Preclinical efficacy of CHK-336: A First-in-Class, Liver-Targeted, Small Molecule Inhibitor of Lactate Dehydrogenase for The Treatment of Primary Hyperoxalurias

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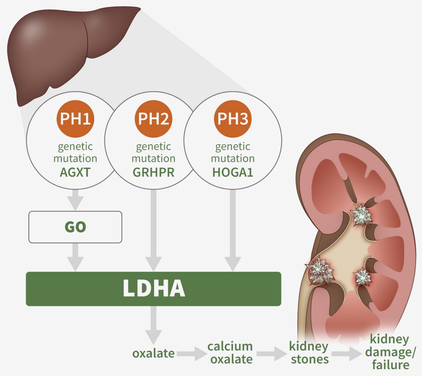
Background

- 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 ESKD at a young age. No oral small molecule agents are currently available.
- Lactate dehydrogenase A (LDHA) catalyzes the final and only committed step in hepatic oxalate synthesis and therefore represents a potential therapeutic target to treat all forms of PH and other disorders caused by oxalate overproduction.



- 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 LDHA inhibitor with a liver-targeted tissue distribution profile which effectively lowers urinary oxalate in mouse PH1 and PH2 models.

Methods and Materials

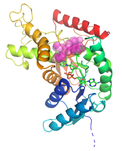
- CHK-336 was evaluated in biochemical and cellular LDHA activity assays, a $^{13}C_2$-glycolate stable isotope tracer pharmacodynamic model, a novel PH1 mouse model generated by *Agxt* deletion, and a *Grhpr* knockout PH2 mouse model.[2] Oxalate excretion was characterized in ZSF-1 rats from 13-21 weeks of age and hepatic gene expression was analyzed.

References

1. Kanno et al *Clinica Chimica Acta* 1980; 108: 267-276
2. Knight et al *Am J Renal Physiol* 2012; 302(6): F688-F693

Results

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

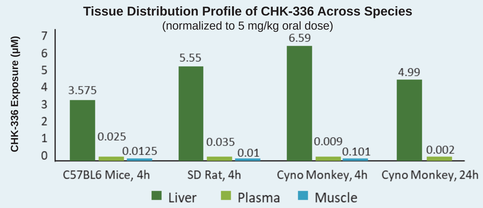


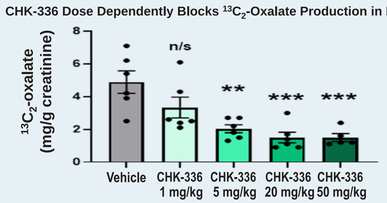
Compound design and sub-nM potency guided by structural biology and X-ray crystallography of LDHA-inhibitor complexes

	Assay	CHK-336 IC_{50}
Enzyme	Human LDHA	0.2 nM
	Mouse LDHA	0.3 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	121 nM
PH1 Hepatocyte	Mouse *Agxt* Knockdown Hepatocytes (Oxalate Production)	165 nM

- CHK-336 demonstrates potent inhibition of LDHA in enzyme assays (IC_{50} = 0.2-0.3 nM) and primary hepatocyte assays across multiple species (IC_{50} = 52-165 nM)
- CHK-336 also demonstrates tight LDHA binding with a very slow off-rate (hours-days)

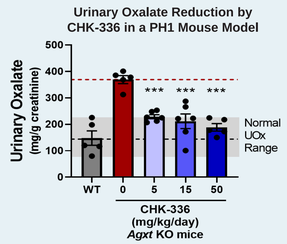
B Liver-targeted tissue distribution of CHK-336 and pharmacodynamic effect on the conversion of $^{13}C_2$-glycolate into $^{13}C_2$-oxalate

