A Phase 2 Study of Peginterferon Lambda, Lonafarnib and Ritonavir for 24 weeks: End-of-Study Results from the LIFT HDV Study

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Disclosures

Christopher Koh, MD MHSc

I have no financial relationship(s) with a commercial interest to disclose.

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Introduction

- ~ 20 million people are infected worldwide with HDV
- Up to 80% of patients with HDV may develop cirrhosis within 5-10 years
- Higher risk for hepatic decompensation leading to death & development of HCC compared to mono-infected patients

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Hughes SA, et al. Lancet 2011;378; Colombo M et al. Gastroenterol 1983; 85
Manesis EK et al. J Hep 2013;59; Fattovich G et al. Gut 2000; 46
Romeo R, et al. Gastroenterol 2009; 136

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The Quest For Better Therapies

- Interferon alfa based therapies are unsatisfactory
- Nucleos(t)ide analogues are ineffective
- Investigational Therapies
  - Immunomodulator - **Peginterferon lambda**
  - Prenylation inhibition – **Lonafarnib**
  - Human sodium-taurocholate cotransporting polypeptide – Myrcludex B
  - Nucleic acid polymers – REP 2139-Ca

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Wedemeyer H, et al. N Eng J Med 2011;27
Wedemeyer H, et al. Hepatology 2013;58
Heller T, et al. Aliment Pharmacol Ther 2014;40
Bogomolov P, et al. Hepatology 2016;65
Bazinet M, et al. J Hepatol 2015;62
Koh C, et al. Lancet Infect Dis 2015;15

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LIFT HDV Study

- Phase 2, Open-Label Study
- Peginterferon lambda (LMD) 180 mcg subcutaneously weekly + Lonafarnib (LNF) 50 mg with ritonavir (RTV) 100 mg orally twice daily
- Primary Endpoints:
  - Therapeutic: >2 log decline in quantitative HDV RNA levels after 24 weeks of therapy.
  - Safety: Ability to tolerate triple combination therapy at the prescribed dose for 24 weeks.

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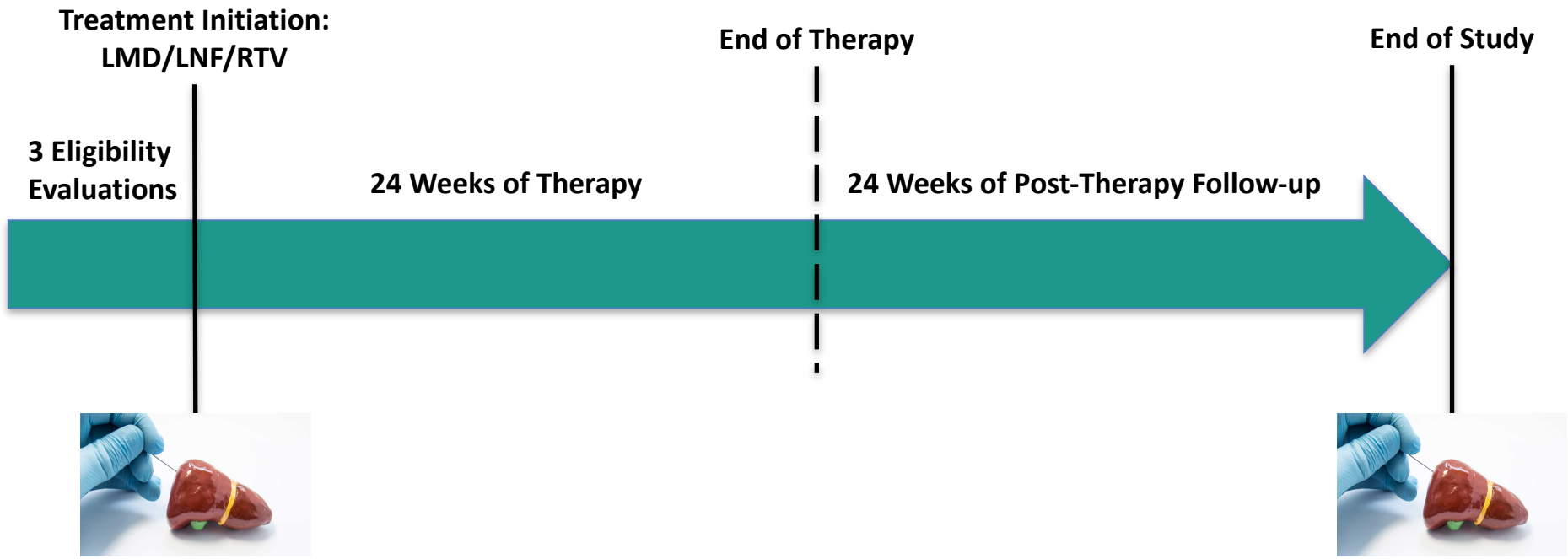
LIFT HDV Study Design



