HBV/HDV Entry Inhibitor Research Webcast

MARCH 31, 2022

Nasdaq: ASMB

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Today's Speakers

John McHutchison AO, MD

Chief Executive Officer & President

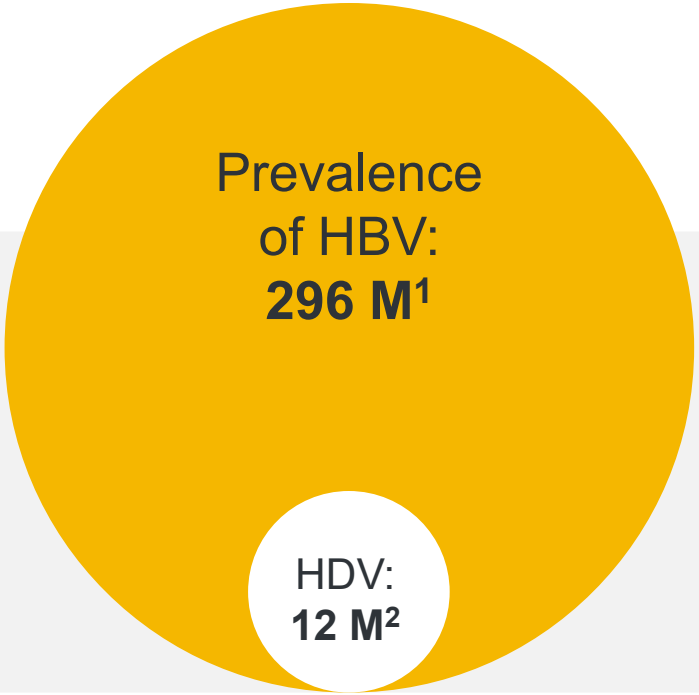
William Delaney, PhD

Chief Scientific Officer

Professor Michael P. Manns, MD

President of Hannover Medical School, Hannover, Germany

HDV is a Major Global Public Health Problem



Only 1 Approved Drug for HDV in Europe†

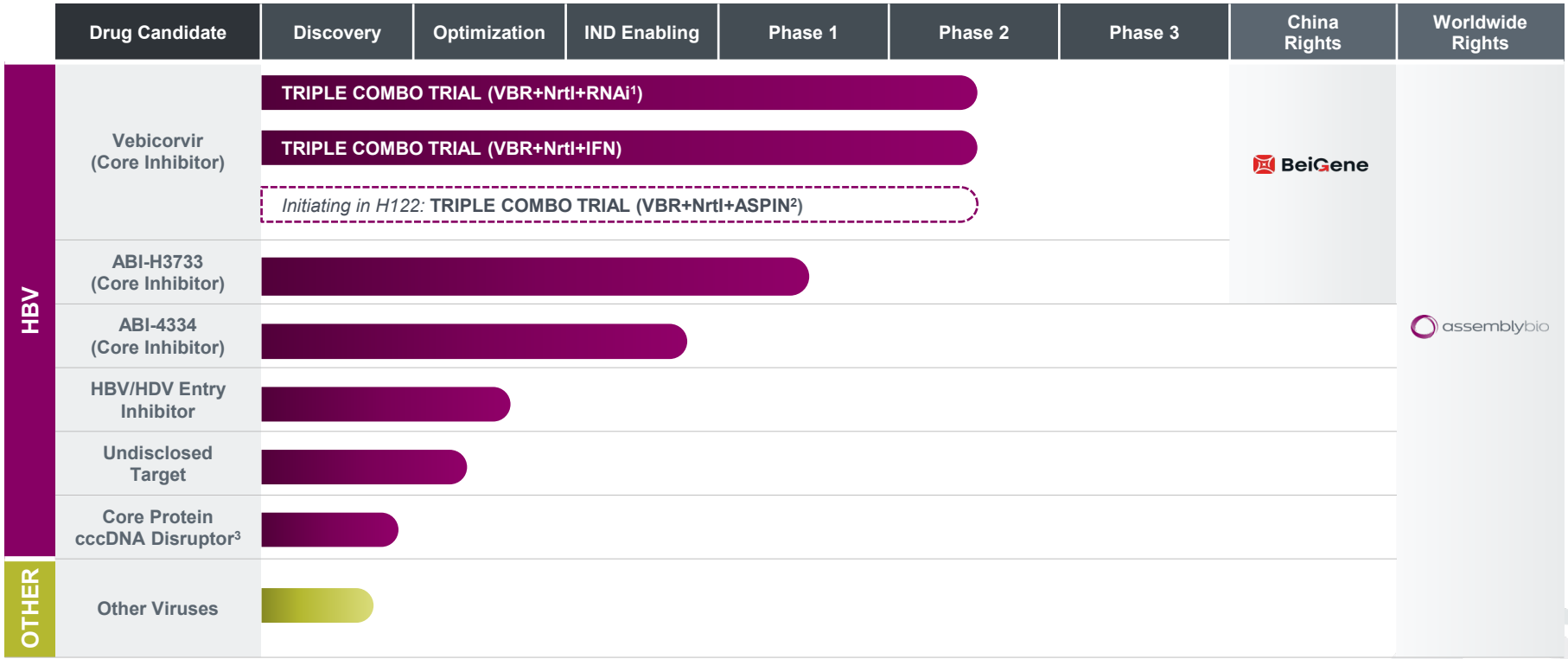
HDV infection occurs only with HBV infection

Among HBsAg positive patients, estimated HDV prevalence is 4.5%[2]

HDV causes 18% of cirrhosis and 20% of hepatocellular carcinoma associated with HBV[2]

[1]Prevalence of HBV 296M per WHO (2021); [2]Stockdale, J Hep 2020; †bulevirtide received conditional approval from EMA in 2020

Broad HBV Clinical & Research Stage Portfolio



[1]RNAi Clinical Collaboration with Arbutus; [2]ASPIN Clinical Collaboration with Antios; [3]Drug Discovery Collaboration with Door Pharma

Professor Michael P. Manns, MD

- International expert in liver diseases and viral hepatitis, including hepatitis B and D (delta), with more than 35 years in clinical and research roles at leading medical and academic institutions
- Currently President and Board Member for Research and Education at Hannover Medical School in Hannover, Germany
- Founder and chairman of HepNet, a national network on viral hepatitis and the German Liver Foundation
- Past president of German Association for the Study of the Liver (GASL), German Society of Gastroenterology (DGVS), German Society of Internal Medicine (DGIM) and United European Gastroenterology (UEG)
- Recipient of numerous awards including the International Hans Popper Award (1995) and EASL Recognition Award (2007)
- According to Thomson Reuters and Clarivate Analytics he ranks among the top 1 % of most cited researchers in clinical medicine (h-Index 166, Google Scholar).

MHH

Hannover Medical School
Germany

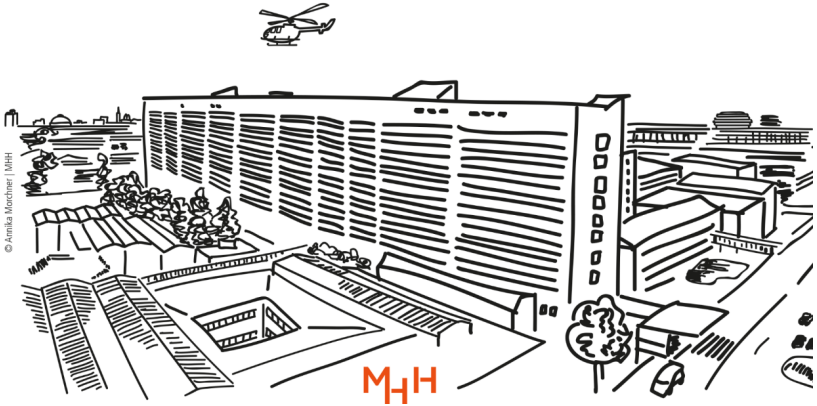
Agenda

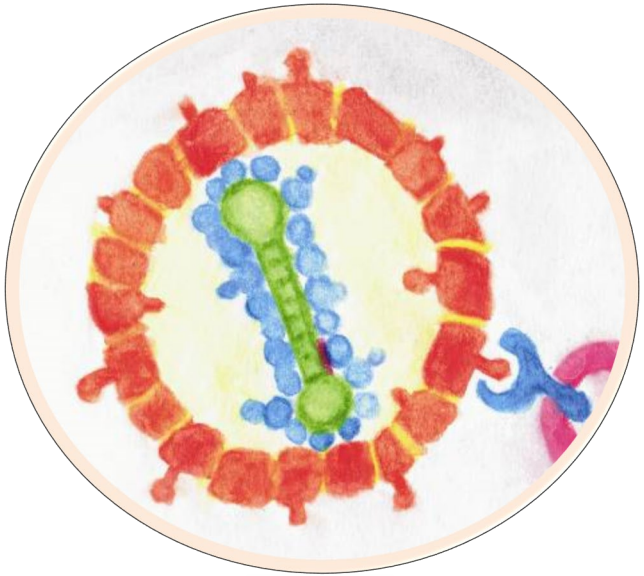
- Assembly Bio Strategy: Leveraging Expertise in Viral Disease to Expand Portfolio
  - John McHutchison AO, MD, Chief Executive Officer & President
- Hepatitis Delta Virus: The Greatest Current Unmet Need in Hepatology
  - Professor Michael P. Manns, MD
- Overview of Assembly Bio's HBV/HDV Entry Inhibitor Research Program
  - William Delaney, PhD, Chief Scientific Officer
- Q&A
- Anticipated 2022 Progress
  - John McHutchison

