New drugs for HDV infection

2020 13th Paris Hepatology Conference

International Conference on the Management of Liver Diseases

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Inserm · Assistance Publique Hôpitaux de Paris · anrs French National Agency for Research on AIDS and Viral Hepatitis, An autonomous agency at Inserm · Université Paris Diderot Paris 7 · CRI Centre de Recherche sur l'Inflammation · unity Addressing Unmet Needs through Innovation in hepatology and gastroenterology


FIFA WORLD CUP
FRANCE 98
adidas
12 Juillet 2008
10ème Anniversaire
10


adidas
adidas
adidas
15

Disclosures

- Employee of Paris Public University Hospitals (AP-HP, Beaujon's Hospital) and University of Paris.

- Principal investigator for research grants : Funds paid to Hospital (AP-HP)

- Consultant, expert and speaker for: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp Dohme, MYR Pharmaceuticals, Roche. Clinical Investigator: Abbvie,Gilead, Janssen, Merck Sharp Dohme, MYR Pharmaceuticals, Eiger pharmaceutical.

- Grants from : ANR, CNRS , INSERM , University of Paris, ANRS.

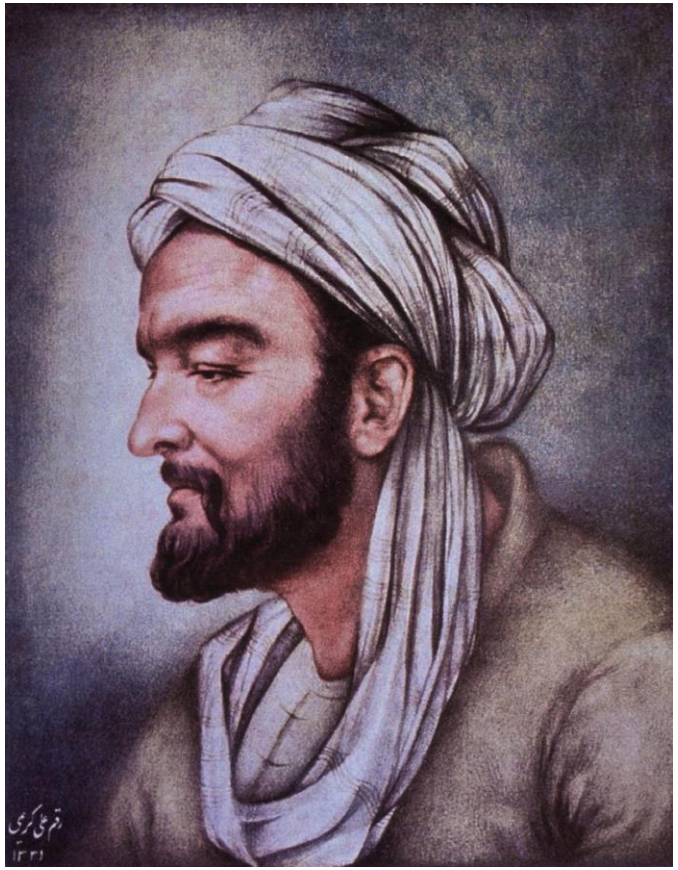
New drugs for HDV infection

1. **Introduction : HDV cure**
2. Entry inhibitor: Bulevirtide
3. Prenylation inhibitors: Lonafarnib
4. Take home messages

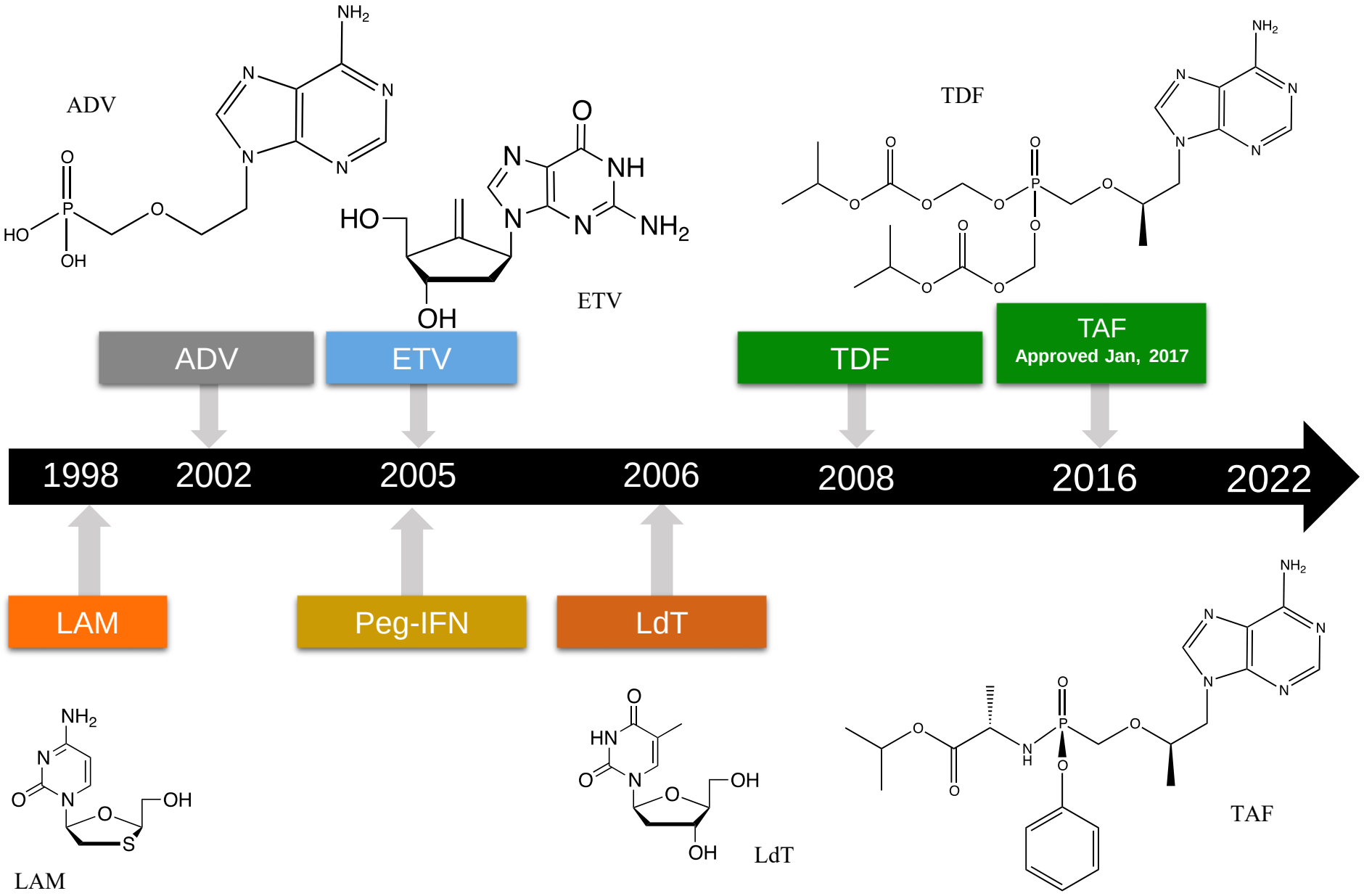
« There are no incurable diseases - only the lack of will.

There are no worthless drugs - only the lack of knowledge »

Ibn Sina / Avicenne (980-1037)



HBV CURE : Drug development



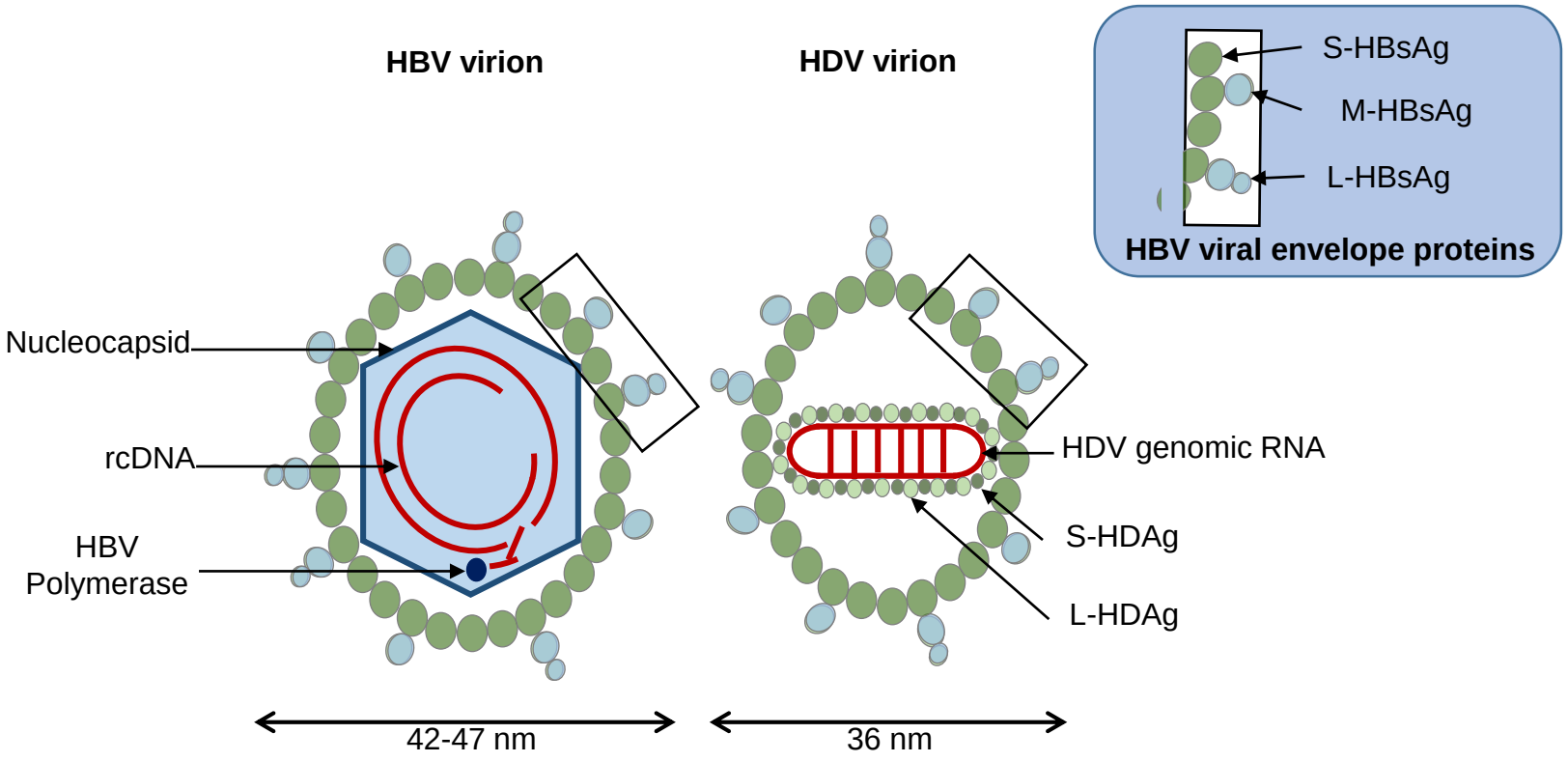
Asselah T. PHC 2020-1/20.

