WCN21-0612

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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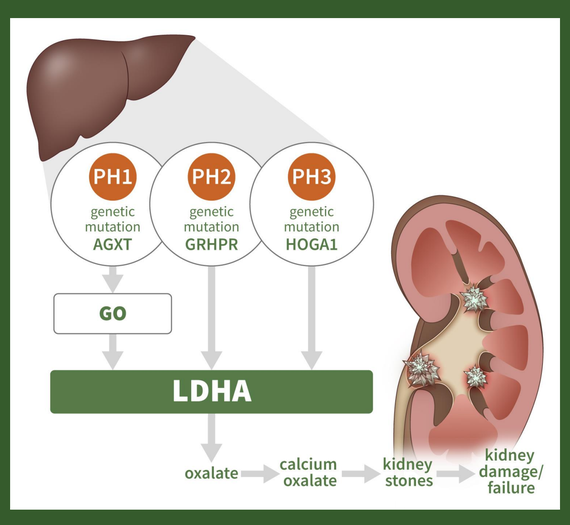
Background

- 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.



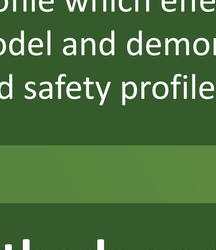
- Complete loss-of-function of LDHA in humans results in an exercise-induced muscle phenotype[1]; therefore a liver-targeted profile with low systemic exposure is desired.
- Herein we describe the profile of a potent, highly selective small molecule LDH inhibitor with a liver-targeted tissue distribution 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 Agxt deletion using CRISPR/Cas9. Additional characterization of drug properties, including off-target activities, ADME, safety pharmacology and toxicity in rodents was also performed.

Results

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



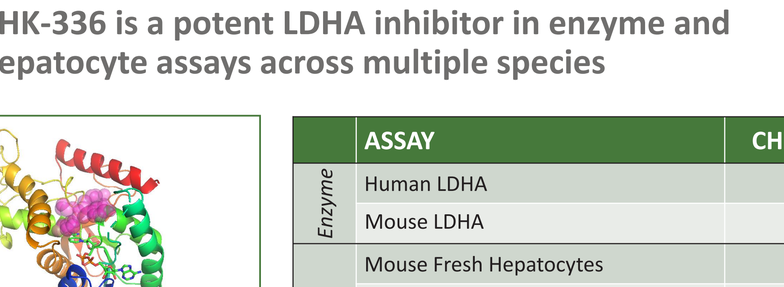
Compound design and sub-nM potency guided by structural biology and X-ray crystallography of LDHA-inhibitor complexes

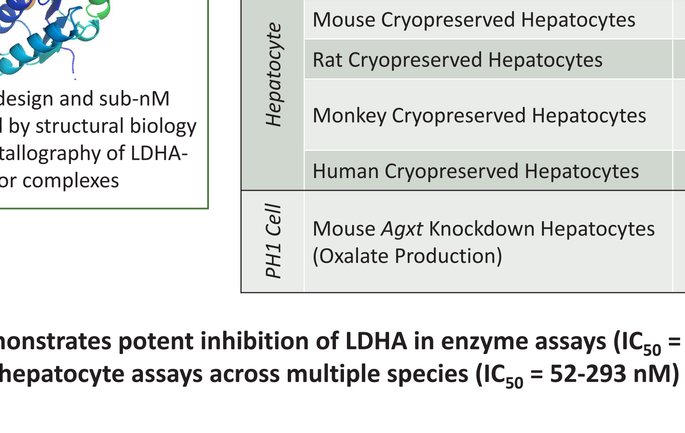
	ASSAY	CHK-336 IC_{50}
Enzyme	Human LDHA	**0.4 nM**
	Mouse LDHA	**0.1 nM**
Hepatocyte	Mouse Fresh Hepatocytes	**52 nM**
	Mouse Cryopreserved Hepatocytes	**80 nM**
	Rat Cryopreserved Hepatocytes	**130 nM**
	Monkey Cryopreserved Hepatocytes	**130 nM**
	Human Cryopreserved Hepatocytes	**131 nM**
PH1 Cell	Mouse *Agxt* Knockdown Hepatocytes (Oxalate Production)	**293 nM**

CHK-336 demonstrates potent inhibition of LDHA in enzyme assays (IC_{50} = 0.1-0.4 nM) and primary hepatocyte assays across multiple species (IC_{50} = 52-293 nM)

CHK-336 also demonstrates tight LDHA binding with a very slow off-rate (hours-days)

