Clinical progress of the Entry Inhibitor Myrcludex B

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Myrcludex B specifically binds to sodium taurocholate co-transporting polypeptide (NTCP) at the basolateral membrane of differentiated hepatocytes. *(Ni et al., Gastroenterology 2014)*

Myrcludex B shows strong inhibitory potential for HBV and HDV infection (IC$_{50}$ ca. 80 pM in PHH). *(Schulze et al., J. Virology 2010)*

Myrcludex B exclusively targets parenchymal liver cells. *(Schieck et al., Hepatology 2013)*

- Myrcludex B has been dosed to 272 hepatitis B and D patients and healthy subjects.
- Myrcludex B induced HDV RNA declines in hepatitis delta patients in the MYR201 trial. *(Bogomolov et al., J of Hepatology 2016)*
Key questions related to the clinical efficacy of entry inhibitors

1. Does persistence of HDV/HBV episomes in a chronically infected liver depend on de novo entry via NTCP?
2. Can HDV RNA be propagated through mitosis of hepatocytes?
3. Can HBV cccDNA be propagated through mitosis of hepatocytes?
4. What are the turnover rates of HBV- and HDV-infected hepatocytes (are there differences to naïve cells)?

External amplification
Internal amplification
Blocked by entry inhibitors

HSPG: heparan sulfate proteoglycan
NTCP: Na^+ taurocholate co-transporting polypeptide
NC: HBV nucleocapsid
RNP: HDV ribonucleoprotein complex
cccDNA: HBV covalently closed circular DNA
circRNA: HDV circular single stranded RNA

Giersch et al., Gut, 2017, Ni et al., unpublished
Allweiss et al., Gut, 2017, Ni et al., HBV meeting 2012

Yes
Yes
No
?

HBV Cure Workshop, Toronto, Nov. 7th 2018
Proof of Concept: The Myrcludex B 202 Study in HDV/HBV co-infected patients

- 120 HBeAg-neg. patients were randomized into 4 treatment arms - 30 patients per arm
- Patients were pretreated with tenofovir for at least 12 weeks
- Myrcludex B was self administered once daily s.c.
- All patients received tenofovir (oral qd) during the entire study period

[Diagram showing the study protocol]

Wedemeyer et al., ILC, 2018, Paris, GS-005
Myr-202 Study Safety Summary

• No SAEs related to myrcludex B during treatment period
• No discontinuations because of AEs related to myrcludex B
• Other AEs related to myrcludex B were mostly mild and moderate, resolved without sequelae or intervention, no dose dependency
• Very low frequency (<5%) of injection site reactions
• High patient adherence to treatment
• Bile acids asymptotically increased in myrcludex B treated patients
  → no worsening of liver function
  → no jaundice
Biochemistry: ALT Levels

1. Dose independent normalization of ALT-levels under Myrcludex B treatment in all arms
2. No ALT normalization in TDF treated patients
3. Re-elevation of ALT levels after Myrcludex B withdrawal

MyrB 2mg vs TDF * p=0.0013; MyrB 5mg vs TDF ** p=0.0002
MyrB 10mg vs TDF ** p=0.0023
Virology: Median HDV Serum RNA responses

Median RNA log_{10} change to BL:
- MyrB 2mg: -1.75
- MyrB 5mg: -1.60
- MyrB 10mg: -2.70
- TDF: -0.18
Individual virological responses (10 mg Myrcludex B)

- All patients in the 10 mg arm responded to Myrcludex B treatment
- No-break through under therapy
- No resistance against Myrcludex B until week 24
- Rebound after drug withdrawal at week 24

Schöneweis et al., ILC, 2018, Paris, SAT-369
HDV serum RNA elimination kinetics

HDV serum RNA-decline follows zero order elimination kinetics (as expected for an entry inhibitor).