Schinazi RS, Ehteshami M, Bassit L, Asselah T. 2018 Liver International, 2018.

There is a need to cure HDV

- HDV might be under-estimated : > 60 millions (Miao et al. JID, 2019)
- Delta Hepatitis increase the risk of cirrhosis
- HDV requires only small amounts of HBsAg to complete viral packaging
- No available therapy except PEG-IFN
- We need an HDV Cure

Comparison of HBV and HDV viral structure



1. HDV : 36 nm (diameter)
2. Same viral envelope HBs
3. HDV genome (RNA)
4. HDV ribonucleocapsid

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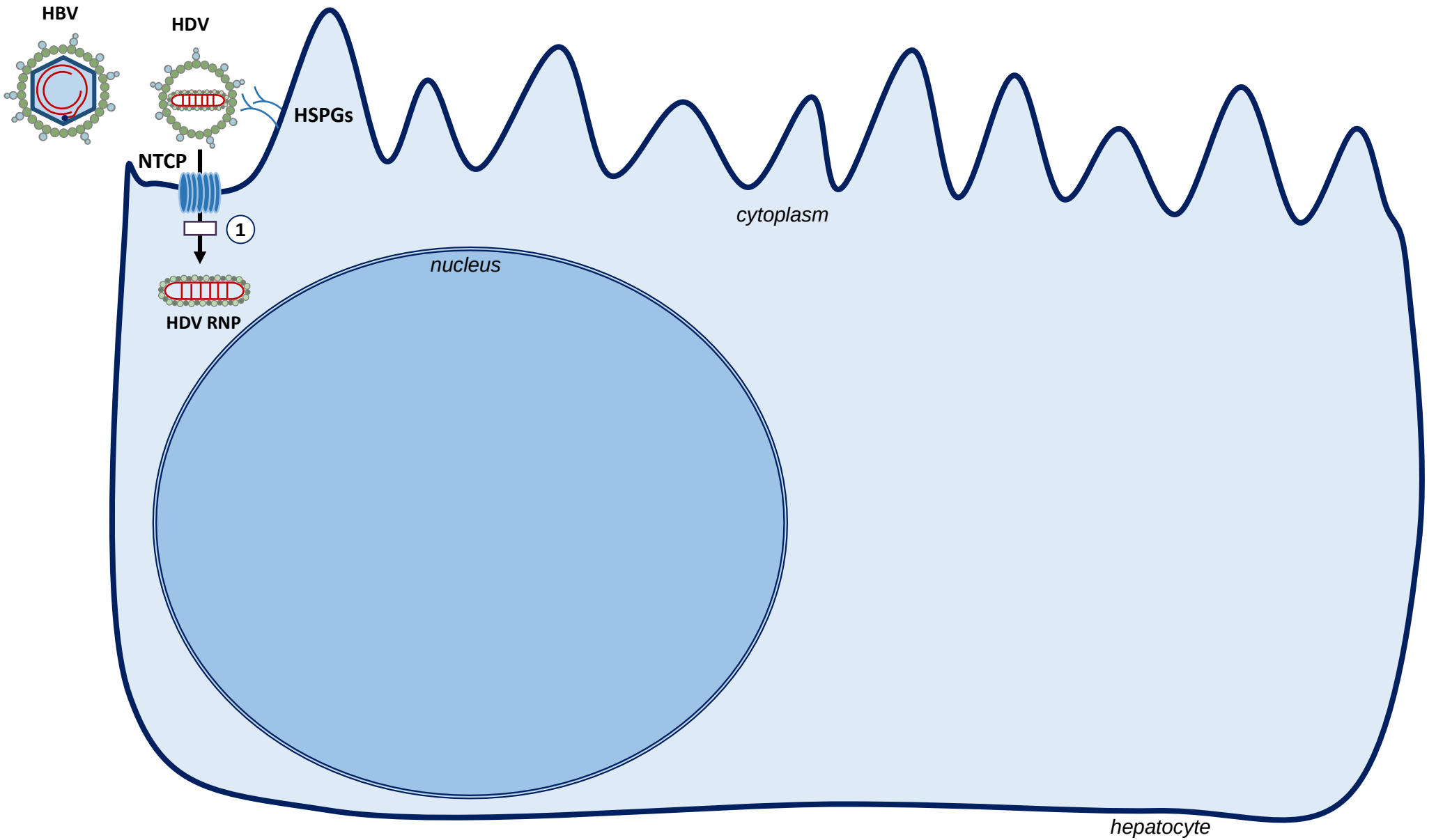
Asselah et al. Liver International, in press, 2020.

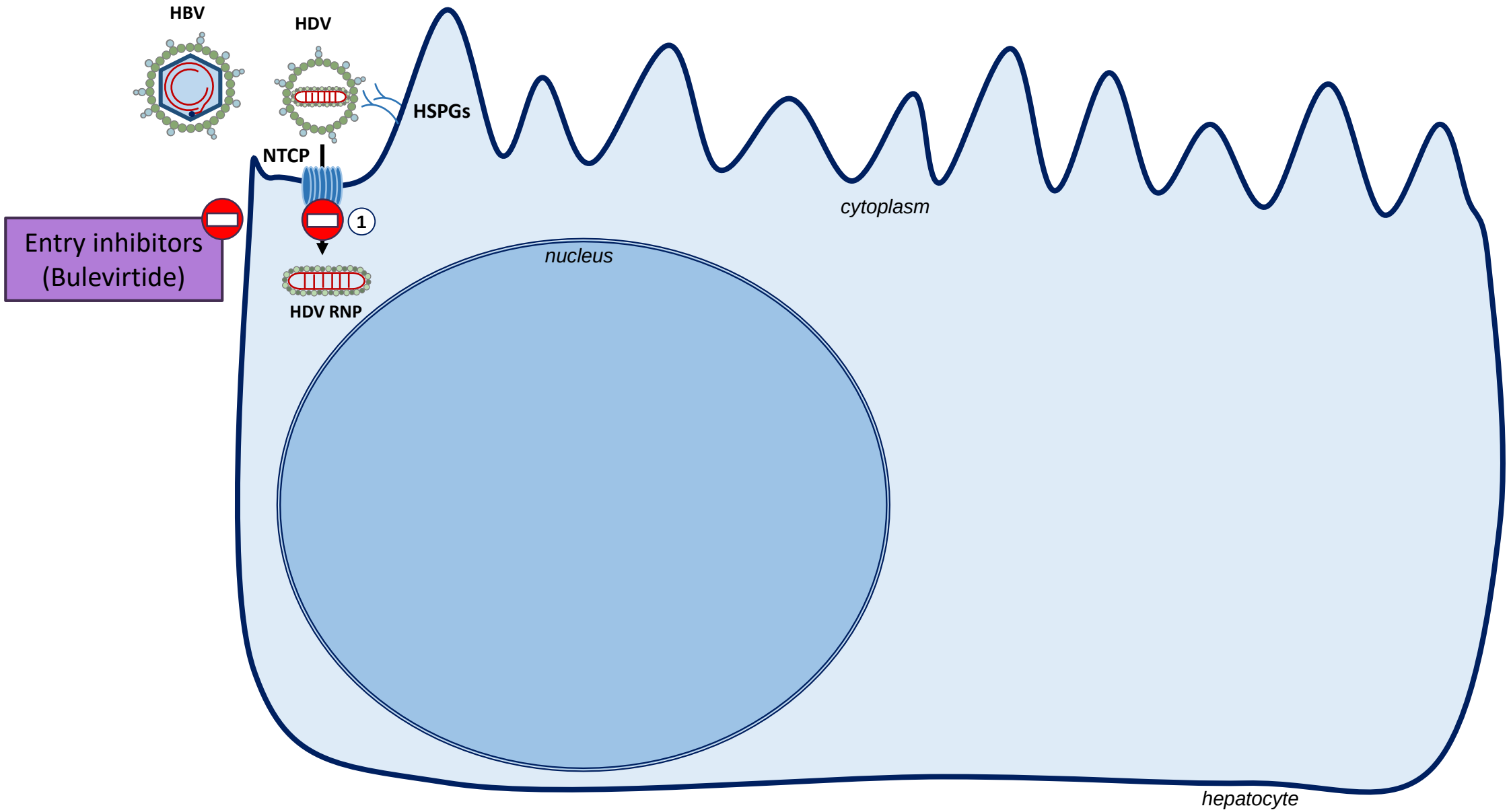
Lifecycle of HDV and targets for new drugs in development.

