24466: HBV RNAi INHIBITOR RG6346 IN PHASE 1b-2a TRIAL WAS SAFE, WELL-TOLERATED, AND RESULTED IN SUBSTANTIAL AND DURABLE REDUCTIONS IN SERUM HBsAg LEVELS

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INTRODUCTION

Chronic Hepatitis B (CHB) virus infection can cause progressive necro-inflammatory liver damage, leading to cirrhosis and hepatocellular carcinoma and typically requires prolonged suppressive treatment with nucleos(t)ide analog inhibitors of the HBV polymerase. Current treatments reduce the risk of CHB sequelae but are associated with very low rates of a functional cure. There is an unmet need for new treatments that lead to a functional cure. RG6346 is an investigational synthetic dsRNAi therapy conjugated to *N*-acetyl-galactosamine that induces cleavage of mRNA encoding all forms of HBsAg in hepatocytes and has the potential to induce functional cure.

Table 1. Trial Design

Group A	Placebo-controlled (2:1 active vs. placebo), single ascending dose study in healthy volunteers	Completed n=30 EOT: D-29	RG6346 dose cohorts: 0.1, 1.5, 3.0, 6.0, 12.0 mg/kg
Group B	Placebo-controlled (5:3 active vs. placebo), single-dose study in participants with no prior use of nucleoside or nucleotide analog (NUC) therapy (NUC-naïve) with chronic HBV infection	Completed n=9* EOT: D-85	RG6346 dose cohort: 3.0 mg/kg (NUCs initiated after 12 weeks)
Group C	Placebo-controlled (2:1 active vs. placebo), multiple-ascending-dose study in NUC-suppressed participants with chronic HBV infection	Ongoing n=18 (3/4 participants reached EOT in 6 mg/kg EOT: D-112	RG6346 dose cohorts: 1.5 (C1), 3.0 (C2), 6.0 (C3) mg/kg; 4 monthly doses

*One additional subject was enrolled in Group B (total N = 9) because a previous Group B subject was ineligible due to receiving another investigational agent within 6 months of RG6346 dosing. Both trial participants were included in the analysis.
After completion of the treatment period, study participants with ≥ 1 $\log_{10}$ IU/mL HBsAg reduction are followed in a conditional follow-up period (CFU).
Data current as of 07 October 2020.

Key Study Inclusion/Exclusion Criteria:

- Groups B and C: HBeAg (+) with HBsAg > 1000 IU/mL, or HBeAg (–) with HBsAg > 500 IU/mL; no evidence of cirrhosis
- Group B: Serum HBV DNA > 2000 IU/mL, and ALT ≥ 35 U/L (males) or ≥ 30 U/L (females)
- Group C: Continuously on NUC therapy for at least 12 weeks prior to screening

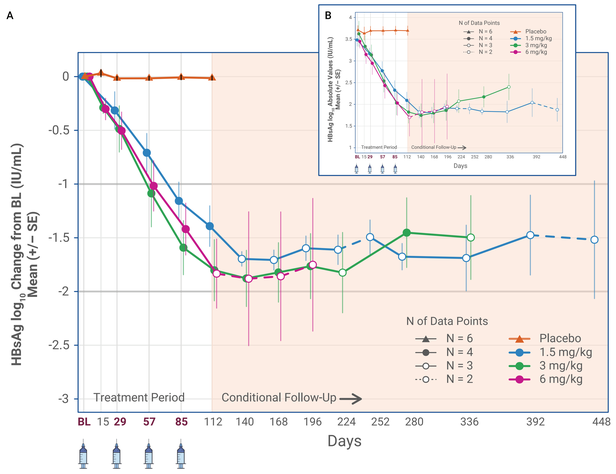
Table 2. Demographics

Patient Baseline Characteristics-Well Balanced Across Cohorts

	Cohort C1 n = 4	Cohort C2 n = 4	Cohort C3 n = 4	Placebo n = 6	Cohort B n = 6	Placebo n = 3
Population	NUC-suppressed				NUC-naive ALT ≥35 U/L (males); ≥30 U/L (females)	
HBV siRNA regimen	4 x QM doses (1.5 mg/kg)	4 x QM doses (3 mg/kg)	4 x QM doses (6 mg/kg)		single dose (3 mg/kg)	
Mean age (years), (min-max)	38 (29-45)	47 (38-51)	52 (34-63)	45 (39-56)	38 (29-49)	40 (34-45)
Race: Asian/non-Asian	4:0	4:0	4:0	5:1	5:1	2:1
Male, n (%)	1 (25)	2 (50)	4 (100)	2 (33)	5 (83)	3 (100)
HBeAg positive, n (%)	2 (50)	2 (50)	2 (50)	2 (33)	4 (67)	1 (33)
HBV genotype, n	–	–	–	–	C (6)	A (1); B (1), C (1)
HBV DNA $\log_{10}$ (IU/mL), mean (SD)	1.6 (1.04)	1.0	1.0 (0.05)	1.1 (0.12)	7.20 (2.06)	6.20 (2.69)
HBsAg $\log_{10}$ (IU/mL), mean (SD)	3.48 (0.29)	3.62 (0.59)	3.45 (0.31)	3.71 (0.26)	4.16 (0.43)	3.82 (0.86)
ALT, n						
≤1 x ULN	4	4	4	5	4	2
>1-2 x ULN				1		
>2-5 x ULN					1	
>5-10 x ULN					1	1

