Jazz Pharmaceuticals Pipeline

Our patient-centric approach to R&D begins with difficult-to-treat, unmet patient needs. We harness the collective talents and expertise of our researchers and partners in order to identify scientific breakthroughs with the potential to result in life-changing medicines that redefine possibilities for patients and their families. Stemming from our robust research and development efforts, we have been able to identify and develop durable, differentiated commercial assets across two therapeutic focus areas – neuroscience and oncology – with significant market opportunities.

This document includes information about investigational products, or investigational indications for products that may have marketing authorizations for other indications in the European Union (EU) or other countries throughout the world. Safety and efficacy may not have been established, and there is no guarantee that pipeline products or investigational uses will receive approval from health authorities. Likewise, any forward-looking statements such as our ability to identify scientific breakthroughs with the potential to result in life-changing medicines are subject to risks and uncertainties, which include, without limitation, risks and uncertainties associated with pharmaceutical product development, and other risks and uncertainties affecting Jazz Pharmaceuticals and its development programs, described in Jazz's periodic reports on file with the Securities and Exchange Commission.

Oncology

PROGRAM	POTENTIAL INDICATION(S)	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	PHASE 4/ REGULATORY
Zanidatamab + SOC chemo ± tislelizumab (1L)	GEA					
Zanidatamab + SOC chemo ± PD-1/L-1 (1L)	BTC					
Zanidatamab + chemo	Previously T-DXd treated mBC					
Zanidatamab + SOC chemo (1L)	BTC, GEA, CRC					
Zanidatamab + fulvestrant + palbociclib (3L)	Previously treated HER2+/HR+ mBC					
Zanidatamab + evorpacept (ALX148 – CD47 blocker) (3L)	Breast cancer					
I-SPY 2 Zanidatamab + SOC	Breast cancer					
Zanidatamab + paclitaxel and ramucirumab	Advanced GEA					
Zanidatamab	Previously treated solid tumors (pan-tumor)					
	Neoadjuvant and adjuvant breast cancer					
	Early-stage breast cancer					
Zanidatamab + chemo (3L)	Advanced cancers					
PRE-I-SPY Zanidatamab + tucatinib	Breast cancer					

Oncology

PROGRAM	POTENTIAL INDICATION(S)	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	PHASE 4/ REGULATORY

Overview: Zanidatamab, or Ziihera® (zanidatamab-hrii) in the United States and the EU, is a bispecific HER2-directed antibody that binds to two extracellular sites on HER2. Zanidatamab has been granted two Fast Track designations by the U.S. Food and Drug Administration (FDA): one as a single agent for refractory biliary tract cancers (BTC) and one in combination with standard-of-care (SOC) chemotherapy for first-line gastroesophageal adenocarcinoma (1L GEA). Zanidatamab has also received Orphan Drug designations from the FDA for the treatment of biliary tract and gastric cancers, as well as Orphan Drug designation from the European Medicines Agency for the treatment of gastric cancer and BTC.

Clinical Trials: Currently, the Phase 3 HERIZON-GEA-01 trial evaluates zanidatamab in combination with chemotherapy and with or without the checkpoint inhibitor tislelizumab as a first-line treatment for metastatic HER2-positive (HER2+) GEA. Read more about the pivotal trial (NCT05152147) **here**.

The Phase 3 HERIZON-BTC-302 trial evaluates zanidatamab and CisGem (cisplatin plus gemcitabine) with or without the addition of a programmed death protein 1/ligand 1 (PD-1/L-1) inhibitor versus CisGem with or without a PD-1/L1 inhibitor in adult participants. Learn more (NCT06282575) **here**.

The Phase 3 EmpowHER trial evaluates zanidatamab compared to trastuzumab, each in combination with physician's choice of chemotherapy, for the treatment of participants with metastatic HER2-positive breast cancer who have progressed on, or are intolerant to, previous T-DXd treatment. Learn more (NCT06435429) **here**.

Additionally, Phase 2 trials are investigating zanidatamab both as a monotherapy and in combination with chemotherapy and/or other agents in BTC, GEA, breast cancer, colorectal cancer (CRC) and HER2-expressing cancers:

