

PRESENTATION SUMMARY & POWERPOINT

Treatment with a Subcutaneous GnRH-Agonist Containing Implant Reversibly Prevents Bitches and Queens from Displaying Puberty, Heat and Ovulation

M.A. Driancourt, S. Rubion, P.O. Desmoulins, A.A.J.J.L. Rutten and A. Flochlay, Intervet Pharma R&D, BP 67131, 49071 Beaucouzé, France

Introduction

In the U.S., early neutering of pets is widely advised by most veterinary surgeons, but the management of the large population of stray dogs and cats still is a problem. In Europe, dog and cat owners usually select one of the three following strategies to manage reproduction of their females. Either they select to neuter before or immediately after first heat, or they let the female produce a litter before neutering or they consider neutering unethical and leave the female intact. With the last two strategies, females may repeatedly display heat and ovulation unless contraceptive treatments are applied. Up to now, the only way to block heat and ovulation and obtain contraception in pets was to use oral or injectable steroidal preparations based on medroxyprogesterone acetate (MPA), Megestrol acetate (MA) or proligestone. While the contraceptive efficacy of such treatments is generally acceptable, long-term administration of such steroids (particularly MPA) is not devoid of side effects (pyometra, mammary tumours).

The development of an alternative long-acting, safe and reversible contraceptive is therefore considered worthwhile. The active included in the selected formulation is a GnRH agonist (azagly-nafarelin). This is because sustained administration of GnRH agonists results in desensitization of the stimulatory effects of GnRH on pituitary cells, therefore reducing LH and FSH concentrations and blocking ovarian function. The final formulation (Gonazon implant) consists of a small silicone implant containing 18.5 mg azagly nafarelin. To allow easy location and removal of implants in bitches, they generally are inserted subcutaneously in the umbilical region, using a user-friendly pre-loaded implantation tool. Alternative implantation sites (neck of queens) have also been used. Insertion is associated with a brief (two weeks long) period of high azagly-nafarelin release, followed by the maintenance of rather steady azagly-nafarelin concentrations, which remain detectable until implant removal (one year in bitches and at least two years in queens). As a consequence, as early as one month post-implantation, FSH concentrations drop to baseline values and remain low until implant removal. Follicular growth, heat and ovulation are therefore prevented. To apply for registration of this controlled release implant, Intervet conducted extensive clinical trials, some of which are summarized below.

Prevention of Heat in Adult Bitches

The ability of Gonazon to safely and efficiently prevent heat and ovulation was assessed in two consecutive one-year-long clinical trials that are summarized below.

First treatment: One hundred and twenty-four animals were enrolled in this clinical trial (run in France, Germany and the Netherlands) and randomly assigned to the Gonazon (n=66) or the placebo (n=58) groups. Bitches were in metestrus at the time of implant administration. They were representative of the overall population for breed, body weight (range 2.5 to 44 kg) and age (1-12 years of age).

After implant insertion, the owner had to check daily if signs of heat occurred up to 12 months post-administration (i.e., at the scheduled time of implant removal). Heat was always confirmed by an extensive veterinary check, including demonstration of ovulation by progesterone measurement following the end of heat. In addition, compulsory veterinary examinations (including collection of blood samples and checks of the presence of the implant) were performed one week and one, six and twelve months after implant administration.

Efficacy was assessed by the duration of heat prevention. The safety criterion was the frequency of adverse effects.

The duration of heat prevention was significantly longer in the Gonazon group (318 ± 97 days) as compared to the placebo group (176 ± 55 days) (Student test, $p < 0.0001$). An effect of age ($p = 0.0343$), but not of body weight ($p = 0.28$), was identified: In young adult bitches (less than 3 years old), the mean duration of prevention of heat was 355 ± 24 days, while in mature bitches (between 3 and 6 years of age), it was 325 ± 93 days. In older bitches, the duration of prevention of heat and ovulation was somewhat shorter.

Clinical signs of treatment-induced heat, when observed, did not interact with the duration of heat prevention. Their frequency was significantly lower in young bitches and when administration of Gonazon was indeed done during metoestrus.

