ALN-HBV
Investigational RNAi Therapeutic for the Treatment of Chronic Hepatitis B Virus (HBV) Infection

Tuesday, October 11, 2016
Agenda

Welcome
• Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Introduction
• Pushkal Garg, M.D., Senior Vice President, Clinical Development

ALN-HBV Program
• Laura Sepp-Lorenzino, Ph.D., Vice President, Entrepreneur-in-Residence

Overview of Chronic Hepatitis D Virus (HDV) Infection
• Heiner Wedemeyer, M.D., Managing Senior Physician and Assistant Professor in the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School

Q&A Session
Reminders

Event will run for approximately 60 minutes

Q&A Session at end of presentation
• Submit questions at bottom of webcast screen
• Questions may be submitted at any time

Replay, slides and audio available at www.alnylam.com
Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.
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Q&A Session
RNAi Therapeutics
New Class of Innovative Medicines

- Harness natural pathway
- Catalytic mechanism
- Silence any gene in genome
- Upstream of today’s medicines
- Clinically proven approach
Alnylam Strategic Therapeutic Areas (STArs)

Investigational pipeline focused in 3 STArs

- **Genetic Medicines**: RNAi therapeutics for rare diseases
- **Cardio-Metabolic Diseases**: RNAi therapeutics for dyslipidemia, NASH, type 2 diabetes, hypertension, and other major diseases
- **Hepatic Infectious Diseases**: RNAi therapeutics for major liver infections beginning with hepatitis B & D
# Alnylam Development Pipeline

## Genetic Medicines
- **Hereditary ATTR Amyloidosis**
  - Development: ALN-TTRsc02
  - Phase 2: Patisiran
- **Hemophilia and Rare Bleeding Disorders**
  - Development: ALN-CC5
  - Phase 2: Fitusiran
- **Complement-Mediated Diseases**
- **Hepatic Porphyrias**
  - Development: ALN-AS1
- **Primary Hyperoxaluria Type 1**
  - Development: ALN-GO1
- **ATTR Amyloidosis**
- **Alpha-1 Antitrypsin Deficiency**
  - Development: ALN-AAT02
- **Beta-Thalassemia/Iron-Overload Disorders**
  - Development: ALN-TMP
- **Hereditary Angioedema**
  - Development: ALN-FT2
- **Additional Genetic Medicine Programs**

## Cardio-Metabolic Diseases
- **Hypercholesterolemia**
- **Hypertriglyceridemia**
  - Development: ALN-AC3
- **Mixed Hyperlipidemia/Hypertriglyceridemia**
  - Development: ALN-ANG
- **Hypertension/Preeclampsia**
  - Development: ALN-AGT
- **Thromboprophylaxis**
  - Development: ALN-F12
- **Additional Cardio-Metabolic Programs**
  - Development: ALN-PCSsc

## Hepatic Infectious Diseases
- **Hepatitis B Virus Infection**
  - Development: ALN-HBV
- **Hepatitis D Virus Infection**
  - Development: ALN-HDV
- **Chronic Liver Infection**
  - Development: ALN-PDL
- **Additional Hepatic ID Programs**
<table>
<thead>
<tr>
<th>GENETIC MEDICINES</th>
<th>DISCOVERY</th>
<th>DEVELOPMENT</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
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Q&A Session
Hepatitis B Virus (HBV) Infection
ALN-HBV

DESCRIPTION
Viral infection leading to cirrhosis and hepatocellular carcinoma (HCC)

DRUG MECHANISM
By silencing all viral products including tolerogenic antigens, ALN-HBV is expected to have direct antiviral effects and increase seroconversion rates

Phase 1/2 Started
July 2016

PATIENT POPULATION*
1/3 of global population exposed
~290M patients worldwide
25M in U.S./EU/Japan with chronic infection

### ALN-HBV for Chronic HBV Infection

<table>
<thead>
<tr>
<th></th>
<th>Genetically validated, liver-expressed target gene</th>
<th>Hepatitis B Virus</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>• Direct acting RNAi against infectious agent</td>
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<tr>
<td></td>
<td></td>
<td>• Multiple, synergistic antiviral mechanisms</td>
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<td></td>
<td></td>
<td>• Silencing of viral lifecycle (pgRNA, POL, S, X, core)</td>
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<td></td>
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<td>• Silencing of tolerogenic antigens (S Ag and e Ag, core)</td>
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<th>Biomarker for POC in Phase 1</th>
<th>Serum viral biomarkers</th>
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<tr>
<td>2</td>
<td></td>
<td>• Viral DNA</td>
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<tr>
<td></td>
<td></td>
<td>• Viral antigens: HBsAg, HBeAg</td>
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<td></td>
<td></td>
<td>• Hepatitis: ALT</td>
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</tbody>
</table>

