Phase I, FIH clinical trial of ARC-520, an siRNA-based therapeutic for treatment of chronic HBV infection, in normal healthy volunteers

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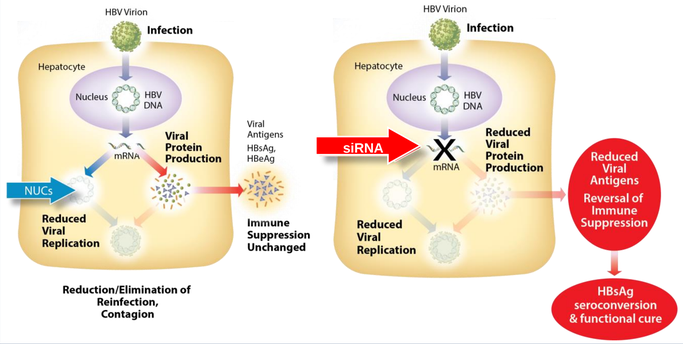
1 Background:

- Functional cure (loss of HBsAg off therapy) in Hepatitis B has been elusive despite the ability to virtually abolish circulating virus in most patients.
- Many consider this to be due to persistent production of viral antigens, especially HBsAg.
- RNA interference (RNAi) has the potential to reduce viral antigen production and thereby allow restoration of effective host immunity.
- As a field, RNAi has been hampered by delivery challenges affecting safety, tolerability and obtainable knockdown.
- Arrowhead Research is testing technology that we believe may address all of these issues and - via substantial viral antigen suppression - lead to functional cure in Hepatitis B.

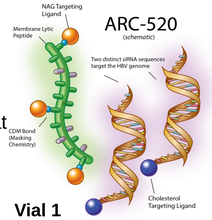


2 ARC-520 for chronic HBV infection

Composed of 2 vials

Vial 1: ARC-520 Excipient
- Lyophilized powder
- Contains a masked, hepatocyte-targeted peptide (NAG-MLP) that promotes endosomal escape of the HBV chol-siRNAs

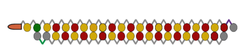
Vial 2: ARC-520 API
- Liquid
- Contains the liver-tropic HBV chol-siRNAs
- Inclusion of 2 siRNAs is predicted to be active against 99.6% of all know HBV genomes



siRNAs

General design features
- Sense strand: 23 nt, cholesterol at 5'end, inv(dT) at 3' end
- Guide strand: 21 nt, single P-S at 3' end
- Alternating 2'OMe/2'F sugar modifications in core sequence
- MW ~ 16000 Da

Structure



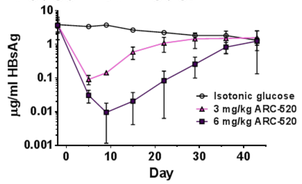
- 2' – H
- 2' – F
- 2' – OMe
- 2' – OH
- Phosphodiester
- Phosphorothioate
- 3'-3' Phosphodiester
- Cholesterol

Distribution
- Liver (10-fold greater than in next highest tissue (spleen) 24 hrs post-injection)

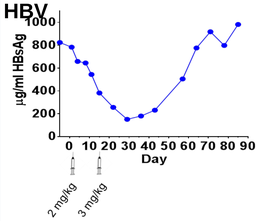
3 Highly effective at reducing antigenemia in animal models

HBsAg

Mouse HBV model



Chimpanzee with chronic HBV



Mouse data: Wooddell et al, Mol Ther 2013 May; 21(5) 973-85
Chimp data: Dr. Robert Lanford, Texas Biomedical Research Institute

