KORRO BIO

Analyst Day 2026

KRRO-121: A Potential First-in-Class Treatment for Ammonia Control

January 27th, 2026

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Today's Speakers

Ram Aiyar

CEO

Loïc Vincent

CSO

Todd Chappell

COO

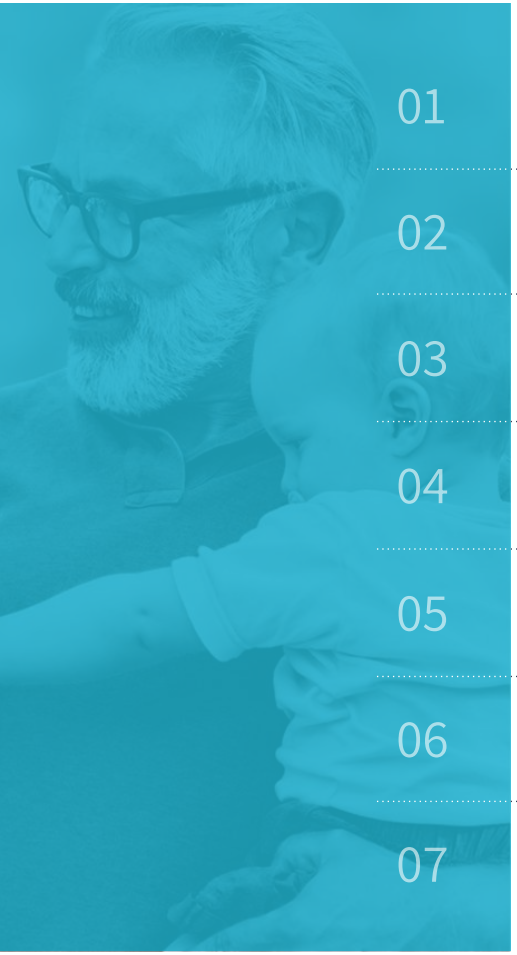
Michelle Dinon

UCD Parent

Bruce Scharschmidt

Clinician

Agenda



01	**Expanding to New Biological Frontiers with RNA Editing**	Ram Aiyar, CEO
02	**Living with UCD: A Mother's Perspective**	Michelle Dinon, UCD Parent
03	**Ammonia-driven Diseases: Urea Cycle Disorders and Hepatic Encephalopathy**	Dr. Bruce Scharschmidt, Clinician
04	**KRRO-121 Scientific Overview and Preclinical Data**	Loïc Vincent, CSO
05	**KRRO-121 Target Product Profile & Market Opportunity**	Todd Chappell, COO
06	**Closing Remarks**	Ram Aiyar, CEO
07	**Q&A**	All Presenters

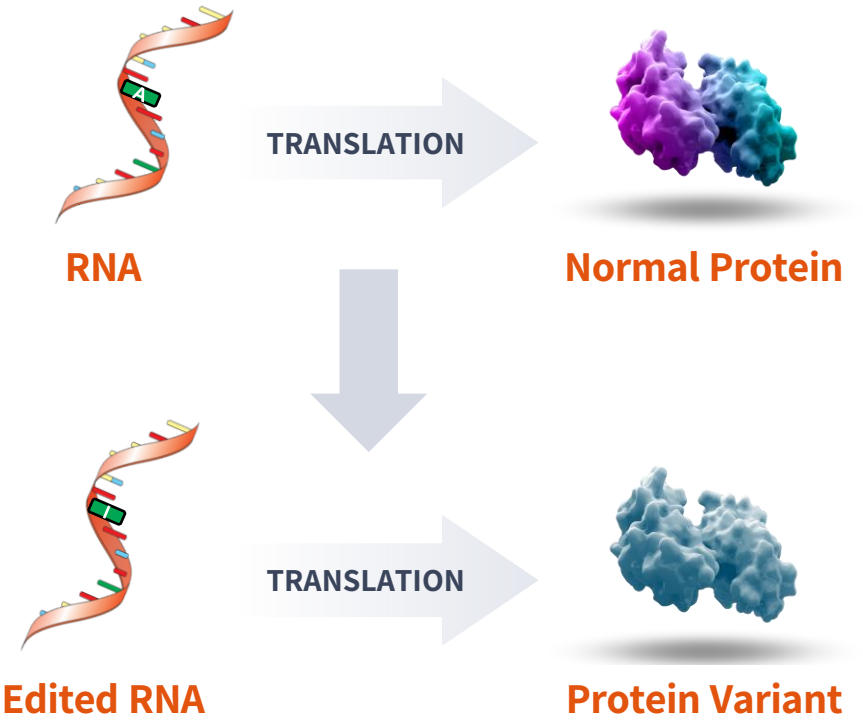
Expanding to New Biological Frontiers with RNA Editing

Ram Aiyar, PhD, MBA

Chief Executive Officer

Developing Transformative Genetic Medicines for Rare and Highly Prevalent Diseases

Modulate Protein Function (Activate pathway)



Examples of Modulate = Hyperammonemia, ALS, MASH, Fibrosis…

Editing RNA
Without permanently modifying DNA

Modular Delivery
Potential to deliver to multiple cell types

Learning from Genetics
To support predictable biological impact

Living with UCD: A Mother's Perspective

Michelle Dinon

UCD Mother

Ammonia-driven Diseases: Urea Cycle Disorders and Hepatic Encephalopathy

Bruce Scharschmidt, MD

Hepatologist, Former CMO of Hyperion Therapeutics

Professional Background / Bruce F. Scharschmidt, MD

UCSF Faculty from 1977-1996: Professor of Medicine & Chief of GI

- Helped start the UCSF liver transplant program with colleagues in surgery & medicine
- Editor-in-Chief of the J. Clinical Investigation & President of the Am Society for Clin Invest

1996-2006: Head of Chiron Clinical Development (Vaccines & Therapeutics)

- 1st Cancer immunotherapeutic; Influenza, pandemic influenza & meningococcal vaccines

2008-2015: Chief Medical & Development Officer, Hyperion Therapeutics

- Development/launch of glycerol phenylbutyrate (GPB, aka Ravicti®) for UCDs; ph2 trial of GPB for HE
- Initial public offering in 2012 and acquisition in 2015

2015-present: Board of Directors, Founder/Co-Founder, Consultant, Patient Advocacy, Children's Book Author (visit: brucescharschmidt.com)

Disclosures: Consultant to Korro, others; Board Member Saccharo, Umecrine

Don't hesitate to ask questions / I have sensorineural hearing loss

Ammonia (NH_3): Most People's First Thoughts

Ammonia is in household cleaners

Surprised to learn that ammonia is in our bloodstream

Imagine: You / your child are / is diagnosed with a urea cycle disorder

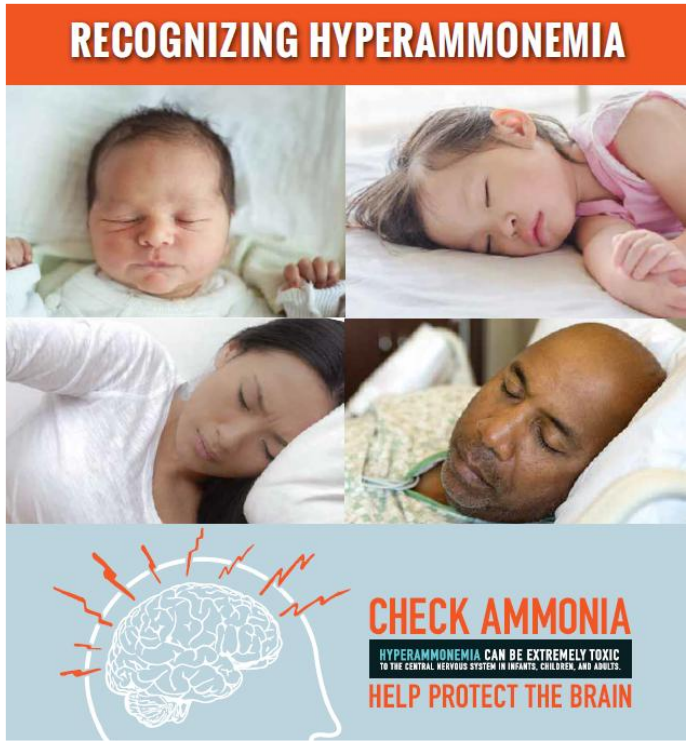
Urea Cycle Disorders (UCDs) are Cruel & Unforgiving

You/your child becomes severely and acutely ill

Your physician/pediatrician orders blood NH_3, refers to a metabolic geneticist

Metabolic geneticist confirms UCD Dx; advises:

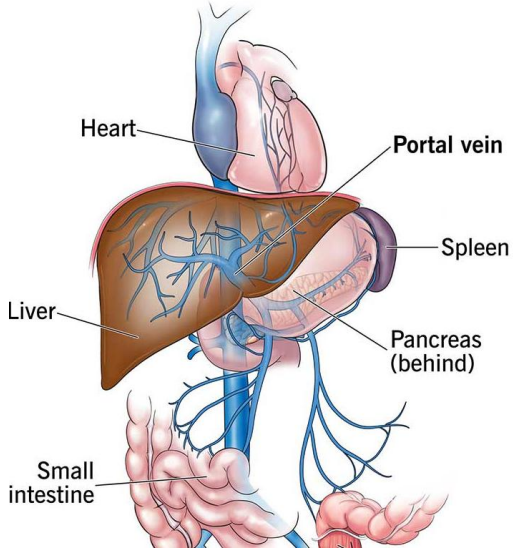
- Severely protein-restricted diet; perhaps with supplements
- A short acting tablet or liquid ≤3-4x/day
- Non-compliance may trigger a hyperammonemic crisis (HAC)
- HACs may require hospitalization, cause disability / death
- HACs may happen anyway; have no apparent cause
- The disorder is lifelong; you/your child won't outgrow it
- Severely affected patients may require a liver transplant



(You're among the fortunate ones whose physician thought to check blood NH_3)

Ammonia Production & Disorders of Hyperammonemia

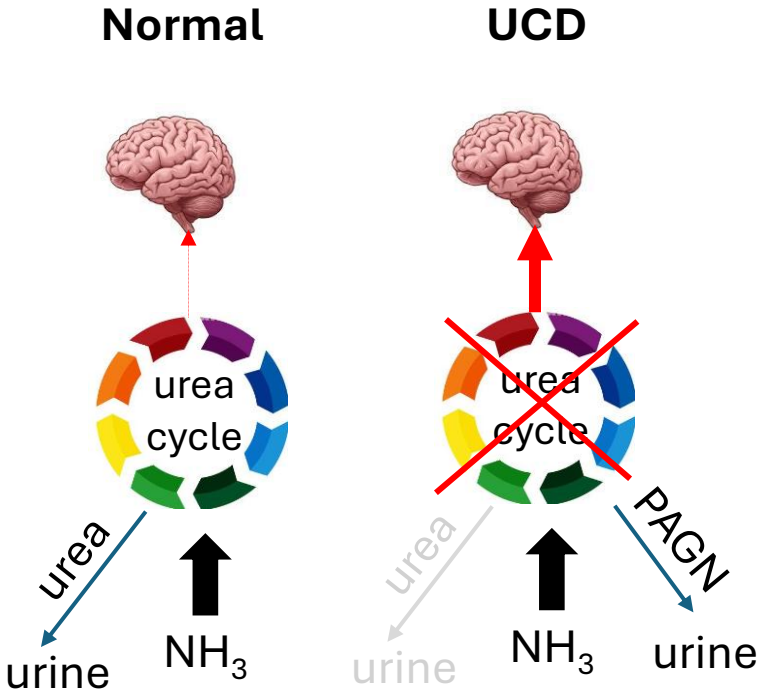
Our Liver is Strategically Positioned



Triage & Cleansing

- Blood from the intestines passes first through the liver
- The liver triages nutrients and clears NH_3 & other toxins

The Urea Cycle Resides in the Liver



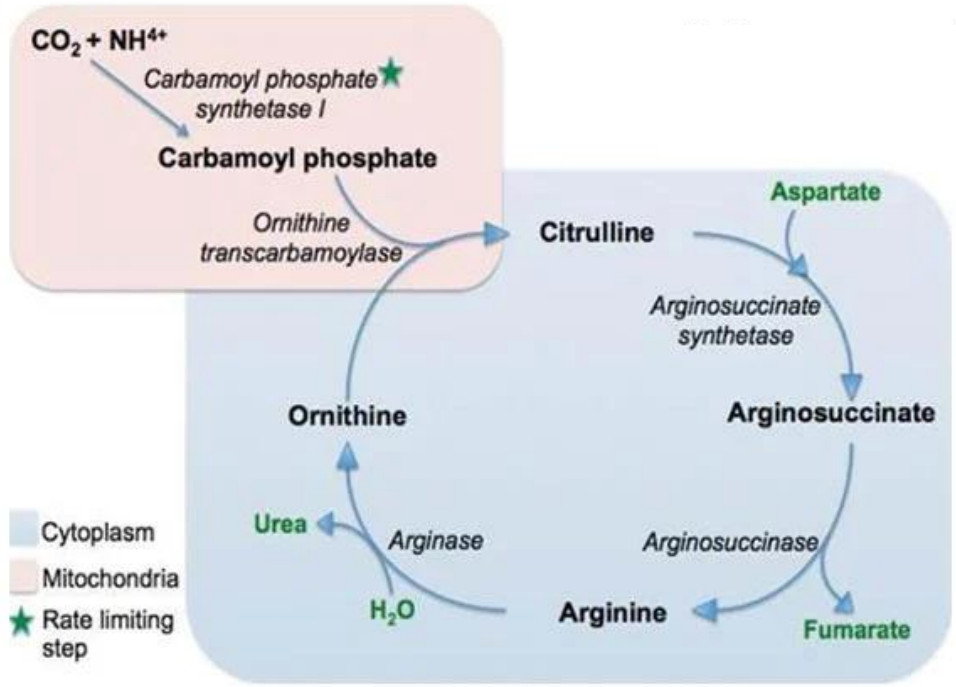
'Alternate Pathway' Drugs

- Sodium phenylbutyrate (NaPBA, Buphenyl®)
- Glycerol phenylbutyrate (GPB, Ravicti®)
- Both are prodrugs of phenylacetic acid, which is converted to phenylacetyl glutamine (PAGN)

- Humans have no nitrogen/protein 'depot'; protein not utilized is broken down, releases ammonia.
- Ammonia is produced in our body/intestines as a byproduct of protein catabolism.
- Ammonia is normally detoxified in the liver through a series of enzymatic steps: the urea cycle.
- Two major disorders of hyperammonemia: liver disease & enzymatic defects in the urea cycle

UCDs: Overview

- Urea Cycle: enzymatic steps NH_3 → urea
- All autosomal recessive except X-linked OTCD
- Genetically heterogeneous
- HACs particularly a problem with proximal UCDs
- The more severe the defect, the earlier the onset
- Severity assessed clinically; measuring urea cycle activity involves stable isotopes (research tool)
- Not all UCD subtypes detected by NBS
- Incidence ~ 1:35,000 births; prevalence uncertain
- Dedicated physician (UCD Consortium; UCDC), patient advocacy groups (National Urea Cycle Disorders Foundation; NUCDF)



Demographics in Hyperion's GPB Trials*

- 49% peds; 51% adult (≥18)
- 67% female; 33% male
- OTC (69%); ASL (13%); ASS (12%)

*Lee, Diaz, Rhead…Scharschmidt, Genet Med 2014

Ammonia Control: Lessons from the GPB Trials

Berry et al (J Ped 2001): "The goal of treatment is to maintain normal levels of plasma ammonia through the use of the low-protein diet and medication while allowing for normal growth."