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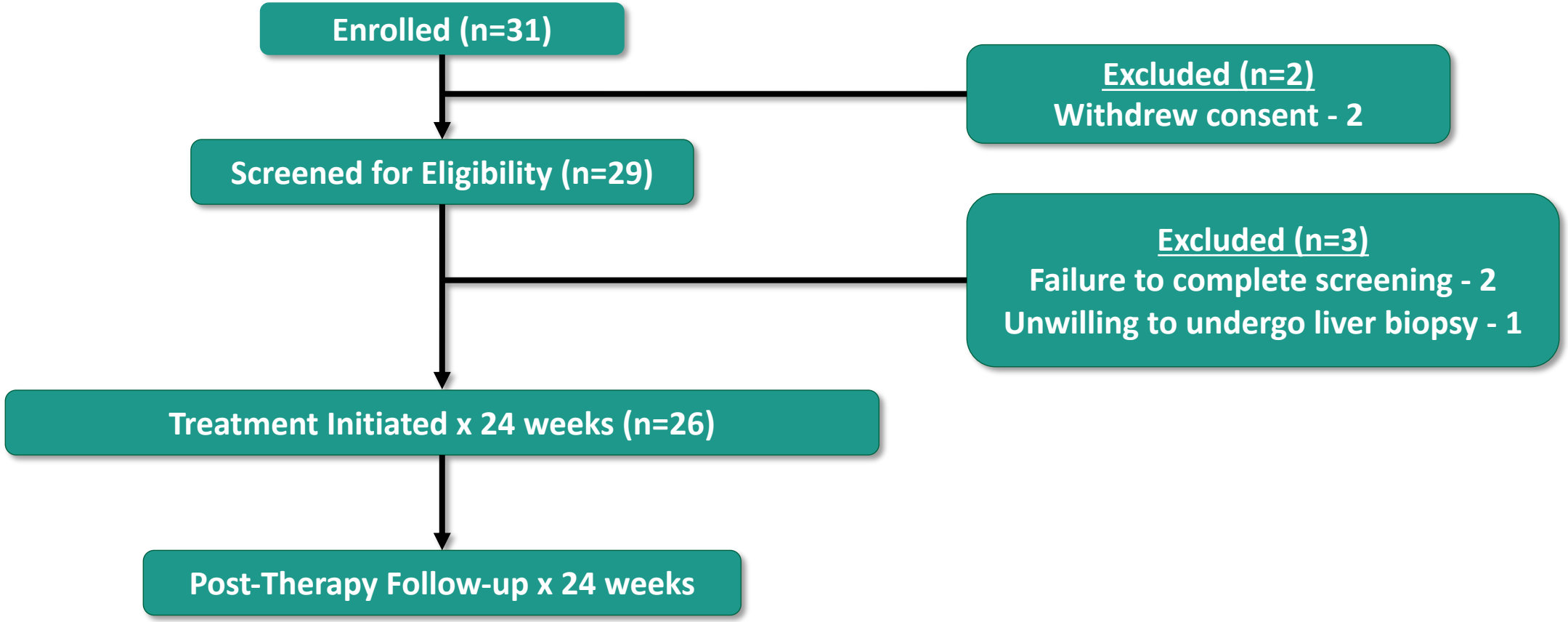
LIFT HDV Study Flow



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* All eligible subjects were placed/maintained on HBV nucleos(t)ide therapy for the duration of the study

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Baseline Patient Characteristics