Hepatitis D (delta) Virus Infection

Michael P. Manns

Hannover Medical School,
Hannover, Germany





Hepatitis D (Delta)

- Epidemiology and natural history of disease
- Standard of care
- New treatment concepts

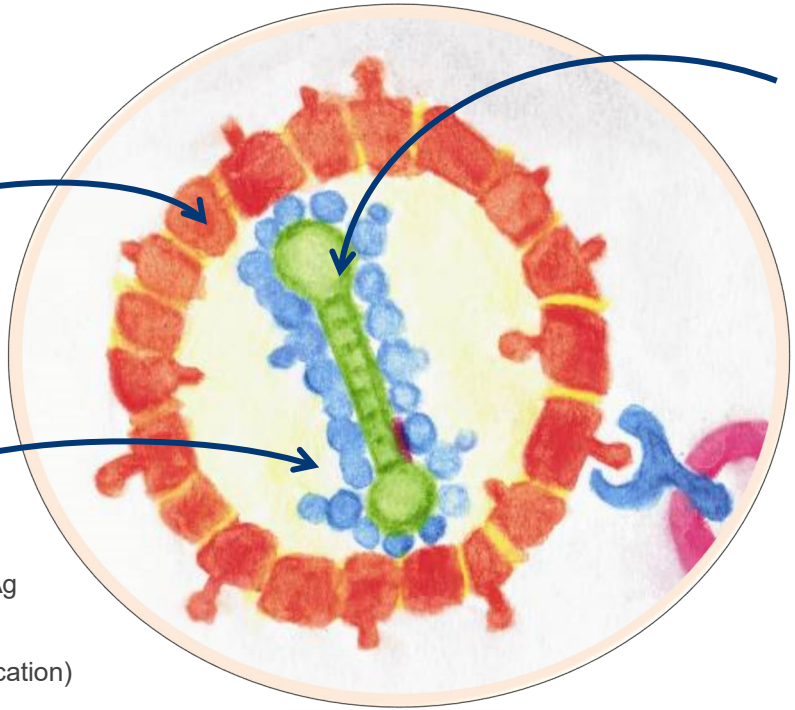
Hepatitis D (Delta)

- **Epidemiology and natural history of disease**
- Standard of care
- New treatment concepts

The pathogen in a nutshell: The hepatitis D virus

HBsAg

- HBsAg particles can self assemble
- HBV: 1 virion x 10^3-10^6 particles



HDV RNA

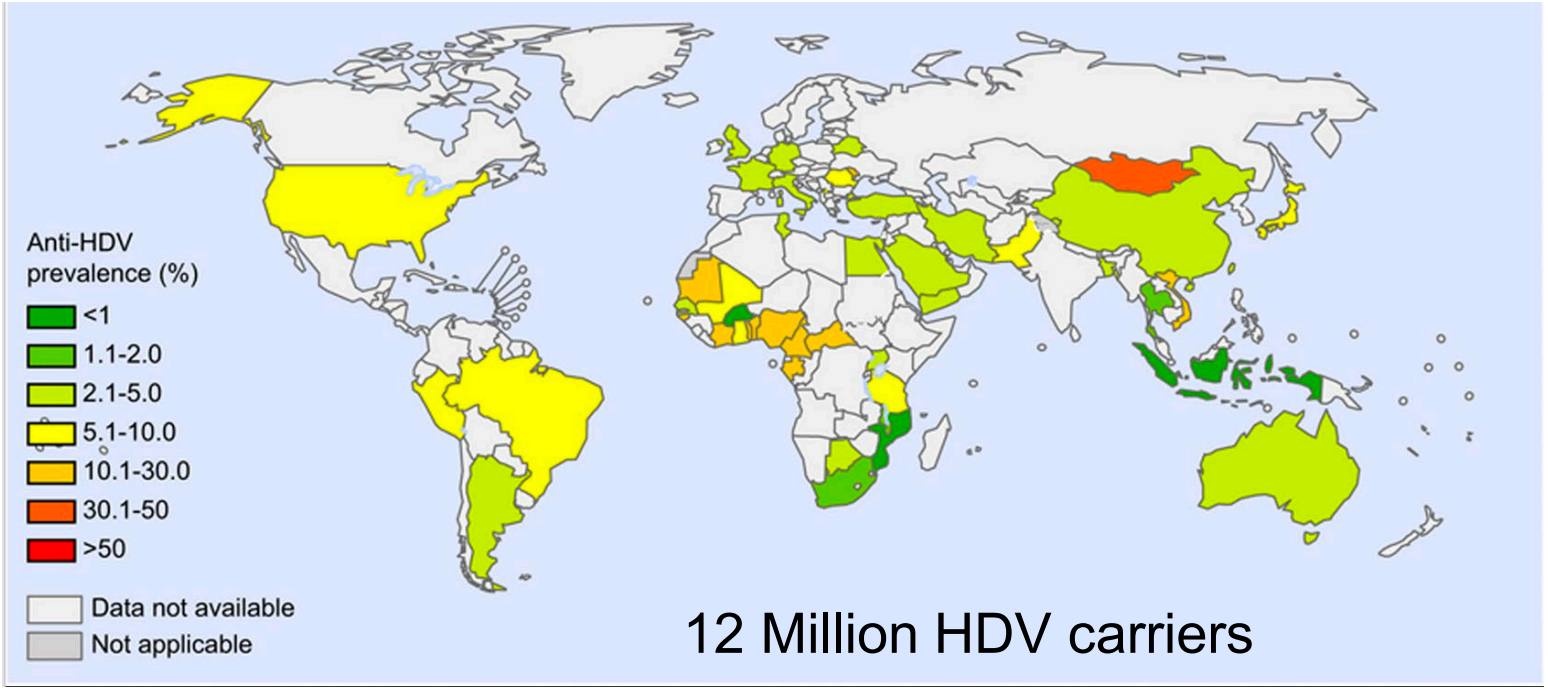
- The smallest of all animal viruses
- Highly paired – rod like structure
- No enzymes but Ribozymes
- Only encodes S-HDAg

HDAg

- 2 forms: S-HDAg and L-HDAg
- S-HDAg: ↑ replication
- L-HDAg: ↑ assembly (↓ replication)

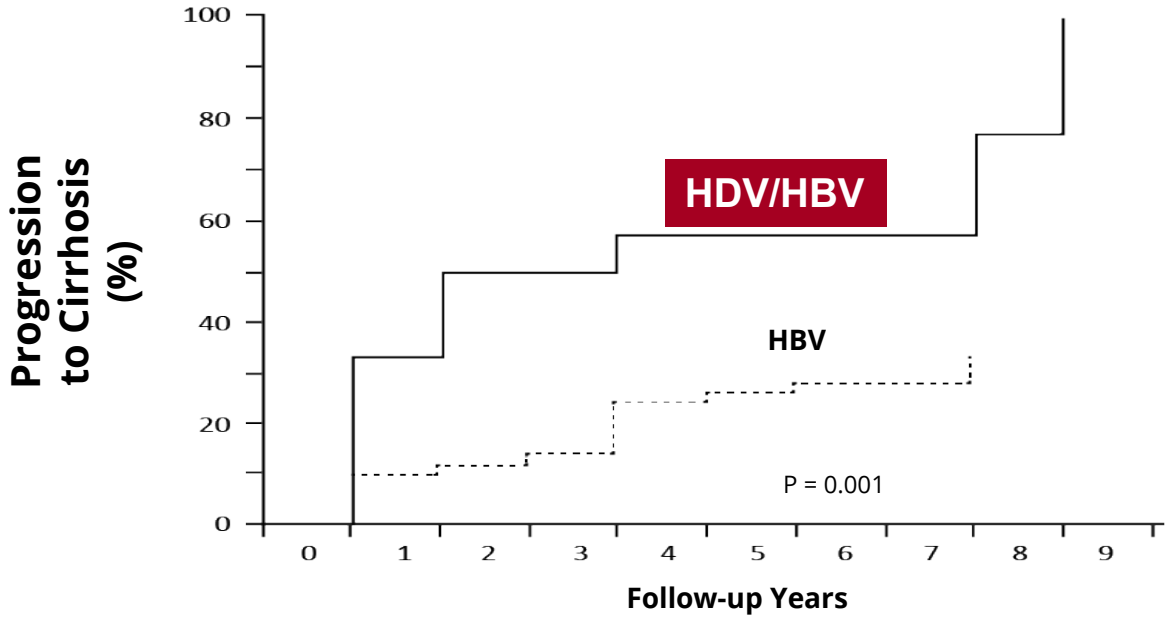
Calle Serrano, Manns, Wedemeyer. ***Semin Liver Dis.*** 2012 May;32(2):120-9.

