HDV Approaches - Clinical and Regulatory

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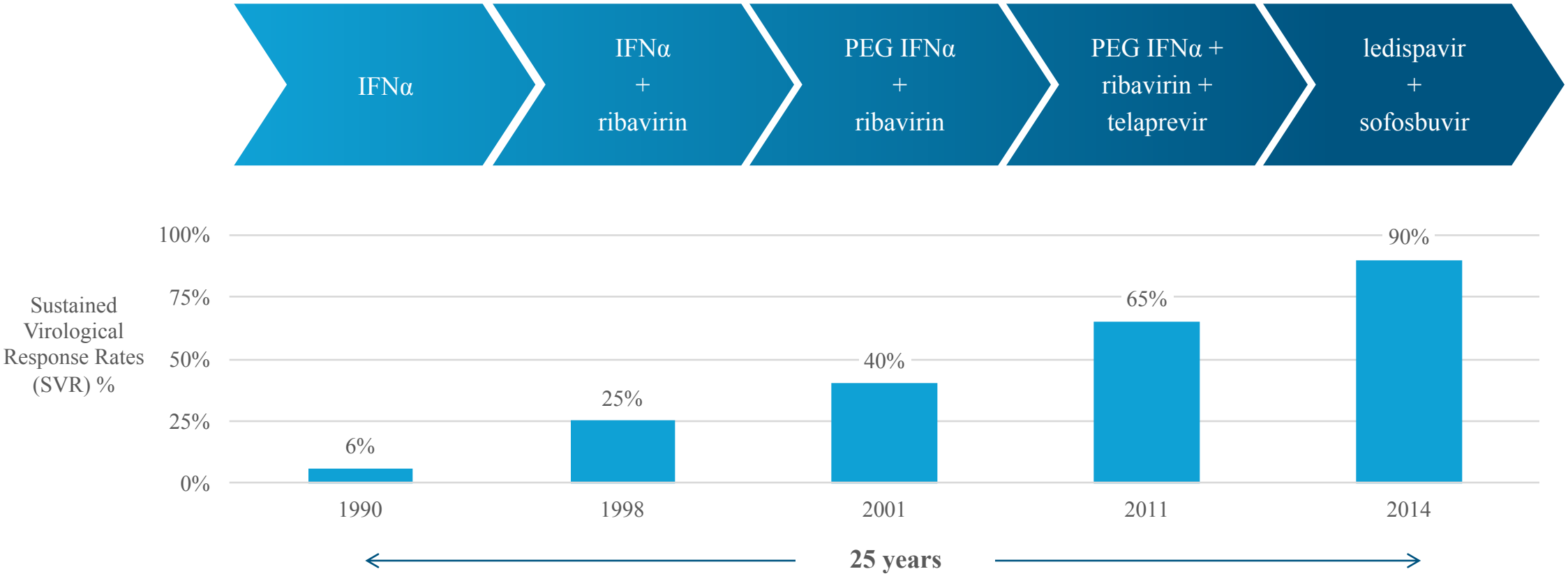
10/20/17

Disclosures: Romark Laboratories, Genentech, Merck, Roche, StemCells Inc., Eiger Group International Inc., Eiger BioPharmaceuticals, Inc., Riboscience, LLC

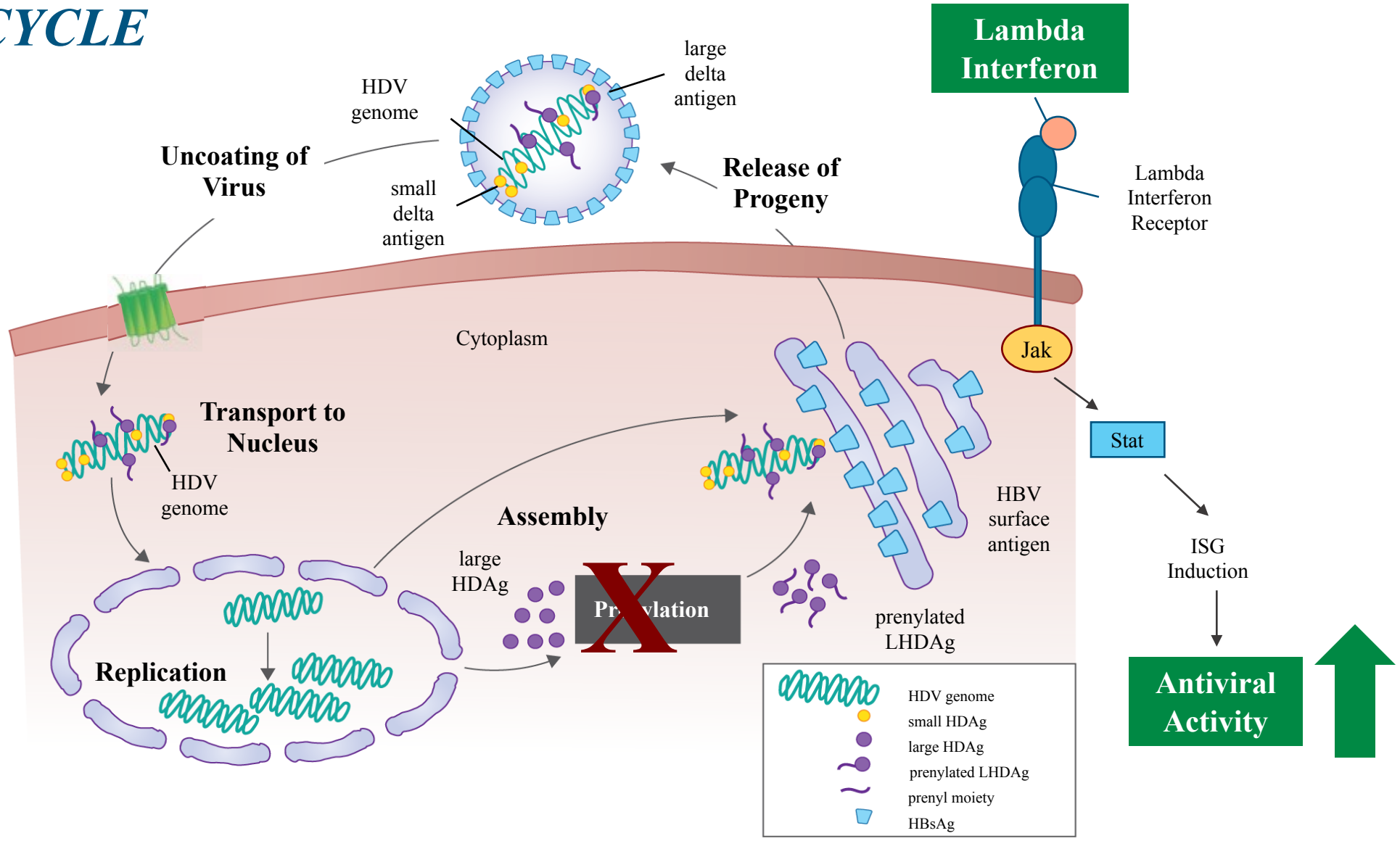
COMBINATION THERAPY MOST EFFECTIVE FOR HEPATITIS C



We Believe Combination Therapy Will Benefit HDV Patients

Source: Frost and Sullivan HCV Reports, Manns et al Nat Rev Drug Dis 12 (2013)

HDV LIFE CYCLE



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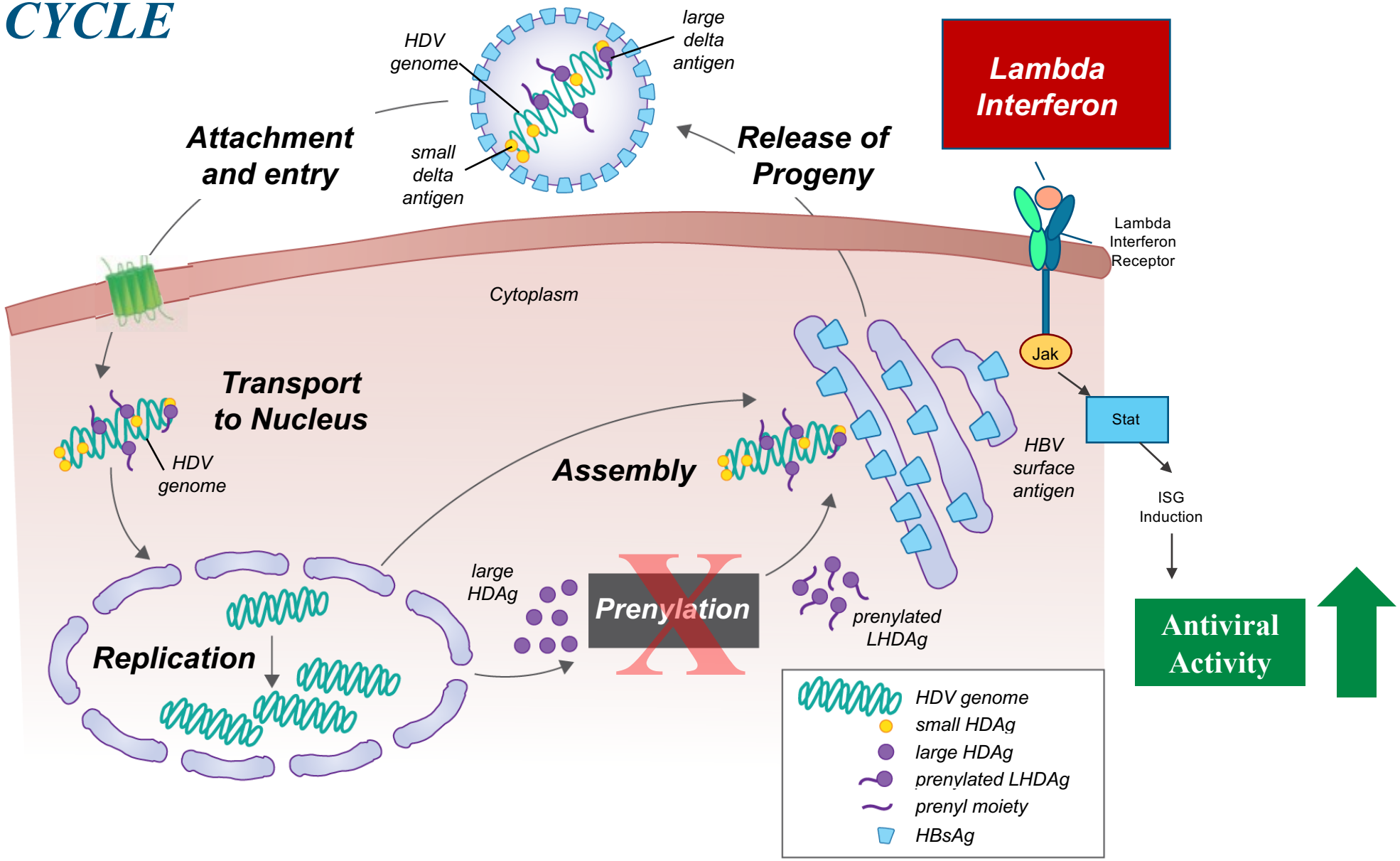