But

- No consensus among investigators regarding ammonia control
- 24-hr monitoring → NH_3 increases up to severalfold after meals

What is meant by keeping NH_3 normal, and does it benefit patients?

- So, we analyzed our unique data set

UCD Patients Benefit from Tight Ammonia Control

Genetics in Medicine; 2014

Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder

Brendan Lee, MD, PhD[1,2], George A. Diaz, MD[3], William Rhead, MD, PhD[4], Uta Lichter-Konecki, MD[5], Annette Feigenbaum, MD[6], Susan A. Berry, MD[7], Cindy Le Mons[8], James A. Bartley, MD[9], Nicola Longo, MD, PhD[10], Sandesh C. Nagamani, MD[1], William Berquist, MD[11], Renata Gallagher, MD, PhD[12], Dennis Bartholomew, MD[13], Cary O. Harding, MD[14], Mark S. Korson, MD[15], Shawn E. McCandless, MD[16], Wendy Smith, MD[17], Stephen Cederbaum, MD[18], Derek Wong, MD[18], J. Lawrence Merritt II, MD[19], Andreas Schulze, MD, PhD[6], Gerard Vockley, MD, PhD[20], David Kronn, MD[21], Roberto Zori, MD[22], Marshall Summar, MD[5], Douglas A. Milikien, MS[23], Miguel Marino, PhD[15], Dion F. Coakley, Pharm D[24], Masoud Mokhtarani, MD[24], the UCD Consortium and Bruce F. Scharschmidt, MD[24]

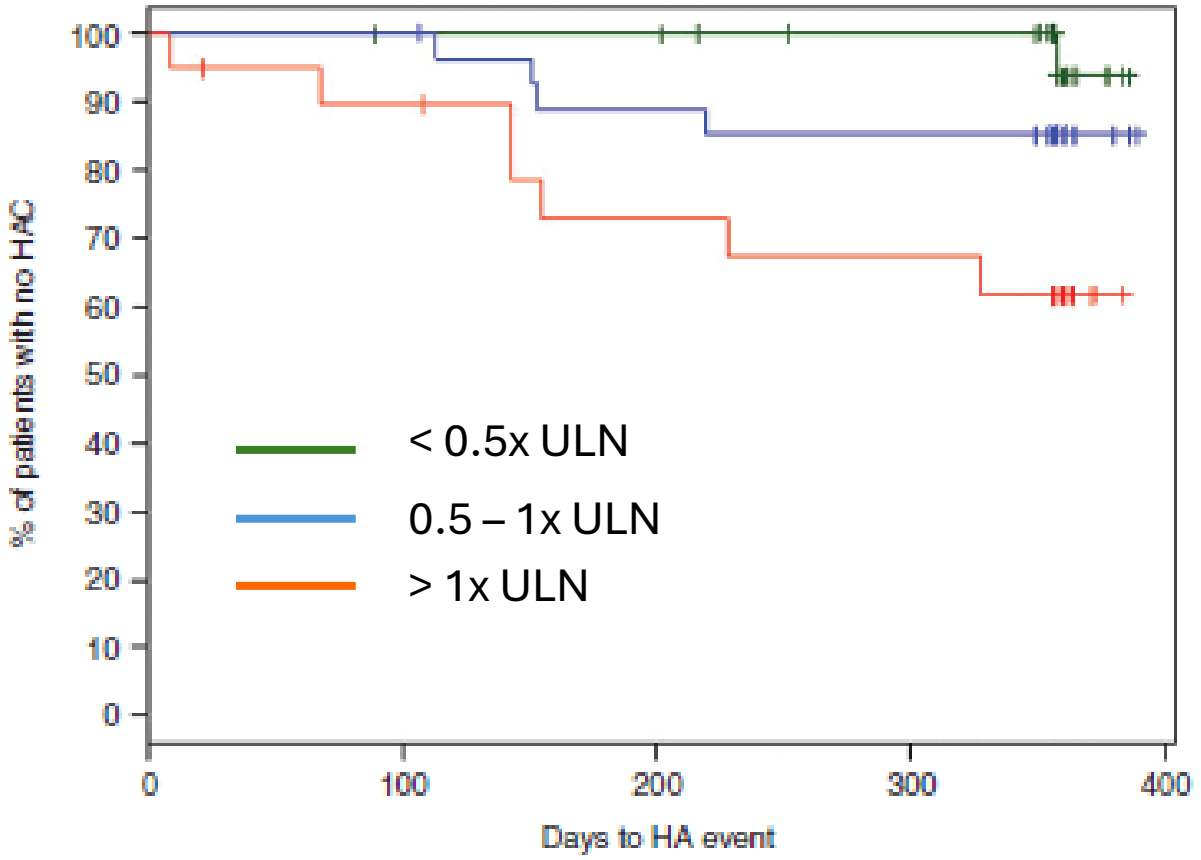
Methods:

- Post-hoc analysis: > 1000 samples, 114 UCD pts
- Examined NH_3 exposure (24-hour AUC) vs. HAC

Results

- HAC risk, frequency correlates with NH_3 exposure
- NH_3 AUC correlates with fasting/morning level
- Patients benefit by fasting/morning NH_3 < ½ ULN

Time-to-event (HAC) 'survival type' analysis



Urea Cycle Disorders (UCDs): Unmet Need

- UCD patients benefit from 'tight' ammonia control, ***but…***
- Treatment is tough
  - Particularly for school age children & adolescents
  - Severely restricted diets sometimes don't resemble food
  - Sodium phenylbutyrate is unpleasant and causes body odor
  - Glycerol phenylbutyrate is easier to take and more slowly absorbed, ***but both drugs…***
    - are short acting and may require multiple times / day dosing
    - may decrease serum levels of BCAA, requiring monitoring, dietary supplements[1]
    - have a narrow therapeutic index, potential for phenylacetic toxicity (PAA)[2]
- We explored the role of compliance/other factors as contributors to HACs

1. **Branched-chain amino acids (BCAA):** Burrage et al., Mol Genet Metab, 2014; Batshaw et al., Mol Genet Metab, 2014
2. **PAA & Safety:** Mokhtarani et al., Mol Genet Metab, 2013; Monteleone et al., J. Clin Pharm, 2013; Glinton et al., Mol Genet Metab, 2023

What We Learned About HACs

CLINICAL TRIAL DATA: HAC Triggers Among 49 Pediatric Patients on NaPBA in the Year Prior to Enrollment*

Trigger	%
Intercurrent illness	26.3%
Infection	15.8%
Drug non-compliance	10.5%
Diet non-compliance	10.5%
Other or 'none'	55.2%

* Berry et al., Glycerol Phenylbutyrate Treatment in Children with Urea Cycle Disorders: Pooled Analysis of Short and Long-term Ammonia Control and Outcomes. Mol Genet Metab, 2014

Additional Considerations

- Role of infection/intercurrent illness consistent with data from UCDC sponsored Longitudinal Study (33%) *
- Role of non-compliance likely understated
  - Infection/illness may cause nausea/vomiting
  - HACs decreased by > 50% after patients enrolled in GPB studies, where compliance is monitored
- Most UCD patients with crises experience several
- A substantial fraction of the ~62% of patients not taking alternate pathway drugs likely also experience HACs

*Batshaw et al., A longitudinal study of urea cycle disorders. Mol Genet Metab, 2014

Some “Asymptomatic” Female OTCD Patients are Not Well

- Most common subtype, X-linked
- It was believed most females were asymptomatic
- Dr. Andrea Gropman’s work has shown that ‘asymptomatic’ female patients exhibit subtle cognitive (executive, fine motor) and functional brain imaging abnormalities
- Among >100 pts in the **UCDC Longitudinal Study** classified as asymptomatic at baseline, 38% developed neuropsychiatric diagnoses (average age 17); 4% HAC (average age 50 years)

“New research shows female OTC carriers (heterozygous females) face more symptoms, risks than expected.” **NUCDF news**, June 2024

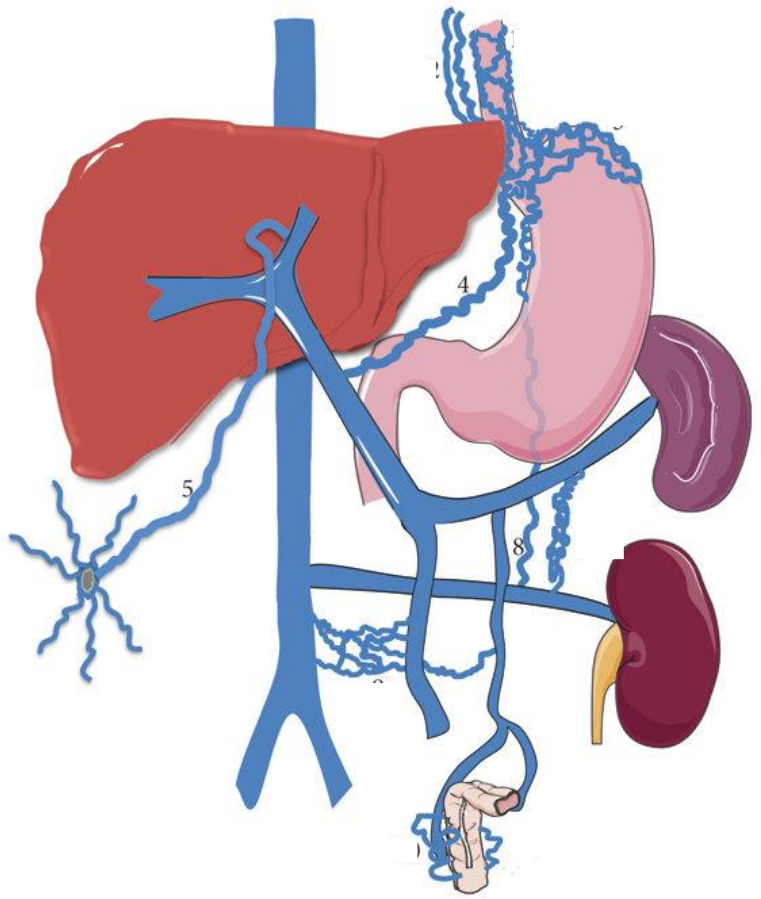
Gropman et al., Altered Neural Activation in Ornithine Transcarbamylase Deficiency During Executive Cognition: An fMRI Study. Human Brain Mapping, 2013.
Gropman et al., Urea cycle defects and hyperammonemia: effects on functional imaging; Met Brain Dis, 2013
Sprouse et al., Investigating Neurological Deficits in Carriers and Affected Patients with Ornithine Transcarbamylase Deficiency, Mol Genet Metab, 2014
Sen et al., Are asymptomatic carriers of OTC deficiency always asymptomatic? A multicentric retrospective study of risk using the UCDC longitudinal study database, Mol Gen Metab, 2024

Decompensated Cirrhosis and Hepatic Encephalopathy (HE)

- Scarred liver impedes portal blood flow → portal hypertension & portal-systemic shunting (PSS) (i.e., shunting of blood around the liver)
- 3 major manifestations of liver failure/PSS : HE, variceal bleeding, fluid retention with ascites/kidney failure
- Liver transplantation is the only 'cure', *but*
  - Severely donor limited -> long wait times
  - Patients may live years
- Can cause brain damage, sometimes death
- Strong pharmaco-economics
- US prevalence likely > 200,000
- Big question when Hyperion started its trial:

Is elevated ammonia a correlate or a cause?

Cirrhosis with PS Shunting



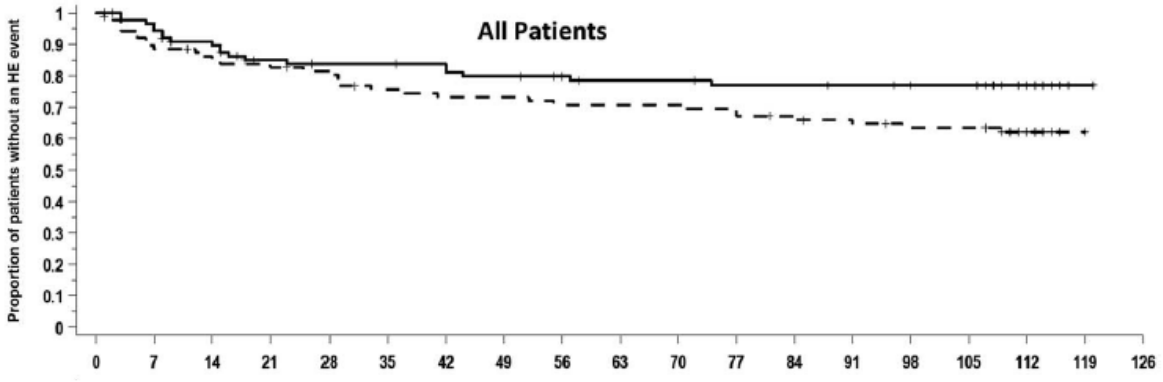
Ammonia Lowering is Effective in Secondary Prophylaxis of HE

2012 AASLD Plenary / Hepatology; 2014

Randomized, Double-Blind, Controlled Study of Glycerol Phenylbutyrate in Hepatic Encephalopathy

Don C. Rockey,[1] John M. Vierling,[2] Parvez Mantry,[3] Marwan Ghabril,[4] Robert S. Brown, Jr.,[5] Olga Alexeeva,[6] Igor A. Zupanets,[7] Vladimir Grinevich,[8] Andrey Baranovsky,[9] Larysa Dudar,[10] Galyna Fadieienko,[11] Nataliya Kharchenko,[12] Iryna Klaryts'ka,[13] Vyacheslav Morozov,[14] Priya Grewal,[15] Timothy McCashland,[16] K. Gautham Reddy,[17] K. Rajender Reddy,[18] Vasyl Syplyviy,[19] Nathan M. Bass,[20] Klara Dickinson,[21] Catherine Norris,[21] Dion Coakley,[21] Masoud Mokhtarani,[21] and Bruce F. Scharschmidt,[21]

Time-to-event (HE event) 'survival type' analysis



Hazard ratio: 0.56
95% CI: (0.32, 0.99)
P = 0.047

—— GPB
--- placebo

Methods:

- RDBPC multi-national trial of GPB
- 178 patients with ≥2 prior HE episodes in ≤ 6 mos
- Cochran-Mantel-Haenszel analysis stratified by country

Results

- GPB lowered ammonia
- GPB lowered HE risk, HE frequency, HE hospitalizations

But... Might the effect of GPB be due to something other than its effect on ammonia?

