



Karyopharm to Evaluate Low Dose Selinexor as a Potential Treatment for Hospitalized Patients with COVID-19

April 7, 2020

– Company to Initiate a Global Randomized Clinical Trial to Treat Patients with COVID-19 –

– XPO1 Inhibitors have Previously Demonstrated Preclinical Activity Against Numerous Respiratory Viruses (Including SARS-CoV) and Associated Inflammation –

– BOSTON sNDA Submission on Target for Q2 2020 –

– Management to Host Conference Call Today at 8:30 AM ET –

NEWTON, Mass., April 07, 2020 (GLOBE NEWSWIRE) -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI) today announced plans to initiate a global randomized clinical trial for low dose oral selinexor in hospitalized patients with severe COVID-19. Selinexor, marketed as XPOVIO[®], is currently approved at higher doses by the Food and Drug Administration (FDA) as a treatment for patients with relapsed or refractory multiple myeloma. Selinexor is an oral, selective inhibitor of nuclear export (SINE) compound which blocks the cellular protein XPO1. In addition to its roles in cancer, XPO1 also facilitates the transport of several viral proteins from the nucleus of the host cell to the cytoplasm¹, and it amplifies the activities of pro-inflammatory transcription factors. SINE compounds have been shown to disrupt the replication of multiple viruses *in vitro* and *in vivo*. They have also been shown to mediate anti-inflammatory and anti-viral effects, including respiratory infections, in several animal models. In particular, SINE compounds have recently been identified as having the potential to interfere with key host protein interactions with SARS-CoV-2, the virus that causes COVID-19.²

Selinexor is currently the only XPO1 inhibitor approved for commercial use by the FDA and has been extensively tested in clinical trials across numerous cancer indications worldwide since 2012. The proposed clinical trial to treat hospitalized patients with COVID-19 would be the first study of an XPO1 inhibitor in patients with severe viral infections.

“While Karyopharm’s clinical development strategy until now has been focused on patients with various types of cancer, there is increasing evidence that XPO1 inhibition could play an important role in the treatment of patients with viral infections including SARS-CoV-2,” said Sharon Shacham, PhD, MBA, President and Chief Scientific Officer of Karyopharm. “As the medical community is urgently seeking innovative ways to address the COVID-19 pandemic, based on recent scientific data, we have decided to evaluate the potential for selinexor in the treatment of patients with COVID-19. We look forward to working with clinical investigators and regulators across the globe as expeditiously as possible to determine the next steps for this new initiative. Additionally, we continue to move our oncology programs forward including the expected submission of our BOSTON supplemental New Drug Application (sNDA) in the second quarter of this year.”

“Given the globally devastating impact of the COVID-19 pandemic, innovative strategies and collaborative efforts are critically needed to bring effective treatment options to patients, who are so desperately in need. I am highly encouraged by the scientific rationale of studying selinexor, which targets both virus and immune-mediated injury, for treatment of patients with severe COVID-19. My staff, colleagues, and I look forward to working with Karyopharm to better understand the role of this novel approach in improving patient outcomes of COVID-19,” said Thomas J. Walsh, MD, Professor of Medicine, Pediatrics, and Microbiology & Immunology, Weill Cornell Medicine, Cornell University.

SINE XPO1 inhibitors have demonstrated activity against over 20 different viruses, including the RNA viruses, influenza, respiratory syncytial virus (RSV) and other common causes of respiratory infection. XPO1 inhibition has been identified in several assays as having potential activity against SARS-CoV-2, although specific animal models have not been available to date. One of the most important aspects of COVID-19 is the marked pulmonary inflammation with high levels of cytokines such as IL6, IL1, IFN γ and others. Along these lines, selinexor and other SINE compounds have demonstrated potent anti-inflammatory activity through the inhibition of Nuclear Factor κ B (NF- κ B), leading to reductions in all of these cytokines in a variety of models, and this may be particularly beneficial to hospitalized patients with COVID-19.

