Hepatitis D Treatment Endpoints:

How Do We Measure Success in the Era of Emerging Therapies?

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Disclosure

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Abbvie, Gilead, MSD, Eiger, HepQuant, Canfite and ChemoMab

Outline

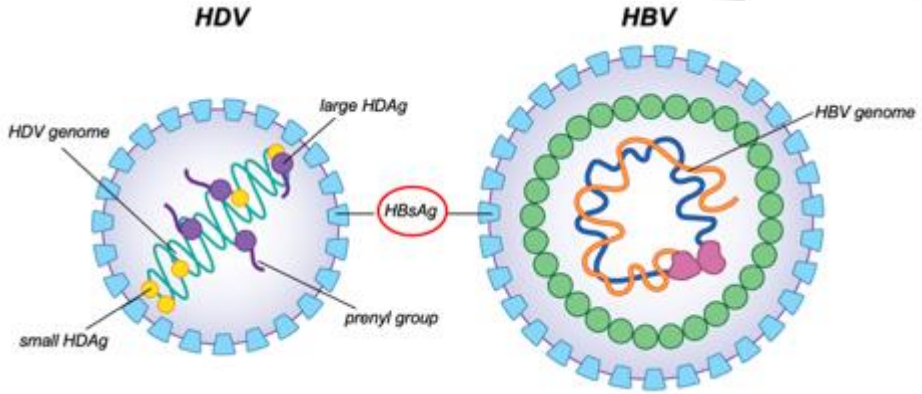
- HDV-epidemiology & clinical aspects
- Current management
- Defining suitable endpoints for clinical trials in HDV
- Review data from recently completed studies and outline of upcoming trials evaluating novel therapies

Hepatitis Delta Virus

- An incomplete RNA virus
- Co-dependent on HBV for packaging
- Dependent on host RNA polymerases for replication
- Single ORF encoding 2 non-structural proteins
- 2 patterns of infection:

  -Coinfecton

  -Super infection



ARTICLE

https://doi.org/10.1038/s41467-019-10117-z OPEN

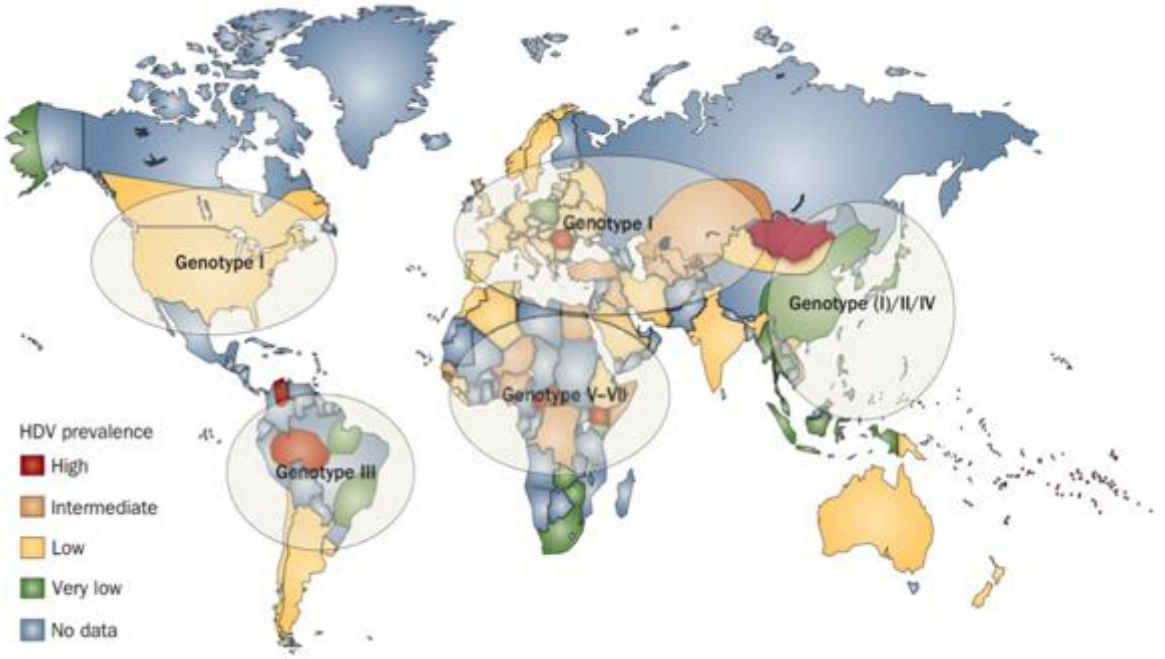
nature COMMUNICATIONS 2019

Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus in vivo

Jimena Perez-Vargas[1], Fouzia Amirache[1], Bertrand Boson[1], Chloé Mialon[1], Natalia Freitas[1], Camille Sureau[2], Floriane Fusil[1] & François-Loïc Cosset[1]

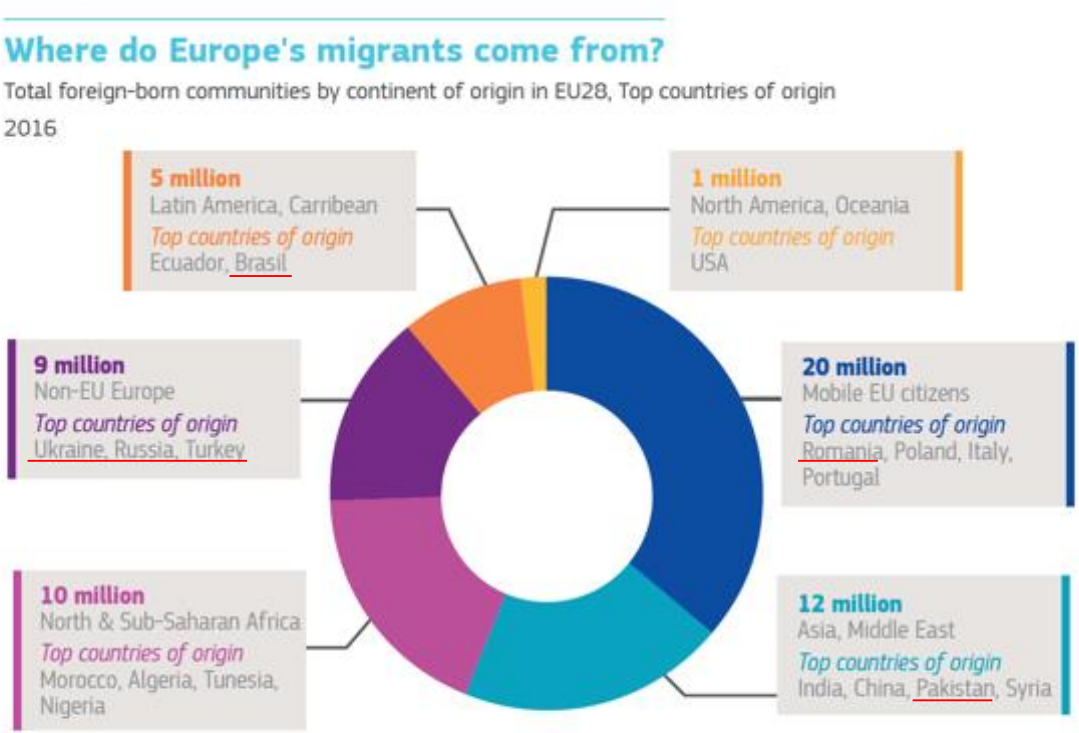
Epidemiology

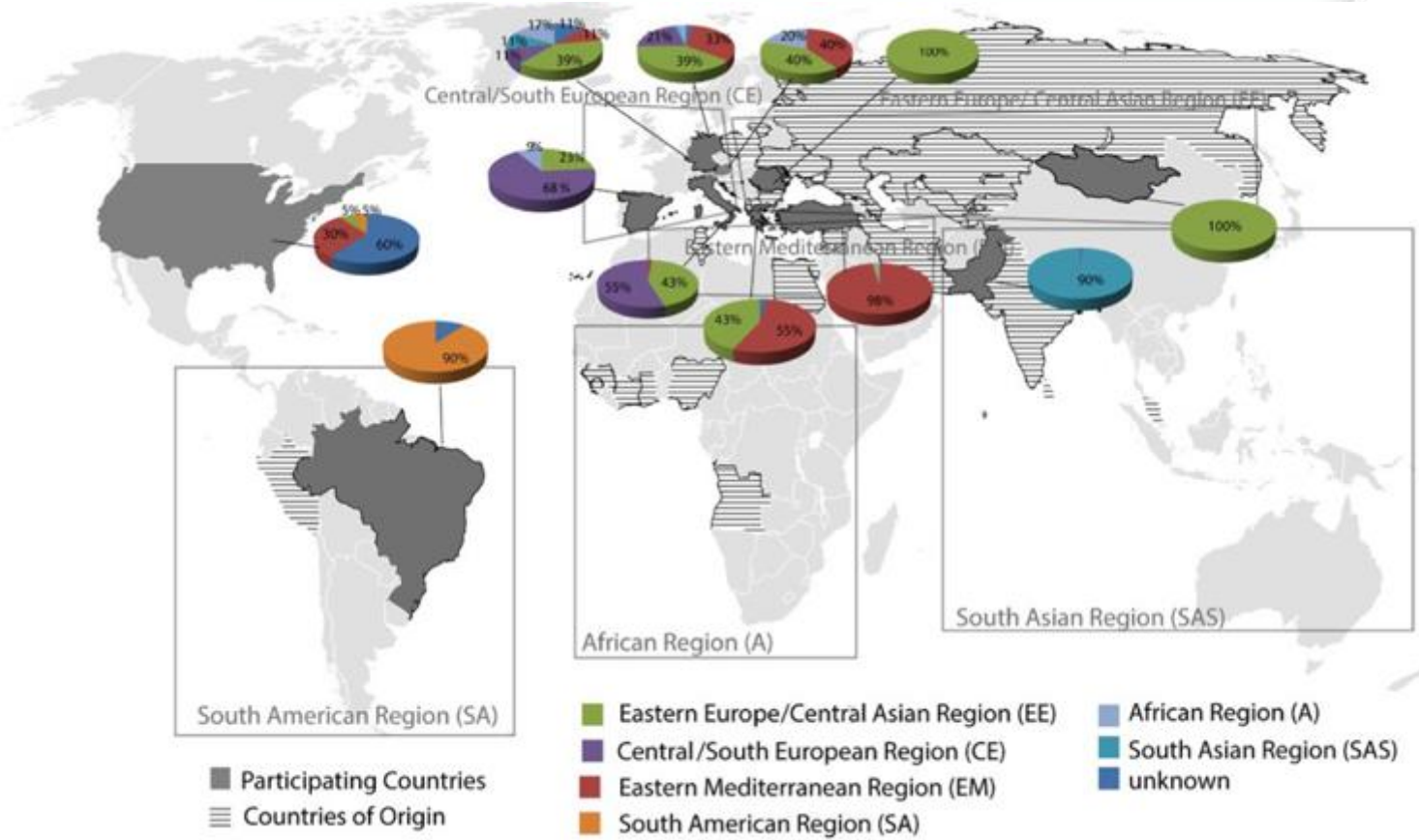
- 15-20 million affected worldwide
- ~5% HBV infected patients
- Genotype 1-most common
- HDV is found in every country except:
  - Where it is not tested for
  - Anti-HDV tests don't work



