

# Efficacy and safety of 4.7mg deslorelin acetate implants in suppressing oestrus cycle in prepubertal female dogs.

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## Supplementary material

**Table S1.** Parameters of inclusion and non-inclusion criteria for the animals entering the study protocol and withdrawal criteria.

| Criteria                                  | Characteristics used in the study protocol  |
|---|---|
| <b>Inclusion criteria</b>                 | Obtention of owner's informed consent (prior to the start of the study)<br>Pre-pubertal intact healthy female dogs<br>Dogs aged between 12 and 18 weeks<br>Normal genital appearance (e.g. no vulvar discharge)<br>Normal ultrasound examination of the reproductive system<br>Animals maintained in a controlled environment that allows for daily observation of pro-oestrus or oestrus (i.e. heat) sign<br>Availability of the animals for the entire duration of the study  |
| <b>Non-Inclusion criteria</b>             | Vulvar deformity<br>Vaginitis<br>Reproduction-related hormonal administration (since birth)<br>Sexually mature animal prior to treatment administration confirmed by clinical or ultrasound examination (e.g. pro-oestrus or oestrus signs, pregnancy)<br>Any concomitant disease that may interfere with the evaluation of the treatment<br>Any animal owned by an Investigator or Dispenser involved in the study   |
| <b>Withdrawal criteria (during study)</b> | Occurrence of an adverse event which may interfere with the evaluation of the study treatment<br>Detection of a sexually mature animal (i.e. silent heat or clinical heat) anytime between D1 and Day 21 post-treatment administration<br>Confirmation of sexual maturity prior to treatment administration upon reception of Day 0 laboratory results<br>Abnormal laboratory results in the pre-treatment sample<br>Sterilization becoming mandatory for the animal during the study<br>Major protocol deviation (from the owner or the investigational team)<br>Withdrawal of the Owner's consent |

**Table S2.** Proportion of the breeds within each group (deslorelin and control) reported at inclusion.

| Reported Breed at Inclusion    | Deslorelin group (n=59) | Placebo group (n=21) |
|--------------------------------|-------------------------|----------------------|
| American bully- exotic         | -                       | 4.8% (n=1)           |
| American Pit Bull Terrier      | 3.4% (n=2)              | -                    |
| American Staffordshire terrier | 1.7% (n=1)              | -                    |
| Andalusian rat - hunting dog   | 1.7% (n=1)              | -                    |
| Australian Shepherd            | 1.7% (n=1)              | -                    |
| Beagle                         | 1.7% (n=1)              | -                    |
| Beauceron                      | 1.7% (n=1)              | -                    |
| Boston terrier                 | 1.7% (n=1)              | -                    |
| Boxer                          | 3.4% (n=2)              | -                    |
| Chihuahua                      | 1.7% (n=1)              | -                    |
| Corso Dog                      | -                       | 4.8% (n=1)           |
| Czechoslovakian Wolfhound      | 1.7% (n=1)              | -                    |
| English Setter                 | 5.1% (n=3)              | 14.3% (n=3)          |
| Fila Brasileiro                | -                       | 4.8% (n=1)           |
| French Bulldog                 | 1.7% (n=1)              | -                    |
| German Shepherd                | 1.7% (n=1)              | 14.3% (n=3)          |
| German Shorthaired Pointer     | 3.4% (n=2)              | -                    |
| Golden Retriever               | 1.7% (n=1)              | -                    |
| Great Dane                     | 1.7% (n=1)              | -                    |
| Labrador Retriever             | 3.4% (n=2)              | -                    |
| Malinois                       | 1.7% (n=1)              | -                    |
| Maltese                        | -                       | 4.8% (n=1)           |
| Miniature Pinscher             | -                       | 4.8% (n=1)           |
| Miniature Schnauzer            | 1.7% (n=1)              | -                    |
| Parson Russell Terrier         | 3.4% (n=2)              | 4.8% (n=1)           |
| Petit Basset Griffon Vendeen   | 3.4% (n=2)              | 4.8% (n=1)           |
| Podengo                        | 1.7% (n=1)              | 9.5% (n=2)           |
| Poodle*                        | 5.1% (n=3)              | -                    |
| Pug                            | 1.7% (n=1)              | -                    |
| Samoyed                        | 1.7% (n=1)              | -                    |
| Shih Tzu                       | 1.7% (n=1)              | -                    |
| Siberian Husky                 | 1.7% (n=1)              | -                    |
| Spanish Greyhound              | 1.7% (n=1)              | -                    |
| Spitz Papillon                 | 1.7% (n=1)              | -                    |

