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CHK-336, a First-in-Class Orally Administered LDH Inhibitor: Safety, PK and Target Engagement in a First-in-Human Phase 1 Healthy Volunteer Study

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Disclosures for Presenting Author

Current Employer: | Chinook Therapeutics

CHK-336 is an investigational agent and has not been approved for any uses in patients

Primary Hyperoxaluria (PH)

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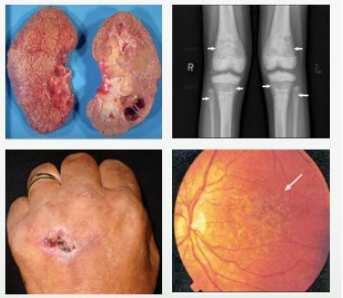
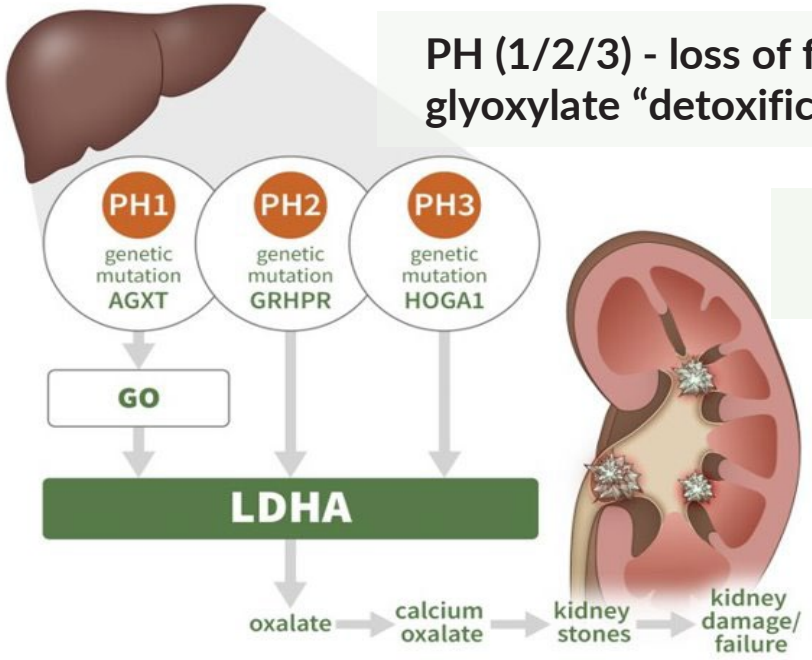
Rare genetic disorder of hepatic oxalate overproduction and potential end stage renal disease (ESRD)

Pathogenesis of Primary Hyperoxaluria

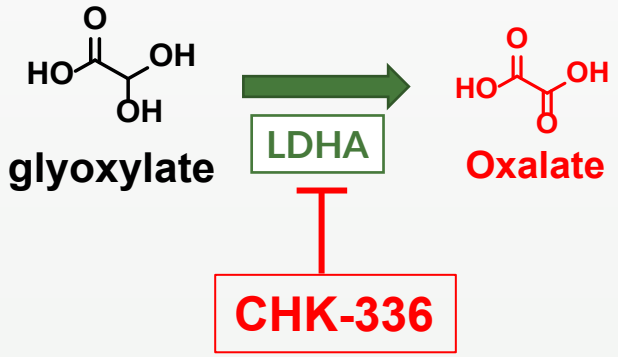
- Impaired hepatic glyoxylate detoxification → **excess oxalate that can accumulate in liver, kidneys, bone, heart, and other tissues**
- Calcium **oxalate crystals form in the kidneys → kidney stones and CKD**
- Progressive liver and kidney failure → **dual liver/kidney transplant**





PH (1/2/3) - loss of function mutations in glyoxylate "detoxification" pathway

↑ conversion of glyoxylate to oxalate (via LDHA)



CHK-336 is in development for PH

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Novel Use of a PD Marker to Enable Proof of Mechanism in HVs