The global prevalence of hepatitis D virus infection: systematic review and meta-analysis



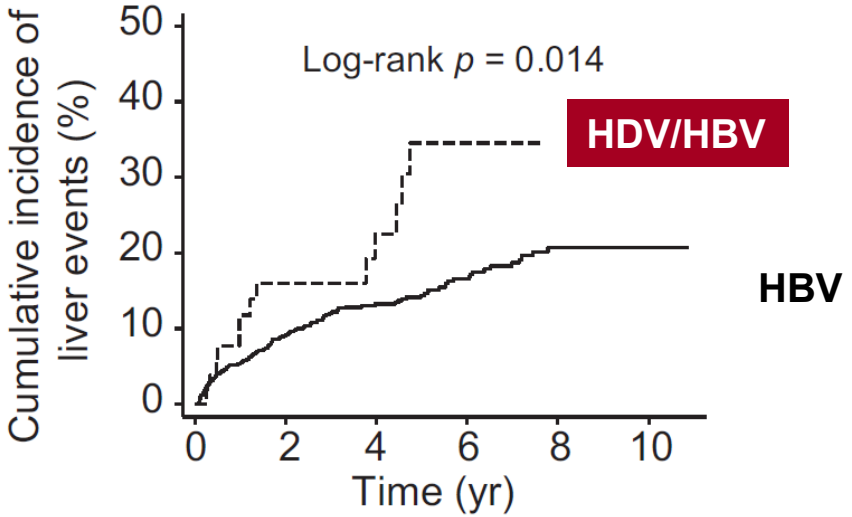
Stockdale et al. ***J Hepatol*** 2020 Sep;73(3):523-532.

Hepatitis delta leads to faster progression to cirrhosis than HBV mono-infection



Fattovich et al, ***J Infect Dis*** 1987; Fattovich et al, ***Gut***, 2000.

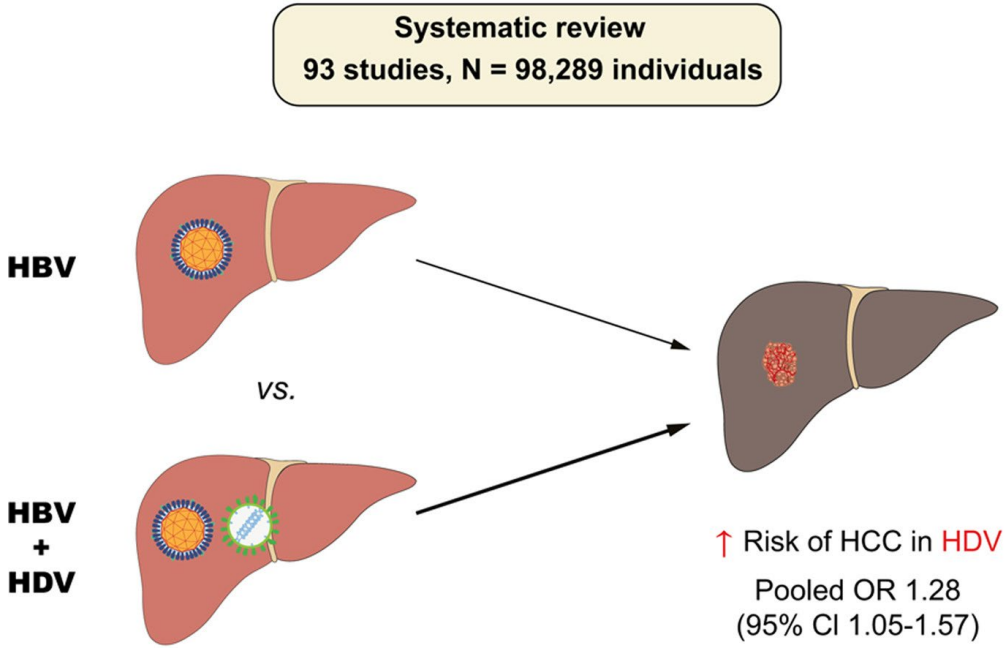
Hepatitis delta takes a more severe long-term course than HBV mono-infection



Number at risk						
HBV monoinfected	1091	685	434	266	123	36
HBV/HDV co-infected	53	33	24	7	2	2

Manesis et al. ***J Hepatol*** 2013 Nov;59(5):949-56.

HDV infection is associated with an increased risk of HCC in HBV-infected patients



Alfaiate et al. ***J Hepatol*** 2020 Sep;73(3):533-539.

The association between HDV and HCC is stronger in the setting of HIV coinfection.

Hepatitis D (Delta)

- Epidemiology and natural history of disease
- **Standard of care**
- New treatment concepts

Guideline recommendations for HDV screening

Whom to Test

HBsAg-positive (all or only at-risk groups?)

↓

Anti-HDV

↓

HDV RNA

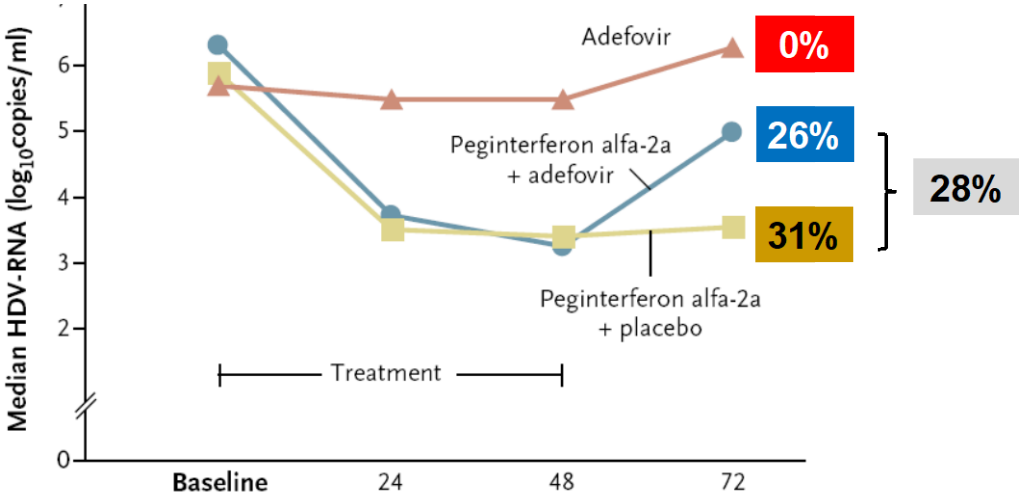
Whom to Test

AASLD[1] (2018)	• HBsAg+ patients with HDV risk factors. • Low/undetectable HBV DNA and high ALT
APASL[2] (2016)	• Patients with chronic HBV infection and chronic liver disease.
EASL[3] (2017)	• All HBsAg positive individuals

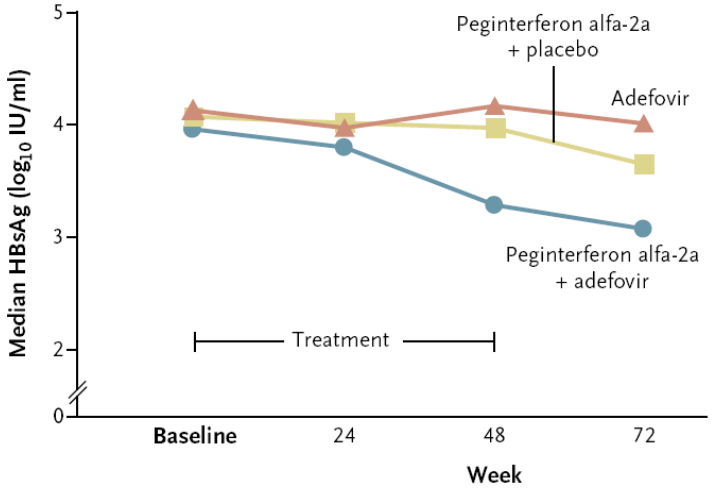
AASLD: American Association for the Study of Liver Diseases; ALT: alanine aminotransferase;
APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HDAg: hepatitis D antigen; HDV: hepatitis D virus; RNA: ribonucleic acid; WHO: World Health Organization.

