Categories of toxicity associated with AAV for pain

Serological immunity
- Neutralizing antibodies will be induced but no related adverse effects to be expected
- No additional pre-clinical studies

General toxicity
- Insertional mutagenesis, germ line transmission or replication escape not reported in large animals or humans
- No additional pre-clinical studies

Effects of serotypes
- AAV2 & AAVrh10 safe for intraparenchymal injection in humans
- AAV8 not tested for safety in the IT/IG route
- AAV9 safe for IT in large animals
- No additional pre-clinical studies for IG
- AAV2/AAVrh10 or for IT AAV9
- Assess biodistribution of AAV8 in large animal model

AAV (vector effect without transgene)
- Cellular immunity: a possibility suggested by some AAV studies targeting the liver in humans; not seen in other studies or in CNS-targeted delivery of AAV in any species
- Animal studies found to be poorly predictive for humans. Focus of translational development therefore on assessment of toxicity in phase I/II clinical studies including histopathological exam of post-mortem tissue specimens to the DRG

Transgene
- ppβEP
  - Toxicity dose-related: use toxicity assessment framework known from pharmacology of opioids
  - MTD in large animals and dose-escalation in humans

Route of Delivery
- IT
  - Lumbar puncture is a safe bedside procedure in patients
  - No additional pre-clinical studies
- IG
  - Minimally invasive CT-guided injection validated in pigs
  - Assess procedure-related safety in large animal model using clinical interventional procedure equipment

- IL-10
  - Flu-like symptoms and potential immunosuppression
  - MTD in large animals and dose-escalation in humans