Preclinical Profiling of ABI-6250, a Novel Orally Bioavailable Small-Molecule Therapeutic Candidate for the Treatment of Chronic Hepatitis D

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Presenter Disclosures

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

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Assembly Biosciences' Drug Pipeline

CAM, capsid assembly modulator; HPI, helicase-primase inhibitor; IFNAR, interferon-alpha receptor; IND, investigational new drug; NNPI, non-nucleoside polymerase inhibitor.

Diagram from https://www.assemblybio.com/pipeline

HDV Background

HDV is a satellite virus that requires the presence of HBsAg to infect hepatocytes.[1,2] Chronic HDV infection affects approximately 12 to 72 million patients worldwide[3,4]

HDV infection is the most severe form of viral hepatitis and accounts for approximately 18% of cirrhosis and approximately 20% of hepatocellular carcinoma associated with hepatitis B[1,5]

➢ There are very limited treatment options for HDV

- Peginterferon-alpha (PEG-IFNα) requires weekly injections[6]

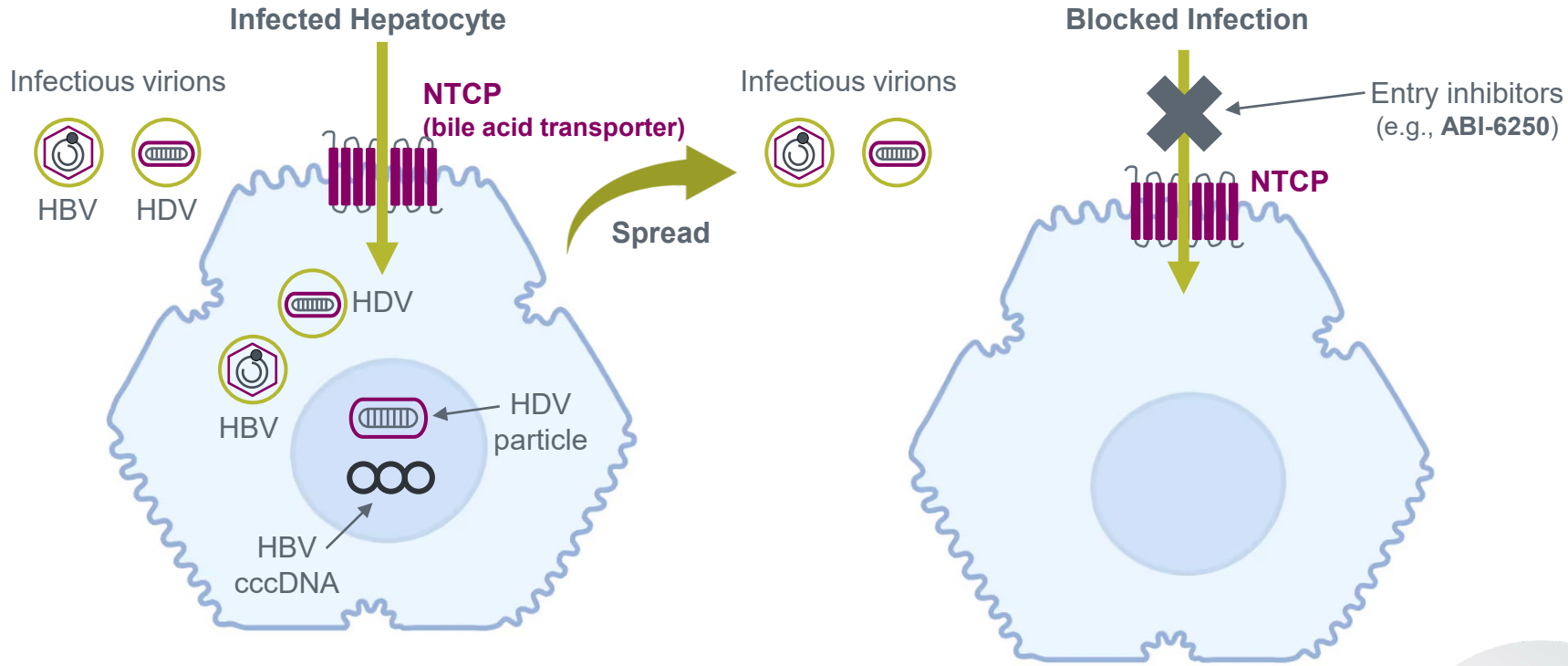
- Bulevirtide (BLV) is the only EMA-approved drug for HDV.[7a] BLV in combination with IFNα can result in HDV cure in some patients,[8] and BLV and PEG-IFNα require daily and weekly injections, respectively[6,9]

→There is a need for an orally bioavailable HDV entry inhibitor

ved Committee; EMA, European Medicines Agency; HBsAg, hepatitis B surface antigen.