1. Terrault N, et al. ***Hepatology*** 2018;67:1560-99;
2. Sarin SK, et al. ***Hepatol Int*** 2016;10:1-98;
3. European Association for the Study of the Liver. ***J Hepatol*** 2017;67:370-98.

Treatment of chronic hepatitis delta: Only PEG-IFNα leads to decline of HDV RNA



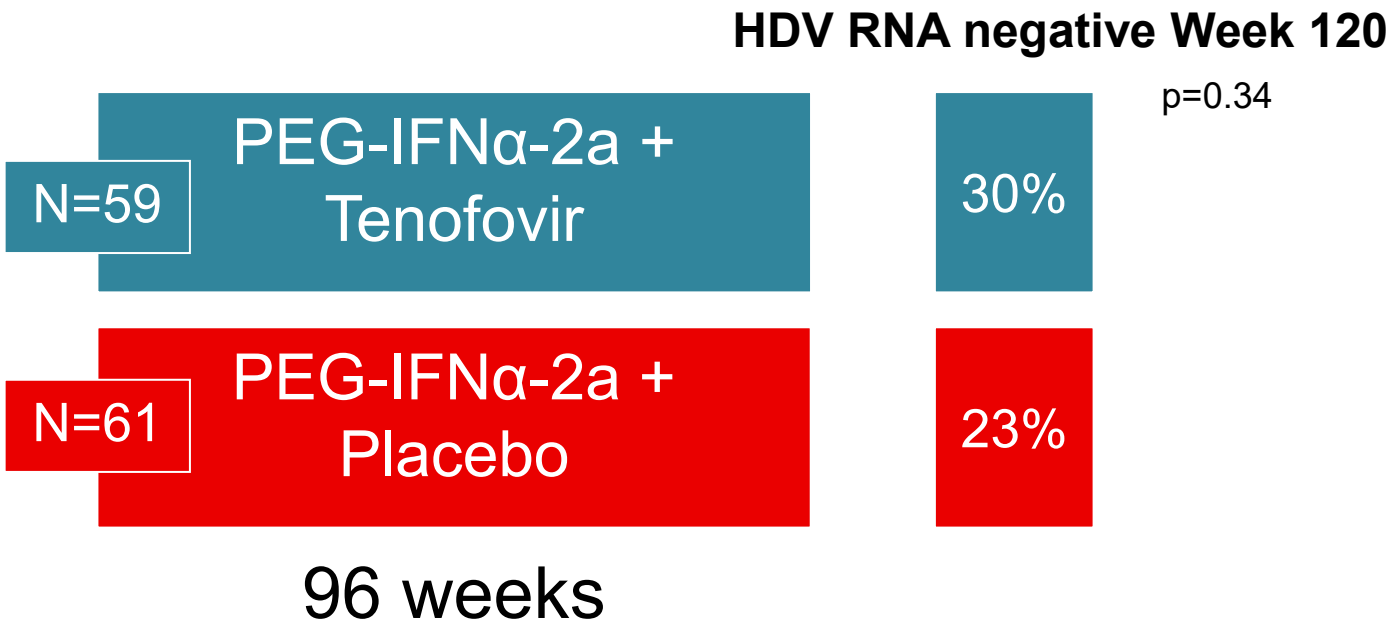
Effect on HBsAg



Wedemeyer et al. ***New Engl J Med*** 2011, 364(4); 322-31.

Note:
PEG-IFNα is not approved for the treatment of hepatitis delta

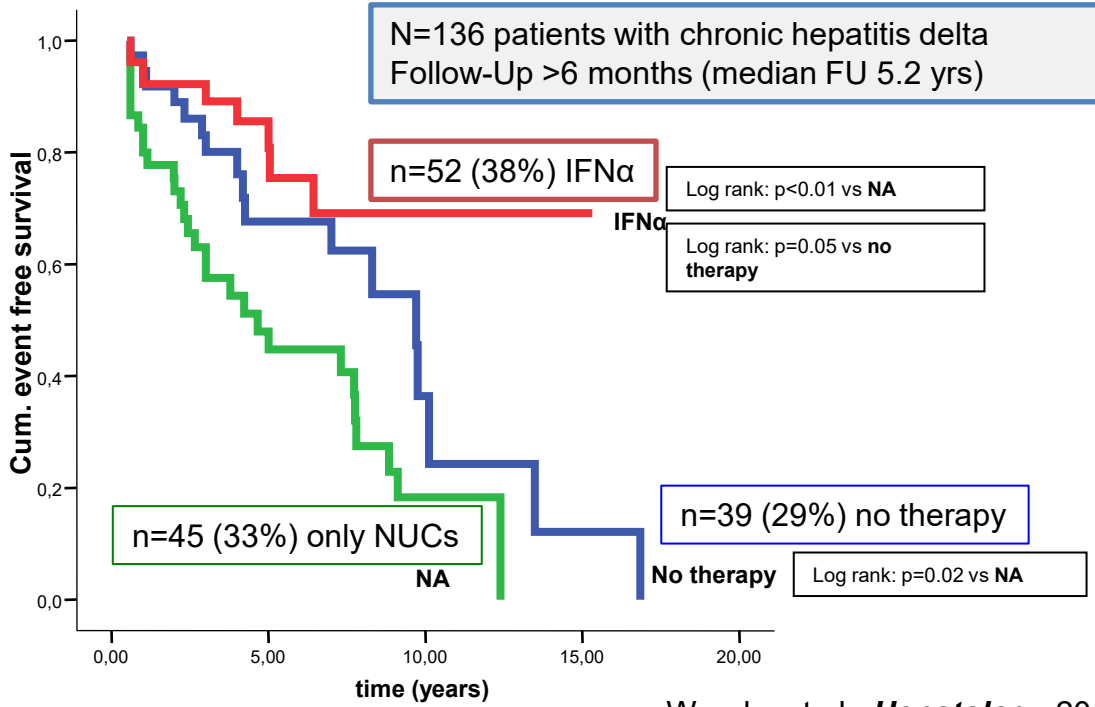
HIDIT-2: Longer treatment with PEG-IFNα does not increase response; no additional benefit of tenofovir



Wedemeyer et al., ***Lancet Infect Dis*** 2019 Mar;19(3):275-286.

Note:
PEG-IFNα is not approved for the treatment of hepatitis delta

IFN therapy is associated with improved clinical long-term outcome of hepatitis D (delta)



Wranke et al., ***Hepatology*** 2016 Oct 22. doi:10.1002/hep.28876.

Note:
PEG-IFNα is not approved for the treatment of hepatitis delta

Hepatitis D (Delta)