GPB Works by Ammonia Lowering

Clinical Gastroenterology & Hepatology; 2016

Fasting Blood Ammonia Predicts Risk and Frequency of Hepatic Encephalopathy Episodes in Patients With Cirrhosis

John M. Vierling,* Masoud Mokhtarani,‡ Robert S. Brown Jr,§ Parvez Mantry,‖ Don C. Rockey,¶ Marwan Ghabril,# Richard Rowell,‡ Marzena Jurek,‡ Dion F. Coakley,‡ and Bruce F. Scharschmidt‡

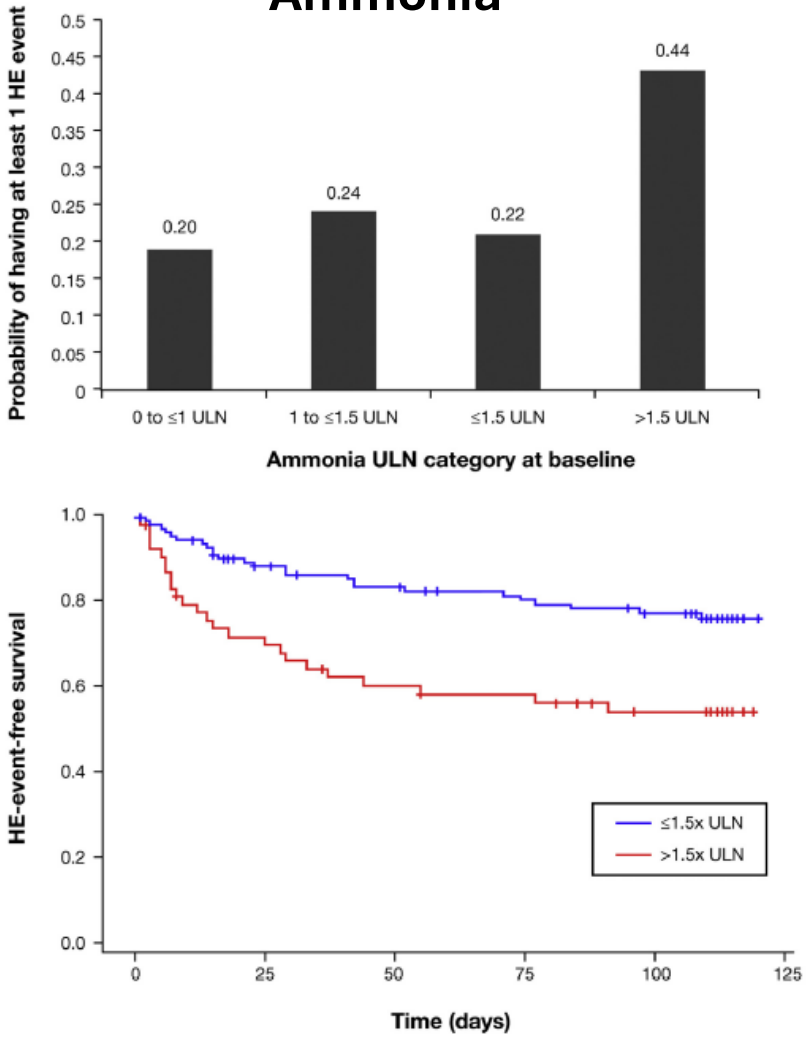
Methods:

- Post-hoc analysis: > 1000 ammonia samples from 178 pts
- Examined fasting ammonia vs. risk, frequency of HE events
- Binary logistic regression & Cox proportional hazard

Results

- Morning/fasting ammonia correlates with HE risk, frequency
- GPB effect explained by ammonia lowering
- Patients benefit by keeping fasting / morning ammonia ≤1.5 x ULN

HE Risk & Frequency vs. Fasting Ammonia



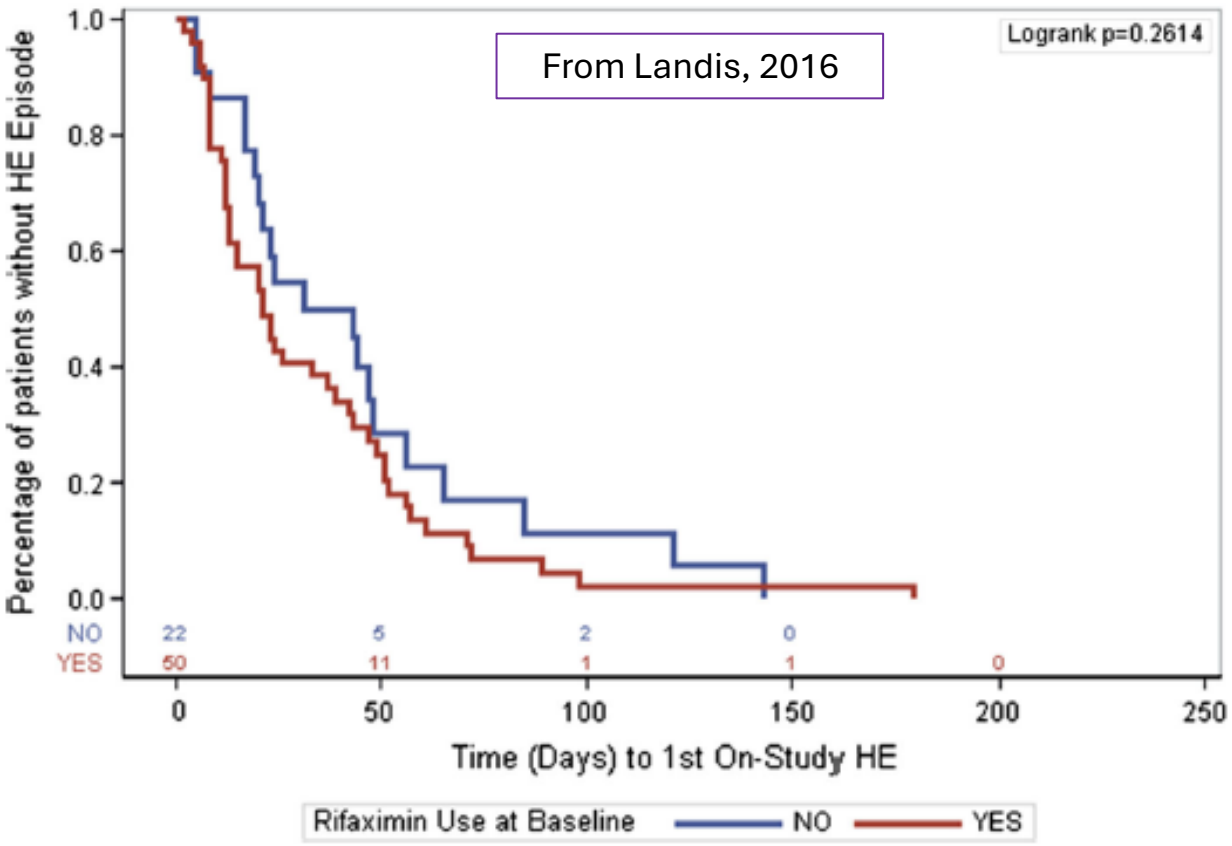
HE is Still a Big and Expensive Problem

HE Observational Study

- 265 pts; 30 sites; ≥1 HE event ≤30 days; 72d mean F/U
- 72 (27%) pts experienced a total of 122 HE events
- 23 (9%) / 13 (5%) had ≥ 2 / ≥ 3 HE events
- 82% of patients with HE were on rifaximin
- 85% of events resulted in hospitalization
- No difference related to rifaximin use at baseline

Big Healthcare Burden; Strong Pharmacoeconomics

- Impacts cognition, HRQoL, outcome
- HE hospitalizations (>>$10K/hospitalization)
- Total US costs: $B's



Landis, Ghabril, Rustgi, … Scharschmidt: Prospective Multicenter Observational Study of Overt Hepatic Encephalopathy, Dig Dis Sci, 2016

Hirode et al., Increasing Burden of Hepatic Encephalopathy Among Hospitalized Adults: An Analysis of the 2010-2014 National Inpatient Sample, Dig Dis Sci, 2019

Bajaj et al. The Burden of Hepatic Encephalopathy use of Albumin as a Potential treatment, Ann Hep, 2025

HE Final Thoughts

Why is HE still such a big problem?

- Drug compliance almost certainly an issue
- Other complications better treated
- HE not prioritized for liver transplant
- Ammonia may not be the only cause, ***and/or***
- Current Rx doesn't lower ammonia enough

> *"Hepatic encephalopathy (HE) is … one of the most debilitating manifestations of liver disease, severely affecting the lives of patients and their caregivers….. results in utilization of more health care resources in adults than other manifestations of liver disease"*
>
> **Hendrik, AASLD/EASL HE practice guidelines, 2014**

Minimal/Covert HE

- Conceptually analogous to 'asymptomatic' OTCD
- Subtle/subclinical cognitive & imaging abnormalities
- Difficulty with executive function, driving
- **No consensus:** Whether to test, how to diagnose and no approved Rx.
- **Consensus:** It is an important problem and more common than overt HE (~50% of cirrhotics)

As a hepatologist: I'm hoping we can do more for these patients!

THANK YOU

KRRO-121 Scientific Overview and Preclinical Data

Loïc Vincent, PhD

Chief Scientific Officer

Mechanism: Stabilizing Glutamine Synthetase to Clear Ammonia

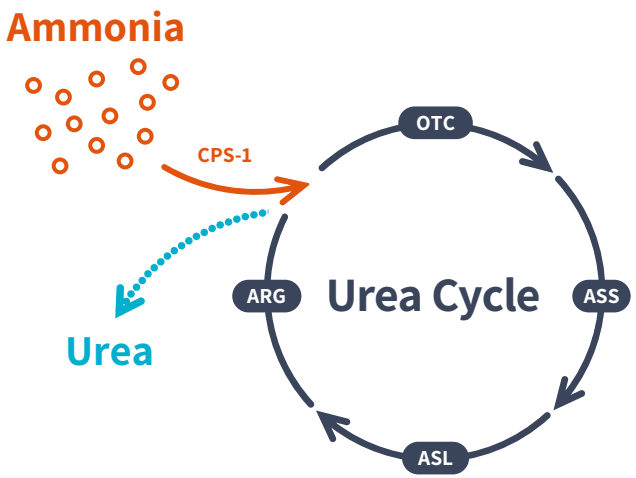
Glutamine Synthetase (GS) is a critical ammonia clearing mechanism

- Genetic evidence uncovers a key amino acid modification that can **augment GS protein stability**
- **Ammonia-lowering benefits** of stabilized GS activity may address substantial unmet need in patients with poor ammonia control, including UCD and hepatic encephalopathy
- KRRO-121 is a GalNAc-conjugated ASO that edits GS mRNA to generate a stable, *de novo* GS variant **specifically in the liver**
- KRRO-121 demonstrates potential to enable **robust ammonia clearance**, supporting a pan-UCD approach that may enable dietary liberalization as well as clinical activity in other **ammonia-driven diseases**, such as HE

KRRO-121 regulatory submission to enable commencement of FIH trial is anticipated in the 2nd half of 2026

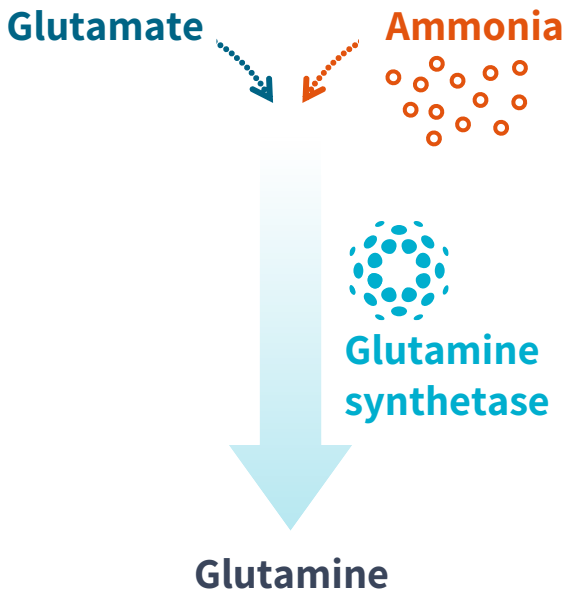
Two Complementary Pathways for Ammonia Clearance: Urea Cycle and Glutamine Synthetase (GS)

Urea Cycle



Expressed primarily in liver

Glutamine Synthetase

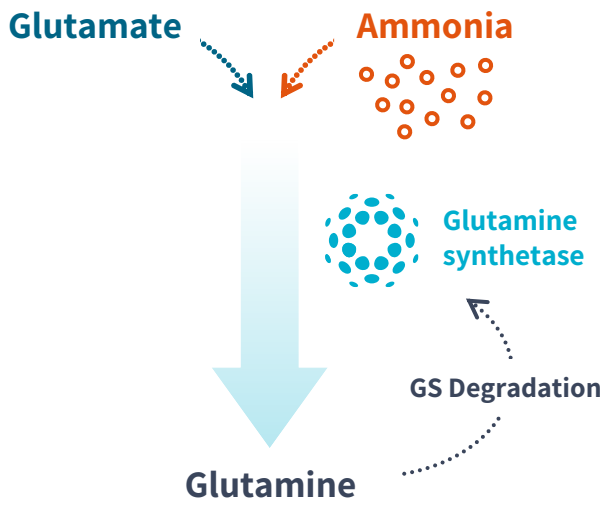


Expressed in many tissues, including liver, brain, and muscle

Source: Inoue at al., Seizure (2015); Bennet et al., Child Neurology Open (2020); Jones et al., The American Journal of Human Genetics (2024); Soria et al., J Inherit Metab Dis (2019); KOL interviews

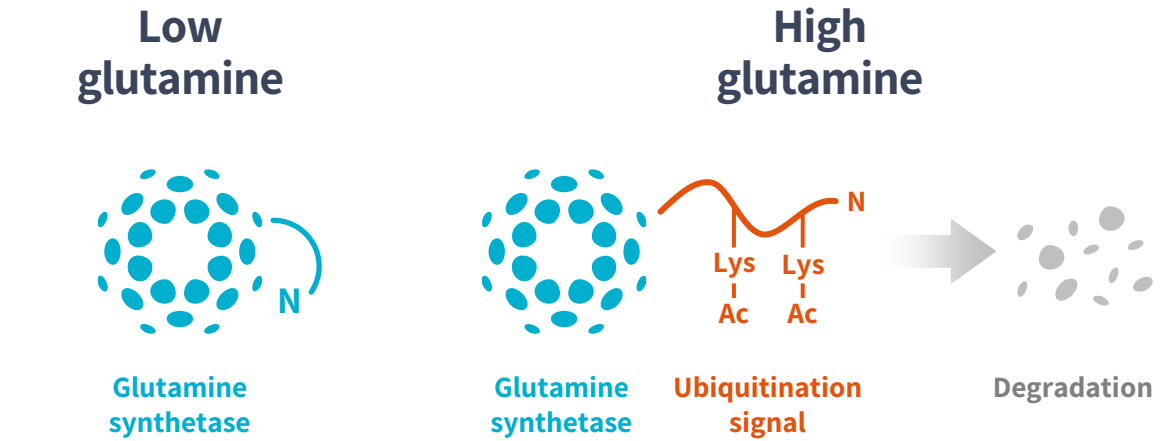
Degradation of GS Controlled by Levels of Glutamine