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

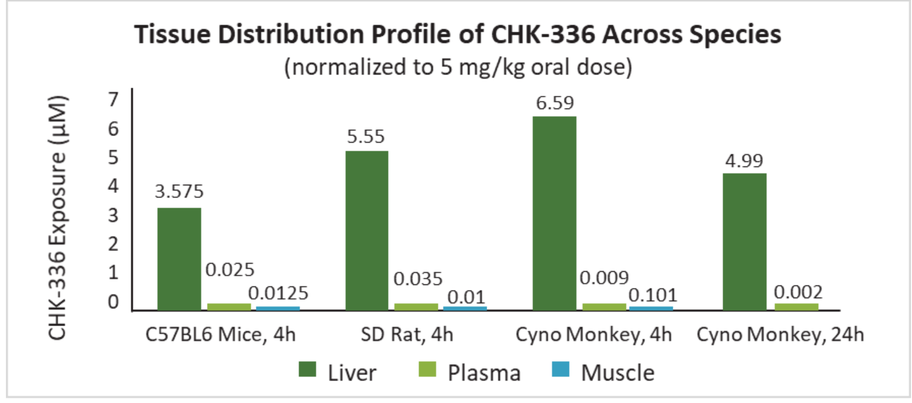


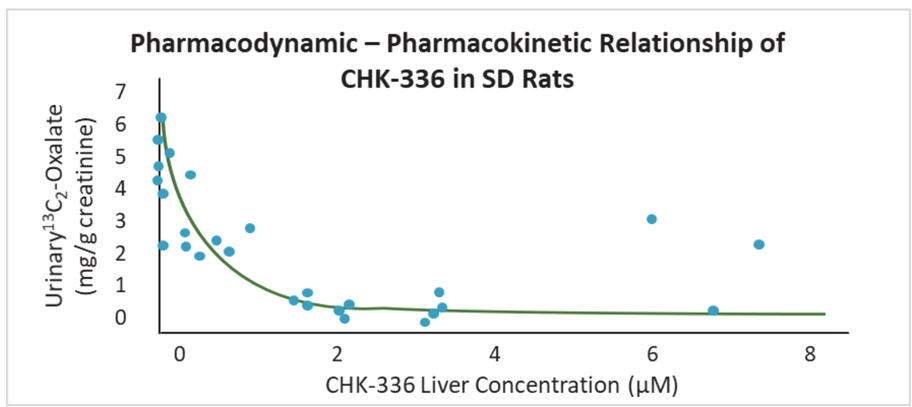


CHK-336 demonstrates active uptake into human, monkey and rat hepatocytes

Results (continued)

C Pharmacokinetic and pharmacodynamic properties of CHK-336





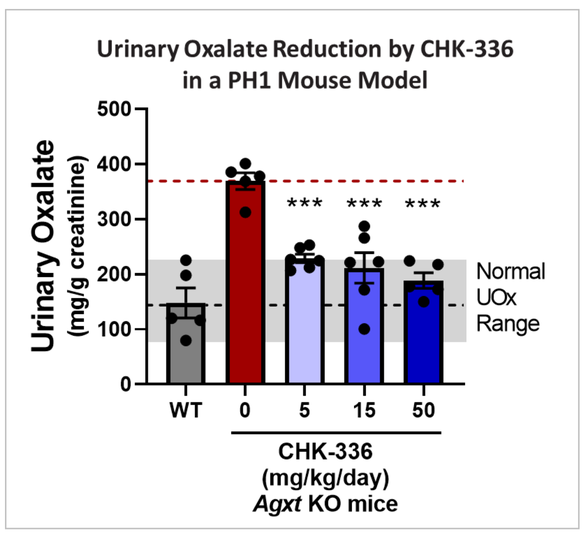
CHK-336 exhibits a liver-targeted tissue distribution profile in mice, rats and monkey with high liver concentrations and low extra-hepatic tissue exposures

Long liver half-life observed across species; driven by good metabolic stability and tight, slow-off rate binding of CHK-336 to LDHA in the liver

Well-profiled pharmacodynamic effect in mice and rats driven by liver concentrations: liver EC_{50} of ≈3 µM

Human PK predictions suggest CHK-336 has the potential to be a low, once-daily oral dose in humans

D CHK-336 produced significant and dose-dependent reductions in urinary oxalate in a PH1 mouse model



CHK-336 was dosed orally, once-daily for 7 days in male *Agxt* KO mice and urinary oxalate concentrations were compared to a vehicle control group

Low, oral, once-daily doses of CHK-336 significantly reduced urinary oxalate; majority of treated mice reached the normal range observed in wild-type mice

Analysis of liver concentrations of CHK-336 resulted in a PK/PD relationship with a liver EC_{50} of 1 – 5 µM CHK-336, consistent with rat liver PD values

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 LDHA inhibitor with the potential to treat all subtypes of primary hyperoxaluria as well as other disorders arising from oxalate overproduction

References

1. Kanno et al *Clinica Chimica Acta* 1980; 108: 267-276