A Phase 2 Dose-Optimization Study of Lonafarnib with Ritonavir for the Treatment of Chronic Delta Hepatitis —End of Treatment Results from the LOWR HDV-2 Study

C Yurdaydin[1], R Idilman[1], C Kalkan[1], F Karakaya[1], A Caliskan[1], O Keskin[1], E Yurdcu[1], S Karatayli[1], M Bozdayi[1], C Koh[2], T Heller[2], JS Glenn[3]

[1]Division of Gastroenterology, University of Ankara Medical School, Ankara, Turkey; [2]Liver Diseases Branch, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bethesda, Maryland; [3]Division of Gastroenterology and Hepatology, Stanford University School of Medicine

April 21, 2017

Disclosures

Cihan Yurdaydin
- Advisory Boards: Merck, Janssen, AbbVie and Gilead
- Speakers Bureau: Roche, AbbVie, Eiger BioPharmaceuticals and Gilead
- Has received research grants from Roche, BMS Pharma and Eiger

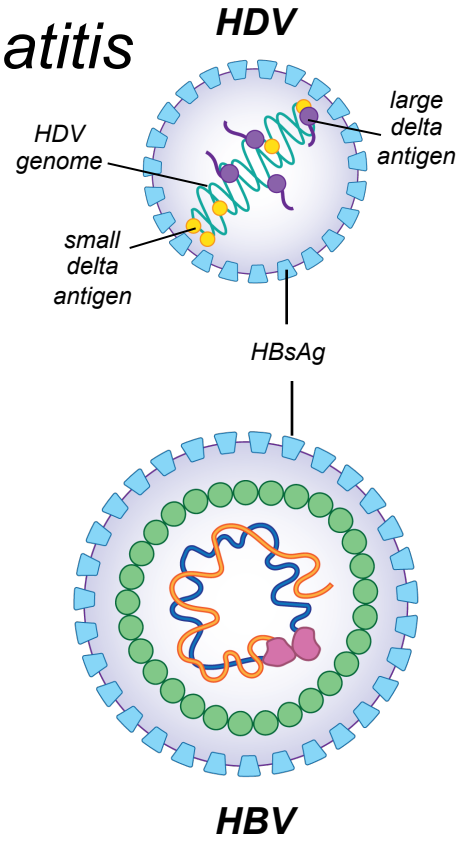
Jeffrey Glenn
- Board, Founder: Eiger, Riboscience
- Consulting: Gilead, Janssen, Sundise, Genentech, Merck, Roche, Romark, StemCells
- Equity interest in Eiger

All remaining authors have no financial relationships to disclose.