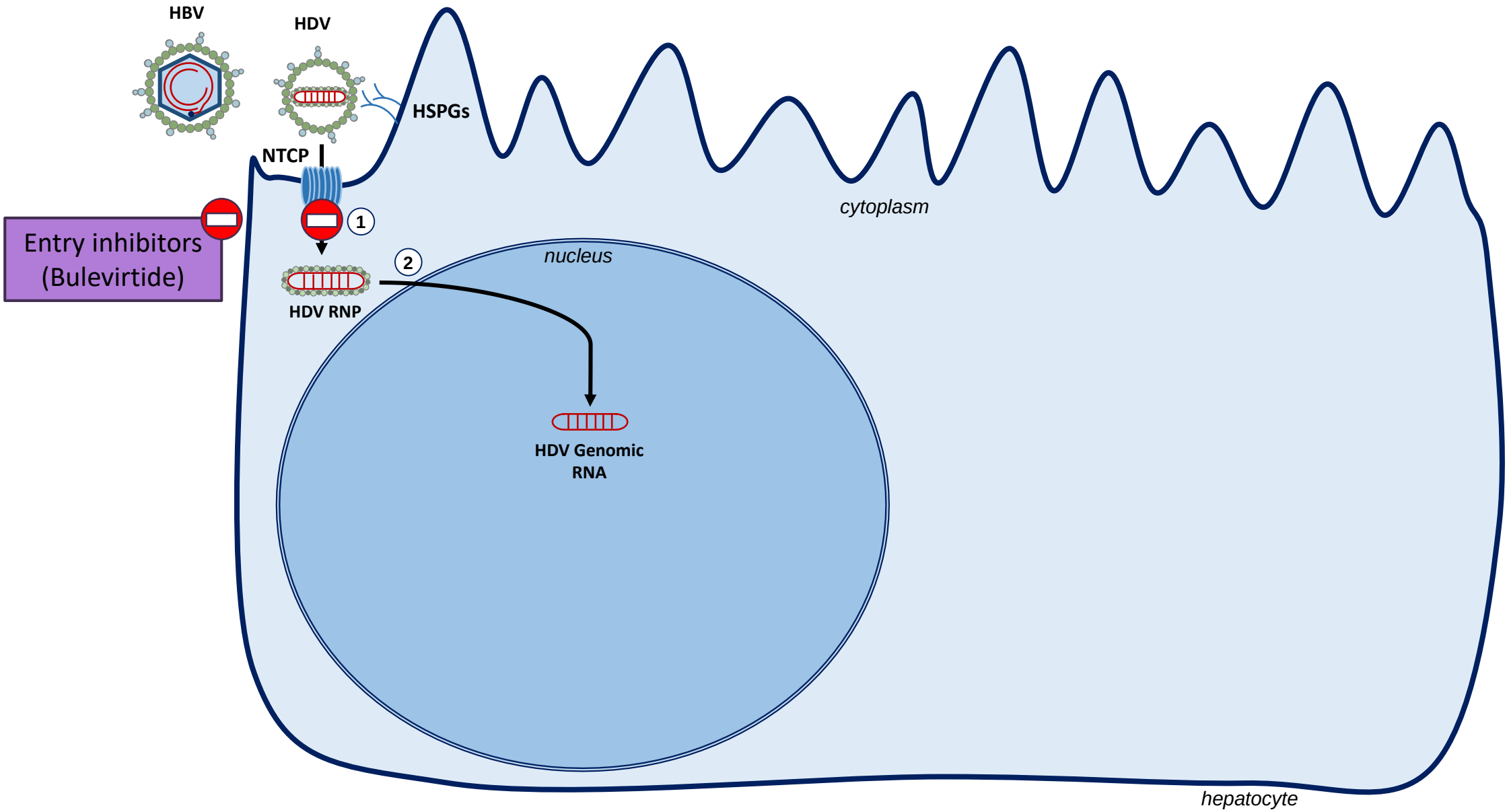


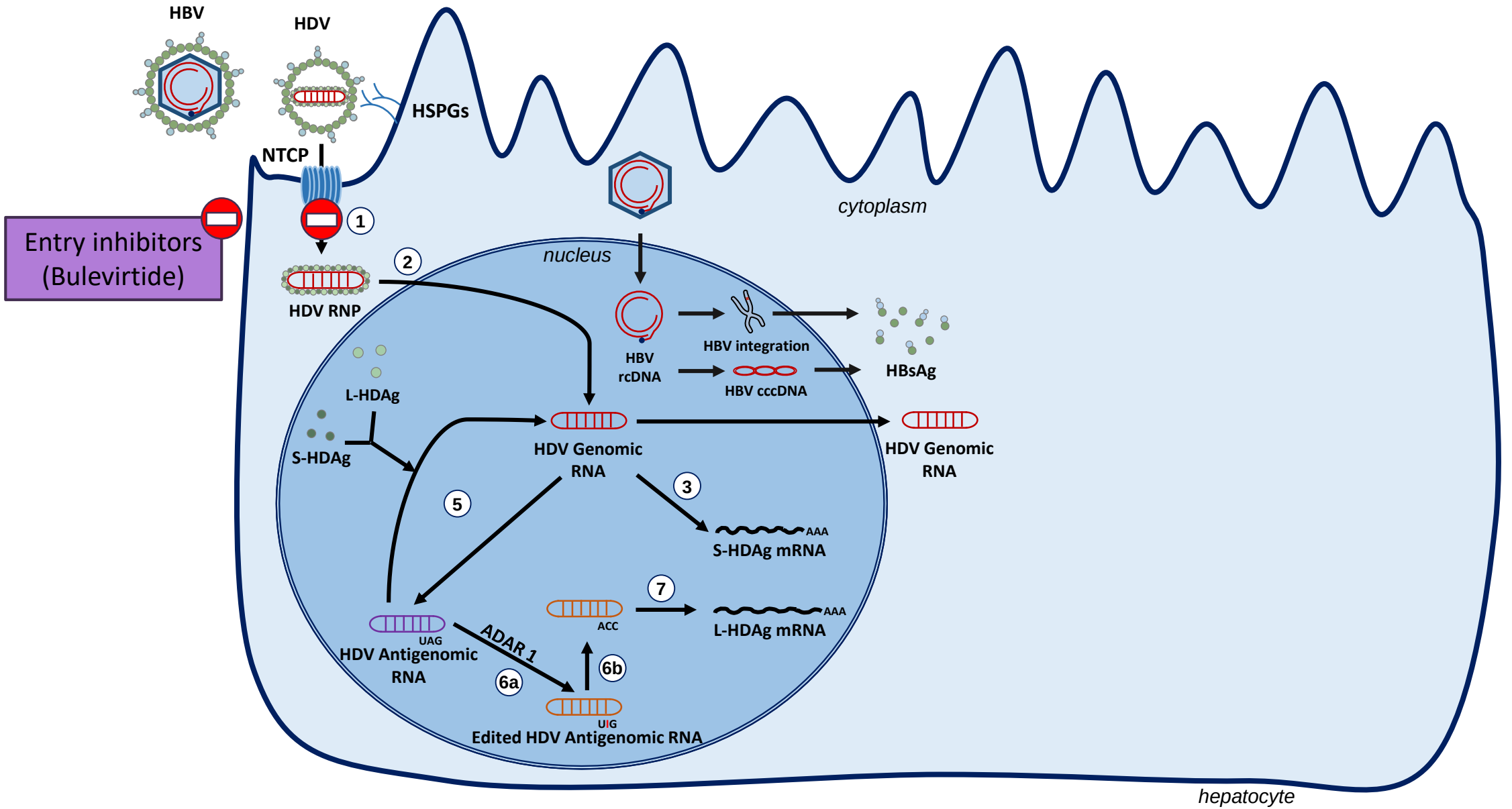
Asselah T. PHC 2020-4/20.

Asselah et al. Liver International, in press, 2020.

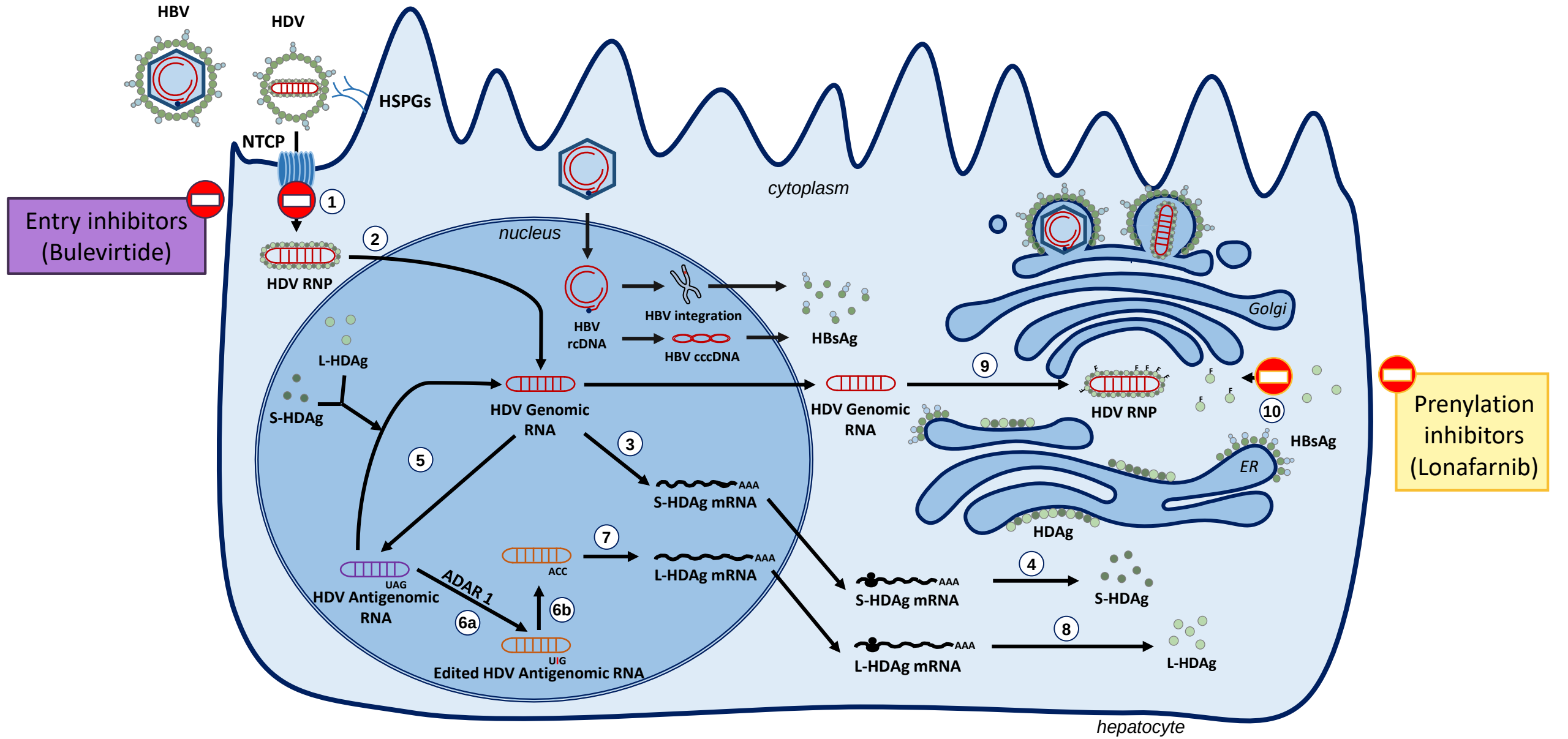
Bulevirtide is an entry inhibitor (binds to NTCP)

