Discovery of CHK-336: A First-in-Class, Liver-Targeted, Small Molecule Inhibitor of Lactate Dehydrogenase for the Treatment of Primary Hyperoxaluria

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Background

• Primary hyperoxalurias (PH) 1-3 are a group of autosomal recessive disorders that result in excess hepatic oxalate production. Patients with PH exhibit frequent kidney stone formation, progressive CKD and in its most severe form, PH1 can lead to ESRD at a young age. No oral small molecule agents are currently available.

• Lactate dehydrogenase (LDH) catalyzes the final and only committed step in hepatic oxalate synthesis and therefore represents a potential therapeutic target to treat all forms of PH.

• Complete loss-of-function of LDH in humans results in an exercise-induced muscle phenotype, therefore a liver-targeted profile with low systemic exposure is desired.

• Herein we describe the profile of a potent, highly selective small molecule LDH inhibitor with a liver-targeted tissue distribution profile which effectively lowers urinary oxalate in a mouse PH1 model and demonstrates an excellent preclinical pharmacokinetic and safety profile.

Methods and Materials

CHK-336 was evaluated in biochemical and cellular LDH activity assays across species and in vivo models of hyperoxaluria, including a novel PH1 mouse generated by Agt deletion using CRISPR/Cas9. Additional characterization of drug properties, including off-target activities, ADME, safety pharmacology and toxicity in rodents was also performed.

Results (continued)

C Pharmacokinetic and pharmacodynamic properties of CHK-336

A CHK-336 is a potent LDHA inhibitor in enzyme and hepatocyte assays across multiple species

B Design of a liver-targeted LDH inhibitor by incorporating moieties that are recognized by liver-selective uptake transporters

Conclusion

• Targeting LDHA, the final step in hepatic oxalate synthesis, represents a potential therapeutic strategy for all forms of PH, as well as other disorders arising from oxalate overproduction.

• By potently blocking LDHA and engineering a liver-targeted tissue distribution profile, CHK-336 represents a potentially safe and effective oral small molecule for the treatment of primary hyperoxaluria.

• CHK-336 shows robust efficacy in a PH1 mouse model at low, once-daily oral doses including the ability to reduce elevated urinary oxalate levels to the normal range.

• The non-clinical safety assessment of CHK-336 conducted to date supports continued advancement into IND-enabling studies.

CHK-336 is a first-in-class oral LDH inhibitor with the potential to treat all subtypes of primary hyperoxaluria as well as other disorders arising from oxalate overproduction.

References


Results

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