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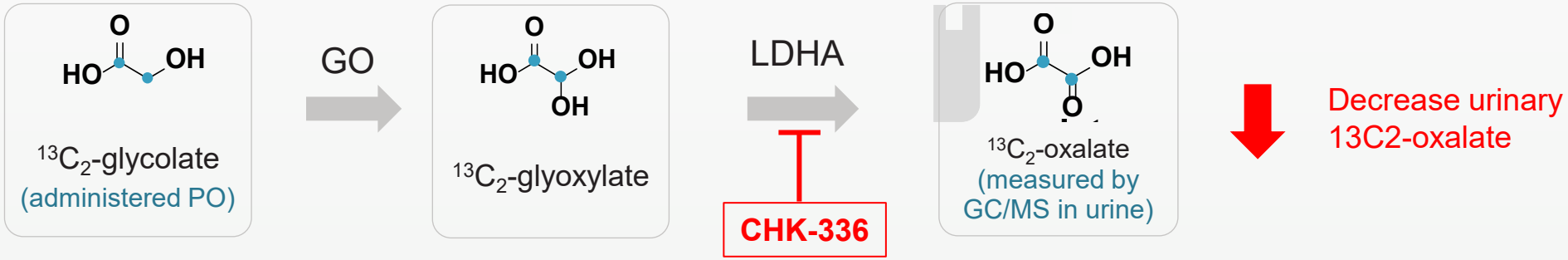
$^{13}C_2$-glycolate tracer was required to demonstrate hepatic LDH inhibition in the FIH study

- Overall contribution of glycolate as endogenous source of urinary oxalate is poor in HVs

Design of $^{13}C_2$-glycolate tracer as a robust PD marker in HVs



Preclinical translation predicts a therapeutic clinical dose of 60 – 125 mg QD

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CHK-336 First-in-Human SAD/ MAD Study

Primary & Secondary Objectives

Safety / Tolerability / Pharmacokinetics

Exploratory Endpoints: urinary $^{13}C_2$-oxalate

(1) To evaluate hepatic target engagement of CHK-336 early in the HV (FIH) studies
(2) To guide starting & target dose for future patient proof-of-concept studies

Co-administer $^{13}C_2$ Glycolate Tracer

A. SAD

15 mg → 30 mg → 60 mg → 125mg → 250 mg → 500 mg

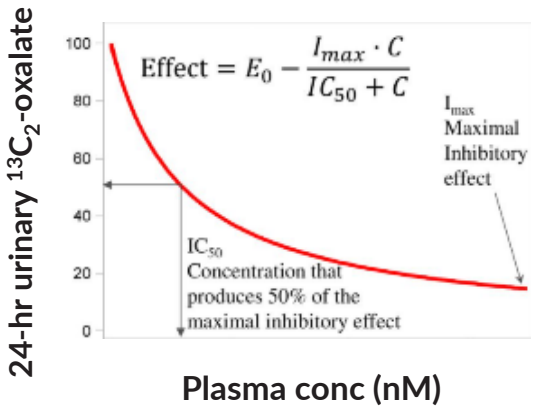
60 mg (food effect)

125 mg (obese)

B. MAD (14 day)

30 mg → 60 mg → 125mg → 250 mg → 500 mg

Imax model – negative effect (I = inhibition)



Objective: Establish exposure-response relationship as Proof of Mechanism in the FIH – HV study

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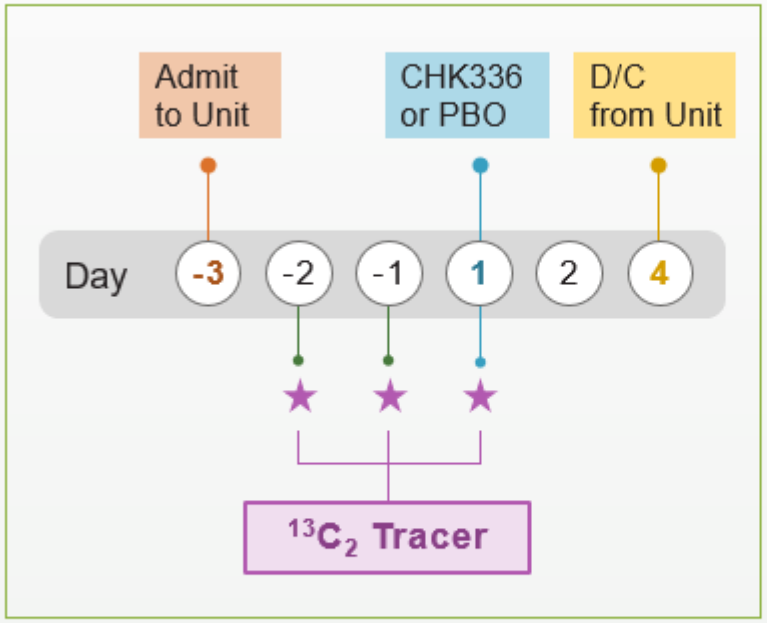
Target Engagement: $^{13}C_2$ Tracer Dosing for SAD and MAD