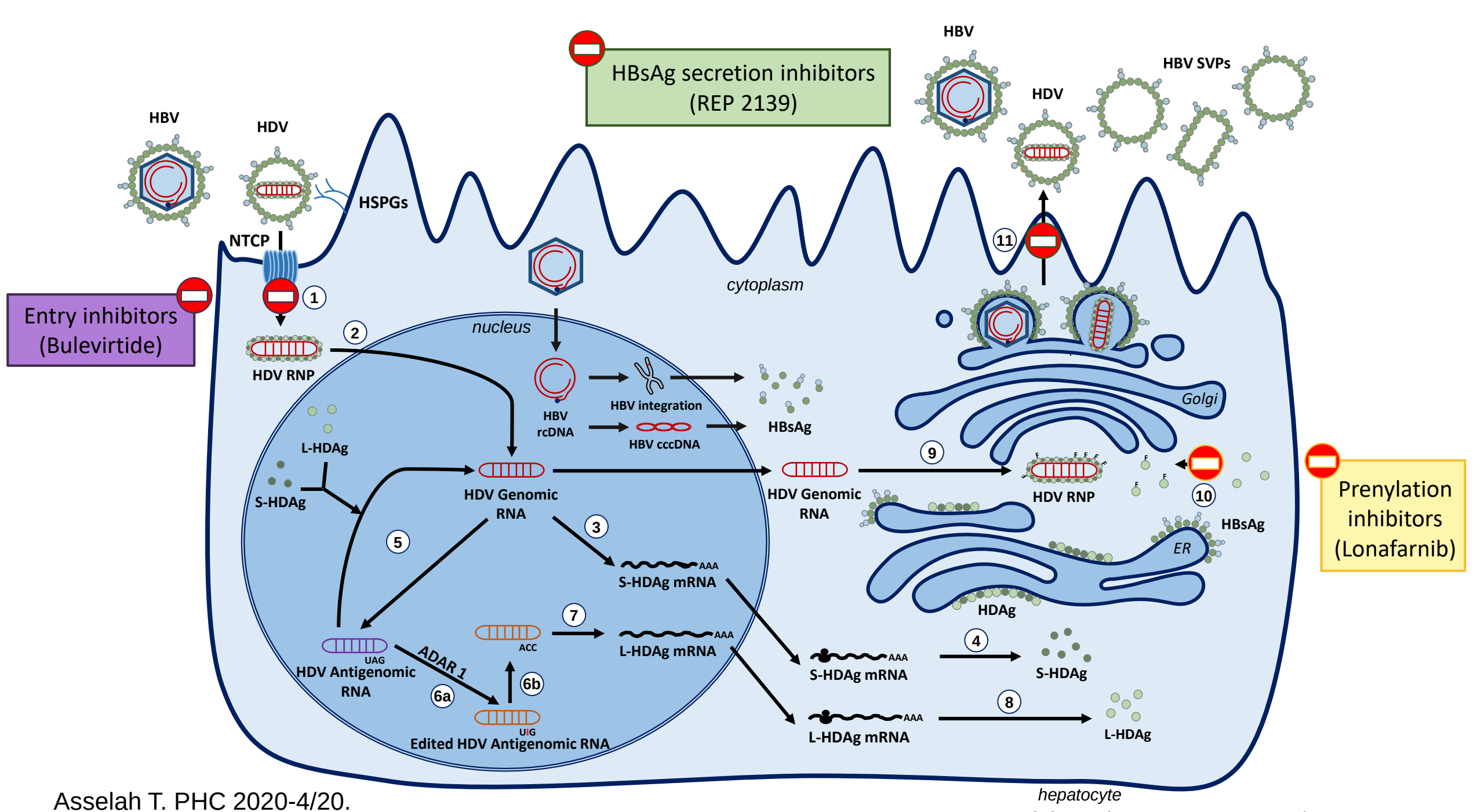



HBV
HDV
HSPGs
NTCP
Entry inhibitors
(Bulevirtide)
1
2
HDV RNP
nucleus
HDV Genomic
RNA
cytoplasm
hepatocyte


HBV
HDV
HSPGs
NTCP
Entry inhibitors
(Bulevirtide)
1
cytoplasm
nucleus
2
HDV RNP
HBV integration
HBV
rcDNA
HBV cccDNA
HBsAg
L-HDAg
S-HDAg
HDV Genomic
RNA
HDV Genomic
RNA
5
3
AAA
S-HDAg mRNA
7
ACC
AAA
L-HDAg mRNA
UAG
HDV Antigenomic
RNA
ADAR 1
6a
6b
UIG
Edited HDV Antigenomic RNA
hepatocyte

Lonafarnib inhibits HDV prenylation (packaging and secretion)





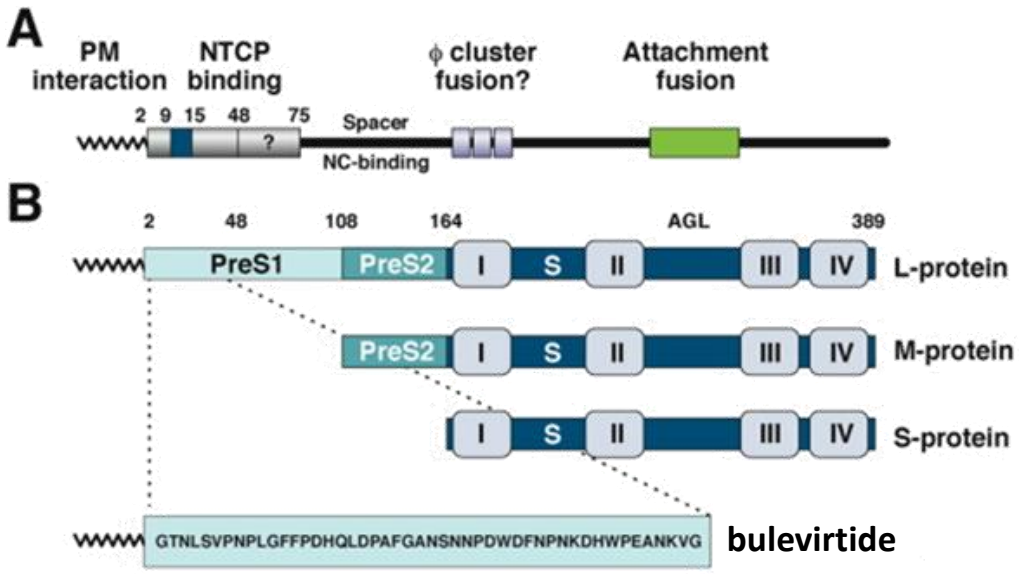
Asselah T. PHC 2020-4/20.

Asselah et al. Liver International, in press, 2020.

New drugs for HDV infection

1. Introduction : HDV cure
2. **Entry inhibitor: Bulevirtide**
3. Prenylation inhibitors: Lonafarnib
4. Take home messages

Bulevirtide Overview (Myrcludex B)



Urban et al., Gastroenterology 2014;147:48-64

- **Specifically binds to sodium taurocholate co-transporting polypeptide (NTCP)** at the basolateral membrane of differentiated hepatocytes *(Ni et al., Gastroenterology. 2014;146:1070-1083; Urban et al., Gastroenterology. 2014;147:48-64)*
- **Strong inhibitory effect for HBV/HDV infection** (IC_{50} ca 80 pM in PHH) **(Schulze et al., J. Virology. 2010;84:1989-2000)**
- Exclusively **targets parenchymal liver cells** **(Meier et al., Hepatology. 2013;58:31-42)**

Bulevirtide Overview (Myrcludex B)

- Has been **dosed to > 600** hepatitis B and D patients and healthy subjects
- Bulevirtide monotherapy induced HDV RNA declines and improved ALT levels in hepatitis D patients in the MYR202 trial (24 weeks of treatment) ***(Wedemeyer et al., EASL 2018)***
- Combination of 2mg or 5mg bulevirtide with PEG-IFNα induced synergistic effects ***(Wedemeyer et al., EASL 2019)***
- Designations: US & EU Orphan, FDA Breakthrough

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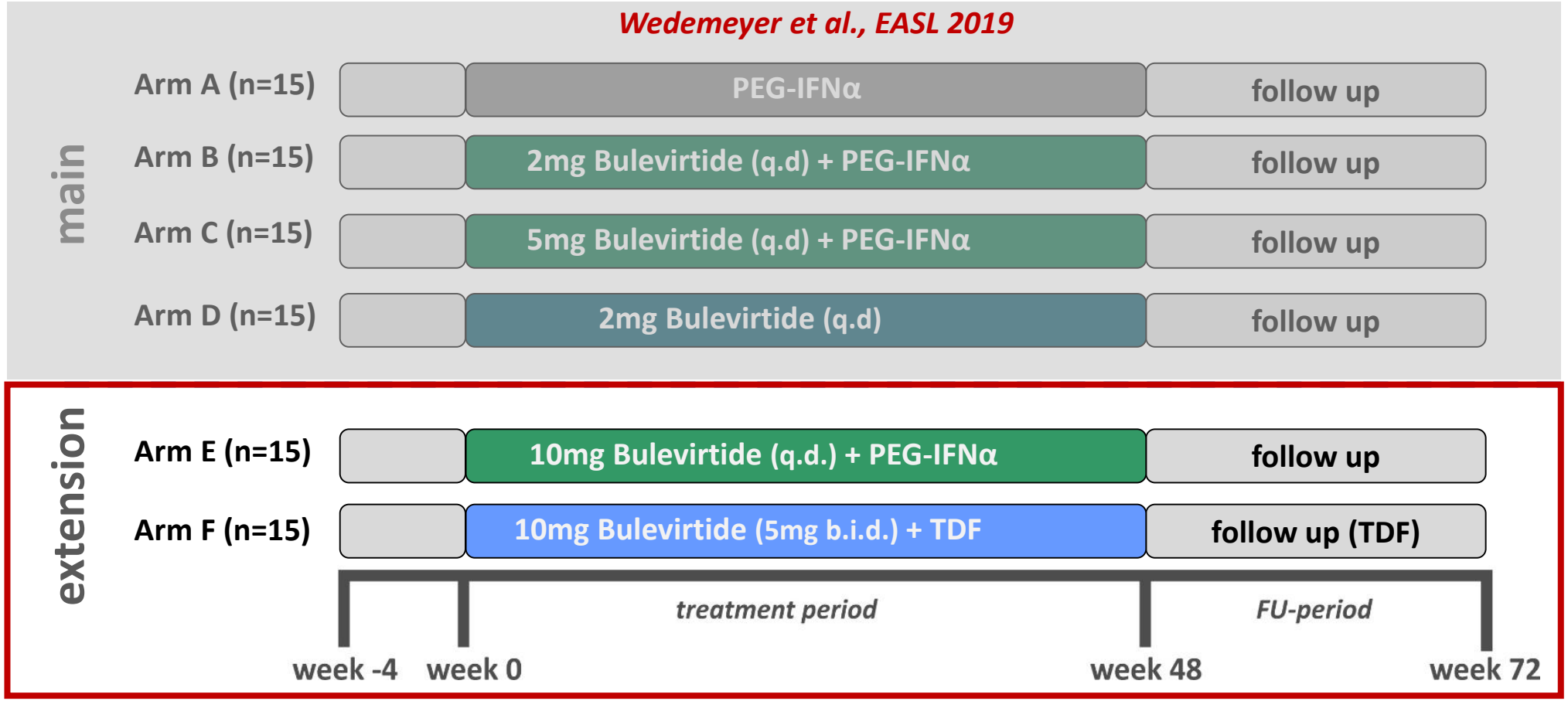
MYR203 extension Study Design

- Bulevirtide was self administered by patients once daily s.c.



