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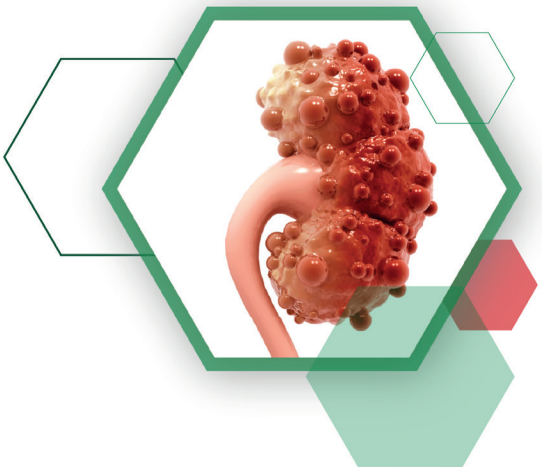


In Vivo ADPKD Mouse Model

Compound testing for polycystic kidney disease via a conditional *Pkd1* knockout model

Polycystic kidney disease is characterized by the development of renal fluid-filled cysts, eventually leading to kidney failure. InnoSer offers a unique in vivo mouse model for Autosomal Dominant Polycystic Kidney Disease (ADPKD), originally developed by LUMC (Leiden University Medical Center)[1]. *Pkd1* is knocked out specifically in the kidneys after Tamoxifen administration. Knockout of *Pkd1* at varying time points, results in different disease progression models. Therefore, we present a unique in vivo model to screen for new drugs and treatments of ADPKD.

Choose the Right *Pkd1* Knockout Model For Your Research

Different *Pkd1* knockout mouse models are available as *Pkd1* knockout can be established by specifically timed Tamoxifen administration. There are three models available depending on which post-natal (P) day Tamoxifen is administered:

P10 model: a quickly progressive model with cyst development in the distal segment of the nephron

P18 model: a slowly progressive model with cyst development in all segments of the nephron

P40 model: a slowly progressive model with cyst development in the proximal part of the nephron

The P10 model is widely used as a first screening platform as it offers quick and robust results, while the P18 and P40 models offer closer clinical phenotypes to Autosomal Dominant Polycystic Kidney Disease.

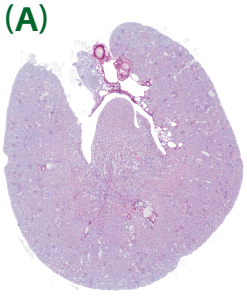
1. Lantinga-van Leeuwen IS, Leonhard WN, van der Wal AM, Bruening MH, de Heer E, and Peters D (2007) 'Kidney-specific inactivation of the Pkd1 gene induces rapid cyst formation in developing kidneys and a slow onset of disease in adult mice', *Hum Mol Genet*, 16(24) 3188-3196.

Evaluate the Efficacy of Your Compound Through Key Endpoints

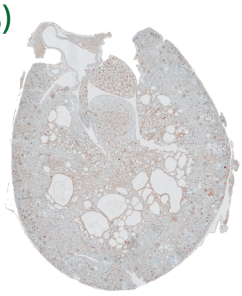
- Survival
- Body weight
- Kidney weight
- Longitudinal ultrasound kidney volume follow-up
- Blood urea evaluation
- Histopathology:
  - Cystic index and associated pathological lesions
  - Special stainings and immunohistochemistry for specific markers of interest:

Indication	Markers
Proliferation	Ki67
Fibrosis	Trichrome, PSR
Apoptosis	TUNEL, Caspase-3, Bcl-2
Renal injuries	Lcn2 (NGAL)
Macrophage infiltration	CCL2 (MCP1)
Cyst growth	Cyclin D
Cyst compression	KIM1 (HAVCR1)
Myofibroblasts	αSMA

(A)



(B)



Example Histopathological Assessment: (A) Tamoxifen treated kidney in P10 model showing picrosirius red application for collagen quantification (B) Tamoxifen treated kidney in P18 model showing IHC application targeting Ki67.