Tracking Conversion of $^{13}C_2$-glycolate into $^{13}C_2$-oxalate

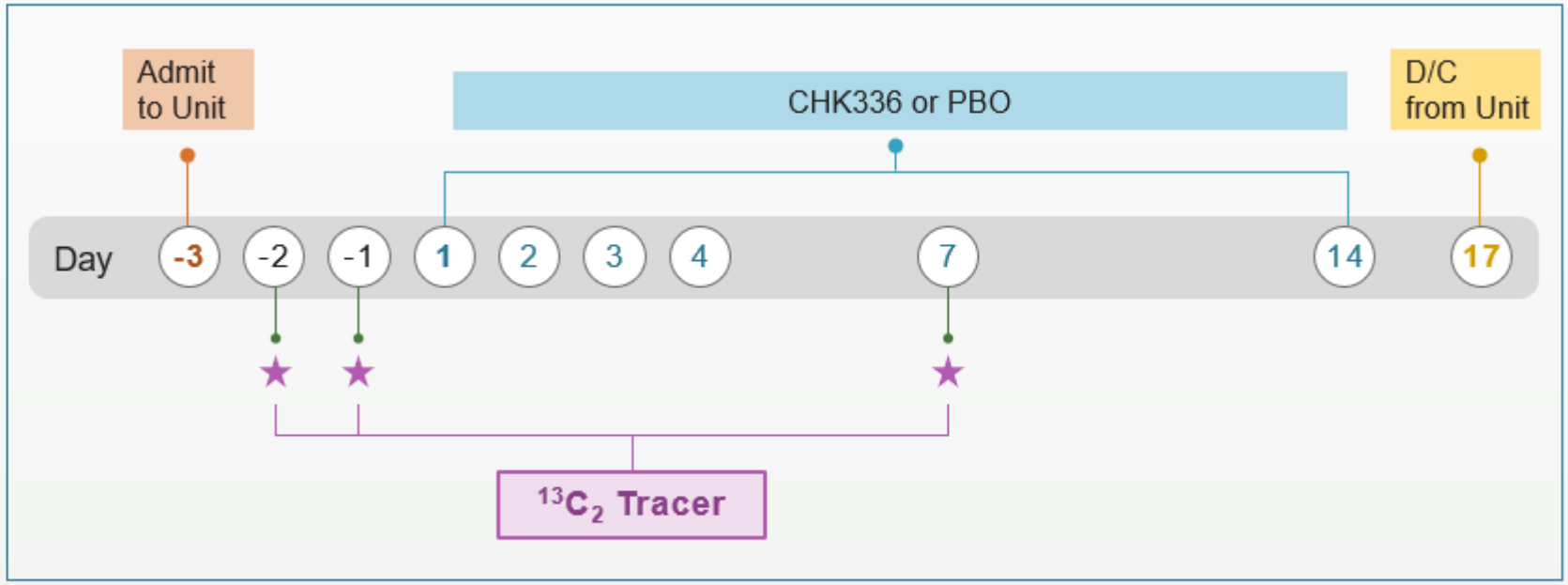
Methods considerations:

- **Timed urine collections (0-24hr) on each tracer day**
- **Controlled oxalate diet (< 50 mg oxalate/day)**
- **Adequate sample pH adjustment (pH <1)**
- **Validated GC/MS assays (Total Ox, ^{13}C-enrichment)**

SAD



MAD



$^{13}C_2$-glycolate tracer was incorporated into the FIH Study along with careful control of dietary oxalate, timed urine collections, validated assays for reliable target engagement

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CHK336-01 Safety Data

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Generally well-tolerated

- Single doses up to 500 mg and multiple doses (14 days) up to 60 mg QD
- No dose related trends in AEs, vital signs or EKG findings
- Most common TEAE: headache in 6 subjects receiving CHK-336 (8.8%) and no placebo subjects; no dose-related trend

One SAE

- Anaphylaxis (related) in a MAD subject who received one 125 mg dose CHK-336 on Day 1
- Rapid onset (1 hr post-dose); resolved rapidly after antihistamine treatment; did NOT require epinephrine administration
- Elevated tryptase level diagnostic of anaphylaxis
  - 4.1 µg/L at baseline vs 13.3 µg/L at time of event
- **This SAE resulted in voluntary study pause for further investigation**