TWO COMPLEMENTARY ASSETS FOR HDV

Multiple Treatment Options

Lonafarnib

- Small molecule oral prenylation inhibitor
- >2000 patients previously dosed in oncology trials
- >120 HDV-patients dosed
- Dose regimens and endpoints defined

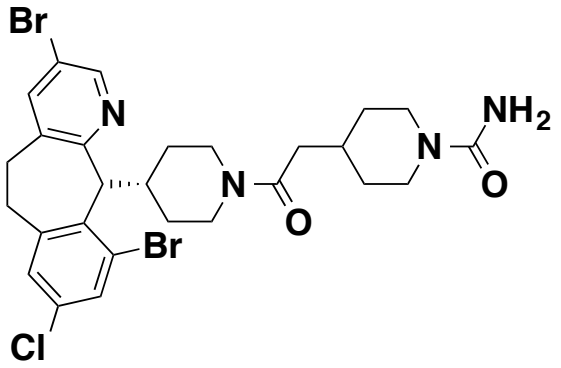
Lambda

- Potential for **less** IFN-associated abnormalities*
- >3000 patients previously dosed in HBV / HCV trials
- 33 HDV-patients dosing
- Interim data to be presented at AASLD 2017

*Chan, HLY et al, J Hepatology 2016.

LONAFARNIB FOR HDV

Well-characterized Clinical Stage Lead Compound



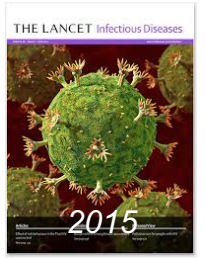
- Small molecule, oral, prenylation inhibitor
- Well-characterized through Phase 3
  - >2,000 patients dosed in oncology program by Merck (Schering)
  - Dose limiting toxicity is GI (class effect)
- Over 120 HDV patients dosed across international sites
- HDV Orphan Designation in US & EU, Fast Track in US
- Prenylation is a host target; potential barrier to resistance

Phase 2 proof of concept study conducted at NIH; NIH Phase 2 study results published: Koh et al, Lancet Infect Dis, 2015.

LONAFARNIB PHASE 2 PROGRESS

Goal: Identify Dose and Regimen for Registration N=129

- **Proof of Concept**
  - Monotherapy — N = 14
- **LOWR HDV – 1**
  - ± RTV or PEG IFN-α — N = 21
- **LOWR HDV – 2**
  - Dose Finding ± PEG IFN-α — N = 58
- **LOWR HDV – 3**
  - QD Dose — N = 21
- **LOWR HDV – 4**
  - Dose-Escalation — N = 15



Manuscript Submitted Hepatology

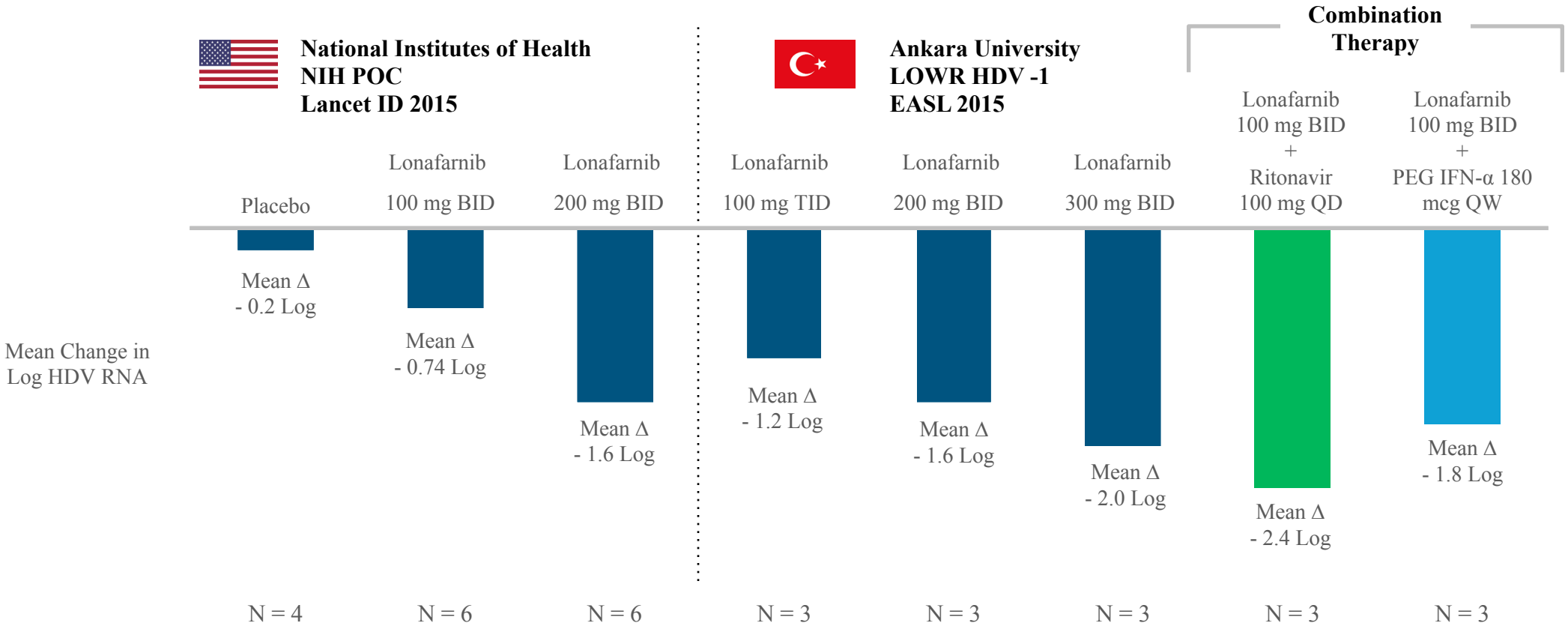
Draft Manuscript

Draft Manuscript

LOWR HDV = **LO**nafarnib **W**ith **R**itonavir in **HDV**

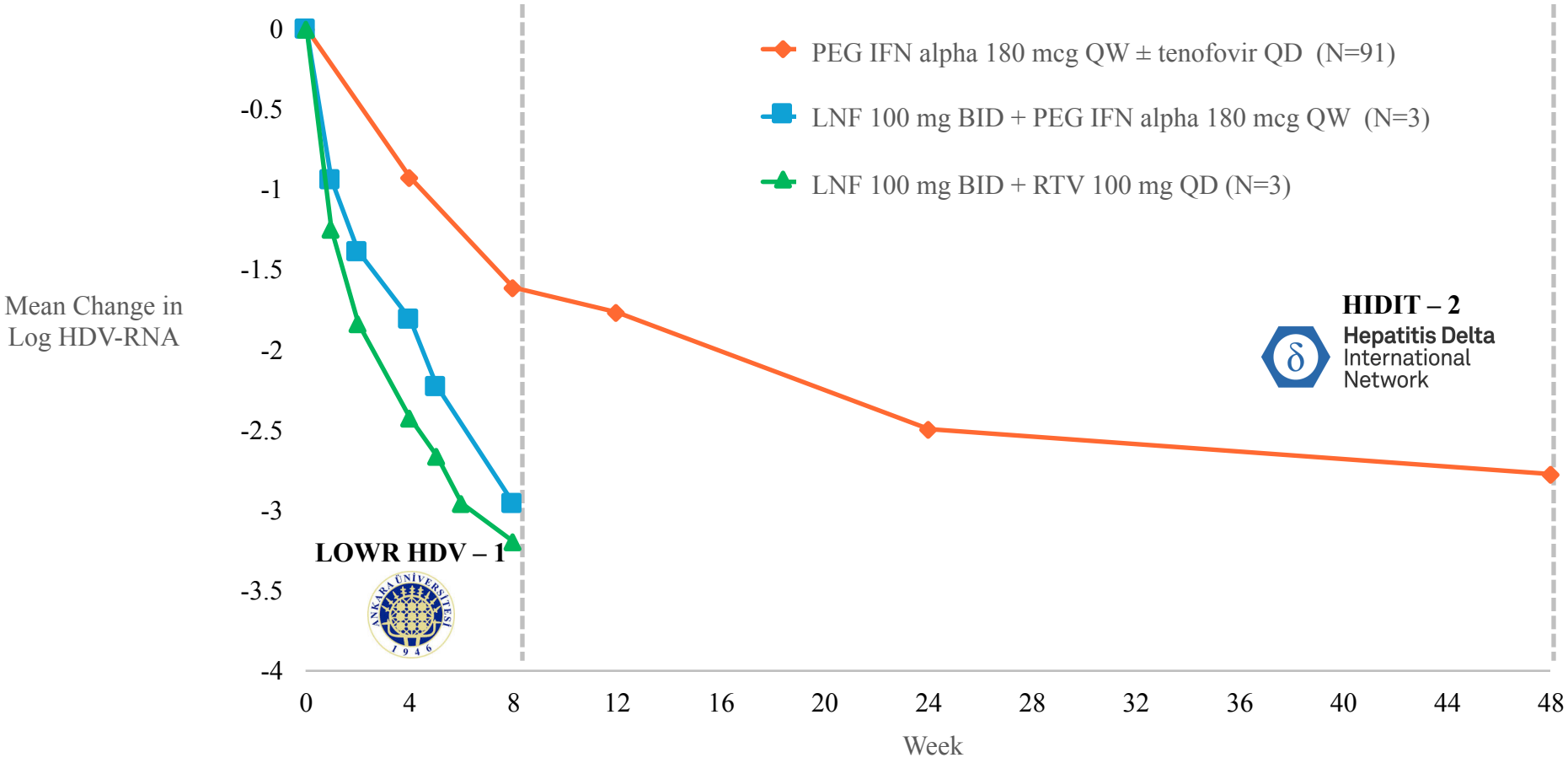
LONAFARNIB DECREASES HDV-RNA VIRAL LOAD

4 Week Reduction in HDV-RNA with Lonafarnib



Koh et al, Lancet Infect Dis, 2015.
LOWR HDV = LOnafarnib With Ritonavir in HDV; Yurdaydin, C. et al, EASL 2015 Abstract #O118