Gonazon proved safe irrespective of body weight, as frequency of pseudo-pregnancy, pyometra, and mammary tumours was low and similar in both treatment and control groups and not higher than in the normal population.

Second consecutive treatment: Bitches that had already had their heat suppressed for one year with a first Gonazon implant in the previous trial (n=28, from Germany, France and the Netherlands) were included in this follow-up trial to document safety and efficacy after a second treatment administration. Following removal of the first implants, bitches were immediately retreated with a new implant. The maximum duration of exposure to this second Gonazon treatment was set at 18 months. After administration of the new implant, the same monitoring that was done during the first year was applied (daily checks by the owner, regular vet checks and confirmation of all heat by a veterinary surgeon).

Session II: What's New in Contraceptive Drugs?

Repeated treatment with Gonazon was very successful, as 92% of the bitches failed to display heat again following the second treatment. Two bitches (20kg-3 years old and 7kg-10 years old) displayed heat before one year, at 11.4 and 11.6 months post-treatment. Induced heat was only observed in two cases (8%).

Finally, it is interesting to note that repeated treatment with Gonazon for two years did not alter body weight of the bitches.

Prevention of Puberty in Young Bitches

To assess the ability of the Gonazon implant to prevent puberty in young (4 months old) bitches, Gonazon (n=10) or a placebo implant (n=10) was administered subcutaneously to prepubertal sister beagle bitches. Duration of treatment was set at one year. Throughout treatment, oestrus behaviour was monitored weekly. Concentrations of progesterone were measured on monthly samples. Body weight and height were also measured monthly. Following implant removal, oestrus detection and progesterone measurement were continued as during treatment until detection of puberty in all bitches.

Control bitches displayed puberty at a mean age of 11.9 months (range 8-16 months) with the first heat always associated with a normal ovulation. There was no induced heat associated with Gonazon administration to prepubertal bitches. Gonazon fully prevented puberty as none of the Gonazon-treated bitches displayed heat during residence of the implant. Side effects such as vaginitis or urinary incontinence were uncommon, irrespective of the treatment group. Body weight and height were unaffected by treatment.

Time to heat after implant removal in the Gonazon-treated group was 8.5 ± 5.2 months (range: 1.2 – 14.3 months). Seven out of 10 bitches naturally displayed their pubertal heat. To keep the study within a reasonable time frame, heat of the remaining 3 bitches was induced using a combined treatment of PMSG (20 UI/kg body weight daily for 5 days) + hCG (500 UI once). In these bitches, signs of heat were observed as early as 4 days (2 bitches) or 5 days (1 bitch) after the beginning of stimulation.

Prevention of Heat and Ovulation in Queens

The efficacy and the safety of Gonazon to prevent oestrus and ovulation in queens was assessed in a study during which queens (6 treated with Gonazon and 6 placebo controls) were continuously housed with vasectomised tomcats.

Efficacy was assessed by the proportion of queens in which ovulation could be demonstrated by high progesterone concentrations in samples collected every other week. Ovulation was detected based on progesterone concentrations reaching at least 10 ng/ml for at least 2 weeks. The proportion of queens ovulating was compared between control and treated groups by chi-square analysis.

Session II: What's New in Contraceptive Drugs?

Results showed that Gonazon was highly efficacious in preventing oestrus in queens for at least 24 months ($p < 0.001$). In the control group, all 6 queens ovulated regularly throughout the treatment period (with 11 periods of high progesterone concentrations per queen for 24 months) while progesterone concentrations of all Gonazon-treated queens declined within the first month of treatment to reach basal levels and none of the 6 queens ovulated later on.

Gonazon also proved to be safe in queens. All subcutaneous implant administrations ($n=6$) were straightforward and painless. No side effects were documented throughout the study.

