OCR-002 (Ornithine Phenylacetate) is a Potent Ammonia Scavenger as Demonstrated in Phase 2b STOP-HE Study

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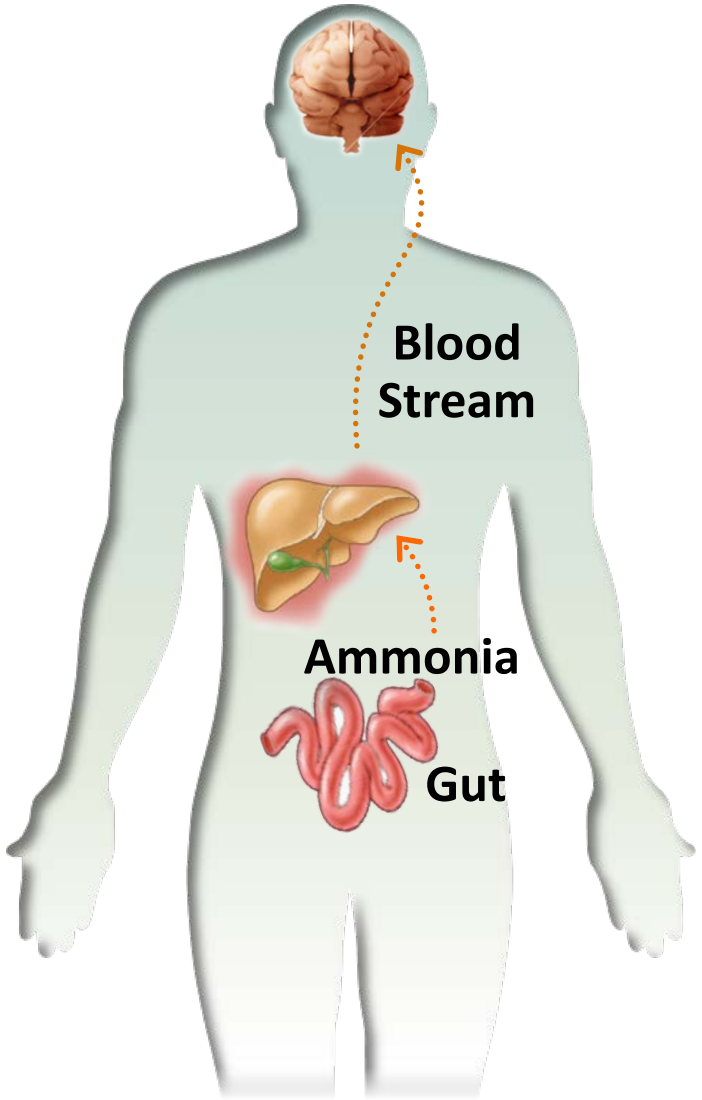
Hepatic Encephalopathy (HE)
Neurocognitive Disorder in Serious Liver Disease