Glutamine Drives Degradation of GS



GS degraded when glutamine rises, reducing ammonia clearance capacity

Degradation Mechanism: Acetylation of Key N-terminal Residues



No lysine acetylation, GS is stable

Acetylation of lysine residues, leading to ubiquitination and protein degradation

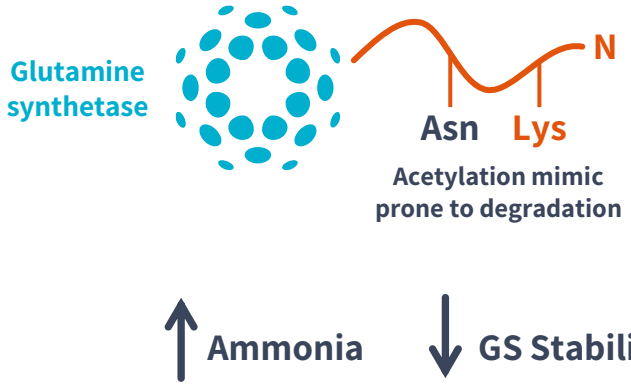
Source: Van Nguyen et al., Mol Cell (2017)

Human Genetic Evidence Supports Stabilization of GS by Preventing Degradation

Loss of Function

Case Report

Two Siblings With Valproate-Related Hyperammonemia and Novel Mutations in Glutamine Synthetase *(GLUL)* Treated With Carglumic Acid

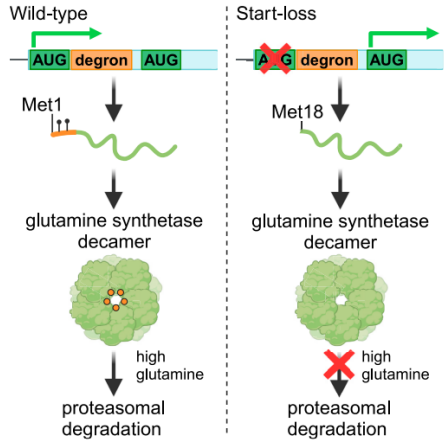


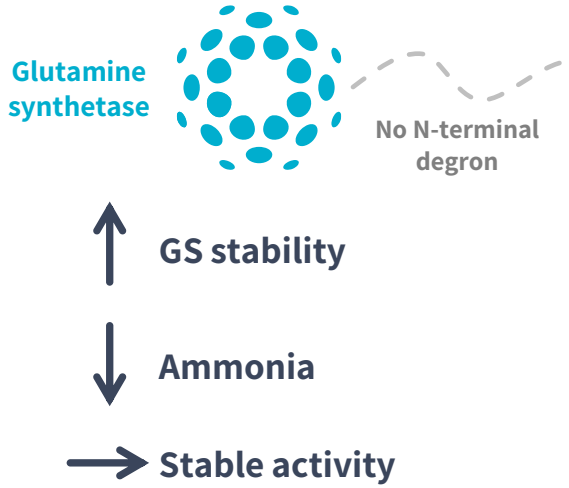
Patient with Lys14Asn mutation (mimicking acetyl-lysine) resulted in GS deficiency, hyperammonemia

Gain of Function

ARTICLE

Clustered *de novo* start-loss variants in *GLUL* result in a developmental and epileptic encephalopathy via stabilization of glutamine synthetase



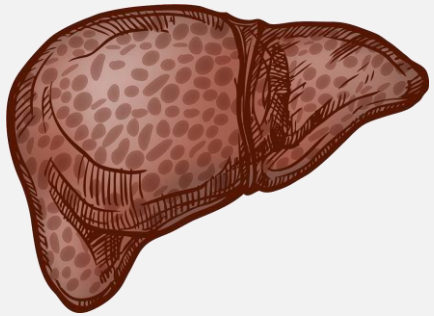


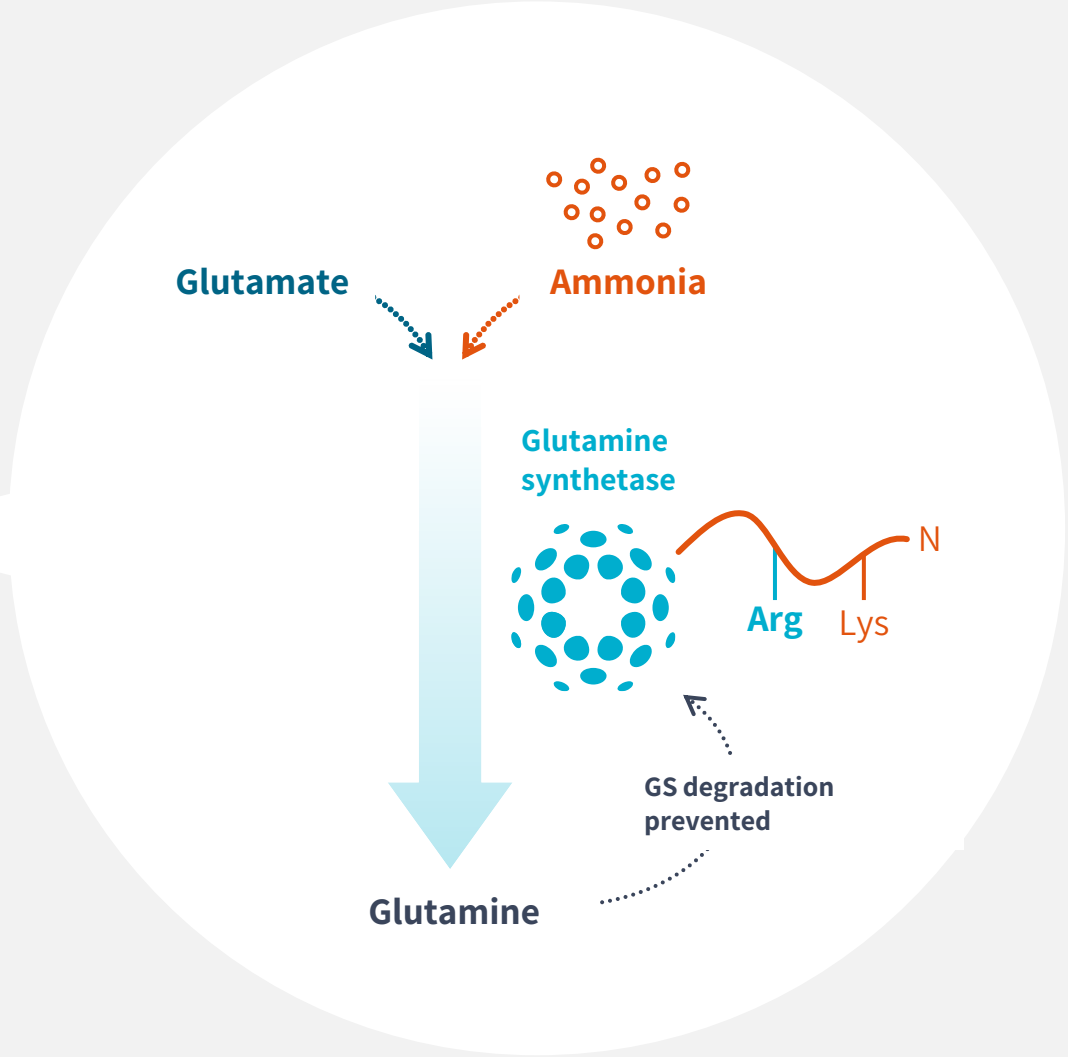
9 patients with start-loss variants, stabilizing GS due to loss of N-terminal Lys residues

Source: Bennet et al., Child Neurology Open (2020); Jones et al., The American Journal of Human Genetics (2024); Van Nguyen et al., Mol Cell (2017)

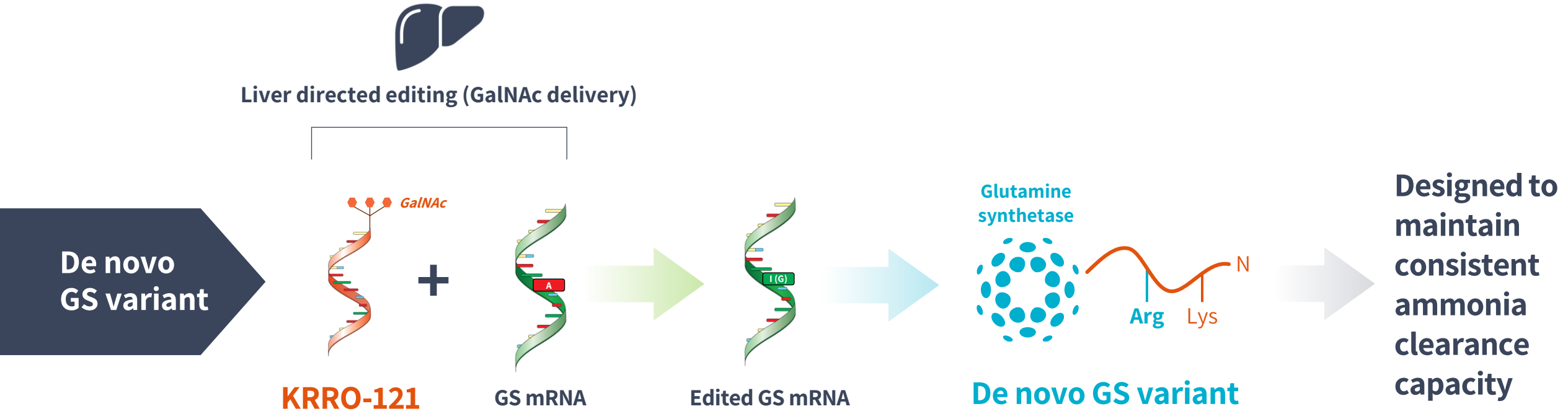
Hypothesis: Preventing GS Degradation Will Stabilize the Protein and Enable Increased Ammonia Clearance

Liver-specific GS modification may prevent degradation, increase ammonia clearance





Our Approach: Liver-specific, GalNAc-ASO to Generate a Stable GS Variant



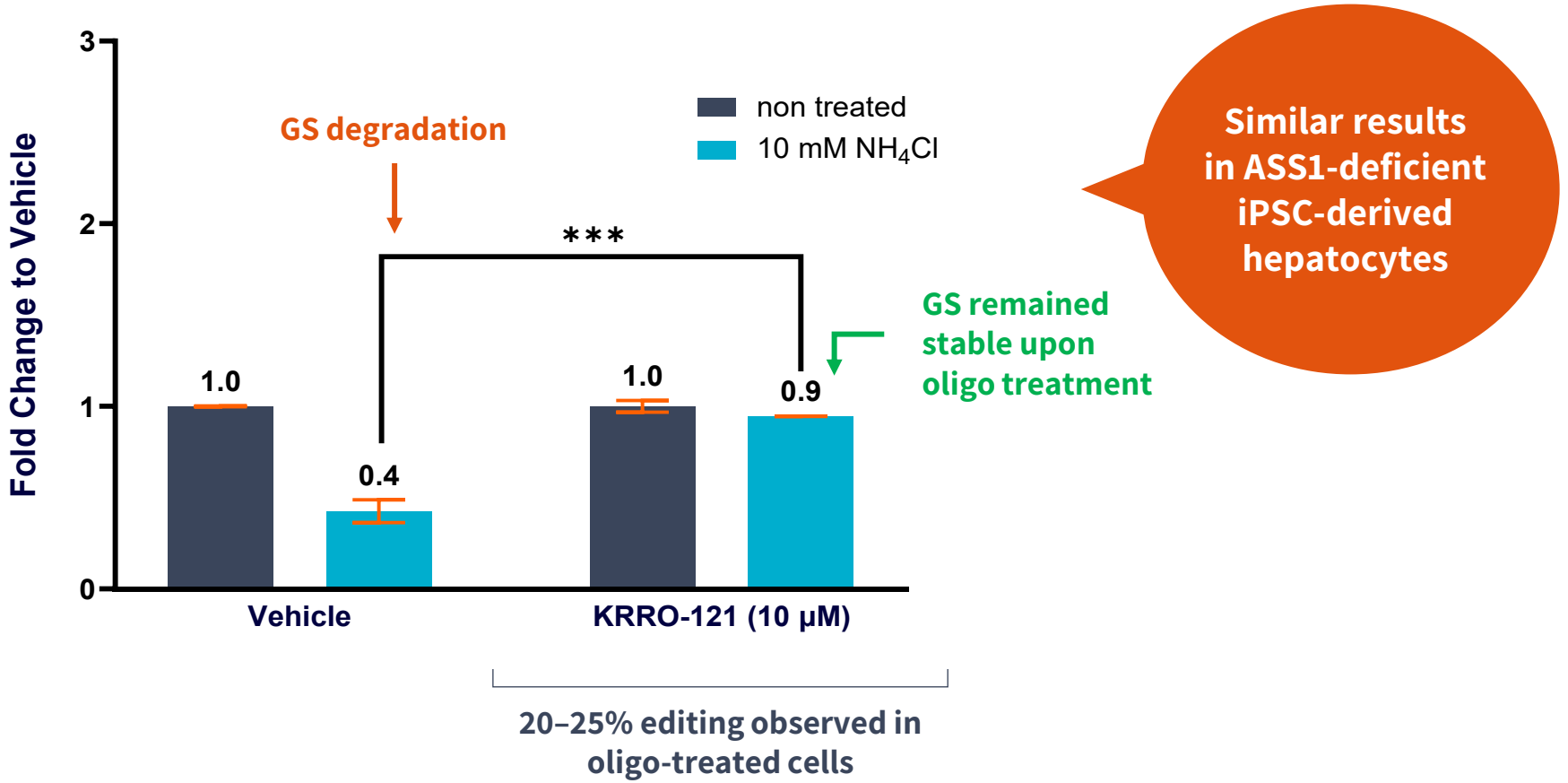
KRRO-121: GalNAc-conjugated oligonucleotide designed for liver-specific RNA editing of GS to enhance ammonia clearance capacity

KRRO-121 Stabilized GS in UCD-derived Human Cell Models

OTC iPSC

KRRO-121

KRRO-121 Stabilized GS in OTC-Deficient iPSC-Derived Hepatocytes

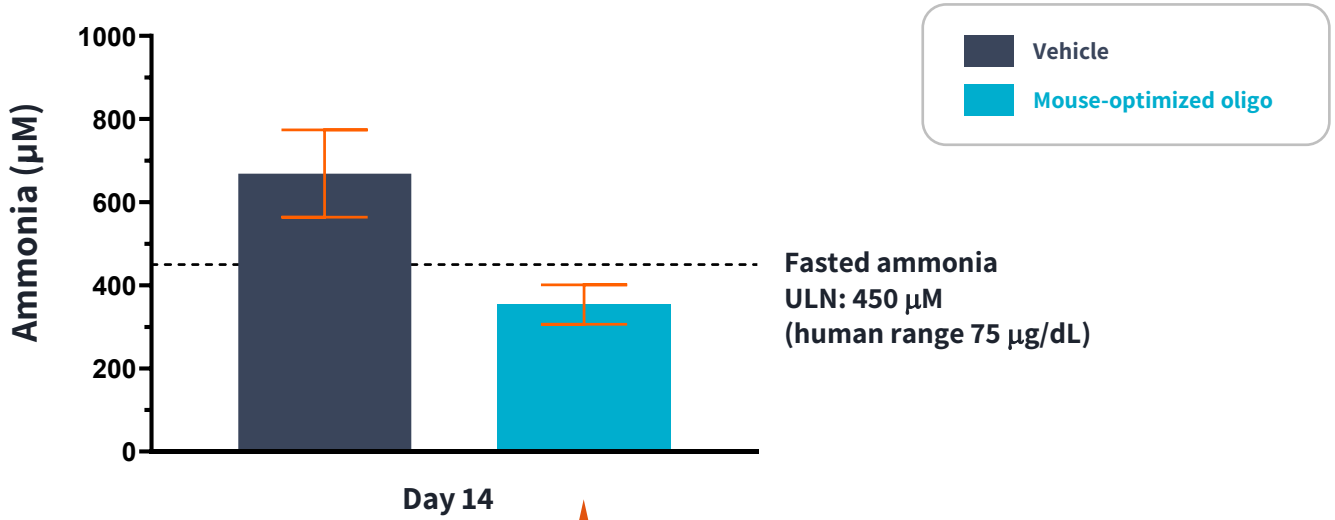


Note: OTC D175V human iPSC-derived hepatocytes differentiated for 14 days, then treated with oligo for 48 hours where indicated (10 mM NH_4Cl added after 24 hours where indicated). GS concentration measured at conclusion of 48-hour incubation.