Conclusion

These data conclusively demonstrate that the Gonazon implant containing 18.5 mg azagly-nafarelin is a safe and efficient approach to obtain long-term and reversible prevention of heat in female pets. Treatment may be started before puberty or once the first pubertal heat has occurred. Treatment may be repeated. Gonazon is therefore a useful strategy to manage reproduction of female pets until owners have made a decision on whether and when they want to neuter. In addition, for bitches that cannot undergo anaesthesia or bitches from breeds prone to urinary incontinence following spaying, the Gonazon implant may be an efficient alternative to neutering. Finally, owing to the long-term efficacy of Gonazon in queens (at least two years), insertion of a Gonazon implant may be a novel approach to keeping the population of stray queens under control.

In addition, preclinical and clinical studies in male dogs have also established the ability of Gonazon to reduce testosterone concentrations (therefore putting androgen-dependent pathologies under control).

This non-surgical technology may therefore be a promising, safe (non-steroidal) and flexible (working in males and females, as well as in dogs and cats) new contraceptive approach for pets.

Session II: What's New in Contraceptive Drugs?

GnRH Analogs: Progress

By Dr. Marc Antoine Driancourt

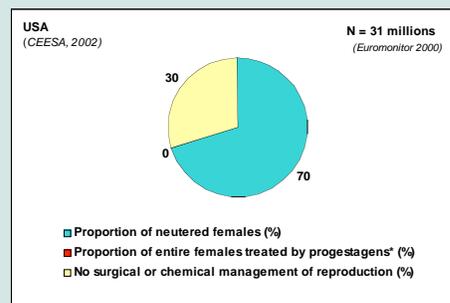
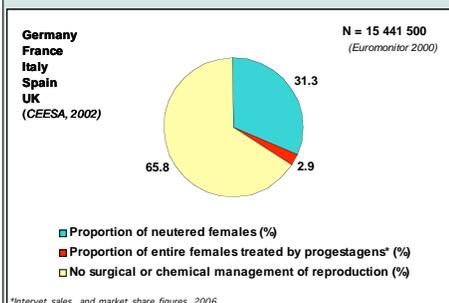
Prevention of puberty, heat and ovulation of bitches and queens by Gonazon, a GnRH agonist implant



M.A. Driancourt, S. Rubion, P.O. Desmoulins, F. Rutten and A. Flochlay
Intervet Pharma R&D, BEAUCOUZE, France



Management of reproduction in bitches... European and U.S. approaches?



But the management of stray dogs and cats remains a difficult issue



Session II: What's New in Contraceptive Drugs?

GnRH Analogs: Progress

By Dr. Marc Antoine Driancourt

Gonazon is a controlled release implant, containing 18.5 mg of azagly-nafarelin, a potent GnRH agonist, and releasing it over a one-year period

- Gonazon is pre-loaded in the needle of a user-friendly disposable implanting tool.
- Its recommended administration site is under the skin of the belly, near the umbilicus (to allow easy retrieval).
- It can also be injected in the neck (queens).



Intervet

RESEARCH • PERFORMANCE • INTEGRITY

Gonazon can safely be used in prepubertal as well as in adult bitches (clinical trials data)

1. In prepubertal bitches
 - No increase in body weight and bitch's size during treatment
 - No side effects detected in the treated group except vaginitis at a low frequency (4%)
2. In adult bitches
 - No increase in body weight associated with treatment
 - No occurrence of urinary incontinence in the treated group
 - No increase in the occurrence of pseudo-pregnancy (control 19% vs. treated 15%), pyometra (2% in each group) and mammary tumors (2% in each group)

