T-4

Trial-in-Progress: A Phase 2 Study of JZP3507 (ONC206) in Patients With Advanced Pheochromocytoma and Paraganglioma

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Objective

- To evaluate the efficacy and safety of JZP3507 (formerly ONC206) in patients with advanced pheochromocytoma and paraganglioma (PCPG) who have locally advanced or metastatic disease and have exhausted or declined available therapy

Study status

- As of October 13, 2026, 10 patients have been enrolled

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Presenting author's potential conflict of interest:
SCR is an employee of Jazz Pharmaceuticals.

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Introduction

- PCPG tumors are rare neuroendocrine tumors originating from chromaffin cells of the adrenal medulla and extra-adrenal paraganglia, respectively
- More than half of patients with PCPG have germline or somatic mutations in genes involved in cellular oxygen sensing and energy metabolism (eg, *SDHB*, *SDHD*, *VHL*, and *RET*, etc)[1–4]
- Despite the chronic and indolent nature of metastatic PCPG, approximately half of therapy-naïve, newly diagnosed patients experience disease progression within 1 year, and most require chronic, life-long antihypertensive medications to control the deleterious effects of excess catecholamine[5]
- Current treatment options for metastatic PCPG are limited and include surgical resection, radiofrequency ablation, radiotherapy, and systemic therapy regimens that may include vascular endothelial growth inhibitors[6–9]
- JZP3507, an oral, brain-penetrant, second-generation imipridone with nanomolar potency, acts as an agonist of mitochondrial caseinolytic protease proteolytic subunit (ClpP) and antagonist of dopamine receptor D2 (DRD2)[10–13]
  - JZP3507 is a potent derivative of dordaviprone, which was previously reported to induce responses in patients with PCPG (**Figure 1**)[14]

Figure 1. Best response by RECIST criteria in dordaviprone-treated patients with PCPG

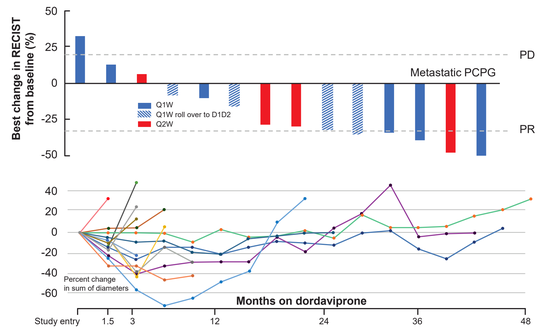
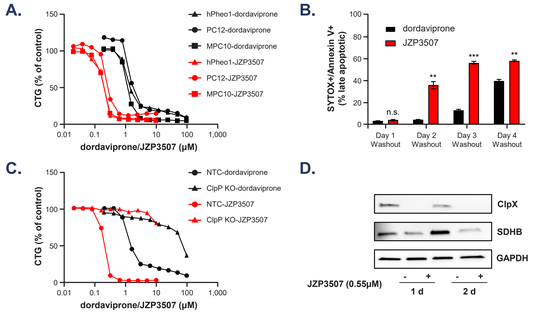


Figure reproduced from Anderson et al.[14]
D1D2, day 1 and day 2; PCPG, pheochromocytoma and paraganglioma; PD, progressive disease; PR, partial response; Q1W, once weekly; Q2W, twice weekly; RECIST, Response Evaluation Criteria in Solid Tumors.

- PCPG demonstrated the highest expression of DRD2 among all cancers
- In preclinical studies, JZP3507 has demonstrated broad-spectrum anticancer activity, including in PCPG. Adrenal gland tumors emerged as most sensitive when JZP3507 cytotoxicity was assessed in a panel of 432 human cancer cell lines. JZP3507 exposure for 48–72 h was needed to impair pheochromocytoma cell viability (**Figure 2**)[15–20]

Figure 2. JZP3507 impairs cell viability, downregulates mitochondrial proteins, and induces apoptosis in PC cell lines with nanomolar potency in a ClpP-dependent manner