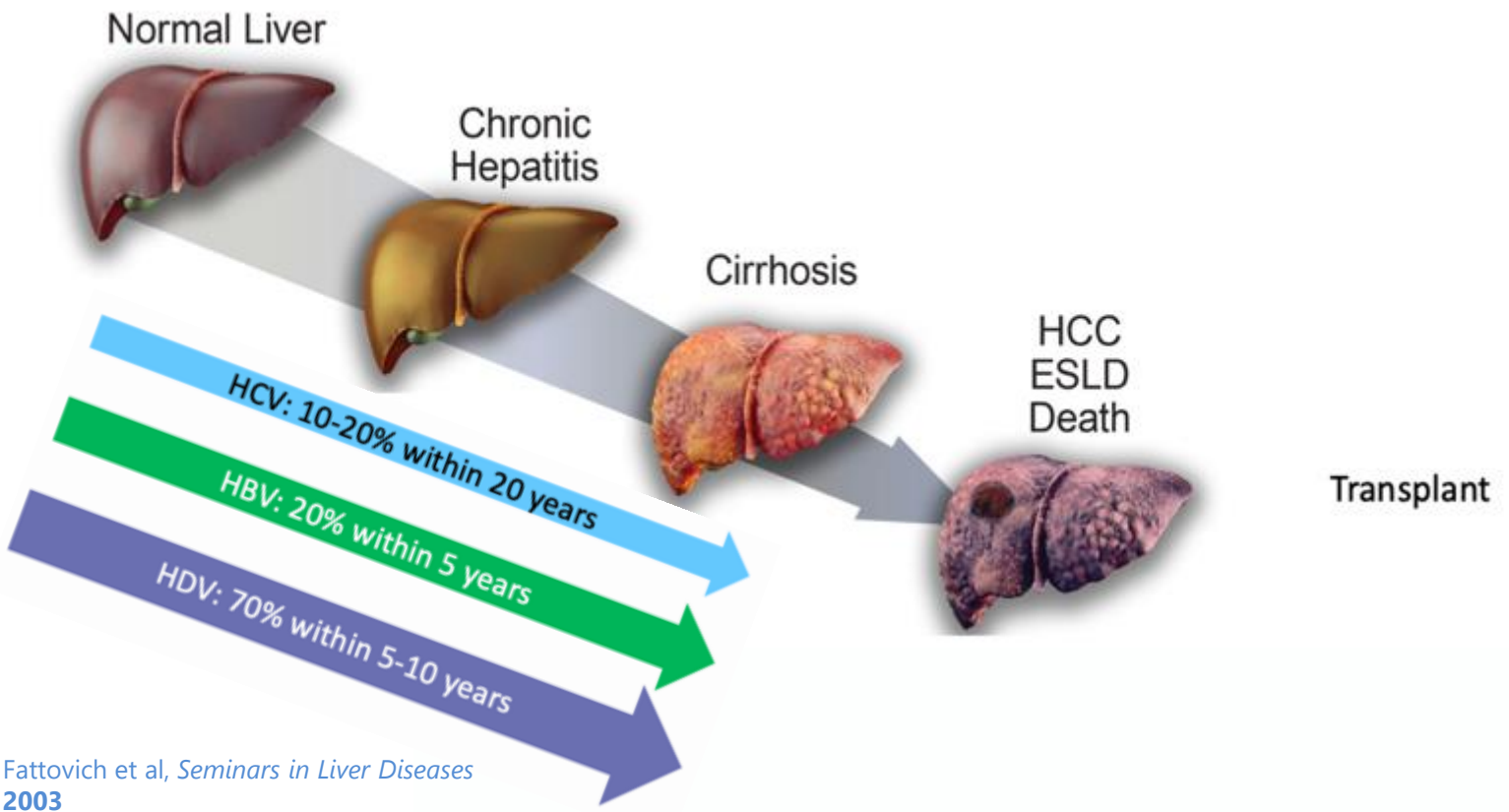
Wedemeyer, H. & Manns, M. P.. Nat. Rev. Gastroenterol. Hepatol. 2010

Recent immigration trends



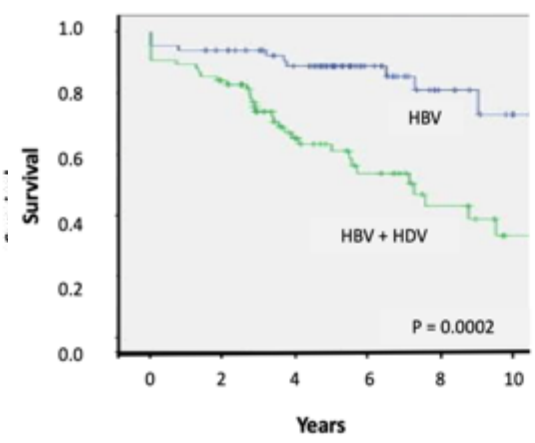

Central/South European Region (CE)
Eastern Europe/ Central Asian Region (EE)
Eastern Mediterranean Region (EM)
South American Region (SA)
African Region (A)
South Asian Region (SAS)
Participating Countries
Countries of Origin
Eastern Europe/Central Asian Region (EE)
Central/South European Region (CE)
Eastern Mediterranean Region (EM)
South American Region (SA)
African Region (A)
South Asian Region (SAS)
unknown

HDV: Most severe form of chronic viral hepatitis

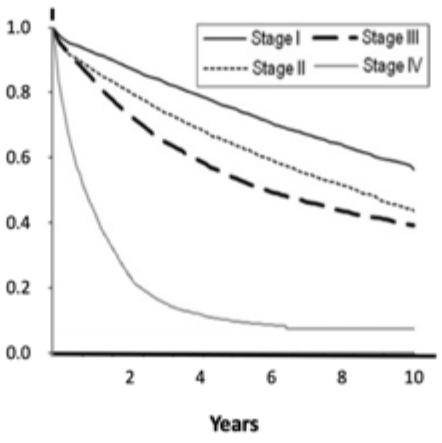


Fattovich et al, *Seminars in Liver Diseases* **2003**
Nourredin et al, *Curr. Gasterol. Rep* ***2013***

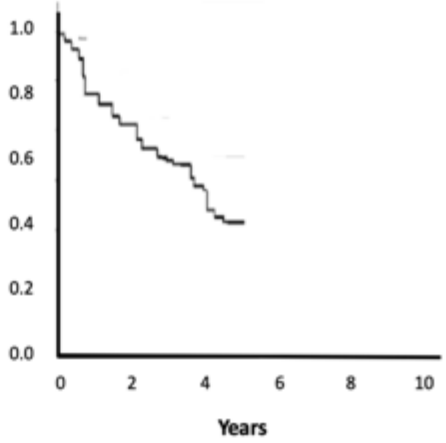
HBV and HDV[1]



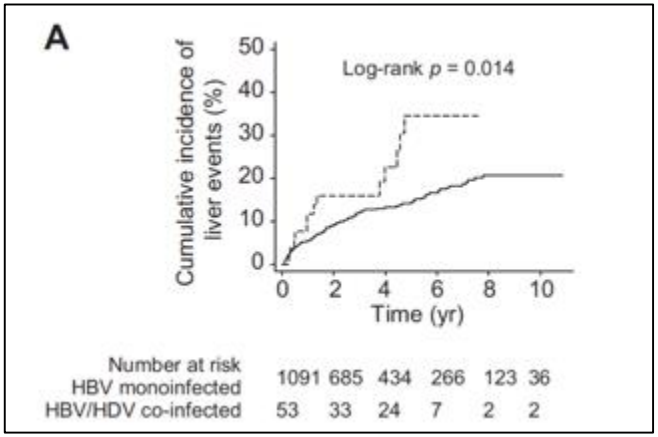
Colorectal Cancer[2]

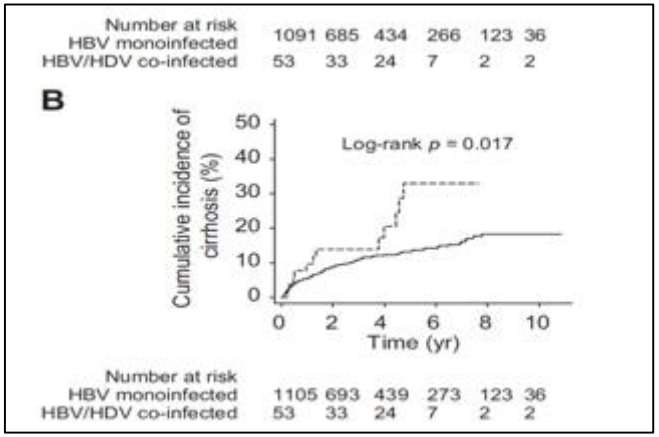


Resected NSCLC[3]

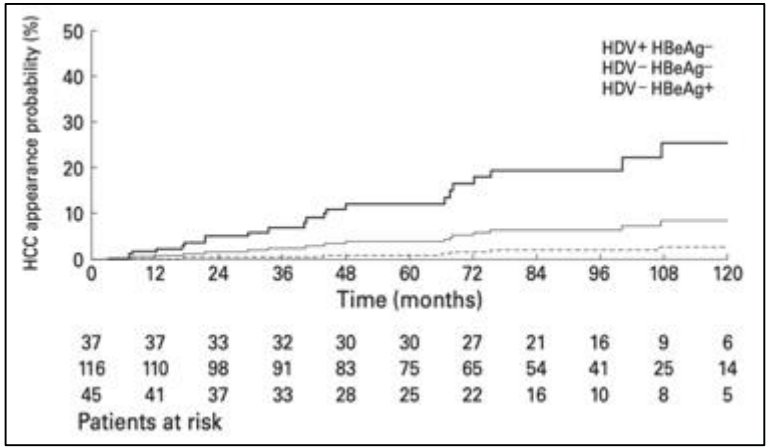


[1]Serrano et al, EASL **2011**; [2]Cancer Causes Control, **2012**, 23:1421–1428; [3]Cerfolio et al, Ann Thorac Surg, **2007**, 84:182–90





Manesis et al, *J Hepatol* **2013**



Fattovich et al, *Gut* ***2000***

CHD-Liver transplantation

Table 1 Prevalence of HDV infection in Israel

	Samples tested, N	HDV negative samples	HDV seropositive samples	% seropositive (95% CI)	Odds Ratio (95% CI)	*p*-value
Total	8969	8382	587	6.5 (6.1-7.1)		
Age (mean± SD)	8452[a]	45.2± 16 (*n*=7919)	47.5± 13.8 (*n*=533)		1.0 (1.0-1.1)	<0.01
Gender (*n*=8744)[a]						
Male	5046	4734	312	6.2 (5.6-6.9)	Reference	0.18
Female	3698	3443	255	6.9 (61.-7.8)	1.1 (0.9-1.3)	

[a]The number of samples for which this information was available

Shirazi et al. BMC Infectious Diseases 2018

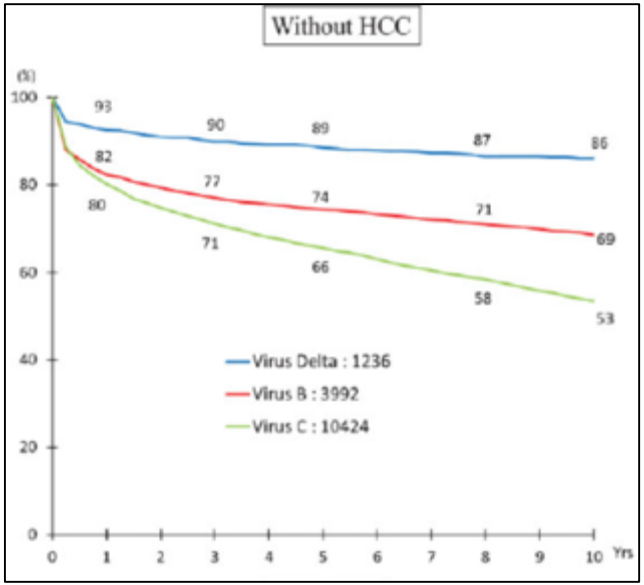
Hadassah Medical Center: 1990-2005

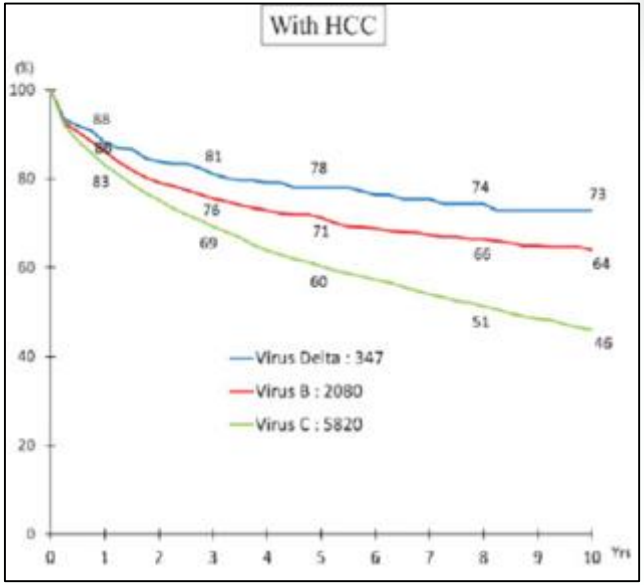
Indication	No	%
HBV positive	71	85%
HBV/HDV coinfected	12	15%*

* 18% after excluding cases where HBV was not the primary indication for liver transplantation

Milgrum Y & Saffadi R personal communication

Survival following LT for CHD



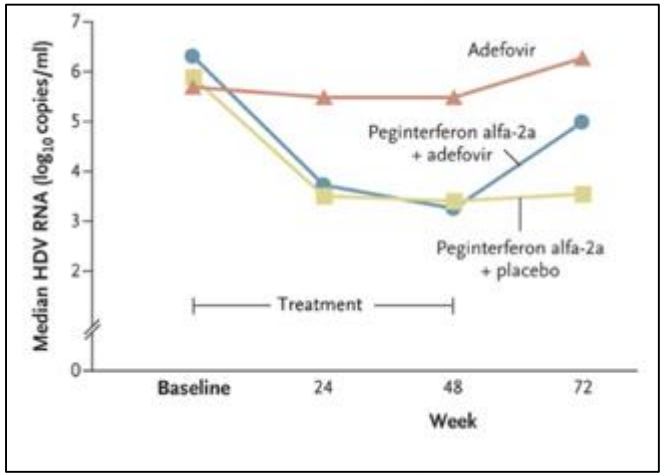


Roche & Samuel. Semin Liver Dis ***2012***

Current management of CHD

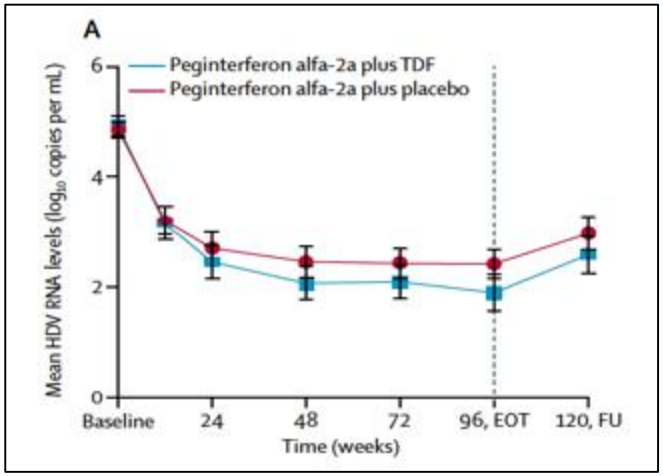
- No approved treatment for CHD!
- No impact of NUCs
- Pegylated IFN-Alpha
  - significant side effects
  - limited efficacy
  - patients with advanced disease not eligible
  - high long-term relapse rates

HIDIT-I



Wedemeyer H. Engl J Med. 2011

HIDIT-II



Wedemeyer H. Lancet Infect Dis 2019

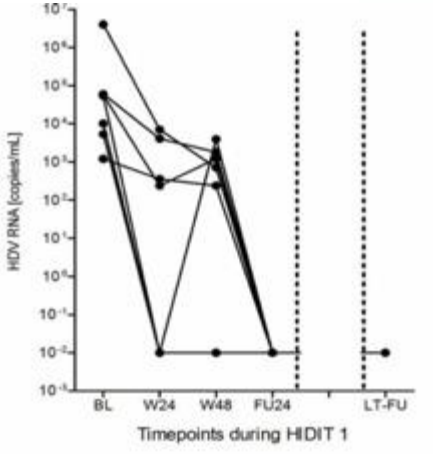
Is SVR feasible with IFN-Alpha?

