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Safety and antibody response elicited by LetiFend® in two multicenter post-authorization studies in Spain

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Background

Canine visceral leishmaniosis (CanL) is a zoonotic disease caused by a parasite of the genus *Leishmania*. As dogs are a main reservoir of infection for humans, vaccinating these animals is key to controlling and eliminating this disease [1].

Currently, there are two registered vaccines against CanL: Leish-Tec® (Ceva) available in Brazil and LetiFend® (LETI Pharma) in the EU. This last vaccine, which contains the multiepitope recombinant protein Q (PQ) and lacks an adjuvant, reduces the risk of developing CanL after a single annual dose [2].

Vaccines are prescribed for healthy seronegative dogs older than six months, so their safety is of special concern. The aim of this study was to evaluate the safety of LetiFend® in dogs of different ages, breeds and sizes under field conditions during two consecutive years in two clinical post-authorization studies.

Materials and methods

The two studies were GCP, multicenter and voluntary and were conducted in areas of Spain endemic for CanL (Alicante, Barcelona, Ibiza, Madrid, Sevilla). Procedures were approved by the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) and by the Independent Ethics Committee for Animal Experimentation of the Universidad Complutense de Madrid.

The dogs enrolled were 61 owned dogs older than 6 months. After their examination on Day -7, 50 animals fulfilling the inclusion criteria (ie, healthy, seronegative) were vaccinated with a single subcutaneous dose (0.5 mL) of LetiFend® on Day 0 (Study I). Testing procedures were conducted on Days 0, 14 and 28. In study II, 38 of the 50 dogs included in the study I were re-examined as candidates for revaccination on Days 275 and 358, and 36 of these dogs were revaccinated on Day 365. These animals were also tested on Days 379, 393, 429 and 533. Examination procedures included local and general tolerance to the vaccine, physical examination and blood sampling for Immunofluorescence Antibody Test (IFAT), ELISA anti –*Leishmania*, ELISA PQ, complete blood count and biochemical profile. Adverse events were recorded, and their causality was assessed according to the ABON system [3].

Results

Throughout the study, all dogs tested seronegative for *L. infantum* except one dog which tested positive from day 393 and was classified as a healthy infected dog.

All clinical-pathological biomarkers remained within the normal range. During the post-vaccination period, 11 non-serious adverse events and one serious adverse event were recorded. Of these events, only mild transient local oedema at the inoculation site which was self-limiting within 24 h was classified as 'possibly-related to treatment'. After revaccination, there were four non-serious adverse events, none considered potentially vaccine-related.

After vaccination on Day 0, anti-PQ antibody titres increased significantly ($p < 0.0001$), and then, after peaking on Day 14 ($p < 0.0001$), started to decline on Day 28, reaching minimum levels on Day 245. After revaccination on day 365, antibody levels peaked on day 379 ($p<0.0001$) and started to decline on day 393, though were still significantly higher than the levels recorded on Days 365, 429 and even 533 (p

< 0.0001). The peak observed after revaccination was clearly higher and longer-lasting than that after the first vaccine, with antibody levels not returning to baseline at the end of the study period.

Conclusions

The safety of vaccination and revaccination with LetiFend® was confirmed under field conditions in CanL endemic areas. Vaccination induced a transient increase in anti-PQ antibodies, and revaccination one year later generated higher and longer-lasting antibody levels, which were still detectable 6 months after revaccination. The antibody response to the vaccine did not interfere with the detection of anti-*L. infantum* antibodies. This allowed for discrimination between vaccinated and naturally infected dogs, thus confirming Letifend® as a DIVA vaccine.

References

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Trial registration: DMV/GEST/CSM, EU/2/16/195/001-008, OH-CEA-UCM-31-2016, PROEX 113/17.