West Haven Scale

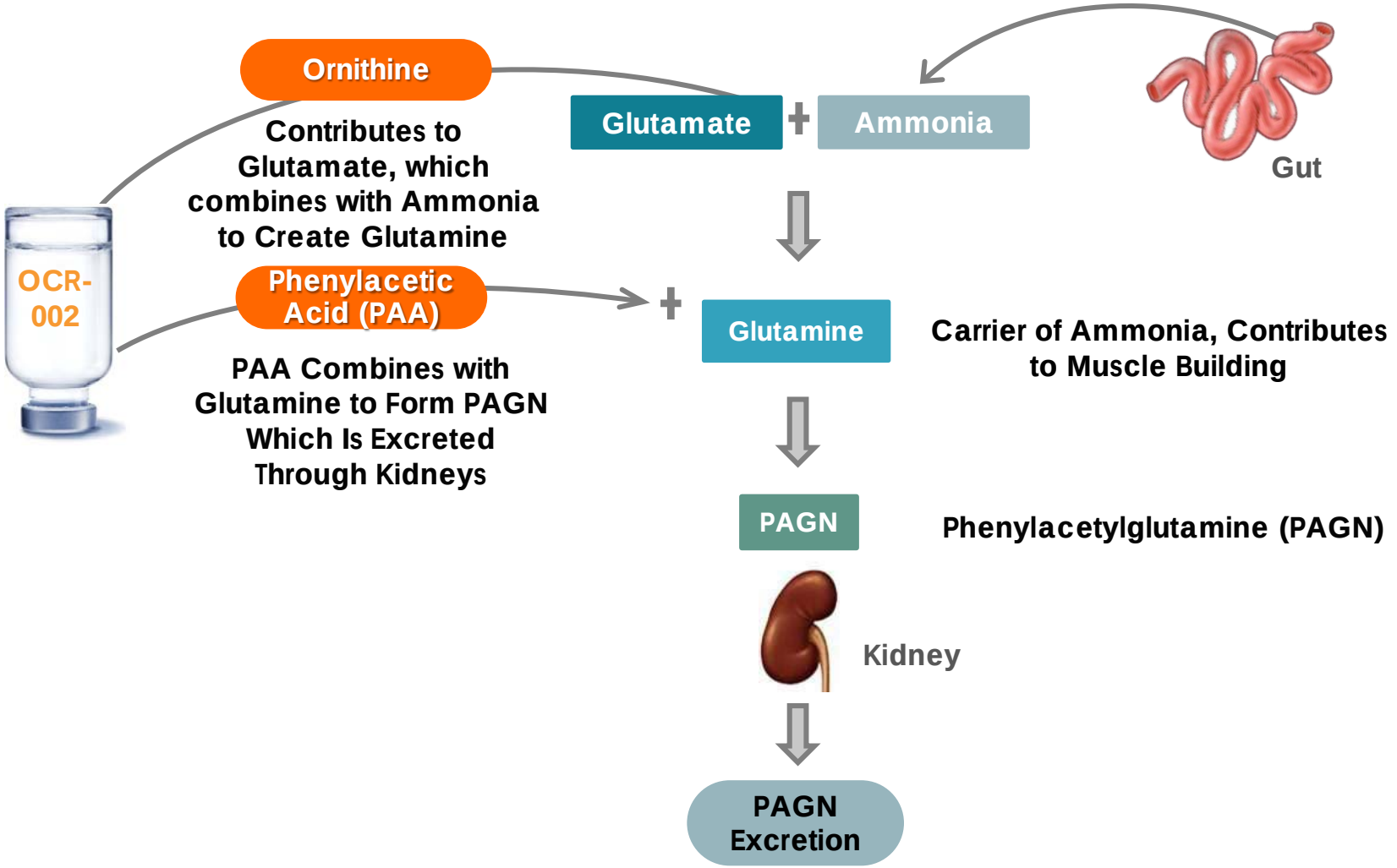
0 — 1 Personality Changes — 2 Disorientation Impaired Motor Skills — 3 Stupor — 4 Coma — Death

Covert (CHE) → *Overt (OHE)*

Elevated Ammonia Levels Drive HE

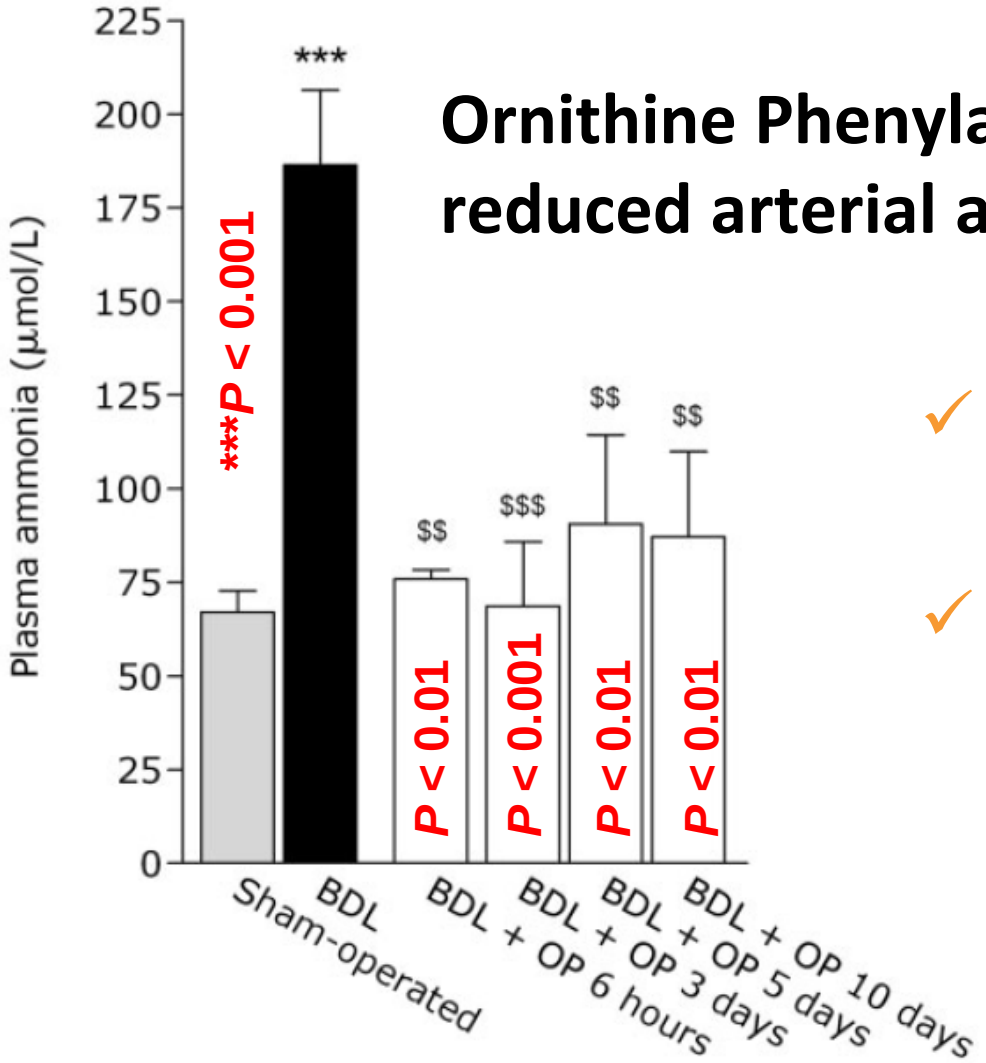
15% mortality rate in hospitals, associated with HE