Ammonia Reduction in OTC-Deficient Mice Challenged with Ammonia Supports Clinical Activity, Diet Liberalization

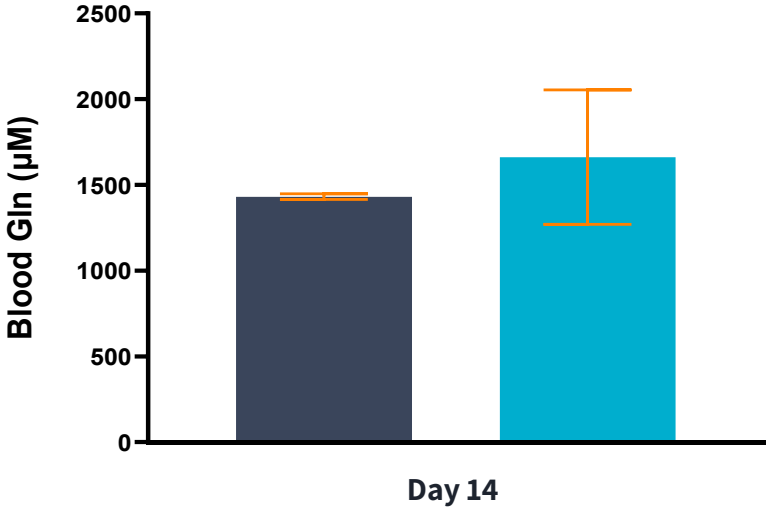
OTC spf/ash

Improved Clearance in Ammonia Challenge Supports Potential to Increase Protein Intake



Ammonia challenge designed to model patient protein consumption

Nonsignificant Increase in Plasma Glutamine Levels

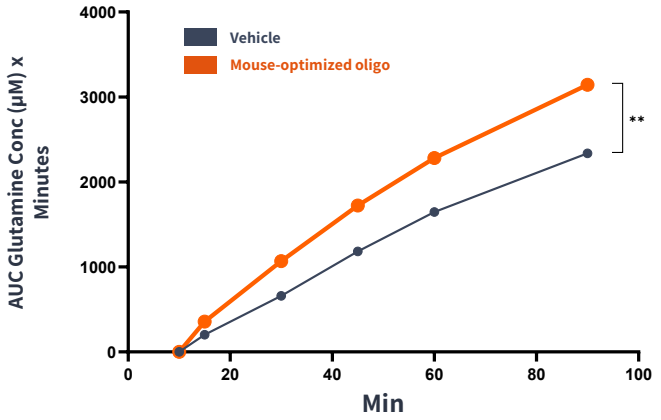


Note: Vehicle or Mouse-optimized oligo dosed at 10 mg/kg-SC daily on Days 0-4. Ammonia and glutamine measured following ammonia challenge (150 mg/kg) on Day 14

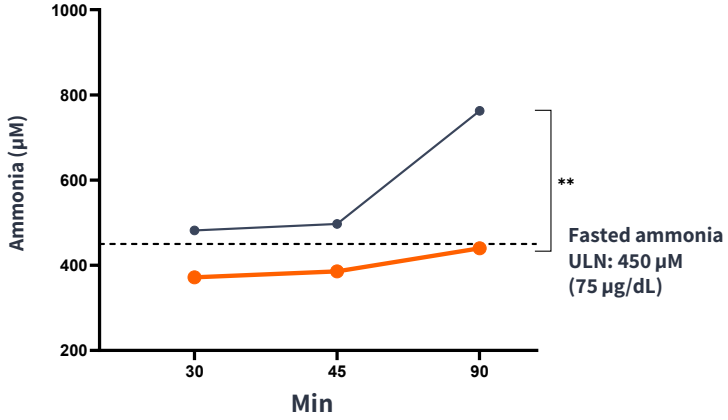
De Novo GS Variant Enabled Ammonia Control in OTC Mice Under Protein Load, with Stable Isotope Tracer Validating MOA

OTC spf/ash

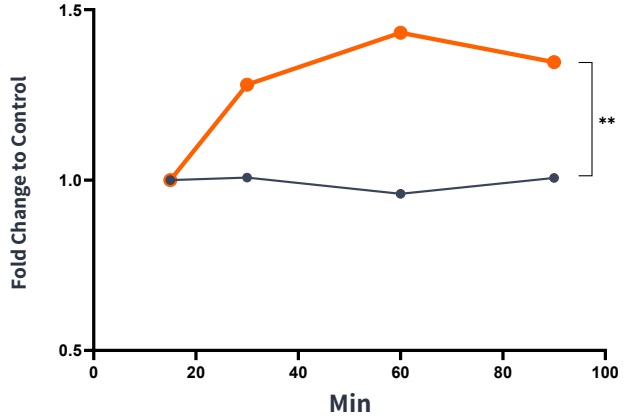
Increased Plasma N-15 Glutamine



Decreased Plasma Ammonia



Increased Total Liver GS Concentration



N-15 glutamate used as target engagement tracer

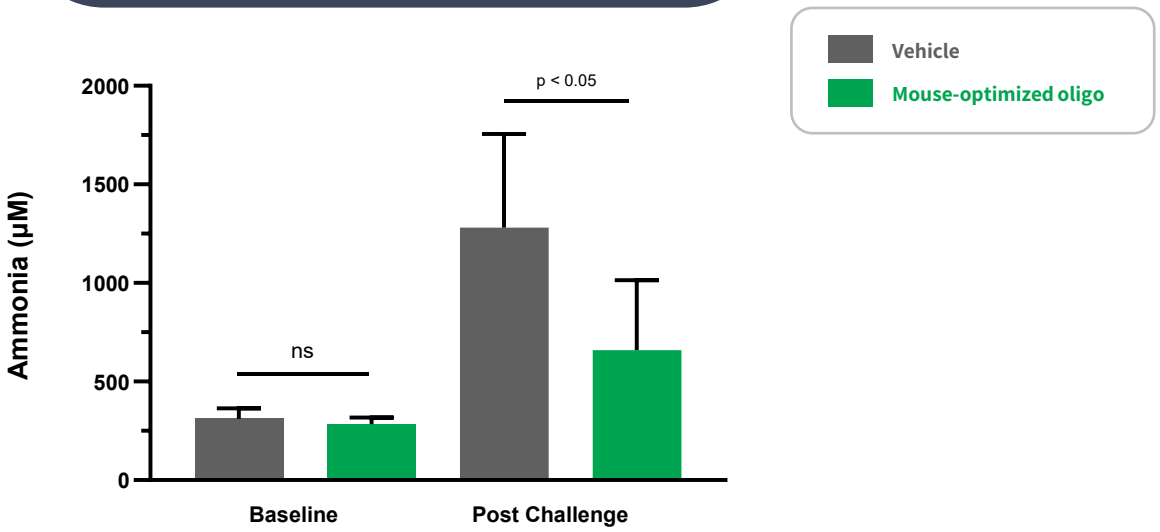
Demonstrated GS target engagement in OTC-deficient mice; similar results observed in wild-type mice (not shown)

Note: Vehicle or Mouse-optimized oligo dosed at 10 mg/kg-SC daily on Days 0-4. Glutamine, ammonia, and GS concentration measured following challenge with 100 mg/kg glutamine + N-15 glutamate on Day 11

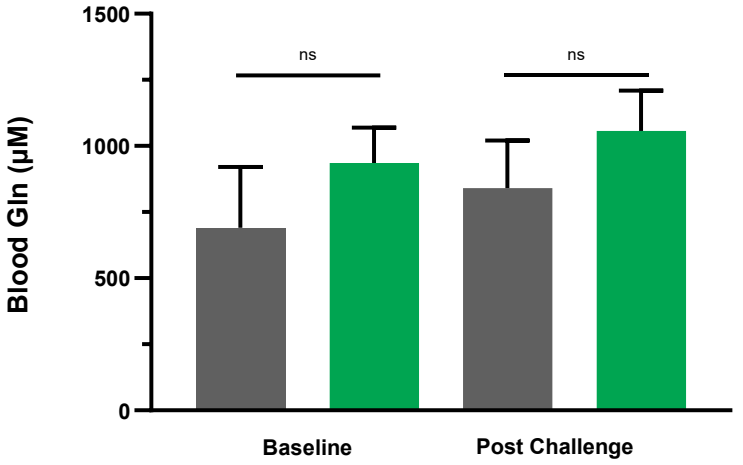
Ammonia Reduction in CPS-1 Deficient Mice Further Validates Potential Pan-UCD Applicability and Diet Liberalization

CPS-1

Reduction in Ammonia Following Ammonia Challenge



Nonsignificant Increase in Plasma Glutamine Levels



"… Korro's RNA editing approach targeting **glutamine synthetase** in hepatocytes has been proven to effectively **redirect excess toxic ammonia** towards the synthesis of glutamine in UCD animal models …"

– Nicola Brunetti-Pierri MD and Leandro R. Soria PhD

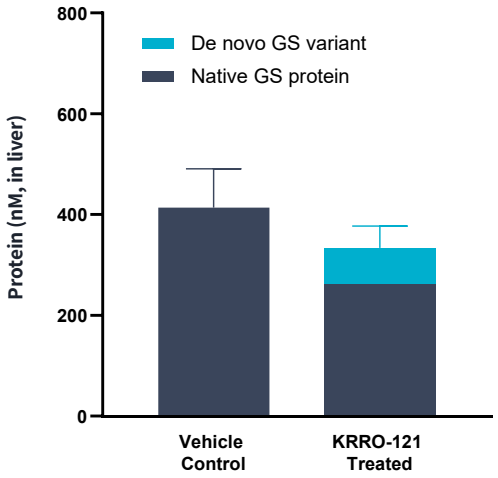
Note: Vehicle or Mouse-optimized oligo dosed at 10 mg/kg-SC daily on Days 0-4. Ammonia and glutamine measured following ammonia challenge (150 mg/kg) on Day 8

KRRO-121 Significantly Reduced Ammonia Levels in Basal State and Following Ammonia Challenge in Humanized Liver Mouse Model

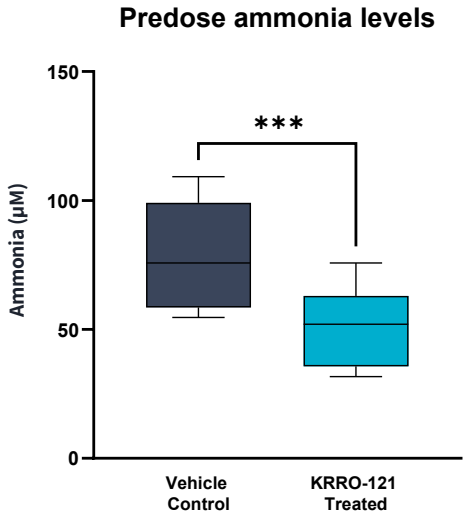
PXB

KRRO-121

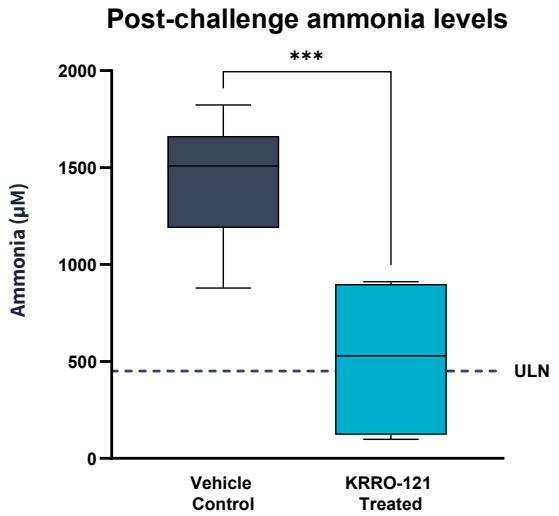
Stabilized GS Variant and Normal GS Protein Levels