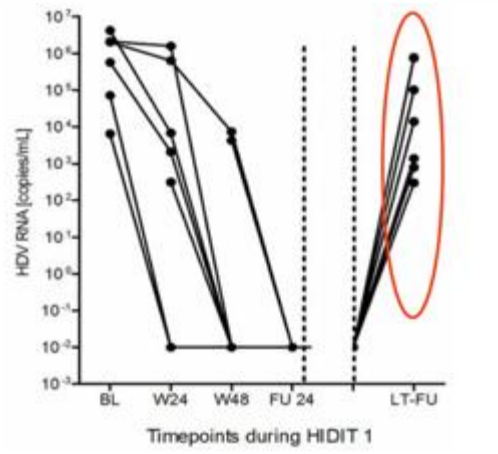
HIDIT-I

HDV Neg at W24 post treatment **28%**

HIDIT-II

HDV Neg at W24 post treatment **27%**

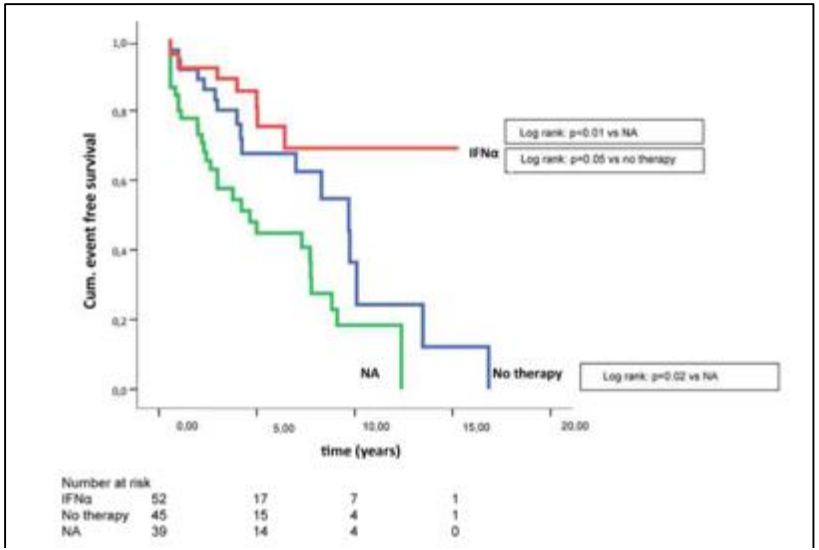




56% of patients that were HDV neg at W24 post treatment
became HDV RNA pos on long-term follow up

Heidrich B. Hepatology 2014

IFN-Alpha is associated with improved long-term clinical outcomes



Wranke A. Hepatology 2017

Prevalence and clinical course of hepatitis delta infection in Greece: A 13-year prospective study

Emanuel K. Manesis[1,*], Georgia Vourli[2], George Dalekos[3], Themistoclis Vasiliadis[4], Nina Manolaki[5], Athina Hounta[6], Sotirios Koutsounas[7], Irini Vafiadis[8], Georgia Nikolopoulou[9], Gregory Giannoulis[10], George Germanidis[11], George Papatheodoridis[12], Giota Touloumi[2]

Manesis et al, *J Hepatol* **2013**

HR for liver related-events in IFN-Alpha treated patients: 0.14 (0.02-0.86); p=0.033

Endpoints in clinical trials in CLD

Goals of treatment

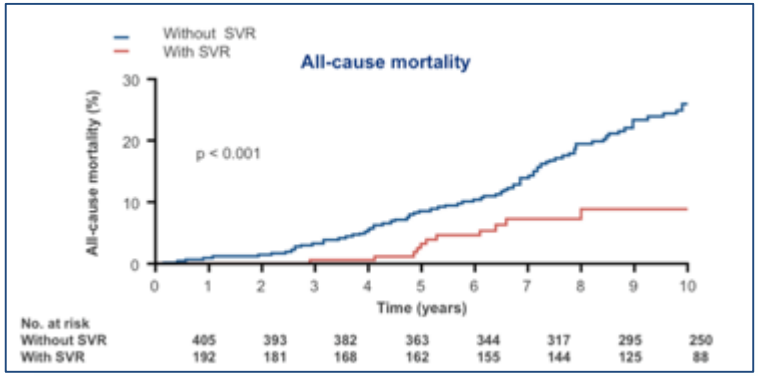
Prevent progression of liver disease and its complications

- Decompensation
- HCC
- Death

Endpoints

Surrogates markers that are reasonably likely to predict clinical benefit

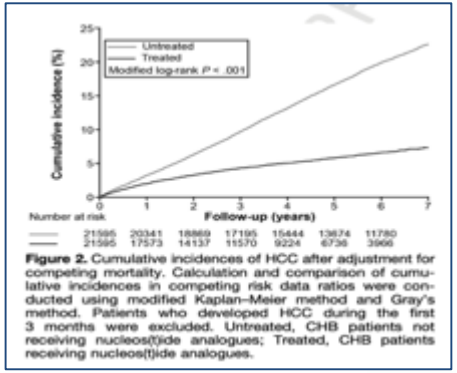
SVR in Hepatitis C



Van Der Meer. JAMA 2012

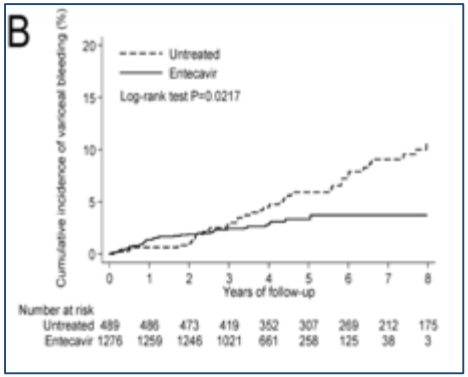
Hepatitis B virus suppression

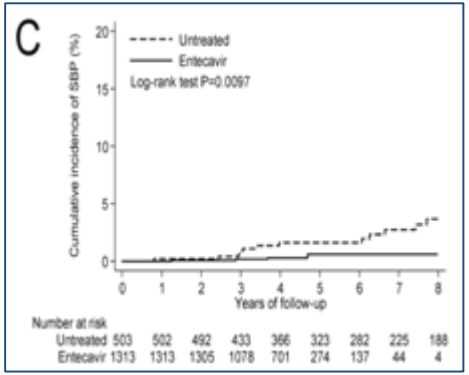
HCC reduction



Wu CY Gastroenterology 2014

ESLD complications

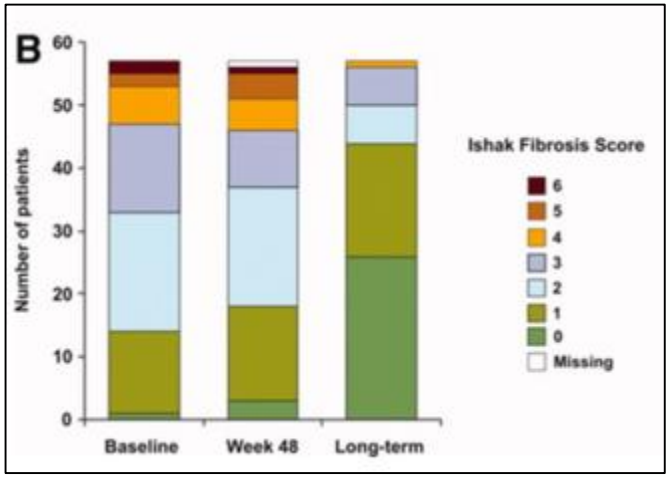




Su TH Liver Int 2016

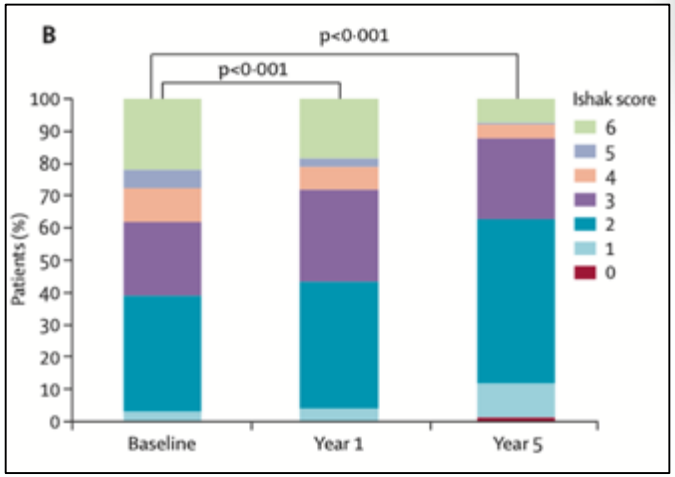
Long-term NUC therapy in HBV is associated with fibrosis regression

Entecavir



Chang TT. Hepatology 2010

Tenofovir



Marcellin P. The Lancet 2013

Choosing endpoints for clinical trials of novel HDV therapies

- Data on specific surrogate endpoints that are associated with long term clinical benefit is sparse
- Cure from HDV may not be feasible
- Selection of endpoints that are reasonably likely to predict clinical benefit is preferable over ideal endpoints that may not yet be achievable (HBsAg loss, SVR)

Choosing endpoints for clinical trials of novel HDV therapies

- Measures of viral suppression
  - ✔ Viral log decline
  - ✔ Virus undetectability
- Markers of improvement in necroinflammation
  - ✔ ALT normalization
  - ✔ Improved histology scores

✓ Composite endpoints have advantage over singular endpoints

✓ Durability of response - assessed by primary or secondary endpoints

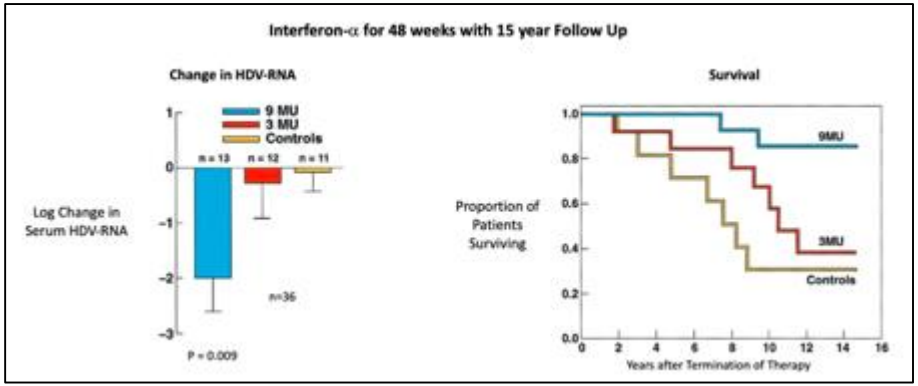
JOURNAL
OF HEPATOLOGY

Treating chronic hepatitis delta: The need for surrogate markers of treatment efficacy

Cihan Yurdaydin[1,*], Zaigham Abbas[2], Maria Buti[3], Markus Cornberg[4], Rafael Esteban[3], Ohad Etzion[5], Edward J. Gane[6], Robert G. Gish[7], Jeffrey S. Glenn[7], Saeed Hamid[8], Theo Heller[9], Christopher Koh[9], Pietro Lampertico[10], Yoav Lurie[11], Michael Manns[4], Raymundo Parana[12], Mario Rizzetto[13], Stephan Urban[14], Heiner Wedemeyer[15], on behalf of the Hepatitis Delta International Network (HDIN)[†]

Yurdaydın et al. J Hepatol 2017

- ≥ 2 log reduction in HDV viral load at EOT compared to baseline- target for the assessment of initial treatment efficacy with drugs currently being evaluated



Farci et al. Gastroenterology 2004

Table 1. Treatment goals for clinical trials in HBV/HDV coinfection.