OCR-002 Novel Mechanism of Action



MOA Shown in Bile Duct Ligated (BDL) Rat Model

The BDL animals fed an additional ammonia- genic diet 1 week prior to the study



Ornithine Phenylacetate administration to BDL rats **reduced arterial ammonia** at:

- ✓ 6 hours,
- ✓ and sustained for 3, 5 and 10 days

HEPATOLOGY, Vol. 50, No. 1, 2009 Davies, Wright, et al. 159

STOP-HE: A Phase 2b Study of SOC for Overt HE ± IV OCR-002

HOSPITALIZED CIRRHOTICS

Key Inclusion

- West Haven* Score ≥2
- Ammonia >ULN

Key Exclusion

- Kidney failure/dialysis
- Life expectancy <2 weeks

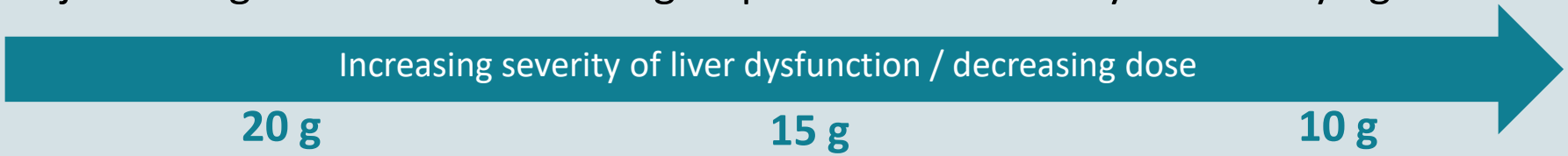
MINIMUM 12-HOUR PRE-SCREEN

- Standard of care (SOC) treatment and observation
- Physician's choice for SOC
- Patients must remain in HE
- Screen out rapid responders

TREATMENT

- Randomized 1:1
  - placebo + SOC
  - drug + SOC
- Continuous infusion for up to 5 days
- Patient assessed 2x/day
- **Primary Endpoint:** Time to meaningful (confirmed) clinical improvement in HE symptoms

Subjects assigned to one of 3 dose groups based on severity of underlying liver disease