Karyopharm’s clinical program in COVID-19 is not expected to impact the timing or prioritization of other key Company milestones, including the planned submission of a sNDA for XPOVIO (selinexor) in combination with once-weekly Velcade[®] (bortezomib) and low-dose dexamethasone as a new second line treatment for patients with relapsed or refractory multiple myeloma (based on the BOSTON Phase 3 trial), which remains on schedule for the second quarter of 2020. Additionally, Karyopharm has sufficient supply of selinexor for current and expected commercial supply for patients with multiple myeloma, for ongoing clinical trials in patients with various cancers, as well as for this proposed study in patients with COVID-19.

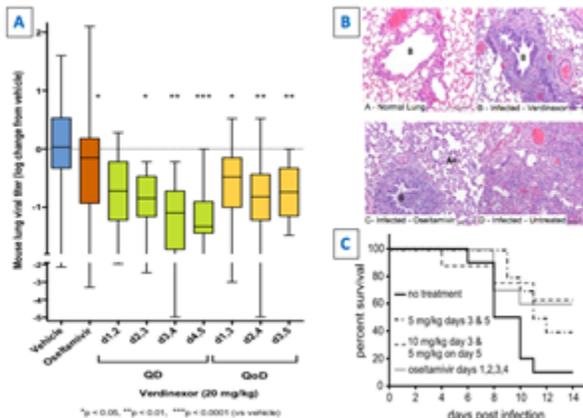
About COVID-19 and the Potential Role of XPO1 Inhibition

The novel coronavirus SARS-CoV-2 that emerged from the Wuhan region of China in December 2019 shares similarity to the original SARS coronavirus, SARS-CoV.³ SARS-CoV was responsible for a 2003 human outbreak of respiratory disease. As such, the wealth of research that has been performed to date on SARS-CoV can serve as important data for predicting the behavior of SARS-CoV-2, which causes COVID-19. The role of XPO1 (also called CRM1) in SARS-CoV replication and pathogenesis was first described in 2009.⁴ XPO1 is solely responsible for exporting certain SARS-CoV proteins, including 9b⁵, N⁶, S⁷, Orf3⁴ and Orf6⁸ out of the nucleus. Blockade of XPO1 is therefore expected to inhibit viral assembly. In a recent analysis using VIPER-based identification of Master Regulator proteins, selinexor was ranked in the top 18 of more than 400 screened drugs

(top 4.5%) for interfering with virus-host interaction in SARS-CoV infected bronchial epithelial cells.⁹ In another study, verdinexor, one of Karyopharm's investigational drugs that is highly similar in structure and biological activity to selinexor, was identified as a drug with the potential to pharmacologically interfere with the interactions of several of the SARS-CoV-2 proteins with their human targets, and was recommended for evaluation in the treatment of SARS-CoV-2 viral infection.² Similarly, a recent bioinformatics study identified XPO1 together with three other proteins, including NPM1, HNRNPA1 and JUN, as "hub proteins" with the highest number of functional connections within 119 host proteins that interact with the human SARS-CoV.¹⁰ Of note, both NPM1 and HNRNPA1 interact directly with XPO1 in normal cells, and JUN is involved in inflammatory responses, including those associated with viral infections.

Severe influenza infection shares many of the features of SARS-CoV infection. Verdinexor demonstrated potent inhibition of influenza viral replication, even when given four days post-infection (Figure 1).^{11,12} In addition, verdinexor induced reductions in markers of disease pathology and improved survival in influenza models in mice and ferrets (Figure 1).^{11,12}

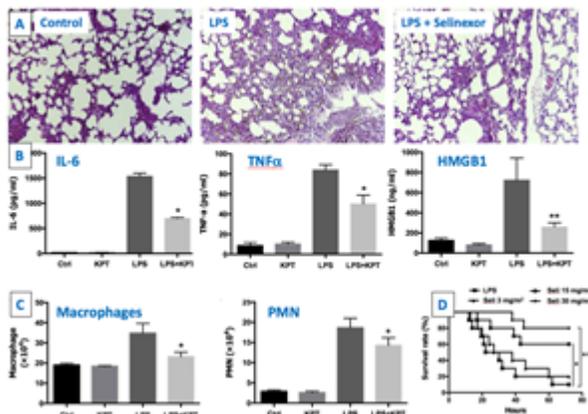
Figure 1: In a mouse H1N1 influenza model, delayed (up to 4 days) verdinexor treatment: (A) significantly reduces influenza virus levels; (B) ameliorated lung injury; and (C) improved survival is available at <https://www.globenewswire.com/NewsRoom/AttachmentNg/ea80c453-8192-4bea-b8f8-74f7ff5670d2>