Get in touch

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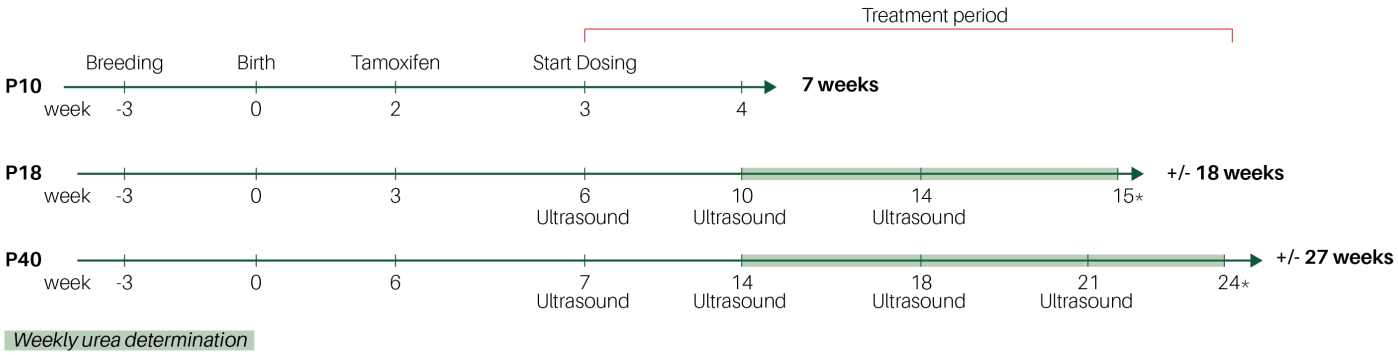
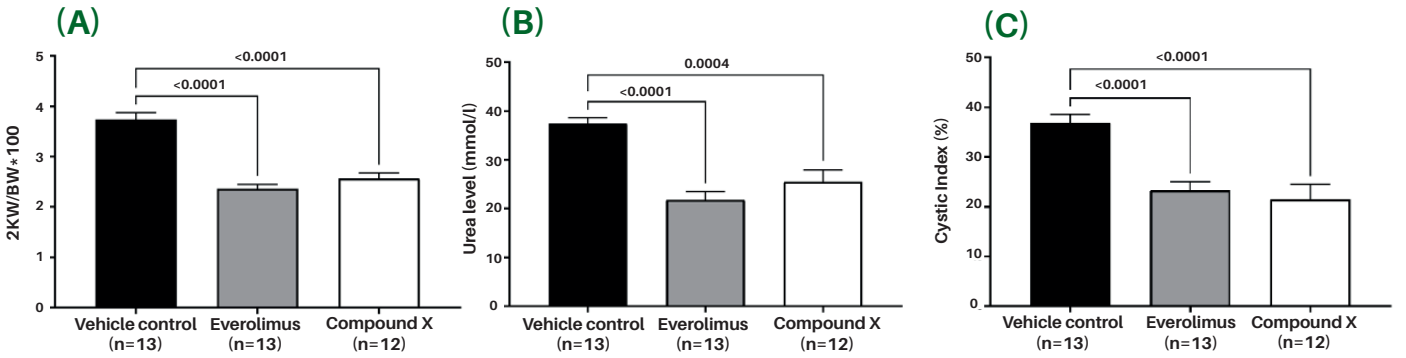
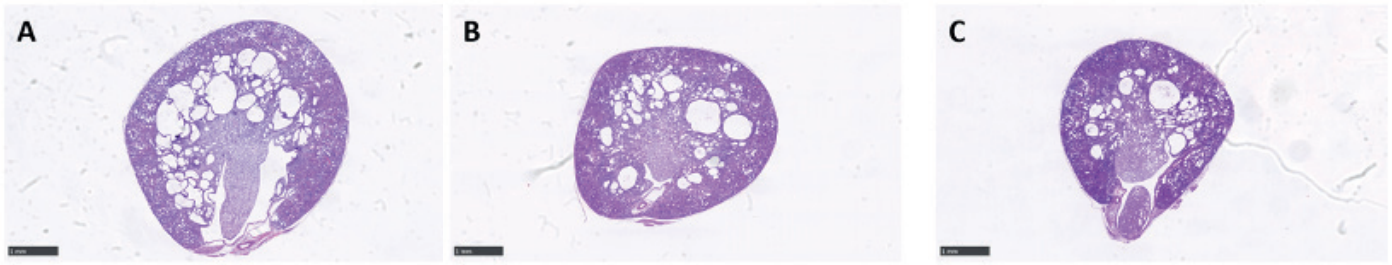
Study Design



Blinded ultrasound data in the P10 model:



Administration of Everolimus and compound X significantly reduces (A) 2kidney weight (KW) corrected for body weight (BW), (B) blood urea levels, and (C) cystic index (cyst area/kidney area %) compared to the vehicle control group in the P10 model (mean ± SEM; one-way ANOVA). Data is proprietary.