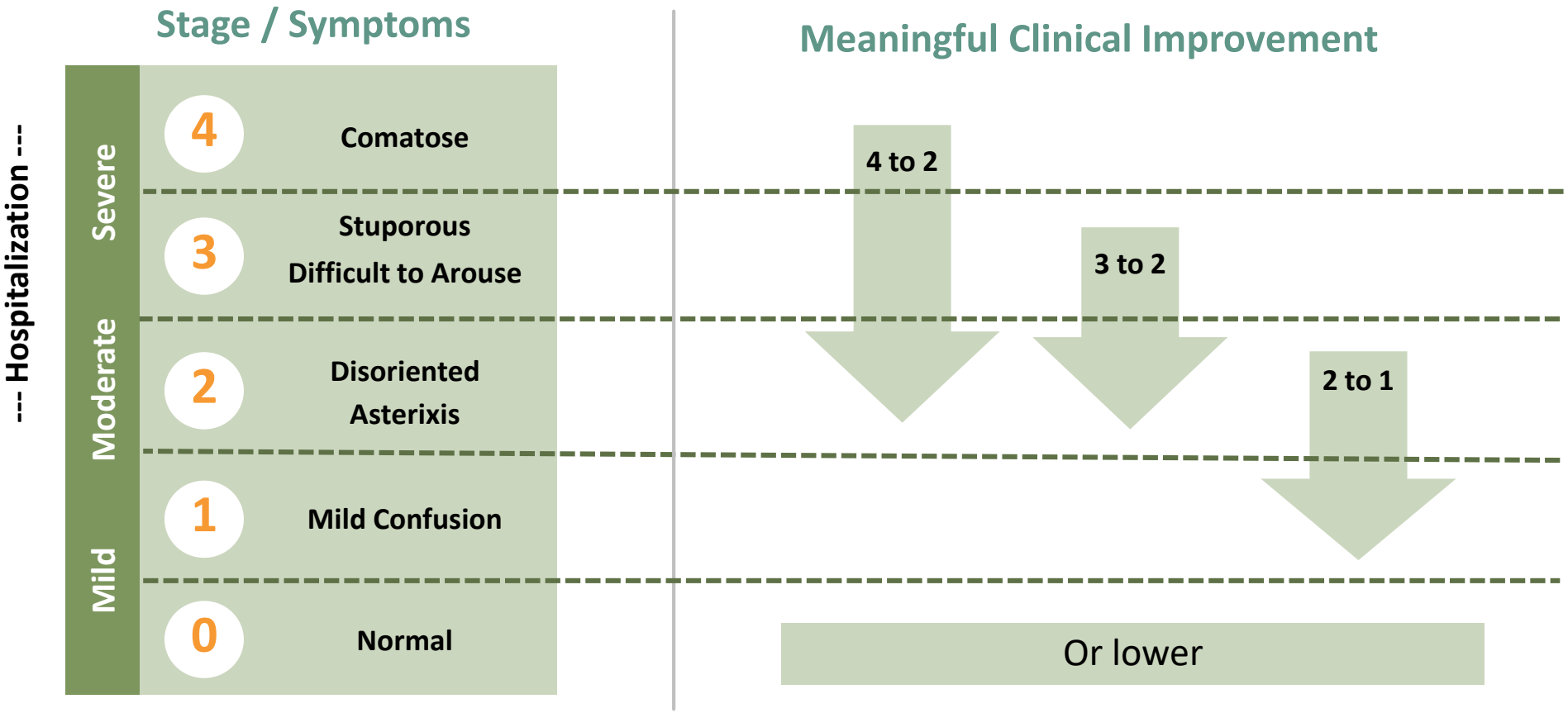
The primary endpoint: Time to Meaningful Clinical Improvement in HE Symptoms

*Scored by a modified version of the West Haven Scale

Meaningful Clinical Improvement

Scored by Hepatic Encephalopathy Scoring Tool (HEST)