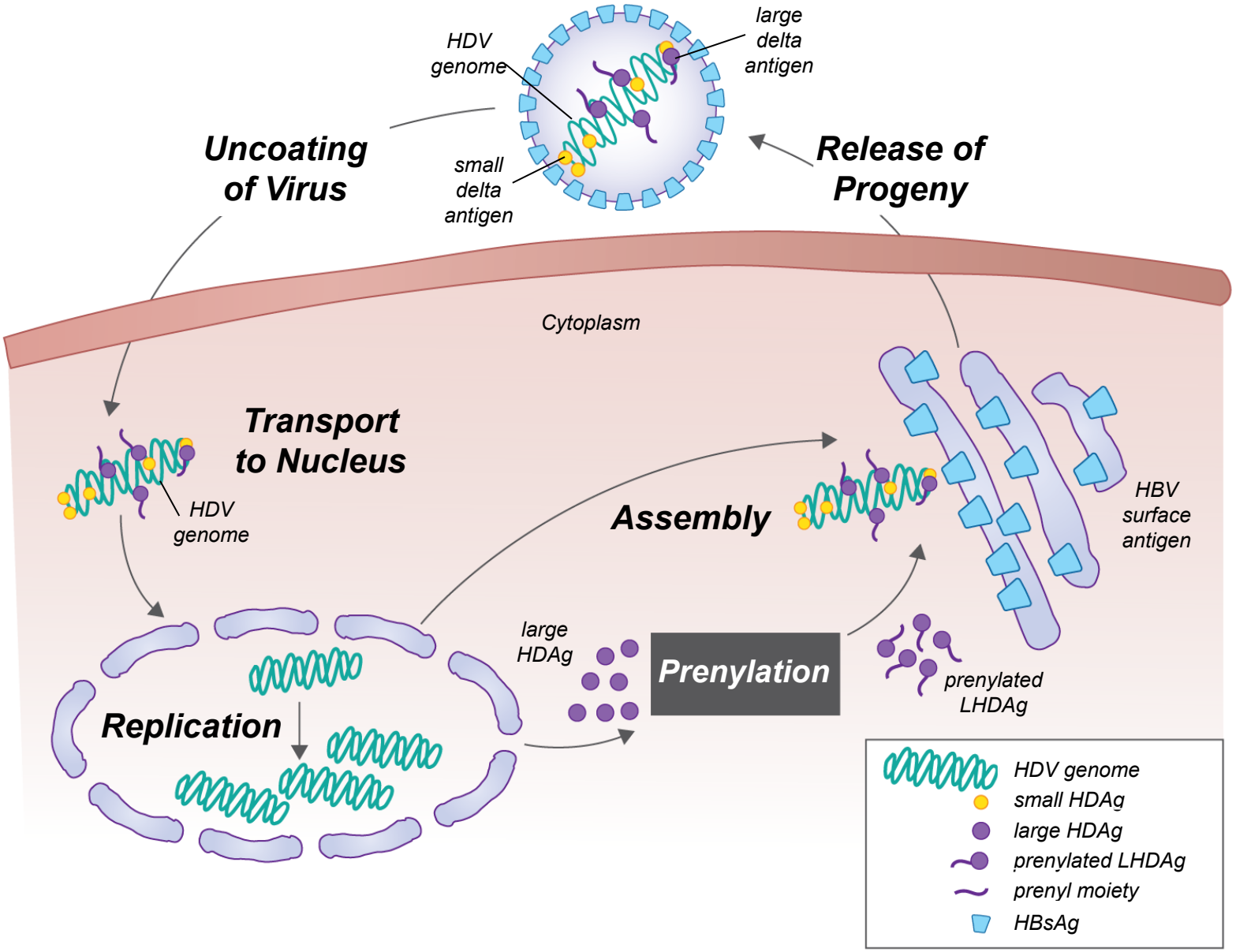
Hepatitis Delta Virus

Leads to the Most Severe Form of Viral Hepatitis

- *HDV leads to the most severe form of viral hepatitis*
  - *More rapid progression to liver cirrhosis*
  - *5-7x more likely to develop cirrhosis and HCC vs HBV*
- *HDV is always associated with HBV infection*
  - *HDV steals HBsAg from HBV for envelopment*
- *Final step in replication involves prenylation*
  - *HDV hijacks prenylation, a host process*
- *No FDA approved Rx for HDV*
  - *PEG IFN-α demonstrates modest benefit*
- *HDV worldwide prevalence is 15 - 20 million*
  - *Approximately 4-6% of HBV worldwide population is infected with HDV*
  - *Orphan status in US and EU*