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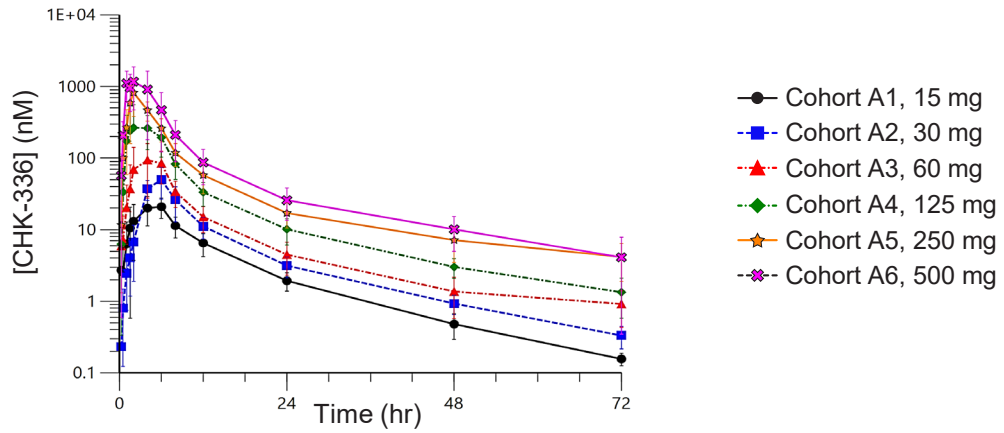
CHK336-01 PK Summary

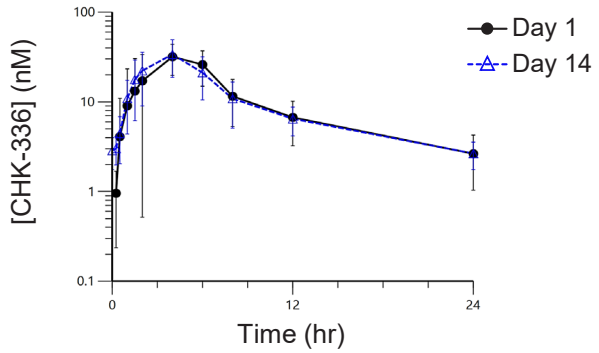
SAD PK Profiles



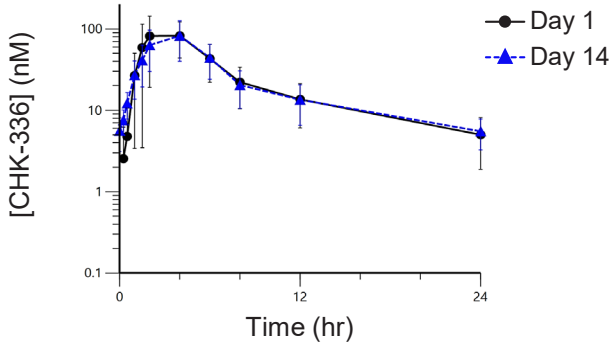
- Dose proportional increases in exposure, $t_{1/2}$ ~18hr consistent with QD dosing
- Urinary excretion of CHK-336 is negligible
- Exposures decrease with high-fat meal (50% ↓ in C_{max}, 30% ↓ $AUC_{0\text{-}24h}$)
- Exposures as predicted with adequate safety margins to nonclinical tox NOAEL at 500 mg SAD

MAD PK Profiles

CHK-336, 30 mg QD



CHK-336, 60 mg QD



- No exposure accumulation with repeat dosing
- Exposures were as predicted at 30 and 60 mg x 14 days