|                              |                 |                 |
|------------------------------|-----------------|-----------------|
| Wirehaired Dachshund         | 1.7% (n=1)      | -               |
| Wirehaired Pointing Griffon  | -               | 4.8% (n=1)      |
| Yorkshire Terrier            | 3.4% (n=2)      | -               |
| % of purebred vs. mixed bred | 54.2% vs. 45.8% | 52.4% vs. 47.6% |
| Not specified breed          | 28.8% (n=17)    | 23.8% (n=5)     |

\* can be either a Poodle, a Miniature Poodle or a Toy Poodle.

**Table S3:** Duration of effect of the deslorelin implant when assessed as the primary efficacy endpoint: the effect was reversible over time, with a maximum duration of 708 days in the deslorelin group (23 months maximum) vs. 436 days in the placebo group (14 months maximum).

| Time interval for sexual maturity occurrence |  | Sexually matured animals<br>deslorelin group<br>(n=59) | Placebo group<br>(n=21)  |
|--|--|--|--------------------------|
| [0 - 6] months post implantation             | N of animals<br>% within the group                     | n=4 *<br>6.7%  | n=6<br>28.6%             |
| [6 - 9] months post implantation             | N of animals<br>% within the group                     | n=9<br>15.3%   | n=10<br>47.6%            |
| [9 - 12] months post implantation            | N of animals<br>% within the group                     | n=16<br>27.1%  | n=1<br>4.8%              |
| [12 -18] months post implantation            | N of animals<br>% within the group<br>Maximum duration | n=23<br>39.0%  | n=4<br>19.0%<br>436 days |
| [18 - 24] months post implantation           | N of animals<br>% within the group<br>Maximum duration | n=7<br>11.9%<br>708 days                               | n=0<br>0.0%              |
| > 24 months post implantation                | N of animals<br>% within the group                     | n=0<br>0.0%  | n=0<br>0.0%              |

\* details for these animals: three dogs, implanted over 16 weeks of age, expressed an induced oestrus after implantation. For one dog, the duration of effect was 5.5 months.

**Table S4:** Adverse events reported in the deslorelin and control groups.

|                              | Deslorelin group (n=62) |                | Placebo group (n=21) |                | p-value |
|------------------------------|-------------------------|----------------|----------------------|----------------|---------|
|                              | Number of animals       | % within group | Number of animals    | % within group |         |
| Lameness                     | 8                       | 12.9           | -                    | -              | -       |
| Emesis                       | 6                       | 9.7            | 1                    | 4.8            | -       |
| Dermatitis and eczema        | 5                       | 8.1            | -                    | -              | -       |
| Diarrhoea                    | 5                       | 8.1            | -                    | -              | -       |
| Vulvovaginitis               | 4                       | 6.5            | 4                    | 19.0           | -       |
| Abnormal oestrus*            | 3                       | 4.8            | -                    | -              | -       |
| Lethargy                     | 3                       | 4.8            | -                    | -              | -       |
| Unclassifiable adverse event | 3                       | 4.8            | -                    | -              | -       |
| Anorexia                     | 2                       | 3.2            | -                    | -              | -       |
| Cough                        | 2                       | 3.2            | -                    | -              | -       |
| Dehydration                  | 2                       | 3.2            | -                    | -              | -       |

