# Preclinical profiling of ABI-6250, a first-in-class oral therapeutic candidate for chronic hepatitis D virus infections

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Presented at the 2025 International HBV meeting, September 8-12, 2023, Berlin, Germany
Session X: Therapy II – September 11, 2025

# Presenter Disclosures

- Marc P Windisch is an employee and stockholder of Assembly Biosciences, Inc.

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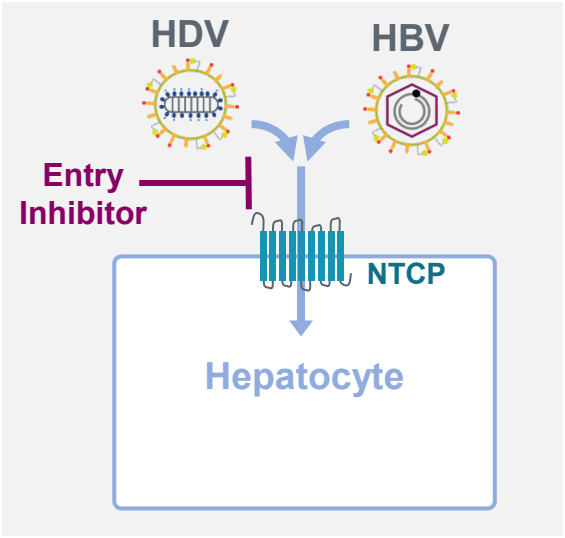
# Chronic HDV is The Most Severe Form of Viral Hepatitis with Limited Treatment Options

- CHD affects ~12-72 million patients worldwide[1,2]

- Most severe form of viral hepatitis
- Increased risk of cirrhosis & hepatocellular carcinoma (HCC)

- Very limited treatment options for HDV
  - Bulevirtide (BLV):
    - NTCP inhibitor
    - Only approved drug for CHD by European Medicines Agency (EMA)
    - Daily injections

## Entry Inhibitors Targeting NTCP Block HDV/HBV Infection

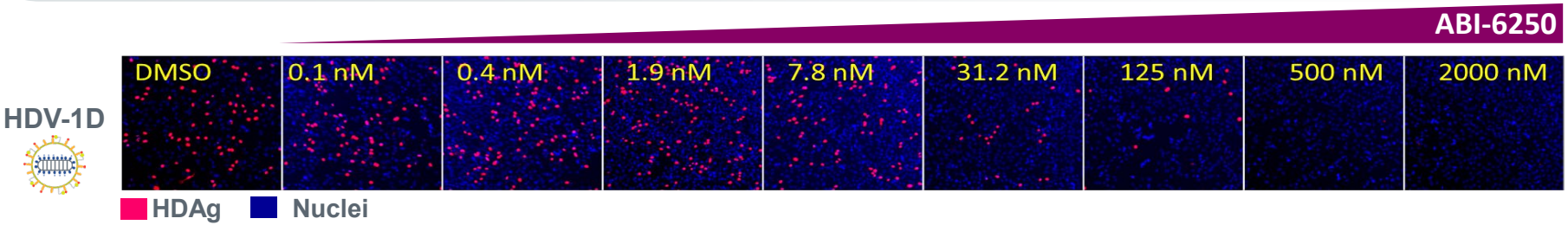



→ Goal: Development of an orally-bioavailable HDV entry inhibitor → ABI-6250

[1]WHO. Hepatitis D Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d; [2]Negro F, *et al*. JAMA. 2023;330(24):2376-87

