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ALG-020572, a GalNAc-conjugated Antisense Oligonucleotide, Demonstrates In Vivo Efficacy and Favorable Preclinical Profile for the Treatment of Chronic Hepatitis B

ALIGOS THERAPEUTICS

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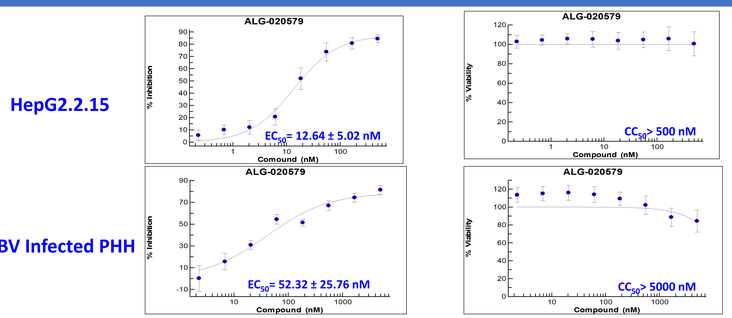
Background

Worldwide, more than 248 million people are affected by chronic hepatitis B (CHB). Current treatment options do not achieve "functional cure," defined as achieving sustained undetectable HBV surface antigen (HBsAg) and HBV DNA levels in serum 6 months after therapy. We are developing ALG-020572, a liver-targeting GalNAc antisense oligonucleotide (ASO) for the reduction of HBsAg via ribonuclease H induced cleavage of hepatitis B viral RNAs.

Methods

ALG-020579, the active unconjugated ASO of ALG-020572, was tested in HepG2.2.15 cells and HBV-infected primary human hepatocytes (PHH) for in vitro activities. The in vivo efficacy was determined in an adeno-associated virus (AAV-HBV) mouse-model from which a Pharmacokinetic/Pharmacodynamic (PK/PD) correlation was established. The PK properties of ALG-020572 were assessed following a single IV infusion in monkeys and subcutaneous (SC) administration in mice and monkeys. Metabolism of ALG-020572 was studied in vitro using mouse liver homogenates and in vivo.

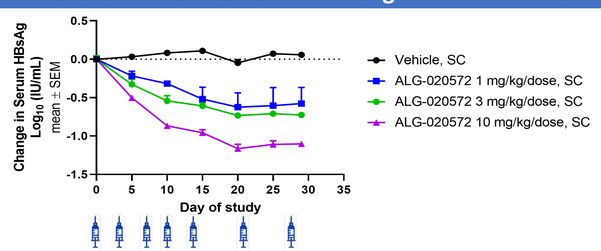
In vitro activity of ALG-020579, the active unconjugated ASO of ALG-020572



HepG2.2.15 N=4, PHH (primary human hepatocytes) N=3

- **ALG-020579 demonstrated potent inhibition of HBsAg release in vitro**
- **No significant cytotoxicity observed at the highest tested concentration**

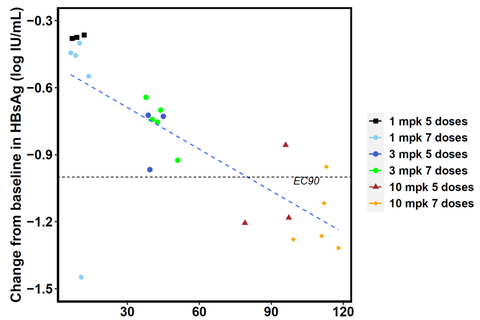
ALG-020572 Reduces Serum HBsAg in AAV-HBV Mice



Dosed on Days 0, 3, 7, 10, 14, 21 and 28; liver samples collected 24 hours after 5 or 7 doses (Days 15 and 29)

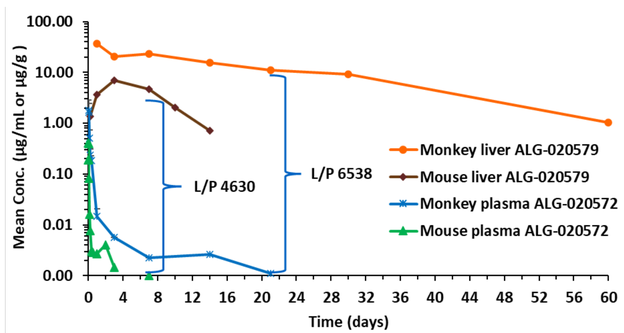
- **HBsAg reduction is ALG-020572 dose-dependent**
- **Maximal 1.1 log_{10} IU/mL reduction in HBsAg at 10 mg/kg/dose, SC**

