INTRODUCTION
Due to the ageing of the population the number of patients suffering from osteoarthritis is increasing. With no cure for the disease yet, an urgent need for new strategies to develop osteoarthritic therapies exists. Patients are currently diagnosed when the disease has already entered a stage with progressive joint damage. Failure to develop therapies for these patients suggests that the degenerative changes in the joint are probably no longer sensitive to treatment. It is therefore important that early diagnosis of osteoarthritis becomes available when treatment can still halt or even reverse the cartilage destruction. Animal models that reflect the early stages of human osteoarthritis are helpful tools to discover early osteoarthritis biomarkers and to test new treatments that are aimed at intervention in this early stage.

Our goal was to develop a guinea pig model with only mild forms of osteoarthritis that could serve as a model for early human osteoarthritis. Classic biomarkers of joint destruction were evaluated in this model for their relevance to monitor early osteoarthritis. Furthermore, treatment strategies able to suppress osteoarthritic features in other animal models were tested for effectiveness in this model.

METHODS
Osteoarthritis was surgically induced by bilateral transection of the meniscus in Dunkin-Hartley guinea pigs. The surgical procedure was minimally invasive to avoid cartilage damage due to inflammatory reactions and/or intra-articular bleeding. The severity of osteoarthritis was assessed both macroscopically and histologically at different time points after surgery (4, 8, and 12 weeks). Serum and urinary biomarkers, i.e., cartilage oligomeric matrix protein (COMP), pyridinoline cross-links (HP and LP), and type II collagen C-telopeptide cross-link (CTX-II), were determined during the development of osteoarthritis. The effectiveness of different treatment strategies was evaluated in a 12-week study design. Guinea pigs were treated daily from the day of surgery onwards with Risedronate (0.15 mg/kg s.c.), Pioglitazone (20 mg/kg p.o.), Anakinra (5 mg/kg s.c.), and Galardin (0.5 mg/kg p.o.). Differences between groups were analysed with ANOVA followed by post hoc Tukey tests. The studies were approved by the Ethical Committee on Animal Experiments of TNO conform the Dutch legislation.

RESULTS
Four weeks after meniscal transection small lesions in the cartilage were macroscopically observed at the medial side of the joint, starting at the femoral head and the central part of the tibial plateau. Clear, but mild progression of osteoarthritis was detectable over time. Within a timeframe of 12 weeks the lesions were still restricted to the medial side of the joint and did not reach into the subchondral bone. At week 8 and 12 mild signs of osteoarthritis were observed in the control and sham groups as well due to the susceptibility of the Dunkin-Hartley strain to the spontaneous development of osteoarthritis. However, at all times the macroscopic score of the meniscal transection group was higher than of these control groups (Fig. 1). Increased cartilage destruction in the meniscal transection group was also histologically observed at week 8 (Fig. 2). Of the urinary biomarkers tested, only CTX-II levels were significantly increased in the meniscal transection group compared to the control group, but only at week 8 after surgery. No increase in HP/LP ratio, a measure for the relative turnover of cartilage bone metabolism, was observed in the meniscal transection group within 12 weeks after surgery. Furthermore, COMP levels in the serum of the meniscal transection group were not different from the sham or control group.

Strategies for treatment were chosen such that different processes in osteoarthritis development were targeted: bone destruction (Risedronate), inflammation (Pioglitazone and Anakinra), and cartilage destruction (Galardin). Unfortunately, none of these treatments showed beneficial effects on the macroscopic osteoarthritis score in the macroscopic transection model.

DISCUSSION
Mild joint destruction was macroscopically and histologically observed in the first 12 weeks after bilateral transection of the medial meniscus in Dunkin-Hartley guinea pigs. However, these early degenerative changes in the cartilage matrix could not be detected by classic biomarkers. Probably, the cartilage destruction is still too mild to be measured in the systemic circulation. Further research into new biomarkers is needed to be able to detect and monitor the early stages of osteoarthritis. Promisingly, we were not able to show sensitivity to treatment in this model with the selected compounds. This further underscores the urgent need for a new generation of drugs.