Treatment goals	Parameter	Readout
Virologic efficacy during treatment	Relative HDV RNA decline during treatment compared to baseline levels	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity
Virologic efficacy off treatment	HDV RNA suppression/decline 24 weeks off-treatment and during further long-term follow-up	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity
Serological efficacy-1	HBsAg levels (log declines and loss) at end-of treatment and off treatment	validated quantitative HBsAg assay (IU/ml)
Serological efficacy-2	Seroconversion to anti-HBs at end-of treatment and off treatment	validated quantitative anti-HBs assay (IU/L)
Biochemical efficacy (1)	ALT normalisation at the end of treatment and off-treatment	Validated assays (IU/L)
Biochemical efficacy (2)	Relative ALT declines during treatment and off treatment	Validated assays (IU/L)
Combined virologic and biochemical response-1	HDV RNA decline of 2log (or PCR negativity if baseline viral load is <100 IU/ml) in combination with ALT normalisation at EOT	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity. ALT (IU/L) with standard biochemical assays.
Combined virologic and biochemical response-2	HDV RNA decline of 2log (or PCR negativity if baseline viral load is <100 IU/ml) in combination with ALT normalisation at 24 weeks off treatment and further during long-term follow-up	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity. ALT (IU/L) with standard biochemical assays.
Histological efficacy – grading	Improvement of HAI of at least 2 points	Total Ishak inflammation score (A + B + C + D); 0–18 points
Histological efficacy – staging	No worsening of fibrosis scores	Ishak score (0–6 points)
Safety – Drug-specific AEs	AEs and SAEs	Severity and relation ot study drug
Safety – Disease-specific AEs	HBV and HDV reactivation	HBV DNA, HDV RNA, ALT and other liver function parameters
ProQOLs	Quality of life during and after end of therapy	EQ5, SF-36, etc.

Table 2. Additional explorative endpoints for clinical trials in HBV/HDV coinfection.

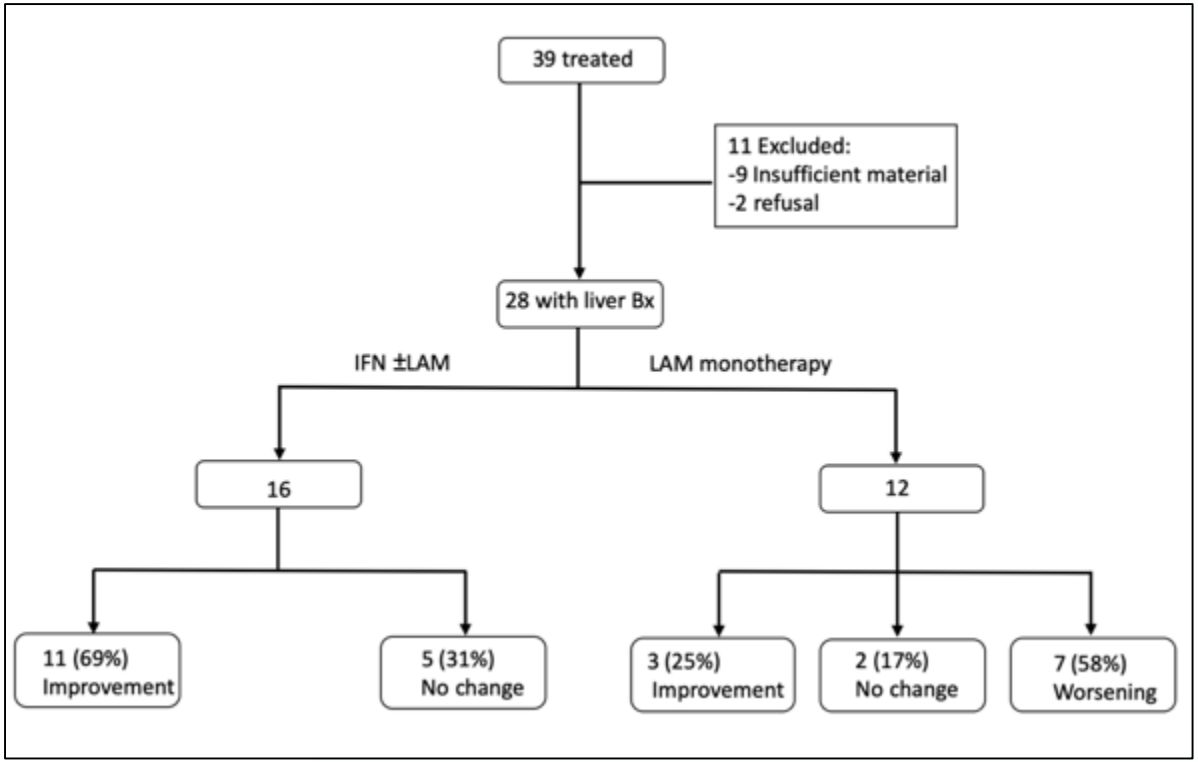
Endpoint	Parameter	Readout
Liver stiffness	Liver elastography	*e.g.* fibroscan, ARFI
Serum biomarkers for inflammation and fibrosis	Established scores (*e.g.* APRI, FIB4, Delta Fibrosis score*) Novel parameters	Serum-/Plasma tests
Intrahepatic virologic response (HDV and HBV)	Intrahepatic HDV RNA, hepatitis D antigen staining, HBV DNA, HBV RNA, HBV cccDNA	Standardized virologic assays
Immune responses	HDV-specific T cells, HBV-specific T cells, NK cell frequency and function, soluble inflammatory mediators	T cell assays, flow cytometry, bead-arrays

AFRI, acoustic radiation force impulse; APRI, aspartate aminotransferase to platelet ratio index; cccDNA, covalently closed circular DNA; FIB4, Fibrosis-4 score; HBV, hepatitis B virus; HDV, hepatitis D virus; ProQOLs: Professional Quality of Life scales.

* Ref. 62.

Yurdaydin et al. J Hepatol ***2019***

Histologic Improvement following IFN-alpha therapy



Adapted from Yurdaydın et al. J Viral Hepatitis. 2008

CHD infection: Developing Drugs for Treatment Guidance for Industry: *DRAFT GUIDANCE* (October 2019)

Endpoints for phase III clinical trials

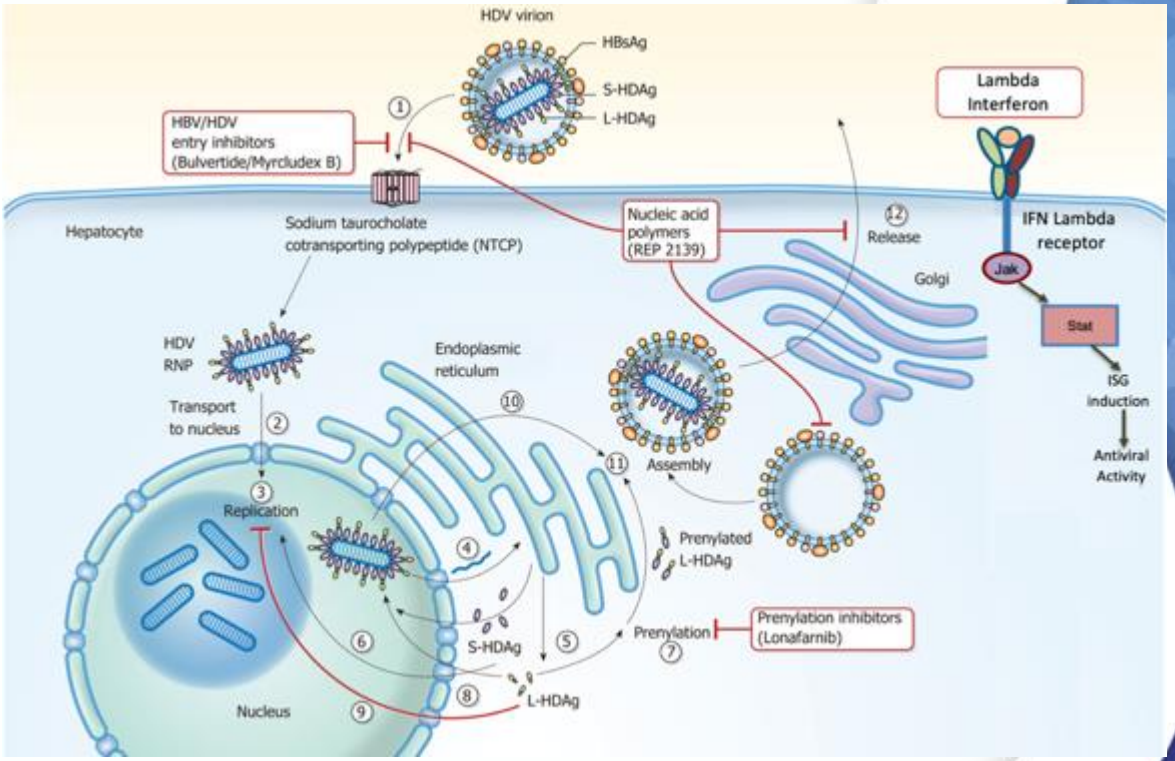
- Surrogate endpoints that are reasonably likely to predict clinical benefit
- Preferred: % of trial patients with undetectable serum HDV RNA and ALT normalization.
- Acceptable: Greater than or equal to 2 log10 decline in HDV RNA and ALT normalization

Timing of primary endpoints assessment

- The optimal timing of the primary endpoint assessment is unknown
- For therapies intended to be administered indefinitely, an on-treatment assessment after a predefined time period can be acceptable for efficacy.
- For therapies intended to be administered for a finite duration, FDA's preferred endpoint is an off-treatment assessment of efficacy.

Novel therapeutic targets for HDV

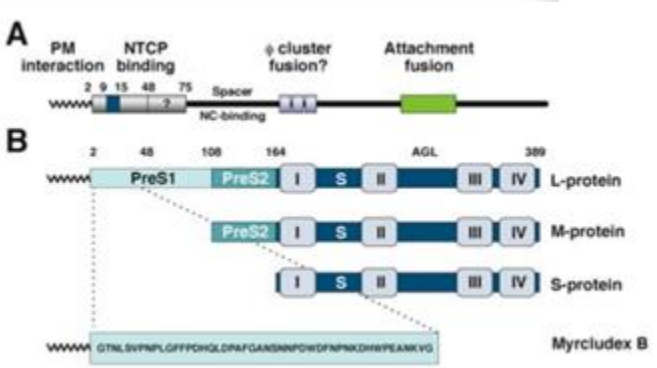
- No RNA polymerase to target
- HDV is dependent on HBsAg



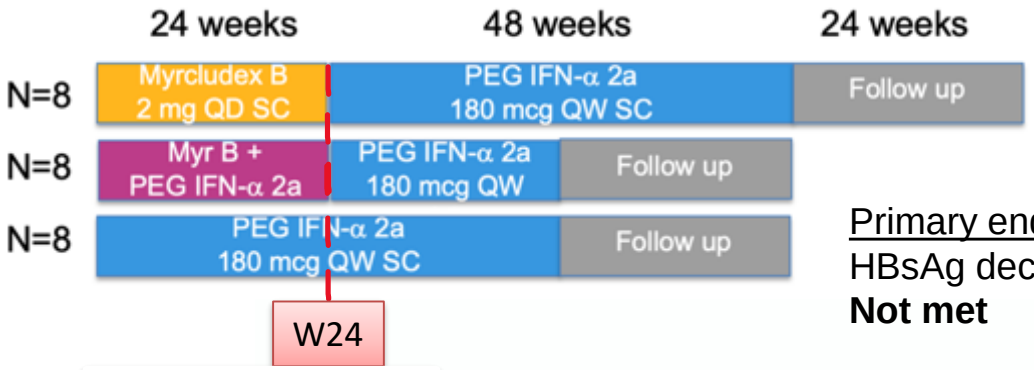
- Inhibition of viral entry (Micrludex-B)
- Interference in viral assembly Lonafarnib
- Interference in HBsAg release (Nucleic acid polymers)
- Immunomodulation (pegIFN-Lambda)

Myrcludex B

- First-in-class entry inhibitor for treatment of chronic HBV and HDV
- Synthetic 47 amino acid, N-acylated preS1 lipopeptide
- Targets Na-taurocholate co-transporting polypeptide (NTCP)
- Exclusively targets parenchymal liver cells
- Blocks receptor functions of NTCP and HBV/HDV virus entry



Myrcludex B- Pilot study

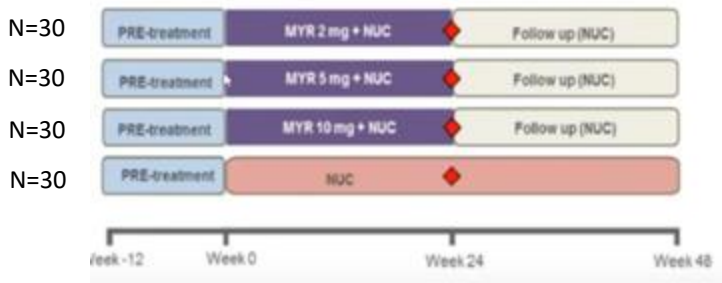


Primary endpoint:
HBsAg decrease at W12
Not met

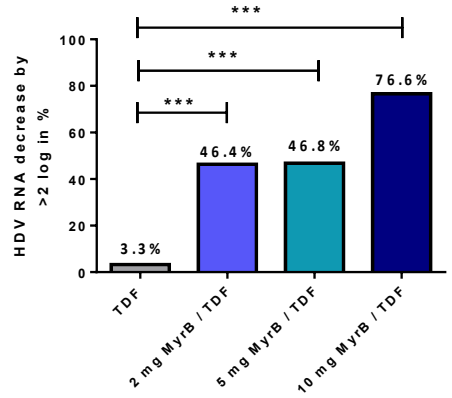
Myr B	HDV RNA -**1.67 log**	2 pts HDV RNA Neg
Myr B+ PEG IFN	HDV RNA **-2.59 log.**	5 pts HDV RNA Neg
PEG IFN	HDV RNA **-2.17 log.**	2 pts HDV RNA Neg