In a mouse H1N1 influenza model, delayed (up to 4 days) verdinexor treatment: (A) significantly reduces influenza virus levels; (B) ameliorated lung injury; and (C) improved survival

XPO1 is also responsible for the nuclear export and functional inactivation of several of the major anti-inflammatory, antioxidant and cytoprotective transcription factors including I κ B, PPAR γ , RXR α , HMGB1 and Nrf2.¹³ Conversely, blockade of XPO1 leads to nuclear retention and functional activation of these critical proteins. High levels of XPO1 are found in multiple inflammatory conditions and may amplify ongoing inflammatory responses leading to severe organ, including pulmonary, damage.¹⁴ In a mouse model for sepsis, selinexor treatment increased survival following a lethal dose of endotoxin (Figure 2).¹⁵

Figure 2: In a lipopolysaccharide (LPS)-induced sepsis model, selinexor (A) attenuated lung injury, (B) reduced serum cytokines levels, (C) reduced macrophage and polymorphonuclear (PMN) subpopulations in the peritoneal exudate and improved survival is available at <https://www.globenewswire.com/NewsRoom/AttachmentNg/964c3643-480c-4cc0-a7df-5b2165502349>



In a lipopolysaccharide (LPS)-induced sepsis model, selinexor (A) attenuated lung injury, (B) reduced serum cytokines levels, (C) reduced macrophage and polymorphonuclear (PMN) subpopulations in the peritoneal exudate and improved survival

In addition, selinexor reduced inflammatory cytokine secretion including TNF α , IL-6 and IFN γ while reducing the numbers of macrophage and polymorphonuclear neutrophils in the mice peritoneal cavity (the site of the LPS injection).¹⁵ Importantly, treatment with selinexor attenuated the acute respiratory distress syndrome (ARDS)-like lung injury observed in this model. Selinexor therapeutic effects were achieved through the inhibition of the inflammatory NF κ B pathway, induction of the anti-inflammatory effects of the DNA binding protein HMGB1 by inducing its nuclear retention and reductions in cytokine levels including TNF- α and IL-6.¹⁵ These findings are significant as COVID-19 disease severity including respiratory symptoms correlates with the patient's cytokine levels. Severe disease is characterized by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon- γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , and tumor necrosis factor- α .¹⁶ Moreover, predictors of fatality of 150 confirmed COVID-19 cases in Wuhan included elevated IL-6 ($p < 0.0001$).¹⁷

Together, these results suggest that SINE compounds such as selinexor could provide both anti-viral and anti-inflammatory activities in patients suffering from severe COVID-19 and therefore warrants clinical investigation.

Conference Call Information

Karyopharm will host a conference call today, Tuesday, April 7, 2020, at 8:30 a.m. Eastern Time, to discuss selinexor as a potential treatment for hospitalized patients with COVID-19. To access the conference call, please dial (855) 437-4406 (local) or (484) 756-4292 (international) at least 10 minutes prior to the start time and refer to conference 6734579. A live audio webcast of the call will be available under "Events & Presentations" in the Investor section of the Company's website, <http://investors.karyopharm.com/events-presentations>. An archived webcast will be available on the Company's website approximately two hours after the event.

About XPOVIO[®] (selinexor)

