Pharmacokinetics and exploratory exposure-response of siRNAs administered monthly as ARB-001467 (ARB-1467) in a Phase 2a study in HBeAg positive and negative virally suppressed subjects with chronic hepatitis B

Timothy Eley[1], Robert Russ[1], Adrian Streinu-Cercel[6], Edward J. Gane[2], Stuart K. Roberts[3], Sang Hoon Ahn[4], Yoon Jun Kim[5], William Symonds[1], Patricia Mendez[1]

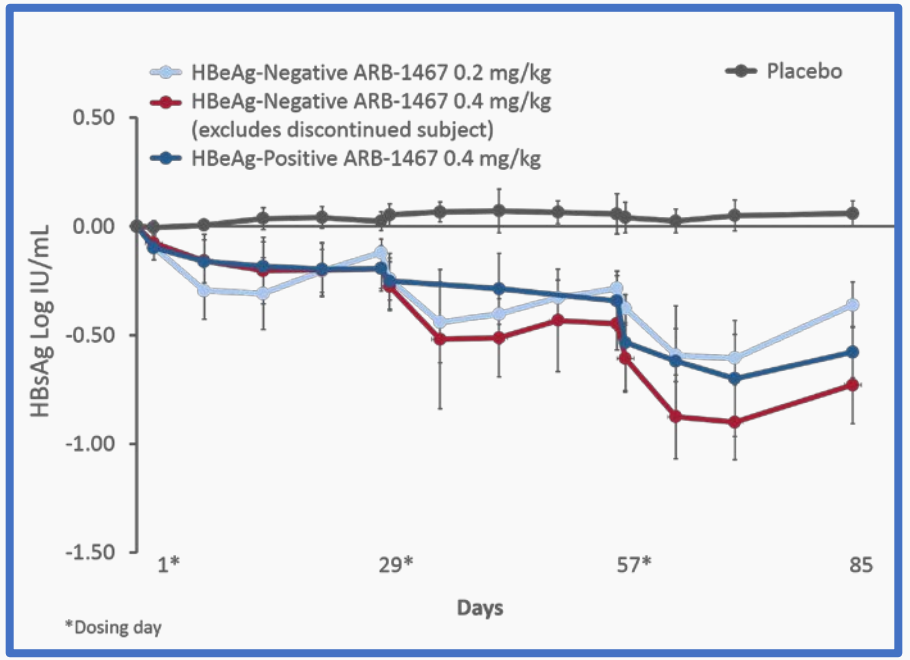
[1]Arbutus Biopharma Corporation, Burnaby, BC, Canada; [2]Auckland Clinical Studies Limited, Auckland, New Zealand; [3]The Alfred, Melbourne, VIC, Australia; [4]Yonsei University College of Medicine, Seoul, Korea (the Republic of); [5]Seoul National University College of Medicine, Seoul, Korea (the Republic of); [6]Carol Davila University of Medicine and Pharmacy, Prof. Dr. Matei Bals National Institute for Infectious Diseases

Disclosures

- T. Eley is a full-time employee and also holds stock options of Arbutus Biopharma

HBV: Converting Control to Cure

- Chronic hepatitis B virus (HBV) infection affects up to 350 million people globally[1]
  - Approximately 887,000 liver-related deaths each year [2]