A. Representative dose-response curves of dordaviprone and JZP3507 in human hPheo1, rat PC-12, and mouse MPC-10 PC cells. Cells were plated in 96-well plates with indicated concentrations and readout with CTG after 3 days treatment. PC-12 and MPC-10 cells were obtained from ATCC. hPheo1 cells were obtained from Evercyte GmbH. **B.** hPheo1 cells were treated with 0.55μM JZP3507 and 3μM dordaviprone for 1, 2, 3, and 4 days, and wells were replenished with fresh media (no drug). Apoptosis was measured with flow cytometry using SYTOX (cell death) and Annexin V (apoptosis) stains on day 7. Unpaired 2-sided *t* test, N = 3. ***P* <0.001, ****P* <0.0001. **C.** Representative dose-response curves of dordaviprone and JZP3507 in human hPheo1 cells with or without CRISPR-mediated ClpP knockout. Cells were plated in 96-well plates with indicated concentrations of JZP3507 and readout with CTG (measures cell ATP content) after 5 days of treatment. **D.** Western blot analysis in hPheo1 cells treated with JZP3507 for 1 and 2 days. GAPDH was used as a loading control.
ATP, adenosine triphosphate; ClpP, caseinolytic protease proteolytic subunit; ClpX, caseinolytic mitochondrial matrix peptidase chaperone subunit X; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CTG, CellTiter-Glo luminescent cell viability assay; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; KO, knockout; NTC, non-targeting control; n.s., not significant; PC, pheochromocytoma; SDHB, succinate dehydrogenase complex iron sulfur subunit B.

Table 1. JZP3507 PK parameters across clinical trials

Dose level; frequency	Weekly dose (mg)	C_{max} > IC_{50}	Weekly AUC > in vivo model	Time above IC_{50}
50 mg; QW	50	0.8×	0.2×	0 h
100 mg; QW	100	0.8×	0.2×	0 h
150 mg; QW	150	>3×	0.6×	3 h
200 mg; QW	200	>7×	1.5×	7 h
250 mg; QW	250	>7×	1.8×	5 h
350 mg; QW	350	>9×	2.4×	17 h
50 mg; BID/TIW	300	0.8×	0.9×	0 h
150 mg; QD/TIW	450	>4×	2.4×	19 h
100 mg; BID/TIW	600	>2×	3.2×	28 h
150 mg; BID/TIW	900	>4×	3.5×	43 h

AUC, area under the curve; BID, twice daily; C_{max}, maximum observed concentration; IC_{50}, half-maximal inhibitory concentration; PK, pharmacokinetic; QD, once daily; QW, once weekly; TIW, on 3 consecutive days a week.

- JZP3507 has oral bioavailability, achieving micromolar concentrations in the plasma, adrenal glands, brain, and various tissues. The starting dose for phase 2 trials was determined based on the lack of observed adverse events (AEs) across various species, with clinical safety and exposures consistent with preclinical therapeutic thresholds (**Table 1**, **Table 2**)
- Downstream effects of JZP3507 in tumor cells include disruption of mitochondrial function, degradation of mitochondrial enzymes commonly altered in PCPG, such as succinate dehydrogenase, and induction of apoptosis (**Figure 2, Figure 3**)[11,15,21,22]

Table 2. TRAEs occurring in >1 patient treated with JZP3507 across clinical trials

n (%)	50–350 mg QW (n = 20)	50 mg BID TIW (n = 1)	150 mg QD TIW (n = 3)	100 mg BID TIW (n = 3)	150 mg BID TIW (n = 3)	All dose levels (N = 30)
Patients with at least 1 TRAE	15 (75.0)	0	2 (66.7)	0	2 (66.7)	19 (63.3)
Fatigue	8 (40.0)	0	2 (66.7)	0	0	10 (33.3)
Headache	3 (15.0)	0	0	0	1 (33.3)	4 (13.3)
Vomiting	4 (20.0)	0	0	0	0	4 (13.3)
Diarrhea	3 (15.0)	0	0	0	0	3 (10.0)
Dizziness	2 (10.0)	0	0	0	1 (33.3)	3 (10.0)
Hematuria	3 (15.0)	0	0	0	0	3 (10.0)
Lymphocyte count decreased	2 (10.0)	0	0	0	1 (33.3)	3 (10.0)
Nausea	2 (10.0)	0	0	0	1 (33.3)	3 (10.0)
ALT increased	1 (5.0)	0	0	0	1 (33.3)	2 (6.7)
AST increased	1 (5.0)	0	0	0	1 (33.3)	2 (6.7)
Decreased appetite	1 (5.0)	0	0	0	1 (33.3)	2 (6.7)

All TRAEs listed above were Grade 1 or 2 in severity. Some patients were enrolled on other dose levels and were not summarized in the table above.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; QD, once daily; QW, once weekly; TIW, on 3 consecutive days a week; TRAE, treatment-related AE.