# ABI-6250 Potently Inhibits Multiple HDV & HBV Genotypes

*NTCP-dependent*

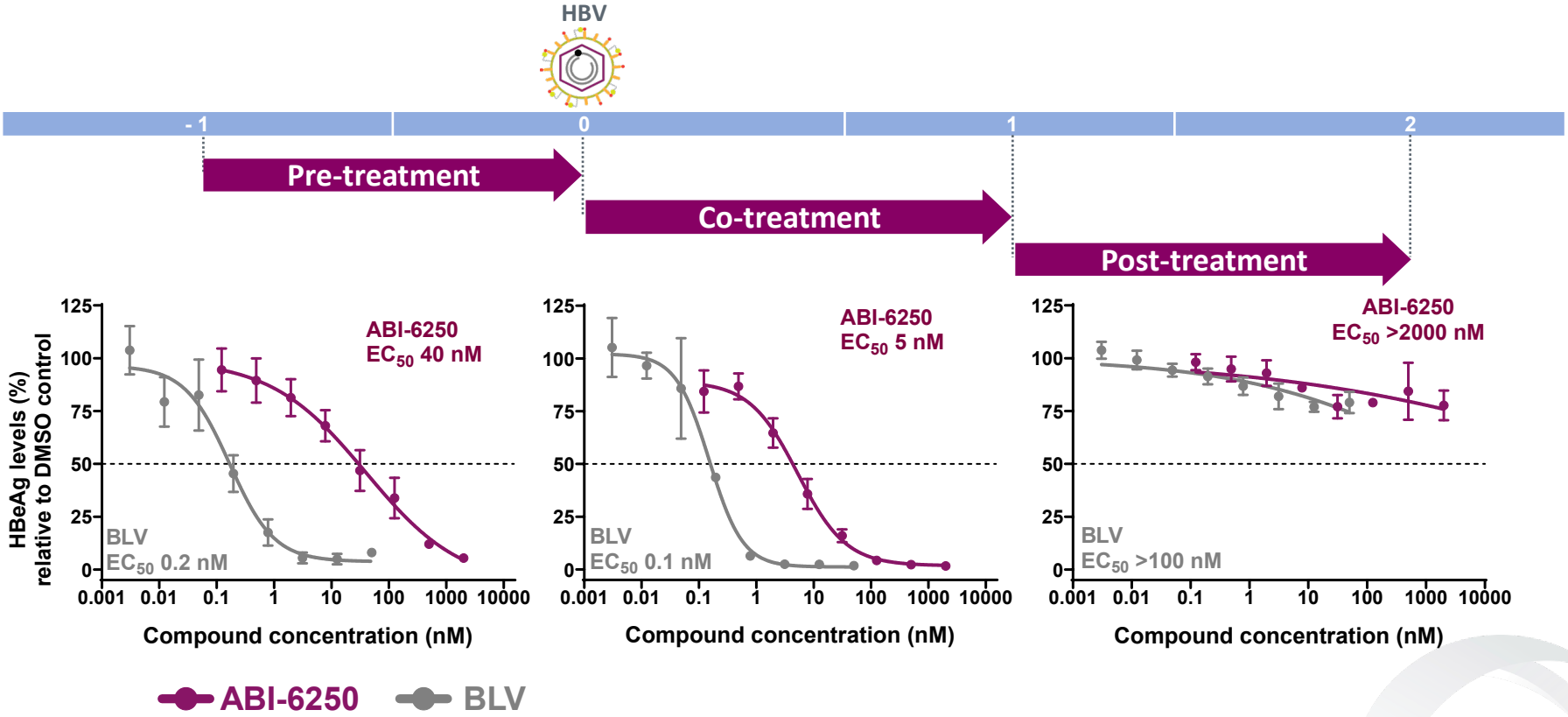



| Compound | Antiviral Activity $EC_{50}$ (nM) | | | | | Bile Acid Uptake Inhibition $IC_{50}$ (nM) | |
|---|---|---|---|---|---|---|---|
| | HDV | | | HBV | | | |
| | Cell Culture | | Patient Isolates | Cell Culture | | | |
| | PHH | HepG2-NTCP | HepG2-NTCP | PHH | HepG2-NTCP | PHH | Huh7-NTCP |
| **ABI-6250** | **11 (GT-3B)** | **5 – 15 (GT-1,2,3, B,D)** | **21*** | **14 (GT-A,C,D)** | **5 (GT-D)** | **3** | **8** |
| Bulevirtide | 0.6 (GT-3B) | 0.5 (GT-3D) | - | 0.2 (GT-D) | 0.2 (GT-D) | 2 | 5 |

