

## PRESENTATION SUMMARY

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### Use of GnRH Agonists and Antagonists for Small Animal Contraception

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**GnRH agonist decapeptides.** The advantages of achieving long-term or chronic contraception by means of GnRH agonist-induced down-regulation of pituitary secretion of LH and FSH in dogs and cats are multiple. The method is non-surgical, it allows for reversibility by discontinuation of re-administrations, it can be applied with a large margin of safety to both male and female animals, either pre-pubertally or as adults, and it represents a choice for pet owners and spay clinics. The resulting hypogonadism also prevents or reduces the occurrence of mammary disease and reproductive tract disease, including pyometra in bitches, and can be expected to prevent prostatic hyperplasia in males. Chronic goserelin treatment has been used to suppress ovarian activity as a means to manage mammary tumor development in bitches with hormone dependent mammary carcinoma, and buserelin has been shown to cause involution of spontaneous benign prostatic hyperplasia in dogs to the same extent as did surgical castration.

GnRH agonists may also have a direct antiproliferative effect on canine mammary tumor cells. GnRH-agonist contraception might also have the benefit of reducing or preventing the occurrence of urinary incontinence in contracepted adult bitches in comparison to the frequency of incontinence observed on ovariectomized bitches. Such is suggested by reported palliative effects of deslorelin treatment on symptom monitored in incontinent ovariectomized bitches.

Several GnRH agonists administered in a variety of ways have been shown to affect gonadal suppression or prevent puberty in male or female dogs, including goserelin, buserelin, nafarelin, aza-gly-nafarelin, and deslorelin. Our own data show the ability of azagly-nafarelin to prevent puberty in beagle and mongrel bitches, without the side effect of estrus induction when administered before 4 mos. of age, and with onset of normal cycles after termination of treatment. The agonist suppressed both LH and FSH below normal levels, and prevented the increase in pulsatile LH release associated with the onset of proestrus in dogs. We have also demonstrated that treatment with azagly-nafarelin or another GnRH agonist (lutrelin) during anestrus often causes the induction of a fertile estrus that can result in normal pregnancy if the treatment is discontinued at or shortly after estrus. This response involves the induction of fertile proestrus by the initial burst release of LH and FSH and an insufficient down-regulation of a spontaneous preovulatory surge release of LH.

With continued treatment at effective doses, the fertile estrus is not followed by a successful pregnancy because continued down regulation of LH (and FSH) also suppresses normal progesterone secretion to levels below that required to sustain

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pregnancy. At least two GnRH agonist products are either available or expected to be soon available for contraception in dogs in one or more countries. The Pepetech Ltd. (Australia) deslorelin-containing (4.7 mg) biodegradable '6-month'-implant product, Suprelorin, following extensive clinical trials, has been approved and marketed in Australia for nearly two years and in New Zealand for over one year, with an indication for suppression of testosterone in male dogs for the management of testosterone dependent disease or abnormal behavior. Applications for approval of repeated treatments and for use in females are ongoing. Available clinical data demonstrate its repeated application is able to prevent and delay puberty in females as well as males, and to prevent recurrence of estrus in adult bitches, with the caveat of an induced estrus that is potentially fertile when administered to adult bitches during anestrus. A second generation '1-year' implant is also undergoing evaluation.

Application for use of Suprelorin in Europe has been initiated. Discussions with USFDA regarding trials that would support application for approval in the U.S. are ongoing. Similarly, the Intervet Pharma R&D group has reported on an aza-gly-nafarelin-containing (18.5 mg) "1-year" implant (Gonazon) now undergoing further testing and clinical trials. Gonazon has been shown to reversibly prevent puberty in dogs and is proposed for marketing in Europe. Gonazon implants prevented puberty throughout one year of treatment following a single implant application at 5 mos. of age, and with estrus occurring 1-14 months after the end of treatment. Reports to date suggest that GnRH agonist implant technology will provide safe, effective contraception at potentially reasonable cost. Competition will depend on the size of the market. There are several additional agonists that could be similarly developed and marketed provided they can be married to an implant technology not covered by patents for the two commercial products mentioned above.

The major drawback of the GnRH agonist approach in female contraception is the induction of a normal or false proestrus and estrus in bitches over 5 months of age as a result of the initial gonadal stimulation. This can be overcome by limiting administration to during a managed estrus or early metestrus or to young prepubertal but not peripubertal animals; and by the use of a progestin pretreatment to prevent the induction of estrus in anestrus animals. Exogenous progestin treatments have been reported to effectively inhibit estrus induction in most deslorelin (Suprelorin)-treated anestrus bitches studied. Whether pretreatment or concurrent treatment with a GnRH antagonist at the start of agonist treatment would obviate the occurrence of any resulting proestrus or estrus response and/or the often-associated ovulation response appears not to have been studied and merits investigation because even short-term treatment with exogenous progestin could have unwanted effects in some bitches.

**GnRH antagonist decapeptides.** The use of GnRH decapeptide antagonists is thought to have less potential for long-term contraception in pets for several reasons. The peptides involved are typically more expensive to manufacture, are often only effective at much higher doses involving doses of mg/kg/d versus the ug/kg/d administered by the GnRH agonist products. The high doses requirement in turn limits the potential for combination

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of the antagonists into current long-term release technologies without involving overly large implants or injection depots.

