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

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CHK-336 is an investigational agent and has not been approved for any uses in patients
Primary Hyperoxaluria (PH)

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

\(^{13}\text{C}_2\)-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 \(^{13}\text{C}_2\)-glycolate tracer as a robust PD marker in HVs**

\begin{align*}
\text{^{13}C}_2\text{-glycolate (administered PO)} & \xrightarrow{\text{GO}} \text{^{13}C}_2\text{-glyoxylate} & \xrightarrow{\text{LDHA}} \text{^{13}C}_2\text{-oxalate} \\
& & \text{(measured by GC/MS in urine)}
\end{align*}

\text{Decrease urinary} \ ^{13}\text{C}_2\text{-oxalate}

\text{CHK-336}

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

B. MAD (14 day)
- 30 mg
- 60 mg
- 125 mg
- 250 mg
- 500 mg

Objective: Establish exposure-response relationship as Proof of Mechanism in the FIH – HV study
Target Engagement: $^{13}\text{C}_2$ Tracer Dosing for SAD and MAD

Tracking Conversion of $^{13}\text{C}_2$-glycolate into $^{13}\text{C}_2$-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**
- Admit to Unit
- CHK336 or PBO
- D/C from Unit
- $^{13}\text{C}_2$ Tracer

**MAD**
- Admit to Unit
- CHK336 or PBO
- D/C from Unit
- $^{13}\text{C}_2$ Tracer

$^{13}\text{C}_2$-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

- 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

Generally well-tolerated

- 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

One SAE
**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% ↓ $AUC_{0-24h}$)
- Exposures as predicted with adequate safety margins to nonclinical tox NOAEL at 500 mg SAD

### MAD PK Profiles

- 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

- $^{13}$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

Unbound IC$_{90} = 0.92$ nM (32% CV)
In Conclusion

- 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

Safety

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

PK

- 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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