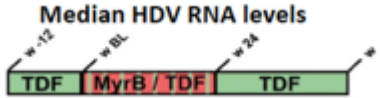
Bogomolov, et al. J Hepatol. 2016

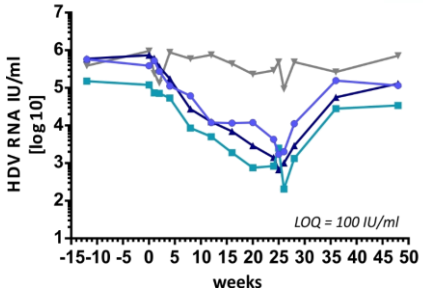
Myrcludex B- Open-label phase 2b study



Primary endpoint:
2 log decline HDV RNA or RNA Neg at Wk 24







Median RNA log change from baseline:
Myr B 2mg: -1.75
Myr B 5mg: -1.60
Myr B 10mg: -2.70
TDF: -0.18

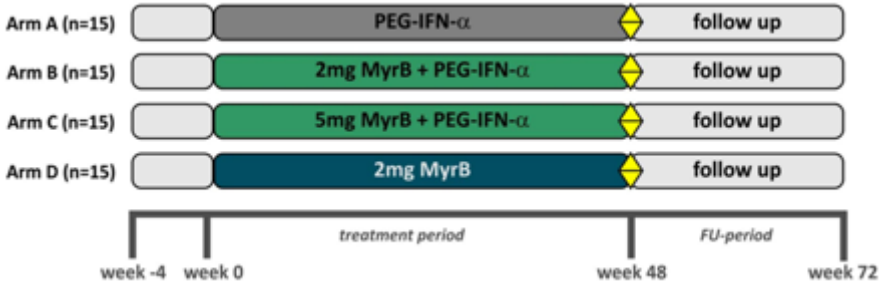
- ALT levels normalize in 40-50% (not dose-dependent)
- HBsAg does not change
- Bile acids increase without pruritus

Conclusion:

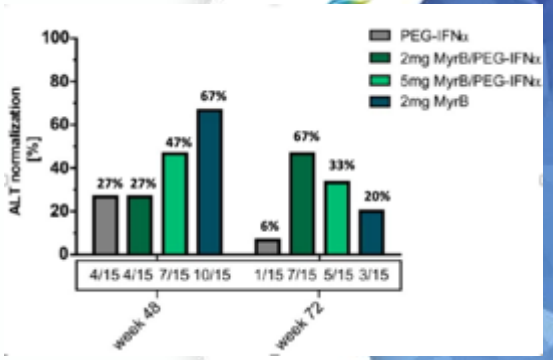
- Bulevirtide monotherapy induced HDV RNA declines and improved ALT levels
- Longer therapies than 24 weeks are needed *(modelling suggests 2-3 years)*

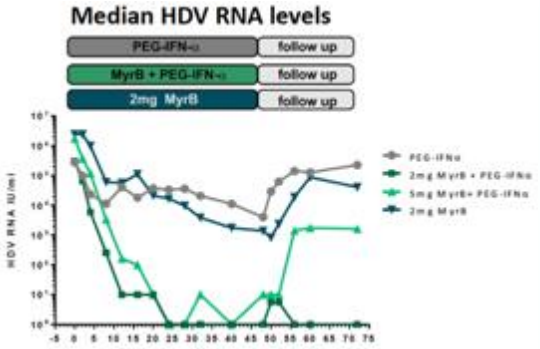
Wedemeyer et al. EASL 2018

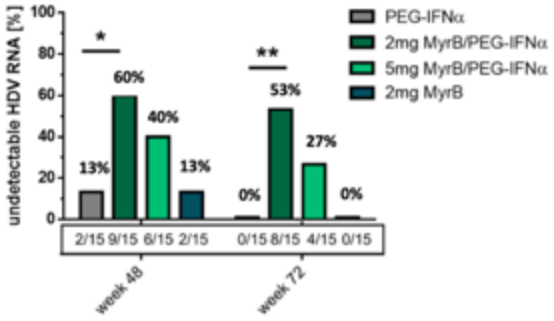
MYR 203 phase 2-End of study results



Primary endpoint:
Undetectable HDV RNA at week 72







weeks

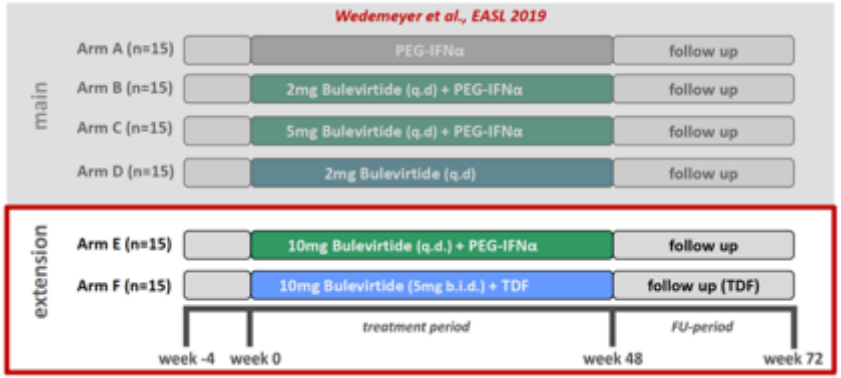
Median serum HDV RNA log reduction	week 48	week 72
PEG-IFNα	-1.30	-0.26
2mg MyrB + PEG-IFNα	-4.81	-4.04
5mg MyrB + PEG-IFNα	-5.59	-1.48
2mg MyrB	-2.84	-1.08

Conclusions:

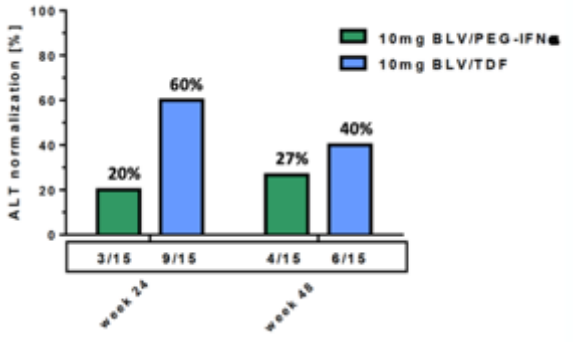
- Myr B monotherapy is safe and induces HDV RNA AND ALT reduction on Rx, but most patients relapse
- Combo therapy shows improved efficacy and may induce cure in a subset of patients

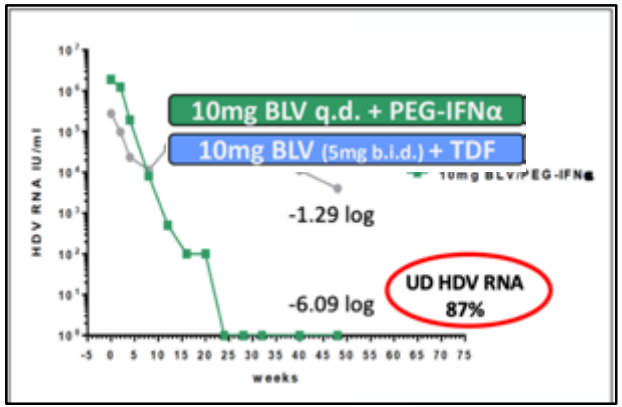
Wedemeyer et al. EASL 2019

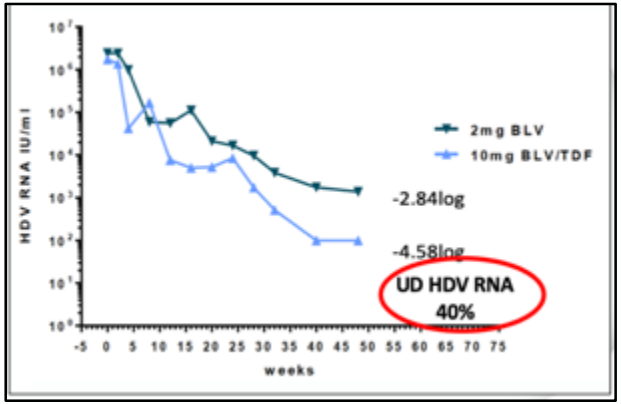
MYR 203-Extension study



<u>Primary endpoint:</u>
Undetectable HDV RNA at W72
W48 results presented





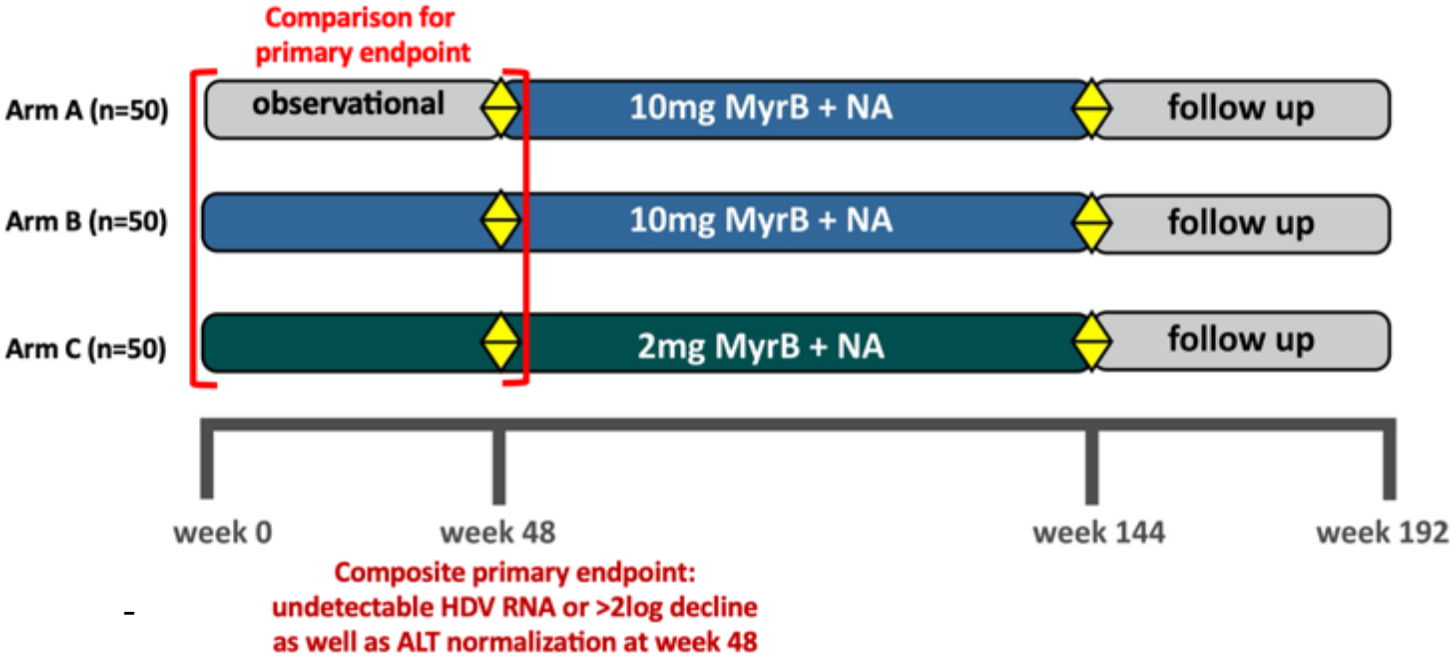


10mg BLV q.d. + PEG-IFNα — **HBsAg response: 6.7%**
10mg BLV (5mg b.i.d.) + TDF — **HBsAg response: 0%**

Conclusions:

- 10mg BLV monotherapy is safe and more suitable for maintenance therapy.
- As shown in lower doses, strong synergism with pegIFN
- No advantage in HBsAg response over lower doses
- Prolonged Rx (2-3y) will be studied in phase III trials

Myrcludex B for HDV: Phase 3 Pivotal Trial MYR301 -> Start Q4 2018

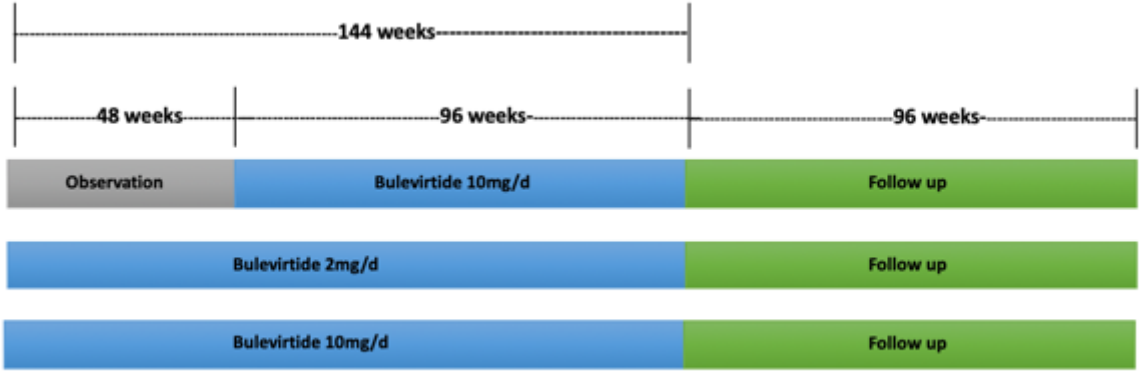


- Only patients with treatment indication for chronic HBV infection (EASL/AASLD guidelines) will be treated with NA