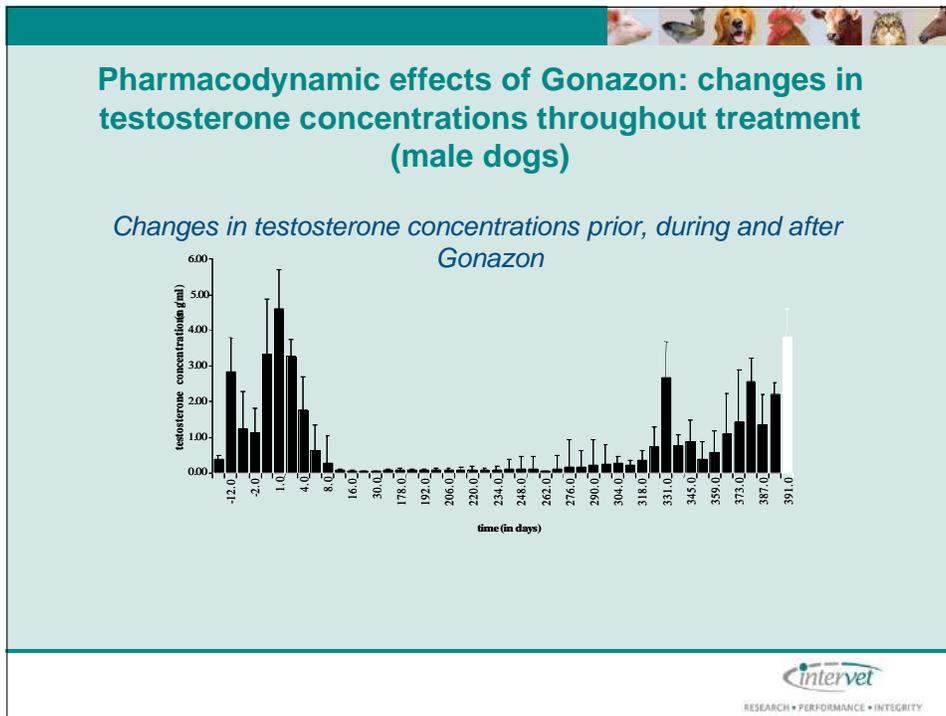
Intervet

RESEARCH • PERFORMANCE • INTEGRITY

Session II: What's New in Contraceptive Drugs?

GnRH Analogs: Progress

By Dr. Marc Antoine Driancourt



Efficacy of Gonazon to prevent heat and ovulation in adult bitches

EXPERIMENTAL PARADIGM: GCP clinical trial involving 124 bitches (66 treated and 58 placebo) in 3 countries. Bitches 1-6 years of age. Weight between 2.5 and 44 kg. Implantation during metestrus for one year.

RESULTS

- Duration of suppression of heat in the Gonazon treated group: 336 +/- 71 days (vs. 161 +/- 72 days for the placebo group)
- Efficacy similar in the three (2.5-15, 15-30 and over 30 kg) body-weight groups
- Proportion of induced heat related to progesterone concentrations at implantation (20% if P4 over 10 ng/ml)

intervet
RESEARCH • PERFORMANCE • INTEGRITY

Session II: What's New in Contraceptive Drugs?

GnRH Analogs: Progress

By Dr. Marc Antoine Driancourt

Repeated treatment with Gonazon: efficacy results

Experimental paradigm

- 28 bitches whose heat and ovulation were successfully suppressed after insertion of a first Gonazon for one year
- Treated with a new Gonazon for one year

Results

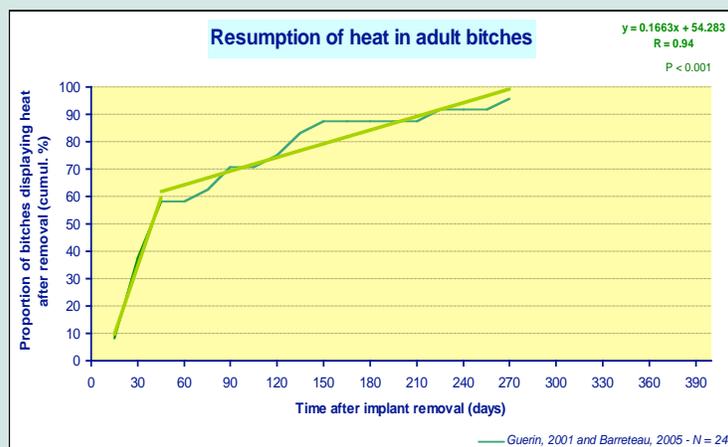
- 92% efficacy (26/28 suppressed again for a year)
- Only two induced heat

Conclusion

REPEATED TREATMENT WITH GONAZON IS SAFE AND EFFECTIVE


RESEARCH • PERFORMANCE • INTEGRITY

Reversibility of treatment effects once Gonazon is removed: heat resumption (adults)