4 Heparc-1001: First-in-human trial of ARC-520

Trial design

- Single dose Phase I study in normal healthy volunteers
- Admitted to unit overnight pre-dose and monitored for 24 hours post-dose in the unit
- Vital signs, telemetry, ECGs, safety labs, PK, adverse events
- Return visits for repeat safety evaluations and recording of adverse events at 48 hrs, 72 hours, day 7, day 14 and day 28 post dosing
- All personnel blinded except research pharmacist at site
- Randomization 2:1 for ARC-520 vs placebo in 6 cohorts of 6 subjects
- 36 subjects enrolled in 6 groups: Placebo (n=12), ARC-520 doses 0.01 mg/kg (n=4), 0.1 mg/kg (n=4), 0.3 mg/kg (n=4), 0.6 mg/kg (n=4), 1.2 mg/kg (n=4), 2.0 mg/kg (n=4)
- **No dropouts for any reason, no serious adverse events or adverse events rated as severe**

	Placebo	ARC-520
Gender	7M, 5F	12M, 12F
Age	28.1+/-9.6	26.9+/-6.7
Weight	70.6+/-9.8	73.2+/-12.8
BMI	23.2+/-1.9	23.4+/-2.4
Caucasian	11	22
Asian	1	2

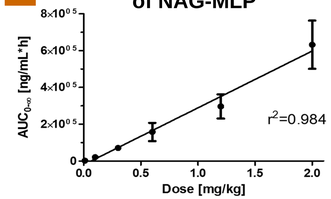
General safety parameters

- No differences relative to Placebo and findings rated Clinically Significant on:
  - Vital Signs, Physical Exams, ECGs, Clinical Labs
- One subject receiving ARC-520 in cohort 3 was noted to have sinus pause with non-conducted beats on telemetry while sleeping
  - Pre-dosing telemetry (1 hr) demonstrated un-observed Winkebach rhythm
  - Follow-up halter demonstrated further pauses and episodes of heart block
  - Cardiology evaluation noted a history of fainting and attributed findings to hypervagal syndrome
- Adverse events reported in 75% of placebo and 75% of ARC-520 subjects
  - Placebo: Mild (64%), Moderate (36%)
  - ARC-520: Mild (63%), Moderate (37%)

Adverse Event	Placebo N=12	0.01 mpk N=4	0.1 mpk N=4	0.3 mpk N=4	0.6 mpk N=4	1.2 mpk N=4	2.0 mpk N=4
Subjects reporting any AE	5 (42%)	0 (0%)	1 (25%)	4 (100%)	1 (25%)	1 (25%)	3 (75%)
Headache	2 Mild, 1 Mod		1 Mod			1 Mild	
Lightheadedness							2 Mild
Abdominal pain				1 Mild			
Generalized flushing				1 Mod			
Hypotension*				1 Mod			
Infusion reaction							1 Mod
Lethargy	1 Mild						
Lost appetite	1 Mild						
Muscle ache							1 Mild
Sinus pause				1 Mod			
Sweet taste in mouth				1 Mild			
Tingling in tongue	1 Mild						
Upper respiratory tract infection					1 Mild		

*BP machine malfunction

5 Pharmacokinetics of NAG-MLP



Heparc-1001: Conclusions

- Heparc-1001 included 36 subjects with 24 receiving rising doses of ARC-520 and 12 receiving placebo.
- Plasma concentrations of the MLP DPC in ARC-520 increased linearly with dose.
- ARC-520 and placebo produced no findings on vital signs, ECGs, physical examinations or clinical laboratories.
- Adverse event frequency and severity did not differ between placebo and ARC-520 and any relationship to dose is tenuous.
- One subject receiving ARC-520 at the highest dose developed an urticarial rash.
- ARC-520 at doses as high as 2.0 mg/kg appears to be safe and well tolerated. A Phase IIa trial is planned to begin in first half of 2014 in patients with chronic Hepatitis B.

Author Disclosures

- **Bruce D. Given, MD** - Arrowhead Research Corp. (COO, options), Leonardo Biosystems, Inc. (CEO, shareholder), Pulmotect, Inc. (Board member, options), Calando Pharmaceuticals, Inc. (Board member, options), ICON, plc (options, shareholder).
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- **Jason Lickliter, MBBS PhD FRACP** – Nucleus Network Ltd. (CMO)