ClinicalTrials.gov Identifier: NCT03852719

Phase 3 Study of Bulevirtide in Patients With CHD

A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients With Chronic Hepatitis Delta



Primary outcome measure

Combined response: Undetectable HDV RNA or decrease by ≥ 2 log10 IU/ml from baseline

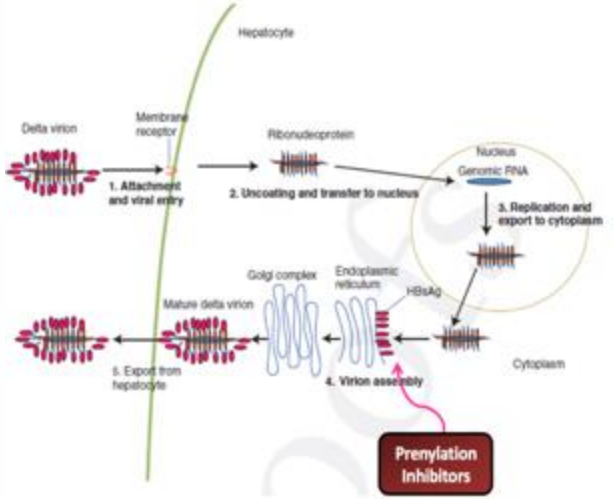
+

ALT normalization at week 48 weeks

ClinicalTrials.gov Identifier: NCT03852719

Lonafarnib

- Prenylation- lipid modification that involves addition of prenyl lipids to proteins resulting in promotion of membrane association and protein–protein interactions



- Small molecule, oral, prenylation inhibitor that inhibits attachment of prenyl lipid farnesyl to LHDAg

- Disruption of prenylation of LHDAg prevents the interaction with HBsAg and formation of secreted particles

- POC study- 14 pts, 28 days, LNF 100mg/200mg vs placebo
  Significant HDV RNA log decline, GI side effects with higher doses, no evidence of virological resistance

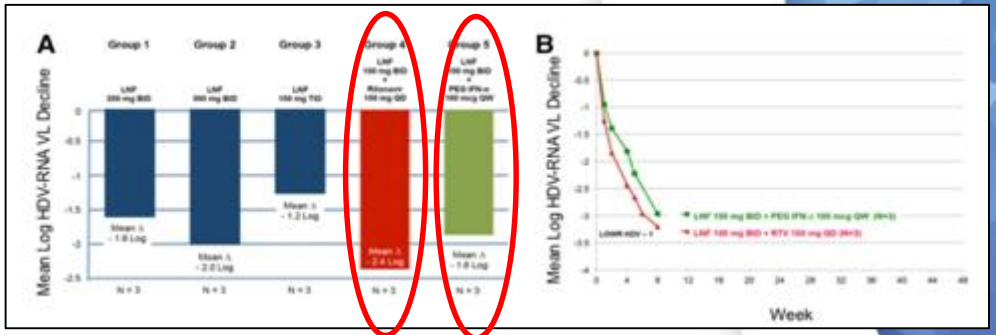
Lonafarnib phase 2 program

Identifying Dose and Regimen for Registration N=129

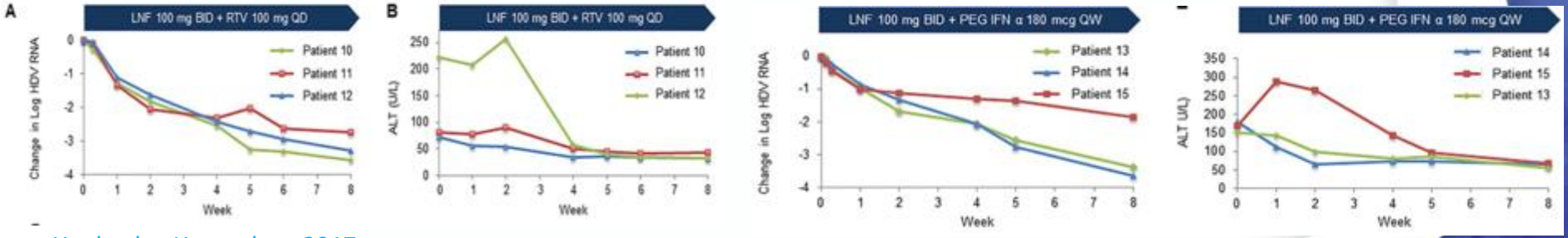
- **Proof of Concept**
  - Monotherapy — N = 14 — NIH
- **LOWR HDV – 1**
  - ± RTV or PEG IFN α — N = 15 — HEPATOLOGY 2017
- **LOWR HDV – 2**
  - Dose Finding +/- PEG IFN α — N = 58 — 2017/2018 EASL
- **LOWR HDV – 3**
  - QD Dose — N = 21 — NIH — 2017 EASL
- **LOWR HDV – 4**
  - Dose-Escalation — N = 15 — MHH Hannover Medical School — 2017 EASL

LOWR HDV-1

- Assess tolerability and viral response of different doses of LNF as monotherapy or in combination with RTV or PEG-IFNa
- Primary endpoint: HDV-RNA decline between baseline and end of treatment (8/12 weeks)
- Combo therapies – significant viral decline and ALT normalization, improved GI tolerance

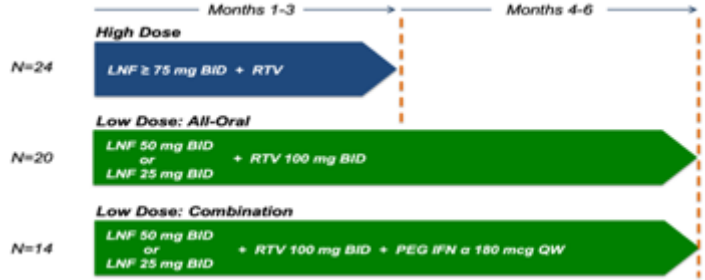


Viral rebound in all but 2 pts who had ALT flares→ HDV UD →HDV UD/LLOQ



Yurdaydın. Hepatology 2017

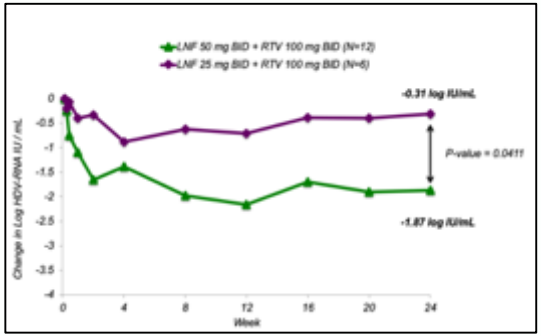
LOWR HDV – 2: "Dose Finding" Study

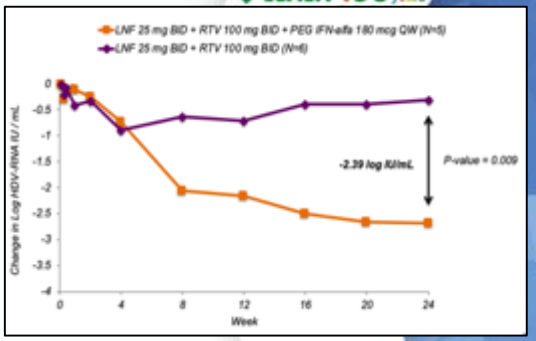


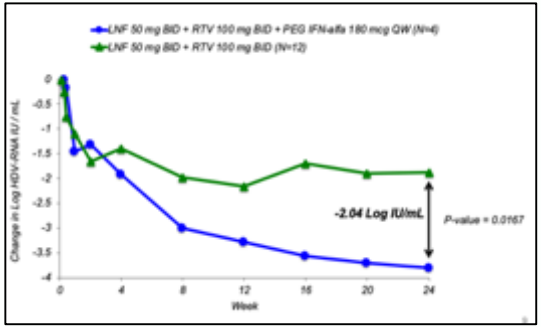
Aim: Identify optimal combination regimens of LNF and RTV ± PEG-IFNα with efficacy and tolerability for longer term dosing

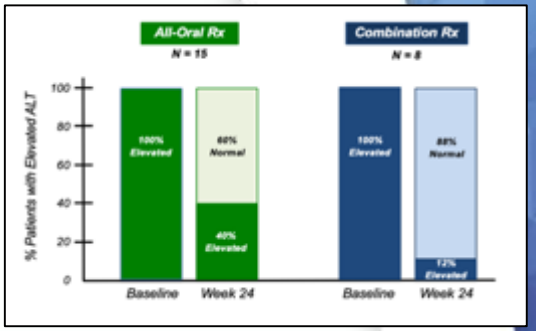
Primary endpoint:
HDV RNA decline from baseline→EOT

Regimen	# of Patients				
	Dosed 24 Wks	BL VL ≤ 4 log (%)		BL VL > 4 log (%)	
		BLOQ (%)	≥ 2 log decline (%)	BLOQ (%)	≥ 2 log decline (%)
LNF 50 mg BID + RTV 100 mg BID + PEG IFN-α	4	0 / 0 (0%)	0 / 0 (0%)	2 / 4 (50%)	4 / 4 (100%)
LNF 25 mg BID + RTV 100 mg BID + PEG IFN-α	5	1 / 1 (100%)	1 / 1 (100%)	2 / 4 (50%)	3 / 4 (75%)
LNF 50 mg BID + RTV 100 mg BID	12	5 / 5 (100%)	5 / 5 (100%)	0 / 7 (0%)	1 / 7 (14%)
LNF 25 mg BID + RTV 100 mg BID	6	0 / 3 (0%)	0 / 3 (0%)	0 / 3 (0%)	1 / 3 (33%)







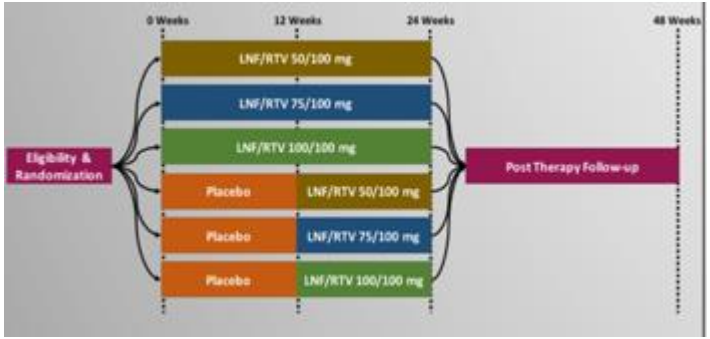


Summary: All-oral LNF +RTV regimens- 39% viral response at W24
Addition of PEG IFN to LNF +RTV- 89% viral response at W24
Post Rx ALT flares followed by HDV RNA negativity
Mild-moderate GI side effects with LNF 25mg/50mg +RTV

Conclusions: All-oral regimens- viable option for patients with low viral load
Combo therapy results in highest response rate

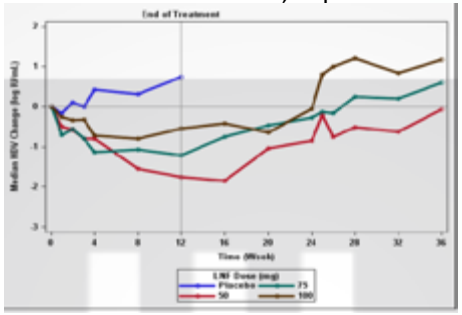
Yurdaydın et al. EASL 2018

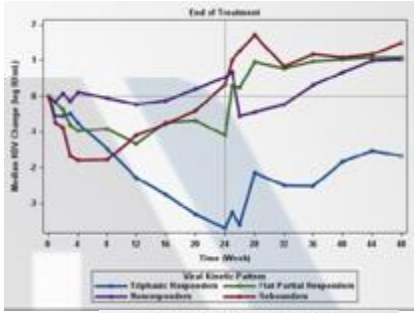
LOWR-3 – Once daily dosing study



Primary objective

-To assess the antiviral effects and safety of once daily RTV boosted LNF, in patients with chronic HDV infection

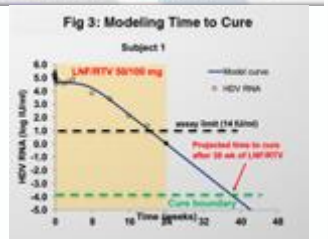




Treatment was safe and generally well tolerated

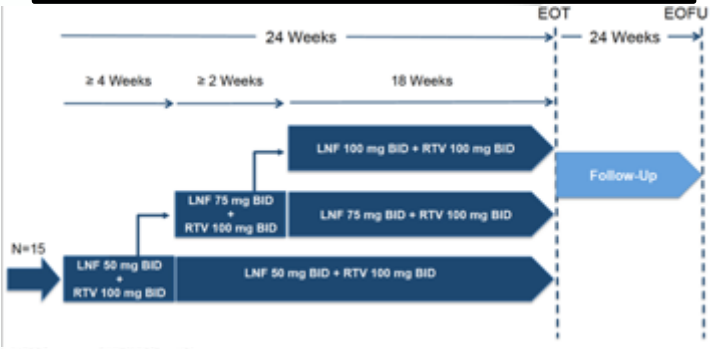
Response guided therapy beyond 6 months may lead to viral clearance