Figure 3. Proposed JZP3507 mechanism of action

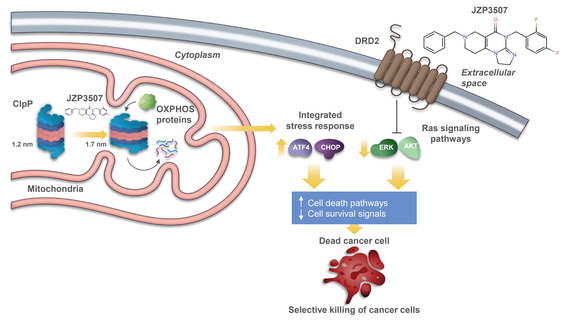
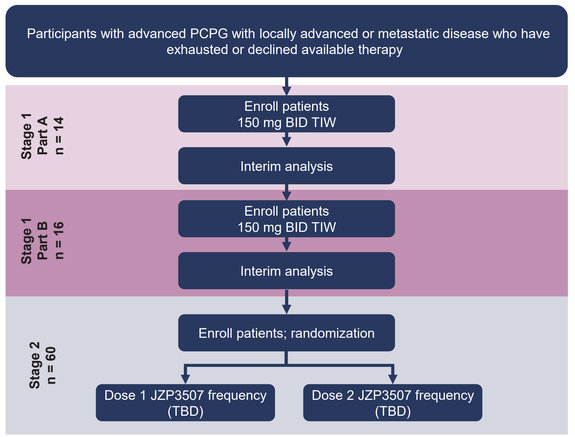


Figure modified from Anderson et al.[14]
AKT, protein kinase B; ATF4, activating transcription 4; CHOP, C/EBP homologous protein; ClpP, caseinolytic protease proteolytic subunit P; DRD2, dopamine receptor 2; ERK, extracellular signal-regulated kinase; OXPHOS, oxidative phosphorylation.

Methods

- This trial is an open-label, multicenter, 2-stage, phase 2 clinical study (NCT07282587) evaluating the efficacy and safety of JZP3507 in patients with advanced PCPG who have locally advanced or metastatic disease and have exhausted or declined available therapy (**Table 3**)
- Each study stage will evaluate JZP3507 at monotherapy doses that have previously been evaluated in phase 1 trials (**Figure 4**)
- JZP3507 will be administered orally in 28-day cycles until patients meet criteria for treatment discontinuation. Each patient's duration of treatment will depend on their individual response, evidence of disease progression, and tolerability
  - JZP3507 will be orally administered twice daily, in the morning and evening, on 3 consecutive days per week

Figure 4. Study schema



BID, twice daily; PCPG, pheochromocytoma and paraganglioma; TBD, to be determined; TIW, on 3 consecutive days a week.

- JZP3507 dosage may be adjusted due to occurrence of treatment-related AEs. Patients who discontinue study treatment should continue study-related follow-up
- All patients will be followed for survival for up to 3 years or to withdrawal of consent
- Sample size determination
  - Stage 1: Under the Simon's 2-stage minimax design criterion, a sample size of 14 patients in part A and 16 patients in part B is required to test a null hypothesis of H_0: π ≤0.1 vs an alternative hypothesis of H_1: π ≥0.3 with a one-sided significance level of 0.025 and >82.5% power, where π is the true proportion of successes
  - Stage 2: A sample size of 30 patients randomized to each dose is required to test a null hypothesis of H_0: π ≤0.1 vs an alternative hypothesis of H_1: π ≥0.3 with a one-sided significance level of 0.025 and >81.2% power, where π is the true proportion of successes. No adjustment will be made for multiple comparisons
- The primary endpoint (overall response rate by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) will be summarized as a proportion with corresponding 95% exact CIs (**Table 4**). Nominal exact 2-sided *P*-values will be presented, testing JZP3507 against a fixed 10% historical/null response rate in stage 1 and testing each JZP3507 dose group independently against a fixed 10% in stage 2. No multiplicity adjustment is planned
- Time-to-event analyses will use Kaplan-Meier methods/plots. Median failure times, Kaplan-Meier estimates every 90 days, and corresponding 95% CIs will be presented