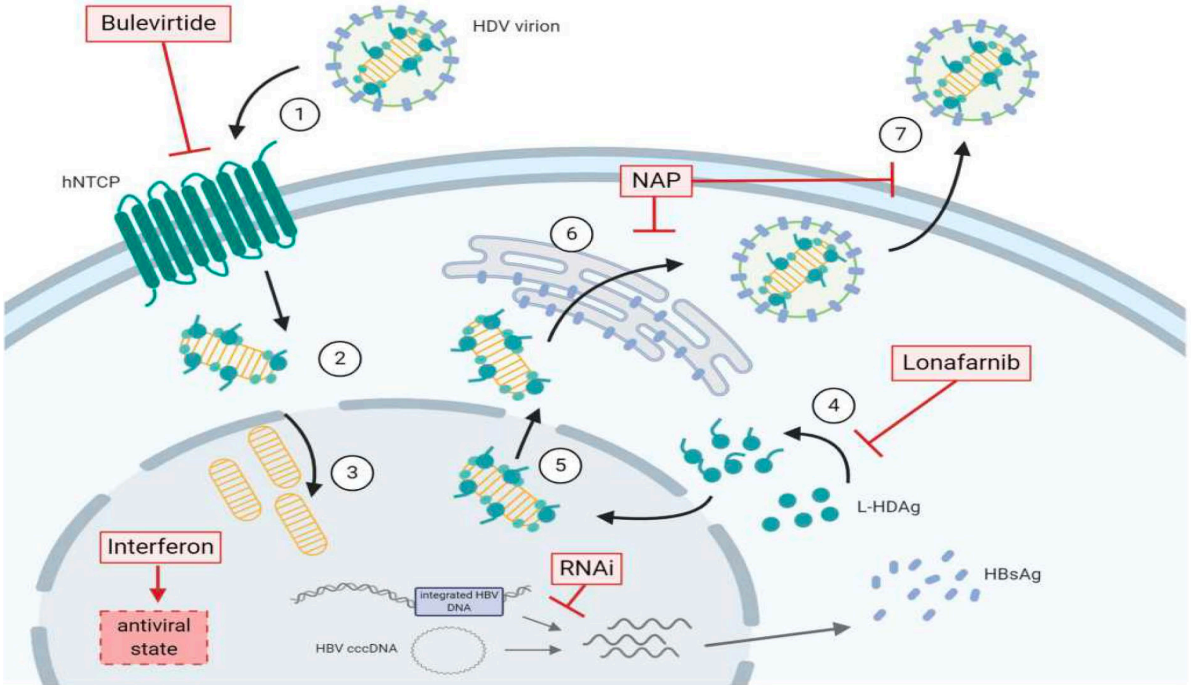
- Epidemiology and natural history of disease
- Standard of care
- **New treatment concepts**

Regulatory and guideline efficacy endpoints

	Chronic On-Therapy Endpoint	Cure Off-Therapy Endpoint
FDA Draft Guidance November 2019[1]	*"…a **greater than or equal to 2-log$_{10}$ decline in HDV RNA and ALT normalization** on-treatment could be considered an acceptable surrogate endpoint"*	*"The proportion of trial patients with **undetectable serum HDV RNA** (defined as less than the lower limit of quantification (LLOQ), target not detected (TND)) and **ALT normalization.**"*
AASLD EASL 2019 EASL-AASLD HBV Treatment Endpoints Conference October 2019[2]	*"…a **2-log reduction in HDV RNA might suffice.**"*	*"…**undetectable serum HDV RNA 6 months after stopping treatment** as the endpoint …Normalisation of ALT is also desired"*

1. FDA. https://www.fda.gov/media/132137/download. Accessed February 2021;
2. Cornberg M, et al. ***J Hepatol*** 2020 Mar;72:539-57. doi: 10.1016/j.jhep.2019.11.003.

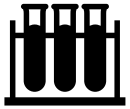
New treatment concepts for hepatitis delta



Sandmann & Cornberg. ***J Exp Pharmacol*** 2021 Apr 16;13:461-468.

Efficacy and safety of bulevirtide monotherapy

- 50-60% HDV RNA decline ≥2log$_{10}$ IU/ml
- ALT normalization 43-73%
- No HBsAg decline



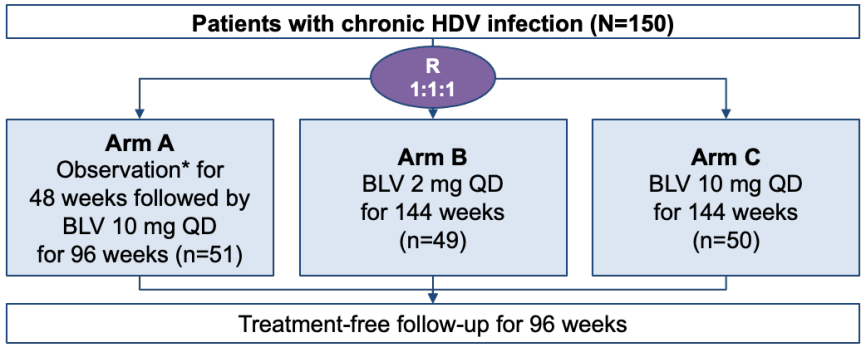
- Asymptomatic and dose-dependent elevation of serum bile salts, reversible upon discontinuation of treatment

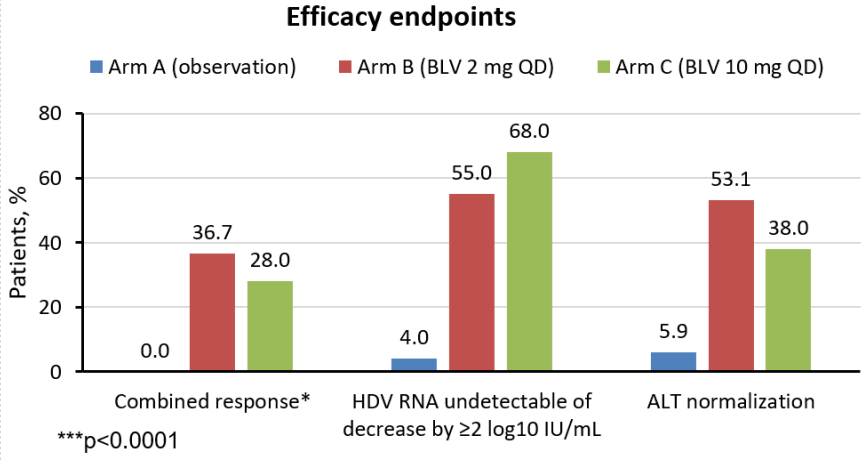
- Injection site reactions such as swelling, redness, irritation, itchiness, infection, haematoma and local pain. Local reactions more likely if injection is accidently misplaced

- Discontinuation of bulevirtide can lead to reactivation of HDV and HBV infection and exacerbation of hepatitis

Bulevirtide, Summary of Product Characteristics. October 2020.

24 week interim analysis of the Phase 3 MYR301 Study





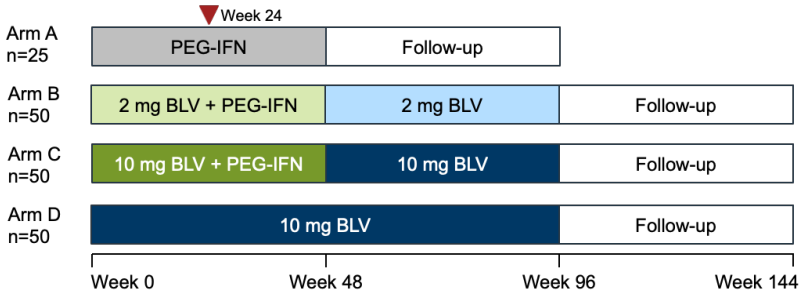
- 57.3% of patients were male, 82.7% white, and the mean age was 41.8 years
- HDV RNA levels were 5.05 log10 IU/mL and ALT mean levels were 110.9 U/L
- 47.3% of patients had compensated liver cirrhosis

Wedemeyer et al., dILC 2021; LBP-2730

24 week interim analysis of the Phase 2b MYR204 study

Bulevirtide as monotherapy and in combination with PEG-IFNα

N=175 HDV randomized 1:2:2:2



Results at Week 24: % of patients with response			
	Undetectable HDV RNA	ALT normalization	Combined response†
PEG-IFN	12.5	12.5	12.5
2 mg BLV + PEG-IFN	24.0	30.0	30.0
10 mg BLV + PEG-IFN	34.0	24.0	24.0
10 mg BLV	4.0	64.0	50.0

Asselah T, et al. dILC 2021; OS-2717

Summary of new treatment concepts for hepatitis delta

			HDV RNA decline	ALT decline	Safety
Bulevirtide Entry inhibitor	Subcutaneous ± PEG-IFNα	Phase 3	☑	☑	Increase bile acids, local reactions
Lonafarnib Prenylation inhibitor	Oral ± PEG-IFNα	Phase 3	☑	☑	Dosing with RTV improves GI tolerability
PEG-IFN lambda	Subcutaneous ± lonafarnib +RTV	Phase 2	☑	On-Tx flares	Less side effects than PEG-IFNα
REP2139 Nucleic Acid Polymers	Intravenous + PEG-IFNα	Phase 2	☑	On-Tx flares	Limited data in HDV
JNJ-3989 RNAi	Subcutaneous	Phase 2	-No data in HDV-		

Note: very subjective and simplified description of the data

HDV - Unmet Needs

- Worst form of viral hepatitis
- 12 million chronic HDV carriers may be an underestimation due to incomplete global epidemiology
- High prevalence in risk groups and migrant populations
- No universal HDV screening of HBsAg carriers