In a subset of patients



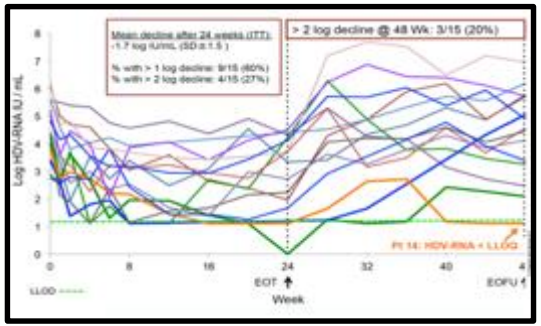
Koh et al. EASL 2017

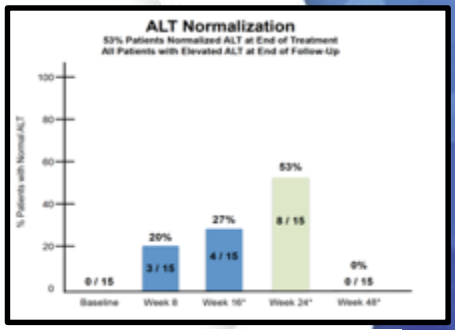
LOWR-4 Dose Escalation study



Primary Objectives

- Dose-escalation / maintenance up to LNF 100 mg BID + RTV for 24 weeks
- Safety and tolerability of LNF + RTV dose-escalation for 24 weeks
- HDV-RNA decline over 24 weeks





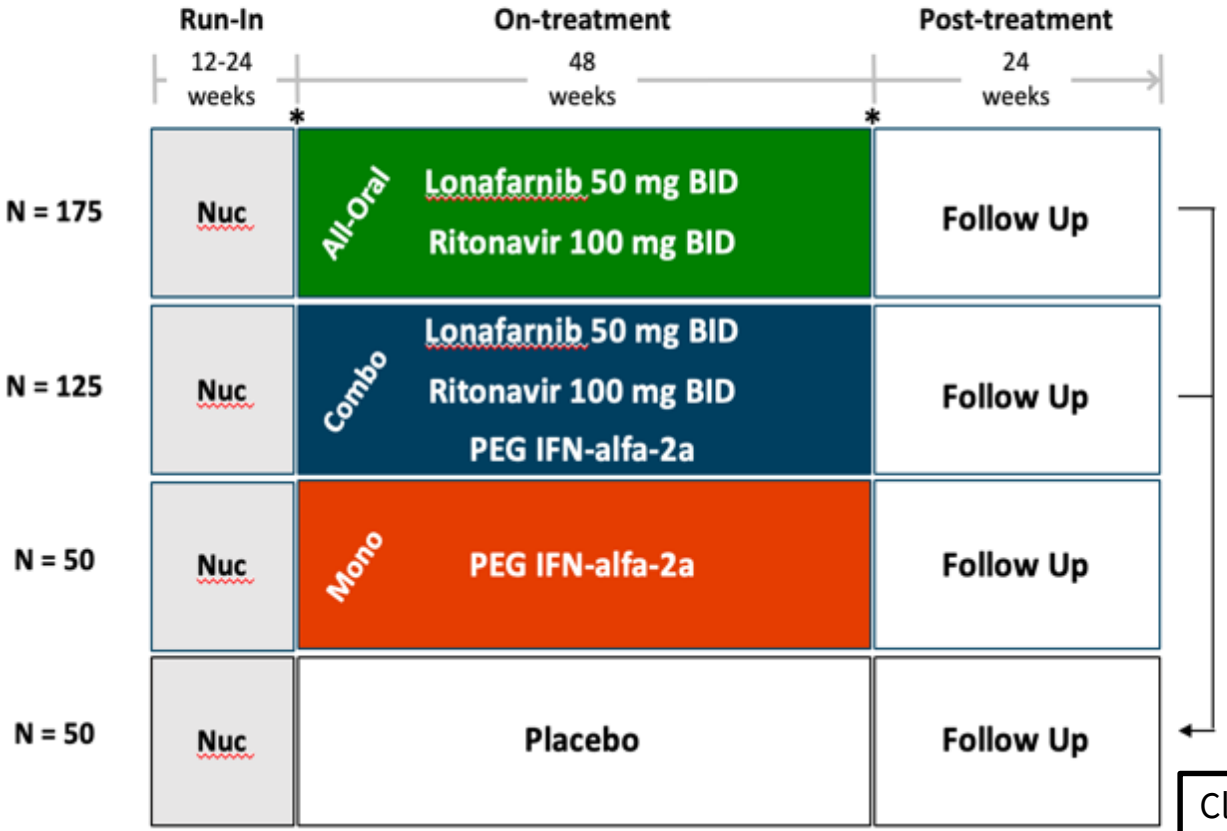
Gastrointestinal AEs

- mostly grade 1-2
- 8/15 (53%) required dose reduction and 2/15 (13%) were discontinued

Wedemeyer et al. EASL 2017

D-LIVR : PHASE 3 GLOBAL STUDY

Delta-Liver Improvement and Virologic Response in HDV



Primary Endpoint at Week 48

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

Secondary Endpoint at Week 48

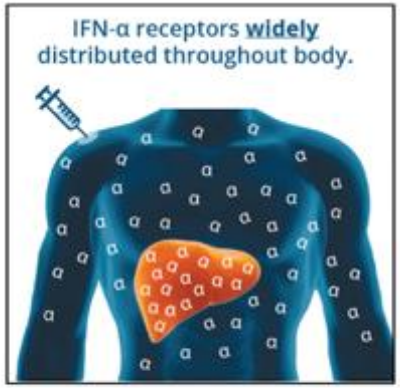
- Histologic improvement
  - > 2-point improvement in HAI inflammatory score
  - No progression in fibrosis
- Improvement of fibrosis

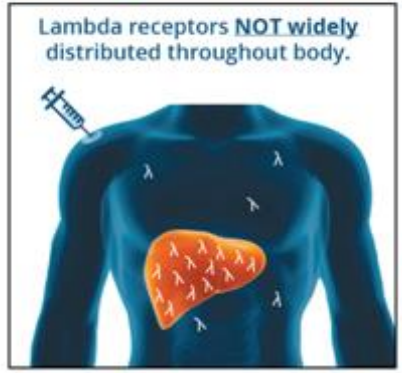
ClinicalTrials.gov Identifier: NCT03719313

Pegylated Interferon Lambda

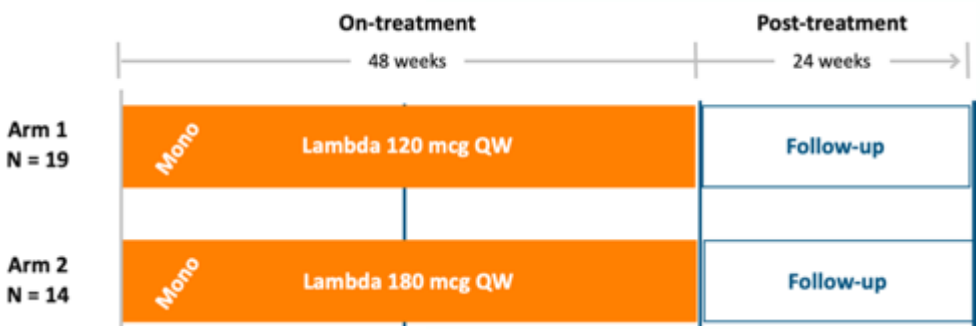
- A novel first in class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells
- Uses similar downstream signaling pathway as Type I interferons
- Greater than 3,000 patients in 17 clinical trials (HCV / HBV)
- Comparable antiviral activity with less of the typical IFN alfa related side effects*

** Chan, HLY et al, J Hepatology 2016*





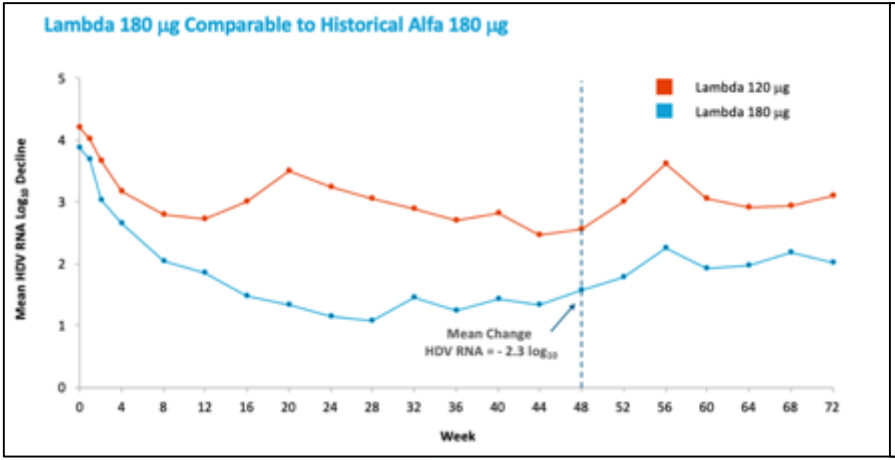
LIMT: Phase 2 Lambda Monotherapy Study

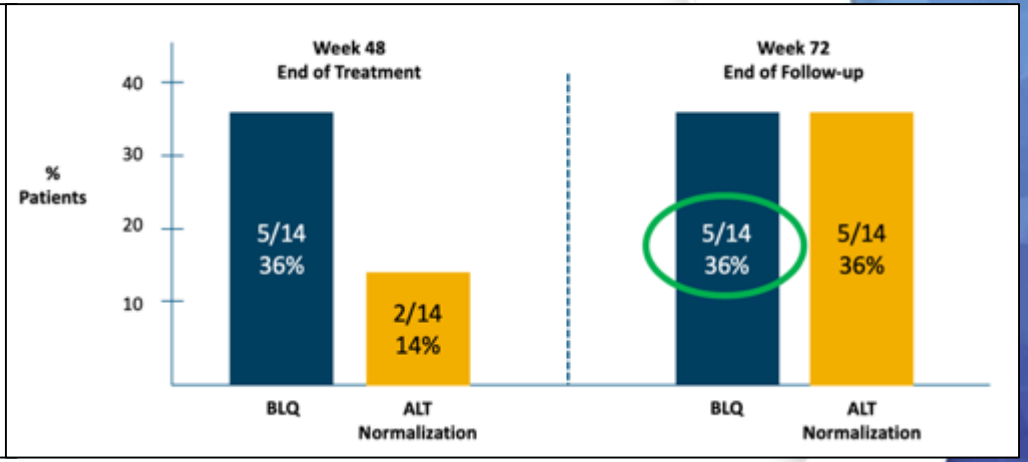


Objectives:

-Evaluate safety and tolerability of Lambda monotherapy for 48 wks

-Efficacy endpoint: Change in HDV RNA from BL to Week 48 and Week 72



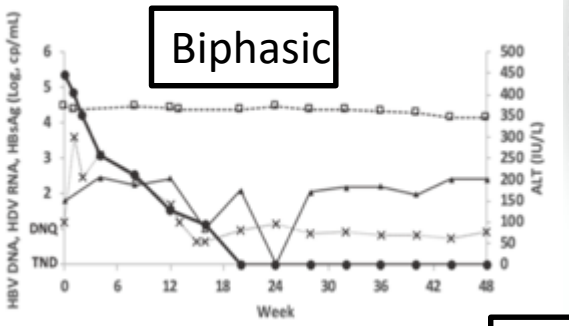


Etzion et al. EASL 2019

LIMT: Phase 2 Lambda Monotherapy Study

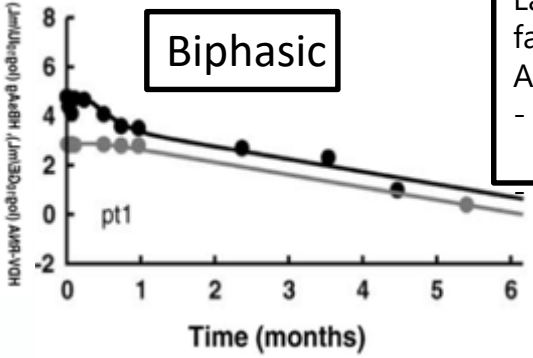
Dose		N	48 Week On-Treatment: Mean Log_{10} Decline	48 Week On-Treatment: # BLQ	24 Week Post-Treatment: # BLQ
180 µg	All	14	-2.3	5 / 14 36%	5 / 14 36%
	High BL VL	8		3 / 8 38%	2 / 8 25%
	Low BL VL	6		2 / 6 33%	3 / 6 50%

LAMBDA



Classification	Adverse Event	Number of Patients Experiencing Grade of AE (N=33)			
		Gr 1	Gr 2	Gr 3	Gr 4
Constitutional	fatigue, asthenia	10	2	-	-
Flu-like	pyrexia, chills, chest pain, flu-like	21	5	-	-
Neurological	dizziness, headache	17	8	-	-
Musculoskeletal	arthralgia, myalgia, back pain, musculoskeletal pain	18	9	-	-
Psychiatric	depression, irritability, insomnia	1	-	-	-
Hematological	neutrophil count decreased	-	-	-	1**
Lab Abnormalities	bilirubin / ALT / AST / GGT increase	2	1	9	1**

ALPHA



Conclusions:
-Durable virologic response of Lambda (36%) compares favorably to historic rates for Alfa 180 µg (28%)
- Better tolerability than Alpha
- Histologic improvement?

