

Answers to Peer Review Comments

At first the authors are thankful and greatly appreciate for reviewing the manuscript and raising some comments. Peer-Review considered that the idea of the study is interesting and the authors aimed to determine a novel small molecule PDGFR+ VEGFR (KDR) dual kinase inhibitor, ANG3070 may have therapeutic benefit and reduce the number of hepato-renal transplants in patients with fibropolycystic kidney disease, ARPKD-CHF. The following changes have been made according to the reviewer's comments.

- Title of manuscript is changed to

A novel PDGFR and VEGFR dual kinase inhibitor for fibropolycystic hepato-renal disease.

- ARRIVE Guidelines Checklist - page numbers - pdf file attached.
- Abstract is revised describing AIM, METHODS, RESULTS and CONCLUSION without exceeding the word count limits for publication.
- Potential toxic effects of ANG3070 compound is addressed
- Decreased the discussion part with slight modification and adjusted references.
- The number of figures decreased by merging and removing one figure.
- References formatted and added PubMed ID and/or DOI numbers if available.
- A new conflict of interest statement attached.
- A new audio-clip attached in MP3 format.
- Now, the authors have revised the manuscript to address all the peer-review comments for publication in the *WJN*.

Dr. Fang-Fang Ji,

Thank you for the request.

Now all the data figures are presented with +/- SD.

The following safety profile was edited in the text.

ANG3070 safety/toxicology profile:

ANG3070 was efficacious and no potential toxic effects were observed in several rodent models. As detailed below, to date, there is no evidence of toxicity (liver or renal) in mice or rats dosed repeatedly over several weeks with ANG3070. In hundreds of mice and rats, dosed several weeks with 150 mg/kg ANG3070 (PO, QD), there were no excursions in BUN (Veh 73 mg/dL; ANG3070 69 mg/dL) or SCr (veh 0.36 mg/dL; ANG3070 0.35 mg/dL) with ANG3070. In other rats dosed for 3 wk with ANG3070 (25 mg/kg, PO, BID x 3 wk), no excursions were seen in liver enzymes *vs* vehicle-dosed rats (ALT - veh: 92 IU; ANG3070: 61 IU; AST - Veh 158 IU; ANG3070 136 IU). There were no adverse events reported in a 14 d toxicology studies in rats and dogs at 9-fold higher doses (450 mg/d) (data not shown) than the efficacious dose of ANG3070 (50 mg/d) at which antifibrotic efficacy was observed in fibropolycystic kidney disease-CHF. These studies indicate that ANG3070 was safe and well tolerated without any potential toxic effects.

In PCK rats, treatment of ANG3070 for several weeks did not increase sCR, BUN, AST and ALT. In fact, sCR and AST were reduced with 3070 treatment. Overall ANG3070 was efficacious in decreasing kidney and liver fibrosis with no potential toxic effects.

Every organ was not evaluated but has no gross morphological tissue/organ damage observed during sacrifice of ANG3070 treated rats.

Thank you very much

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