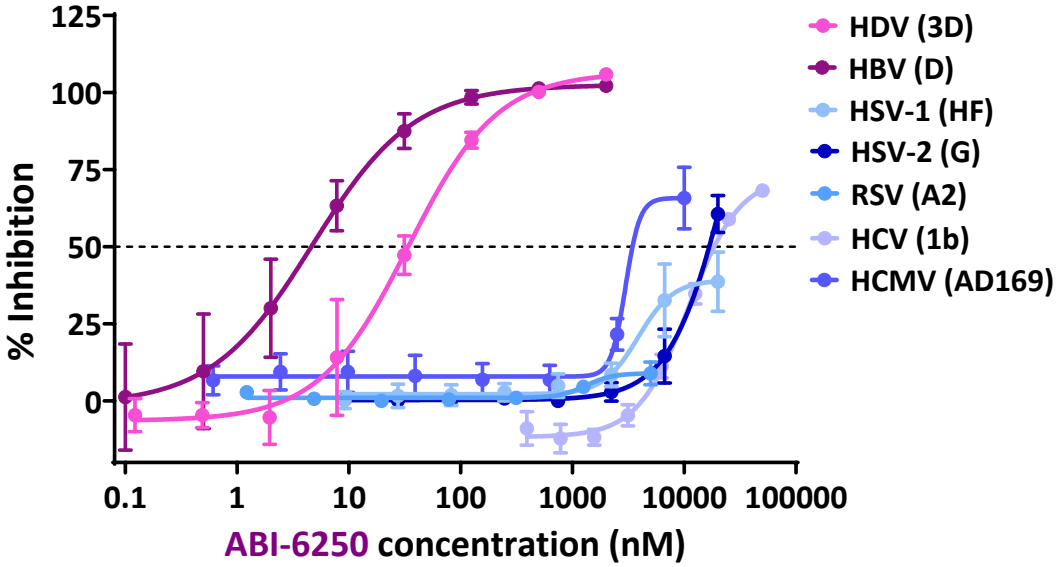
GT, genotype; *median value of N=18 patient isolates; HDV GT-1: 17, GT-8: 1; HBV GT-D: 11, GT-E: 2, GT unknown: 5

# ABI-6250 Inhibits HBV During Pre & Co-treatment

*Time-of-addition study*



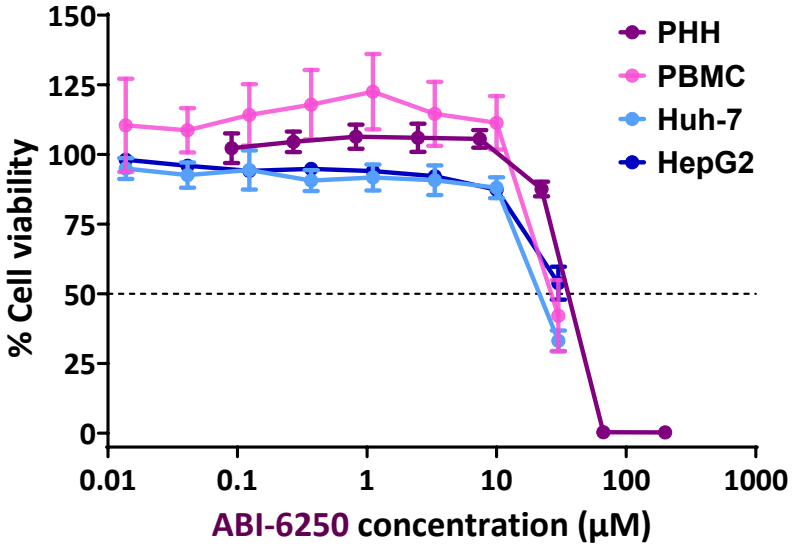
# ABI-6250 Specifically Inhibited HDV & HBV Infection




| Virus | ABI-6250 Selectivity Indices (SI) | |
|---|---|---|
| | HBV | HDV |
| HSV-1 | >4,000 | >1,300 |
| HSV-2 | >3,200 | >1,000 |
| RSV | >1,000 | >300 |
| HCV | >2,800 | >900 |
| HCMV | >1,300 | >400 |