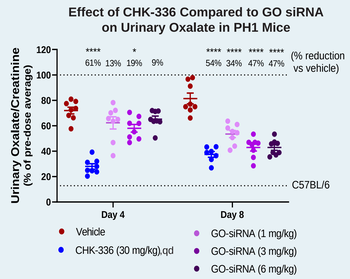




- CHK-336 exhibits a liver-targeted tissue distribution profile in mice, rats and monkey with high liver concentrations and low extra-hepatic tissue exposures
- Liver-targeted profile driven by OATP-mediated uptake results in high liver/plasma unbound ratios of 180-fold (rat) to 450-fold (monkey)
- Since LDHA catalyzes the final step of oxalate production from glycolate, a $^{13}C_2$-glycolate stable isotope tracer was used to assess CHK-336 target engagement by measuring urinary excretion of $^{13}C_2$-oxalate in Sprague Dawley rats
- Human PK predictions suggest CHK-336 has the potential to be a low, once-daily oral dose therapeutic in humans

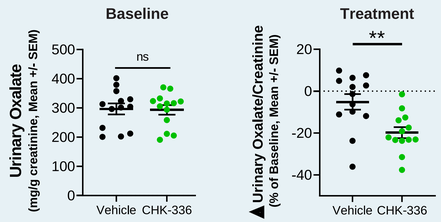
C CHK-336 produced significant and dose-dependent reductions in urinary oxalate in a PH1 mouse model





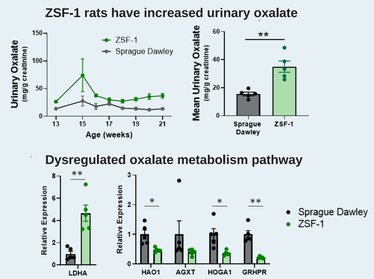
- CHK-336 was dosed orally, once-daily for 7 days in male *Agxt* KO mice and urinary oxalate concentrations were compared to a vehicle control group
- Low, oral, once-daily doses of CHK-336 significantly reduced urinary oxalate; majority of treated mice reached the normal range observed in wild-type mice
- CHK-336 had a more rapid onset of action and comparable magnitude of urinary oxalate reduction compared to a GO-targeting siRNA
- GO-siRNA was administered on day 0; Doses of 1, 3, and 6 mg/kg caused 56%, 75%, and 78% knockdown, respectively

D CHK-336 significantly reduced urinary oxalate excretion in a genetic mouse model of PH2



- CHK-336 was dosed orally, once-daily for 7 days at 25 mg/kg in male *Grhpr* KO mice and urinary oxalate concentrations were compared to a vehicle group

E Obese, hypertensive, and diabetic ZSF-1 rats have elevated urinary oxalate excretion and dysregulated expression of oxalate metabolism genes

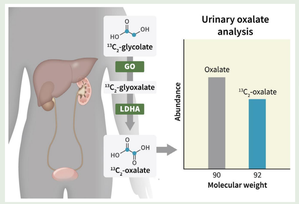


- Increased urinary oxalate and altered hepatic expression of genes involved in oxalate metabolism was observed in ZSF-1 rats compared to Sprague Dawley controls
- Data supports potential therapeutic benefit of CHK-336 in non-genetic oxalate nephropathies associated with increased endogenous production of oxalate

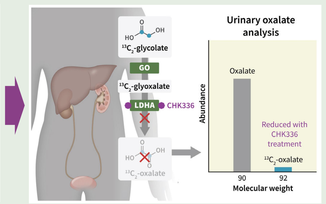
Conclusions

- CHK-336 is a potent LDHA inhibitor, with liver-targeted tissue distribution, that is efficacious in PH1 and PH2 mouse models of primary hyperoxaluria and has potential benefit in non-genetic hyperoxalurias caused by oxalate overproduction.
- The human safety and pharmacokinetic profiles of CHK-336 are currently under investigation in a healthy volunteer SAD/MAD study (NCT05367661).
- Target engagement will be assessed in humans using a novel stable isotope glycolate tracer approach (depicted below).

Pre-Treatment Glycolate Tracer



Post-Treatment Glycolate Tracer



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

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*CHK-336 is an investigational drug that has not been approved by regulatory authorities. Efficacy and safety have not been established. There is no guarantee that it will become commercially available for the use(s) under investigation.