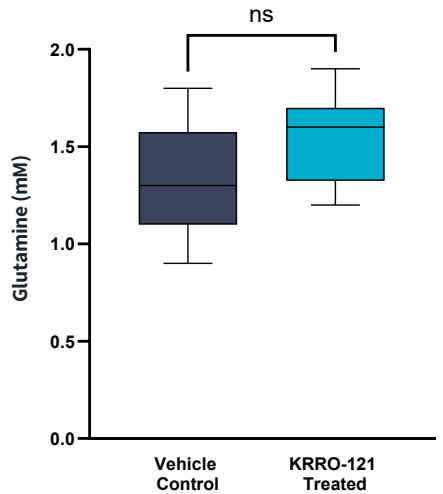
Reduction in Basal Ammonia



Enhanced Ammonia Clearance in Challenge



Steady Glutamine Post-Challenge



Potent ammonia lowering through a minimal amount of de novo GS

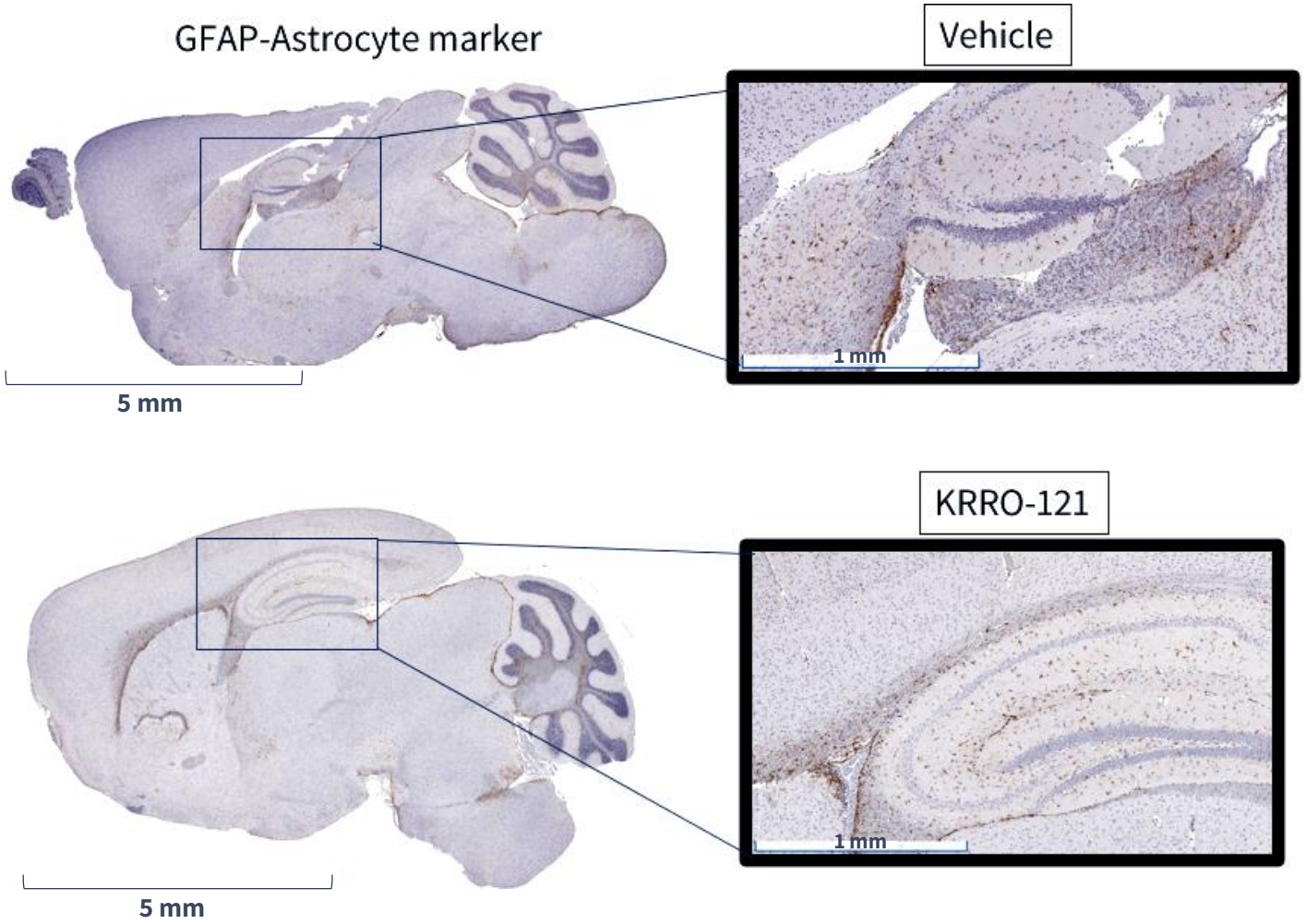
KRRO-121 stabilized GS levels, providing robust ammonia control in a humanized mouse model

Note: Vehicle or KRRO-121 dosed at 50 mg/kg-SC on Days 0, 14 and 28. Mice challenged with 350 mg/kg ammonia on Day 21. GS levels measured on Day 31. PXB mice retain zonal GS expression.
Source: J Toxicol Pathol 2025; 38: 183–189

KRRO-121 Showed No Increase in Astrocyte Activation in Brain

OTC spf/ash

KRRO-121



GFAP+ cells represented as brown dots

Note: Vehicle or KRRO-121 dosed at 20 mg/kg-SC daily on Days 0-4. Editing and GFAP measured following ammonia challenge (150 mg/kg) on Day 14

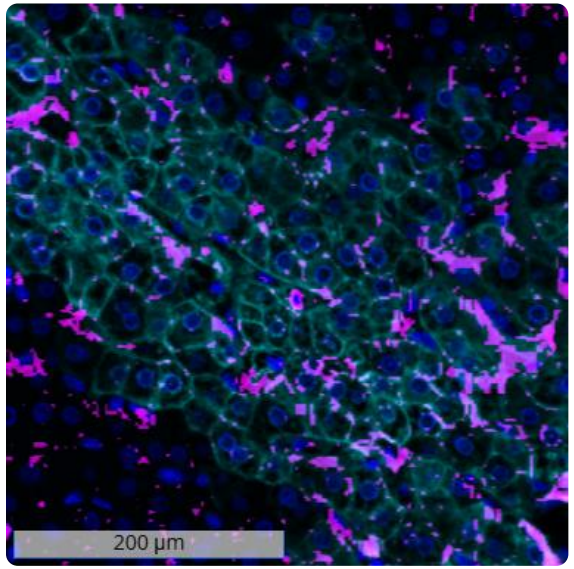
KRRO-121 Displayed Strong Liver Uptake and No Adverse Findings in Non-Human Primates

KRRO-121

>90% Delivery of KRRO-121 to Liver

<0.05% delivery to bone marrow, brain, heart, lymph nodes and muscle

Confirmed Liver Localization of KRRO-121 with Pericentral GS

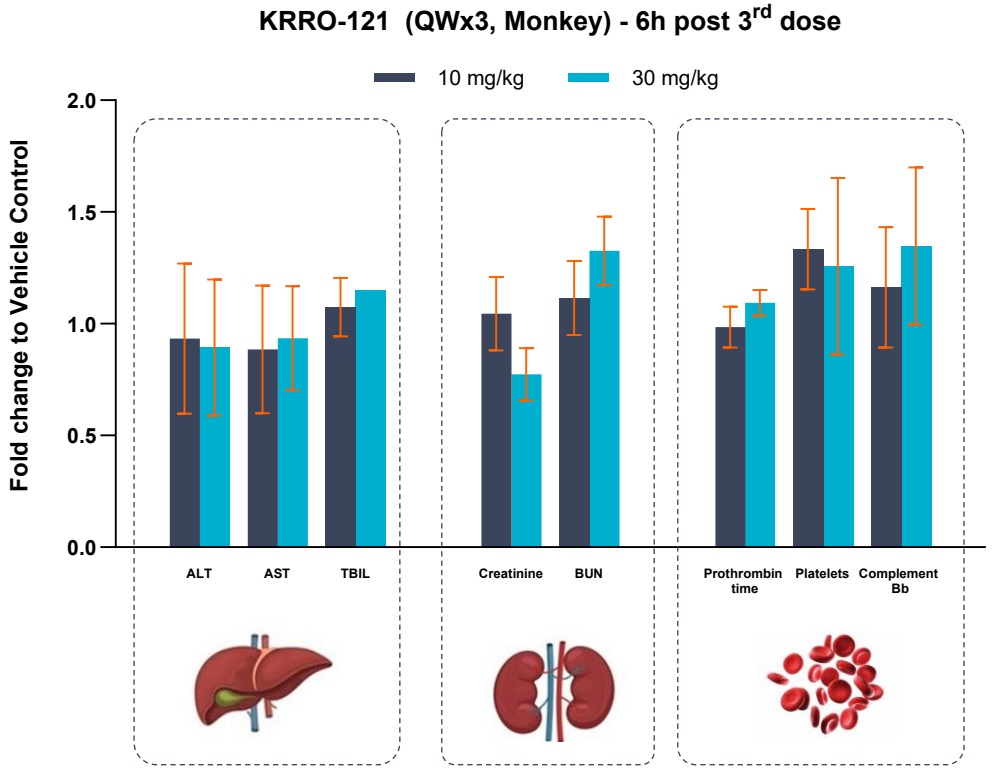


Cy5 (purple) = KRRO-121

Cy7 (teal) = GS

DAPI (blue) = nuclei

No Changes in Liver or Kidney Function



Note: Vehicle or KRRO-121 dosed to cynomolgus monkeys (n=3 male/group) QWx3 (10 or 30 mg/kg), samples collected for biodistribution and histopathology 48h post third dose and clinical chemistries and hematology 6 and 48h post first and last dose

KRRO-121: A Potential First-in-class Treatment For Ammonia Control

Preclinical Activity

- **Pan-UCD potential** impacting multiple UCD subtypes
- **Robust ammonia control** in OTC and CPS-1 mice challenged with ammonia[1]
- **Diet liberalization potential** demonstrated by ammonia reduction during protein challenge

Preclinical Safety

- **NHP: No adverse safety signals** in repeat QWx3 dose range finding tox studies
- **NHP:** No impact on **coagulation, complement, platelets, cytokines**
- No evidence of editing observed in **mouse brain tissue**
- No increase in **mouse astrocyte staining** in KRRO-121 treated mice relative to vehicle treatment

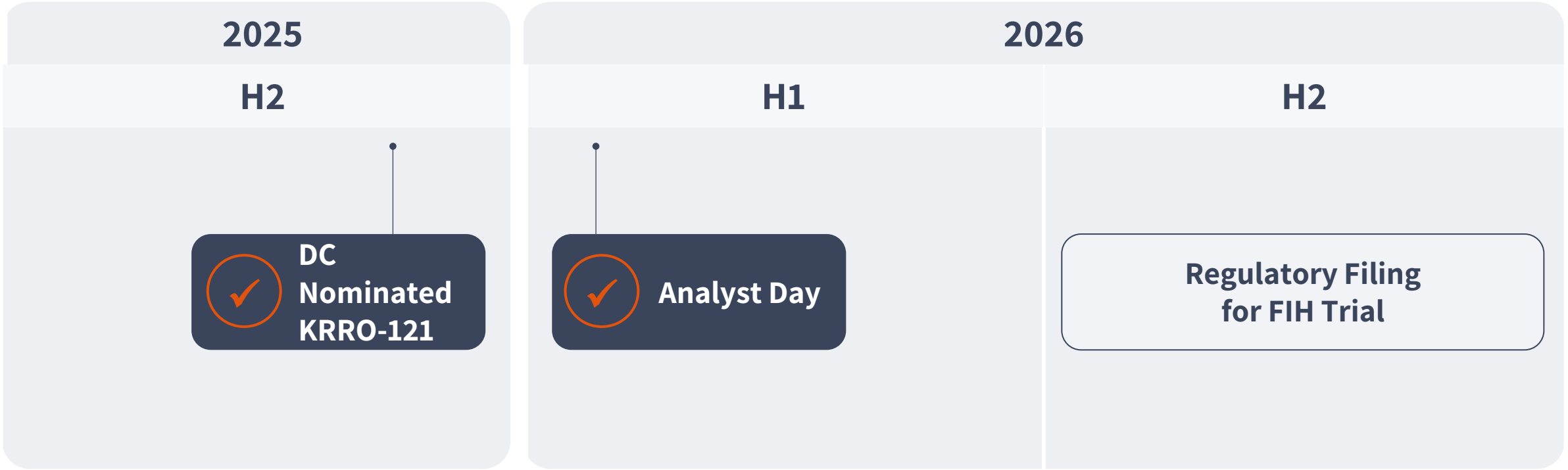
Demonstrated Translation

- Production of **stable, *de novo* GS variant** which increased ammonia clearance and maintained normal glutamine levels
- Scaled from **mouse to monkey** and showed **targeted liver delivery**

Strong preclinical data support KRRO-121's anticipated regulatory submission

Note: 1. As demonstrated using a surrogate mouse-optimized oligo

KRRO-121: Anticipated Regulatory Filing in Second Half of 2026



Compelling product profile for controlling ammonia expected to drive strong patient engagement and recruitment

KRRO-121 Market Opportunity

Todd Chappell, MBA

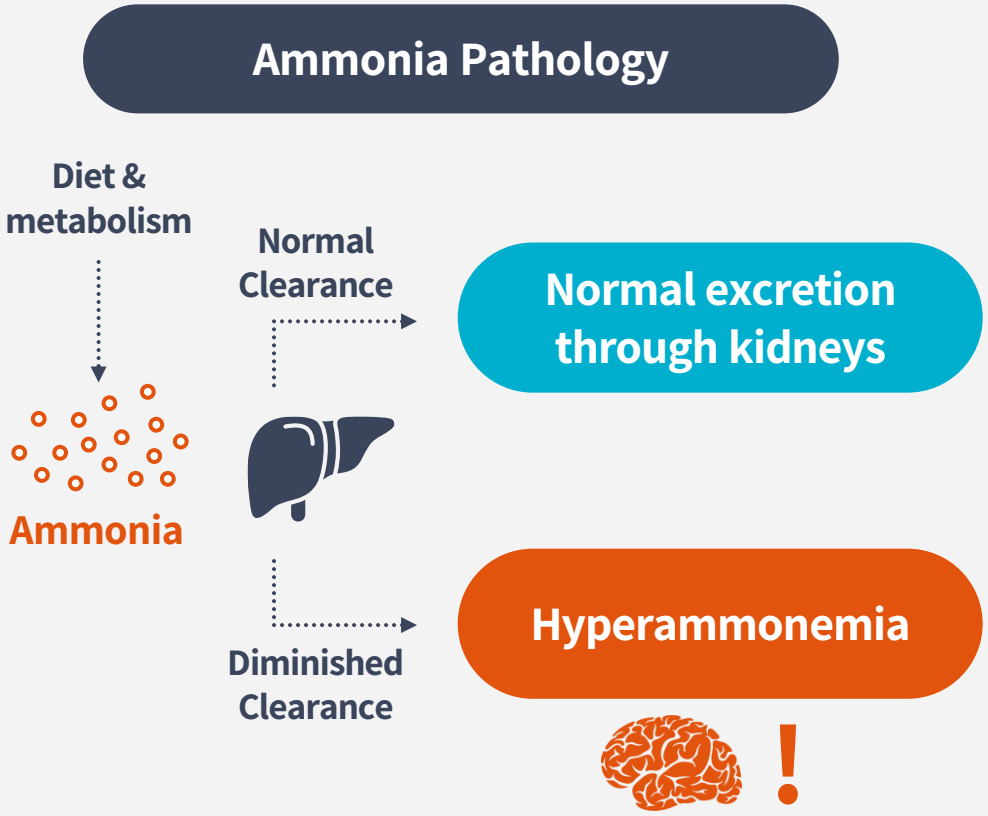
Chief Operating Officer

KRRO-121 Has Blockbuster Potential in Multiple Indications

	Urea Cycle Disorders	Hepatic Encephalopathy
Addressable Patients	4,200 U.S.[1] 5,100 EU + UK[1]	80,000 U.S.[2] 150,000 EU + UK[3]
Market Opportunity	$1.5B	$2B+

Note: 1. Severe late-onset UCD patients; 2. Patients prescribed rifaximin +/- lactulose with ≥1.5x normal ammonia and satisfactory liver function as assessed by laboratory values; 3. EU + UK estimate applies U.S. epidemiology assumptions to estimated EU + UK cirrhosis population
Source: 3rd party primary market research study (April 2025); KOL interviews; GlobalData; Electronic medical records analysis (data from 2022). All figures approximate.