Modified Version of West Haven Scale



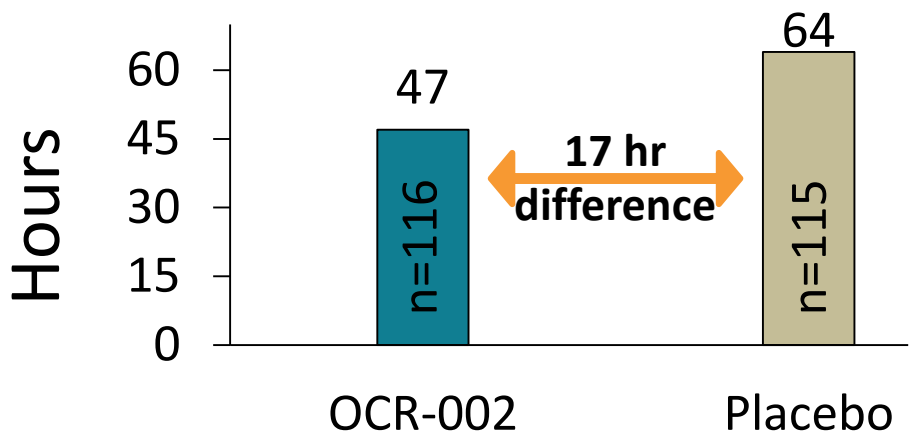
Results

Baseline Characteristics

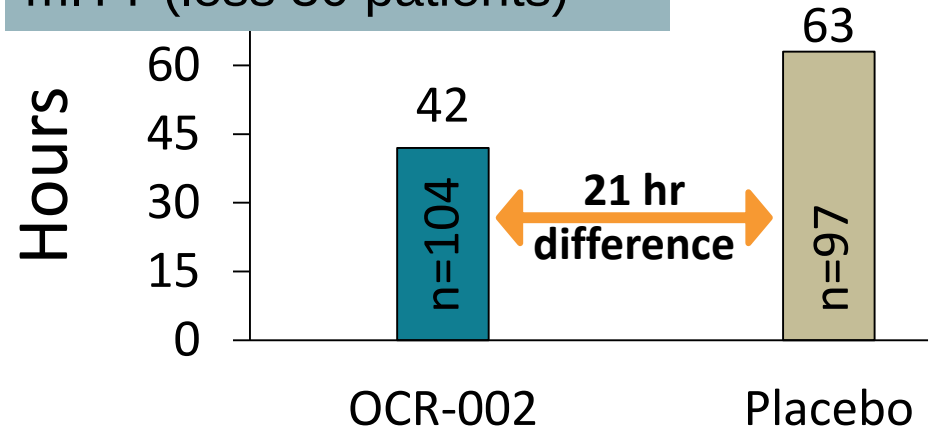
Characteristic	OCR-002 (n=116)	Placebo (n=115)
Male	62%	68%
Mean age, y (range)	59 (26,74)	60 (27,79)
Child-Pugh and MELD		
Child-Pugh A	2%	<1%
Child-Pugh B	33%	24%
Child-Pugh C	66%	75%
MELD (Median)	18	18
HEST Stage		
HEST Stage 2	60%	61%
HEST Stage 3	34%	32%
HEST Stage 4	5%	7%
Etiology of Inciting Factors (most common)		
Bacterial infection	15 (13%)	14 (12%)
Poor compliance (lactulose)	15 (13%)	13 (11%)
Dehydration	16 (14%)	9 (8%)
Transjugular intrahepatic portosystemic shunt	7 (6%)	9 (8%)