- The DiscovHER-Pan-206 trial evaluating zanidatamab monotherapy in previously-treated patients with HER2+ (IHC 3+) cancers including breast, gastric, esophageal, gastroesophageal, colorectal, endometrial, non-small cell lung, ovarian, urothelial, salivary and pancreatic. Learn more (NCT06695845) **here**.
- The Phase 2 EmpowHER-BC-208 trial to evaluate zanidatamab in patients with HER2-positive neoadjuvant and adjuvant breast cancer. Learn more (NCT07102381) **here**.
- Zanidatamab in addition to SOC chemotherapy is being evaluated in Phase 2 trial for BTC, GEA and CRC. Learn more (NCT03929666) **here**.
- Phase 2a study investigating the safety, tolerability and anti-tumor activity of zanidatamab in combination with fulvestrant and palbociclib in patients with locally advanced and/or metastatic HER2+/hormone receptor-positive breast cancer. Learn more (NCT04224272) **here**.
- Phase 2 trial evaluating the safety and tolerability of zanidatamab with evorpacept (ALX148) in patients with advanced HER2-expressing cancer. Learn more (NCT05027139) **here**.
- Phase 2 investigation of serial studies to predict the therapeutic response with imaging and molecular analysis 2 (I-SPY 2) trial assessing the efficacy of novel drugs in sequence with standard chemotherapy to advance approaches to personalized medicine. This trial is conducted in collaboration with QuantumLeap Healthcare Collaborative. Learn more about I-SPY 2 (NCT01042379) **here**.
- In collaboration with the Canadian Cancer Trials Group, the efficacy of zanidatamab in combination with usual care, paclitaxel and ramucirumab, is being evaluated in Phase 2 trial in HER2+ advanced GEA. Learn more (NCT06043427) **here**.
- Phase 2 single-arm open-label pilot trial evaluating zanidatamab in patients with early-stage, low-risk, HER2-positive breast cancer. This study is being completed as part of the collaboration with the MD Anderson Cancer Center. Learn more (NCT05035836) **here**.

Zanidatamab is also being investigated in Phase 1 studies, including the I-SPY Phase 1/1b platform trial with multiple ongoing drug regiment arms, evaluating single agents or combinations for breast cancer patients. Promising treatment regiments are to be transferred into the I-SPY 2 SMART Design Trial (NCT01042379). Learn more about Pre-I-SPY/I-SPY-P1 (NCT05868226) **here**.

Lurbinectedin	2L SCLC	
	Relapsed SCLC	
Lurbinectedin + atezolizumab (1L)	SCLC	

Overview: Lurbinectedin, or Zepzelca® in the United States and Canada, is an alkylating drug that binds guanine residues within DNA, which triggers a cascade of events that can affect the activity of DNA binding proteins, including some transcription factors, and DNA repair pathways, resulting in disruption of the cell cycle and eventual cell death.

Clinical Trials: In addition to being approved for small cell lung cancer (SCLC), the effectiveness of lurbinectedin is being evaluated in adult patients with extensive-stage SCLC (ES-SCLC). The Phase 4 prospective, multi-center observational study aims to collect safety and outcome data of lurbinectedin in adult participants with ES-SCLC previously exposed to at least one line of chemotherapy. Learn more about the study (NCT04894591) **here**.

Currently, lurbinectedin is also being evaluated in combination with other agents for the following:

- Phase 3 trial evaluating and comparing the activity and safety of lurbinectedin as a single agent and in combination with irinotecan in SCLC patients. This trial is being conducted by PharmaMar as part of Jazz Pharmaceuticals' **partnership** with the company. Learn more about the study (NCT05153239) **here**.
- Phase 3 trial evaluating lurbinectedin in combination with the PD-L1 inhibitor, atezolizumab, as a first-line maintenance treatment for patients with ES-SCLC. The trial will measure the progression-free survival and overall survival benefits of lurbinectedin and atezolizumab administered in combination compared to atezolizumab alone. The trial is conducted in collaboration with F. Hoffmann-La Roche Ltd. Learn more about the IMforte Phase 3 trial (NCT05091567) **here**.

Dordaviprone (ONC201)	Newly diagnosed H3 K27M-mutant diffuse glioma	
	Multiple indications/ combinations	

Overview: Dordaviprone, or Modeyso™ in the United States, (formerly known as ONC201) is a protease activator of the mitochondrial caseinolytic protease P (ClpP) and also inhibits dopamine D2 receptor (DRD2). In vitro, dordaviprone activates the integrated stress response, induces apoptosis, and alters mitochondrial metabolism, leading to restored histone H3 K27 trimethylation in H3 K27M-mutant diffuse glioma.

Clinical trials: Currently, the Phase 3 ACTION confirmatory trial is evaluating the safety and clinical benefit of Modeyso in newly diagnosed patients with H3 K27M-mutant diffuse glioma following radiotherapy. Learn more (NCT05580562) **here**.

Oncology

PROGRAM	POTENTIAL INDICATION(S)	PRE-CLINICAL / PHASE 1 / PHASE 2 / PHASE 3 / PHASE 4/ REGULATORY
JZP351	Newly diagnosed adults with standard- and HR-AML (AMLSG)	
	AML or HR-MDS >60yrs (AML18)	
	Newly diagnosed older adults with HR-AML	
	HR- MDS (EMSCO)	
	Low-intensity dosing for higher risk MDS	
JZP351 + other approved therapies	R/R AML or HMA Failure MDS	
	de novo or R/R AML	

Overview: JZP351, or Vyxeos®/Vyxeos Liposomal in approved markets, is a liposomal combination of daunorubicin, an anthracycline topoisomerase inhibitor, and cytarabine, a nucleoside metabolic inhibitor.

Clinical Trials: Jazz Pharmaceuticals is collaborating with the University of Texas MD Anderson Cancer Center on one Phase 1 and two Phase 2 trials investigating JZP351 on its own and in parallel with other approved therapies, respectively, for potential indications in higher-risk myelodysplastic syndromes (MDS), relapsing/refractory acute myeloid leukemia (R/R AML) or hypomethylating agents (HMA) failure MDS.

