Clinical trial of Venglustat, a glucosylceramide synthase (GCS) inhibitor, is supported by preclinical and Phase 1 study data

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of end stage renal disease (ESRD). Studies in the 1990s showed that levels of two glycosphingolipids— glucosylceramide (GL-1) and lactosylceramide—were higher in the kidneys of PKD patients and in mouse models of PKD than in those of healthy controls.

METHODS

Mouse models of ADPKD were treated with GCS inhibitor or control. Phase 1 study with venglustat was conducted in healthy volunteers.

RESULTS

In three mouse models of PKD, treatment with a GCS inhibitor resulted in decreased kidney and plasma levels of glucosylceramide (GL-1) and reduced formation of kidney cysts compared with untreated controls. Analysis of kidney tissue from treated mice showed that inhibiting GCS blocked signaling between protein kinase B (PKB; Akt) and mammalian target of rapamycin (mTOR; FRAP; RAFT1). In three completed Phase 1 studies in healthy subjects, the GCS inhibitor venglustat was generally safe and well tolerated. After repeated-dosing up to 15mg (14 days QD) with venglustat, time- and dose-dependent reductions in plasma GL-1 concentration were observed. No effect on serum creatinine, blood pressure or urinary output was observed in subjects treated with venglustat.

CONCLUSION

Glucosylceramide synthase inhibition ameliorates ADPKD in mouse models. Venglustat is a glucosylceramide synthase inhibitor (GCSi) that has demonstrated reduction in plasma glucosylceramide (GL-1) levels and is safe and well tolerated in humans. Based on the following data, a new clinical trial in ADPKD will be initiated, SAVE-PKD, to evaluate the effect of venglustat in ADPKD.