Primary Endpoint: Median Time to Clinical Improvement

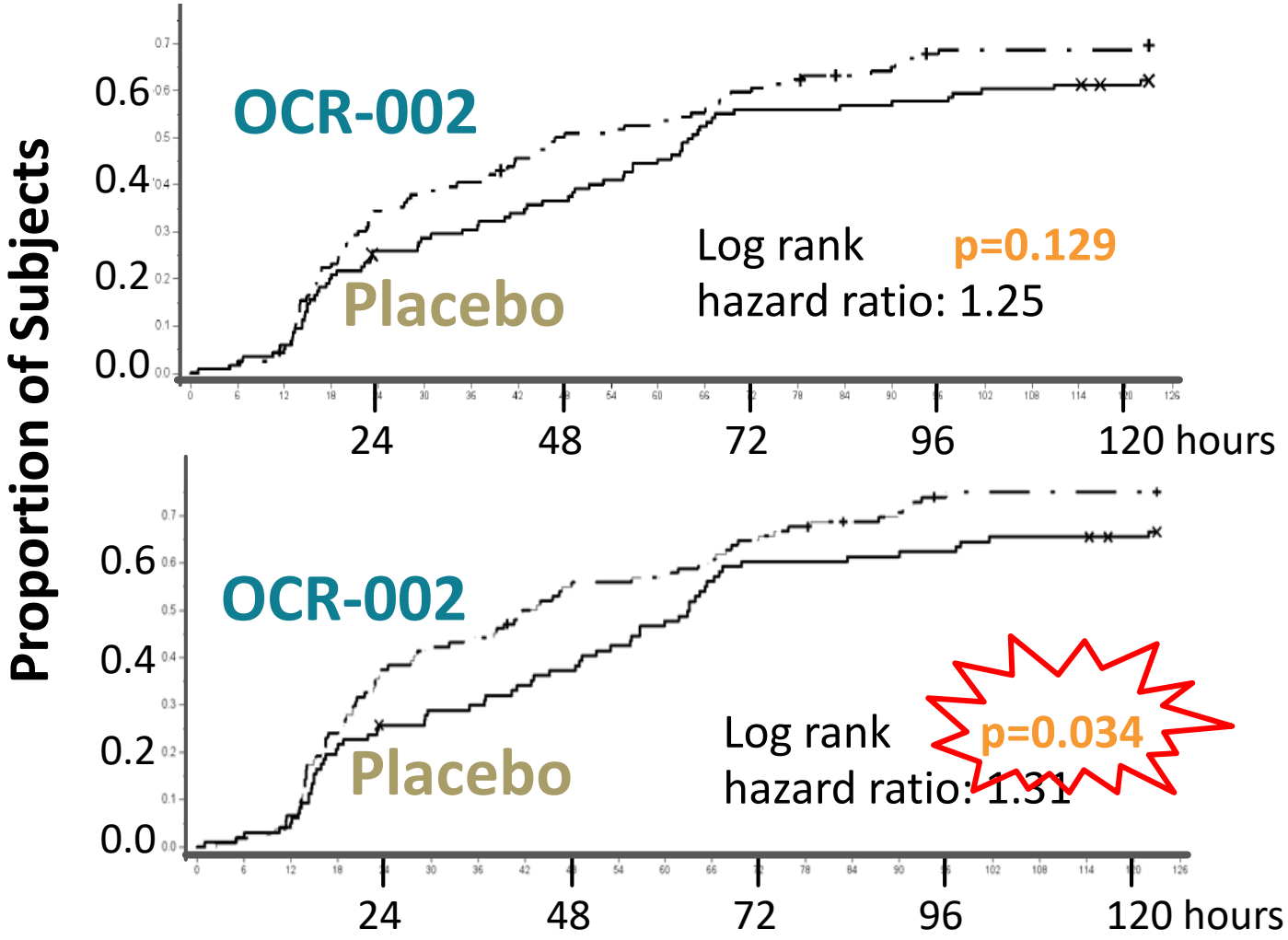
ITT – Primary Endpoint



mITT (less 30 patients)



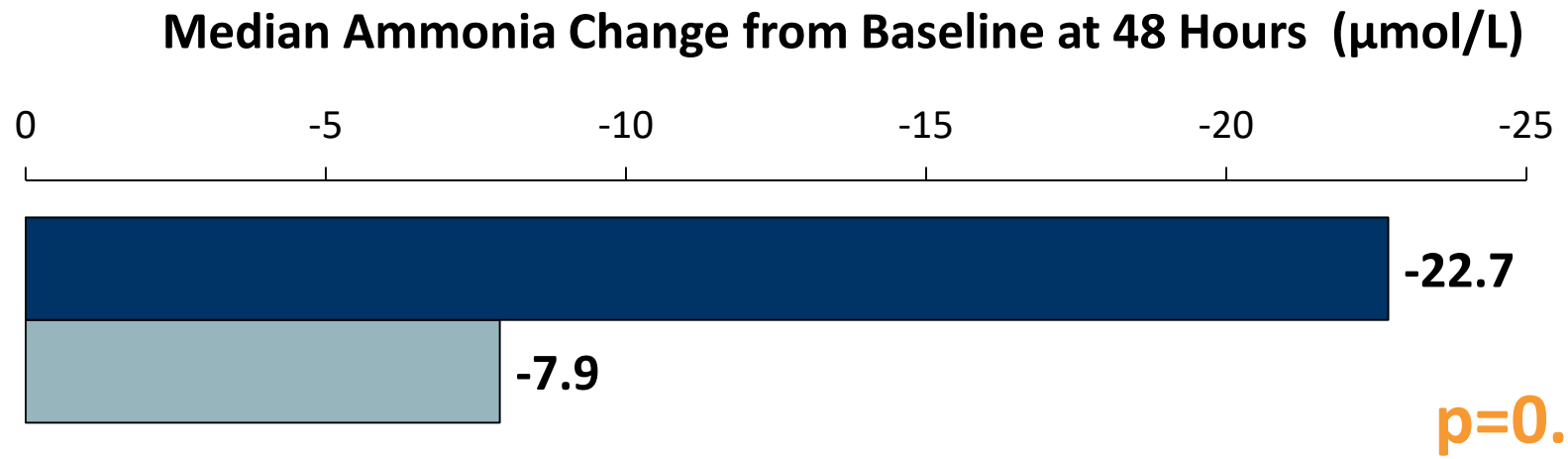
Time to Clinical Improvement in HE Symptoms [hours]