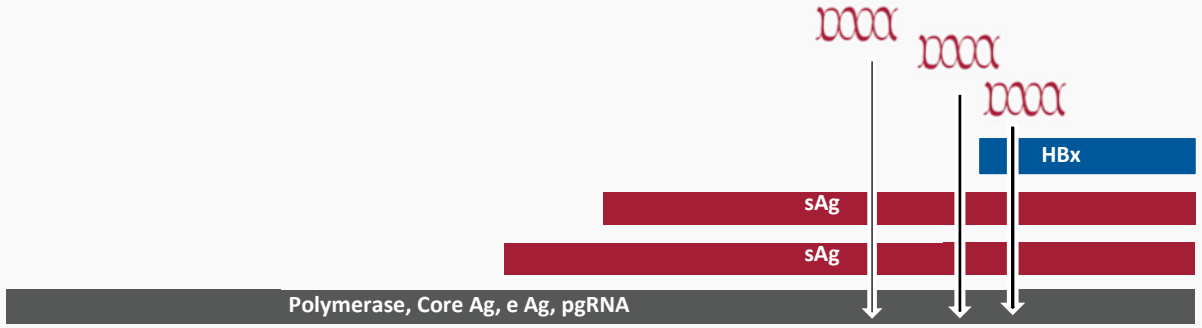


- Reducing all HBV viral proteins, particularly HBsAg, may mitigate viral suppression of and reactivate the immune response
- Monthly dosing of ARB-1467 caused significant reductions in HBsAg, regardless of HBeAg status, in nucleos(t)ide-suppressed patients in the ARB-1467-002 phase 2 study[3]

1. https://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html;
2. WHO Global Hepatitis Report 2017
3. Streinu-Cercel A, et al. J Hepatol 2017;66(suppl 1):S688–S689 (NCT02631096)

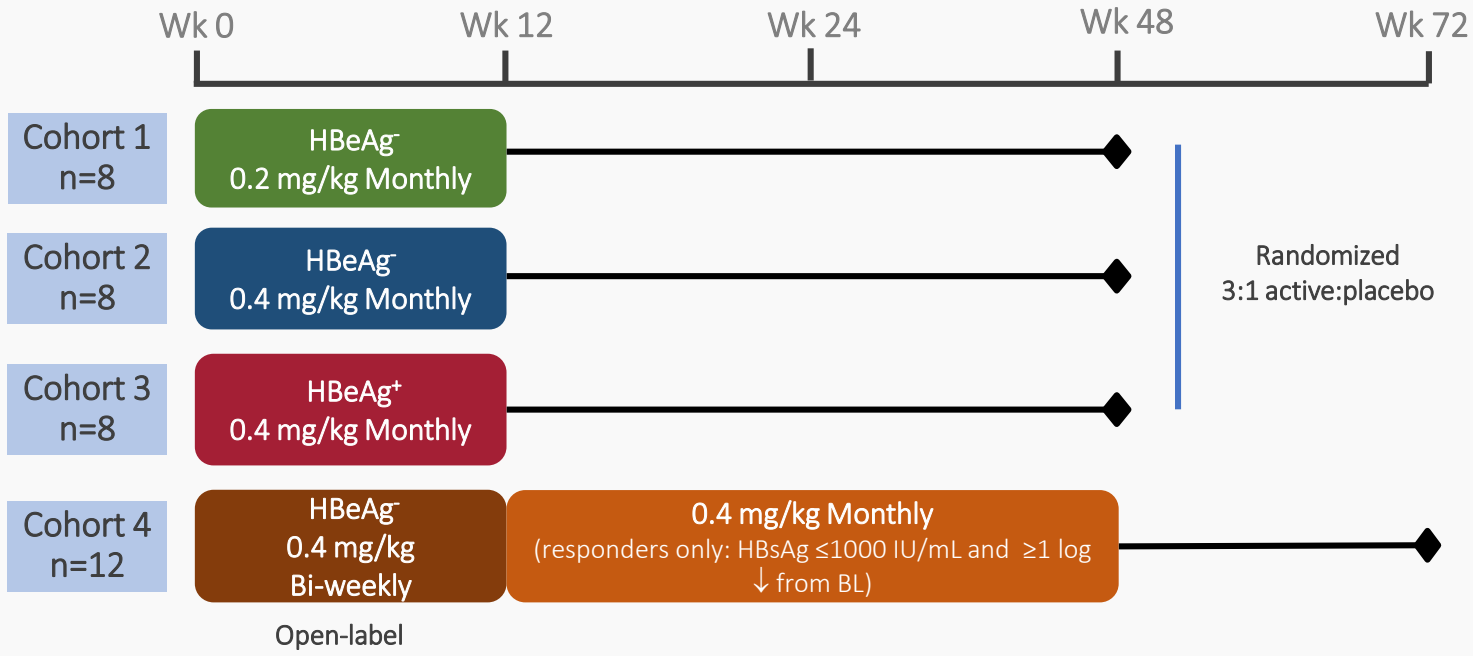
ARB-1467

- Novel RNA Interference Product
- Unique 3-trigger design inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens
- Delivered via proprietary lipid nanoparticle (LNP) technology
- Generally safe and well tolerated to date