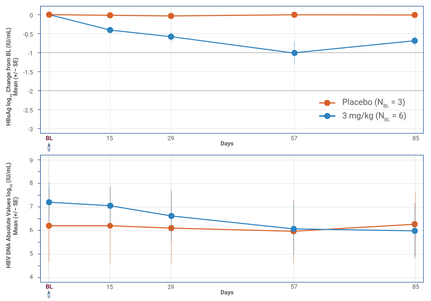
RESULTS

Figure 1A & **Figure 1B** (inset): RG6346 Showed Strong, Durable Reduction in HBsAg Levels in NUC-suppressed CHB participants (Group C)



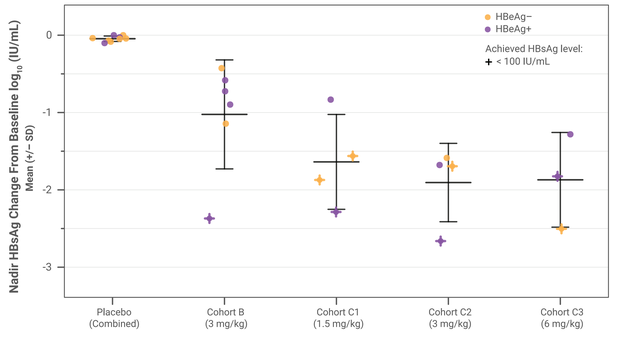
- Mean HBsAg $\log_{10}$ reduction (IU/mL) from baseline at D-112 (EOT) (**Figure 1A**)
  - 1.39 (SE 0.19) for 1.5 mg/kg cohort.
  - 1.80 (SE 0.28) for 3 mg/kg cohort.
  - 1.83 (SE 0.32) for 6 mg/kg cohort (3/4 participants on RG6346 completed D-112).
- Mean HBsAg $\log_{10}$ absolute value (IU/mL) at D-112 (EOT) (**Figure 1B**)
  - 2.09 (SE 0.19) for 1.5 mg/kg cohort.
  - 1.82 (SE 0.26) for 3 mg/kg cohort.
  - 1.70 (SE 0.43) for 6 mg/kg cohort (3/4 participants on RG6346 completed D-112).
- Durability of response has been observed up to D-448
  - The subject with the maximum HBsAg change from baseline in C1 maintained > 2.0 $\log_{10}$ IU/mL HBsAg reduction up to D-448.
  - The majority of patients (7/9) who entered into conditional follow-up had ≥ 1 $\log_{10}$ IU/mL HBsAg reduction from baseline at the last observed time point, which ranged from D-196 to D-448.

Figure 2A (upper) & **Figure 2B** (lower): RG6346 Induces Reduction in HBsAg (2A) and HBV DNA (2B) in Immune Active NUC-naïve Participants with HBV (Group B, Single Dose)



- D-85 (EOT): Mean HBsAg $\log_{10}$ reduction (IU/mL) from baseline is 0.69 for 3 mg/kg cohort (**Figure 2A**).
- Max mean reduction of HBsAg $\log_{10}$ (IU/mL) from baseline was 1.01 on D-57 (**Figure 2A**).
- The absolute mean of HBV DNA value change from 7.20 IU/mL at baseline to 5.98 IU/mL at D-85 (**Figure 2B**).

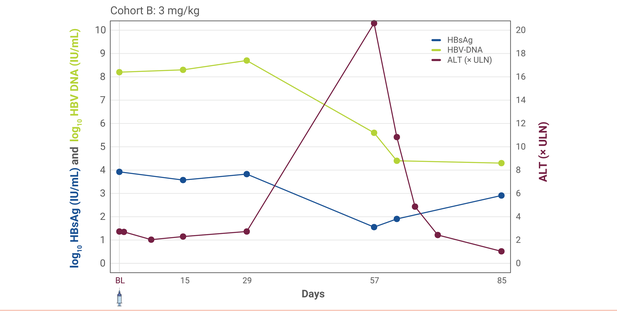
Figure 3. Individual and Average Max Reductions in HBsAg Levels Due to Administration of RG6346 (Groups B and C)



Note 1: Only the subjects that completed the treatment period are shown in the figure.
Note 2: HBeAg+/–: status of HBeAg at baseline.