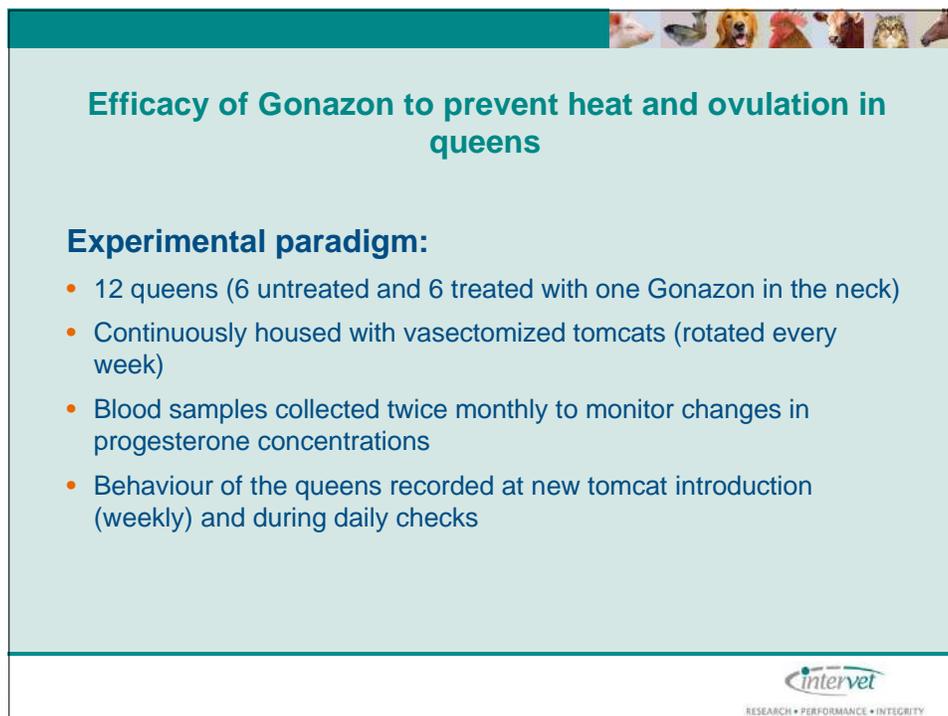
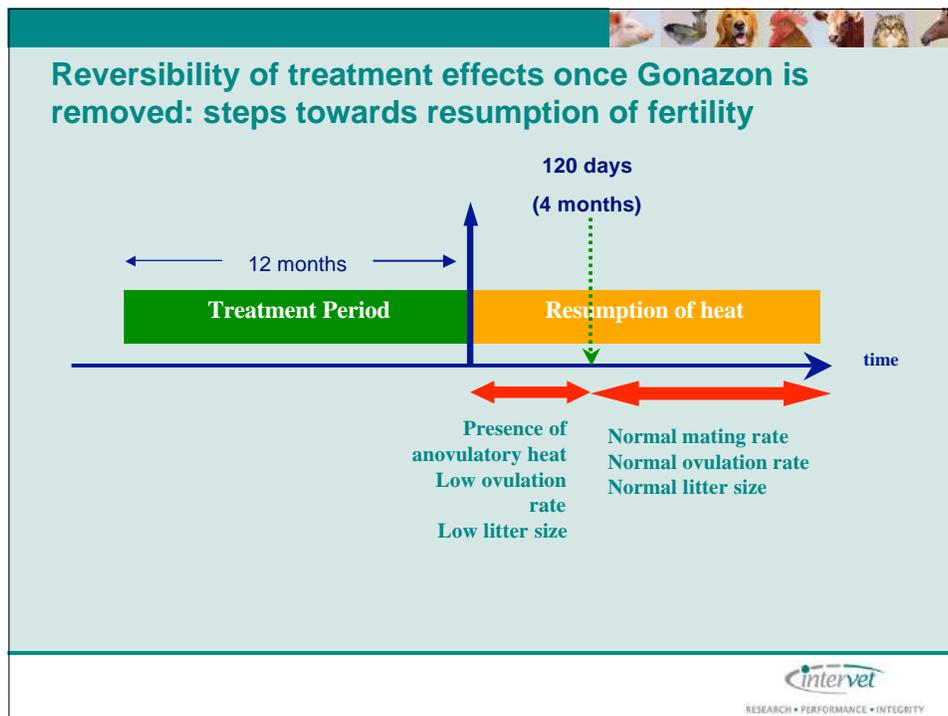
The blocking effects of Gonazon on heat are therefore fully reversible