First-generation GnRH antagonists like detirelix also had the problem of histamine release activity, most or much of which has been overcome in many second-generation antagonists like azaline, acyline, degarelix, abarelix, cetorelix, and ganirelix. Some have nevertheless been reported to have significant side effects in some human patients. For example, adverse reactions to cetorelix include nausea and injection site reactions such as redness, bruising, pruritus, and swelling. Peripheral edema and immediate-onset systemic allergic reactions may occur with abarelix and other GnRH antagonists. The GnRH decapeptide antagonists can be effectively and easily used for pregnancy termination. Detirelix was shown to terminate pregnancy following a single 2 mg/kg injection, but was less effective before implantation than after implantation or after day 25. The agonist in combination with a prostaglandin analog preimplantation was more effective than either treatment alone, and prevented pregnancy in 80% of the bitches.

Acyline, a potent second-generation GnRH antagonist shown to suppress pituitary and gonadal activity in men for 15 days after a single dose of 300 ug/kg, was recently reported by Gobello and colleagues to terminate confirmed pregnancies by resorption or abortion in each of 12 bitches within 12 days (avg. 7) following a single application of 110 ug/kg, s.c., at 30-35 days after mating, and did so without observable undesirable side effects. Whether efficacy earlier in pregnancy can be routinely obtained with this or similar analogs alone, or in combination with acceptable doses of a prostaglandin, remains to be determined. Newer third- and fourth-generation decapeptide antagonists have been reported to have increased potency and durations of action and are likely to see further R&D at least for human applications. However, durations are reported in days rather than weeks and even micro-particle preparations have effective durations reported in weeks rather than months. Further, as mentioned above, short-term GnRH antagonist regimens might be useful to prevent the undesired effect of estrus induction in agonist-treated anestrous animals.

**Non-peptide GnRH antagonists.** This new area of research involving non-peptide neuro-modulating drugs that act on the receptors of endogenous releasing-hormone peptides expanded greatly with the Merck Laboratory development of non-peptide orally active molecules that have somatotropin releasing activity.

Nonpeptide GnRH antagonists have been reported and have the potential for not only oral, mucosal or dermal administration, but also the potential to be incorporated into drug release modalities that could differ in technology from the peptide release implants used for the traditional decapeptide agonists and antagonists. Such non-peptide antagonists include CMPD-1 (Pfizer), quinolone-derivatives reported by Merck Labs, thienopyrimidine derivatives (Takada), benzimidazole derivatives (Bayer), and even cyclic derivatives of erythromycin (Abbott Labs). Interesting in this regard was the discovery by Merck researchers that while the dog GnRH receptor has an affinity for GnRH and GnRH-analog peptides similar to that of the human GnRH receptor, the dog receptor had a greatly diminished affinity for at least one class (quinolone-derived) of

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non-peptide GnRH antagonists. The occurrence within the dog GnRH-R of a leucine rather than phenylalanine at AA position 313 accounted entirely for the 150-fold decrease in agonist affinity to the dog GnRH-R. Thus, even though the dog GnRH-R is 92% identical to the human receptor, and responds nearly equivalently to peptide analogs, even some of the very minor differences in AA sequence in their GnRH-Rs may nevertheless adversely affect the application to dogs of non-peptide analogs developed for human medicine.

In humans, *orally* administered daily doses of non-peptide GnRH antagonist (NBI 56418) developed as a potential treatment for endometriosis, at approximately 2 mg/kg, were estradiol-suppressive throughout the 42 days of administration. A sister-compound caused dose-dependent LH-suppression in post-menopausal women during *oral* administration. The biopotencies of these or other non-peptide GnRH antagonists in dogs and their potential for pregnancy termination in bitches merit evaluation, with the goal of developing orally active modalities for prevention and/or termination of pregnancy on an outpatient basis. As the chemistry of GnRH-agonist compounds becomes better understood, their incorporation into long-term release formulations could also have application in long-term pet contraception and chronic management of reproductive hormone dependent diseases, without the side effects of the initial gonadal stimulation seen with the agonists. Chronic administration as a food supplement could also be developed.

**Cats.** Information on efficacy of GnRH analogs in cats is limited. The extent to which modalities successful in dogs can be readily applied to cats is not clear. In female cats, 6 mg Peptech deslorelin implants were reported to suppress ovarian activity for 8-14 months except for one cat that had a breakthrough after 155 days. Additional trials, including other doses and/or implant formulations, may need to be examined before conclusions about expected efficacy in cats can be made. The GnRH peptide antagonist antide was reported to suppress estradiol secretion and estrus activity in cats during a 30-day "treatment period" for which two treatments of 6 mg/kg were administered 15 days apart with estrus activity recurring during the subsequent 90-day period.

Cats may have unique responses to GnRH agonists. One study demonstrated alteration in adrenal fasciculata cell histology following administration of testis stimulating doses of a GnRH agonist, with alterations present even after the reproductive responses had subsided.

**Conclusions and comments.** GnRH-receptor agonists and antagonists clearly have a place in addressing the need of dog and cat owners to have access to effective contraception, estrus suppression and pregnancy termination for their pets. Marketing of the initial agonist products for dogs is likely to expand greatly geographically over the next decade. More research is needed on applications in cats, and on species differences in potencies of non-peptide GnRH antagonists, including study of the latter in both dogs and cats. The ability of these products, as they become more readily available, to address the larger problem of dog and cat overpopulation, to replace surgical methods, or to ease the financial burden of dealing with unwanted animals will depend on the relative costs

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of the products and the marketing strategies of the companies involved. It is important for these products to be approved for and marketed with an indication for use in females. Each sterile or infertile female represents a known prevention of the birth of 1.5 or more litters of puppies or kittens each year. In contrast, the neutering of an individual male simply removes his gene pool from the reproducing population but does not necessarily reduce the number of litters born each year, considering that mating with multiple males during estrus is common in both species.

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