1) et al. *Lancet*. 2011;278:73-85. **2)** Urban S, et al. *Gut*. 2021;70:1782-94. **3)** World Health Organization. Hepatitis D fact sheet. Accessed June 10, 2024. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d. **4)** Negro F, et al. *JAMA*. 2023;330(24):2376-87. **5)** Stockdale A, et al. *J Hepatol*. 2020;73(3):523-32. **6)** Pegasys. Prescribing information. Hoffmann-La Roche, Inc., c/o Genentech, Inc.; 2021. **7)** Kang C, et al. *Drugs*. 2020;80:1601-5. **8)** Asselah T, et al. *N Engl J Med*. 2024 (online ahead of print); DOI: 0.1056/NEJMoa2314134. **9)** European Medicines Agency. Summary of product characteristics, Hepcludex 2 mg powder for solution for injection. August 2020. Accessed June 14, 2024. https://www.ema.europa.eu/en/documents/product-information/hepcludex-epar-product-information_en.pdf.

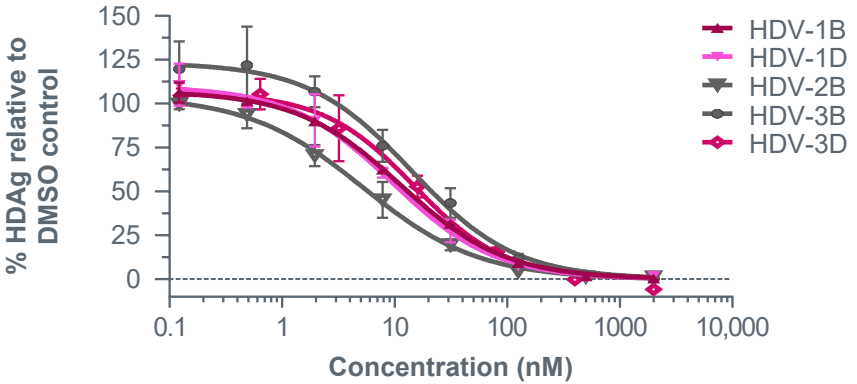
Entry Inhibitors Targeting NTCP Block HBV and HDV Infection of Hepatocytes



cccDNA, covalently closed circular DNA; NTCP, sodium taurocholate cotransporting polypeptide.

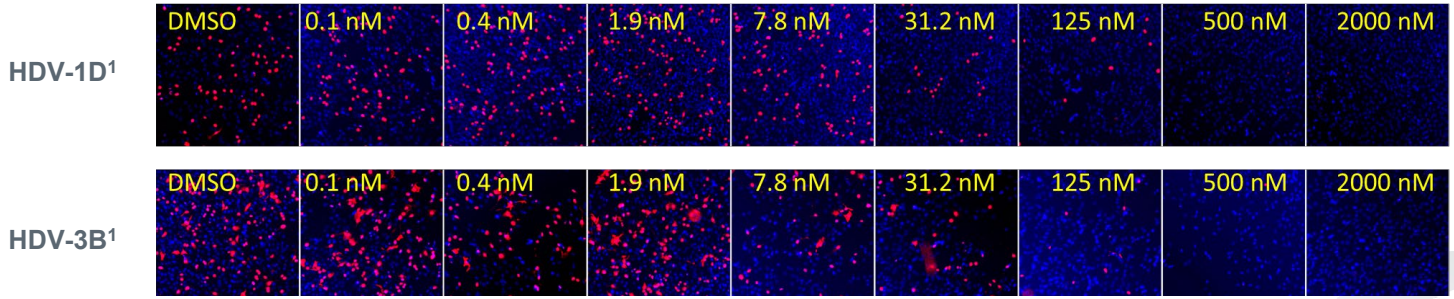
ABI-6250 Efficiently Inhibited HDV Infection of the Most Prevalent Genotypes in HepG2-NTCP Cells

Anti-HDV Activity in HepG2-NTCP Cells[2]



ABI-6250 EC_{50} Values in HepG2-NTCP Cells[2]