Characteristic	Result (n=26)
Male Sex (%)	17 (65)
Median Age (IQR)	40 (36, 46)
BMI	25 (23.2, 28.7)
Race (%)	
Caucasian	8 (31)
Asian	14 (54)
Black	4 (15)
Median Laboratory Results (IQR)	
ALT U/L	64 (45, 93)
AST U/L	47 (38, 64)
HBV DNA IU/mL	<20 (<20, <20)
HDV RNA log IU/mL	4.74 (4.18, 5.65)

Characteristic	Result (n=26)
Fibroscan Stiffness kPa	11.8 (6, 15)
Median Histology Results (IQR)	
Modified HAI Inflammation	9 (8-10)
Ishak Fibrosis	3 (2-4)
Median Portal Pressures (IQR)	
HVPG	4.0 (3.0-5.5)

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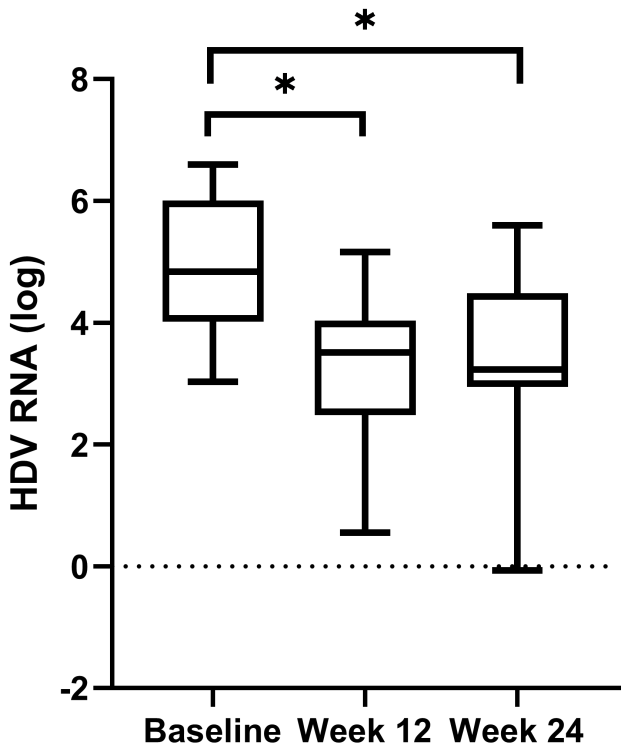
Treatment Response at 12 and 24 Weeks

Treatment Duration	n	Mean Change in log HDV RNA (IU/mL)	Confidence Interval	p-value
12 Weeks	26	3.36	(2.86-3.85)	<0.0001
24 Weeks	22	3.23	(2.94-4.49)	<0.0001



*P=<0.0001

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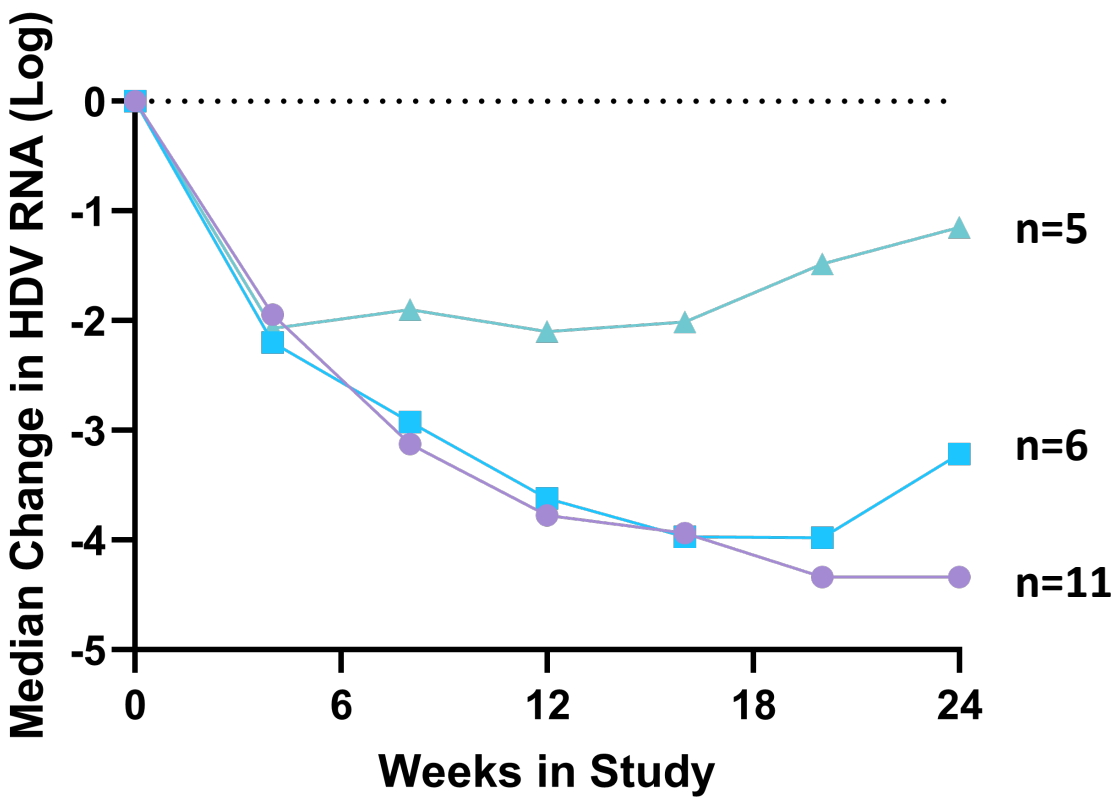
HDV RNA Change from Baseline to End of Therapy



