PharmaMar and Jazz Pharmaceuticals Announce Initiation of Confirmatory Phase 3 Clinical Trial of Zepzelca® (lurbinectedin) for the Treatment of Patients with Relapsed Small Cell Lung Cancer

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The confirmatory trial is designed to secure full approval in the U.S. and serve as a registrational trial for the European Medicines Agency

The multi-center, open-label global trial will enroll 705 patients from over 100 centers mainly in North America and Europe

MADRID and DUBLIN, Dec. 13, 2021 /PRNewswire/ -- PharmaMar (MSE: PHM) and partner Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced the initiation of a confirmatory Phase 3 clinical trial, LAGOON, evaluating Zepzelca® (lurbinectedin) for the treatment of patients with relapsed small cell lung cancer (SCLC). The trial will measure overall survival (OS) as the primary endpoint and progression-free survival (PFS) as a secondary endpoint of lurbinectedin monotherapy or lurbinectedin in combination with irinotecan compared with investigator's choice of topotecan or irinotecan, in patients with SCLC whose disease has progressed following prior platinum-containing chemotherapy with or without anti-PD-1 or anti-PD-L1 agents.

"We are very excited about this trial, which is designed to reinforce lurbinectedin as a second-line treatment of choice in the U.S. and has the potential to bring our treatment to European patients," said Ali Zeaiter, director of clinical development, PharmaMar Oncology Business Unit.

"There has been strong clinical demand for *Zepzelca* following the FDA's accelerated approval, which demonstrates that this important therapy is filling a significant unmet need for the metastatic small cell lung cancer community," said Rob Iannone, M.D., M.S.C.E., executive vice president, research and development and chief medical officer at Jazz Pharmaceuticals. "We are committed to working with PharmaMar and the FDA to further demonstrate the clinical benefit of *Zepzelca* and support conversion to full regulatory approval in the U.S."

LAGOON is a Phase 3, randomized (1:1:1), multicenter, open-label clinical trial with three arms: one arm to receive lurbinectedin 3.2 mg/m^2 as monotherapy (the approved dose in the U.S.), the second arm to receive lurbinectedin 2.0 mg/m^2 in combination with irinotecan 75 mg/m^2, and the third arm to receive topotecan or irinotecan based on the investigators' choice. The trial will be conducted in patients with SCLC, whose disease has progressed following prior platinum-containing chemotherapy with or without anti-PD-1 or anti-PD-L1 agents. LAGOON is expected to enroll 705 patients from more than 100 sites mainly in North America and Europe.

The FDA approved *Zepzelca* under accelerated approval in June 2020 for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. The approval is based on overall response rate (ORR) and duration of response demonstrated in an open-label, monotherapy clinical study. If successful, LAGOON will serve as the confirmatory trial for *Zepzelca* to secure full approval in the U.S. LAGOON will also be used as a registrational trial with the European Medicines Agency (EMA) to obtain marketing authorization in Europe. Jazz Pharmaceuticals holds the commercial rights for *Zepzelca* in North America.

In 2021, lurbinectedin received marketing authorization in the United Arab Emirates, Canada, Australia and Singapore. Additional marketing authorizations are expected in 2022 and beyond.

About Zepzelca® (lurbinectedin)

Zepzelca is an alkylating drug that binds guanine residues within DNA. This 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.[i]

Zepzelca is a prescription medicine used to treat adults with small cell lung cancer that has spread to other parts of the body (metastatic) and who have received treatment with chemotherapy that contains platinum, and it did not work or is no longer working. *Zepzelca* is approved based on response rate and how long the response lasted. Additional studies will further evaluate the benefit of *Zepzelca* for this use. *Zepzelca* is not approved as part of a combination therapy or as a first-line maintenance treatment for patients with extensive-stage small cell lung cancer.

Important Safety Information for Patients

Before receiving ZEPZELCA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems.
- are pregnant or plan to become pregnant. ZEPZELCA can harm your unborn baby.

Females who are able to become pregnant:

  - Your healthcare provider should do a pregnancy test before you start treatment with ZEPZELCA.
  - You should use effective birth control (contraception) during treatment with and for 6 months after your final dose of ZEPZELCA.
  - Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with ZEPZELCA.

Males with female partners who are able to become pregnant should use effective birth control during treatment with and for 4 months after your final dose of ZEPZELCA.

- are breastfeeding or plan to breastfeed. It is not known if ZEPZELCA passes into your breastmilk. Do not breastfeed during treatment with ZEPZELCA and for 2 weeks after your final dose of ZEPZELCA. Talk to your healthcare provider about the best way to feed your baby during treatment with ZEPZELCA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain other medicines may affect how ZEPZELCA works.

What should I avoid while using ZEPZELCA?

