Karyopharm Therapeutics Initiates a Phase IIb Efficacy Study with its Novel, Oral Selective Inhibitor of Nuclear Export (SINE) KPT-335 in Dogs with Non-Hodgkin Lymphomas (NHL)

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Karyopharm Therapeutics Inc., a leader in the new field of nuclear transport modulators, announced dosing of dogs with newly diagnosed or relapsed lymphoma in clinical trial KARYO-2. KARYO-2 is designed to support an application of KPT-335 for Conditional Approval to the FDA's Center for Veterinary Medicine (CVM). KARYO-2 follows the successful completion of KARYO-1, Karyopharm's first study of KPT-335 in dogs with spontaneous tumors.

Both KARYO-1 and KARYO-2 are being led by Cheryl London, DVM, PhD, from The Ohio State University (OSU). Dr. London will present the KARYO-1 trial results at the upcoming American Society of Hematology meeting in Atlanta. Her oral presentation, "Results of a Phase I Dose Escalation Study of the Novel CRM1 Selective Inhibitor of Nuclear Export (SINE) KPT-335 in Dogs with Spontaneous Non-Hodgkin's Lymphomas (NHL)," is in Session 625 on Sunday, December 9, 2012: 5:30 PM, in Building B, Level 4, Room B405-B407.

KARYO-2 is being run at OSU and eight additional centers in the United States. The trial is being coordinated by Animal Clinical Investigation LLC.

Karyopharm is developing KPT-335 initially as a single agent oral therapy for treatment of dogs with NHL. KPT-335 represents the first ever SINE to be tested in client-owned dogs with cancer, and is closely related to KPT-330, currently undergoing Phase 1 testing in humans with cancer. At the present time, NHL in dogs (and in humans) is often treated with parenteral multi-agent chemotherapy such as CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone). Dilara McCauley, PhD, Sr. Director and KPT-335 Product Leader at Karyopharm commented, "We are very excited about the initiation of KARYO-2 in dogs with lymphoma. We are hopeful that KPT-335 can provide a relatively simple, oral alterative to multi-agent chemotherapy for dogs with lymphoma, giving owners and veterinarians another option for the treatment of this common malignancy."

KARYO-2 will enroll up to thirty dogs with newly diagnosed or relapsed NHL who have progressive disease on study entry. All dogs will receive oral KPT-335 tablets at a starting dose of 1.5 mg/kg three times each week and continue on drug until disease progression or intolerability. The primary endpoint of the study is progression free survival. It is anticipated that data from KARYO-2 will be included in an application for Conditional Approval of KPT-335 for the veterinary market (analogous to an accelerated approval for an orphan indication in humans).

SINEs specifically and irreversibly inhibit the nuclear export protein CRM1 (chromosome region maintenance protein 1), also called exportin 1 (XPO1). CRM1 is the exclusive mediator of nuclear export of p53, p73, pRb, FOXO, p21, p27, BRACA1, the endogenous inhibitor of Nuclear Factor kB (NF-kB) known as IkB, and other tumor suppressor and growth regulatory proteins. Nuclear export of these key proteins leads to their functional inactivation. Blockade of CRM1 with SINEs forces the accumulation and activation of tumor suppressor and growth regulatory proteins in the nucleus, leading to potent and selective tumor cell apoptosis while sparing normal cells.

LYMPHOMA IN DOGS
Lymphoma is a common malignancy in dogs, comprising about 15 of all canine cancer patients. The clinical course and treatment response of canine and human NHL are quite similar. Like humans, the most common type of canine NHL is Diffuse Large B Cell Lymphoma (DLBCL). Both human and canine NHL are often treated with multi-agent chemotherapy such as CHOP, which requires substantial supportive care and monitoring. Nearly all dogs with NHL eventually relapse from their initial therapy, and novel treatments, particularly with good tolerability, are needed.

About Karyopharm Therapeutics Inc.
Karyopharm is a pharmaceutical company leading the development of small molecule modulators of nuclear transport. The Company was founded by Drs. Sharon Shacham and Michael Kauffman in 2008. Karyopharm has raised approximately $34M since its inception and has won several grants/awards including a Biotech Investment Award by the Multiple Myeloma Research Foundation in 2010. Karyopharm's first program is directed towards the Selective Inhibition of Nuclear Export – its SINE program – targeting CRM1, the major nuclear export protein. SINE compounds, including KPT-330 and KPT-335, force the activation of the cell's key tumor suppressor proteins and anti-inflammatory pathways including p53, p21, pRB, FoxO, and IkB, a key cellular inhibitor of nuclear factor NF-kB. Karyopharm is currently evaluating two oral SINE compounds in clinical trials. KPT-330 oral is being evaluated in patients with cancer, and KPT-335 oral is being studied in dogs with relapsed/refractory non-Hodgkin's Lymphomas. The Company is also evaluating the use of SINEs in autoimmune/inflammatory disorders, viral infections and dermatologic diseases. Karyopharm Therapeutics is located in Natick, Massachusetts.

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