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<tr>
<th></th>
<th>Definable path to approval and market</th>
<th>Endpoint: sustained virological response off all therapies after finite therapy</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td>Combination with standard of care Polymerase inhibitors (NUCs) and novel agents</td>
</tr>
</tbody>
</table>
ALN-HBV Targets a Highly Conserved Sequence in HBV X Orf

- Target site is conserved across genotypes A-J
  - Perfect homology (2-18): 97.2%
  - Allow 1 mismatch: 99.7%
- Site is upstream from integration hotspot
ALN-HBV Mediates Potent and Highly Durable HBsAg Knockdown in AAV-HBV Murine Model

- Up to $3.6 \log_{10}$ HBsAg reduction
- Single SC dose achieves $>2 \log_{10}$ HBsAg reduction lasting $>30$ days

Pre-dose HBsAg titer range ~10-500 ng/mL
ALN-HBV Target Product Profile

Functional Cure of CHB

ALN-HBV, by suppressing the production of tolerogenic HBV antigens, promotes the emergence of effective host immunity to HBV, with potential to achieve long-term functional cure.

<table>
<thead>
<tr>
<th>ALN-HBV</th>
<th>Target Product Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>• Chronic hepatitis B (CHB) treatment – enable functional cures</td>
</tr>
<tr>
<td>Dose and Regimen</td>
<td>• 100-200 mg fixed dose monthly</td>
</tr>
<tr>
<td></td>
<td>• 12-24 months in combination standard of care</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>• Subcutaneous injection, 1-2 mL injection volume, self-administration</td>
</tr>
<tr>
<td>Efficacy</td>
<td>• Long-term treatment-free suppression of HBV DNA</td>
</tr>
<tr>
<td>POM/POC Endpoints</td>
<td>• Proof-of-mechanism (1o endpoint)</td>
</tr>
<tr>
<td></td>
<td>• &gt;2 log_{10} nadir in serum HBsAg (or ≤100 IU/mL)</td>
</tr>
<tr>
<td></td>
<td>• Clinical proof-of-concept: 6 months post-treatment suppression of HBV DNA</td>
</tr>
<tr>
<td>Safety</td>
<td>• &lt;1% incidence of drug discontinuation due to ALN-HBV related AEs</td>
</tr>
<tr>
<td></td>
<td>• Well-tolerated, including in combination with immune-modulator therapy</td>
</tr>
</tbody>
</table>
ALN-HBV Phase 1/2 Study

**Primary objectives**
Safety, tolerability

**Secondary objectives**
PK & antiviral activity (sAg, eAg, HBV DNA)

**Part A: Single-Ascending Doses in HV (SAD)** |
| 0.1 mg/kg dose |
| 0.3 mg/kg dose |
| 1.0 mg/kg dose |
| 3.0 mg/kg dose |
| 2 Optional cohorts |

Part A initiated July 2016

**Part B: Single-Ascending Doses in Pts on NUC tx for >12 months (SAD)** |
| 0.1 mg/kg as starting dose |
| 0.3 mg/kg dose |
| 1.0 mg/kg dose |
| 3.0 mg/kg dose |
| 3 Optional cohorts |

**Part C: Multiple-Ascending Dose (MAD) in Pts on NUC tx for >12 months** |
| Starting dose TBD, Q4W*4 doses |

Randomized 3:1, 4-6 cohorts, N=16-24

Randomized 3:1, 4-7 cohorts, N=16-28

Randomized 6:2, 3-6 cohorts, N=24-48

[clinicaltrials.gov](https://clinicaltrials.gov) _NCT02826018_
# RNA Therapeutic Strategies for HBV