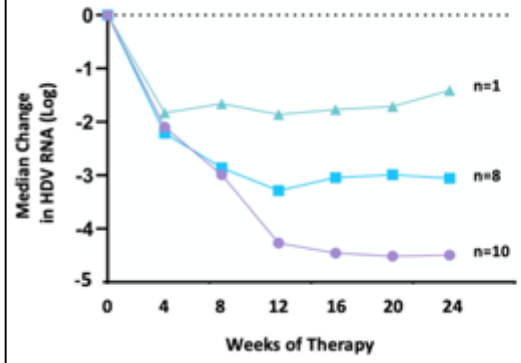
Etzion et al. AASLD 2019

LIFT HDV Study

- Phase 2a, Open-Label Study
- Lambda 180 mcg/w+ LNF 50mg/RTV 100 bid for 24 weeks
- Primary Endpoints:

  >2 log decline HDV RNA at W24

  Safety of triple combination for 24 weeks



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

Most Common Adverse Events								
Nausea	Diarrhea	Anorexia	Abdominal Bloating	GERD	Fatigue	Weight Loss	Anemia	Hyperbilirubinemia
63%	100%	47%	63%	63%	32%	37%	32%	21%

Dose Reductions/Discontinuations			
	Hyperbilirubinemia	Anemia	Ascites
Dose Reduction	2	1	
Discontinuation	3		1

Summary

- Therapy with LMD/LNF/RTV was relatively safe in most patients for up to 6 months.
- Per protocol discontinuation of triple combination therapy was mostly due to known side effects related to peginterferon lambda.

Koh et al. AASLD 2019

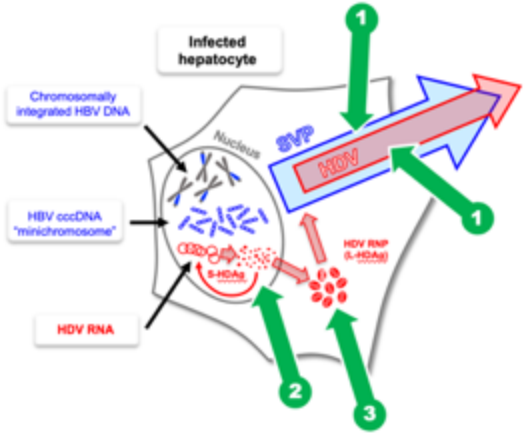
Nucleic Acid Polymers—REP 2139

- Nucleic acid polymers (NAPs) are oligonucleotides with broad spectrum in vitro antiviral activities
- Proposed to bind to amphipathic protein structures

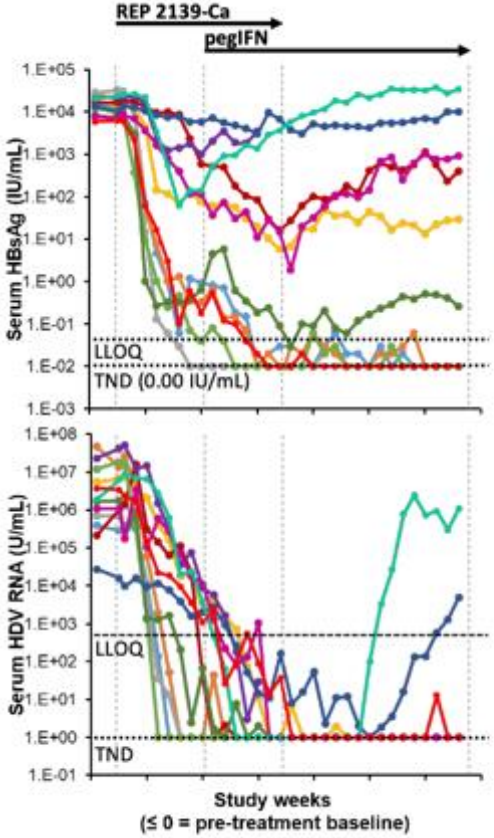
1 Inhibition of HBV SVP assembly / secretion and HDV envelopment
- Allows host mediated clearance of HBsAg / HDV
- Blocks release of HDV

2 Interaction with S-HDAg
- Potential upstream inhibition of HDV RNA synthesis

3 Interaction with L-HDAg
- Potential upstream inhibition of HDV RNP assembly



REP 2139-Ca / Pegasys™ Combination Therapy in HBV / HDV Co-infection



Rapid HBsAg clearance prior to pegIFN

Universal and rapid HBV RNA response

Target not detected in 11/12 participants during therapy

Even in participants with moderate HBsAg response

Likely due to upstream direct effects against HDV replication

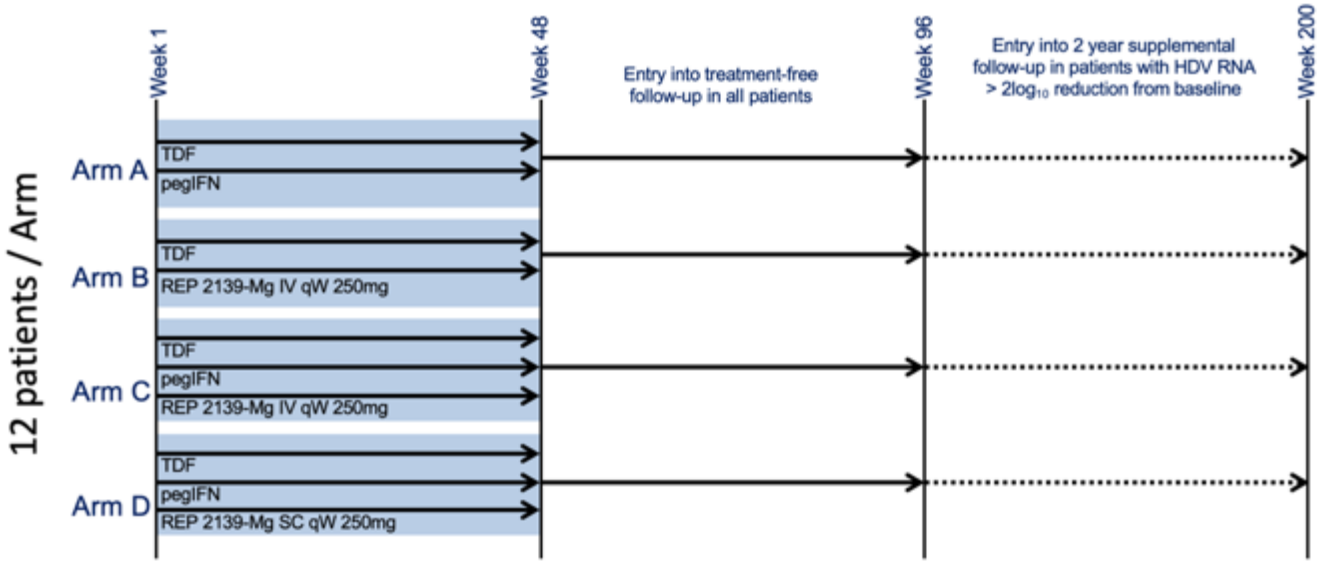
Completed treatment and 3.5 years of follow-up		**11**
Clinical response	Normal ALT	8/11 (73%)
	Normal / declining liver median stiffness	7/11 (64%)
HBsAg response	< 1 IU/ml	6/11 (55%)
	≤ LLOQ (0.05 IU/mL)	5/11 (42%)
	Seroconversion	4/11 (36%)
HDV RNA response	**> 2 log_{10} reduction from baseline**	**9/11 (82%)***
	TND	**7/11 (64%)**

***2 participants maintaining 2.67 and 2.12 log_{10} HDV RNA reduction from baseline at 3.5 years follow-up did not maintain normal liver function during follow-up.**

Functional cure of HDV at 3.5 years of follow-up (HDV RNA TND, ALT normal)		**7**
HBV DNA response	≤ 2000 IU/mL	7/7 (100%)
	Target not detected (TND)	5/7 (71%)
HBV virologic response	Virologic control HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)	3/7 (43%)
	Functional cure HBV (HBsAg < LLOQ, HBV DNA TND, normal ALT)	4/7 (57%)
	HBV clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)	**7/7 (100%)**
On-therapy flare	Asymptomatic transaminase flare while HBsAg ≤ 1IU/mL	7/7 (100%)

REP 501

REP 2139-Mg IV vs SC in HBV / HDV co-infection



Objectives:

Assessment of safety tolerability and efficacy

Endpoints:

-HBsAg and HDV RNA loss during therapy

-HBsAg seroconversion

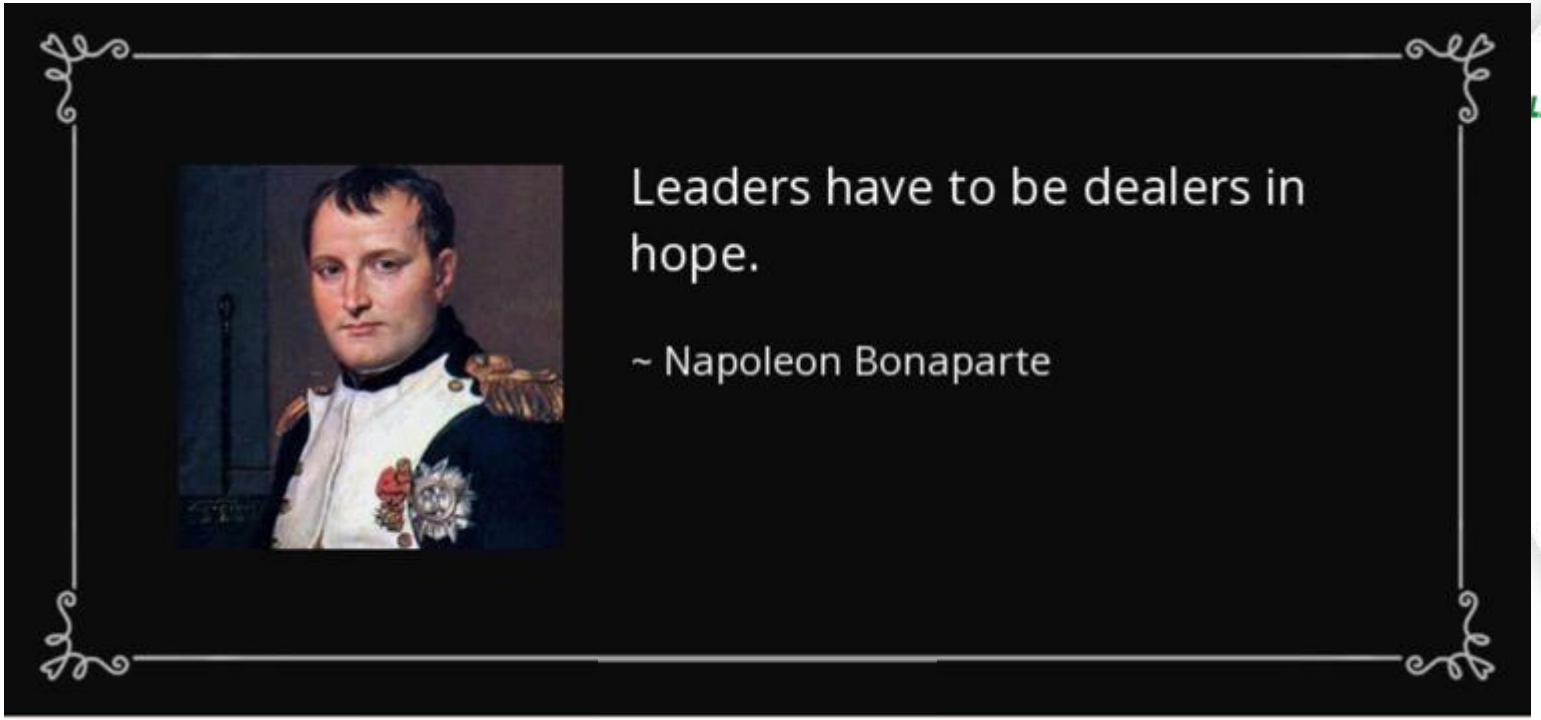
Therapeutic transaminase flares

-functional cure of HBV & HDV >6 months following treatment cessation

Tentative starting date: Tentative Q4 2020 .

In summary

- CHD is a severe disease for which current management is unsatisfactory
- Data on surrogate endpoints predicting long term clinical benefit is sparse
- Clinical trials assessing novel therapies for HDV rely on endpoints that are reasonably likely to predict clinical benefit
- Long term follow up will be required to establish the validity of these endpoint as surrogate markers of clinical benefit
- Therapies allowing viral suppression/elimination are on the horizon



Thank You!

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