RAPID DECLINE WITH LONAFARNIB COMBINATIONS



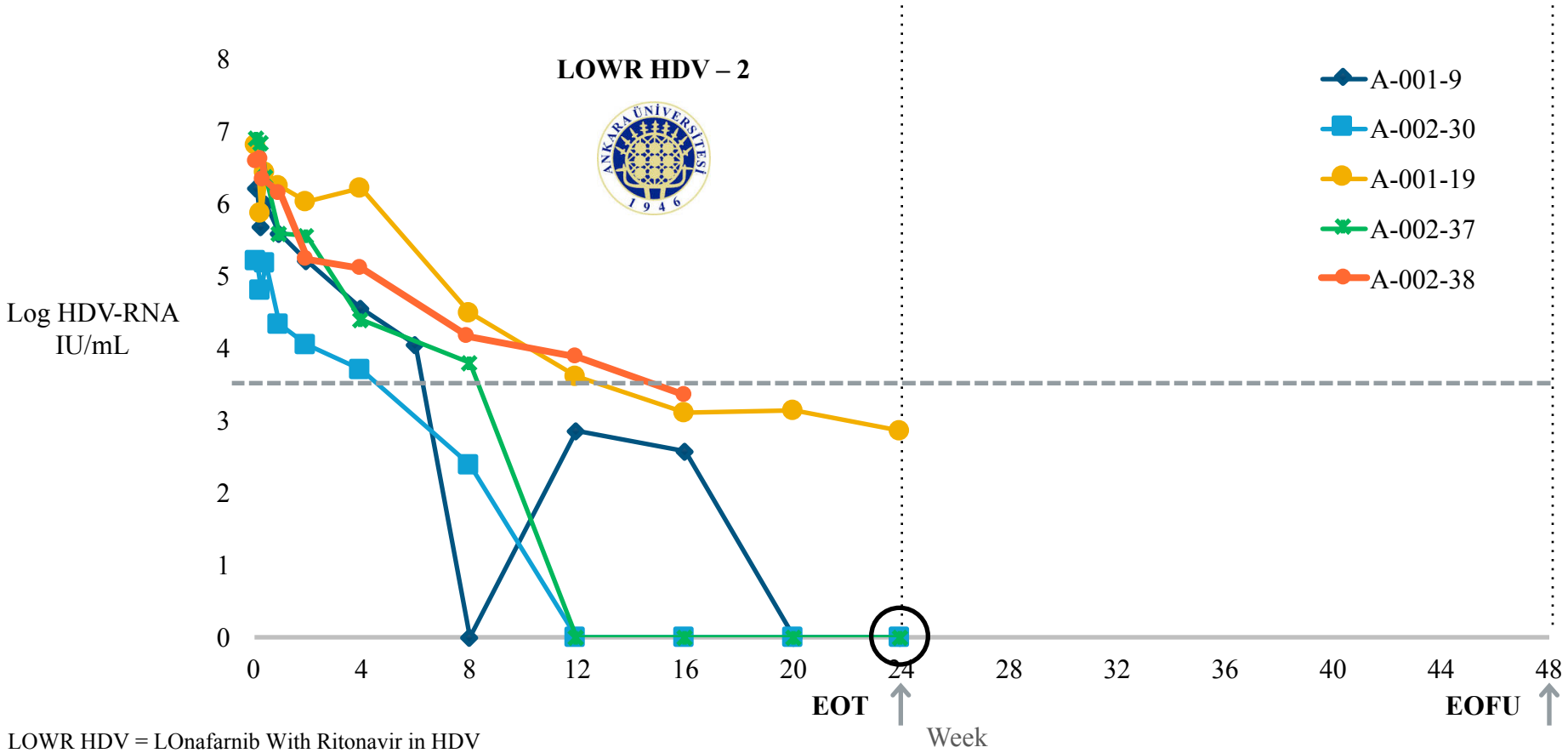
Rapid Viral Load Decline After 2 Months

Next steps: Explore dose-ranging, combinations, longer duration

LOWR HDV = LOnafarnib With Ritonavir in HDV
Meta-analysis of LOWR HDV-1 and HIDIT-2 studies

COMBINATION: HIGHEST RESPONSE RATES

LNF 25 mg BID + RTV + PEG IFN α



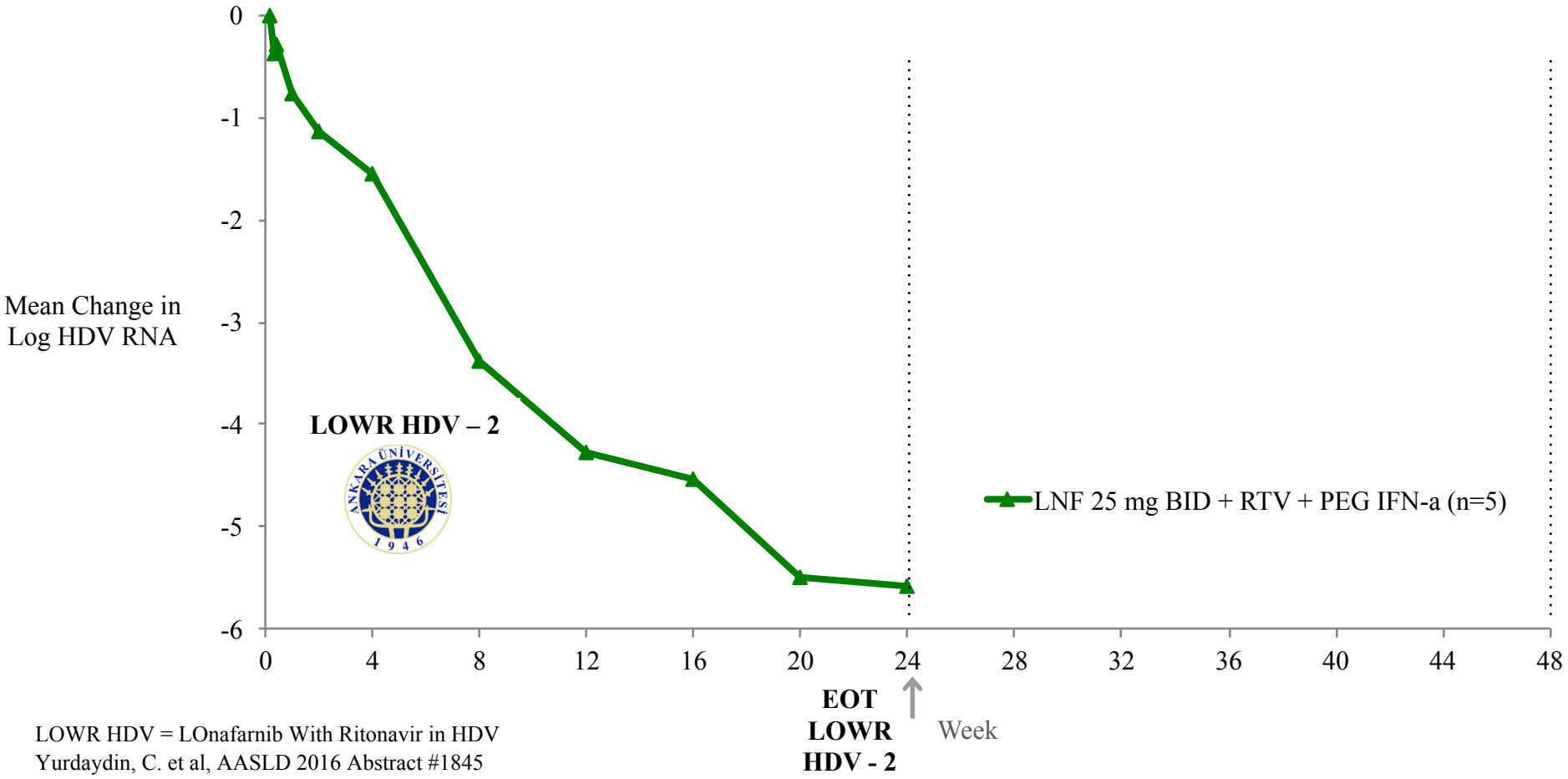
Highest Percent of Patients Achieving PCR-Negative Levels @ Week 24

LOWR HDV = LOnafarnib With Ritonavir in HDV
Yurdaydin, C. et al, AASLD 2016 Abstract #1845