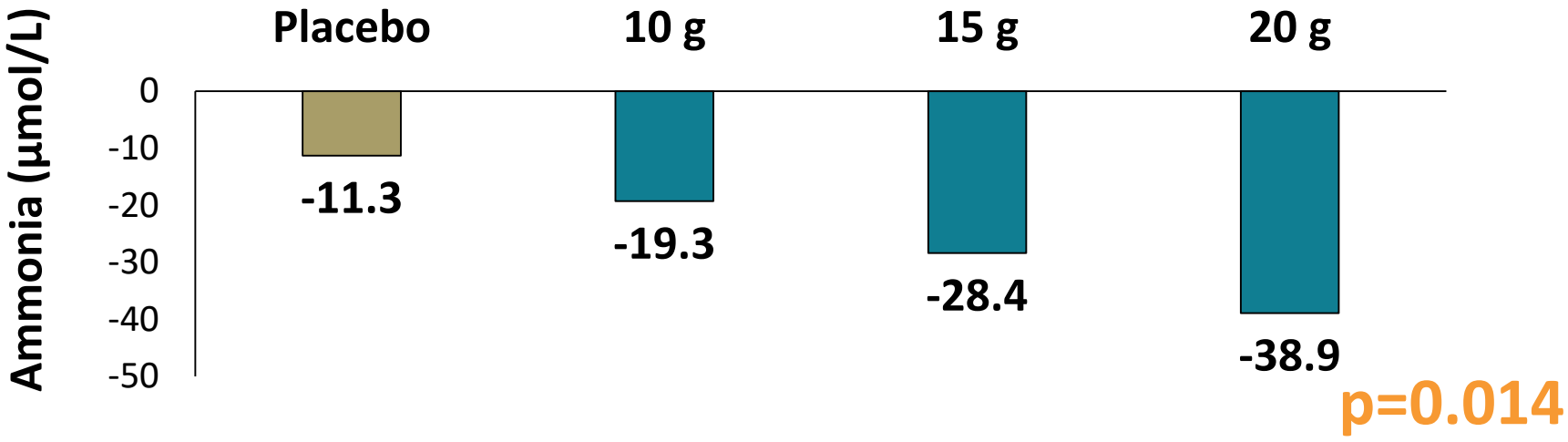
30 Patients Were Randomized with Normal (or missing) Baseline Ammonia
Primary Endpoint Would Have Been Met Without These 30 Patients (modified ITT)

Median Ammonia Change from Baseline (µmol/L)