|  | Deslorelin group (n=62) |                | Placebo group (n=21) |                | p-value |
|--|-------------------------|----------------|----------------------|----------------|---------|
|  | Number of animals       | % within group | Number of animals    | % within group |         |
| Gastritis  | 2                       | 3.2            | -                    | -              | -       |
| Joint pain*                                      | 2                       | 3.2            | -                    | -              | -       |
| Pruritus   | 2                       | 3.2            | -                    | -              | -       |
| Trauma*  | 2                       | 3.2            | 1                    | 4.8            | -       |
| Aggression                                       | 1                       | 1.6            | -                    | -              | -       |
| Alopecia   | 1                       | 1.6            | -                    | -              | -       |
| Bacterial skin infection                         | 1                       | 1.6            | -                    | -              | -       |
| Bronchitis                                       | 1                       | 1.6            | -                    | -              | -       |
| Cartilage degeneration                           | 1                       | 1.6            | -                    | -              | -       |
| Conjunctivitis                                   | 1                       | 1.6            | 1                    | 4.8            | -       |
| Death  | 1                       | 1.6            | -                    | -              | -       |
| Dermal cyst(s)                                   | 1                       | 1.6            | -                    | -              | -       |
| Dermal mass                                      | 1                       | 1.6            | -                    | -              | -       |
| Dyspnoea   | 1                       | 1.6            | -                    | -              | -       |
| Fracture   | 1                       | 1.6            | -                    | -              | -       |
| Haemorrhagic diarrhoea                           | 1                       | 1.6            | -                    | -              | -       |
| Hyperactivity                                    | 1                       | 1.6            | -                    | -              | -       |
| Hyperthermia                                     | 1                       | 1.6            | -                    | -              | -       |
| Infarction                                       | 1                       | 1.6            | -                    | -              | -       |
| Localised pain*                                  | 1                       | 1.6            | -                    | -              | -       |
| Myopathy   | 1                       | 1.6            | -                    | -              | -       |
| Nail disorder*                                   | 1                       | 1.6            | -                    | -              | -       |
| Neuromuscular disorder*                          | 1                       | 1.6            | -                    | -              | -       |
| Oedema*  | 1                       | 1.6            | -                    | -              | -       |
| Otitis externa                                   | 1                       | 1.6            | -                    | -              | -       |
| Otitis*  | 1                       | 1.6            | -                    | -              | -       |
| Pica*  | 1                       | 1.6            | -                    | -              | -       |
| Polydipsia                                       | 1                       | 1.6            | -                    | -              | -       |
| Polyuria   | 1                       | 1.6            | -                    | -              | -       |
| Sexual disorder*                                 | 1                       | 1.6            | -                    | -              | -       |
| Skin oedema                                      | 1                       | 1.6            | -                    | -              | -       |
| Tachycardia                                      | 1                       | 1.6            | -                    | -              | -       |
| Tachypnoea                                       | 1                       | 1.6            | -                    | -              | -       |
| Anxiety  | -                       | -              | 1                    | 4.8            | -       |
| Cataract   | -                       | -              | 1                    | 4.8            | -       |
| Corneal ulcer                                    | -                       | -              | 1                    | 4.8            | -       |
| Genital tract pruritus                           | -                       | -              | 1                    | 4.8            | -       |
| Lens disorder*                                   | -                       | -              | 1                    | 4.8            | -       |
| Sneezing   | -                       | -              | 1                    | 4.8            | -       |
| Uveitis  | -                       | -              | 1                    | 4.8            | -       |
| Total of animals with at least one adverse event | 31                      | 50.0           | 6                    | 28.6           | 0.0877  |

\* No further details provided by the investigators or owners

Table S5: Details of reproductive performances over up to 24 months after the occurrence of the first heat.

| Group      | Breed   | Time period after the first heat | Litter size (number of puppies) | Observations  |
|------------|---|----------------------------------|---------------------------------|---|
| Placebo    | English setter                                  | 6 months                         | 2                               |   |
| Deslorelin | Great dane                                      | First heat                       | 9 + 1 stillborn                 |   |
| Deslorelin | Parson russell terrier x basset griffon vendeen | First heat                       | 5                               |   |
|            |   | 13.5 months                      | N/A                             | The female died in labor.   |
| Deslorelin | Pitbull terrier                                 | First heat                       | 7                               |   |
|            |   | 7 months                         | N/A                             | The female was spayed at one month of gestation to end this unwanted pregnancy. |
| Deslorelin | Beagle  | 8 months                         | 6                               |   |
| Deslorelin | Wire-haired dachshund                           | 9 months                         | 1                               | The female was inseminated and mated.   |
| Deslorelin | Pitbull terrier                                 | 7 months                         | N/A                             | The female was spayed at one month of gestation to end this unwanted pregnancy. |
| Deslorelin | French bulldog                                  | 2 years                          | 6                               | Caesarean.  |

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