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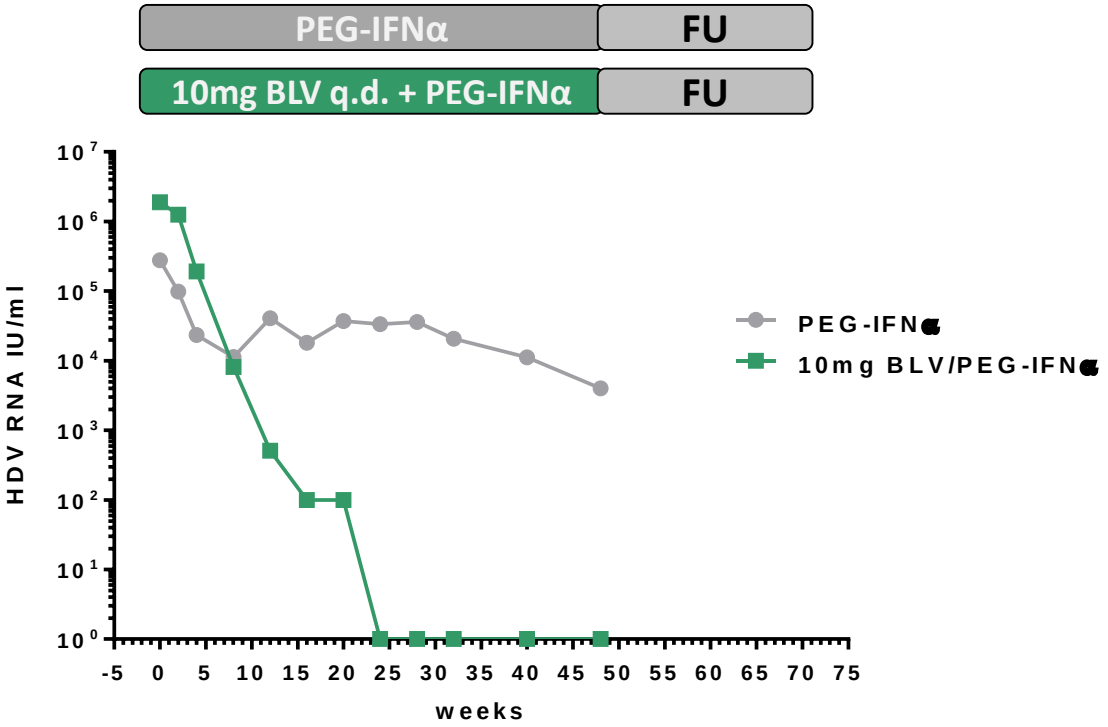
Wedemeyer et al., AASLD 2019

Virological Response (Median HDV RNA)



Virological respons: week 48	Median HDV RNA reduction [log]	undetectable HDV RNA
PEG-IFNα	-1.29	13.3%
2mg BLV + PEG-IFNα	**-5.21**	**80.0%**
5mg BLV + PEG-IFNα	**-6.13**	**86.7%**
10mg BLV + PEG-IFNα	**-6.09**	**86.7%**

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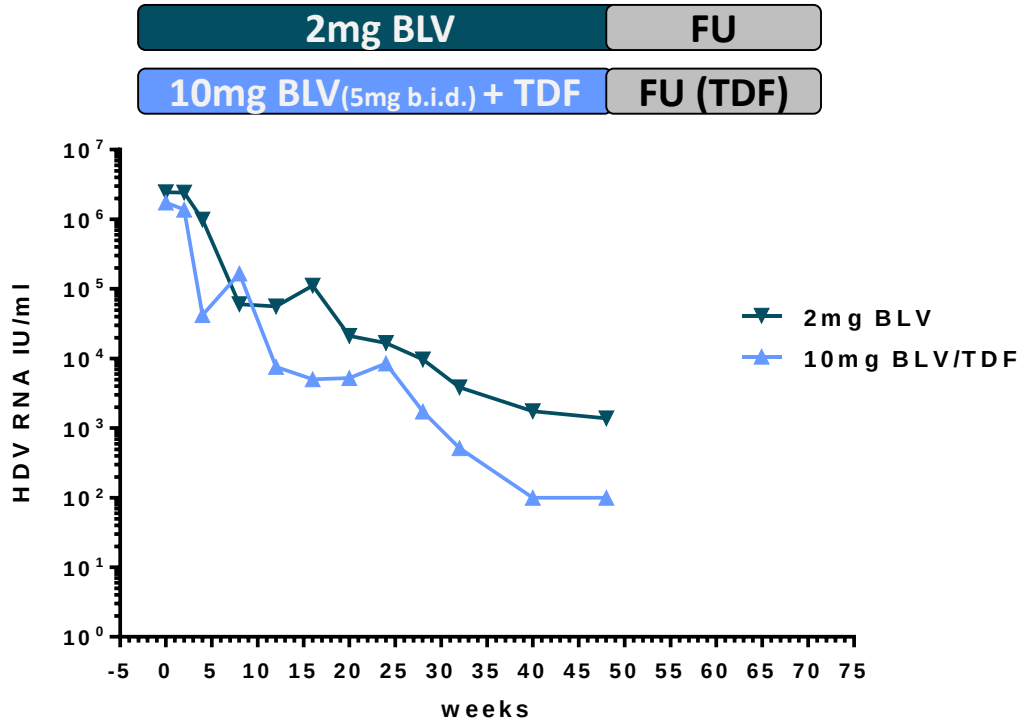
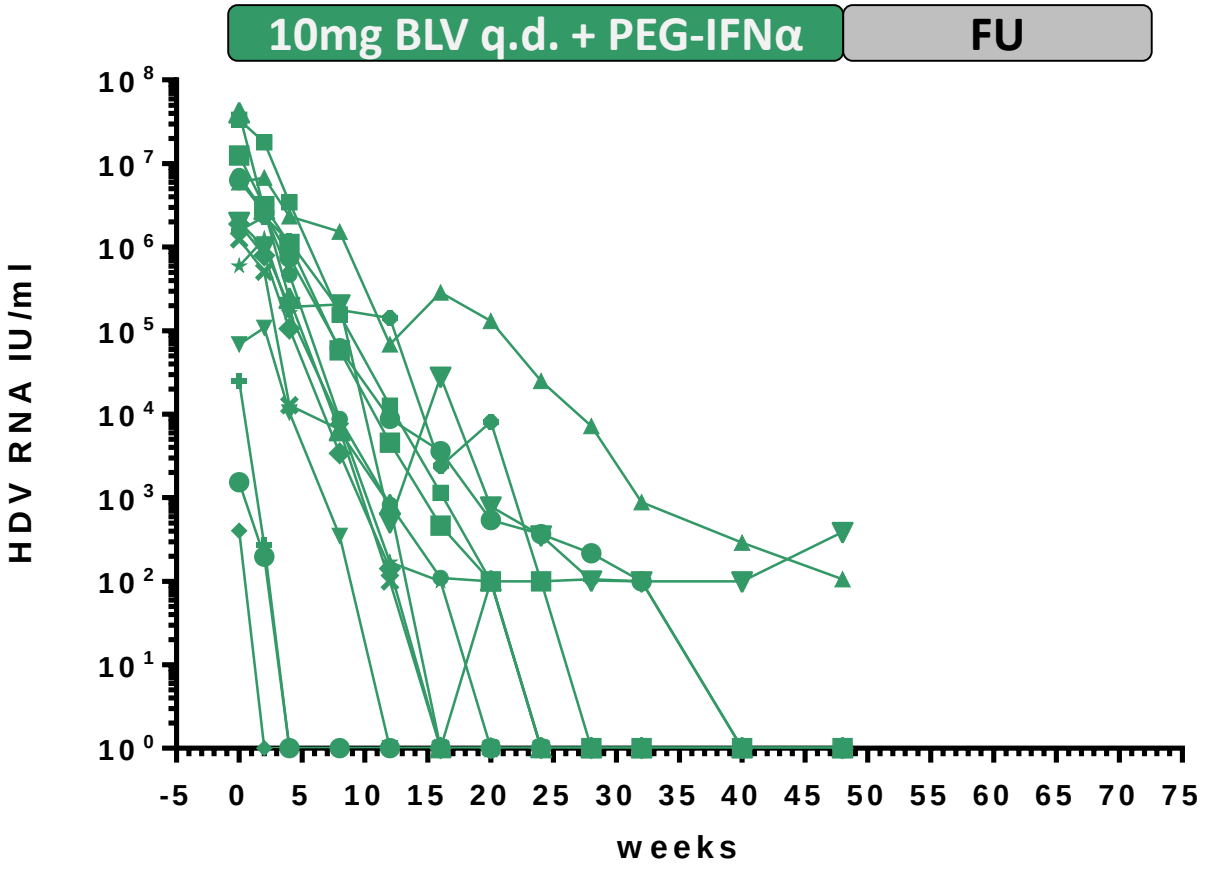