By Response



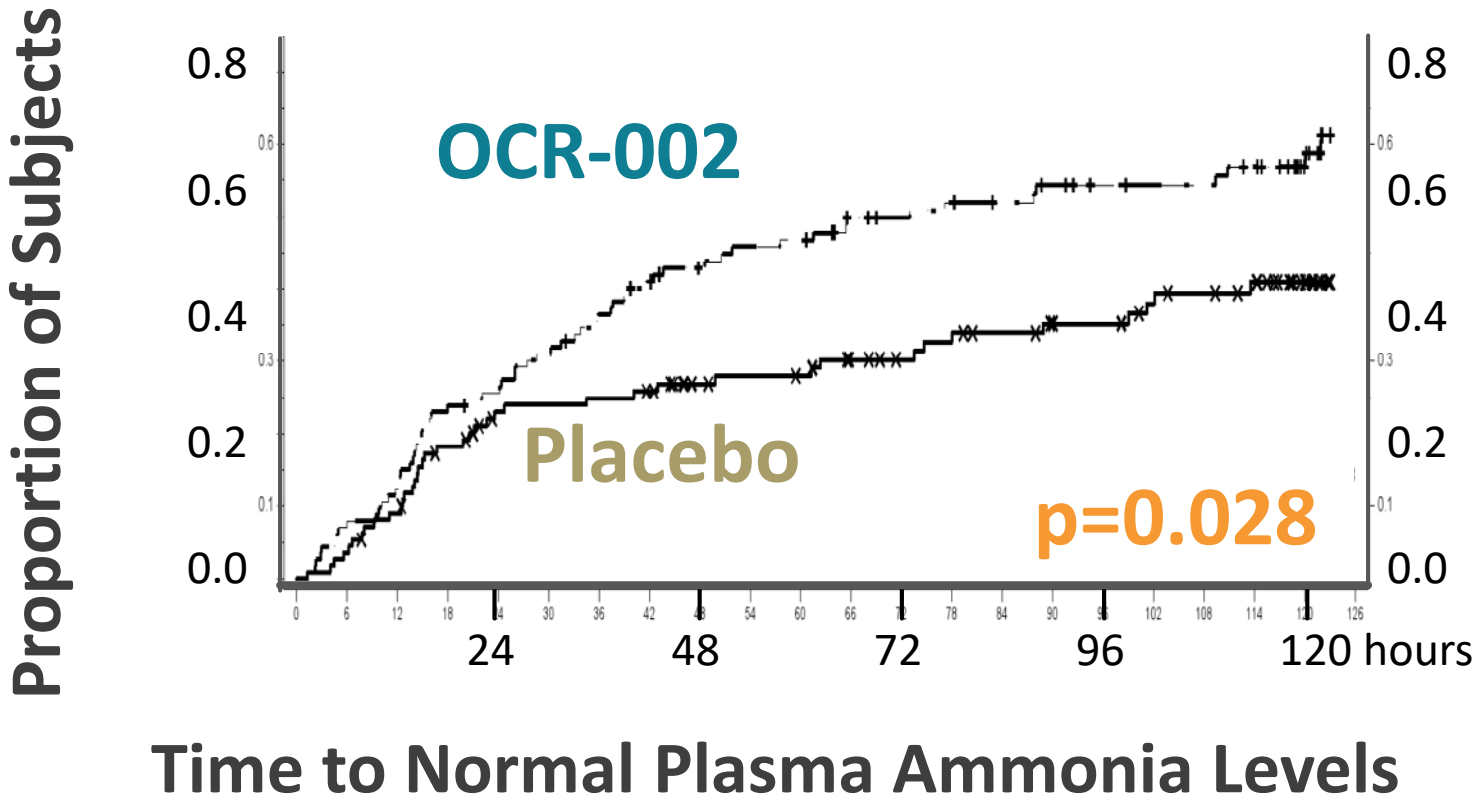
By Dose



ANCOVA, 2 sided p-value was calculated from an analysis of covariance (ANCOVA) model with a fixed effect for achieving vs. not achieving primary clinical response, adjusting for the randomization strata

Time to Achieve Normal Plasma Ammonia Level (≤ULN)

Probability of achieving plasma ammonia ≤ULN was 69% greater for OCR-002 *vs.* placebo (hazard ratio = 1.691)



Additional Potential Clinical Benefit for OCR-002

There was an improvement in MELD scores on OCR-002 *vs.* PBO (p = 0.051), with greatest improvement in sickest patients

Treatment	Baseline (SD)	3h after last Study Drug Dose (SD)
OCR-002	18 (6.6)	↓ 16 (6.1)
Placebo	19 (6.4)	↑ 21 (6.3)

Additionally, the death rate was numerically lower for OCR-002 than Placebo.

Serious Adverse Event (SAE) n (%)	OCR-002 Total n=114	Placebo n=112
Death	11 (9%)	15 (13%)

Safety: Incidence of Adverse Events

Adverse Event (AE)* n (%)	OCR-002 10g n=29	OCR-002 15g n=59	OCR-002 20g n=26	OCR-002 Total n=114	Placebo n=112
Hypokalaemia	3 (10%)	4 (7%)	2 (8%)	9 (8%)	8 (7%)
Pyrexia	1 (3%)	3 (5%)	2 (8%)	6 (5%)	8 (7%)
Urinary Tract Infection	2 (7%)	3 (5%)	3 (12%)	8 (7%)	4 (4%)
Hepatic Encephalopathy	2 (7%)	7 (12%)	1 (4%)	10 (9%)	11 (10%)
Anemia	5 (17%)	6 (10%)	3 (12%)	14 (12%)	8 (7%)

*Treatment Emergent with an incidence of >5%

Serious Adverse Event (SAE) n (%)	OCR-002 10g n=29	OCR-002 15g n=59	OCR-002 20g n=26	OCR-002 Total n=114	Placebo n=112
Serious Adverse Event	10 (34%)	13 (22%)	6 (23%)	29 (25%)	33 (29%)

The incidence of adverse events (AEs) was comparable between treatment groups. No significant differences were observed between placebo and OCR-002

Conclusions

- STOP-HE confirms the MOA of OCR-002 being a potent ammonia scavenger
- OCR-002 use in cirrhotic patients hospitalized with HE reduced plasma ammonia levels to a greater extent than placebo
  - **AND** reduced ammonia levels faster than placebo and SOC
  - **AND** leads to faster clinical improvement than placebo and SOC
- Safety/tolerability comparable to placebo + SOC
- Results from this study will be used for study design for continued OCR-002 development

Acknowledgements

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