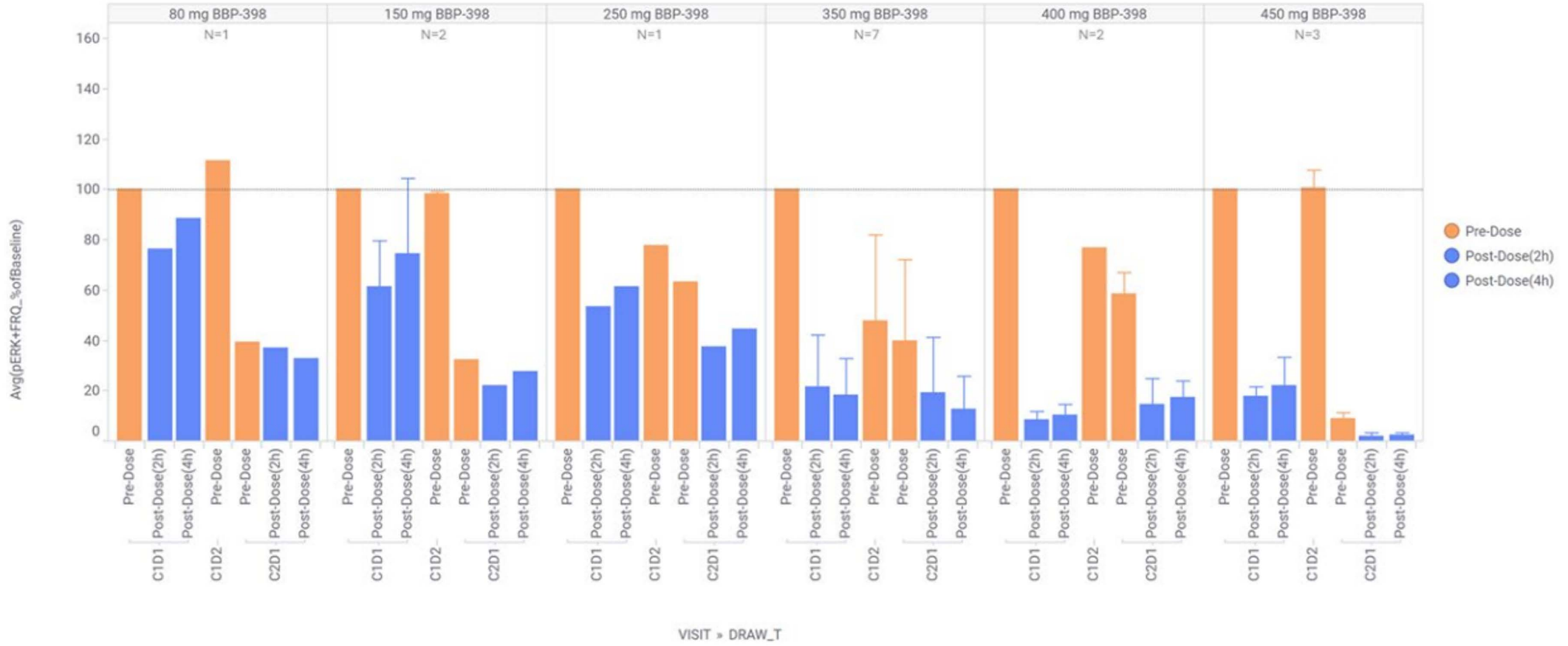
1000
100
10
1
0
1
2
4
6
24
Time Post-Dose (hours)
Lower Limit of Quantification (5 ng/mL)
150 mg (n = 1)
350 mg (n = 12)
450 mg (n = 6)
80 mg (n = 1)
250 mg (n = 1)
400 mg (n = 2)


80 mg BBP-398
N=1
150 mg BBP-398
N=2
250 mg BBP-398
N=1
350 mg BBP-398
N=7
400 mg BBP-398
N=2
450 mg BBP-398
N=3
Avg(pERK+FRQ_%ofBaseline)
160
140
120
100
80
60
40
20
0
Pre-Dose
Post-Dose(2h)
Post-Dose(4h)
C1D1
C1D2
C2D1
VISIT » DRAW_T