- Efficacious, tolerable and affordable HDV-targeted therapies

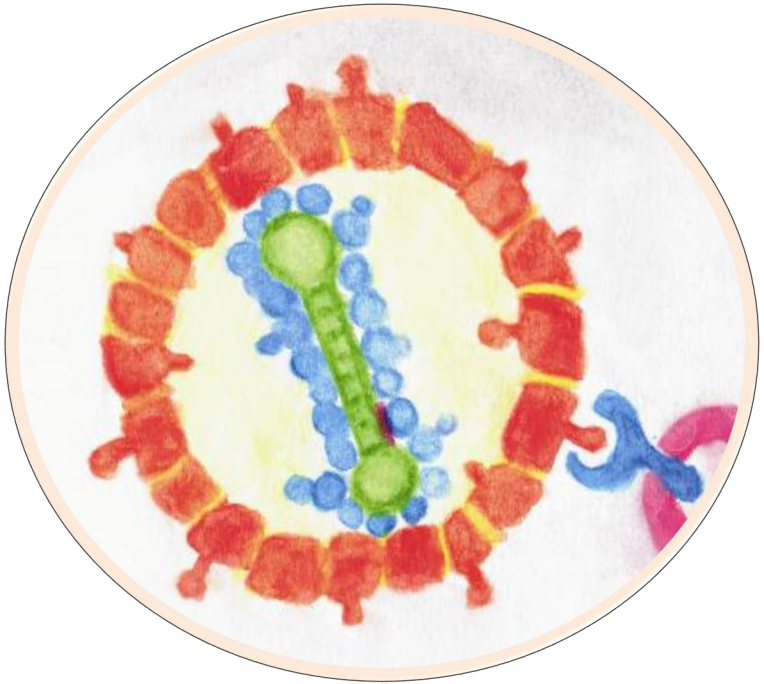
HDV - Opportunities

- ➡ Greatest unmet needs in viral hepatitis are therapies for chronic hepatitis D
- Many molecular targets have been identified and there are several molecules at various stages of clinical development
- Interferon a candidate for combination therapy
- Curing HBV would also cure HDV, but development of a cure for HBV is still early

Acknowledgements

Markus Cornberg, Hannover

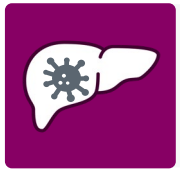
Thank you for your attention!



Agenda

- Assembly Bio Strategy: Leveraging Expertise in Viral Disease to Expand Portfolio
  - John McHutchison AO, MD, Chief Executive Officer & President
- Hepatitis Delta Virus: The Greatest Current Unmet Need in Hepatology
  - Professor Michael P. Manns, MD
- Overview of Assembly Bio's HBV/HDV Entry Inhibitor Research Program
  - William Delaney, PhD, Chief Scientific Officer
- Q&A
- Anticipated 2022 Progress
  - John McHutchison

Chronic HDV Infection – Current Unmet Need



HDV infection results in the most severe form of viral hepatitis with few treatment options

Lowering viral load improves patient outcomes, however…..

Current treatment options have drawbacks in convenience and side effects

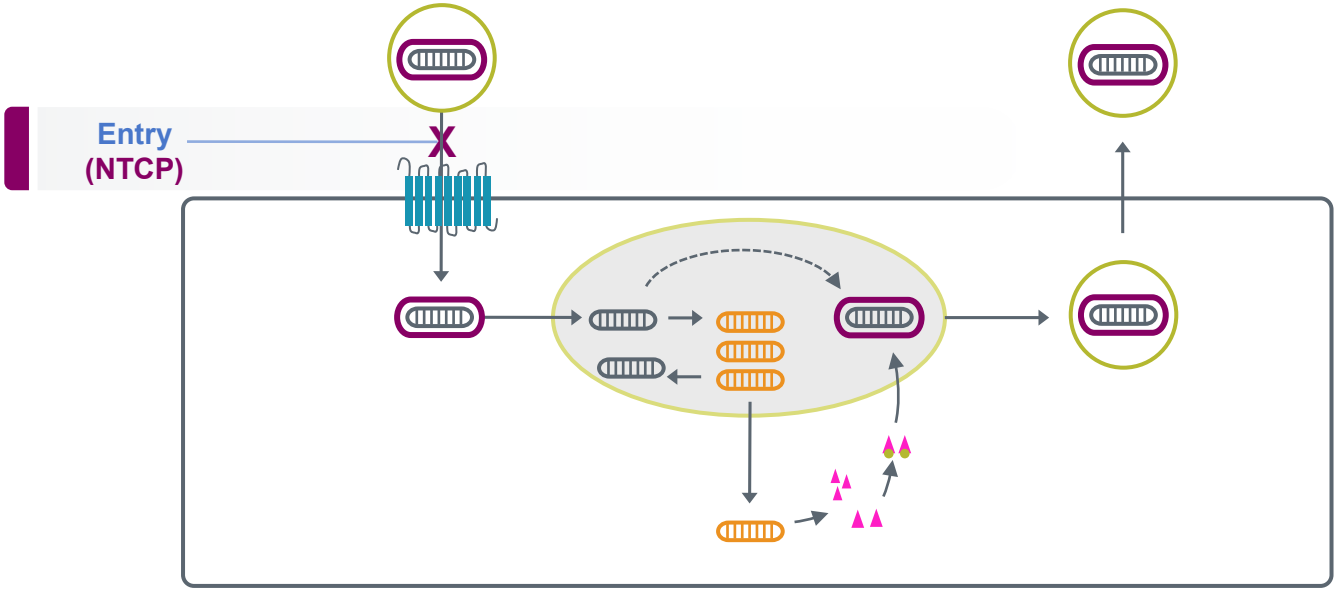
There is a need for safe, simple, and effective oral therapies

Hepatitis B Virus and Hepatitis Delta Virus

- Small enveloped DNA virus
- Infects human hepatocytes
- Partially double-stranded 3.2 kb DNA genome
- Encodes HBcAg, HBeAg, HBV Pol, HBsAg, HBxAg
- Replicates by reverse transcription using its own Pol

- Small enveloped RNA virus
- Infects human hepatocytes
- Single-stranded 1.7 kb circular RNA genome.
- Encodes only two proteins: S- and L-HDAg
- Replicates using host RNA Pols I & II
- Is a “satellite” virus of HBV (requires HBsAg)

HDV Replication Cycle: Target for Antiviral Intervention



Sodium Taurocholate Cotransporting Polypeptide (NTCP)

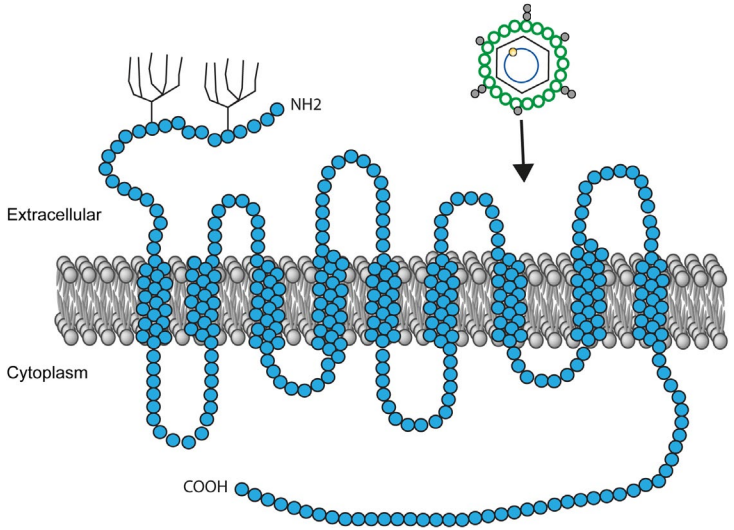
Bile acid/Na+ uptake transporter with multiple transmembrane domains

Selective expression on hepatocytes

- regulates uptake of bile acids into the liver

Identified as the receptor for HBV and HDV

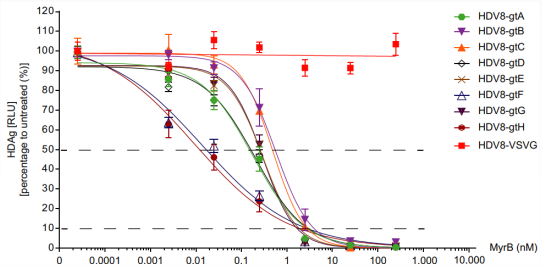
- HBsAg binds specifically to human NTCP to mediate viral entry