SI value = $EC_{50}$ given virus/$EC_{50}$ HBV or HDV

# ABI-6250 Had Minimal Effects on Cell Viability

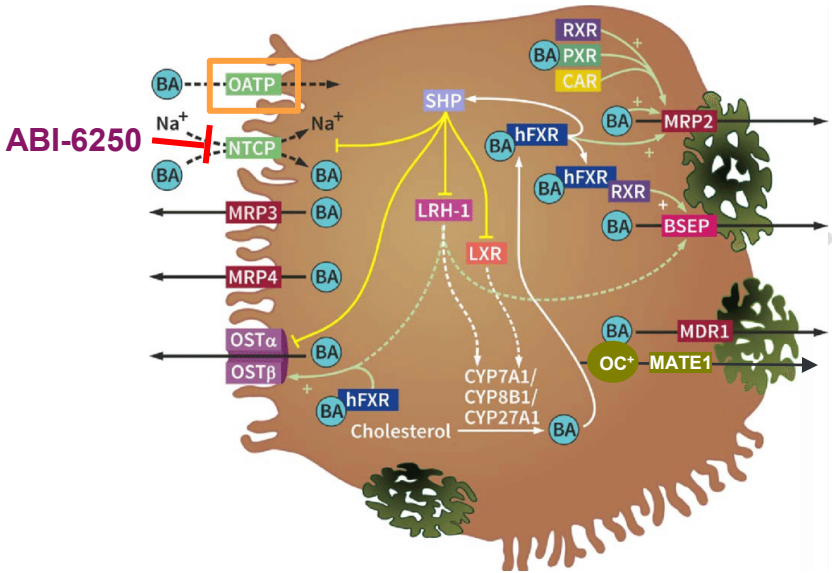



| Cell Type | Cytotoxicity $CC_{50}$ (µM) | |
|---|---|---|
| | ABI-6250 | Puromycin |
| PHH | >29* | 1.1 |
| PBMC | >24 | 0.4 |
| Huh-7 | >24 | 1.2 |
| HepG2 | >30 | 1.4 |
| MOLT-4 | >15 | 0.3 |
| NCI-H226 | >30 | 0.4 |
| MT-4 | >30 | 0.2 |
| HEK293 | >30 | 0.7 |
| HeLa-H1A | >23 | 0.7 |

