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 (2L)	BTC					
Zanidatamab + SOC chemo ± tislelizumab (1L)	GEA					
Zanidatamab + SOC chemo ± PD-1/L-1 (1L)	BTC					
Zanidatamab + chemo	Previously T-DXd treated HER2+ breast cancer					
Zanidatamab + SOC chemo (1L)	BTC, GEA, CRC					
Zanidatamab + fulvestrant + palbociclib (3L)	Previously treated HER2+/HR+ breast cancer					
Zanidatamab + evorpacept (ALX148 – CD47 blocker) (3L)	HER2-expressing breast cancer					
I-SPY 2 Zanidatamab + SOC	Breast cancer					
Zanidatamab + paclitaxel and ramucirumab	HER2+ advanced GEA					
Zanidatamab	Previously treated HER2+ solid tumors (pan-tumor)					
	Early-stage HER2/Neu+ breast cancer					
	HER2-expressing solid tumors in Japan					
	Advanced HER2-expressing cancers					
Zanidatamab + chemo (3L)	Advanced HER2-expressing cancers					

Oncology

PROGRAM	POTENTIAL INDICATION(S)	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	PHASE 4/ REGULATORY
PRE-I-SPY Zanidatamab + tucatinib	Breast cancer					

Overview: Zanidatamab is an investigational HER2-targeted bispecific antibody that can simultaneously bind two non-overlapping epitopes of 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. Read more about the trial (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. Read more about the trial (NCT06435429) **here**.

Additionally, Phase 2 trials are investigating zanidatamab both as a monotherapy and in combination with chemotherapy and/or other agents:

- Zanidatamab in addition to SOC chemotherapy is being evaluated in a Phase 2 trial for BTC, GEA and CRC. Read more about the trial (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 about the study (NCT04224272) **here**.
- Phase 2 trial evaluating the safety and tolerability of zanidatamab with evorpacept (ALX148) in patients with advanced HER2-expressing cancer. Learn more about the trial (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. Read more about the study (NCT06043427) **here**.
- Phase 2b HERIZON-BTC-01 trial evaluating zanidatamab as a second-line (2L) monotherapy for treatment of HER2-amplified BTC. Learn more about the pivotal trial (NCT04466891) **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 about the study (NCT05035836) **here**.

Zanidatamab is also being investigated in Phase 1 studies as a monotherapy as well as in combination with selected chemotherapies:

- Phase 1 of the ZW25-102 study investigates the safety, preliminary antitumor activity and pharmacokinetics of zanidatamab in Japanese patients with HER2-expressing solid tumors.
- Safety, tolerability and effectiveness, as well as how the body absorbs, distributes, and eliminates zanidatamab, are being evaluated in a three-part study on locally advanced and/or metastatic HER2-espressing cancers. Part 1 of the study evaluates dose maintenance and recommended dosing; part 2 further evaluates the safety and tolerability of zanidatamab; and part 3 tests the safety, tolerability and effectiveness of zanidatamab in combination with selected chemotherapy agents. Learn more about the multi-part study (NCT02892123) **here**.
- 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**.

Oncology

PROGRAM	POTENTIAL INDICATION(S)	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	PHASE 4/ REGULATORY
JZP351	Newly diagnosed <22 yrs with AML (COG)					
	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.

Additionally, five Phase 2 and Phase 3 trials of JZP351 are evaluating the agent in various age populations, including older adults, adults over 60 as well as newly diagnosed patients younger than 22. These studies are conducted with cooperative groups such as the Children's Oncology Group (COG), 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**.

JZP341	Solid tumors	

Overview: Long-acting *Erwinia* asparaginase.

KRAS Inhibitor	Solid tumors	

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

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.

Suvecaltamide	Parkinson's disease tremor					

Overview: Suvecaltamide (JZP385) is an orally available, highly selective small molecule and works by selectively blocking T-type calcium channels.

Clinical Trials: Learn more about the study (NCT05642442) evaluating the efficacy and safety of suvecaltamide for the treatment of moderate-to-severe residual tremor in adult participants with Parkinson's disease **here**.

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 healthy sleep-deprived adults. NCT05651152 **here** and NCT05720494 **here**.

JZP324	Narcolepsy					

Overview: Planned. Extended-release oxybate formulation.

Undisclosed Targets	Sleep					
	Epilepsy					
	Other neuroscience					

LGS = Lennox-Gastaut syndrome, **DS** = Dravet syndrome, **TSC** = Tuberous sclerosis complex, **SOC** = standard-of-care, **1L** = first line, **GEA** = gastroesophageal adenocarcinoma, **2L** = second line, **BTC** = biliary tract cancer, **CRC** = colorectal cancer, **3L** = third line, **SCLC** = small cell lung cancer, **AML** = acute myeloid leukemia, **COG** = Children's Oncology Group, **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.