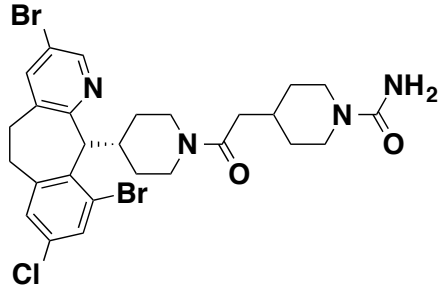


HDV Life Cycle



Sarasar® (lonafarnib) for HDV

Well-Characterized Clinical Stage Lead Compound

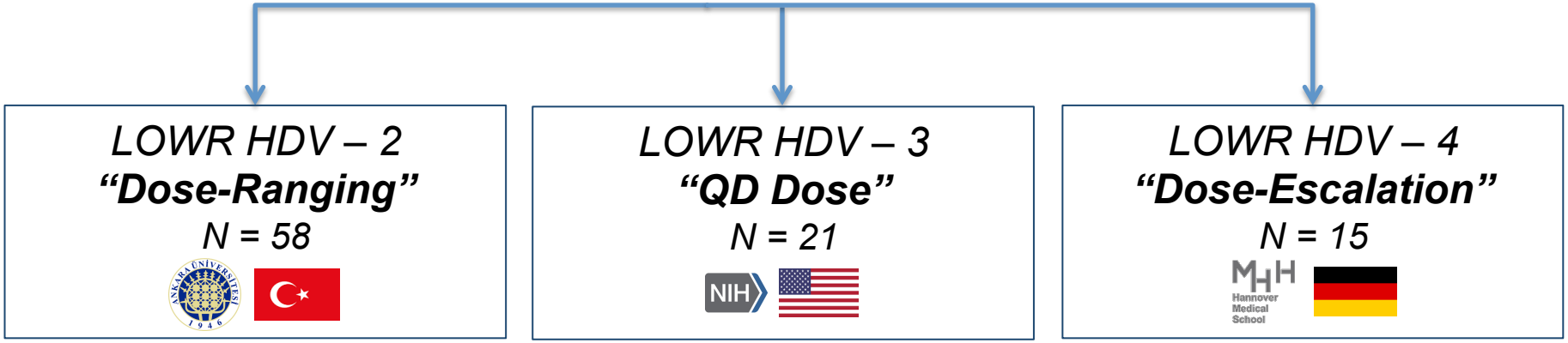


- *Small molecule, oral, prenylation inhibitor*
- *Well-characterized through Phase 3*
  - *>2,000 patients dosed in oncology program by Merck (Schering)*
  - *Dose limiting toxicity is GI (class effect)*
- *Prenylation is a host target; potential high barrier to resistance*
- *Over 120 HDV patients dosed across international sites*
  - *NIH Phase 2 study results published in Lancet Infectious Diseases 2015**
- *Orphan Designation in US & EU, Fast Track in US*

** Koh et al, Lancet Infect Dis, 2015.*

LOWR HDV - 2, - 3, - 4

Week 48 Results Presented at EASL 2017



LOWR HDV – 2

- *Identify LNF-RTV combination +/- PEG IFN*

*LOWR HDV – 3**

- *Once-daily dosing*

*LOWR HDV – 4***

- *Is rapid dose-escalation possible and / or required?*

** Koh et al., EASL 2017 Abstract #LBP-519, ** Wedemeyer et al., EASL 2017 Abstract #PS-039*

LOWR HDV – 2 Study

***LO**nafarnib **W**ith **R**itonavir ± PEG IFN-α*

Purpose

- *To identify combination regimens of **LNF and RTV ± PEG IFN-α** which demonstrate efficacy and tolerability for longer term dosing to enable HDV-RNA clearance.*

