Karyopharm and Menarini Group Receive Positive CHMP Opinion for NEXPOVIO® (selinexor) for the Treatment of Patients with Refractory Multiple Myeloma

– European Commission Decision Anticipated within Approximately 60 Days –

NEWTON, Mass. and FLORENCE, Italy, May 20, 2022 /PRNewswire/ -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI), a commercial-stage pharmaceutical company pioneering novel cancer therapies, and the Menarini Group ("Menarini"), a privately-held, leading international pharmaceutical company, today announced that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending approval of NEXPOVIO® (selinexor), a first-in-class, oral exportin 1 (XPO1) inhibitor, in combination with once weekly bortezomib (Velcade®) and low-dose dexamethasone (SVd) for the treatment of adults with multiple myeloma who have received one to three prior lines of therapy.

The positive CHMP opinion is a scientific recommendation for marketing authorization and one of the final steps before the European Commission (EC) makes a decision on Karyopharm's NEXPOVIO application. The EC's decision is expected within approximately 60 days following the CHMP recommendation. In December 2021, Karyopharm and Menarini Group entered into an exclusive license agreement to commercialize NEXPOVIO® (selinexor) in Europe.

"Despite therapeutic advances, multiple myeloma remains an incurable disease that is difficult to treat," said Richard Paulson, President and Chief Executive Officer of Karyopharm. "Today's positive CHMP opinion brings us one step closer to our goal of making NEXPOVIO available to patients globally who may benefit from its novel mechanism of action. We are pleased to have Menarini as a partner in this effort given its commercialization expertise as well as strong heritage and footprint in Europe."

"We are thrilled with the CHMP's recommendation in favor of NEXPOVIO and what it represents for multiple myeloma patients in need of new and innovative treatment options," said Elcin Barker Ergun, Chief Executive Officer of Menarini. "Pending potential marketing authorization from the EC, we will work closely with appropriate authorities to ensure this important treatment can be made available to patients in Europe."

Karyopharm's application is supported by data from the Phase 3 BOSTON study, which evaluated the SVd triplet regimen in patients with relapsed or refractory multiple myeloma and were published in The Lancet (Grosicki, et al.) in November 2020. This CHMP opinion follows the approval of XPOVIO® (selinexor) by the U.S. Food and Drug Administration in December 2020 in the SVd combination in patients with multiple myeloma after at least one prior therapy.

About the Pivotal Phase 3 BOSTON Study

The Phase 3 BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) study was an multi-center, randomized study (NCT03110562), which evaluated 402 adult patients with relapsed or refractory multiple myeloma who had received one to three prior lines of therapy. The study was designed to compare the efficacy, safety and certain health-related quality of life parameters of once-weekly SVd versus twice-weekly bortezomib and low-dose dexamethasone (Vd). The primary endpoint of the study was progression-free survival (PFS) and key secondary endpoints included overall response rate (ORR), rate of peripheral neuropathy, and others. Additionally, the BOSTON study allowed for patients on the Vd control arm to crossover to the SVd arm following objective (quantitative) progression of disease verified by an Independent Review Committee (IRC). The BOSTON study was conducted at over 150 clinical sites internationally.

Despite the study having a high proportion of patients with high-risk cytogenetics (~50%) compared to other Velcade®-based studies in previously treated myeloma, the median PFS in the SVd arm was 13.93 months compared to 9.46 months in the Vd arm, representing a 4.47 month (47%) increase in median PFS (hazard ratio (HR)=0.70; p=0.0075). The SVd arm also demonstrated a significantly greater ORR compared to the Vd arm (76.4% vs. 62.3%, p=0.0012). Patients who had received only one prior line of therapy also demonstrated a higher ORR on the SVd arm as compared to the Vd arm (80.8% vs. 65.7%, p=0.0082). Importantly, SVd therapy compared to Vd therapy showed consistent PFS benefit and higher ORR across several important subgroups.

In addition, the following results favored SVd therapy as compared to Vd therapy:

- SVd therapy demonstrated a significantly higher rate of deep responses, defined as ≥ Very Good Partial

Response compared to Vd therapy (44.6% vs. 32.4%) as well as a longer median duration of response (20.3 months vs. 12.9 months). Additionally, 16.9% of patients on the SVd arm achieved a complete response or a stringent complete response as compared to 10.6% of patients receiving Vd therapy. All responses were confirmed by an IRC.

- Data as of the cut-off date of February 15, 2021 showed a trend toward an overall survival (OS) benefit associated with SVd therapy with fewer deaths, numerically, reported on the SVd arm (68 vs. 80). Median OS for the SVd arm was 36.7 months, while the median OS for the Vd arm was 32.8 months.
- Peripheral neuropathy (PN) rates were significantly lower on SVd compared to Vd (32.3% vs. 47.1%; p=0.0010). In addition, PN rates of grade ≥2 were also significantly lower in the SVd arm compared to Vd (21.0% vs. 34.3%, P=0.0013).