AASLD 2016

COMBINATION: LNF 25 MG BID + RTV + PEG IFNα

Most Rapid and Profound Decline in HDV-RNA



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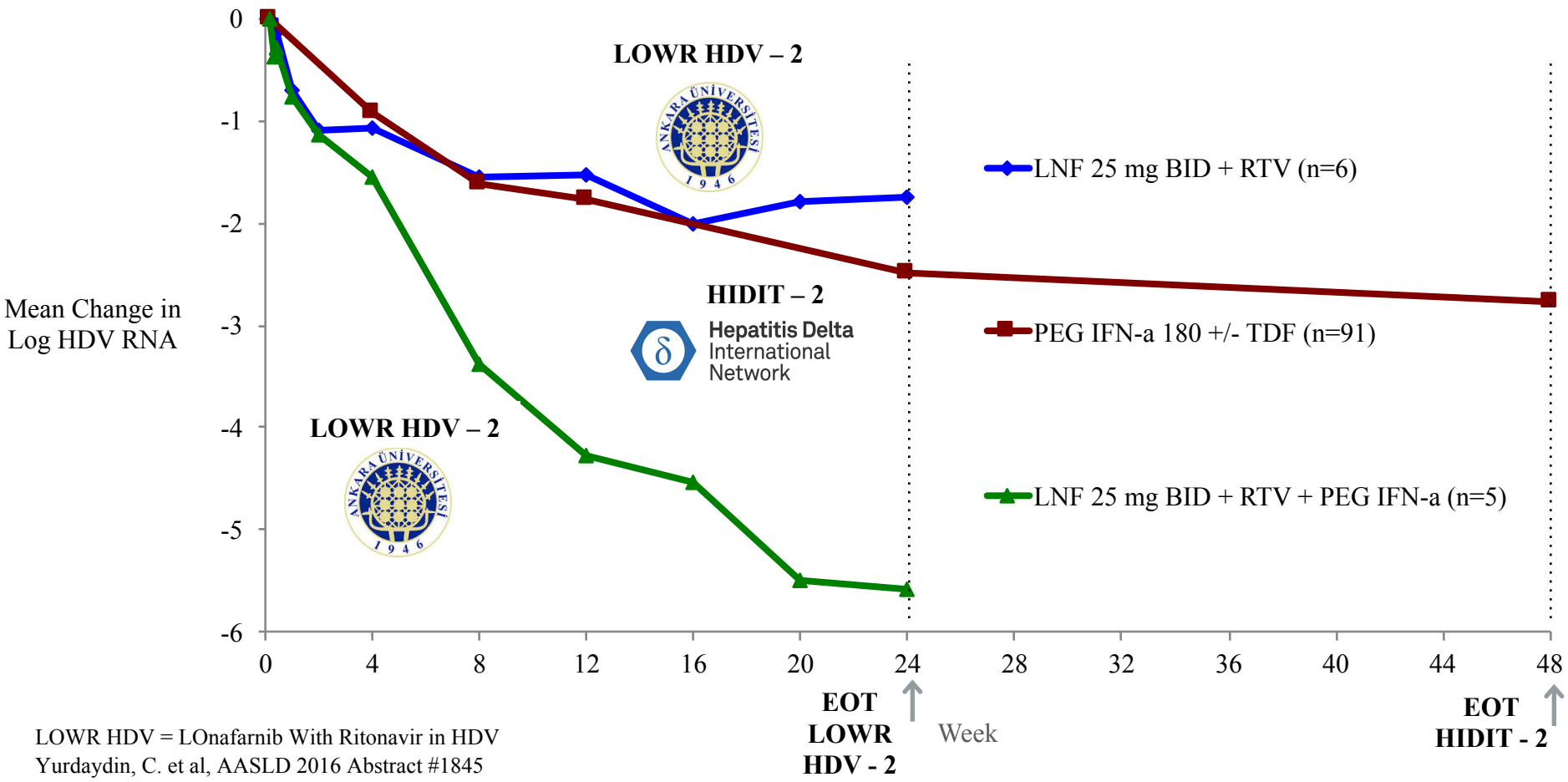

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Yurdaydin, C. et al, AASLD 2016 Abstract #1845

AASLD 2016

*PHASE 2: LOWR HDV PROGRAM**

Key Findings from EASL 2017

- All-oral LNF + RTV suppresses HDV-RNA < LOQ
- Addition of PEG IFN α to LNF 25 mg BID + RTV
  - results in highest response rates
- Majority of patients normalized ALT at Week 24
- GI AEs predominantly mild / moderate

Goal: Define Dose Regimens and Endpoints

Basis of Agency Discussions

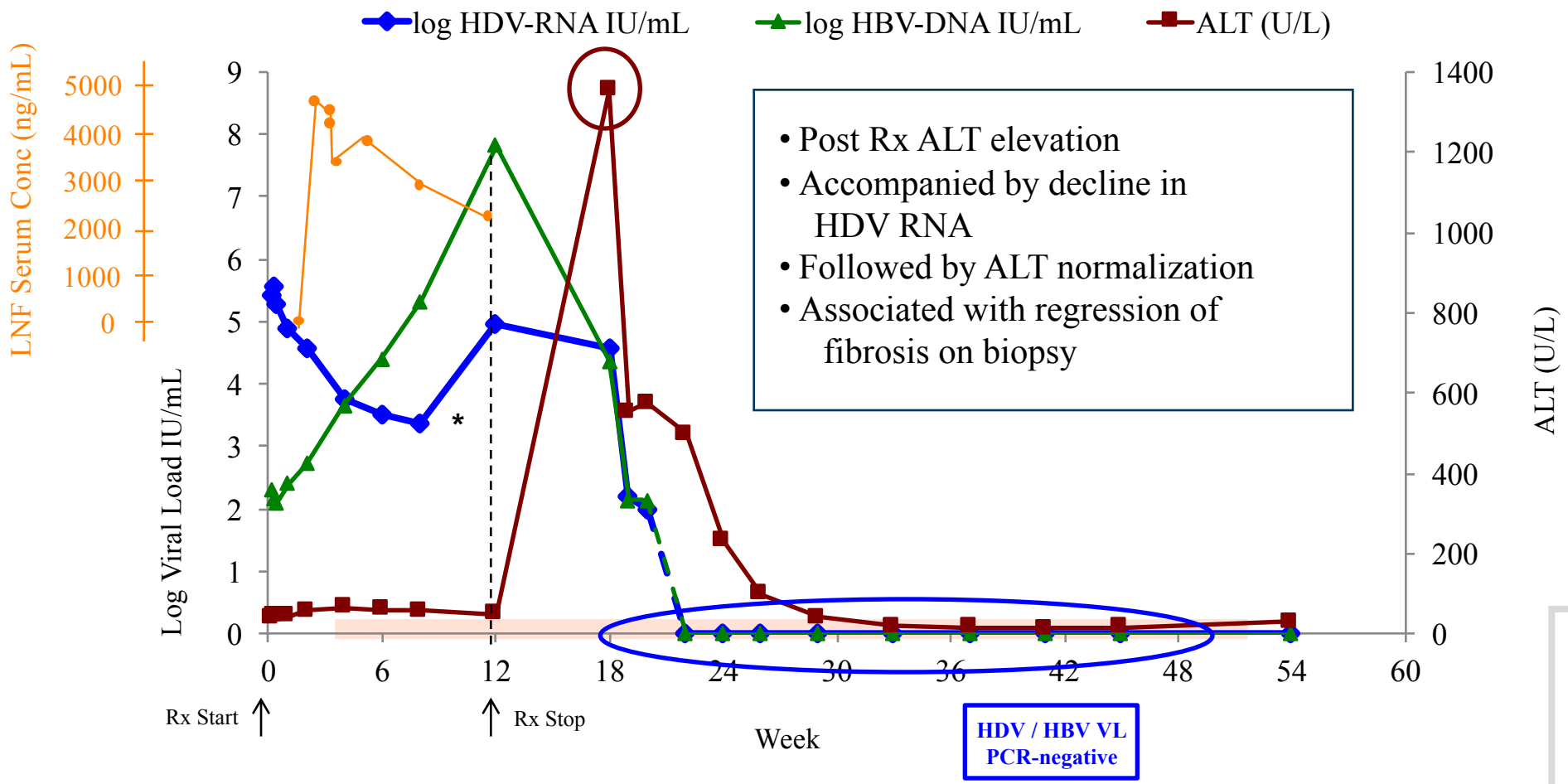
* LOWR HDV = LOnafarnib With Ritonavir in HDV

Yurdaydin et al., EASL 2017 Abstract #GS-008, Koh et al., EASL 2017 Abstract #LBP-519, Wedemeyer et al., EASL 2017 Abstract #PS-039

