still present for the patients that were under therapy after 42 months.

**Results:** Following section of the ACL, all dogs developed functional impairment, but there was less loss of PVF in dogs treated with any of the tested doses of AS902330 than in controls. In placebo-treated dogs, the evolution of structural damage over time (weeks 4–26) correlated with worsening limb function as expressed by PVF. As early as week 8 (i.e. at the end of intra-articular therapy), differences in joint functionality could be detected between AS902330-treated dogs and placebo-treated dogs. At week 8, mean PVF loss in the AS902330-treated group given 30 μg/joint was 36.3% of baseline values, versus 47.8% in controls (p = 0.082; Mann-Whitney U test). A significant difference in PVF loss was also seen between AS902330 30 μg and saline at week 14 (26.2% vs 44.4%, p = 0.007). The difference between groups (AS902330 30 μg vs saline) was less pronounced at weeks 20 and 26 (35.2% vs 38.5%; 23.9% vs 33.5%, respectively). Measures of contact area followed a similar pattern to PVF. Macroscopic gross pathology and microscopic evaluation of cartilage using the International Cartilage Repair Society scoring system revealed clear reduction in the severity of cartilage lesions in AS902330-treated dogs compared with controls at the end of therapy (8 weeks) and after longer term follow-up (26 weeks). In addition, immunostaining for catabolic factors (e.g. matrix metalloproteinases, inducible nitric oxide synthase) revealed a reduction in staining in the cartilage of AS902330-treated dogs, which was maintained up to the end of the study period (26 weeks). Systemic exposure after intra-articular administration of AS902330 was below the lower limit of quantification (50 pg/mL).

**Conclusions:** Intra-articular injection with the anabolic agent AS902330 was shown to reduce progression of structural damage and alleviate limb impairment in an ACL model of OA in dogs. The reduction in catabolic parameters in the OA joint of treated animals, improved histopathology scoring, and the improved functionality compared with saline-treated controls support the hypothesis that treatment with rHGF18 may influence the course of OA and reduce functional impairment.