Study 002 Design

Chronic HBV Patients on Stable Nucleos(t)ide Therapy



- ARB-1467 or placebo given as a 2-hour IV infusion
- Broad inclusion criteria
  - Non-cirrhotic, chronic HBV infection receiving NA therapy with ETV or TDF for ≥ 12 months
  - HBsAg ≥ 1000 IU/mL, HBV-DNA negative
  - ALT or AST ≤ 2x ULN
  - Fibroscan ≤ 9 kPa
- Pre-medications given the evening prior and 30 minutes prior to each infusion

Objectives:

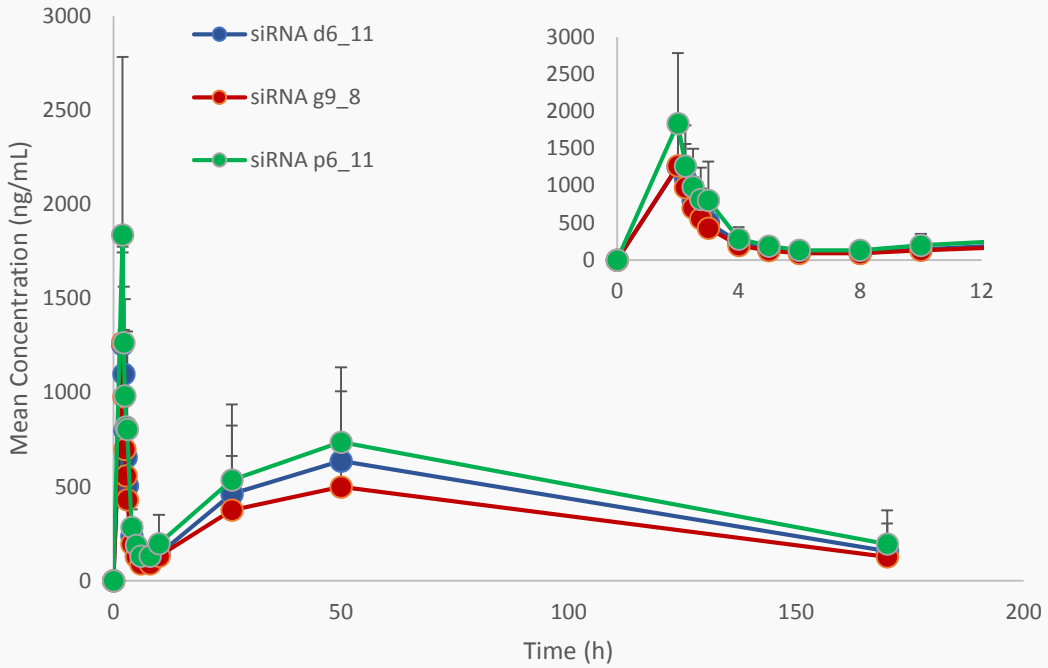
- To characterize plasma pharmacokinetics of the siRNA within ARB-1467 when dosed monthly
- To explore relationships between the plasma PK of the siRNA and reductions in HBsAg

Methods: PK and Exploratory Exposure-Response Analysis

- Blood samples for PK analysis up to 168h post-infusion after the 1st dose and either 2nd or 3rd dose
- Concentrations of siRNA were obtained by separate validated hybridization ELISAs
- Noncompartmental PK, descriptive statistics and graphical explorations via Phoenix WinNonlin
- Only HBeAg-negative subjects were selected for exploratory Exposure-Response
  - Potential for greater range of exposure with two dose levels
  - No apparent difference between e-negative and e-positive response at 0.4 mg/kg
- Only includes subjects that received all 3 monthly doses

siRNA PK: Comparable Exposures and Minimal Accumulation

Cohort 2 Dose 1
[siRNA] vs. Time



Cohort 2 Dose 1 Summary Statistics of PK Parameters				
siRNA Trigger	Dose Level	N	Cmax (ng/mL) Geometric Mean (CV%)	AUC[0-t] (ng*h/mL) Geometric Mean (CV%)
D6_11	0.4 mg/kg	6	1303 (31)	38183 (80)
G9_8	0.4 mg/kg	6	1197 (36)	31857 (75)
P6_11	0.4 mg/kg	6	1694 (46)	47438 (76)