Additional Phase 2 and Phase 3 trials of JZP351 are evaluating the agent in various age populations and are being conducted with cooperative groups such as the AML Study Group (AMLSG) and the European Myelodysplastic Neoplasms Cooperative Group (EMSCO).

JZP815	Solid tumors and hematologic malignancies	

Overview: An investigational pan-RAF inhibitor for the treatment of solid tumors and hematologic malignancies that contain mutations in the mitogen-activated protein kinase (MAPK) pathway. JZP815 targets specific components of the MAPK pathway that, when activated by oncogenic mutations, can be a frequent driver of human cancer. JZP815 potentially inhibits both monomer- and dimer-driven RAF signaling (e.g., RAS-induced), prevents paradoxical pathway activation induced by BRAF selective inhabitation and is active against class 1, class 2 and class 3 BRAF mutants as well as BRAF fusions and CRAF mutants.

Clinical Trials: Learn more about the Phase 1, open-label, first-in-human study (NCT05557045) **here**.

JZP898	Solid tumors	

Overview: Investigational JZP898, previously WTX-613, is a conditionally activated IFNα2b cytokine pro-drug.

Clinical Trials: The safety, tolerability, pharmacokinetics, immunogenicity and preliminary antitumor activity of JZP898 both as a monotherapy and in combination with pembrolizumab is being investigated in Phase 1, first-in-human study. Read more about the study (NCT06108050) **here**.

JZP3507 (ONC206)	Central nervous system tumors	
	Non-central nervous system tumors	

Overview: JZP3507 (formerly ONC206) is a dual targeted investigational therapy that is an agonist of the mitochondrial protease ClpP and an antagonist of the G protein-coupled receptor DRD2.

KRAS Inhibitor	Solid tumors	

Overview: KRAS (Kirsten rat sarcoma virus) inhibitor program, including G12D selective and pan-KRAS molecules, acquired from Redx Pharma.

JZP3508 (ONC212)	IND-enabling studies	

Overview: JZP3508 (formerly ONC212) is a dual agonist of the mitochondrial protease ClpP and the G protein-coupled receptor GPR132.

Oncology

PROGRAM	POTENTIAL INDICATION(S)	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	PHASE 4/ REGULATORY
CombiPlex	N/A					

Overview: Evaluating patented CombiPlex® platform in a wide range of tumor types. Evaluating improvement in cancer therapy by using extremely small (nano-scale) carriers to deliver optimal ratios of multiple anticancer agents directly to cancer cells over a prolonged period of time.

Undisclosed Targets	N/A					

Neuroscience

PROGRAM	POTENTIAL INDICATION(S)	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	PHASE 4/ REGULATORY
Cannabidiol	Seizures associated with LGS, DS, TSC in Japan					

Overview: Epidiolex® (cannabidiol), known as Epidyolex® in the EU, United Kingdom (U.K.), Australia and Israel, is a prescription, plant-derived cannabis-based medicine administered as an oral solution. In the United States, Epidiolex is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older. In the EU and U.K., Epidyolex is indicated for use as adjunctive therapy of seizures associated with LGS or DS, in conjunction with clobazam, for patients 2 years of age and older. Epidyolex is also indicated for use as adjunctive therapy of seizures associated with TSC for patients 2 years of age and older.

Clinical Trials: Jazz's GW Pharmaceuticals initiated clinical trials of Epidyolex in Japan in October 2022. The study tests the efficacy and safety of the drug in patients with LGS, DS and TSC.

JZP441	Narcolepsy					

Overview: JZP441, previously referred to as DSP-0187, is a potent and highly selective oral orexin-2 receptor agonist with potential applications for the treatment of narcolepsy, idiopathic hypersomnia and other sleep disorders.

Clinical Trials: The safety, tolerability, pharmacokinetics and pharmacodynamics of JZP441 are being investigated in narcolepsy Type 1 patients.

JZP324	Narcolepsy					

Overview: Planned. Extended-release oxybate formulation.

SAN2355	Epilepsy					
Undisclosed Targets	Sleep					
	Epilepsy					
	Other neuroscience					

LGS = Lennox-Gastaut syndrome, **DS** = Dravet syndrome, **TSC** = Tuberous sclerosis complex, PTSD = post-traumatic stress disorder, **SOC** = standard-of-care, **1L** = first line, **GEA** = gastroesophageal adenocarcinoma, **2L** = second line, **BTC** = biliary tract cancer, **CRC** = colorectal cancer, **3L** = third line, **mBC** = metastatic breast cancer, **SCLC** = small cell lung cancer, **AML** = acute myeloid leukemia, **HR** = high-risk, **MDS** = myelodysplastic syndromes, **AMLSG** = acute myeloid leukemia study group, **EMSCO** = European Myelodysplastic Neoplasms Cooperative Group, **R/R** = relapsing/refractory, **HMA** = hypomethylating agents.