EASL The Home of Hepatology 2017

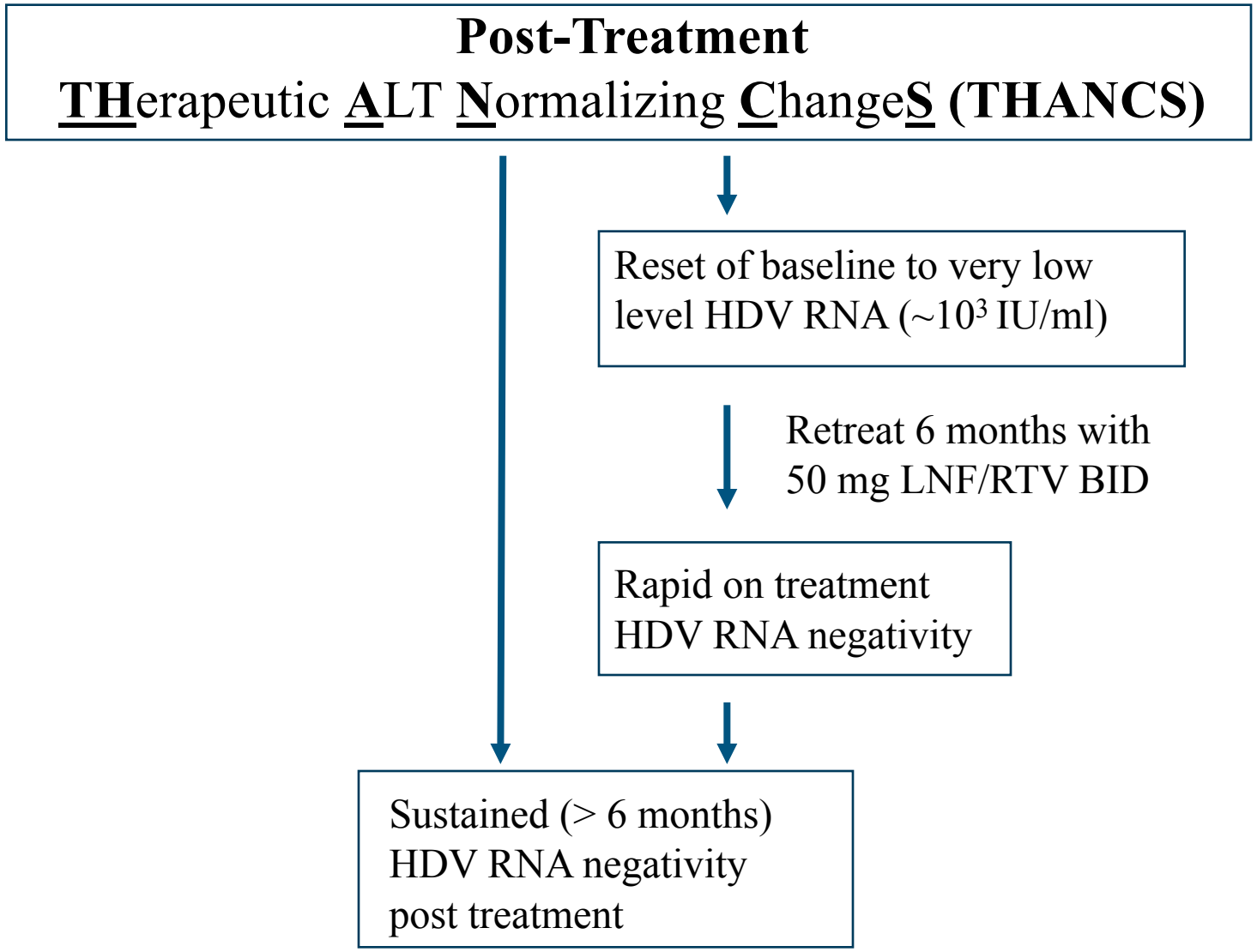
POST-TREATMENT: LNF 100 MG BID + RTV 50 MG BID

Post-Treatment THerapeutic ALT Normalizing ChangeS (THANCS)



AASLD 2016

TWO OUTCOMES OF THANCS REACTIONS



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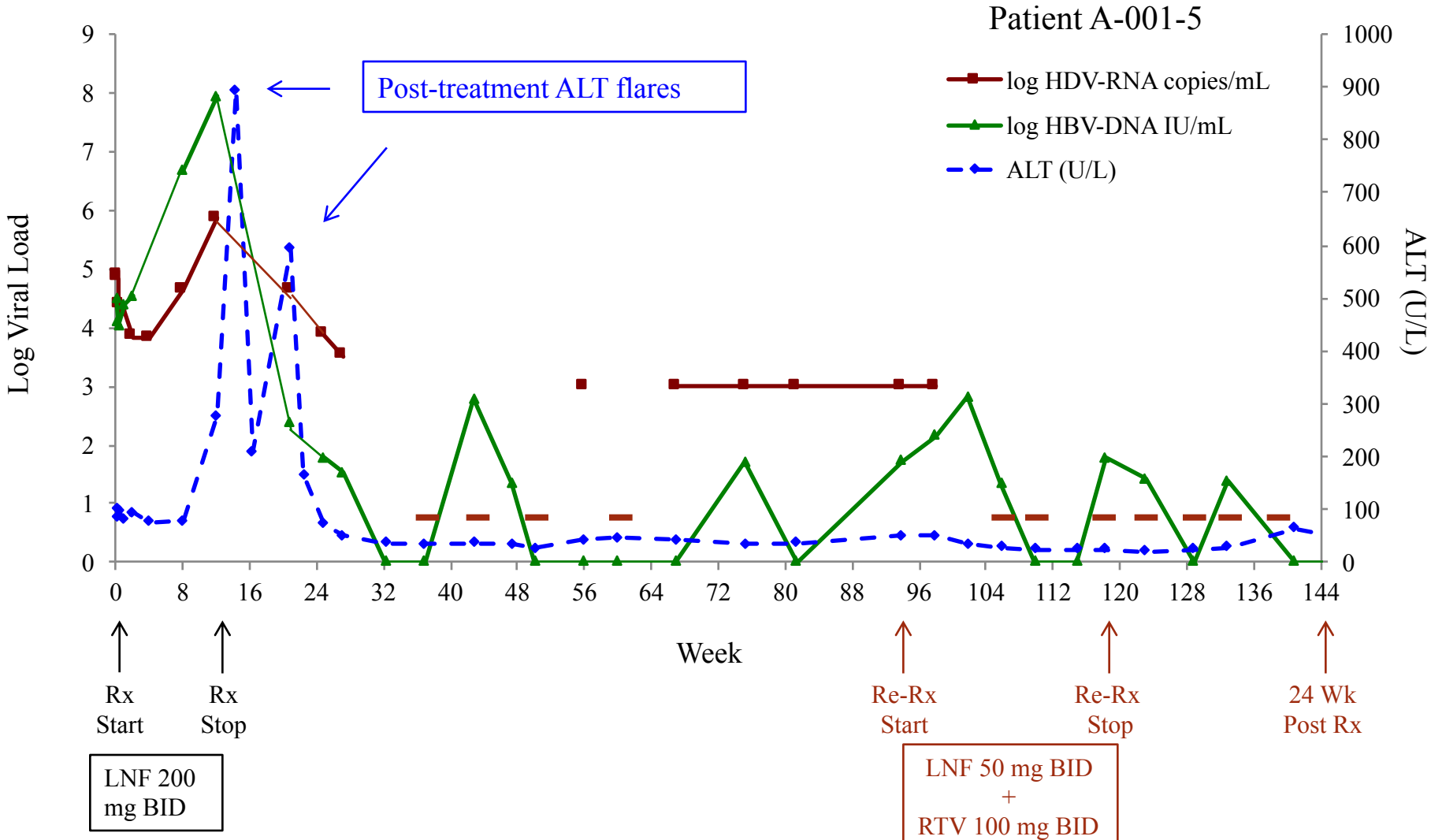
POST-TREATMENT: LNF 200 MG BID

HDV-RNA Negative for 24 Weeks Post-Retreatment



AASLD 2016

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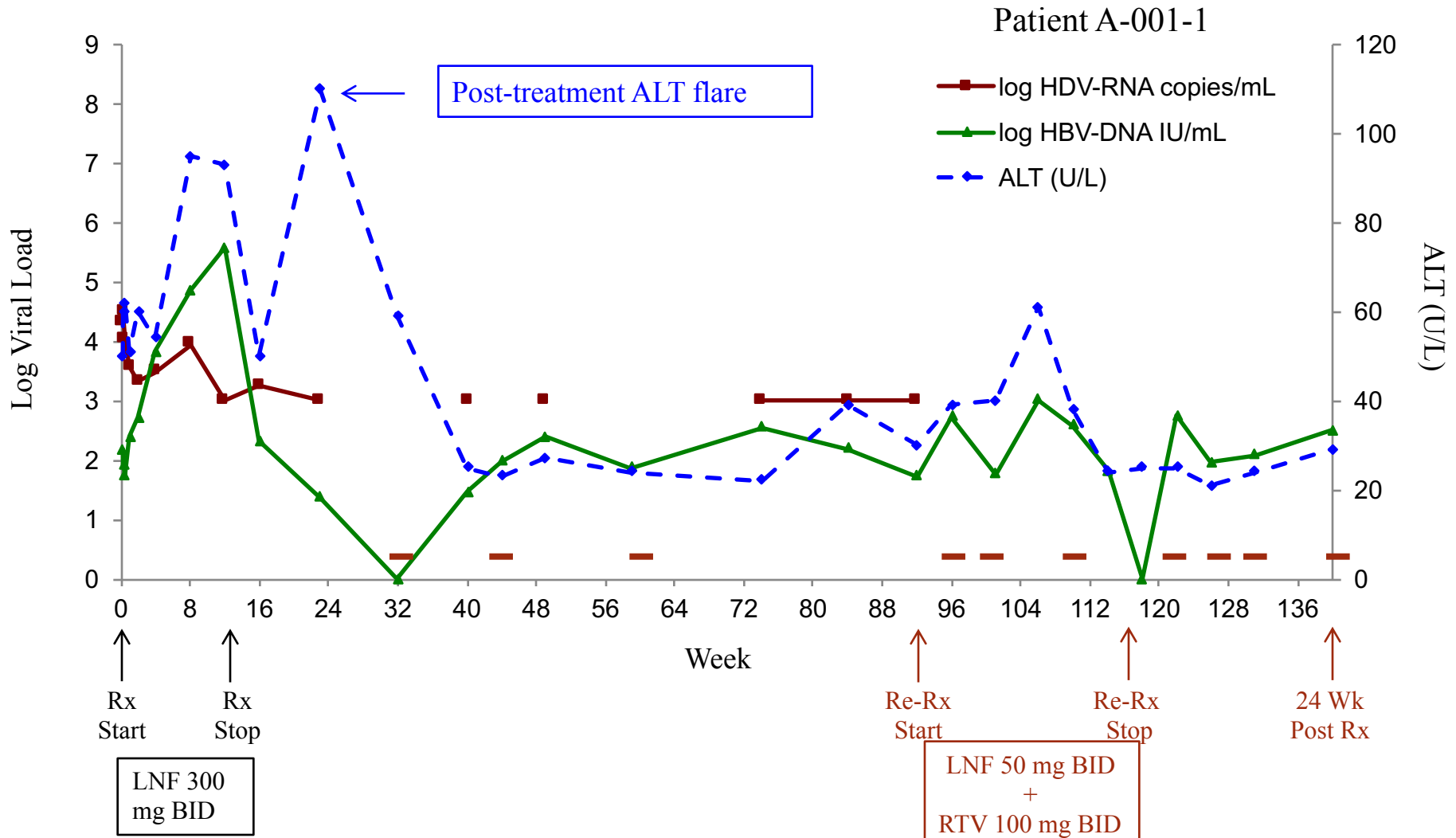
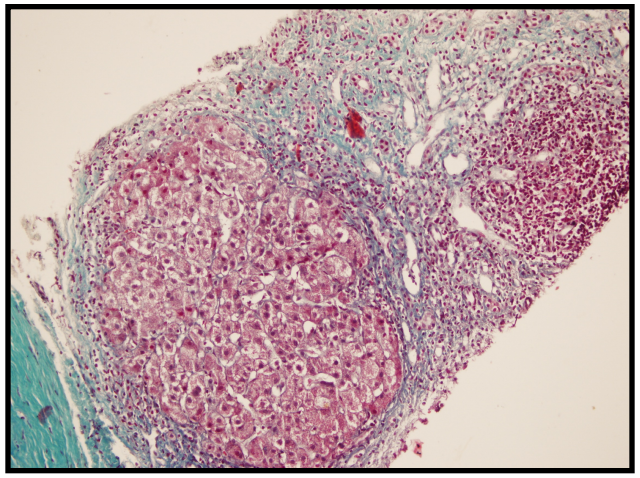


