A Phase 2 Study Exploring Once Daily Dosing of Ritonavir Boosted Lonafarnib for the Treatment of Chronic Delta Hepatitis – End of Study Results from the LOWR-3 Study

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Introduction

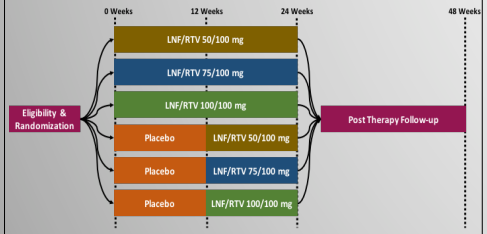
- 15-20 million people are infected worldwide with chronic hepatitis D (HDV).
- Up to 80% of patients with HDV may develop cirrhosis within 5-10 years.
- Interferon-based therapies are unsatisfactory, <30% achieve HBsAg loss and become HDV RNA negative.
- The prenylation inhibitor lonafarnib (LNF) +/- ritonavir (RTV) boosting has demonstrated effectiveness against HDV in early phase clinical trials.

Aims

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

Methods

- 21 chronically infected HDV patients on hepatitis B nucleos(t)ide analogue therapy were enrolled into 1 of 6 groups in a phase 2a double-blinded, randomized, placebo-controlled study.



- Serial measurements of safety parameters, liver tests, virologic (HDV RNA & HBV DNA) and pharmacokinetic markers and symptom questionnaires were performed.

Results

Table 1: Demographics

	Result (n=21)
M/F (%)	67/33
Median Age	40
Ethnicity(%)	
Caucasian	45
Black	5
Asian	50
Median VCTE* (kPa)	7.9
Entecavir/Tenofovir	11/10

*VCTE= Vibration Controlled Transient Elastography

Fig 1: HDV RNA response during 12 weeks of therapy

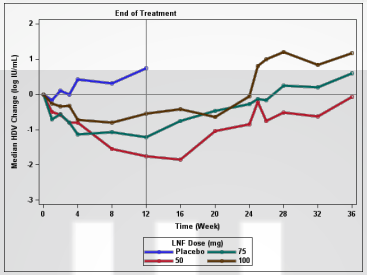


Fig 2: Viral kinetic response patterns during 24 weeks of therapy

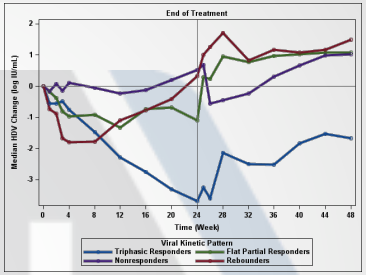


Table 2: Median Changes over 12 Weeks of Therapy

	Baseline		Δ at 12 weeks
Dosing Group	ALT (U/L)	HDV RNA (log IU/mL)	HDV RNA (log IU/mL)
LNF 50 mg (n=7)	60	4.31	-1.60
LNF 75 mg (n=7)	64	4.67	-1.33
LNF 100 mg (n=7)	88	4.67	-0.83
Placebo (n=9)	71	4.11	0.75

*Values in red indicate p-value < 0.05 compared to Placebo

Table 3: Median Changes over 24 Weeks of Therapy

	Baseline		Δ at 24 weeks	
VK Pattern*	ALT (U/L)	HDV RNA (log IU/mL)	ALT (U/L)	HDV RNA (log IU/mL)
Triphasic Responders	76	4.58	-57	-3.70
Flat Partial Responders	99	4.67	-46	-1.90
Non Responders	46	4.56	-8	0.18
Rebounders	70	4.77	-6	-0.49

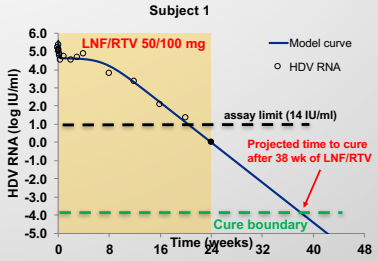
* n=3 in each VK pattern group

Table 4: Subjects reaching <250 IU/mL HDV RNA

	Baseline		Nadir	
Subject	ALT (U/L)	HDV RNA (IU/mL)	ALT (U/L)	HDV RNA (IU/mL)
1	134	1.7×10^5	25	Negative
2	61	5.9×10^4	37	124
3	41	3.7×10^2	22	<14
4	26	2.4×10^4	21	<14
5	71	2.8×10^3	48	<14
6	76	3.8×10^4	26	19

*Lower limit of quantification is 14 IU/mL

Fig 3: Modeling Time to Cure



Discussion

- Compared to placebo, serum HDV RNA levels significantly declined during 12 and 24 weeks of therapy.
- 6 subjects achieved HDV RNA levels <250 IU/mL of which 67% normalized ALT during therapy.
- Viral kinetic analysis identified 4 distinct patterns of response in each LNF dosing group (Figure 2).
- 100% of the triphasic responders and 67% of the partial responders normalized ALT on therapy.
- Mathematical modeling projects that patients with a triphasic response (Figure 3) may achieve cure by extending therapy duration.
- Lonafarnib was safe and generally well tolerated at the prescribed doses for up to 24 weeks.

Conclusion

- The all-oral combination of once-daily ritonavir boosted lonafarnib was safe and tolerable in patients for up to 6 months of therapy and demonstrated antiviral activity.
- Administration of prenylation inhibitors beyond 6 months with response guided therapy may result in continued anti-HDV activity with possible viral clearance.

References

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Disclosures

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- All patients provided informed consent for IRB approved studies.
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