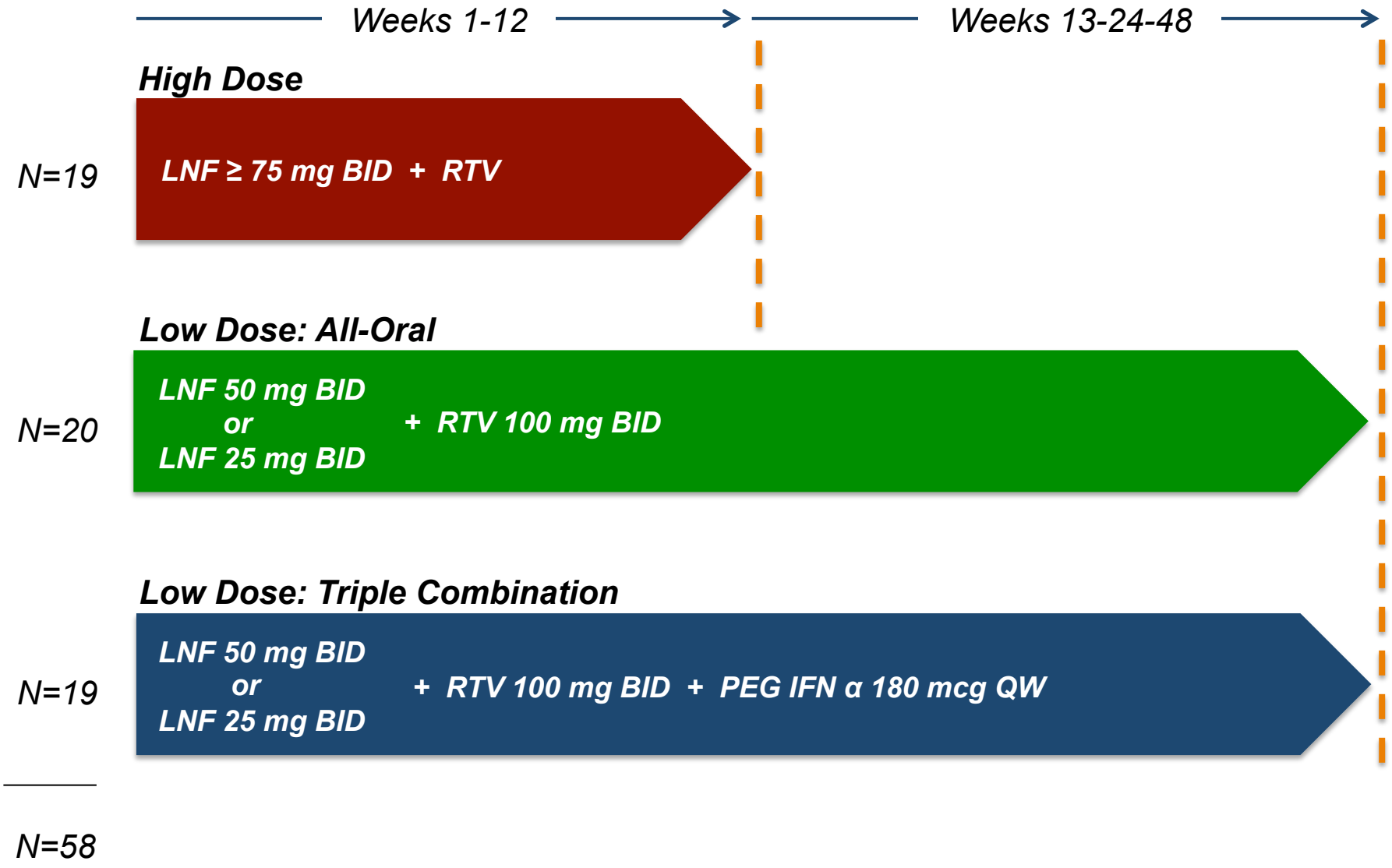
Patients and Methods

- *Treatment duration 12 or 24 or 48 weeks*
- *72 hour PK and PD evaluation on day 1 and day 28*
- *Testing frequency: days 1, 2, 3, 7, 14, 28 and then 4W*
  - *Biochemical parameters, HBV DNA*
  - *HDV-RNA (by in-house qPCR with LOQ ~ 3 log copies/mL)*

LOQ = limit of quantitation

LOWR HDV – 2: "Dose Finding" Study

Tolerability, Longer Dosing, and Triple Combination



LOWR HDV – 2: "Dose Finding" Study

Low Doses Tested for Longer Durations

	Regimen	Duration (Weeks)	# Patients	# Discontinuations Due to AE
High Dose	L100B + R100Q	12	4	1
	L150Q + R100Q	12	3	0
	L100B + R50B	12	4	0
	L100Q + R100Q	12	5	2
	L75B + R100B (+ P180QW on Wk 12)	24	3	0
	L50B + R100B (+ P180QW on Wk 12)	24	5	1
Low Dose N = 34	L50B + R100B	24	12	0
		48	2	0
	L25B + R100B	24	1	0
		48	5	0
	L50B + R100B + P180QW	24	3	1
		48	2	0
	L25B + R100B + P180QW	24	6	1
		48	3	0
	Total		58	6

L=LNF in mg, R=RTV in mg, P=PEG IFN-α in mcg, B=BID, Q=QD

Baseline Characteristics

LOWR HDV – 2: Low Dose Groups

Characteristic	Values
N	27*
Median age, years (range)	50 (24 - 59)
Male, n (%)	12 (44%)
Race, n (%) White	27 (100%)
Median BMI, kg/m^2 (range)	24.5 (18.5 – 33.9)
Median HDV-RNA, log_{10} copies/mL (range)	5.36 (3.30 – 6.94)
Median ALT, U/mL (range)	64 (24 - 229)
Prior interferon treatment, n (%)	12 (44%)

* Excludes 7 patients < LOQ at baseline

LOWR HDV – 2: Efficacy

As-Treated Analysis: Patients Dosed for 24 Weeks

	# of Patients			
	All-Oral Rx		Triple Rx	
	LNF 25 mg BID + RTV	LNF 50 mg BID + RTV	LNF 25 mg BID + RTV + PEG	LNF 50 mg BID + RTV + PEG
Week 24	**N = 6**	**N = 8**	**N = 5**	**N = 4**
HDV-RNA < LOQ	3 / 6	2 / 8	4 / 5	3 / 4
HDV-RNA PCR negative	0 / 6	1 / 8	3 / 5	0 / 4
> 2 log decline*	3 / 5	1 / 3	3 / 4	3 / 3