HDV/HBV genotype	EC_{50} (nM)
1B	11.4
1D	9.6
2B	5.2
3B	14.2
3D	14.9

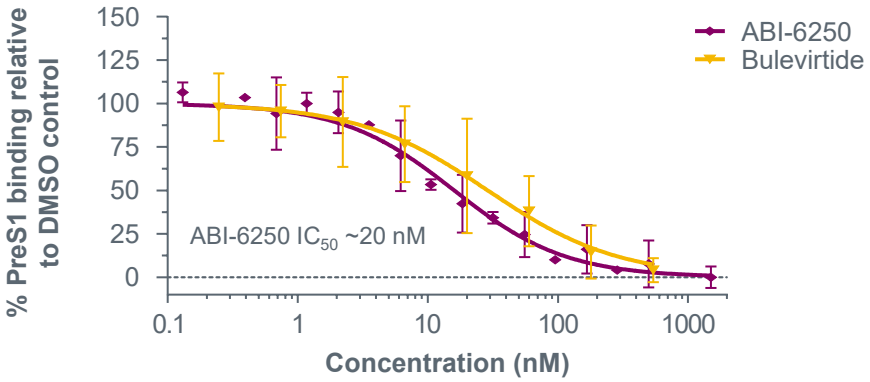


HDAg is shown in red and cell nuclei are shown in blue.
DMSO, dimethyl sulfoxide; EC_{50}, half-maximal effective concentration; HDAg, hepatitis D antigen.

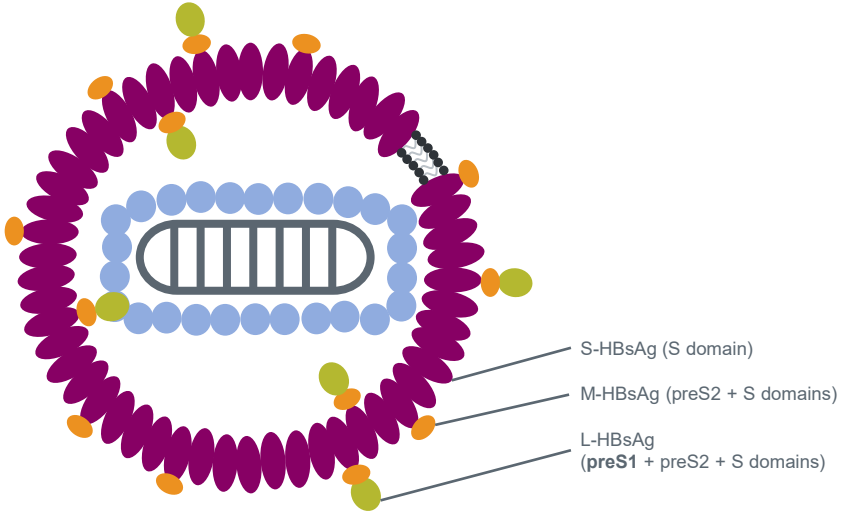
1) Windisch M, et al. Poster presented at EASL 2024. WED-377. **2)** Windisch M, et al. Oral presentation at the International HBV Meeting 2024. Session IV: Drug discovery in preclinical models.

ABI-6250 Inhibited PreS1-NTCP Binding and NTCP-Mediated Bile Acid Uptake

PreS1-NTCP Binding Inhibition

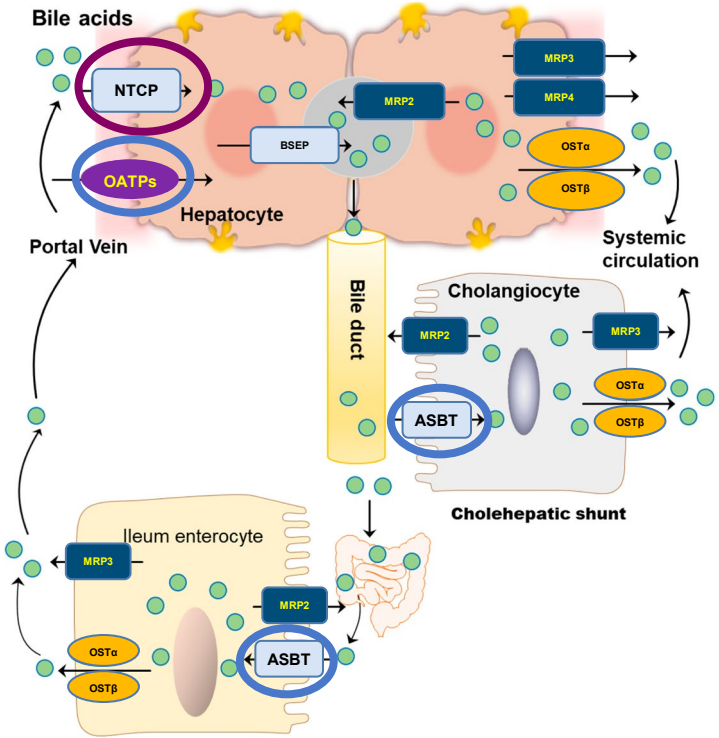


HDV Virion[a]



[a]Adapted from Tan W, et al. *World J Gastroenterol*. 2014;20:11650-70 per the terms under https://creativecommons.org/licenses/by/4.0/.
HBsAg, hepatitis B surface antigen; IC_{50}, half-maximal inhibitory concentration; L-, large; M-, medium; S-, small.