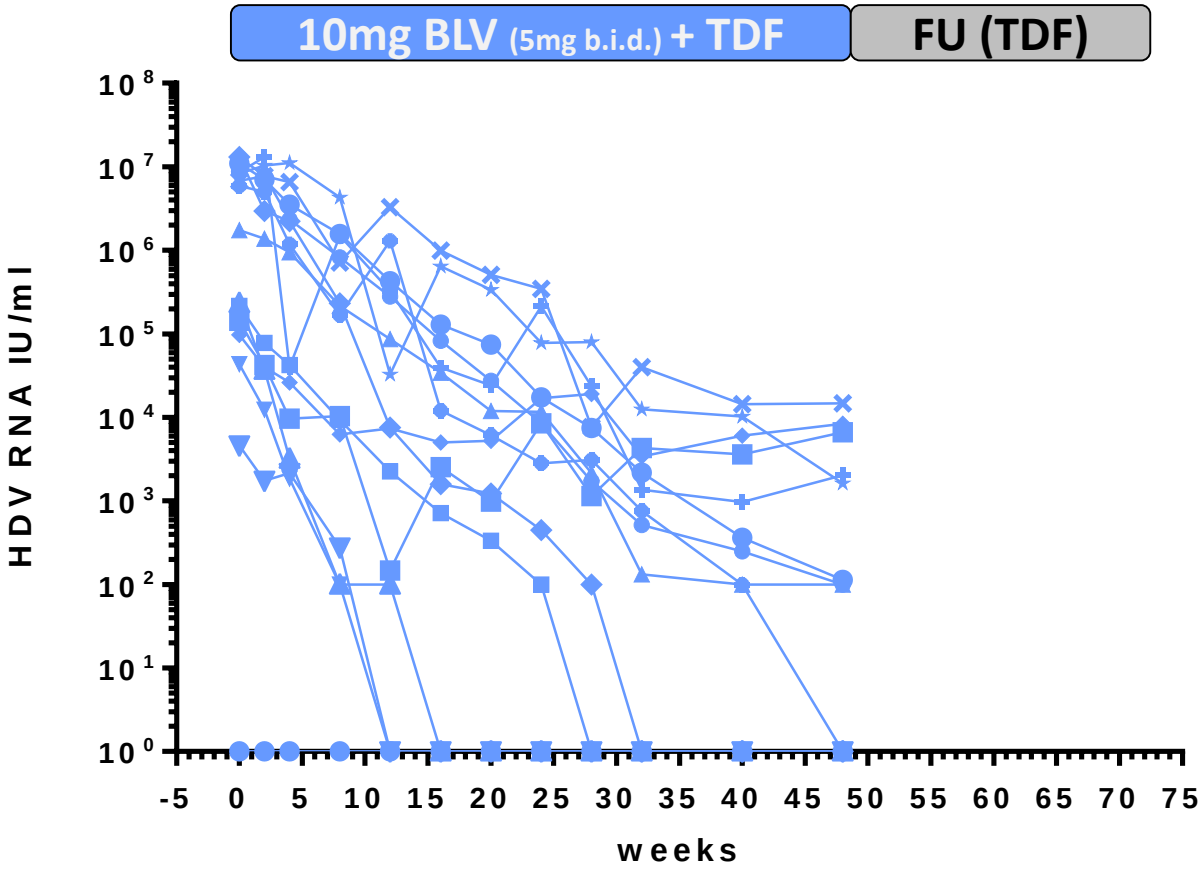
Virological response: week 48	Median HDV RNA reduction [log]	undetectable HDV RNA
2mg BLV	-2.84	13.3%
10mg BLV + TDF	-4.58	40.0%

BLV = bulevirtide

Wedemeyer et al., AASLD 2019

Individual HDV RNA kinetics





- All patients in both treatment arms achieved a more than $1\log_{10}$ HDV RNA decline (no non-responders were observed)

BLV = bulevirtide; LOD = 10 IU/ml

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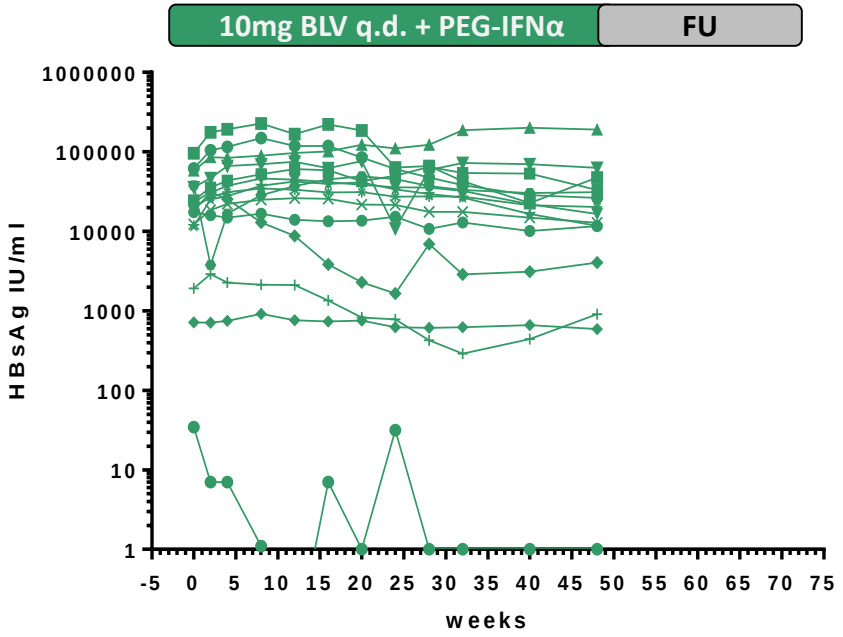
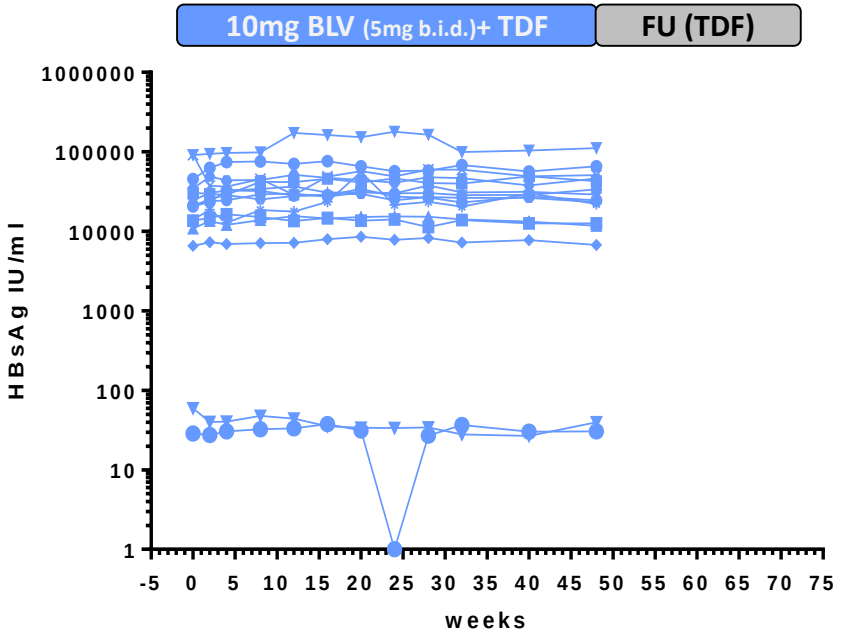
Wedemeyer et al., AASLD 2019

HBsAg Response (≥ 1log$_{10}$ decline or undetectable)





HBsAg response at week 48	>1log$_{10}$ HBsAg decline [%]	undetectable HBsAg [%]
PEG-IFNα	0.0%	0.0%
2mg BLV + PEG-IFNα	**46.7%**	**20.0%**
5mg BLV + PEG-IFNα	**20.0%**	**0.0%**
10mg BLV + PEG-IFNα	**6.7%**	**6.7%**

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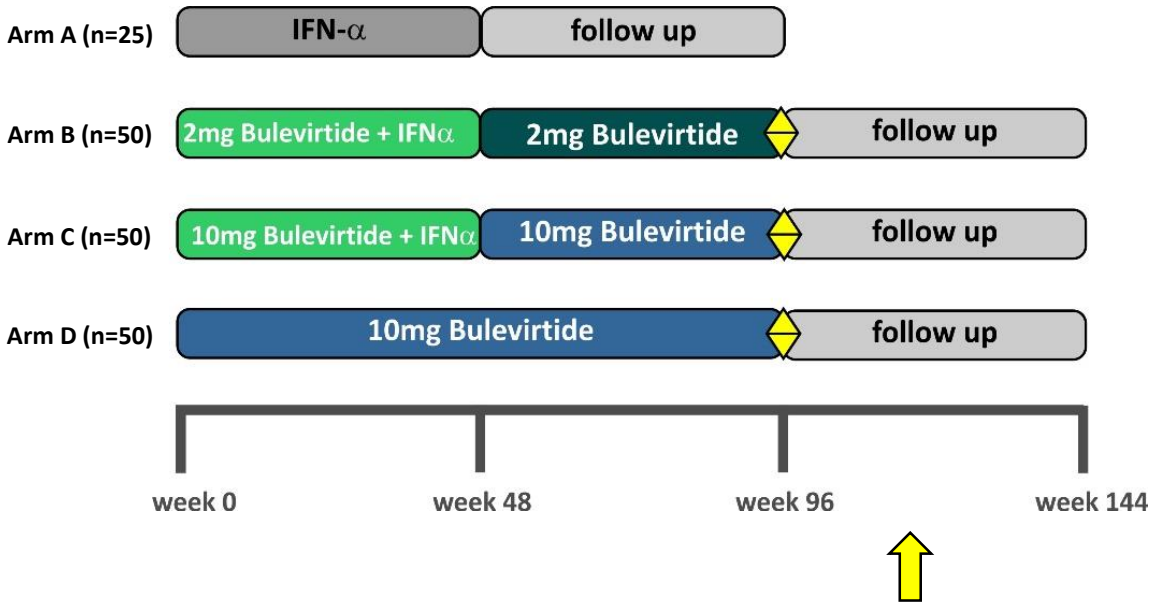
HBsAg response at week 48	>1log$_{10}$ HBsAg decline [%]	undetectable HBsAg [%]
2mg BLV	0.0%	0.0%
10mg BLV + TDF	0.0%	0.0%

Wedemeyer et al., AASLD 2019

Ongoing clinical trial MYR 204



- **175 HDV patients**, in combination with PEG-IFNα
- **Enrolment completed** December 2019
- Patients **randomized in 4 treatment arms**
- In 4 countries: **France**, Russia, Romania, Moldova

- Primary endpoint:
  Sustained virologic response defined as negative PCR result for HDV RNA at week 24 after end of treatment