Pharmacokinetic/pharmacodynamic correlation



- **The dose-dependent reduction of HBsAg in ALG-020572-treated groups correlated with ALG-020579 liver concentration**
- **Antiviral EC_{90} is projected at the liver concentration of 72.4 µg/g ALG-020579**
- **Lower efficacy observed with ALG-020579 dosing despite high liver concentrations (data not shown), confirming hepatocyte targeting with ALG-020572**

Plasma profile following a single SC 3 mg/kg dose in mouse and monkey



L/P = Liver to plasma ratio in the equilibrium Phase

Matrix	Analyte	Mouse			Monkey			
		C_{max} (µg/mL or µg/g)	AUC_{last} (µg·h/mL or µg·h/g)	$t_{1/2}$	C_{max} (µg/mL or µg/g)	AUC_{last} (µg·h/mL or µg·h/g)	$t_{1/2}$	F%[a]
Plasma	ALG-020572	0.42	0.83	1.1 h	1.83	8.76	3.5 h	45.5
Liver	ALG-020579	7.00	1210	2.6 d	37.1	14208	11.9 d	
Kidney	ALG-020579	5.56	1194	4.1 d	NA	NA	NA	

[a]From AUC_{inf} following IV-infusion for 1 h at 1 mg/kg: CL 2.7 ml/min/kg and Vd=10.9 L/kg, NA=not applicable, h=hour, d=day; Plasma analysis by PNA hybridization method, Tissue analysis by LC-HRAM
Liver collection in monkey by laparoscopic biopsy

ALG-020572 displays a favorable ADME profile

Single Dose SC PK

- **ALG-020572**
  - **Rapid absorption and distribution with short plasma half-life**
  - **Good systemic bioavailability in monkey**
  - **BQL in tissues at all timepoints; rapid uptake and efficient conversion to ALG-020579 in liver and kidney**
- **ALG-020579**
  - **Long half-life in liver (3 days in mouse and 12 days in monkey) supports at least weekly regimen in humans; half-life in mouse kidney was 4 days**

Repeat Dose SC PK

- **Greater than dose-proportional increase, no accumulation and no sex difference in plasma exposures of ALG-020572**
- **Rapid uptake in liver with efficient conversion to ALG-020579; ALG-020572 was not detected in tissues**

Metabolism

- **In mouse liver homogenate the major metabolites were formed by the loss of N-acetyl galactosamine units; ALG-020579, a minor analyte was formed at 48-72 hours only**
- **The major in vivo analytes in monkey were ALG-020572 in plasma and ALG-020579 in liver and kidney**

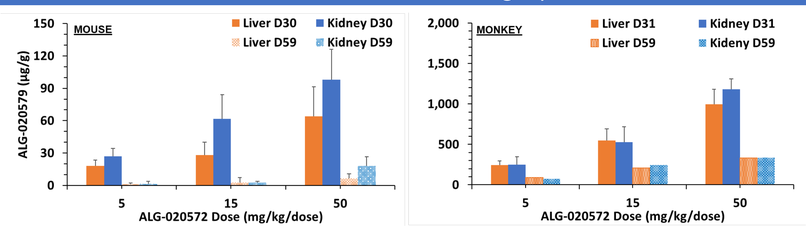
Excretion

- **Urinary excretion of total ASO within 7 days following a single SC dose at 3 mg/kg in monkey was <1% of dose**

In Vitro DDI of ALG-020572 and ALG-020579

- **Low potential of DDI due to inhibition of CYP450s (IC_{50} >100 µM each for full panel) or transporter (BCRP, P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2)**

Tissue distribution and half-life following repeated SC doses



Dose regime: Days 1, 4, 8, 11, 15, 22 and 29; Tissues at 24 h (mouse) and 48 h (monkey) after the last dose and at end of the recovery phase (Day 59)

- **Liver and kidney concentrations of ALG-020579 increased with dose albeit less than dose proportionally**
- **Half-life of ALG-020579 in liver was 8 days in mouse and 19 days in monkey**
- **ALG-020572 (GalNAc conjugate) was BQL at all timepoints**

Conclusions

The in vitro and in vivo efficacy, hepatocyte targeting, a favorable PK profile of ALG-020572 and long half-life of ALG-020579 in liver following SC administration warrant its advancement into clinical development as a potential treatment for chronic hepatitis B. This compound is currently being evaluated in Phase 1 studies (NCT05001022).

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