- Marked distribution phase – preferential delivery to hepatic tissue
- Comparable PK Profiles – use only one siRNA for Exploratory Exposure-Response
- Accumulation in plasma was negligible with monthly dosing – use Dose 1 PK Data

siRNA PK: Greater than Dose Proportional Exposure

Panel Dose # (dose) [N]	Cohort 1 Dose 1 (0.2 mg/kg) [6]	Cohort 2 Dose 1 (0.4 mg/kg) [6]	Cohort 3 Dose 1 (0.4 mg/kg) [6]
Population	HBeAg -	HBeAg -	HBeAg +
Cmax◊ [ng/mL] Geometric Mean (CV%)	420 (30)	1303 (31)	973 (32)
AUC(0-t)◊ [ng*h/mL] Geometric Mean (CV%)	14292 (101)	38183 (80)	31926 (54)

- Plasma PK data suggest that siRNA exposures are greater than dose proportional
- AUC appears to be more variable than Cmax

◊ D6-11 siRNA

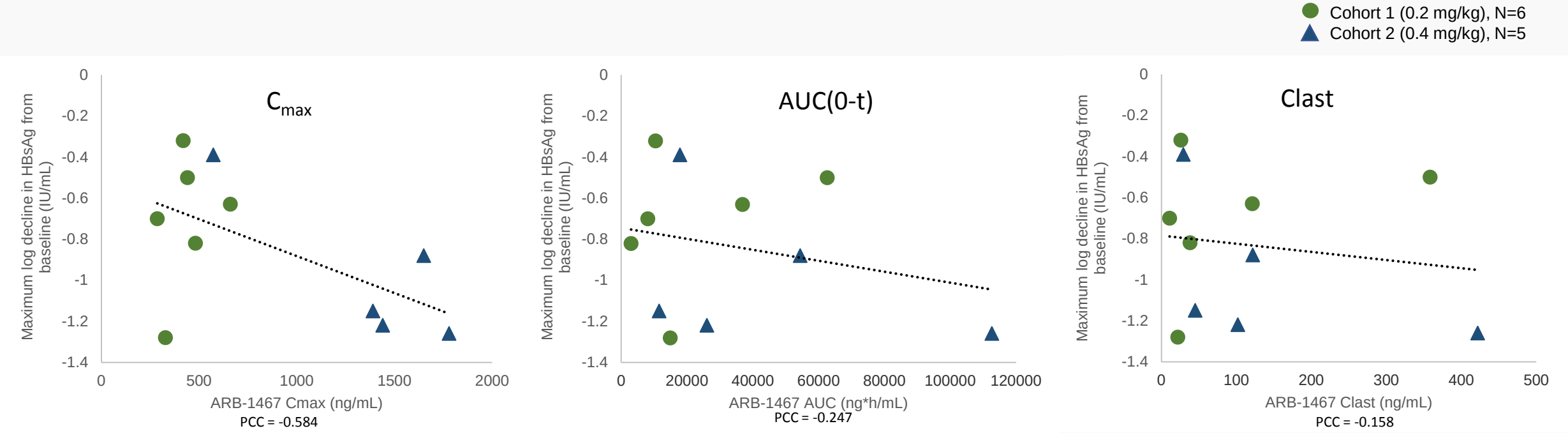
siRNA PK: Greater than Dose Proportional Exposure

Panel Dose # (dose) [N]	Cohort 1 Dose 1 (0.2 mg/kg) [6]	Cohort 2 Dose 1 (0.4 mg/kg) [6]	Cohort 3 Dose 1 (0.4 mg/kg) [6]
Population	HBeAg -	HBeAg -	HBeAg +
Cmax◊ [ng/mL] Geometric Mean (CV%)	420 (30)	1303 (31)	973 (32)
AUC(0-t)◊ [ng*h/mL] Geometric Mean (CV%)	14292 (101)	38183 (80)	31926 (54)

- Plasma PK data suggest that siRNA exposures are greater than dose proportional
- AUC appears to be more variable than Cmax
- PK appears to be comparable between HBeAg- and HBeAg+