24 Week Dosing

- *All-oral LNF 25 and 50 mg BID + RTV suppress HDV-RNA < LOQ in 36% of patients*
- *Addition of PEG IFN to LNF 25 mg BID + RTV enhances antiviral activity*

* Patients with high baseline viral load (HDV RNA > 5 log copies/mL)

LNF 25 mg BID + RTV + PEG

2 Patients HDV-RNA negative at EOT (Week 24) and Week 48

	# of Patients			
	All-Oral Rx		Triple Rx	
	LNF 25 mg BID + RTV	LNF 50 mg BID + RTV	LNF 25 mg BID + RTV + PEG	LNF 50 mg BID + RTV + PEG
Week 24	**N = 6**	**N = 8**	**N = 5**	**N = 4**
HDV-RNA < LOQ	3 / 6	2 / 8	4 / 5	3 / 4
HDV-RNA PCR negative	0 / 6	1 / 8	**3 / 5**	0 / 4
> 2 log decline*	3 / 5	1 / 3	3 / 4	3 / 3

- 3 of 5 patients (60%) PCR-negative at Week 24
  - 2 had low viremia off-therapy, PCR-negative at 24 weeks post-treatment
  - 1 continued treatment for another 24 weeks

* Patients with high baseline viral load (HDV RNA > 5 log copies/mL)

LOWR HDV – 2: Efficacy

As-Treated Analysis: Patients Dosed for 48 Weeks

	# of Patients			
	All-Oral Rx		Triple Rx	
	LNF 25 mg BID + RTV	LNF 50 mg BID + RTV	LNF 25 mg BID + RTV + PEG	LNF 50 mg BID + RTV + PEG
Week 24	N = 6	N = 8	N = 5	N = 4
HDV-RNA < LOQ	3 / 6	2 / 8	4 / 5	3 / 4
HDV-RNA PCR negative	0 / 6	1 / 8	3 / 5	0 / 4
> 2 log decline*	3 / 5	1 / 3	3 / 4	3 / 3
Week 48	**N = 5**	**N = 2**	**N = 3**	**N = 2**
HDV-RNA < LOQ	2 / 5	1 / 2◆	2 / 3	0 / 2
HDV-RNA PCR negative	0 / 5	0 / 2◆	2 / 3	0 / 2
> 2 log decline*	1 / 4	0 / 0	3 / 3	0 / 2