PBMC, peripheral blood mononuclear cells

*SI HDV >2,600

# ABI-6250 Selectively Inhibited NTCP



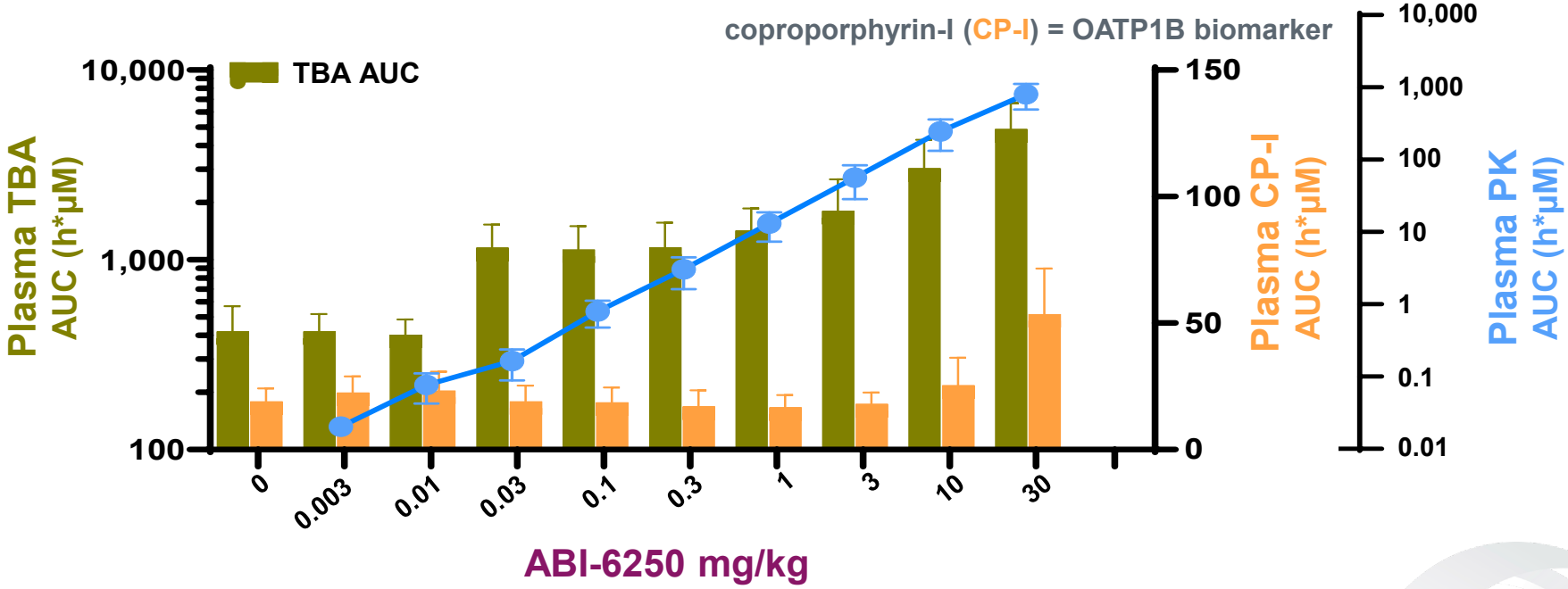

De Haan *et al.*, J Clin Transl Res. 2018 May *(modified)*

| Transporter | ABI-6250 Fold-selectivity |
|---|---|
| NTCP | 1 |
| MRP2 | >2400 |
| MATE1 | >1800 |
| MATE2K | >1800 |
| OCT1 | >1800 |
| OCT2 | >1800 |
| OSTα/β | >1800 |
| OAT1 | >1200 |
| OAT2 | >1000 |
| MDR1 | >1200 |
| BSEP | >1200 |
| BCRP | 250 |
| OATP2B1 | 200 |
| OATP1B1 | 75 |
| OATP1B3 | 13 |

OATP, organic anion transporting polypeptide

Fold-selectivity = $IC_{50}$ given transporter/$IC_{50}$ NTCP

# ABI-6250 Elevates Plasma Total Bile Acids in Cynomolgus Monkeys Indicating Target Engagement




TBA, total bile acid; AUC; area under the curve; PK, pharmacokinetics

# Conclusions

- ABI-6250 is a highly potent, specific, orally bioavailable small molecule HDV/HBV entry inhibitor
- At projected clinically relevant concentrations, ABI-6250 elevates total bile acids in cynomolgus monkeys, without elevating coproporphyrin-I levels, indicating selective target engagement
- The PK profile in monkeys supports low once-daily oral dosing for chronic HDV treatment

➢ **ABI-6250 Phase 1a clinical trial is ongoing**

– **Interim & blinded data:**

- **PK: ABI-6250 half-life of ~4 days → supporting once-daily dosing**
- **PD: Dose-dependent TBA elevations → target engagement**

# Acknowledgments


- The authors would like to thank the members of the HDV entry team at Assembly Biosciences, Inc. for their contributions to these experiments

- This study was sponsored by Assembly Biosciences, Inc.

# Thank you!

# Questions?

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