## Competitive Landscape

<table>
<thead>
<tr>
<th></th>
<th>ALN-HBV</th>
<th>ARC-520</th>
<th>ARC-521</th>
<th>ABUS-1467</th>
<th>IONIS-HBV-LRx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potency in Humans (mean sAg ↓)</strong></td>
<td>TBD</td>
<td>0.3-0.4 log in eAg + ETV-Rx eAg +/- pt 1 log in Rx naïve eAg+ pt at 4 mg/kg</td>
<td>Undisclosed</td>
<td>0.2-0.3 &amp; 0.6 log in eAg- pt at 0.2 mg/kg SD &amp; MD</td>
<td>Undisclosed</td>
</tr>
<tr>
<td><strong>Phase</strong></td>
<td>Phase 1/2</td>
<td>Phase 2</td>
<td>Phase 1</td>
<td>Phase 1/2</td>
<td>Phase 2</td>
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<tr>
<td><strong># of Target Sequences</strong></td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
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<tr>
<td><strong>Orf Targeted</strong></td>
<td>X</td>
<td>X</td>
<td>X and S</td>
<td>X and S</td>
<td>X</td>
</tr>
<tr>
<td><strong>Delivery</strong></td>
<td>GalNAc-siRNA (ESC)</td>
<td>Cholesterol siRNA plus GalNAc-Mellitin-Like Peptide (MLP)</td>
<td>Lipid Nanoparticle</td>
<td>GalNAc-ASO</td>
<td></td>
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<tr>
<td><strong>Administration</strong></td>
<td>SC injection</td>
<td>IV infusion</td>
<td>IV infusion</td>
<td>SC injection</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-medication</strong></td>
<td>None</td>
<td>Oral Antihistamine</td>
<td></td>
<td>Steroids</td>
<td>None</td>
</tr>
</tbody>
</table>

Source: ARWR, ABUS and Ionis company websites
Chronic Hepatitis D Virus (CHD) Infection

Chronic HBV/HDV infection is more aggressive than CHB
No therapies available

- HDV is RNA sub-virus, which can only propagate in presence of HBV
- 15-20M patients infected WW, 80K in US
- Acquired at same time or subsequent to HBV infection
- No curative therapies available

Target Product Profile for ALN-HBV in HDV

- **HDV Suppression**
  - Chronic, on-going therapy to inhibit HBsAg production thereby suppressing HDV replication and HDV viremia

- **HDV Cure**
  - Finite treatment resulting in functional CHB cure thereby resulting in CHD cure

Potential for CHB functional cures & CHD chronic treatment

• Potent and durable silencing of all HBV gene products
  ◦ Elicit multiple synergistic antiviral mechanisms in both CHB and CHD

• Pan-genotypic, conserved site
  ◦ Combination with NUCs increases barrier for development of resistance

• Tolerability profile supporting combination with immune therapies

• Improved compliance expected due to convenience of infrequent subcutaneous dosing

• Expected efficacy across CHB patient segments, including young immune tolerant and patients outside treatment guidelines

• Rapid physician/patient acceptance of novel treatment paradigm

• Room temperature stability simplifies global distribution
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Q&A Session
Hepatitis (Delta): An Underestimated Liver Disease!

Heiner Wedemeyer

Hannover Medical School

Germany
Disclosures

Honoraria for consulting or speaking (last 5 years):
Abbott, AbbVie, Biolex, BMS, Boehringer Ingelheim, Eiger, Gilead, ITS, JJ/Janssen-Cilag, Medgenics, Merck/Schering-Plough, MyrGmbH, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, ViiV

Research grants:
Abbott, Abbvie, BMS, Gilead, Merck, Novartis, Roche, Roche Diagnostics, Siemens
The Hepatitis Delta Virus

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

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

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

- Acute HBV
- Acute HDV

95% recovery
More frequent fulminant

HDV Super-Infection

- Acute HDV
- Chronic Hepatitis B

90% chronic
More severe disease
High anti-HDV prevalence in HBsAg-positive HIV-infected individuals

Fernandet-Montero, Sorriano et al., CID 2014

HDV coinfection associated with increased liver-related morbidity and mortality (HR7.5) in HIV-infected persons

Overall prevalence: 14.5%!
Only a small number of HBsAg positive patients is tested for anti-HDV

... e.g. only 8.5% of HBsAg-positive patients were tested for anti-HDV in a USA–VA cohort

Kushner et al. J Hepatol Sept. 2015
Hepatitis delta takes a more severe long-term course than HBV monoinfection.
Hepatitis delta: evolution of clinical presentation

- young patients
  - locally acquired
  - special risk groups (IVDU)

- older patients
  - Immigrant populations
  - special risk groups

Severe
Acute + Chronic Disease

Mild chronic Disease

Severe chronic Disease

High frequency of liver-related morbidity

- Romeo, Colombo: Gastroenterology 2009+PlosOne 2014
- Calle-Serrano, Wedemeyer JVH 2014
- Niro, Rizzetto: Journal of Hepatology 2010
- Buti, Esteban: JVH2010

1980 1990 2000 2010
Different HDV genotypes are associated with different clinical outcomes

Su et al, Gastroenterology 2006
### HDV genotype 3 infection: Particular Severe Courses

#### Table 3. Advanced fibrosis and associated variables of 64 patients with chronic HDV/HBV co-infection included in the study assessed by multiple logistic regression.