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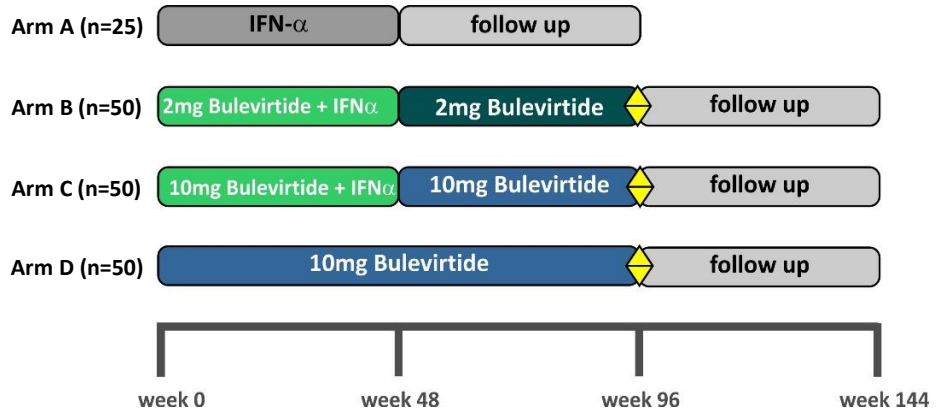
Ongoing clinical trials

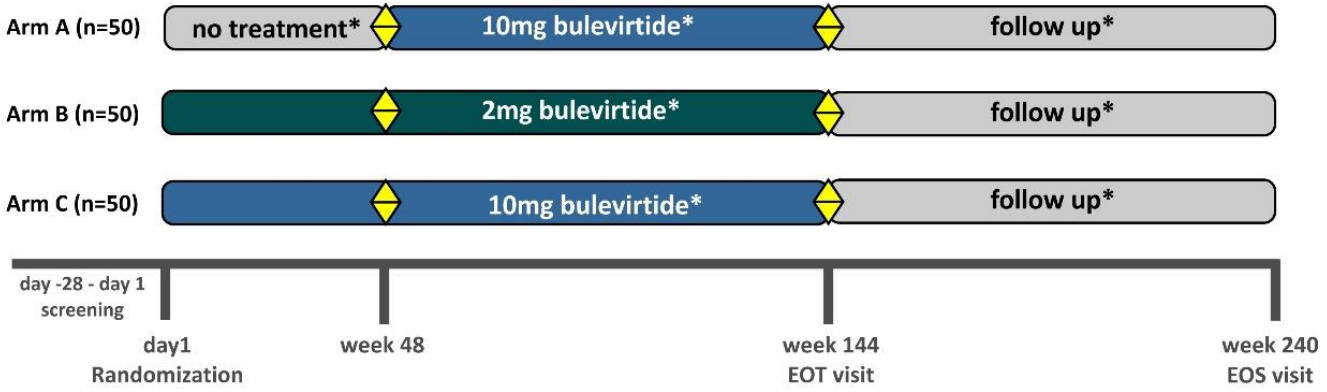
MYR 204

- Primary endpoint: Negative PCR result for HDV RNA at week 24 after end of treatment
- 175 HDV patients, in combination with PEG-IFNα
- Patients randomized in 4 treatment arms
- In 4 countries: **France**, Russia, Romania, Moldova



MYR 301

- Composite primary endpoint: HDV RNA negativation or >2log decline as well as ALT normalization at week 48
- 150 HDV patients
- Patients randomized in 3 treatment arms
- In 6 countries: Germany, Russia, USA, Georgia, Sweden, Italy



MXB: Myrcludex B ; EOT: end of treatment; EOS: end of study
no treatment: no treatment for HDV infection
* if indicated treatment with NA according to EASL/AASLD guidelines

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Cohort ATU in France

Bulevirtide 2mg, self administered by patients once daily s.c.

> 90 patients are included

Inclusion criteria:

Adult patients (>18 years) with chronic HDV infection since at least 6 months assessed by positive HDV RNA and/or HDV antibody testing and

- **Compensated liver cirrhosis or severe fibrosis grade 3** (evaluated by liver biopsy or Fibroscan) or
- **Fibrosis grade 2** (evaluated by liver biopsy or Fibroscan) **with persistent ALT elevation** (ALT > or = 2N since at least 6 months)

Exclusion criteria:

Presence of decompensated liver disease, creatinine clearance < 60 ml/min, pregnancy

➢ More information on ANSM website

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Bulevirtide: Summary

- Entry inhibitor (binds NTCP)
- High efficacy and favorable tolerability
- High-dose therapy (10 mg) was safe and well tolerated
- **Bulevirtide monotherapy with 10mg (5mg b.i.d.)**

- continuous linear HDV RNA decline over 48 weeks
- rapid ALT reduction and normalization
- 5mg bulevirtide b.i.d. was comparable to 10mg bulevirtide q.d.

- **Bulevirtide 10mg q.d./PEG-IFNα combination therapy:**

- undetectable HDV RNA in 87% at 48 weeks of therapy

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New drugs for HDV infection

1. Introduction : HDV cure
2. Entry inhibitor: Bulevirtide
3. **Prenylation inhibitors: Lonafarnib**
4. Take home messages

Lonafarnib Overview

- Small molecule, first-in-class, oral, prenylation inhibitor
- Well-characterized in patients
  - > 2,000 patients dosed in oncology program by Merck (Schering)
  - > 90 children dosed in Progeria program by Boston Children's Hospital
  - > 170 patients dosed in HDV program
  - Longest duration of dosing > 10 years
- Most commonly-reported adverse events are GI-related (class effect)
  - Well-managed with prophylactic treatment with anti-diarrheals and anti-emetics
- Designations: US & EU Orphan, FDA Breakthrough, EMA PRIME

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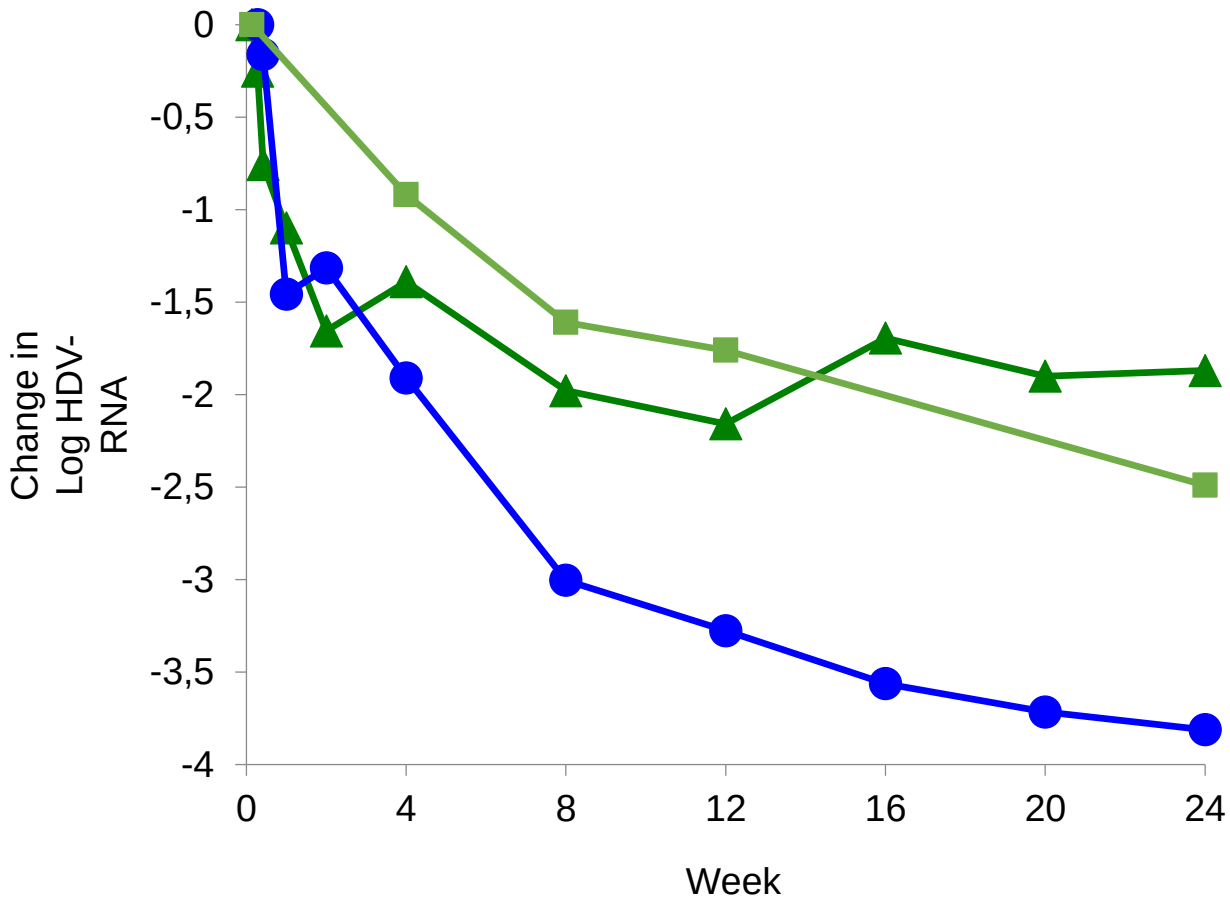
Lonafarnib: Phase 2 Data

Two Lonafarnib-based Regimens Identified for Registration



LNF 50 mg BID + RTV (N=12)
LOWR-2 STUDY

PEG IFN-alfa-2a ± tenofovir (N=91)
HIDIT-1 STUDY

LNF 50 mg BID + RTV + PEG IFN-alfa-2a (N=4)
LOWR-2 STUDY

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Yurdaydin et al, *J Hepatology* **2018**, Abstract #PS-161

Lonafarnib: Phase 2 Program

Dose, Combinations and Endpoints Defined

- **All-oral:** Lonafarnib boosted with Ritonavir
  - 33% (6 of 18) patients **≥ 2 log decline** or BLQ at Week 24
  - 47% (7 of 15) patients **normalized ALT** at Week 24
  - **Composite endpoint: 29% (4 of 14)**