Appelman et al. BBA – Mol. & Cell Biology of Lipids, 2021

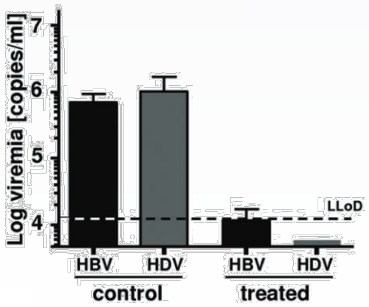
Target Validation for NTCP by Bulevirtide

IN VITRO



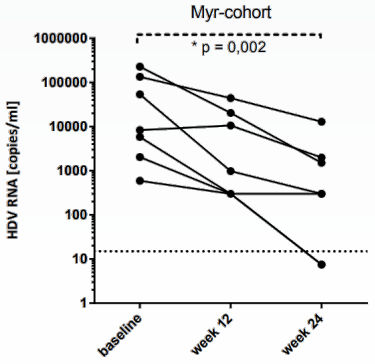
Wang et al. JHep, 2021

HUMANIZED MOUSE



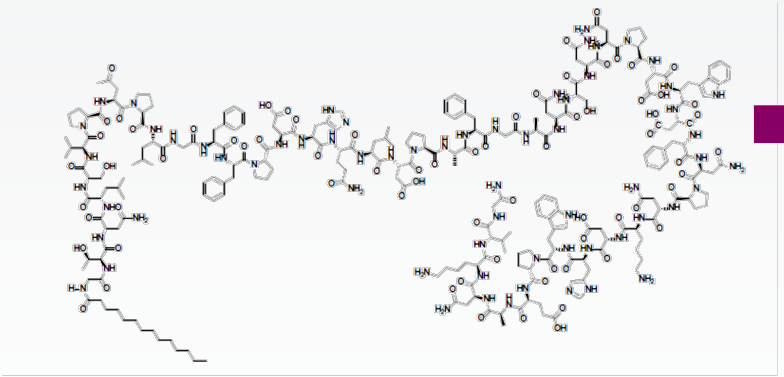
Lütgehetmann et al. Hepatology, 2012

PHASE 2



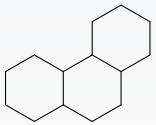
Bogomolov et al. JHep, 2016

Assembly Small Molecule Approach



Bulevirtide has shown safety & efficacy in clinical trials, but…..

- Requires daily injections
- Is a very large, complex molecule



- Opportunity to develop a safe & effective oral small molecule
- Improved convenience
- Potential for enhanced treatment uptake and diagnosis rates

HBV/HDV Entry Inhibitor Target Product Profile (TPP)

Virologic Profile

- Potent HBV and HDV antiviral activity (EC_{50} ≤ 10 nM)
- Pan-genotypic for HBV & HDV

PK Profile

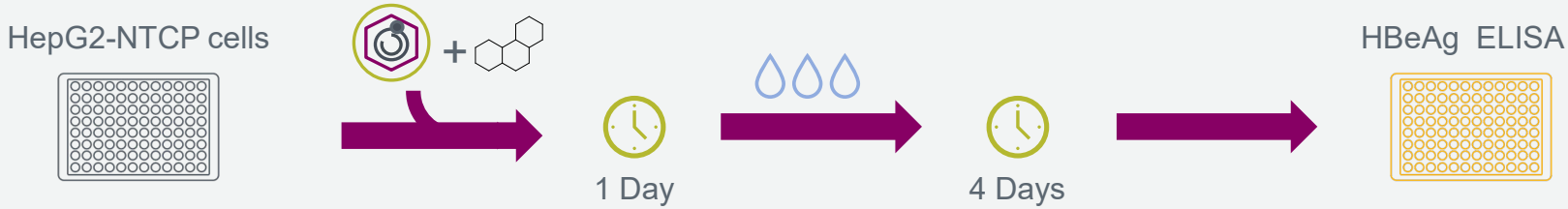
- Once daily oral dose (≤ 300 mg)
- Plasma C_{min} ≥ 10-fold above protein adjusted antiviral EC_{50}
- Conventional formulation suitable for coformulation

Safety Profile

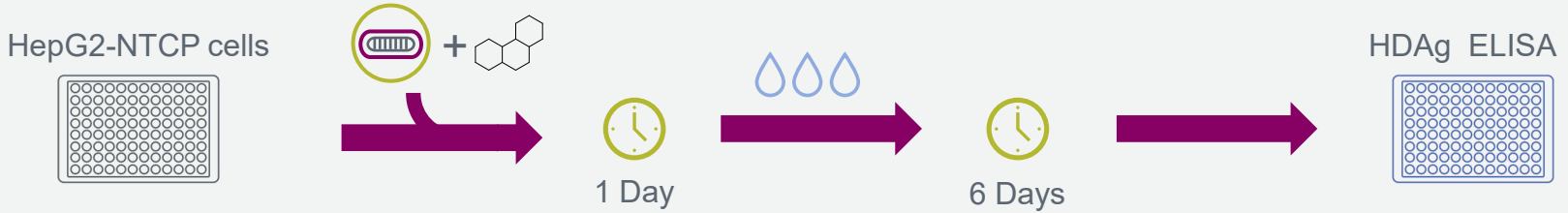
- No clinically-significant side effects; suitable for chronic dosing
- Low potential for drug-drug interactions

Identification of Novel Potent HBV/HDV Entry Inhibitors

Cell-based Preclinical Antiviral Activity



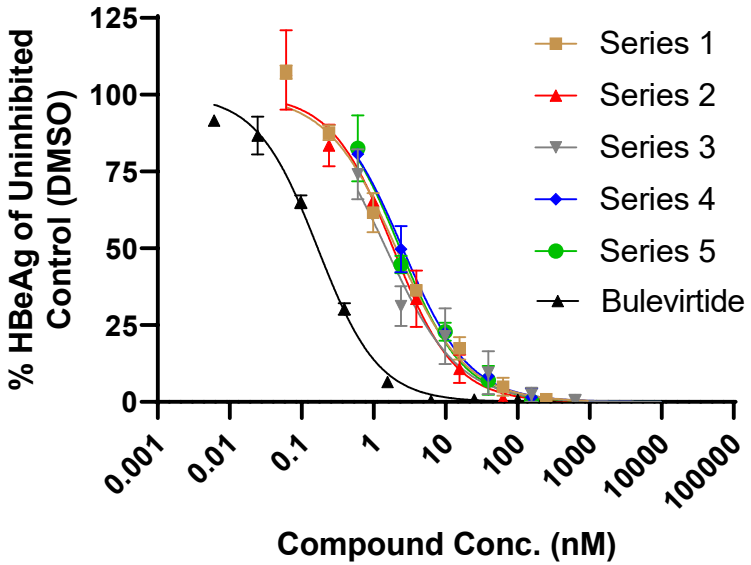
Inhibition of HBeAg indicates HBV entry and cccDNA formation are inhibited



Inhibition of HDAg indicates HDV entry and HDV RNA replication are inhibited

Identification of Novel Potent HBV/HDV Entry Inhibitors

Cell-based Preclinical Antiviral Activity

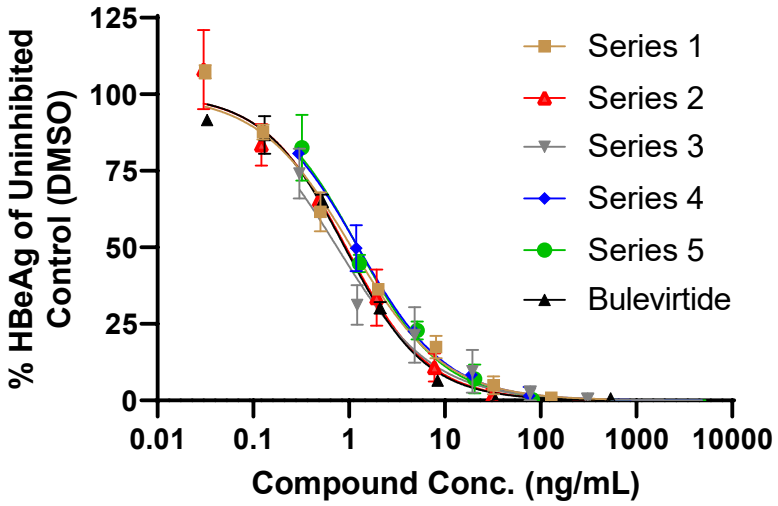


Compound	HBeAg EC_{50} (nM)
Series 1 Inhibitor	2.1
Series 2 Inhibitor	1.9
Series 3 Inhibitor	1.5
Series 4 Inhibitor	2.5
Series 5 Inhibitor	2.3
Bulevirtide	0.2