<table>
<thead>
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<th>Variable</th>
<th>N</th>
<th>Advanced fibrosis</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
<th>OR*</th>
<th>95% CI*</th>
<th>p value</th>
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<td>Total</td>
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<td>32</td>
<td>1.53</td>
<td>0.53-4.38</td>
<td>0.42</td>
<td>4.05</td>
<td>1.13-14.50</td>
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<tr>
<td>M</td>
<td>43</td>
<td>23</td>
<td>2.82</td>
<td>1.01-7.87</td>
<td>0.04</td>
<td>4.05</td>
<td>1.13-14.50</td>
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<td>F</td>
<td>21</td>
<td>9</td>
<td>3.73</td>
<td>1.31-10.61</td>
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<td>&gt;25</td>
<td>28</td>
<td>18</td>
<td>2.23</td>
<td>0.50-9.83</td>
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<td>Y</td>
<td>36</td>
<td>23</td>
<td>5.00</td>
<td>1.70-14.6</td>
<td>0.003</td>
<td>6.47</td>
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<td>N</td>
<td>28</td>
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<td>HBV viral load</td>
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<td>≥2 log</td>
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<td>&lt;2 log</td>
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</table>
Identification of patients with a higher risk for disease progression
Presence of anti-HDV IgM is associated with the development of clinical events

Cumulative event free survival

Time (years)

Survival

IgM status
- negative
- medium
- high
- positive
Survival according to the BEA-score

Event free survival: Hannover

Percent survival:

Time (years)

Patients at risk:

BEA-A 19
BEA-B 27
BEA-C 7

BEA-A (ref.)

BEA-B (HR=9.01, CI=1.17-69.34)

BEA-C (HR=25.27, CI=3.02-211.11)

p=0.0004
Survival according to the BEA-score

Barcelona: n=77

- BEA-A (ref.)
- BEA-B (HR=31.79; CI=4.1-249.4)
- BEA-C (HR=278.79 CI=29.5-2829.6)

Düsseldorf: n=58

- BEA-A (ref.)
- BEA-B (HR=6.08 CI=1.3-27.8)
- BEA-C (HR=90.77 CI=6.0-90.8)

M. Homs, M. Buti et al.

A. Erhardt et al.
Treatment of Hepatitis Delta
The Hepatitis Deltas Virus: No viral enzyme → no direct acting antiviral

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

- HDAC particles contain HDV-RNA:
  - The smallest of all animal viruses
  - Highly paired – rod like structure
  - No enzymes but Ribozymes

- 2 forms: S-HDAg and L-HDAg
- S-HDAg: ↑ replication
- L-HDAg: ↑ assembly (↓ replication)
Treatment of Hepatitis Delta with PEG-IFNa-2a: ~25% Sustained HDV RNA clearance

Figure 1. Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.
PEG-IFNa-2a – Adefovir combination resulted in a more pronounced HBsAg suppression.
... and combination with tenofovir?
The Hep-Net-International Delta-Hepatitis Intervention Trial 2: HIDIT-2

96 weeks 5 years FU

PEG-Interferon alpha-2a 180µg oiw + Placebo

Follow-up

N=61

PEG-Interferon alpha-2a 180µg oiw + Tenofovir disoproxilfumarat 245mg daily

Follow-up

N=59

Primary efficacy endpoint: HDV RNA negativity Week 96

Stratification:
Country
Previous therapy
Gender

Heiner Wedemeyer: 10-2016
Hepatitis Delta
HDV RNA response until week 120 (Intent-to-treat analysis)

% of patients HDV RNA negative

PEG-IFNa-2a + Tenofovir
PEG-IFNa-2a + Placebo

Relapse 11/25 (44%)
Relapse 8/20 (40%)

HDV RNA Clearance after Therapy

Neg post Tx 1 patient
Neg post Tx 3 patients

Week 96

Treatment
FU

Baseline W12 W24 W48 Week 96

Week 120 24 w post Tx

p=0.10

p=0.34
**HBsAg response until week 120**

(Intent-to-treat analysis)

% of patients with HBsAg-decline >0.5 Log10IU/ml

- HBsAg loss: 4/59 patients (6.7%)
- HBsAg loss: 3/61 patients (4.9%)

**Mean HBsAg levels**

PEG-IFNa-2a + Tenofovir
PEG-IFNa-2a + Placebo

**Mean HBsAg levels**

Baseline Week 12 Week 24 Week 48 Week 72 Week 96 Week 120
Long-term-Follow-up after IFN therapy
Late HDV RNA relapses after initial response!