Categorized by response at week 24 of therapy

- <2 log decline
- >2 log decline
- Undetectable or BLOQ

- **77% of patients achieved >2 log HDV RNA decline after 24 weeks of therapy.**
- **50% had undetectable or BLOQ* HDV RNA after 24 weeks of therapy.**

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*Lower limit of quantification of HDV RNA in serum: <40 IU/mL or 1.6 Log, Quest Diagnostics Assay

Adverse Events

Most Common Adverse Events								
Nausea	Diarrhea	Anorexia	Abdominal Bloating	GERD	Fatigue	Weight Loss	Anemia	Hyperbilirubinemia
69%	100%	46%	63%	65%	42%	31%	23%	19%

Dose Reductions/Discontinuations			
	Hyperbilirubinemia	Anemia	Ascites
Dose Reduction	1	1	
Discontinuation	4		1

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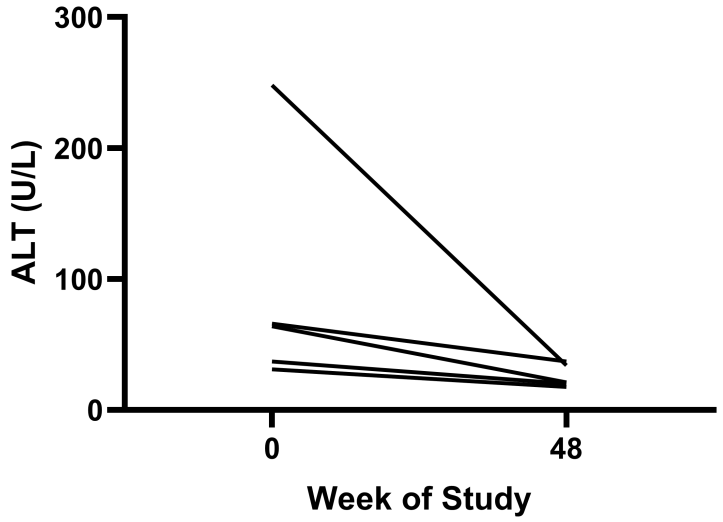
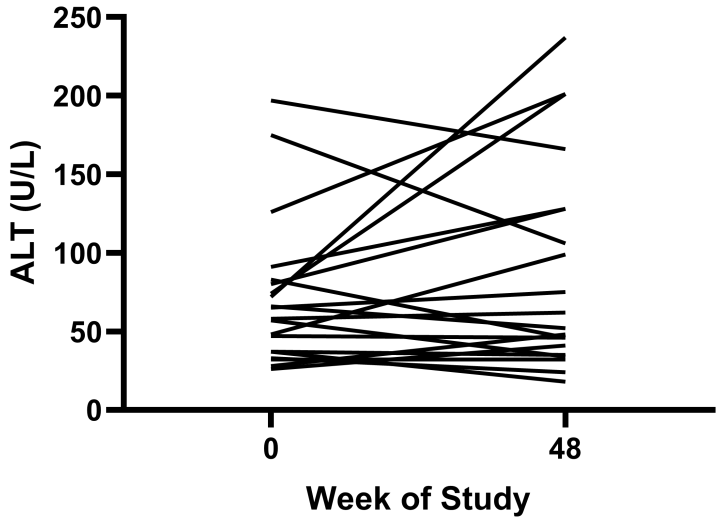
End of Study: ALT Changes from Baseline

