Introduction
Subcutaneous apomorphine is currently used for the management of sudden, unexpected and refractory oral LD-induced "off" states in fluctuating PD patients either as intermittent rescue injections or continuous infusions [1].

Apomorphine hydrochloride provides a similar level of motor benefit to LD as well as a possible anti-dyskinetic effect [2]. These have also been sporadic reports of its possible beneficial effect on non-motor symptoms, commonly appearing in PD patients and affecting their quality of life. Nevertheless, its long-term use is limited by compliance and injection site skin reactions, resulting in the formation of nodules that can cause discomfort and may impact the effectiveness of the drug therapy [3].

Neuroderm Ltd (Rehovot, Israel) has developed a novel apomorphine formulation, ND0701, for continuous subcutaneous delivery that contains apomorphine-base. In preclinical studies we detected superior local safety and tolerability with equivalent PK of up to 5 fold concentrated apomorphine in comparison to a commercially available apomorphine-HCl.

Objective
The aim of this study was to investigate the local safety and PK of a newly developed, concentrated, formulation of apomorphine-base, ND0701-2.5%, as compared to a commercially available apomorphine-HCl, in pigs.

Methods
Domestic Landrace × Large White pigs, 3 males and 3 females, weighting 45±3 kg were administered a single continuous SC infusion of 50 mg apomorphine for 20 - 24 hours. ApoGo® 10 mg/ml apomorphine-HCl (Britannia Pharmaceuticals, UK), was used as a reference. In all experiments, 4 formulations were compared: 1% ND0701, 2.5% ND0701, 0.5% apomorphine-HCl or 1% apomorphine-HCl.

The following analyses were made:
PK analysis
Was quantified using LC-MS/MS.

In vivo MRI
MRI scans of infusion site were performed using a 0.35 T/0.3T Magnetom-C Siemens MRI machine.

Ex-Vivo MRI
MRI scans of fixed tissue samples (i.e., injection sites) were performed, from using a 1 Tesla M2TM Aspect imaging MRI machine.

Histopathological evaluation
The histological evaluation consisted of a subjective description of the observed tissue reaction. The scoring of the lesions was done using a semi quantitative system based on the criteria explained by Shackleford et al. [4].

Results
The pharmacokinetic (PK) profile of apomorphine following continuous SC administration was similar among all 4 tested formulations.

Lesions’ volume was significantly smaller following administration of ND0701 as compared to apomorphine-HCl. Size of the lesions was reduced by 5-5.5 fold 4 weeks following ND0701 versus only 3-3.2 fold following apomorphine-HCl administration.

The SC inflammation seen in the ND0701 infused sites exhibited only a minimal, chronic inflammatory reaction characterized by the presence of mixed inflammatory cell infiltration, with no multinucleated giant cells.

Conclusions
Results suggest that even at concentrations 2.5-5 times higher than apomorphine-HCl, ND0701 causes a considerably milder infusion site reaction when compared to apomorphine-HCl.

MRI may provide a quantitative tool for the assessment of subcutaneous reactions and for monitoring the progression and recovery of lesions following infusion of newly developed drug products.

The findings set forth the development of a new apomorphine product that could provide a safer, more tolerable and convenient alternative to current apomorphine commercial preparations, that could be delivered by a small volume, discrete patch pump for the treatment of motor complications in advanced PD.

References