Table 3. Select eligibility criteria

Inclusion criteria	Exclusion criteria
• Provided written informed consent • Aged ≥18 years • Unresectable, histologically confirmed PCPG • Failed, is not a candidate for, or has declined standard-of-care treatment for PCPG • Measurable disease per RECIST v1.1 (investigator-assessed) • Adequately controlled blood pressure (≤150/90 mm Hg); no change in antihypertensive medications for ≥14 days before first JZP3507 dose • Eastern Cooperative Oncology Group Performance Status of 0 to 2 • Adequate organ function • Expected survival of ≥12 weeks • Has pharmacologic control of catecholamine-associated symptoms • If available, ≥15 unstained formalin-fixed paraffin-embedded slides from tumor tissue	• Known JZP3507 hypersensitivity • Active cardiac disease/condition including — Corrected QT interval >480 ms — Documented congestive heart failure (New York Heart Association function classification III–IV) — Unstable angina, acute myocardial infarction, or arterial bypass or percutaneous transluminal coronary angioplasty within 6 months before the first JZP3507 dose • Prior JZP3507 or dordaviprone exposure • Known additional malignancy that is progressing or has required active treatment within the past 2 years. Exceptions include — Basal cell carcinoma of the skin — Squamous cell carcinoma of the skin that has undergone potentially curative therapy — In situ cervical cancer — Von Hippel-Lindau disease–associated tumors not requiring immediate surgery or intervention • Has received — Any prior anticancer medication within 4 weeks/5 half-lives (denosumab and zoledronic acid are permissible) — Any treatment with somatostatin analog or lanreotide within 21 days of baseline positron emission tomography scan — Strong cytochrome P450 inhibitors or inducers within 14 days — Radiotherapy within 14 days — Major surgery, biopsy, or trauma within 30 days

PCPG, pheochromocytoma and paraganglioma; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 4. Objectives and endpoints

Objectives	Endpoints
Primary	
• Evaluate antitumor activity of JZP3507	• Overall response rate by RECIST v1.1
Secondary	
• Evaluate the effect of JZP3507 on PCPG growth and symptoms	• Duration of response • Time to response • Disease control rate • Progression-free survival • Overall survival (up to 3 years) • Change from baseline in antihypertensive medication dose • Change from baseline in biochemical response (metanephrines/disease markers)
• Assess the safety and tolerability of JZP3507	• Incidence of AEs • Change from baseline in clinical laboratory parameters or ECG parameters • Distribution of graded clinical laboratory parameters
• Assess plasma concentrations and estimate PK parameters for JZP3507	• Plasma concentrations of JZP3507 • PK parameters for JZP3507
• Evaluate impact of JZP3507 on health-related QoL	• Change from baseline in EORTC-QLQ-C30 and FACT-BP

AE, adverse events; ECG, electrocardiogram; EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; FACT-BP, Functional Assessment of Cancer Therapy–Bone Pain; PCPG, pheochromocytoma and paraganglioma; PK, pharmacokinetic; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.

- Interim futility analyses
  - The first futility interim analyses will be completed after 14 patients in stage 1, part A have been treated and followed for response and confirmation. If ≤1 patient experiences a confirmed response, the study will be stopped for futility
  - The second interim analysis will be conducted after 16 patients in stage 1, part B are treated and followed for response and confirmation. To meet the prespecified efficacy criterion, ≥7 confirmed responses among 30 patients will be required
- As of October 13, 2026, 10 patients have been enrolled across 8 study sites (**Figure 5**)

Figure 5. Study site locations