Median (IQR)	Undetectable or BLOQ (n=5)	Remaining Cohort (n=20)	p value
			
ALT at Baseline	64.7 (46, 125.3)	58.2 (44.7, 84.7)	>0.1
Change in ALT	-43.7 (-91.3, -26)	-2.17 (-17.2, 41.8)	0.0151

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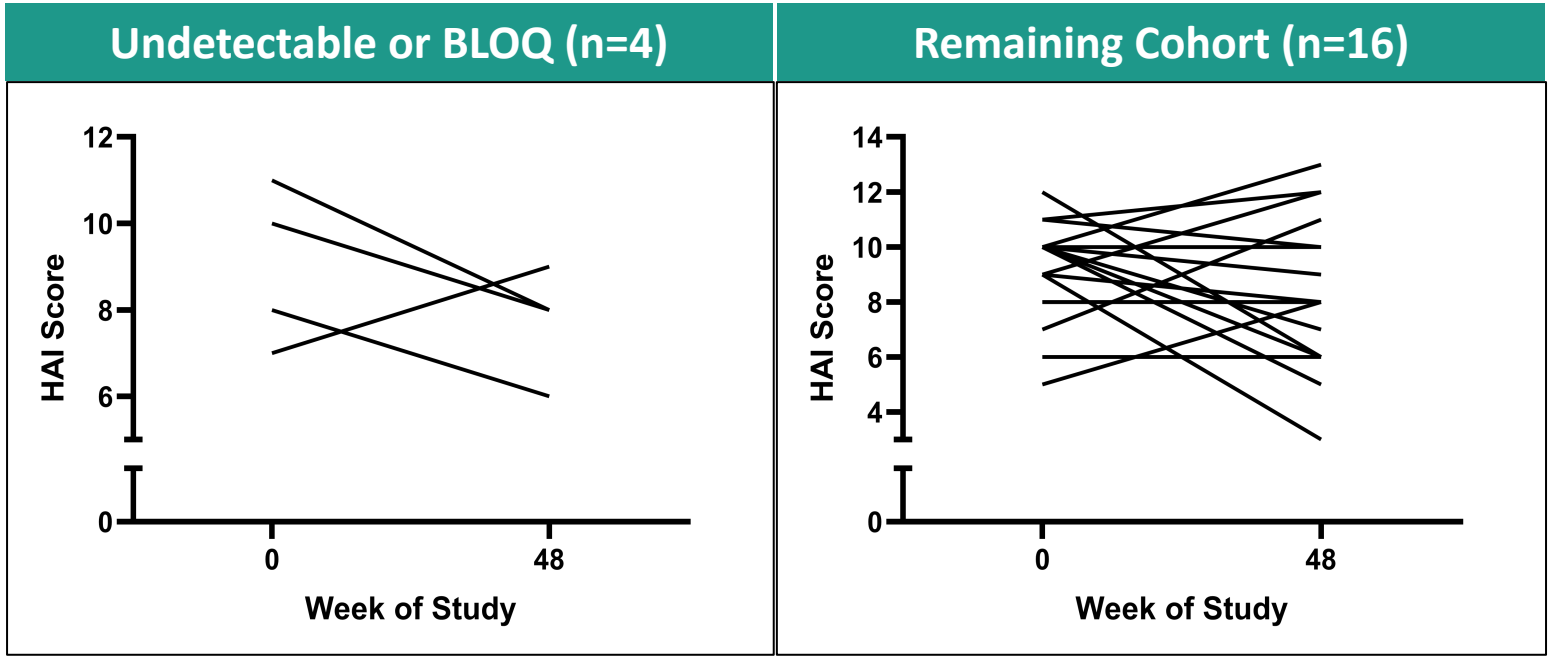
End of Study: Histologic Changes from Baseline



Changes in Inflammation at the End of Study			
> 2 Improvement in HAI	1 – 2 Improvement in HAI	No Change in HAI	Worsening in HAI
6 / 20	5 / 20	4 / 20	5 / 20