- NUC-naïve patients (Group B, 3 mg/kg single dose): Mean (SD) nadir HBsAg $\log_{10}$ (IU/mL) reduction was 1.02 (0.70).
- In NUC-suppressed patients (Group C, 4 monthly doses): Mean (SD) nadir HBsAg $\log_{10}$ IU/mL reduction was 1.64 (0.61) for 1.5 mg/kg, 1.91 (0.51) for 3 mg/kg; 1.87 (0.61) for 6 mg/kg cohorts.
- The maximum HBsAg $\log_{10}$ (IU/mL) reduction observed was 2.37 for Group B and 2.66 for Group C.
- Approximately 82% of patients who reached at least D-112 (Group C) achieved > 1.5 $\log_{10}$ (IU/mL) reduction, and approximately 64% achieved HBsAg < 100 IU/mL, regardless of HBeAg status.

Figure 4. RG6346 Induces Self Resolving ALT Flares With Reduction in HBsAg and HBV-DNA in Immune Active NUC-naïve Participants with HBV (Group B, Single Dose)



Note: A single representative ALT flare associated with concomitant HBsAg and HBV-DNA reductions is shown here.

- 3 patients from NUC-naïve 3 mg/kg (Group B, Single Dose) on active treatment exhibited self-resolving protocol defined ALT flares, which are defined as substantial ALT elevations (> 3 times baseline, or post-baseline nadir value, and > 7 times ULN).
- Overall hepatic synthetic and excretory function were preserved in all patients.
- These ALT flares are suggestive of treatment-induced immune-mediated responses, as demonstrated by a decrease in viral markers and overall preserved liver function.
- There were no protocol defined ALT flares seen in NUC-suppressed Group C cohorts.

Table 3. RG6346 is Safe and Well Tolerated (Groups B and C)

	Cohort C1 1.5 mg/kg n = 4	Cohort C2 3 mg/kg n = 4	Cohort C3 6 mg/kg n= 4	Placebo n = 6	Total C Cohorts n = 18	Cohort B n = 6	Placebo n = 3	Total B Cohort n = 9
Number of participants with at least 1 possibly-related AE	2	3	1	2	8	4	1	5
Number of participants with at least 2 AEs[1]								
Injection site erythema, Injection site vesicles, Injection site bruising, Injection site rash, Injection site pain[2]	2 Mild	2 Mild 1 Moderate	1 Mild	1 Mild	7	1 Mild	0	1
Fatigue	0	1 Mild	0	0	1	1 Mild	0	1
Headache	0	2 Mild	0	1 Moderate	3	0	0	0
ALT increased, AST increased, GGT increased	0	0	0	0	0	2 Mild 2 Moderate 1 Severe	0	2

1. *MedDRA Preferred Term (PT) aggregated based on similarity. Possibly, Probably, or Definitely Drug-Related AEs in ≥ 2 participants.*
2. *Inclusive of all ISR regardless of onset time is < 4 hours or ≥ 4 hours (≥ 4 hours case is defined an ISR by protocol).*

- No SAEs, dose-limiting toxicities, or withdrawals due to AEs were observed with treatment of RG6346.
- There were no dose-exposure or regimen-dependent increase in frequency or severity of AEs, safety labs, ECG, and vital signs.
- The most common AEs in Groups B and C were related to mild injection site reactions.

CONCLUSIONS

- Treatment with RG6346 for up to 4 monthly doses was safe and well tolerated.
- Several participants treated with RG6346 exhibited self-resolving ALT elevations in NUC-naïve patients with overall preserved liver function, suggestive of treatment-induced immune-mediated responses.
- RG6346 has demonstrated proof of mechanism with significant and durable reductions of HBsAg levels in IU/ml up to 448 days, regardless of HBeAg status.

DISCLOSURES AND REFERENCES

Disclosures:
- MFY, JHY, ED, has consulting interest in Dicerna Pharmaceuticals, Inc.
- BDB and HEA are employees of Dicerna Pharmaceuticals, Inc.

References:
1. Terrault NA, Bzowej NH, Chang KM. AASLD guidelines for treatment of chronic hepatitis B. *Hepatol.* 2016; 63: 261-283.
2. Fontana RJ, Avigan MI, Janssen HLA, et al., Liver safety assessment in clinical trials of new agents for chronic hepatitis B. *J Viral Hepat.* 2019;00:1–14.

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