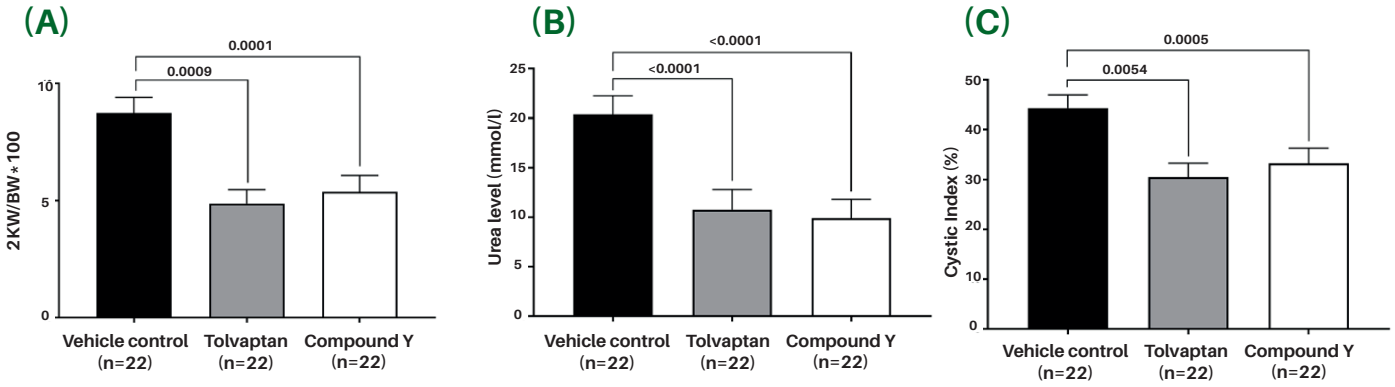
Vehicle control
CI: 32%

Everolimus
CI: 25%

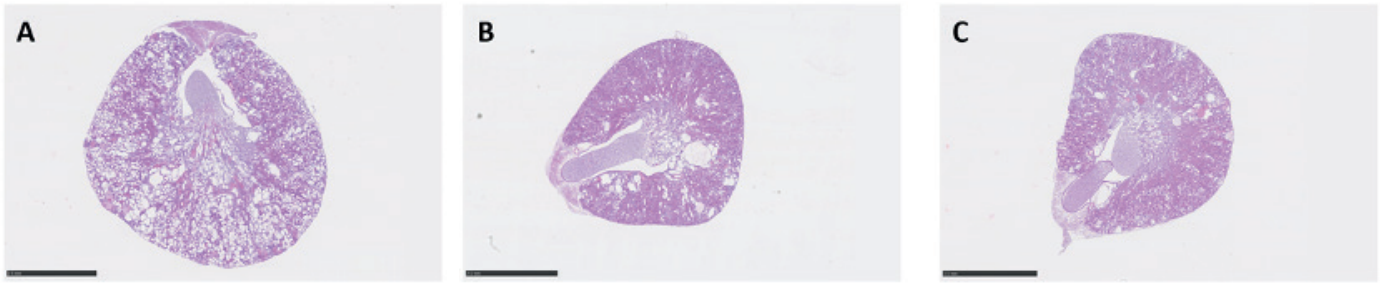
Compound X
CI: 21%

Overview pictures of transverse kidney sections stained with H&E for cystic index determination. Cystic index (CI) is significantly lower in the (B) Everolimus and (C) compound X groups compared to the (A) vehicle control group, which is visible in these overview pictures as there are less and smaller cysts present in the Everolimus and Compound X groups.

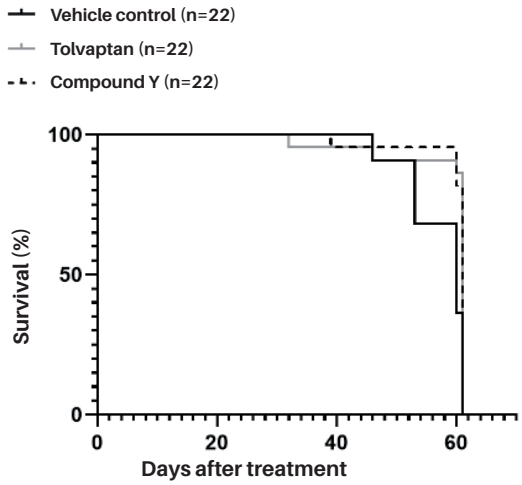
Blinded ultrasound data in the P18 model:



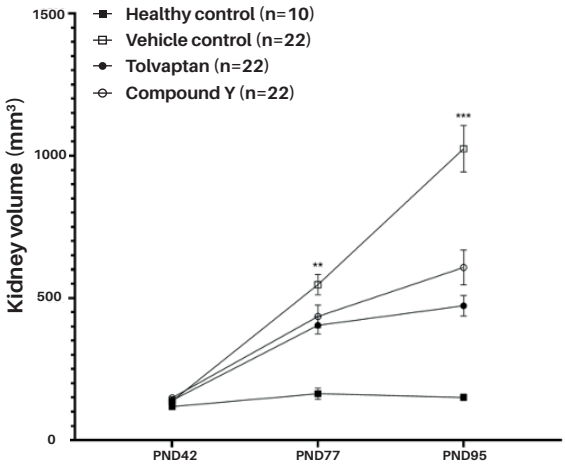
Administration of Tolvaptan and compound Y significantly reduces (A) 2kidney weight (KW) corrected for body weight (BW), (B) blood urea levels, and (C) cystic index (cyst area/kidney area %) compared to the vehicle control group in the P18 model (mean ± SEM; one-way ANOVA). Data is proprietary.



Overview pictures of transverse kidney sections stained with H&E for cystic index determination. Cystic index (CI) is significantly lower in the (B) Tolvaptan and (C) compound Y groups compared to the (A) vehicle control group, which is visible in these overview pictures as there are less cysts present in the Tolvaptan and Compound Y groups.



Administration of Tolvaptan and compound Y increases survival compared to the vehicle control group.



Right kidney volume (mm^3) is significantly lower in the Tolvaptan and compound Y groups compared to the vehicle control group. Cyst development is aberrant in the vehicle control group compared to the healthy control (mean ± SEM; one-way ANOVA; ** p<0,01, *** p<0.001). Data is proprietary.

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