The most common adverse events (AEs; ≥20%) were cytopenias, along with gastrointestinal and constitutional symptoms and were consistent with those previously reported from other selinexor studies. Most AEs were manageable with dose modifications and/or standard supportive care. The most common non-hematologic AEs were fatigue (59%), nausea (50%), decreased appetite (35%), diarrhea (32%), peripheral neuropathy (32%), upper respiratory tract infection (29%), decreased weight (26%), cataract (22%) and vomiting (21%) and were mostly Grade 1 and 2 events. The most common Grade 3 and 4 AEs (≥10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia.

About Multiple Myeloma in Europe

Multiple myeloma is an incurable cancer with significant morbidity and the second most common hematologic malignancy. According to the World Health Organization, in 2020, there were approximately 51,000 new cases and 32,000 deaths from multiple myeloma in Europe[1]. While the treatment of multiple myeloma has improved over the last 20 years, and overall survival has increased considerably, the disease remains incurable, and nearly all patients will eventually relapse and develop disease that is refractory to all approved anti-myeloma therapies. Therefore, there continues to be a high unmet medical need for new therapies, particularly those with novel mechanisms of action.

About NEXPOVIO® (selinexor)

NEXPOVIO, which is marketed as XPOVIO in the U.S., is a first-in-class, oral exportin 1 (XPO1) inhibitor. NEXPOVIO functions by selectively binding to and inhibiting the nuclear export protein exportin 1 (XPO1, also called CRM1). NEXPOVIO blocks the nuclear export of tumor suppressor, growth regulatory and anti-inflammatory proteins, leading to accumulation of these proteins in the nucleus and enhancing their anti-cancer activity in the cell. The forced nuclear retention of these proteins can counteract a multitude of the oncogenic pathways that, unchecked, allow cancer cells with severe DNA damage to continue to grow and divide in an unrestrained fashion. NEXPOVIO has been granted conditional marketing authorization by the European Commission in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Therapeutic indication for NEXPOVIO in the EU Member States as well as Iceland, Liechtenstein, Norway and Northern Ireland. NEXPOVIO is also approved in the UK under a Conditional Marketing Authorisation.

NEXPOVIO is indicated in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

IMPORTANT SAFETY INFORMATION

Contraindications: Hypersensitivity to selinexor.

Special warnings and precautions for use:

Recommended concomitant treatments
Patients should be advised to maintain adequate fluid and caloric intake throughout treatment. Intravenous hydration should be considered for patients at risk of dehydration.

Prophylactic concomitant treatment with a 5-HT3 antagonist and/or other anti-nausea agents should be provided prior to and during treatment with NEXPOVIO.

Haematology:

Patients should have their complete blood counts (CBC) assessed at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment.

Thrombocytopenia:
Thrombocytopenic events (thrombocytopenia and platelet count decreased) were frequently reported in adult patients receiving selinexor, which can be severe (Grade 3/4). Patients should be monitored for signs and symptoms of bleeding and evaluated promptly.

Neutropenia:
Severe neutropenia (Grade 3/4) has been reported with selinexor.

Patients with neutropenia should be monitored for signs of infection and evaluated promptly.

Gastrointestinal toxicity:
Nausea, vomiting, diarrhoea, which sometimes can be severe and may require the use of anti-emetic and anti-diarrhoeal medicinal products.

Weight loss and anorexia:
Patients should have their body weight, nutritional status and volume checked at baseline, during treatment, and as clinically indicated. Monitoring should be more frequent during the first two months of treatment.

Confusional state and dizziness:
Patients should be instructed to avoid situations where dizziness or confusional state may be a problem and to not take other medicinal products that may cause dizziness or confusional state without adequate medical advice. Patients should be advised not to drive or operate heavy machinery until symptoms resolve.

Hyponatraemia:
Patients should have their sodium levels checked at baseline, during treatment, and as clinically indicated. Monitoring should be more frequent during the first two months of treatment.

Tumour lysis syndrome (TLS):
TLS has been reported in patients receiving therapy with selinexor. Patients at a high risk for TLS should be monitored closely. Treat TLS promptly in accordance with institutional guidelines.

Fertility, pregnancy and lactation
Women of childbearing potential/contraception in males and females:
Women of childbearing potential and male adult patients of reproductive potential should be advised to use effective contraceptive measures or abstain from sexual intercourse while being treated with selinexor and for at least 1 week following the last dose of selinexor.

Pregnancy:
There are no data from the use of selinexor in pregnant women. Selinexor is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding:
It is unknown whether selinexor or its metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with selinexor and for 1 week after the last dose.

Undesirable effects
Summary of the safety profile
The most frequent adverse reactions (≥30%) of selinexor in combination with dexamethasone were nausea, thrombocytopenia, fatigue, anaemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatraemia, neutropenia and leukopenia.

