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PRESS RELEASE

Solid scientific evidence for Oasmia product candidate Paccal® Vet

Two clinical studies have now been completed in client owned dogs with Oasmia's product candidate Paccal® Vet. The first was a Phase I/II study on different types of cancers and showed an overall response rate of 74 %. The other was a Phase III study on mastocytoma grade II and III and showed a response rate of 70 %. No unexpected severe side-effects were observed.

Oasmia Pharmaceutical AB, Uppsala Sweden has performed two clinical trials in tumor bearing dogs with their new nanoparticulate water soluble formulation of paclitaxel. The extremely lipid soluble, well known cytotoxic drug Paclitaxel has practically been impossible to administer to dogs due to the deleterious side effects caused by the excipient Cremophor® EL.

- Mast cell tumors are infamous for being chemo-resistant. The results in the two clinical studies on the new water soluble nanoparticulate formulation from Oasmia Pharmaceutical AB are very remarkable both regarding the response rate and also the new possibility to actually conveniently treat dogs with paclitaxel without obvious deleterious side effects, says Dr Henrik von Euler, PhD and Associate professor at the Swedish University of Agricultural Sciences, study coordinator of both trials.

Phase I/II study of Paccal® Vet in tumors in dogs refractory to standard treatment Paclitaxel (Taxol®) requires extensive premedication and slow infusion (3-24h) due to side effects caused by the solvent Cremophor EL®. The purpose of the phase I/II study was to determine the maximum tolerated dose, toxicity and efficacy of a new micellar, nanoparticulate, water-soluble and Cremophor® EL-free formulation of paclitaxel in 32 dogs with refractory/recurrent solid tumors and high-stage lymphomas.

Paccal® Vet dissolved in Ringer-Acetate, was given as a 15-30 min IV infusion of 175 mg/m² with subsequent dose reduction if toxicity was observed (range 175-100 mg/m²). Treatment was repeated every 21 days for at least 3 cycles or until disease progression. No premedication was needed to be administered. A pharmacokinetic study was performed in 24 dogs.

Results

Thirty-two dogs received paclitaxel. Dose-limiting neutropenia day 6 was observed at 175 mg/m². The mean dose 150 mg/m² was generally tolerated. Other side effects included alopecia, transient inappetence and vomiting/diarrhea. Mild hypersensitivity only occurred in one dog in 96 doses administered. Best overall response (complete- and partial response) per protocol measured after the 3rd treatment was 73.9 %. Mastocytomas (8) and squamous cell carcinomas (4) responded 100 %. The longest complete response (CR) detected was over 30 months (935 days) in a grade II, clinical stage III mastocytoma. The

dog died without any signs of mast cell tumor progression. The quality of life was measured according to a standardized Performance Status Score. According to this; 70 % stayed normal, 17 % mildly decreased, 9 % improved and 1 dog decreased from bad to worse due to progressive disease. In the pharmacokinetic study paclitaxel plasma concentration showed a typical 2-compartment behavior. The α -phase, half-life 10 minutes, accounted for half of the AUC. The β -half-life was 2-7 hours and clearance 16.6 L/h/m² (range 11-33 L/h/m²). Drug distribution into tissues was extensive with a V_{ss} of 57 L/m². This supports the findings in humans.

- This is the first successful trial of a paclitaxel formulation in dogs, also useful in comparative oncology. The extraordinary tumor response and controllable side-effects called for a multicenter trial in selected diagnoses, says Dr Henrik von Euler.

Multicenter one armed open label phase III trial in mast cell tumors grade II and III in dogs refractory to surgery

An open single arm multi-center trial investigates the efficacy and safety in dogs with mastocytoma grade II or III was conducted where curative intent surgery could not be performed. The primary endpoint was efficacy with regard to tumor response documented according to the RECIST criteria. Twenty-nine client-owned dogs were treated and there were no restrictions on age, breed or sex. Prior use of chemotherapy or radiotherapy was not permitted and the life expectancy should be at least one month. The protocol design was one infusion every three weeks for three cycles with a dose of 150 mg/m² administered intravenously during approx 30 minutes. If dose limiting toxicity was experienced the dose could be reduced by 10 mg/m² or the treatment was delayed a maximum of two weeks.

The study was performed at eight sites, six in Sweden and one in Austria, and Germany respectively and was approved by the Regulatory Agencies and Ethics Committees concerned.

Results

Twenty-nine dogs received paclitaxel. The side effects seen in the first trial were present, including alopecia, transient inappetence and vomiting/diarrhea. The neutropenias in the trial was less prominent than in the phase I/II trial and no hypersensitivity reaction was reported. Best overall response (complete- and partial response) per protocol measured after the 3rd treatment in 23 dogs was 69.5 %. If including also stable disease in the per protocol analysis, the response was 100 %, meaning that no one of the 23 receiving three doses of Paccal® Vet relapsed before the time of evaluation. The median progression free survival was 235 days. The quality of life was measured according to a standardized Performance Status Score. According to this; the dogs were almost all normal (score 0) at study entry and they were rarely influenced by the study drug and were practically all normal at the study termination visit.

- There are still no chemotherapeutic agents registered for veterinary use. The usefulness of paclitaxel is well documented in human oncology, but the use has been hampered in dogs due to severe side-effects. Thus, a tolerable formulation would be highly appreciated in veterinary medicine, says Dr Henrik von Euler.

About Paccal® Vet

With the retinoid based unique platform XR-17, Oasmia has managed to produce a water soluble formulation of Paclitaxel (Paccal® Vet), that does not require premedication and abolish Cremophor® EL related side effects. Two clinical trials have been performed in client owned dogs with tumors refractory to standard treatment. The results are very promising,

both regarding tolerability and tumor response. Moreover, the studies show that the findings in the dog are supporting parallel trials in humans, regarding pharmacokinetics and reported side effects. The studies therefore supports the further development towards a registration of the first cytotoxic drug on the large cancer market for companion animals, as well as serves a good comparative model for human oncology.

About mastocytoma (Skin cancer)

Mastocytoma is a malignant form of cancer, originating from the mastocytom cells of the skin. The disease is graded I - III depending on the seriousness of the disease. This form of cancer accounts for approximately 20 % of all malignant skin tumours in dogs. Today, the most common form of treatment is surgery, although chemotherapy developed for human use is also used. Unfortunately, surgery as a treatment of grade III tumours is mostly ineffective, and euthanasia is often the only remaining alternative.

About Oasmia

Oasmia Pharmaceutical AB develops second and third generation cancer drugs based on nanotechnology for human and veterinary use. The broad portfolio is focused on oncology and contains several promising products in clinical and pre-clinical phase. Oasmia cooperates with leading universities and other biotech companies to discover and optimize substances with a favourable safety profile and better efficacy. The company was founded in 1998 and is based in Uppsala, Sweden.

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