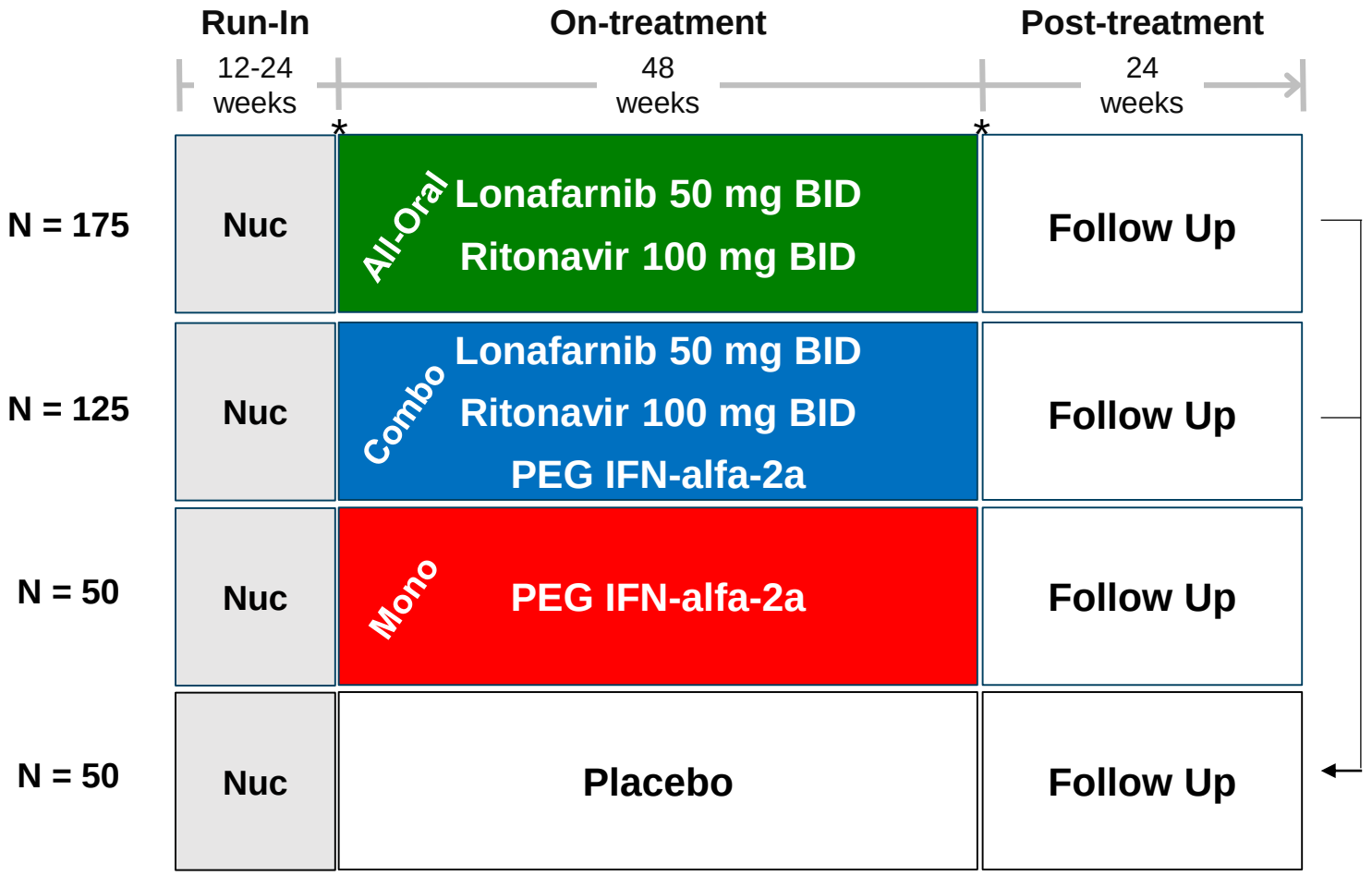
- **Combination:** Lonafarnib boosted with Ritonavir + PEG IFN-alfa-2a
  - 78% (7 of 9) patients **≥ 2 log decline** or BLQ at Week 24
  - 88% (7 of 8) patients **normalized ALT** at Week 24
  - **Composite endpoint: 63% (5 of 8)**

- Predominant AEs were GI-related (mild / moderate)

Yurdaydin et al, *J Hepatology* **2018**, Abstract #PS-161
Most common reported AEs: nausea, diarrhea, fatigue, weight loss, anorexia, vomiting

D-LIVR: Phase 3 study

Delta-Liver Improvement and Virologic Response in HDV (400 patients)



Primary Endpoint at Week 48

- ≥ 2 log decline in HDV RNA
  +
  Normalization of ALT

Secondary Endpoint at Week 48

- Histologic improvement
  - > 2-point improvement in HAI inflammatory score
  - No progression in fibrosis
- Improvement of fibrosis

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All patients will be maintained on background HBV nucleoside therapy.
Superiority over PEG IFN-alfa-2a not required.

* biopsy

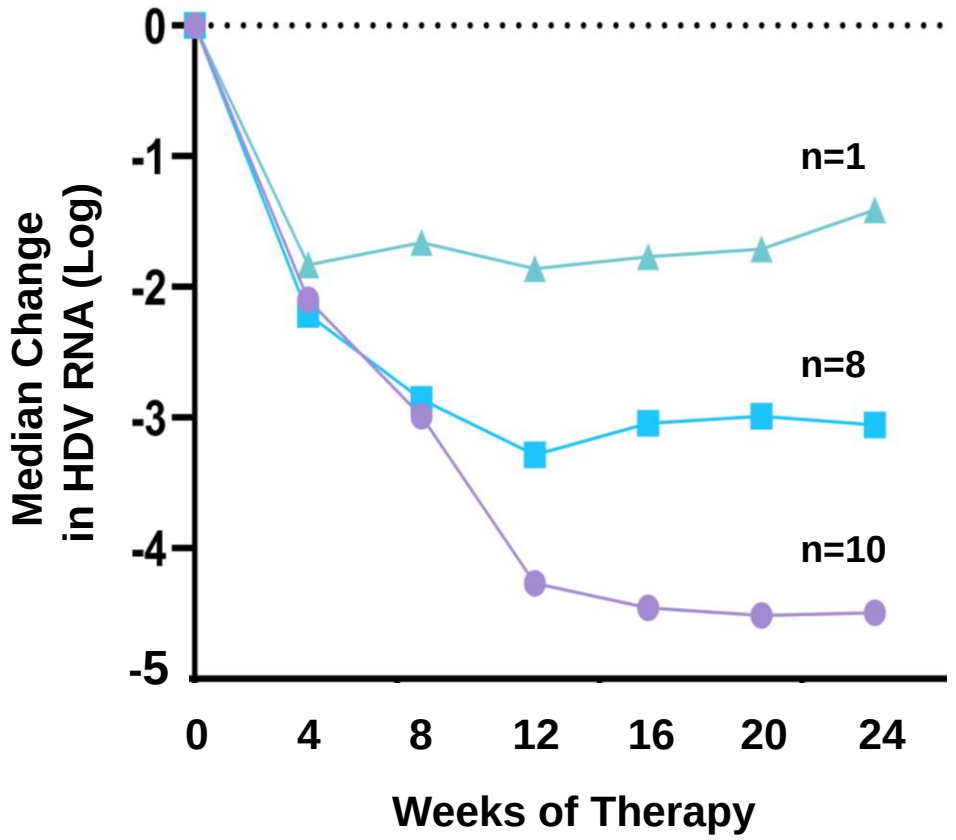
LIFT Study:
Lonafarnib, Ritonavir and Lambda Interferon for HDV

Interim End-of-Treatment Results

Aims: Evaluate the safety and antiviral effects with LNF, RTV and lambda interferon in patients with chronic HDV

Methods: Phase 2a, open-label, prospective treatment trial in 26 patients for 24 weeks, with 24 weeks of post-therapy follow-up

Conclusion: Combination therapy with LNF/RTV/LMD in chronic HDV patients appears to be safe and tolerable for up to 6 months in most patients



Results

% of Patients	Week 24 HDV RNA
95%	> 2 Log Decline
53%	BLQ
37%	Undetectable

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Koh et al, AASLD 2019, LO-8

Lonafarnib: Summary

- High efficacy in Phase 2 studies
- Favorable tolerability, most common AEs are GI (class effect)
- Synergistic effect with PEG-IFN
- Ongoing Phase 3 D-LIVR global study
- PEG-IFN lambda + lonafarnib combinations in development
- Regulatory Designations
  - US & EU Orphan
  - FDA Breakthrough
  - EMA Prime

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New drugs for HDV infection : Take home messages

1 – HDV is a defective virus which needs HBV presence for its own viral cycle infection.

2 - HDV, similarly to HBV, infects hepatocytes via high specificity interaction with human NTCP expressed on basolateral membrane of hepatocytes.

3 - Current treatment of HDV is PEG-IFN for 48 weeks. For patients who failed PEG-IFN, there is no therapeutic option available.

New drugs for HDV infection : Take home messages

1 – HDV is a defective virus which needs HBV presence for its own viral cycle infection.

2 - HDV, similarly to HBV, infects hepatocytes via high specificity interaction with human NTCP expressed on basolateral membrane of hepatocytes.

3 - Current treatment of HDV is PEG-IFN for 48 weeks. For patients who failed PEG-IFN, there is no therapeutic option available.

4 - Drugs in development include entry inhibitors, prenylation inhibitors, and HBsAg release inhibitors.

5 - For Bulevirtide and Lonafarnib, the addition of PEG-IFN appears to be synergistic

6 - There is a need for long-term end-points

7 – HBV cure program will also lead to HDV cure, but in a long-term.

8 – We need an HDV cure program

Hepatitis Delta: ongoing trials

Mode of Action Compound Company	Official Title	Number (participants)	Stage of devlopment	Reference; Clinicaltrials.gov
Entry Inhibitor; Bulevirtide; MYR GmbH	Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients With Chronic Hepatitis Delta	150	3	NCT03852719
	A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination With Pegylated Interferon Alfa-2a in Patients With Chronic Hepatitis Delta	175	2b	NCT03852433
	A Multicenter, Open-label, Randomised, Comparative, Parallel-Arm, Phase II Study to Assess Efficacy and Safety of Myrcludex B in Combination With Peginterferon Alfa-2a Versus Peginterferon Alfa-2a Alone in Patients With Chronic Viral Hepatitis B With Delta-agent	60	2b	NCT02888106
Prenylation Inhibitor; Lonafarnib; Eiger BioPharmaceuticals	A Phase 3, Matrix Design, Partially Double-Blind, Randomized Study of the Efficacy and Safety of 50 mg Lonafarnib/100 mg Ritonavir BID With and Without 180 mcg PEG IFN-alfa-2a for 48 Weeks Compared With PEG IFN-alfa-2a Monotherapy and Placebo Treatment in Patients Chronically Infected With Hepatitis Delta Virus Being Maintained on Anti-HBV Nucleos(t)Ide Therapy (D-LIVR)	400	3	NCT03719313
	Treatment of Chronic Delta Hepatitis With Lonafarnib, Ritonavir and Lambda Interferon	32	2A	NCT03600714

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