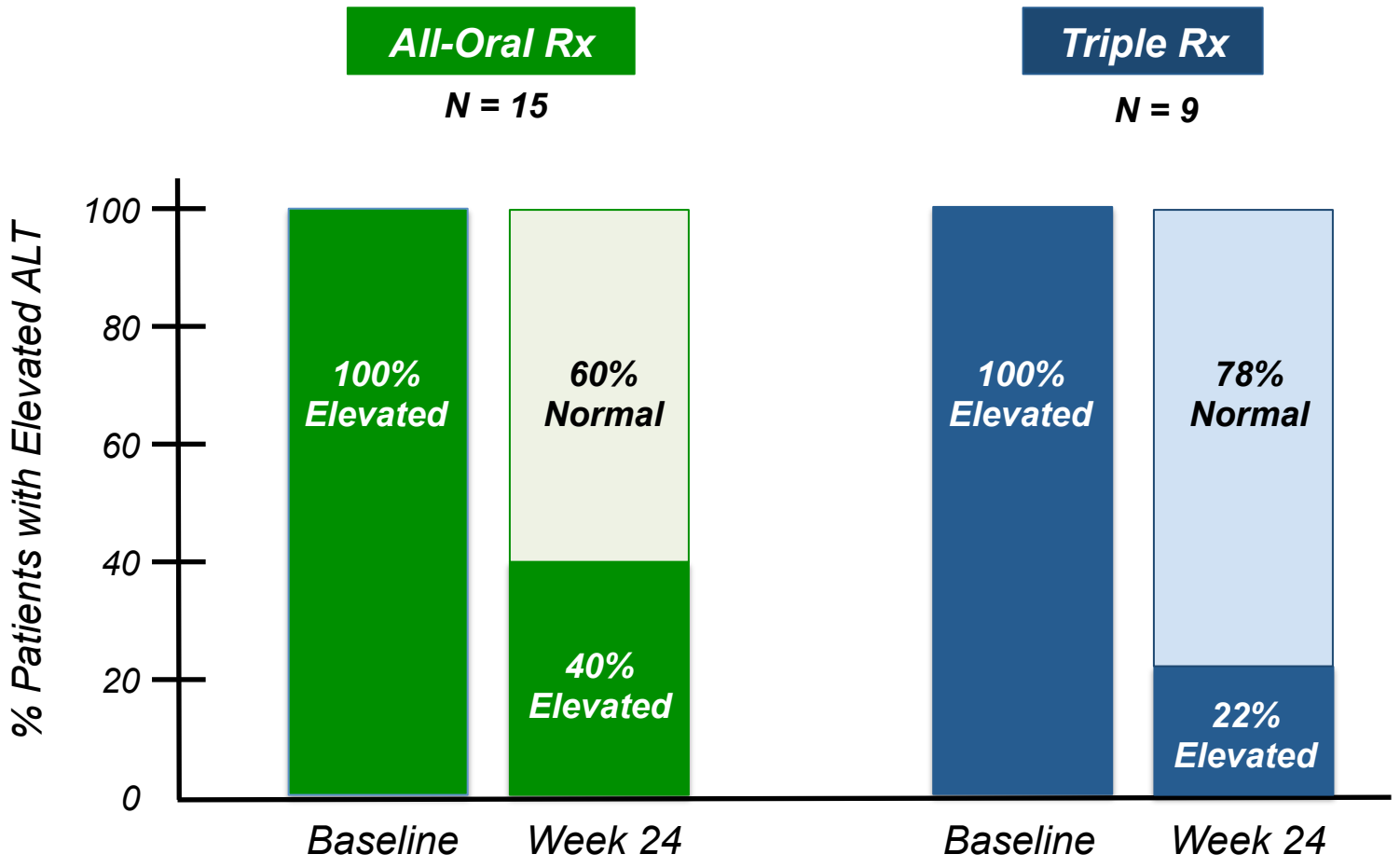
48 Week Dosing

- All-oral LNF: 3 of 7 patients (43%) < LOQ
- Triple LNF 25 mg BID + RTV + PEG: 2 of 3 patients (67%) PCR-negative

* Patients with high baseline viral load (HDV RNA > 5 log copies/mL); ◆ Week 40-44 data

60-78% of Patients Normalized ALT at Wk 24*

Addition of PEG Improves ALT Normalization



** LNF 25 and 50 mg BID regimens with elevated ALT at baseline*

All-Oral Rx = LNF 25/50 mg BID + RTV 100 mg BID; Triple Rx = LNF 25/50 mg BID + RTV 100 mg BID + PEG IFN 180 mcg QW

Adverse Events: Low Dose LNF

LNF 25 / 50 mg Regimens Demonstrate Tolerability

	# of Patients Experiencing AE[1]			
	All-Oral Rx		Triple Rx	
AE Grade	LNF 25 mg BID + RTV N = 6	LNF 50 mg BID + RTV N = 14	LNF 25 mg BID + RTV + PEG N = 9	LNF 50 mg BID + RTV + PEG[2] N = 10
Grade 1	3	8	4	5
Grade 2	1	3	2	4
Grade 3	2	2	0	1
SAE[3]	1	2	1	1

- AEs predominantly mild / moderate for LNF 25 / 50 mg regimens
- Generally tolerable through Week 48

Highest grade GI AE reported

[1] *Most common and severe reported AEs: nausea, diarrhea, fatigue, weight loss, anorexia, vomiting*

[2] *Includes cohort: LNF 50 mg BID + RTV for first 12 weeks + PEG for second 12 weeks*

[3] *All reported to be "unlikely related to LNF"*

LOWR HDV – 2

Conclusions

- *All-oral LNF 25 or 50 mg BID + RTV suppresses HDV-RNA < LOQ*
  - *5 of 14 (36%) patients < LOQ at Week 24*
  - *1 patient PCR-negative at Week 24*
- *Addition of PEG IFN to LNF 25 mg BID + RTV results in highest response*
  - *4 of 5 (80%) patients < LOQ at Week 24*
  - *3 of 5 (60%) patients PCR-negative at Week 24*
    - *2 patients PCR-negative at 24 weeks post-treatment*
- *60-78% of patients normalized ALT at Week 24*
- *> 2 log decline AND normalized ALT warrants evaluation for clinical benefit*
- *AEs predominantly mild / moderate for LNF 25 / 50 mg regimens*