Individual differences in elimination rates observed

Treatment extension predicts virus elimination

<table>
<thead>
<tr>
<th>Time under Myrcludex Treatment*</th>
<th>Percentage of Patients with HDV Load = 0</th>
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<tbody>
<tr>
<td>2 Years</td>
<td>&gt; 60%</td>
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<tr>
<td>3 Years</td>
<td>&gt; 87%</td>
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*calculation based on Snoeck E, et al., Clin Pharmacol Ther. 2010
Elimination of HDV infected hepatocytes

Intrahepatic HDV RNA decline:

- 0.78 log IU/ml in 2 mg (n=7)
- 1.07 log IU/ml in 5 mg (n=5)
- 1.34 log IU/ml in 10 mg (n=7)
- 0.30 log IU/ml in TDF (n=3)

⇒ Myrcludex B monotherapy induces elimination of HDV hepatocytes!
No effect of Myrcludex B monotherapy on HBsAg

Consistent with the assumption that HDV preferentially replicates in cells with HBs-encoding integrates
Can combination with IFN-α accelerate elimination of HBV/HDV infected hepatocytes?

Can Myrcludex B/IFN-a combination induce HBsAg clearance?

⇒ AASLD, Wedemeyer et al., presidential talk, Monday November 12th, 8.45 a.m.; Hepatology Vol 68, suppl 1, abstract 16.
The Myrcludex B pegIFN-α pilot study Myr-201

- Chronic HDV infected HBeAg-negative patients
- Active hepatitis: ALT increase or biopsy

- 24 patients: equally randomized 1:1:1
- Myrcludex B: 2mg/day, s.c.
- PEG-IFNα: 180µg/week (Pegasys ®, Roche)

Interim results reported in: Bogomolov et al., J. Hepatol., 2016
Synergistic effect of Myrcludex B and pegIFN-α on HDV serum RNA

⇒ RNA negativation in 5/7 at the end of combination (w 24)
⇒ HDV RNA incline after withdrawal of Myrcludex B during IFNα in 5/6 evaluable patients
Different fates of HBV cccDNA and HDV circRNA during mitosis

- **HDV-infected cell**
  - Survival of HDV RNA during cell mitosis
    - Giersch et al., Gut, 2017, Ni et al., unpublished

- **HBV-infected cell**
  - Loss of HBV cccDNA during cell mitosis
    - Allweiss et al., Gut, 2017, Ni et al., HBV meeting 2012

Possible mode of action of IFN-α on HDV replication
HDV is not sensitive to IFNs in infected hepatocytes

- HDV replicates in the presence of IFN.
- IFN treatment doesn’t abolish HDV replication.

Cell division-mediated HDV spread depends on innate immune competence

HuH7^{NTCP}
deficient for IFN activation

P0

1:200
split

HDAg, Nuclei

P1

Cell to cell spread of HDV by cell division is controlled in innate immune competent HepaRG cells

Knock out of MDA5, the sensor for HDV promotes uncontrolled HDV spread by cell division
IFN treatment suppresses HDV spread during cell division

IFN-α, IFN-β, and IFN-λ all suppress HDV cell to cell spread
Possible synergism of Myrcludex B and IFNα on HBsAg (Myr 201)

→ No significant HBsAg changes during 24w of MyrB monotherapy

→ 4/7 of patients (57%) experience HBsAg decline by $>1.5 \log_{10}$ upon switch to PEG-IFNα
The MYR-203 Study design

Interim results on HDV and HBV markers (HBsAg) will be presented at the AASLD

⇒ Myrcludex B is an important player for HBV cure in combination with IFN-α
Myrcludex B, the prototypic NTCP-specific entry inhibitor shows clinical efficacy in CHB & CHD

Virological responses reflect the loss of infected hepatocytes (shown for HDV, assumed for HBV)

Entry inhibition is an efficient way to block de novo HBV cccDNA and HDV RNA formation

Entry inhibition in chronically infected patients results in loss of HDV infected hepatocytes

Myrcludex B monotherapy has curative potential for HDV infected patients

Curative potential in combination with immune modulators

**Status/ ongoing activities**

• Myrcludex B received “orphan drug status” by the FDA and EMA
• Myrcludex B received prime eligibility status from EMA
• Myrcludex B received “breakthrough therapy designation” by the FDA
• Development of an oral formulation is in progress
• Phase III study is intended to starts early 2019
• Aiming at provisional approval for HBV/HDV co-infected patients in 2019
Thanks, Acknowledgments and Funding

- All patients participating in the trial.
- All trial physicians and study nurses.
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  - MYR GmbH (Bad Homburg, Germany)

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