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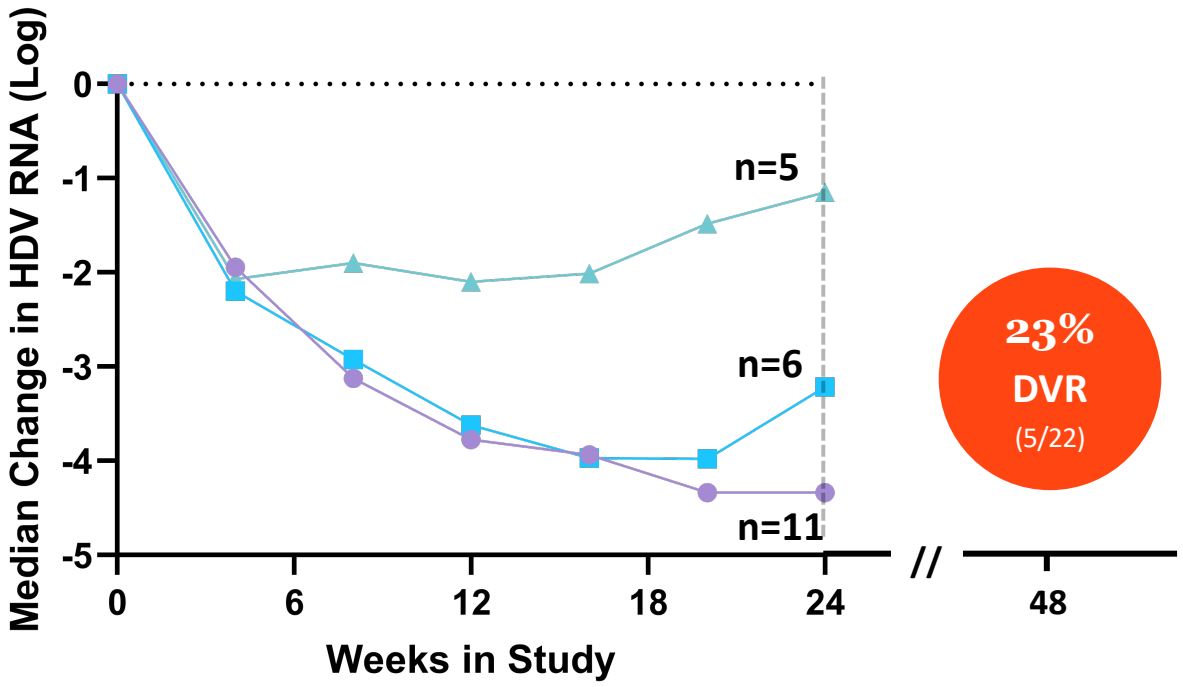
End of Study: HDV RNA Change from Baseline



23% DVR (5/22)

Categorized by response at week 24 of therapy

- <2 log decline
- >21 U/L
- Undetectable or BLOQ

- **5 (23)% maintained undetectable or BLOQ HDV RNA at the end of follow-up**
- **3 (14%) maintained undetectable HDV RNA at the end of follow-up**

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Summary

- At 24 weeks of treatment with LMD/LNF/RTV:
  - 17 of 22 (77%) patients achieved >2 log decline in HDV RNA
  - 11 of 22 (50%) patients achieved BLOQ or undetectable HDV RNA

- At 24 weeks post-treatment (Week 48):
  - 5 of 22 (23%) patients maintained undetectable or BLOQ at the end of study
  - 11 of 20 (55%) patients demonstrated improvement in HAI
    - In comparison: in HIDIT-2 study, 9 of 26 (34.6%) patients showed improvement in HAI after 96 weeks of PEG IFN-alfa

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Summary

- For patients who maintained undetectable or BLOQ responses at the end of study:
    - Significant ALT declines
    - Improvements in HAI
- Therapy was relatively safe in most patients for up to 6 months with per protocol discontinuations due to known side effects related to peginterferon lambda

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Conclusion

- After 24 weeks of therapy, >75% of subjects achieve >2 log decline in HDV RNA with 50% achieving undetectable or BLOQ HDV RNA levels.

- These end of study results support continued exploration of this therapeutic combination in HDV.

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Thank you!

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