Plasma Ammonia Significantly Impacts Pathology Across Multiple Diseases

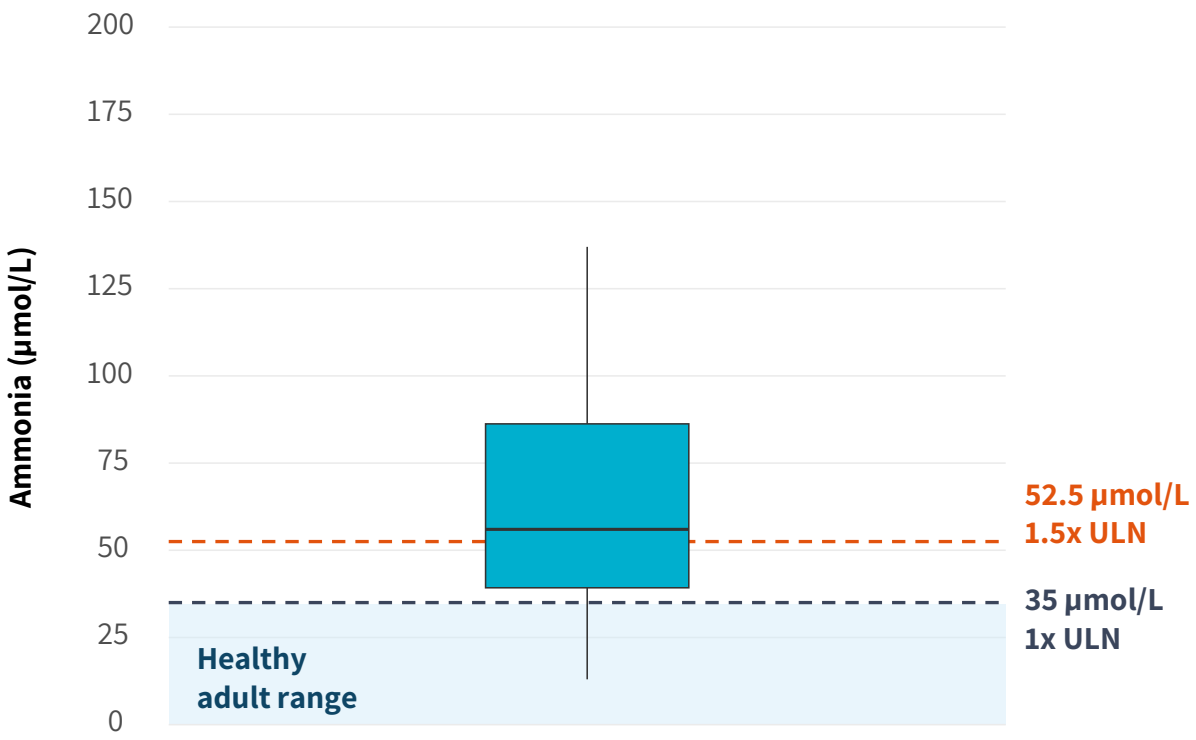


- **High ammonia** leads to:
  - Neurological impairment, potentially permanent
  - Frequent hospitalization
  - Highly restricted diet
  - Elevated infection risk
  - Additional non-neurological complications
- Can be caused by **cirrhosis or urea cycle dysfunction**
- Clinical studies have shown benefit of **lowering ammonia** in multiple indications

Source: 3rd party primary market research study and analysis (April 2025); KOL interviews

Uncontrolled Ammonia is a Persistent Danger for UCD Patients

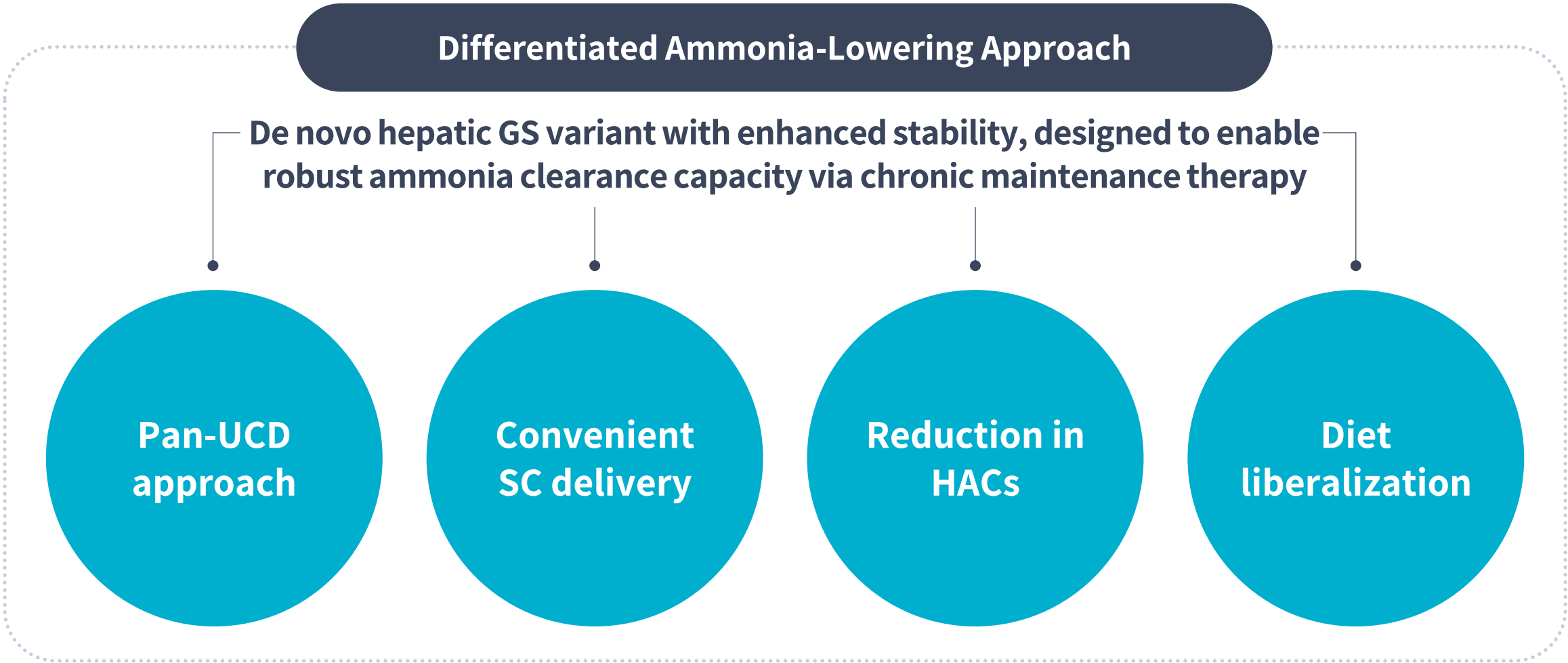
Ammonia Frequently >1.5x ULN in UCD, Leading to Increased Hyperammonemia Risk



Ammonia control is highly challenging in UCD patients today, often requiring nitrogen scavengers + strict diet that can lead to malnutrition

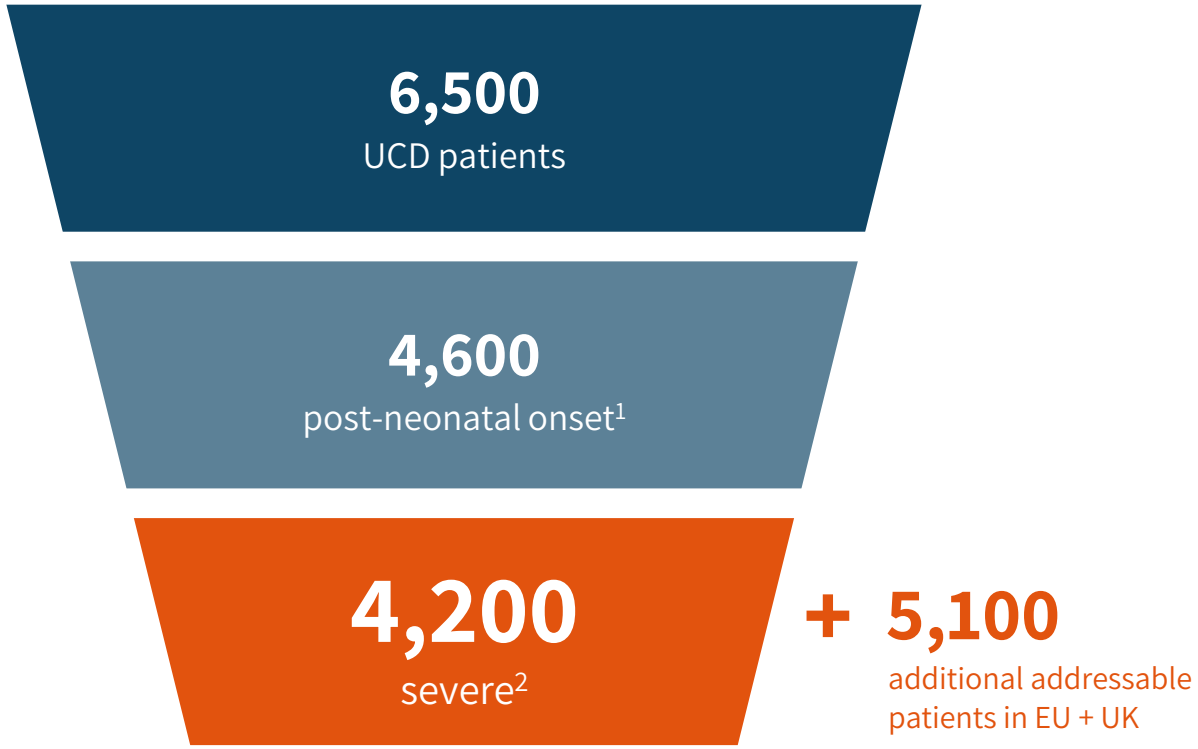
Note: 1. ~150 measurements in 16 patients with confirmed SNPs associated with urea cycle enzymes. ULN – Upper limit of normal
Source: Electronic medical records analysis (data from 2022)

KRRO-121 is Designed to Have a Compelling Product Profile to Potentially Address UCD Patients with Substantial Unmet Need



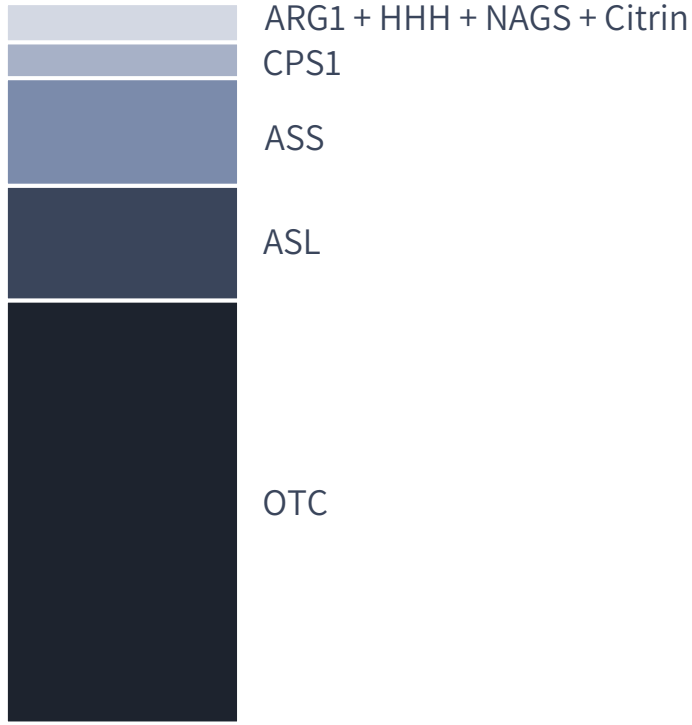
KRRO-121 Can Potentially Address Patients Across All UCD subtypes

U.S. UCD Epidemiology



+ 5,100
additional addressable patients in EU + UK

UCD Subtypes

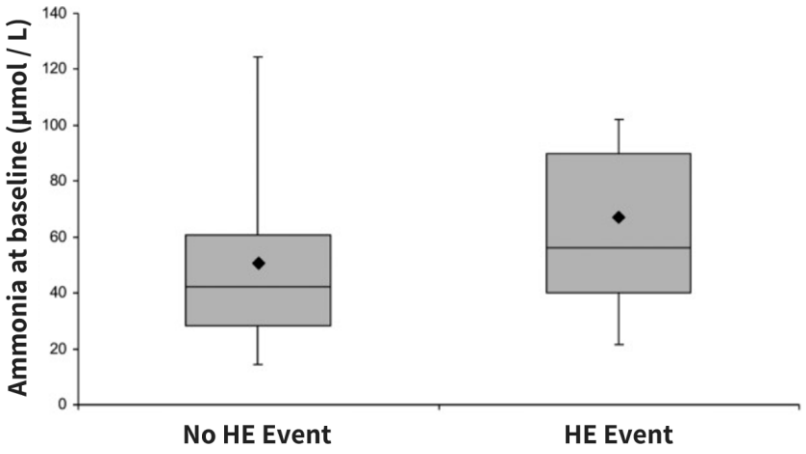


Note: 1. Onset of symptoms at age >1 month; 2. Severe defined as symptomatic patients expected to benefit from pharmacological therapy
Source: 3rd party primary market research study (April 2025); KOL interviews; GlobalData. All figures approximate.

