Effects of ANG-3070 in a Mouse Model of Alport Syndrome

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Background – Alport Syndrome

- Alport syndrome
  - hereditary kidney disease that presents in childhood and progresses to end-stage kidney disease (ESKD) in adolescence\(^1\)
  - no cure and no treatment completely stops kidney failure

- Caused by mutations in the type IV collagen genes Col4a3, Col4a4 or Col4a5
  - reduced structural integrity of the glomerular basement membrane, triggering activation of fibrogenic cytokines, and causing proteinuria and fibrosis\(^2,3\)

- Aberrant signaling of receptor tyrosine kinases (RTK) shown in preclinical models of fibrotic kidney and lung diseases\(^4-6\)
  - platelet-derived growth factor receptor (PDGFR)
  - vascular endothelial growth factor receptor (VEGFR)
  - discoidin domain receptor (DDR)

- ANG-3070 is an orally bioavailable RTK inhibitor with selectivity for PDGFR\(\alpha/\beta\) and DDR1/2, among other tyrosine kinases

- ANG-3070 was tested in a preclinical model of AS using Col4a3 knockout mice (AS mice)
  - Alport mice develop kidney failure by 8–10 weeks of age

Objective: To evaluate the effect of ANG-3070 on AS in transgenic mice with a Col4a3 mutation

Study design

- 4-week-old AS mice randomized to Vehicle or ANG-3070 (25 mg/Kg, PO, BID) and treated for 5 weeks
- Age-matched, wild-type (WT) mice controls
- Spot urines at baseline, 4 and 5 weeks for proteinuria and protein to creatinine ratio (PCR)
- Fibrosis in renal tissue by hydroxyproline (HYP) content, Trichrome and picrosirius red staining (PSR)
- Collagen-1, TGFβ1, and αSMA determined by Western blot analysis and immunohistochemistry
- Blots were quantitated using calibrated densitometry
- Renal damage was assessed using H&E staining
- All histological analyses performed blindly by two observers using a 0–4 scale (0, normal; 4 ≥75% injured or stained)
ANG-3070 increased survival

- ANG-3070 treatment significantly decreased AS mouse mortality compared with AS-Vehicle mice \((P=0.03)\)
- Body and kidney weights were not significantly different between AS-Vehicle and AS-ANG-3070 mice
ANG-3070 reduced proteinuria and protein to creatinine ratio

- AS-Vehicle mice had significantly higher proteinuria and protein to creatinine ratio compared to WT mice.
- AS-ANG-3070 mice had significantly decreased proteinuria and protein to creatinine ratio compared to AS-Vehicle at 5 weeks but not 4 weeks post treatment.
ANG-3070 decreased renal damage

- ANG-3070 treatment significantly decreased renal damage score of AS mice compared with AS-Vehicle mice ($P=0.002$) determined from H&E-stained sections.
ANG-3070 reduced renal fibrosis

- ANG-3070 treatment significantly decreased kidney HYP in AS mice compared with AS-Vehicle mice ($P=0.002$)
- ANG-3070-treated AS mice had significantly decreased renal fibrosis scores determined by Trichrome staining and PSR staining sections compared with AS-Vehicle mice ($P=0.03$ and $P=0.001$ respectively)
ANG-3070 reduced fibrotic markers (Collagen-1, TGFβ1 and αSMA)

- Western blot analysis showed that ANG-3070 treatment reduced protein levels of fibrotic markers collagen-1, TGFβ1, and αSMA in AS mice compared with AS-Vehicle mice.

- ANG-3070-treated AS mice had reduced staining for kidney fibrotic markers collagen-1, TGFβ1 and αSMA compared with AS-Vehicle mice.
Conclusions

- ANG-3070 increased survival and reduced proteinuria and protein to creatinine ratio in a mouse model of AS
- Treatment with ANG-3070 reduced renal damage and renal fibrosis in AS mice
- ANG-3070 may represent a novel therapeutic for AS

Key takeaway: These data suggest that oral administration of the novel tyrosine kinase inhibitor ANG-3070, may be an effective treatment and novel therapeutic to Alport Syndrome