Avoid eating or drinking grapefruit, or products that contain grapefruit juice during treatment with ZEPZELCA.

ZEPZELCA can cause serious side effects, including:

- **Low blood cell counts.** Low blood counts including low neutrophil counts (neutropenia) and low platelet counts (thrombocytopenia) are common with ZEPZELCA, and can also be severe. Some people with low white blood cell counts may get fever, or an infection throughout the body (sepsis), that can cause death. Your healthcare provider should do blood tests before you receive each treatment with ZEPZELCA to check your blood cell counts.
  Tell your healthcare provider right away if you develop:
  - fever or any other signs of infection
  - unusual bruising or bleeding
  - tiredness
  - pale colored skin
- **Liver problems.** Increased liver function tests are common with ZEPZELCA, and can also be severe. Your healthcare provider should do blood tests to check your liver function before you start and during treatment with ZEPZELCA.
  Tell your healthcare provider right away if you develop symptoms of liver problems including:
  - loss of appetite
  - nausea or vomiting
  - pain on the right side of your stomach area (abdomen)

Your healthcare provider may temporarily stop treatment, lower your dose, or permanently stop ZEPZELCA if you develop low blood cell counts or liver problems during treatment with ZEPZELCA.

The most common side effects of ZEPZELCA include:

- tiredness
- low white and red blood cell counts
- increased kidney function blood test (creatinine)
- increased liver function blood tests
- increased blood sugar (glucose)
- nausea
- decreased appetite
- muscle and joint (musculoskeletal) pain
- low level of albumin in the blood
- constipation
- trouble breathing
- low levels of sodium and magnesium in the blood
- vomiting
- cough
- diarrhea

These are not all of the possible side effects of ZEPZELCA.

Call your doctor for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. You may also report side effects to Jazz Pharmaceuticals at 1-800-520-5568.

More information about Zepzelca, including Full Prescribing Information and Patient Information, is available here.

ZEPZELCA is a trademark of PharmaMar, S.A. used by Jazz Pharmaceuticals under license.

About PharmaMar
PharmaMar is a biopharmaceutical company focused on the research and development of new oncology treatments, whose mission is to improve the healthcare outcomes of patients afflicted by serious diseases with our innovative medicines. The Company is inspired by the sea, driven by science, and motivated by patients with serious diseases to improve their lives by delivering novel medicines to them. PharmaMar intends to continue to be the world leader in marine medicinal discovery, development and innovation.

PharmaMar has developed and now commercializes Yondelis® in Europe by itself, as well as Zepzelca® (lurbinectedin), in the US; and Aplidin® (plitidepsin), in Australia, with different partners. In addition, it has a pipeline of drug candidates and a robust R&D oncology program. PharmaMar has

other clinical-stage programs under development for several types of solid cancers: lurbinectedin and PM14. Headquartered in Madrid (Spain), PharmaMar has subsidiaries in Germany, France, Italy, Belgium, Austria, Switzerland and The United States. PharmaMar also wholly owns other companies: GENOMICA, a molecular diagnostics company; and Sylentis, dedicated to researching therapeutic applications of gene silencing (RNAi). To learn more about PharmaMar, please visit us at www.pharmamar.com.

About Jazz Pharmaceuticals plc
Jazz Pharmaceuticals plc (NASDAQ: JAZZ) is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases—often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we are identifying new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in nearly 75 countries. For more information, please visit www.jazzpharma.com and follow @JazzPharma on Twitter.

Caution Concerning Forward-Looking Statements
This press release contains forward-looking statements, including, but not limited to, statements related to Jazz Pharmaceuticals' belief in the potential of Zepzelca to provide a potentially new SCLC therapeutic option in the first-line setting and other statements that are not historical facts. These forward-looking statements are based on Jazz Pharmaceuticals' current plans, objectives, estimates, expectations and intentions and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, effectively launching and commercializing new products; obtaining and maintaining adequate coverage and reimbursement for the company's products; delays or problems in the supply or manufacture of the company's products; and other risks and uncertainties affecting the company, including those described from time to time under the caption "Risk Factors" and elsewhere in Jazz Pharmaceuticals' Securities and Exchange Commission filings and reports (Commission File No. 001-33500), including Jazz Pharmaceuticals' Quarterly Report on Form 10-Q for the quarter ended September 30, 2021 and future filings and reports by Jazz Pharmaceuticals. Other risks and uncertainties of which Jazz Pharmaceuticals is not currently aware may also affect Jazz Pharmaceuticals' forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. The forward-looking statements herein are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by Jazz Pharmaceuticals on its website or otherwise. Jazz Pharmaceuticals undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.

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[i]ZEPZELCA (lurbinectedin) Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals.

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