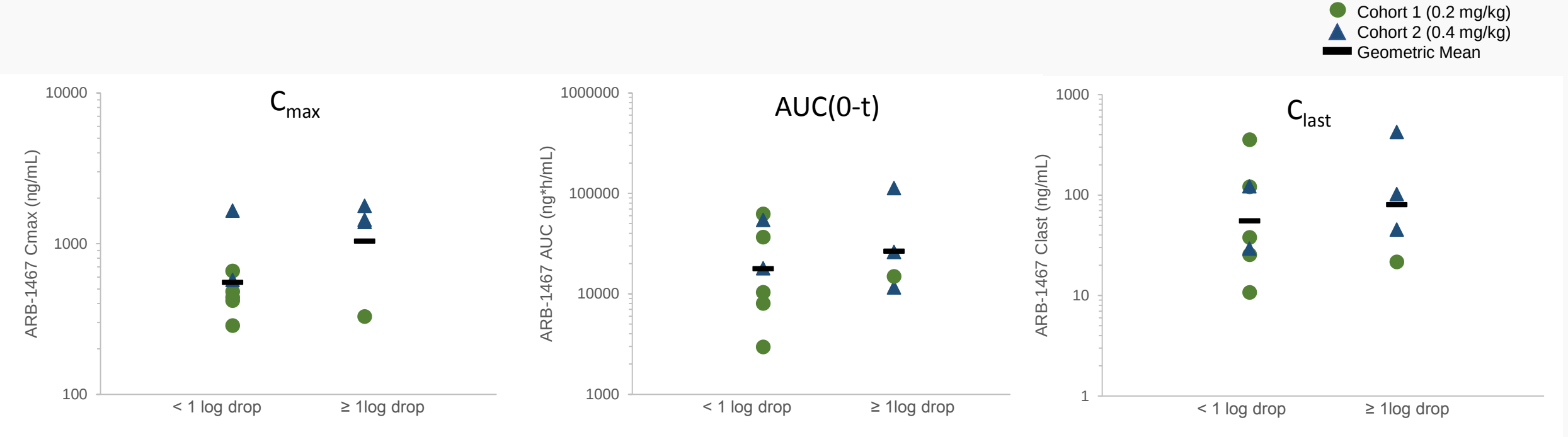
◊ D6-11 siRNA

No clear relationship between siRNA PK and HBsAg decline



- Plasma Cmax has a fairly weak association with HBsAg decline; AUC and Clast show none
- Cmax unlikely explanation; transient, response persists and peaks typically 2 weeks later
  - Lowest Cmax had fastest drop in HBsAg
- Cmax vs response is artifact of dose response

Comparable Exposures in Subjects with/without 1 log Decline in HBsAg



- Considerable overlap between those with and without 1 log decline
- Plasma Cmax shows trend toward higher values in those with 1 log decline
- AUC and Clast show no meaningful trends
- Other factors influencing exposure-response such as RISC kinetics, other viral markers, etc

Additional Considerations and Future Directions

Alternate assessments

- Substitution of % change in HBsAg for log change produced similar findings
- Measures of exposure from the second peak in plasma similarly did not reveal any useful trends

Next Steps

- Re-evaluate trends including biweekly Cohort 4 data
- Investigate/Incorporate additional predictive factors for antiviral response
- Investigate alternate measures of antiviral response

Conclusions

- Following monthly dosing with ARB-1467 siRNA PK was modestly greater than dose proportional
- No clear trends between HBsAg decline and PK parameters
- Differences in individual patient response were not well explained by plasma PK parameters
- Patient- and disease-specific factors require further evaluation as predictors of/covariates on response

Acknowledgements

- Subjects who participated in ARB-1467-002 and their families
- Study Coordinators/Site Staff for each of the Investigators
- Arbutus Biopharma siRNA Project Team
  - Alexis Carpenter
  - Nana Collett
  - Andy Cuconati
  - Merete Eisenhardt
  - Tom Frohlich
  - Amy Lee
  - Jim List
  - Pete Lutwyche
  - Susan Oakley
  - Scott Oglesby
  - Sean Semple
  - Heather Sevinsky