AASLD 2016

2 POINT IMPROVEMENT IN FIBROSIS

Patient 3: LNF 50 mg BID + RTV 100 mg BID

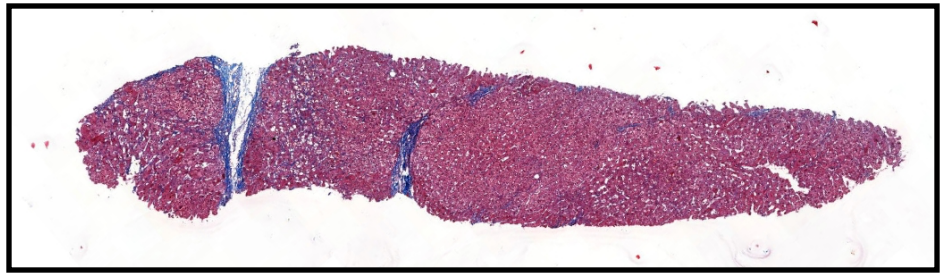
Pre-Treatment



Baseline

Ishak Fibrosis Score 6

Post-LNF-Induced ALT Normalization



Week 84
6 months post-ALT normalization
and
HDV-RNA PCR-negative

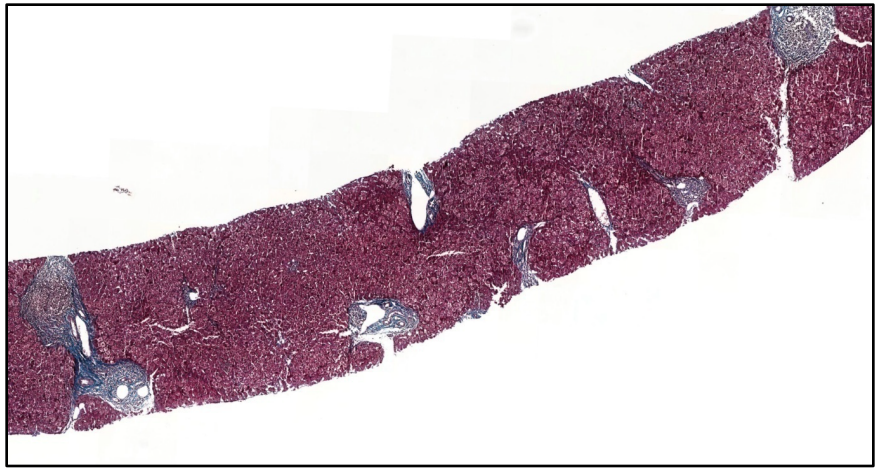
Ishak Fibrosis Score 4

AASLD
2016

2 POINT IMPROVEMENT IN FIBROSIS

Patient 5: LNF 300 mg BID

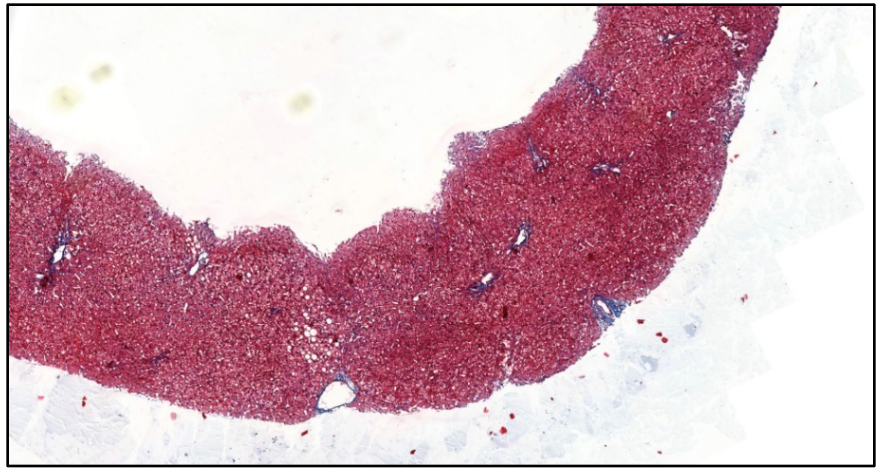
Pre-Treatment



Baseline

Ishak Fibrosis Score 2

Post-LNF-Induced ALT Normalization



Week 128
18 months post-ALT normalization
and
HDV-RNA PCR-negative

Ishak Fibrosis Score 0

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IMMUNE REACTIVATION IN HDV PATIENTS

Potential New Mechanism for Viral Clearance

Two potential pathways for achieving HDV-RNA PCR-negativity with LNF therapy:

- On-treatment LNF-induced HDV-RNA suppression

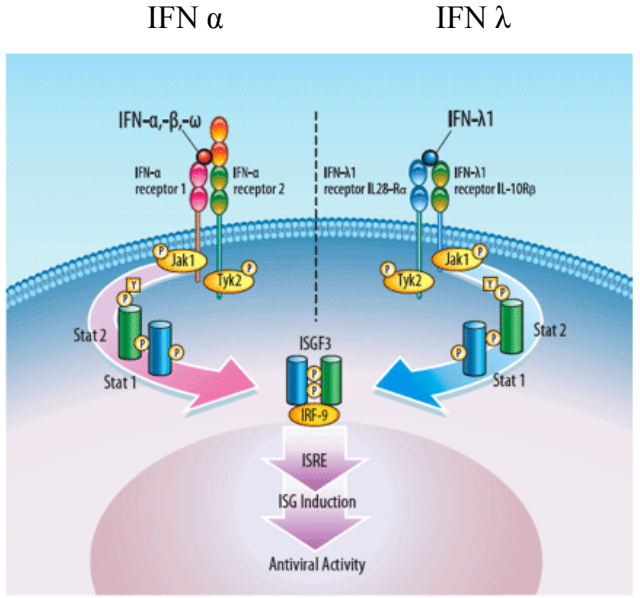
  → More classical antiviral approach, e.g.

  LOWR HDV – 2, – 3, and – 4 studies

- Post-treatment LNF-induced **THANCS**

PEGYLATED INTERFERON LAMBDA

A Targeted Interferon for HDV

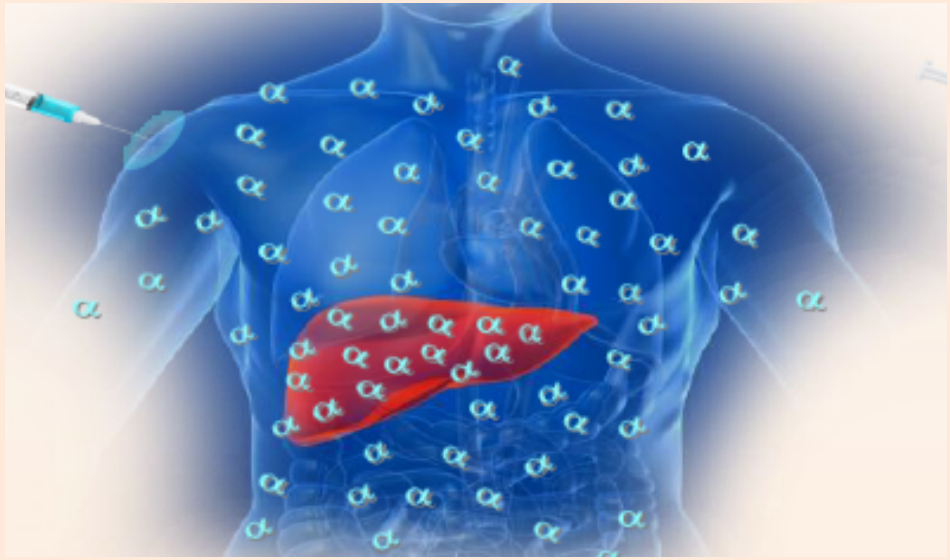


- A novel first in class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells
- Uses similar downstream signaling pathway as Type I interferons
- Greater than 3,000 patients in 17 clinical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

*Chan, HLY et al, J Hepatology 2016

LIMITED EXTRA-HEPATIC LAMBDA RECEPTOR DISTRIBUTION

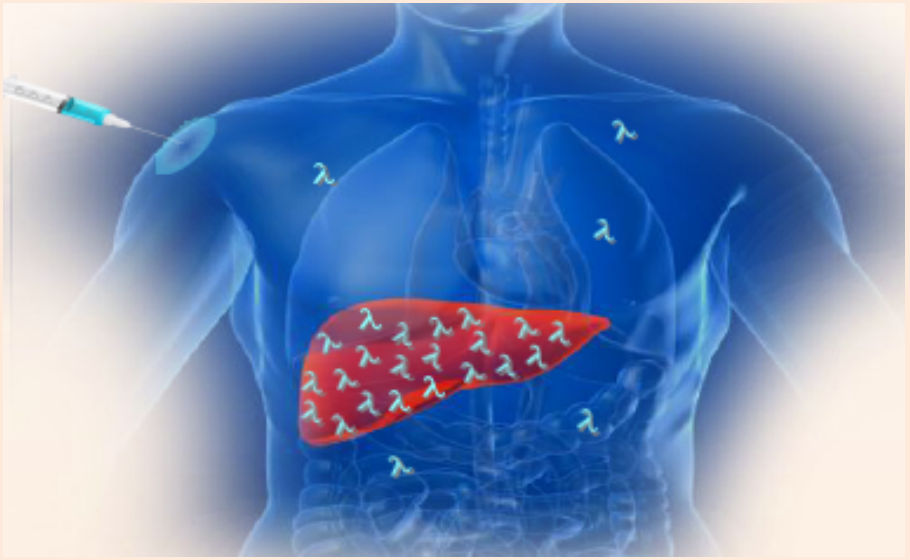
Alfa receptors **widely** distributed throughout body.