RESEARCH • PERFORMANCE • INTEGRITY

Session II: What's New in Contraceptive Drugs?

GnRH Analogs: Progress

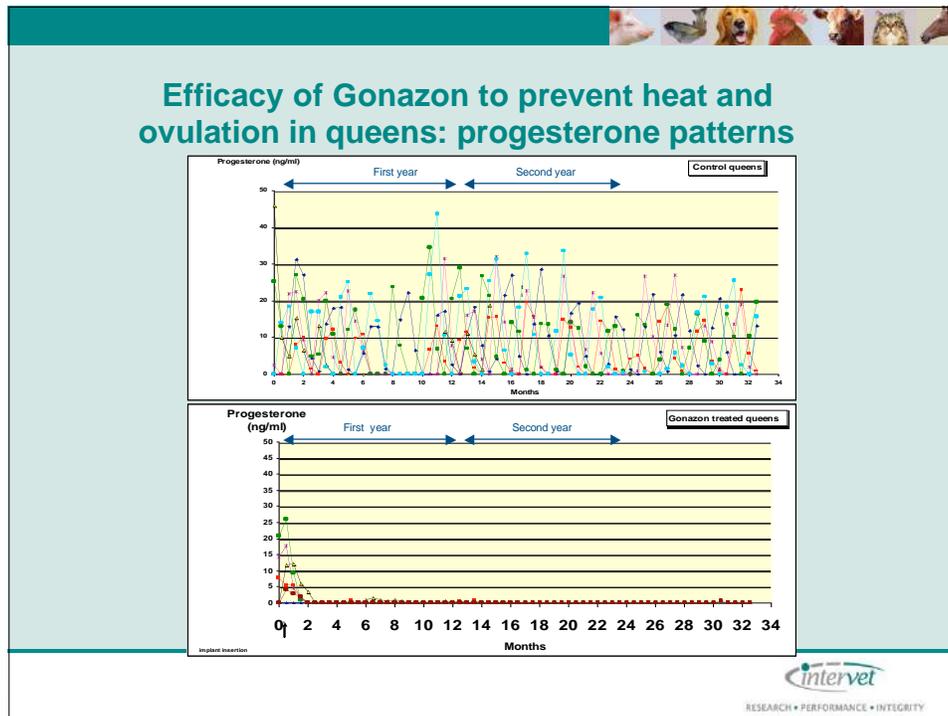
By Dr. Marc Antoine Driancourt



Session II: What's New in Contraceptive Drugs?

GnRH Analogs: Progress

By Dr. Marc Antoine Driancourt



CONCLUSIONS

GONAZON IS

- The first long-term (one year long) chemical contraceptive undergoing the last pre-approval steps in Europe (CVMP) for bitches
- Under patent protection until 2008
- A very safe contraceptive owing to the high safety margin of GnRH agonists
- If the Gonazon implant is not removed, prevention of heat lasts for around 16 months in bitches and close to 3 years in queens
- A very **flexible tool** to manage reproduction of pets (cats and dogs), irrespective of their sex (females and males), their age (prepubertal and adults) and (when adult) of the stage of their cycle at treatment

intervet
RESEARCH • PERFORMANCE • INTEGRITY

Session II: What's New in Contraceptive Drugs?

GnRH Analogs: Progress

By Dr. Marc Antoine Driancourt



CONCLUSIONS

A novel and humane approach to limit reproduction of stray cats?

A new tool for vets to manage dog reproduction

Bloody hell! I will have to wait until her implant is removed!



intervet
RESEARCH • PERFORMANCE • INTEGRITY