Bulevirtide molecular weight: 5,399 g/mol
Series 1-5 molecular weight: ~500 g/mol

Identification of Novel Potent HBV/HDV Entry Inhibitors

Cell-based Preclinical Antiviral Activity



Compound	HBeAg EC_{50} (ng/mL)
Series 1 Inhibitor	1.1
Series 2 Inhibitor	0.9
Series 3 Inhibitor	0.8
Series 4 Inhibitor	1.2
Series 5 Inhibitor	1.2
Bulevirtide	0.9

Bulevirtide molecular weight: 5,399 g/mol
Series 1-5 molecular weight: ~500 g/mol

HBV/HDV Entry Inhibitor: Progress and Goals

Project is in Lead Optimization

- Highly resourced to progress to development candidate nomination quickly
- Multiple chemically-differentiated leads with single digit nM potency
- HBV entry assays in place, HDV assay in development
- Currently optimizing DMPK properties
- Anticipate advancing compounds into preclinical safety profiling throughout 2022

Development candidate nomination expected in first half of 2023

HBV/HDV Entry Inhibitor Project: Summary

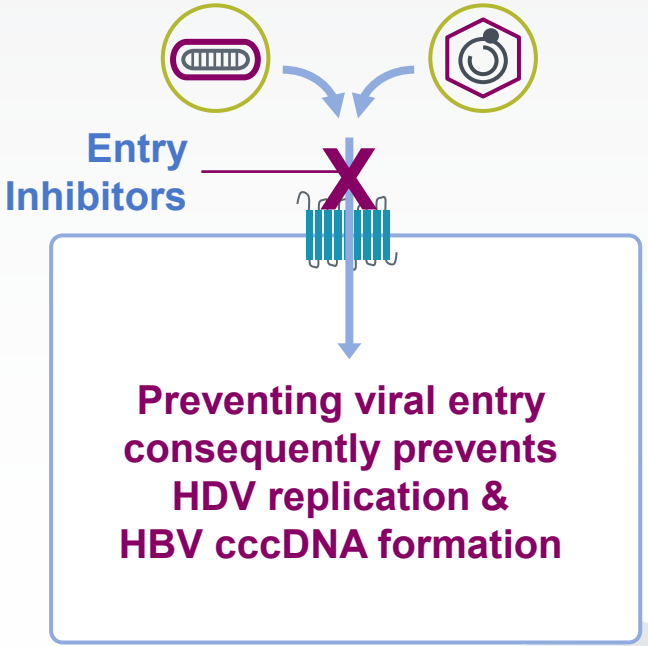
HDV: most severe form of viral hepatitis; an important subgroup of HBV patients with high unmet need

Progress in HDV therapeutics encouraging; significant room for improvement (convenience and side effects)

An oral, QD HDV entry inhibitor meeting our target profile would be a significant advance to currently used therapies; potential to increase diagnosis and treatment rates

We have discovered novel single digit nM entry inhibitors; aim to nominate a candidate within a year

- Potential to simplify and improve access to HDV therapy
- Potential to intensify antiviral pressure on HBV



Agenda

- Assembly Bio Strategy: Leveraging Expertise in Viral Disease to Expand Portfolio
  - John McHutchison AO, MD, Chief Executive Officer & President
- Hepatitis Delta Virus: The Greatest Current Unmet Need in Hepatology
  - Professor Michael P. Manns, MD
- Overview of Assembly Bio's HBV/HDV Entry Inhibitor Research Program
  - William Delaney, PhD, Chief Scientific Officer
- Q&A
- Anticipated 2022 Progress
  - John McHutchison

Q&A

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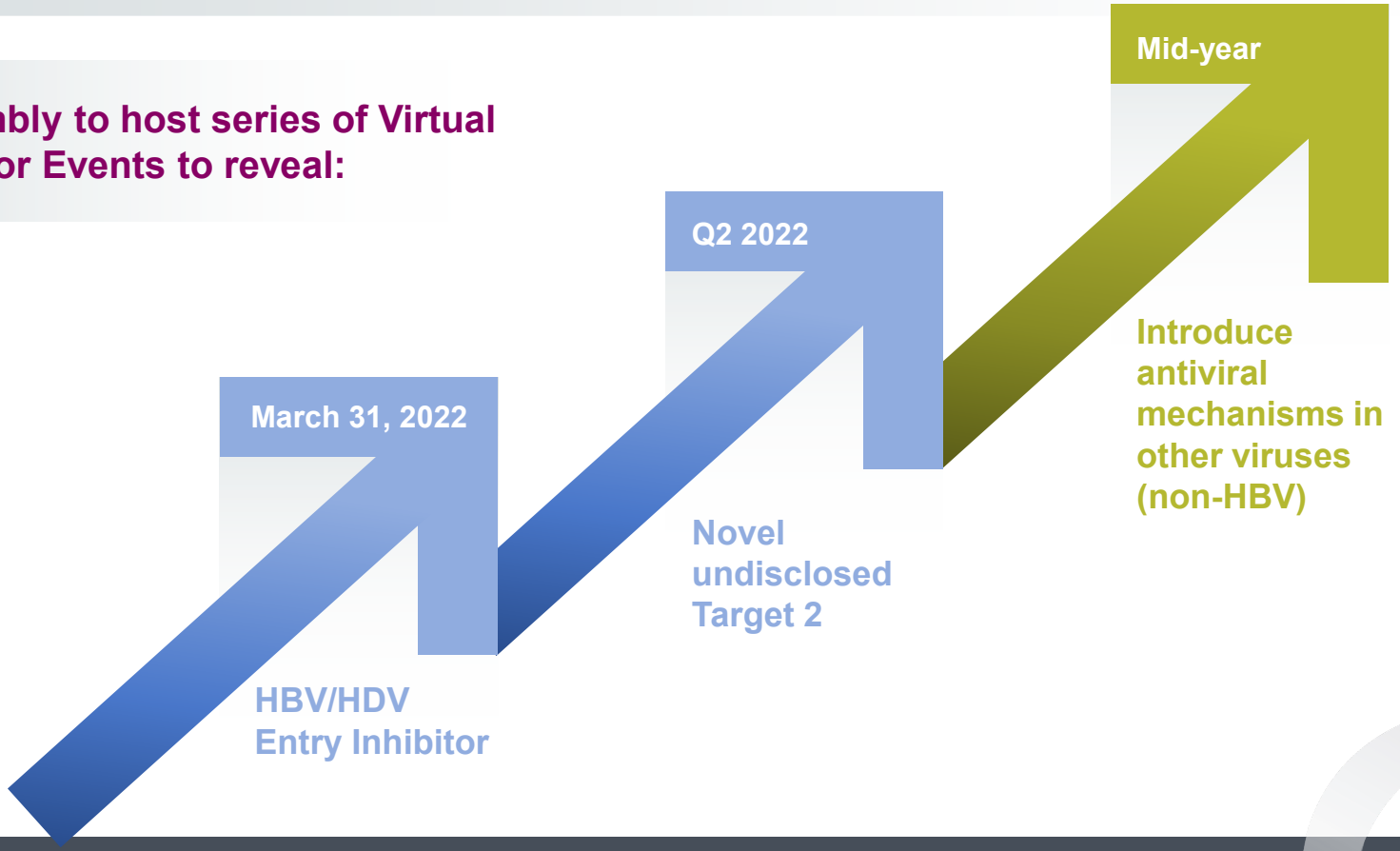
Expanded Research Engine - Expectations for 2022

Assembly to host series of Virtual Investor Events to reveal:



2022 Key Objectives and Anticipated Progress

1H 2022

- Introduce HBV/HDV entry inhibitor program ✓
- Reveal novel undisclosed HBV Target 2
- Introduce R&D initiatives aimed at other viruses (non-HBV) – *mid-year*
- Both Phase 2 Triple Combo Studies (IFN and RNAi) fully enrolled ✓
- Initiate Phase 2 Triple Combo Study – ASPIN
- Initiate Phase 1b Study – 3733

2H 2022

- Interim Phase 2 On-Treatment Data Triple Combo Study – IFN
- Interim Phase 2 On-Treatment Data Triple Combo Study – RNAi
- Initiate Phase 1a Study – 4334
- Interim Phase 1b Data – 3733

Balance Sheet

~$175M in cash (as of 12/31/21) sufficient to fund operations into 2H 2023

HBV/HDV Entry Inhibitor Research Webcast

MARCH 31, 2022