Proof of Mechanism Achieved in HVs for CHK-336

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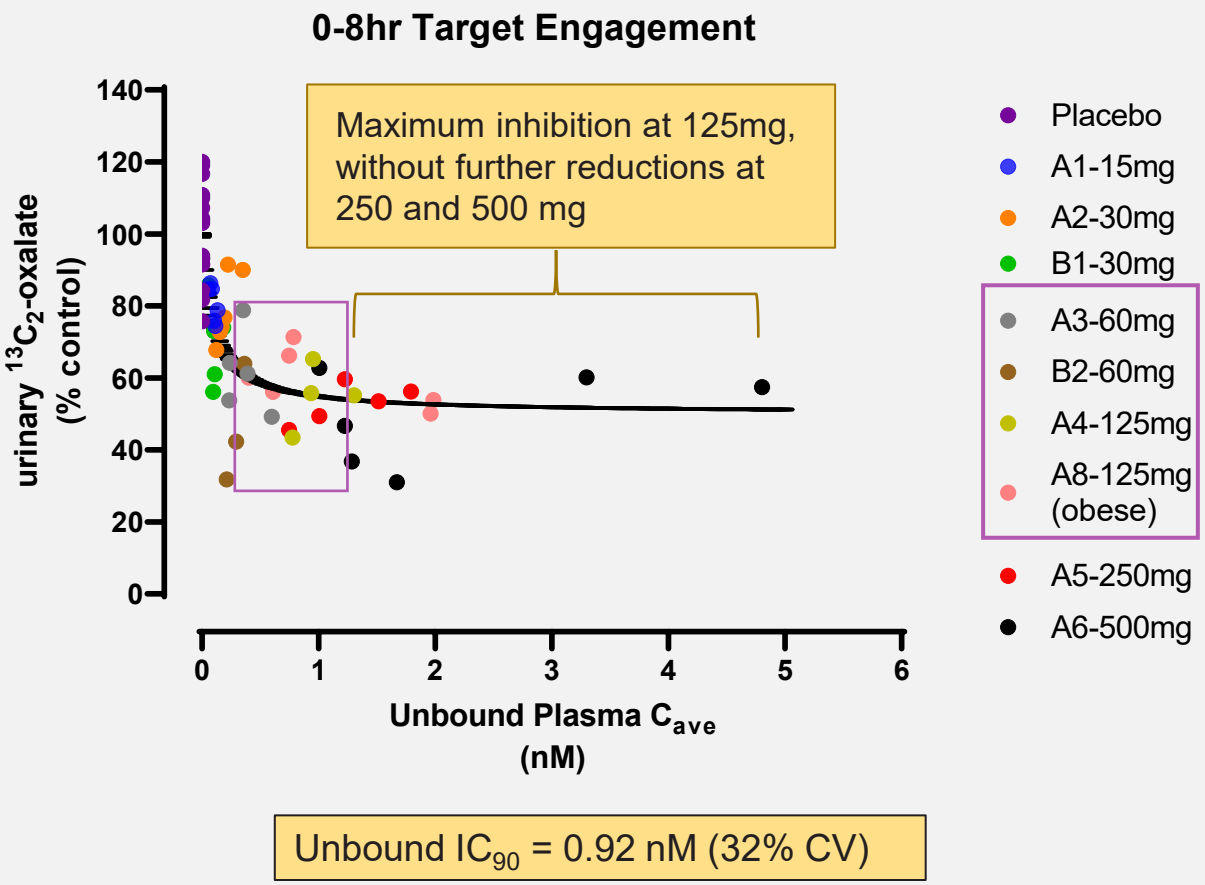

- $^{13}C_2$-glycolate tracer used successfully to demonstrate hepatic LDH inhibition in HVs
- Of the $^{13}C_2$-oxalate recovered in urine, the majority was excreted in the first 8hr after tracer administration
- Dose dependent decrease of urinary $^{13}C_2$-oxalate
- Exposure-response relationship demonstrated complete hepatic LDH inhibition in HVs
- Based on unbound plasma concentration, hepatic LDH IC_{90} achieved at 60-125mg, **as predicted**

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In Conclusion

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Safety

- CHK-336 was generally well-tolerated with single doses up to 500 mg and multiple doses up to 60 mg (14days)
- One SAE (anaphylaxis) in a subject receiving CHK-336 resulted in study pause

CHK-336 PK

- PK was well characterized (moderate variability, dose proportional exposures)
- Plasma $t_{1/2}$ consistent with QD dosing
- No exposure accumulation following repeat dosing

CHK-336 PD

- Successfully implementation of novel use of $^{13}C_2$-glycolate tracer in a healthy volunteer study
- Established proof of mechanism of CHK-336 as a small molecule, orally administered, LDH inhibitor
- Single dose of 60 – 125 mg resulted in maximum hepatic LDH inhibition

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Acknowledgements

- Jenis Bhavsar (Clin Ops)
- Marc-Olivier Boily (DMPK)
- Alex Caron (Pharmacology)
- Jennifer Cox (Biology)
- Jim Ding (Med Chem)
- Russell Eyre (Toxicology)
- Erin Freeman (Biomarkers)
- Samuel Gaudreault (Pharmacology)
- Donette Goldsmith (CMC Supply)
- Chandra Garapati (CMC Formulation)
- Matt Laughlin (Data Management)
- David Powell (Med Chem)
- Jayakumar Surendradoss (DMPK)
- Xiaowei Teng (DMPK)
- Stephanie Turner (Regulatory)
- Jessica Vedder (Clin Ops)
- Daniel Watson (CMC)
- Joyce Wu (Biology)
- Libo Yang (CMC)
- Chris Young (Statistical Programming)
- Leon Zhang (CMC)

John Knight, PhD
Sonia Fargue, PhD

Harvey Wong, PhD

David Wagner, PhD