Long Term Virological Response

Late Relapse

Therapy

Therapy

Timepoints during HIDIT 1

Timepoints during HIDIT 1

Heiner Wedemeyer: 10-2016
Hepatitis Delta

Heidrich et al., Hepatology 2014
Clinical effects of antiviral therapy
Improved long-term outcome of hepatitis delta with high dose of IFNα
Improved outcome of hepatitis delta in IFNa-treated patients

All patients

Patients with platelets >90000/µl only

Log rank: p<0.01

Log rank: p=0.04
HDV Patients experiencing an HBsAg loss had a better clinical long-term outcome
Current Management of Hepatitis Delta

- Patients with a very mild course can be identified possibly not requiring immediate treatment
- PEG-IFNa remains the only effective treatment option against HDV—however, long-term follow-up is required
  - my recommendation: Treat Bea-B patients
- Treat HBV according to hepatitis B guidelines
Patients experiencing an **HDV RNA loss** have a better clinical long-term outcome.
Current Management of Hepatitis Delta

- Patients with a very mild course can be identified *(possibly not requiring immediate treatment)*
  - Clinical markers: Calle Serrano J Viral Hepatitis 2014
  - Anti-HDV IgM Levels: Wranke et al., PlosOne 2014
  - NK cell responses: Lunemann et al., GUT 2015

- PEG-IFNa remains the only effective treatment option against HDV
  - stopping rules week 24: Keskin et al., CGH 2015
  - however, long-term follow-up is required
  - my recommendation: Treat Bea-B patients

- Treat HBV according to hepatitis B guidelines
Relapse after PEG-IFNa2a

Currently treated with tenofovir (Sorriano et al.)

Any novel clinical trials?

♀ 42 years, born in Russia
HBsAg positive
(known since >10 years)
ALT 64 U/l; AST 52 U/l
HBV DNA 79 IU/ml
Anti-HDV positive
HDV RNA 7.6 x10^6 cop/ml
Histology: Liver cirrhosis
Platelet count 93.000/µl
INR 1.2; bilirubin normal
HDV Replication

1. Hepatocyte membrane receptor
2. Ribonucleoprotein
3. Nucleus
4. Genomic RNA
5. mRNA
6. Antigenomic RNA
7. Endoplasmic reticulum
8. Golgi complex
9. Delta virion

S-HDAg, L-HDAg, M-HBsAg, L-HBsAg

Heiner Wedemeyer: 10-2016
Hepatitis Delta
Hughes, Wedemeyer, Harrison Lancet 2011
Entry Inhibitor „Myrcludex“

Heiner Wedemeyer: 10-2016
Hepatitis Delta
Hughes, Wedemeyer, Harrison Lancet 2011
Prenylation inhibition
Blocks virion assembly and packing of viral particles
Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial

Christopher Koh*, Laetitia Canini, Harel Dahari, Xiongce Zhao, Susan L Uprichard, Vanessa Haynes-Williams, Mark A Winters, Gitanjali Subramanya, Stewart L Cooper, Peter Pinto, Erin F Wolff, Rachel Bishop, Ma Ai Thanda Han, Scott J Cotler, David E Kleiner, Onur Keskin, Ramazan Idilman, Cihan Yurdaydin, Jeffrey S Glenn*, Theo Heller*
Blocking of subviral particle formation
Summary

- PEG-IFNa is currently the only treatment option for HDV infection
- HBV entry inhibition, prenylation inhibition and block of particle formation are currently explored in clinical trials but have all limitations
- Novel strategies to achieve HBsAg clearance need to be explored in hepatitis delta!

Cure of HBV = Cure of HBV/HDV
And... if you want to be more involved in hepatitis delta:
Agenda

Welcome
• Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Introduction
• Pushkal Garg, M.D., Senior Vice President, Clinical Development

ALN-HBV Program
• Laura Sepp-Lorenzino, Ph.D., Vice President, Entrepreneur-in-Residence

Overview of Chronic Hepatitis D Virus (HDV) Infection
• Heiner Wedemeyer, M.D., Managing Senior Physician and Assistant Professor in the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School

Q&A Session
Thank you

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