The most commonly reported serious adverse reactions (≥3%) were pneumonia, sepsis, thrombocytopenia, acute kidney injury, and anaemia.

Description of selected adverse reactions
Infections: Infection was the most common non-haematological toxicity. Upper respiratory tract infection and pneumonia were the most commonly reported infections with 25% of reported infections being serious and fatal infections occurring in 3% of treated adult patients.

Elderly population
Patients 75 years and older had a higher incidence of discontinuation due to an adverse reaction, higher incidence of serious adverse reactions, and higher incidence of fatal adverse reactions.

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Please see NEXPOVIO Summary of Product Characteristics and European Public Assessment Report at https://ec.europa.eu/health/documents/community-register/html/h1537.htm

About Karyopharm Therapeutics

Karyopharm Therapeutics Inc. (Nasdaq: KPTI) is a commercial-stage pharmaceutical company pioneering novel cancer therapies. Since its founding, Karyopharm has been the industry leader in oral Selective Inhibitor of Nuclear Export (SINE) compound technology, which was developed to address a fundamental mechanism of oncogenesis: nuclear export dysregulation. Karyopharm's lead SINE compound and first-in-class, oral exportin 1 (XPO1) inhibitor, XPOVIO® (selinexor), is approved in the U.S. and marketed by the Company in three oncology indications and has received regulatory approvals in various indications in a growing number of ex-U.S. territories and countries, including Europe and the United Kingdom (as NEXPOVIO®), China and Singapore. Karyopharm has a focused pipeline targeting multiple high unmet need cancer indications, including in endometrial cancer, myelodysplastic syndromes and myelofibrosis. For more information about our people, science and pipeline, please visit www.karyopharm.com, and follow us on Twitter at @Karyopharm and LinkedIn.

About Menarini Group

The Menarini Group is a leading international pharmaceutical and diagnostics company, with a turnover of over $4 billion and over 17,000 employees. Menarini is focused on therapeutic areas with high unmet needs with products for oncology, cardiology, pneumology, gastroenterology, infectious diseases, diabetology, inflammation, and analgesia. With 18 production sites and 9 Research and Development centers, Menarini's products are available in 140 countries worldwide.

Menarini has a deep commitment for developing treatments addressing oncological and hematologic diseases. Menarini actively develops Elzonris (marketed in US and Europe for BPDCN) for multiple hematologic malignancies, including AML, CMML and myelofibrosis, and elacestrant and felezenexor for oncology as well. Additionally, the FDA recently granted MEN1703 an orphan drug designation for AML. For further information, please visit www.menarini.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential approval and commercial launch of NEXPOVIO in the European Union[Europe]; the ability of selinexor to treat patients with multiple myeloma; and expectations related to future clinical development and potential regulatory submissions of selinexor. Such statements are subject to numerous important factors, risks and uncertainties, many of which are beyond Karyopharm's control, that may cause actual events or results to differ materially from Karyopharm's current expectations. For example, there can be no guarantee that Karyopharm will successfully commercialize XPOVIO or that any of Karyopharm's drug candidates, including selinexor and eltanexor, will successfully complete necessary clinical development phases or that development of any of Karyopharm's drug candidates will continue. Further, there can be no guarantee that any positive developments in the development or commercialization of Karyopharm's drug candidate portfolio will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other factors, including the following: the risk that the COVID-19 pandemic could disrupt Karyopharm's business more severely than it currently anticipates, including by negatively impacting sales of XPOVIO, interrupting or delaying research and development efforts, impacting the ability to procure sufficient supply for the development and commercialization of selinexor or other product candidates, delaying ongoing or planned clinical trials, impeding the execution of business plans, planned regulatory milestones and timelines, or inconveniencing patients; the adoption of XPOVIO in the commercial marketplace, the timing and costs involved in commercializing XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; the ability to obtain and retain regulatory approval of XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; Karyopharm's results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. Food and Drug Administration and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, including with respect to the need for additional clinical studies; the ability of Karyopharm or its third party collaborators or successors in interest to fully perform their respective obligations under the applicable agreement and the potential future financial implications of such agreement; Karyopharm's ability to enroll patients in its clinical trials; unplanned cash requirements and expenditures;

development or regulatory approval of drug candidates by Karyopharm's competitors for products or product candidates in which Karyopharm is currently commercializing or developing; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any of its products or product candidates. These and other risks are described under the caption "Risk Factors" in Karyopharm's Quarterly Report on Form 10-Q for the quarter ended March 31, 2022, which was filed with the Securities and Exchange Commission (SEC) on May 5, 2022, and in other filings that Karyopharm may make with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and, except as required by law, Karyopharm expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

References

[1] World Health Organization. 2020. https://gco.iarc.fr/today/data/factsheets/cancers/35-Multiple-myeloma-fact-sheet.pdf

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