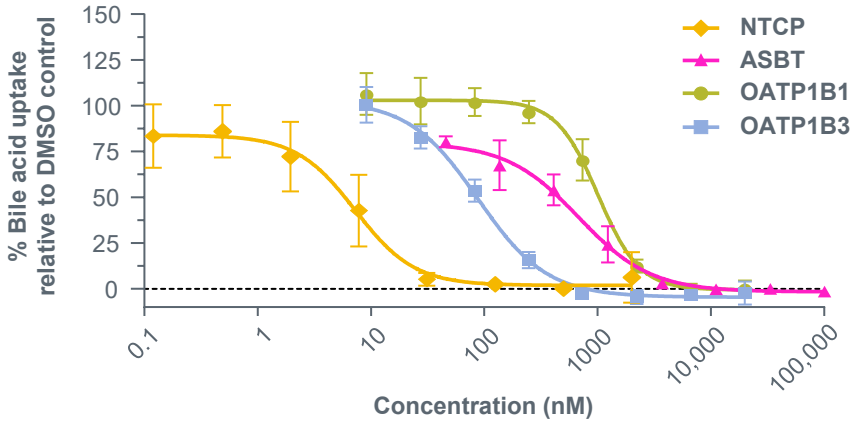
Key Transporters Involved in Bile Acid Homeostasis ASBT and OATP



Adapted from Xue R, et al. *Cells*. 2021;10:2806 per the terms under https://creativecommons.org/licenses/by/4.0/.
ASBT, apical sodium-dependent bile acid transporter; OATP, organic anion-transporting polypeptide.

ABI-6250 Selectively Inhibited NTCP *In Vitro*

Limited OATP1B and ASBT Bile Acid Uptake Inhibition



ABI-6250 Fold Selectivity

Transporter	ABI-6250 IC_{50} (nM) [fold selectivity][a]
NTCP	7.3
OATP1B1	1000 [>135]
OATP1B3	90 [>12]
ASBT	700 [>95]

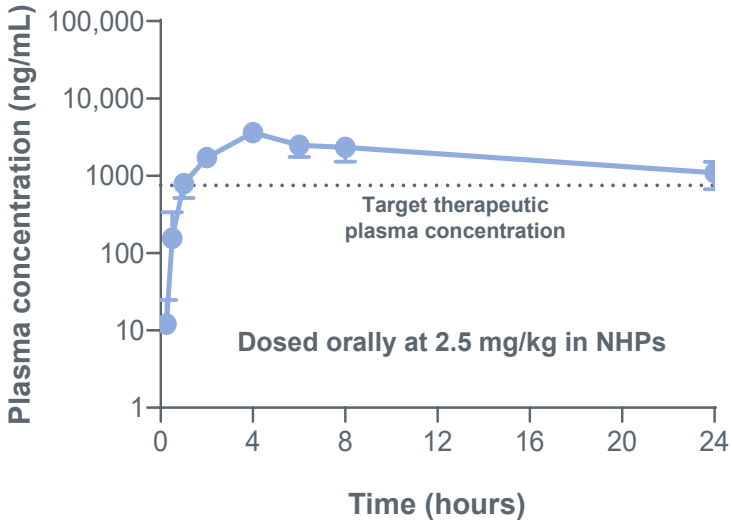
[a]Numbers in brackets indicate fold selectivity calculated as the ratio of bile acid transporter IC_{50} to NTCP IC_{50}.
IC_{50}, half-maximal inhibitory concentration.