Potential for **MORE** IFN-associated abnormalities:

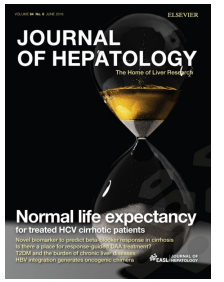
- ↑ Neutropenia
- ↑ Thrombocytopenia
- ↑ Flu-like Symptoms
- ↑ Musculoskeletal Symptoms

Lambda receptors **NOT widely** distributed throughout body.



Potential for **LESS** IFN-associated abnormalities:

- ↓ Neutropenia
- ↓ Thrombocytopenia
- ↓ Flu-like Symptoms
- ↓ Musculoskeletal Symptoms



LAMBDA vs. ALPHA IN HBV PATIENTS

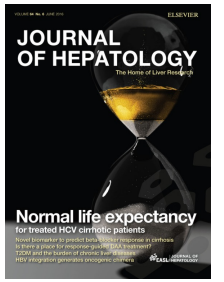
On-treatment safety summary.

Patients, n (%)	Lambda 180 µg N = 80	Alfa 180 µg N = 83
Serious adverse events	7 (8.8)	5 (6.0)
Adverse events leading to discontinuation	6 (7.5)[a]	8 (9.6)[b]
Adverse events (any grade) in >15% in any group		
Pyrexia	8 (10.0)	38 (45.8)
Alopecia	9 (11.3)	25 (30.1)
Fatigue	26 (32.5)	24 (28.9)
Headache	11 (13.8)	24 (28.9)
Neutropenia	0	20 (24.1)
Myalgia	3 (3.8)	18 (21.7)
Dizziness	5 (6.3)	13 (15.7)
Pruritus	7 (8.8)	13 (15.7)
ALT increased	15 (18.8)	8 (9.6)
Adverse event categories of special interest[c]		
Constitutional	28 (35.0)	26 (31.3)
Neurologic	18 (22.5)	30 (36.1)
Flu-like	13 (16.3)	45 (54.2)
Musculoskeletal	5 (6.3)	23 (27.7)
Psychiatric	11 (13.8)	15 (18.1)

Patients, n (%)	Lambda 180 µg N = 80	Alfa 180 µg N = 83
Grade 3-4 laboratory abnormalities		
ALT increases (>5 × ULN)	33 (41.3)	19 (23.2)
AST increases (>5 × ULN)	27 (33.8)	15 (18.3)
Hyperbilirubinemia (>2.5 × ULN)	3 (3.8)	0
Neutropenia (<750 cells/mm³)	2 (2.5)	17 (20.7)
Thrombocytopenia (<50,000 cells/mm³)	0	1 (1.2)
Hemoglobin <9 g/dl or ≥4.5 g/dl ↓ from baseline	0	0
ALT flare[d]	13 (16.3)	6 (7.2)
Dose reductions	12 (15.0)[e]	23 (27.7)[b]
Dose interruptions	8 (10.0)[e]	4 (4.8)[b]

[a]Mostly elevations in hepatobiliary enzymes.
[b]Mostly neutropenia or elevations in hepatobiliary enzymes.
[c]AE categories of special interest are based on preferred terms found in the alfa label reported in at least 5% of patients: Constitutional (fatigue); neurologic (headache and/or dizziness); flu-like (pyrexia and/or chills and/or pain); musculoskeletal (arthralgia and/or myalgia and/or back pain); and psychiatric (depression and/or irritability and/or insomnia).
[d]ALT flare defined as ALT >2 × baseline and >10 × ULN.
[e]In majority of cases, reason was on-treatment ALT flare.

Chan et al, J Hepatology 2016



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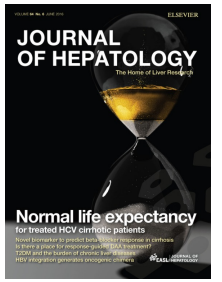
Chan et al, J Hepatology 2016



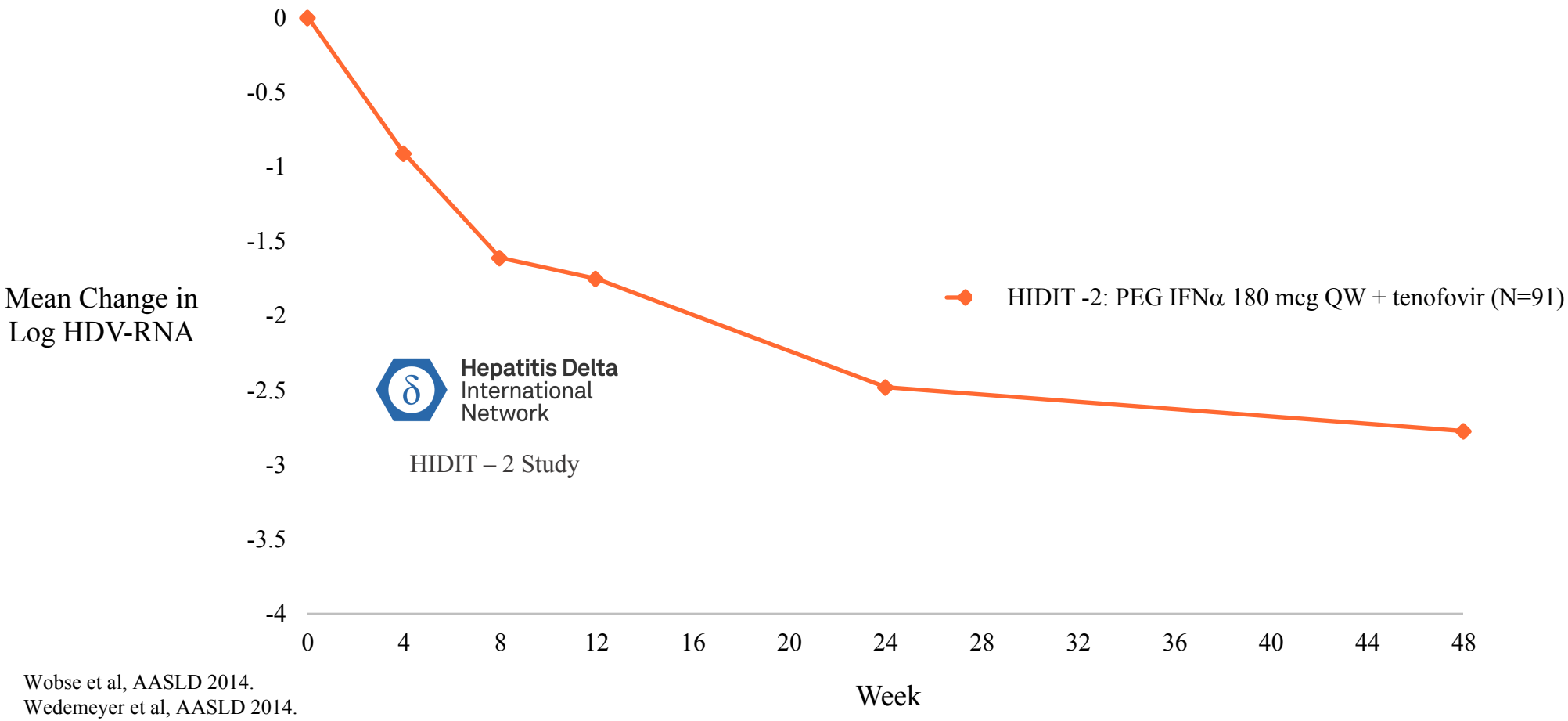
LAMBDA vs. ALPHA IN HBV PATIENTS

- Comparable HBV antiviral activity at end of treatment
- Lambda was generally well tolerated
- Comparable rates of SAEs and discontinuations due to AEs (lambda vs alpha)
  - Lambda: related to hepatobiliary events
  - Alpha: related to cytopenias, neutropenia, thrombocytopenia or hepatic enzyme elevations
- Frequency of ALT flares[1] was higher with lambda than alpha
  - Most ALT flares were asymptomatic; no clinical or laboratory signs of hepatic impairment

Chan et al, Hepatology 2016
[1]ALT > 2x BL and 10x ULN

PEG IFNα DEMONSTRATES ACTIVITY IN HDV PATIENTS

Lambda Expected to Demonstrate Comparable Activity



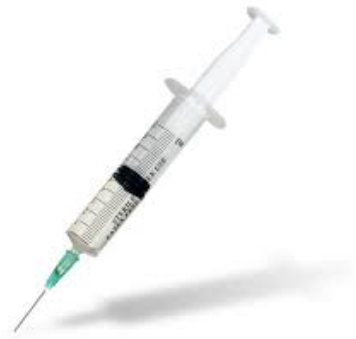
Wobse et al, AASLD 2014.
Wedemeyer et al, AASLD 2014.