XPOVIO is a first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) compound. XPOVIO functions by selectively binding to and inhibiting the nuclear export protein exportin 1 (XPO1, also called CRM1). XPOVIO 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. Karyopharm received accelerated U.S. Food and Drug Administration (FDA) approval of XPOVIO in July 2019 in combination with dexamethasone for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. Karyopharm has also submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) with a request for conditional approval of selinexor. A supplemental New Drug Application was submitted to the FDA seeking accelerated approval for selinexor as a new treatment for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and selinexor has received Fast Track and Orphan designation and Priority Review from the FDA with a scheduled PDUFA date of June 23, 2020 for this patient population. Selinexor is also being evaluated in several other mid-and later-phase clinical trials across multiple cancer indications, including in multiple myeloma in a pivotal, randomized Phase 3 study in combination with Velcade[®] (bortezomib) and low-dose dexamethasone (BOSTON), for which Karyopharm announced positive top-line results in March 2020. Additional, ongoing trials for selinexor include as a potential backbone therapy in combination with approved myeloma therapies (STOMP), in liposarcoma (SEAL) and in endometrial cancer (SIENDO), among others. Additional Phase 1, Phase 2 and Phase 3 studies are ongoing or currently planned, including multiple studies in combination with approved therapies in a variety of tumor types to further inform Karyopharm's clinical development priorities for selinexor. Additional clinical trial information for selinexor is available at www.clinicaltrials.gov.

For more information about Karyopharm's products or clinical trials, please contact the Medical Information department at:

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IMPORTANT SAFETY INFORMATION

Thrombocytopenia

XPOVIO can cause thrombocytopenia, leading to potentially fatal hemorrhage. Thrombocytopenia was reported as an adverse reaction in 74% of patients, and severe (Grade 3-4) thrombocytopenia occurred in 61% of patients treated with XPOVIO. The median time to onset of the first event was 22 days. Bleeding occurred in 23% of patients with thrombocytopenia, clinically significant bleeding occurred in 5% of patients with thrombocytopenia and fatal hemorrhage occurred in <1% of patients.

Monitor platelet counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia

XPOVIO can cause neutropenia, potentially increasing the risk of infection. Neutropenia was reported as an adverse reaction in 34% of patients, and severe (Grade 3-4) neutropenia occurred in 21% of patients treated with XPOVIO. The median time to onset of the first event was 25 days. Febrile neutropenia was reported in 3% of patients.

Obtain neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF). Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity

Gastrointestinal toxicities occurred in patients treated with XPOVIO.

Nausea/Vomiting

Nausea was reported as an adverse reaction in 72% of patients, and Grade 3 nausea occurred in 9% of patients treated with XPOVIO. The median time to onset of the first nausea event was 3 days.

Vomiting was reported in 41% of patients, and Grade 3 vomiting occurred in 4% of patients treated with XPOVIO. The median time to onset of the first vomiting event was 5 days.

Provide prophylactic 5-HT₃ antagonists and/or other anti-nausea agents, prior to and during treatment with XPOVIO. Manage nausea/vomiting by dose interruption, reduction, and/or discontinuation. Administer intravenous fluids and replace electrolytes to prevent dehydration in patients at risk. Use additional anti-nausea medications as clinically indicated.

Diarrhea

Diarrhea was reported as an adverse reaction in 44% of patients, and Grade 3 diarrhea occurred in 6% of patients treated with XPOVIO. The median time to onset of diarrhea was 15 days.

Manage diarrhea by dose modifications and/or standard anti-diarrheal agents; administer intravenous fluids to prevent dehydration in patients at risk.

Anorexia/Weight Loss

Anorexia was reported as an adverse reaction in 53% of patients, and Grade 3 anorexia occurred in 5% of patients treated with XPOVIO. The median time to onset of anorexia was 8 days.

Weight loss was reported as an adverse reaction in 47% of patients, and Grade 3 weight loss occurred in 1% of patients treated with XPOVIO. The median time to onset of weight loss was 15 days.

Monitor patient weight at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Manage anorexia and weight loss with dose modifications, appetite stimulants, and nutritional support.

Hyponatremia

XPOVIO can cause hyponatremia; 39% of patients treated with XPOVIO experienced hyponatremia, 22% of patients experienced Grade 3 or 4 hyponatremia. The median time to onset of the first event was 8 days.

Monitor sodium level at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Treat hyponatremia per clinical guidelines (intravenous saline and/or salt tablets), including dietary review. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Infections

In patients receiving XPOVIO, 52% of patients experienced any grade of infection. Upper respiratory tract infection of any grade occurred in 21%, pneumonia in 13%, and sepsis in 6% of patients. Grade ≥ 3 infections were reported in 25% of patients, and deaths resulting from an infection occurred in 4% of patients. The most commonly reported Grade ≥ 3 infections were pneumonia in 9% of patients, followed by sepsis in 6%. The median time to onset was 54 days for pneumonia and 42 days for sepsis. Most infections were not associated with neutropenia and were caused by non-opportunistic organisms.