Ammonia Measurements in Uncontrolled HE Patients Are Frequently Above Normal, Correlating with Higher HE Risk

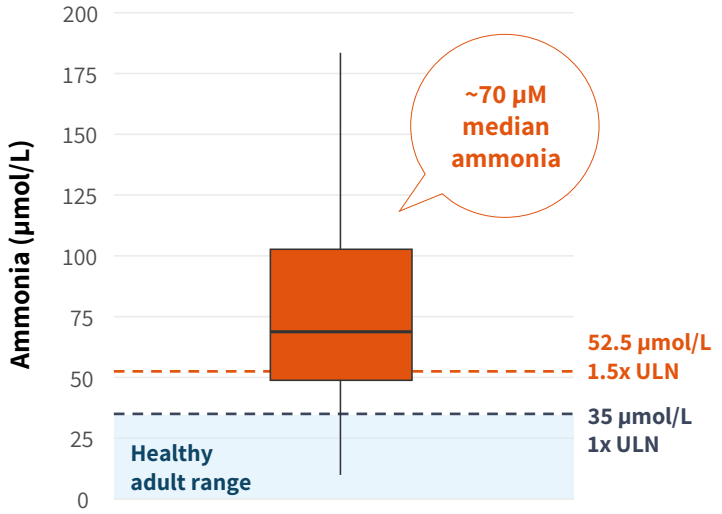
HE Events Correlate with Ammonia

Glycerol Phenylbutyrate Phase 2 HALT-HE Study

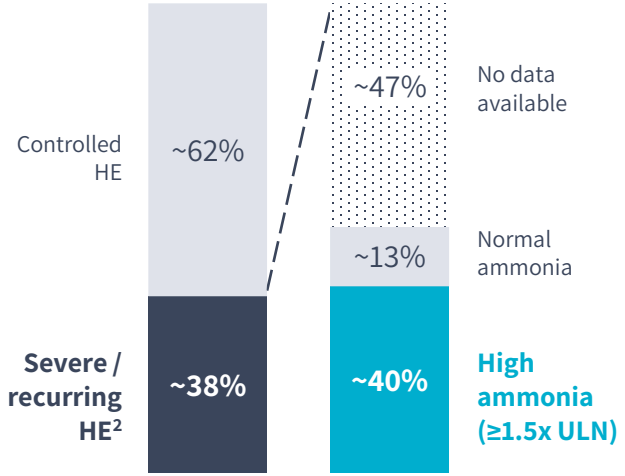


Ammonia Elevated in Many Severe / Recurring HE Patients[1]

Ammonia Measurements: Severe / Recurring HE



HE Patient Segmentation

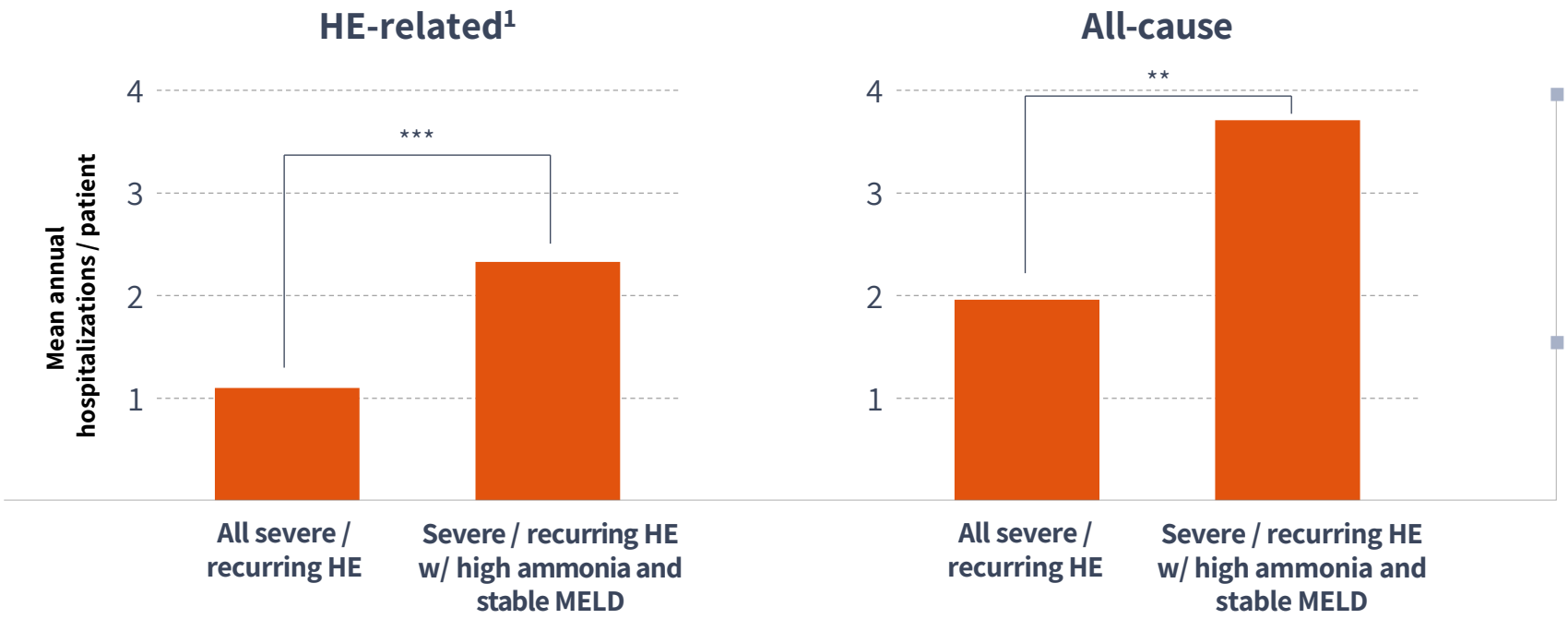


~76% of severe/ recurring HE patients with available ammonia data have an elevation ≥1.5x ULN[3]

Note: 1. 523 measurements from HE patients with rifaximin exposure in 2022 (27 outliers excluded from graph as defined by Q3 + 1.5 x IQR or Q1 – 1.5 x IQR); 2. Cirrhosis patients with exposure to rifaximin (+/- lactulose);
3. Excluding patients with no available ammonia data. ULN – Upper limit of normal
Source: Rockey et al., Hepatology (2014); Electronic medical records analysis (data from 2022)

Elevated Ammonia Levels Are Associated with a Greater Healthcare Burden in HE

High Ammonia Significantly Increases Hospitalization Risk



- **>2-fold increase** in HE-related hospitalization for addressable HE patients[2] vs all severe / recurring HE
- **>$10B** inpatient charges for HE in the U.S. each year; average cost per hospitalization **over $75K[3]**

Clear shift towards greater healthcare utilization in HE underscores strong pharmacoeconomic case for treatments that can reduce this burden

Note: 1. HE-related hospitalization defined as an inpatient visit with a concurrent lactulose prescription; 2. Addressable HE defined as HE patients prescribed rifaximin +/- lactulose with ≥1.5x normal ammonia and MELD ≤20; 3. Average payer costs for HE hospitalization in 2020 based on commercial claims database analysis; ** p <0.01; *** p <0.001
Source: Harris et al., Clinics in Liver Disease (2024); Wong et al., Clin Transl Gastroenterol (2025); Electronic medical records analysis (data from 2022)

KRRO-121 Also Has an Opportunity to Potentially Address Significant Unmet need in HE

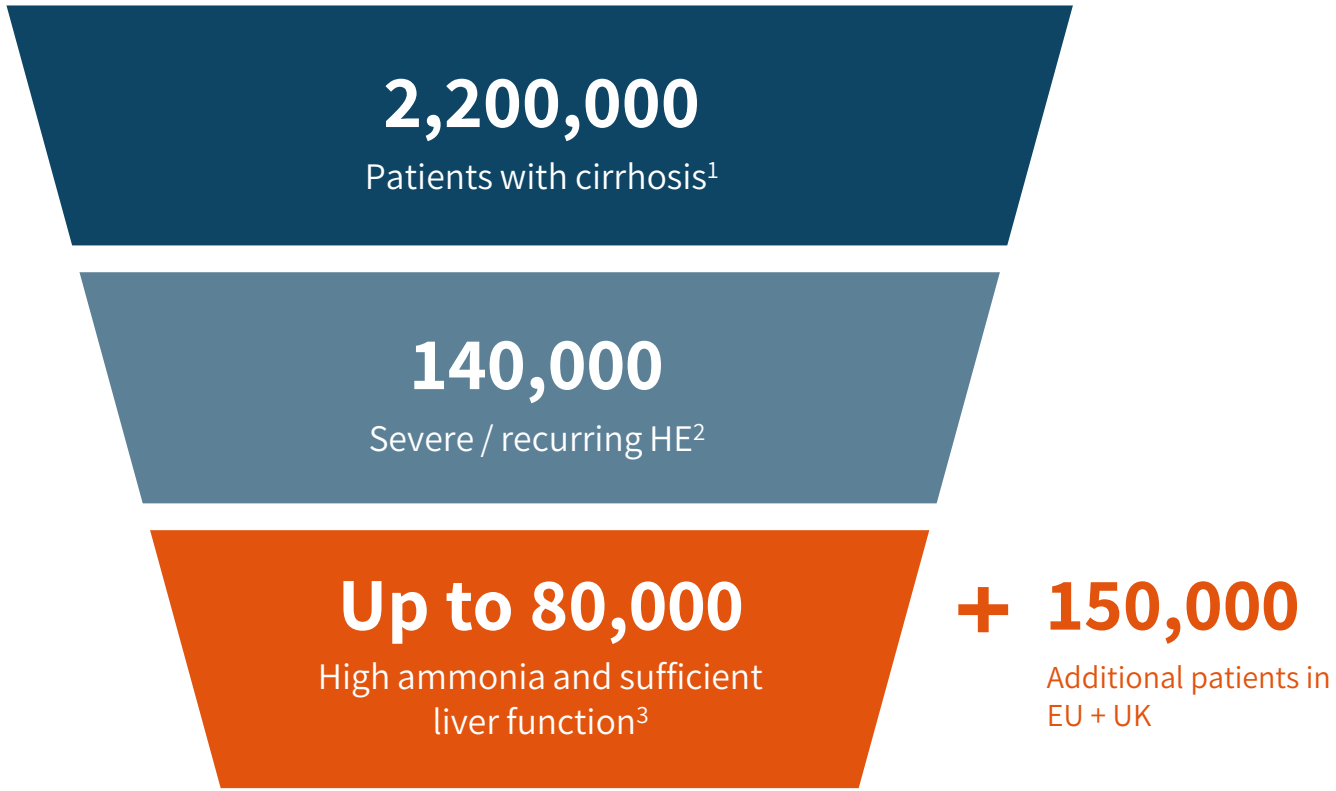
Differentiated Ammonia-Lowering Approach

De novo hepatic GS variant with enhanced stability, designed to enable robust ammonia clearance capacity via chronic maintenance therapy

- Direct ammonia control
- Convenient SC delivery
- Reduction in HE events
- Improved survival and quality of life

Up to ~80K Addressable Patients in the U.S. with Severe / Recurring HE May Benefit from Ammonia-Lowering Treatment

U.S. HE Epidemiology



+ 150,000
Additional patients in EU + UK

Additional opportunity can be unlocked in prevention of initial HE episode

Note: 1. U.S. cirrhosis prevalence as estimated by Tapper et al (2023); 2. Cirrhosis patients with exposure to rifaximin (+/- lactulose); 3. Ammonia measurement ≥52.5 µM (1.5x upper limit of normal) and average MELD score below 20 (excluding patients where no ammonia data was available)
Source: Tapper et al., JAMA (2023); Electronic medical records analysis (data from 2022). All figures approximate.

Closing remarks

Ram Aiyar, PhD, MBA

Chief Executive Officer

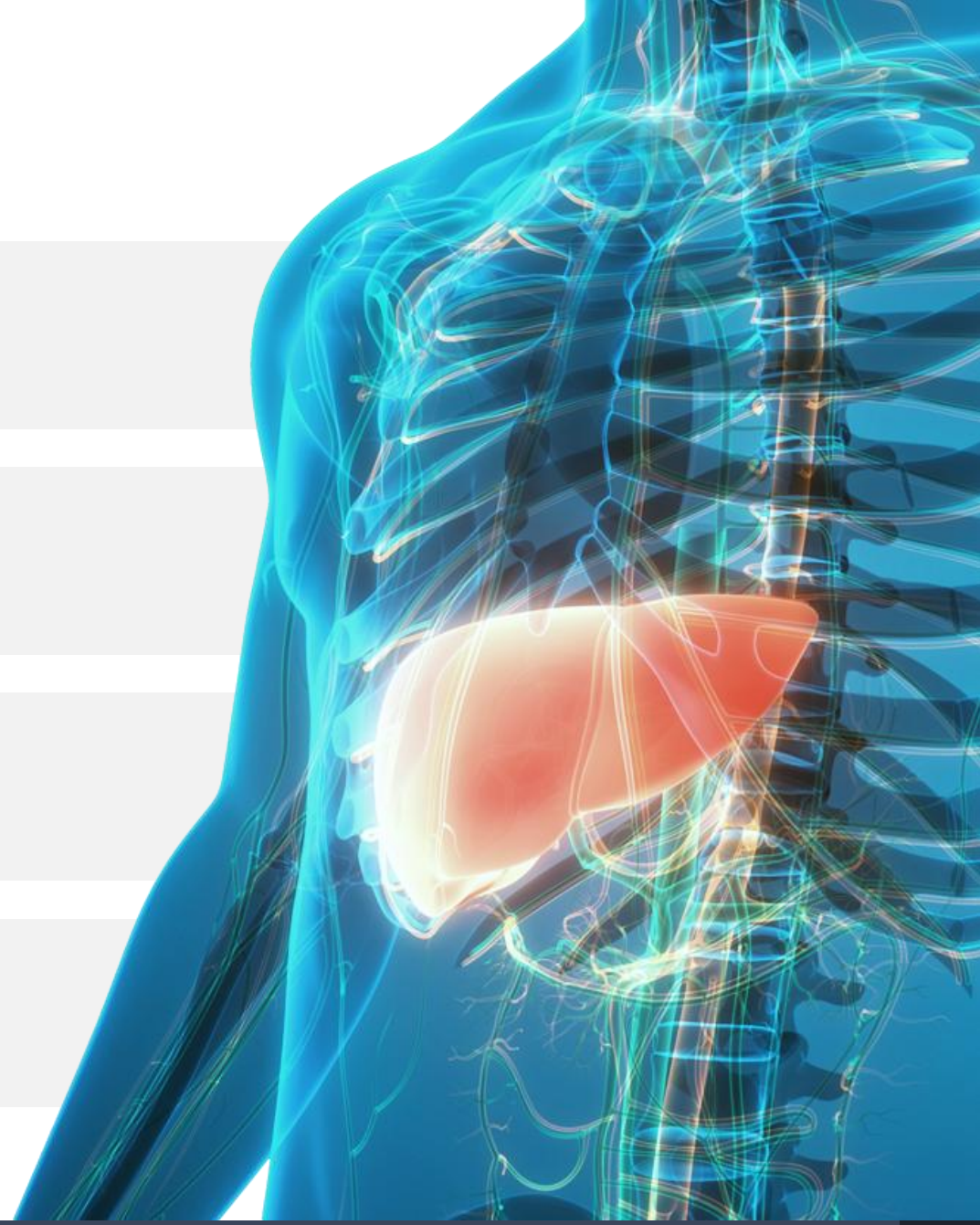
Key Takeaways from KRRO-121

Significant unmet medical need
for controlling ammonia

Robust scientific / genetic evidence
supporting GS stabilization approach

Transformative potential
to impact patients

Vision for the future
as a leader in modulating disease biology



Q&A

Ram Aiyar

CEO

Loïc Vincent

CSO

Todd Chappell

COO

Bruce Scharschmidt

Clinician

Edit the message.
Rewrite the future.