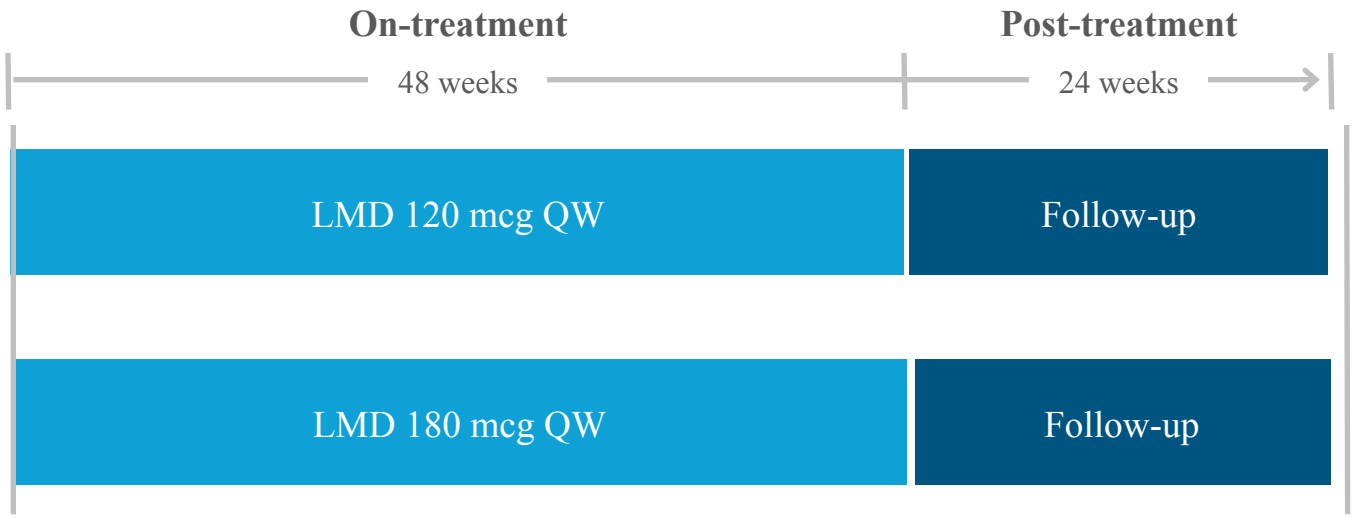
AASLD 2014

LIMT HDV "MONO": PHASE 2 STUDY

Lambda Interferon MonoTherapy Study in HDV

Bridging to Registration: Supportive Study





- Safety / tolerability
- HDV-RNA negativity

Enrollment Completed N=33

To be presented at

AASLD

2017

Hamid, S. et al; AASLD 2017 Abstract #927

2017 AASLD ABSTRACT: INTERIM 8-WEEK SUMMARY

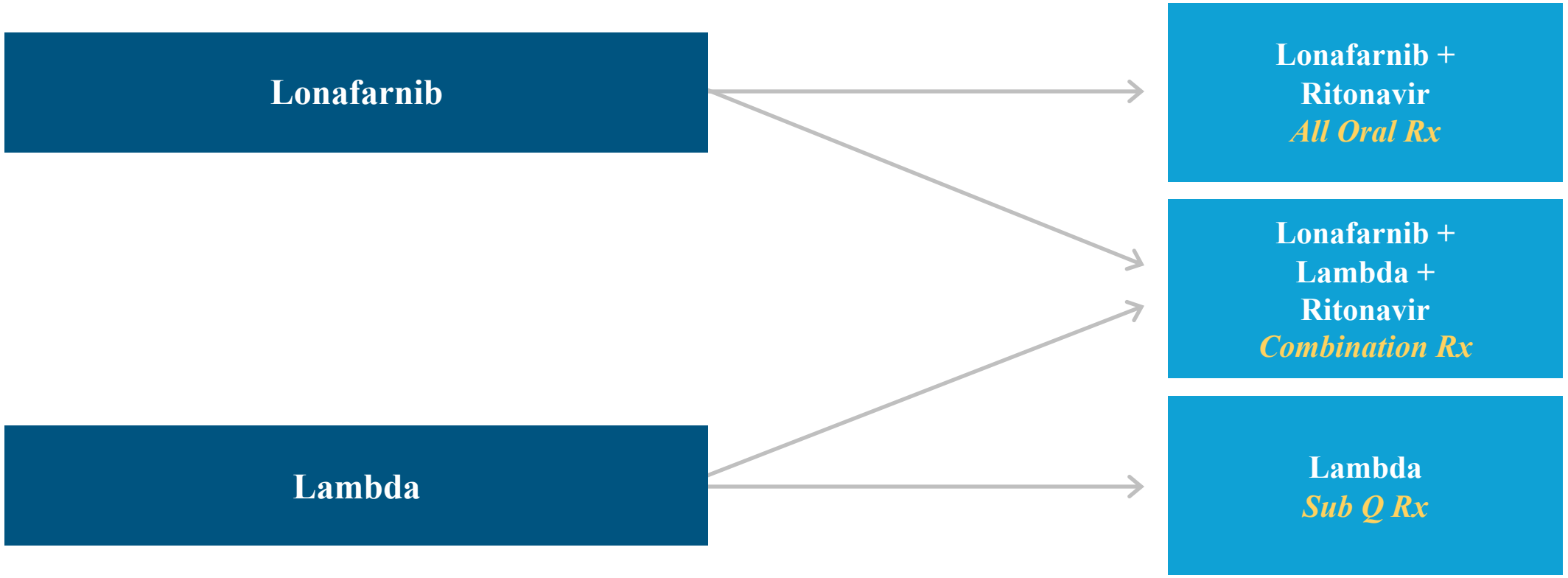
LIMT HDV Study

- 20 of 33 patients enrolled at time of AASLD abstract submission
  - Baseline HDV RNA 4.5 log IU/mL (SD ±1.36)
  - 11 of 20 patients reached Week 8
- 6 of 11 (55%) patients had HDV RNA < LLOQ*
- 3 of 11 (27%) were HDV-RNA PCR-negative
- Safety:
  - Three patients had Grade 3 elevations of ALT
  - Hyperbilirubinemia events in three patients responded to dose reduction or discontinuation
- Constitutional symptoms were less frequent and milder than historical data with PEG IFN-alpha
- Lambda was well-tolerated

Hamid, S. et al; AASLD 2017 Abstract #927

TWO COMPLEMENTARY ASSETS FOR HDV

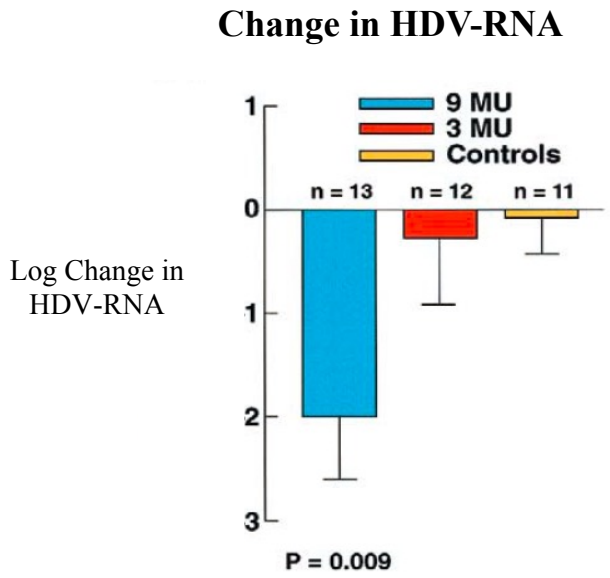
Multiple Treatment Options

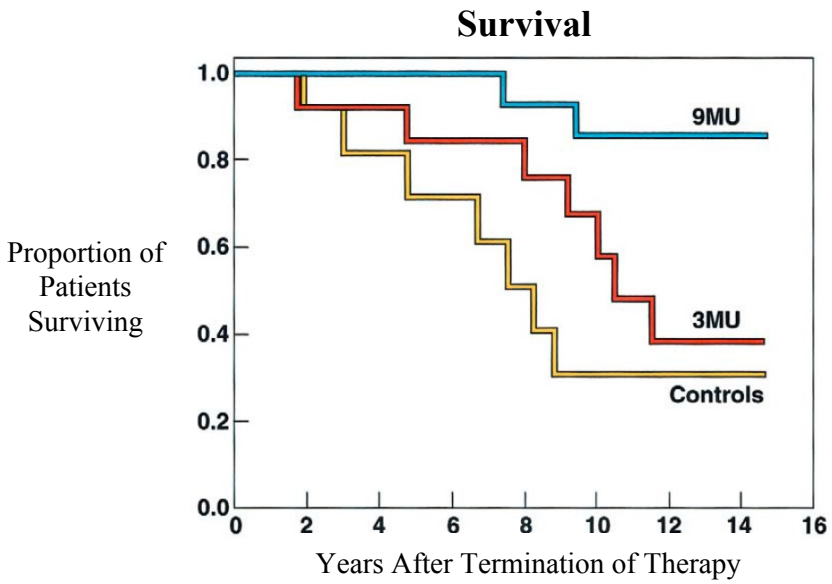


Lambda to Replace Alpha in Next Studies

PROPOSED ENDPOINTS IN HDV

- Primary Endpoint:
  - ≥ 2 Log Reduction in HDV RNA at EOT





Farci et al, Gastroenterology **2004**: Long-Term Benefit of Interferon-α Therapy of Chronic HDV: Regression of Advanced Hepatic Fibrosis

PROPOSED ENDPOINTS IN HDV

Consensus endpoints for clinical trials in HBV/HDV coinfection

Endpoint	Parameter	Readout
Primary efficacy endpoint	HDV RNA decline of 2log (or PCR negativity if baseline viral load is <100 IU/ml) at end of therapy	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity
Secondary efficacy - virological	off-treatment HDV RNA response (e.g. 24 weeks after end-of-therapy): HDV RNA decline of 2log (or PCR negativity if baseline viral load is <100 IU/ml) at end of therapy)	
Secondary efficacy - virological and immunological	HBsAg levels (log declines and loss) at end-of treatment and off treatment	validated quantitative HBsAg assay (IU/ml)
Secondary efficacy - biochemical	ALT improvements: 1 grade decline in CTC grade (or grade 0 if CTC grade 0 at baseline) at end-of treatment and off treatment	IU/L
Secondary efficacy – histological	Grading: improvement of HAI of at least 2 points Staging: no worsening of fibrosis	Ishak score
Secondary - safety	Drug-specific items	
Secondary – safety	HBV reactivation:	HBV DNA

White Paper to be submitted by Hepatitis Delta International Network (HDIN) in October

Hepatitis Delta International Network