Neurological Toxicity

Neurological toxicities occurred in patients treated with XPOVIO.

Neurological adverse reactions including dizziness, syncope, depressed level of consciousness, and mental status changes (including delirium and confusional state) occurred in 30% of patients, and severe events (Grade 3-4) occurred in 9% of patients treated with XPOVIO. Median time to the first event was 15 days.

Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. Selinexor administration to pregnant animals during organogenesis resulted in structural abnormalities and alterations to growth at exposures below those occurring clinically at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 20\%$) are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.

The treatment discontinuation rate due to adverse reactions was 27%; 53% of patients had a reduction in the XPOVIO dose, and 65.3% had the dose of XPOVIO interrupted. The most frequent adverse reactions requiring permanent discontinuation in 4% or greater of patients who received XPOVIO included fatigue, nausea, and thrombocytopenia. The rate of fatal adverse reactions was 8.9%.

Please see XPOVIO Full Prescribing Information available at www.XPOVIO.com.

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About Karyopharm Therapeutics

Karyopharm Therapeutics Inc. (Nasdaq: KPTI) is an oncology-focused pharmaceutical company dedicated to the discovery, development, and commercialization of novel first-in-class drugs directed against nuclear export and related targets for the treatment of cancer and other major diseases. Karyopharm's Selective Inhibitor of Nuclear Export (SINE) compounds function by binding with and inhibiting the nuclear export protein XPO1 (or CRM1). Karyopharm's lead compound, XPOVIO[®] (selinexor), received accelerated approval from the U.S. Food and Drug Administration (FDA) in July 2019 in combination with dexamethasone as a treatment for patients with heavily pretreated multiple myeloma. A Marketing Authorization Application for selinexor is also currently under review by the European Medicines Agency. A supplemental New Drug Application was recently accepted by the FDA seeking accelerated approval for selinexor as a new treatment for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). In addition to single-agent and combination activity against a variety of human cancers, SINE compounds have also shown biological activity in models of neurodegeneration, inflammation, autoimmune disease, certain viruses and wound-healing. Karyopharm has several investigational programs in clinical or preclinical development. For more information, please visit www.karyopharm.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 Karyopharm's expectations and plans relating to selinexor as a potential treatment for hospitalized patients with severe COVID-19; the initiation and design of a global randomized clinical trial to study this potential application of selinexor, including the dosing regimen; submissions to, and the review and potential approval of selinexor in this indication by, regulatory authorities, including the anticipated availability of data to support such submissions, timing of such submissions and actions by regulatory authorities and the potential availability of accelerated approval pathways; and the therapeutic potential of and potential clinical development plans for Karyopharm's drug candidates, including the impact of a selinexor clinical trial on the timing or prioritization of other key company milestones, such as its expected submission of a supplemental new drug application in the second quarter of 2020 for XPOVIO in combination with once-weekly Velcade[®] and low dose dexamethasone. 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 complete necessary clinical development phases of selinexor in this indication; that data from a clinical trial of selinexor would support its use in treatment of hospitalized patients with severe COVID-19; that regulators will approve the use of selinexor in hospitalized patients with severe COVID-19, or that such approval will be made on an accelerated timeline. 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 reducing 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 selinexor for treatment of COVID-19 in the commercial marketplace, the timing and costs involved in commercializing selinexor for such indication or any of Karyopharm's drug candidates that receive regulatory approval; the ability to retain regulatory approval of selinexor for such indication 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 obtain and maintain requisite regulatory approvals and to enroll patients in its clinical trials; unplanned cash requirements and expenditures; development of drug candidates by Karyopharm's competitors for indications in which Karyopharm is currently developing its drug candidates; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any drug candidates it is developing. These and other risks are described under the caption "Risk Factors" in Karyopharm's Annual Report on Form 10-K for the year ended December 31, 2019, which was filed with the Securities and Exchange Commission (SEC) on February 26, 2020, 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.

Velcade® is a registered trademark of Takeda Pharmaceutical Company Limited.

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