ABI-6250 Has Favorable ADME and PK Profiles

ABI-6250 ADME and PK Profile[1,a]

ADME properties		
Percentage of ABI-6250 remaining at 45 min after incubation in LMs (human | NHP | rat | mouse)	97 | 97 | 97 | 93	
Caco-2 A-B[b] | B-A[b] | ER	4.8 | 4.7 | 1.0	
PK properties	**Rat**	**NHP**
$t_{1/2}$ (hr)	4.9[c] | 5.4[d]	6.7[c] | 14.8[d]
%F	100	99

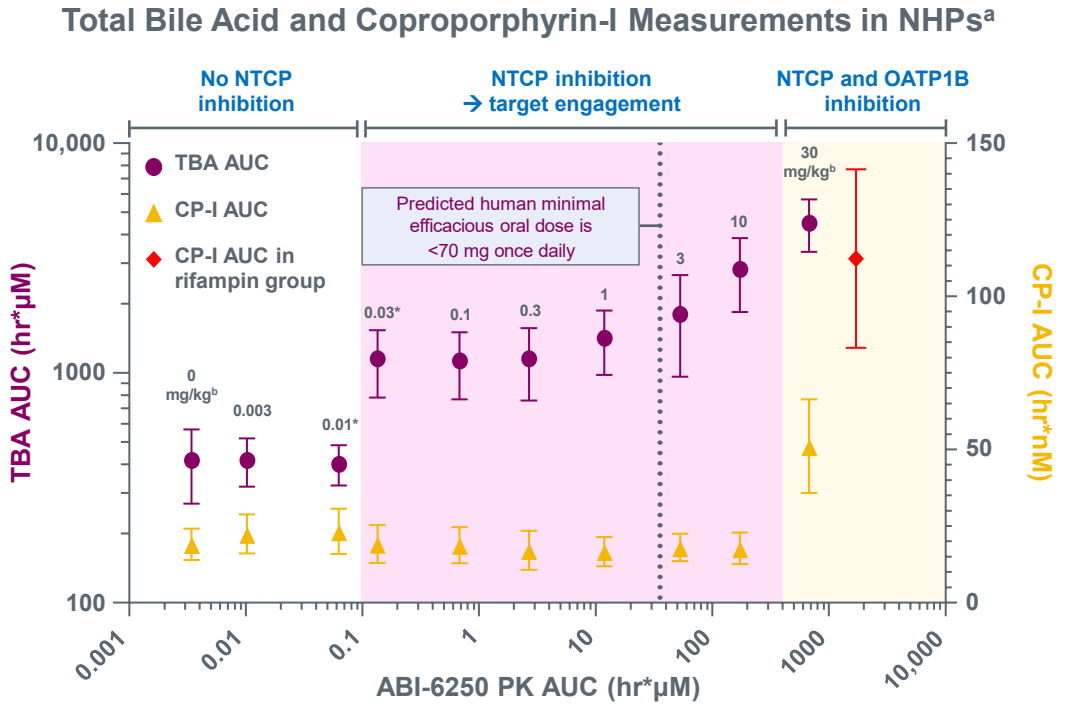
ABI-6250 Exceeds Therapeutic Plasma Concentration[2]



[a]n = 2 or 3. [b]10^{-6} cm/s. [c]If ABI-6250 is administered intravenously. [d]If ABI-6250 is administered orally.
A-B, A to B permeability; ADME, absorption, distribution, metabolism, and excretion; B-A, B to A permeability; ER, efflux ratio; %F, bioavailability; LM, liver microsome; NHPs, non-human primates; PK, pharmacokinetics; $t_{1/2}$, terminal half-life.

1) Windisch M, et al. Poster presented at EASL 2024. WED-377. **2)** Windisch M, et al. Poster presented at EASL 2024. SAT-195.

ABI-6250 Has Favorable PK/PD Profiles



[a]The x-axis values for vehicle, 0.003 mg/kg, and rifampin groups are arbitrarily set. [b]Doses of ABI-6250 in NHPs; n = 6 per dose. *For TBA AUC P<0.01 between 0.01 mg/kg and 0.03 mg/kg. Vertical line indicates human PK projection using allometric scaling.
AUC, area under the curve; CP-I, coproporphyrin-I; PD, pharmacodynamics; TBA, total bile acid.

Conclusions

- ABI-6250 is a highly potent, NTCP-selective, orally bioavailable HDV and HBV entry inhibitor
- At clinically relevant concentrations, ABI-6250 elevates total bile acids in NHPs, indicating target engagement without increasing CP-I plasma levels, a biomarker for OATP1B inhibition
- The preclinical PK profile of ABI-6250 supports low once-daily dosing in patients with chronic HDV infection
- ABI-6250 is expected to enter Phase 1 clinical trials by the end of 2024

Acknowledgements

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- Data have been previously presented at EASL 2024 (Milan, Italy), EASL 2023 (Vienna, Austria), and the International HBV Meeting 2024 (Kobe, Japan)
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Thanks for your attention!

Questions?

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