Disclosure

- This study was sponsored by Pfizer, Inc.
- All authors are employees of Pfizer, Inc. with ownership of stock in Pfizer, Inc.

Effects of 12 Weeks of Treatment with RN316 (PF-04950615), a Humanized IgG2Δa Monoclonal Antibody Binding Proprotein Convertase Subtilisin Kexin Type 9, in Hypercholesterolemic Subjects on High- and Maximal-Dose Statins

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RN316: Mechanism of Action

- Although statins are first-line therapy for reducing LDL-C and CV events, many patients are unable to achieve LDL-C goals or tolerate their medication
- Proprotein convertase subtilisin kexin type 9 (PCSK9) is a new target for LDL-C lowering
- PCSK9 reduces the number of LDL receptors, particularly in the liver, resulting in diminished hepatic clearance capacity for plasma LDL-C and increased LDL-C levels
- RN316, a humanized IgG2Δa monoclonal antibody, binds to PCSK9, preventing PCSK9-mediated down-regulation of the LDL receptor thereby improving LDL-C clearance and reducing LDL-C levels

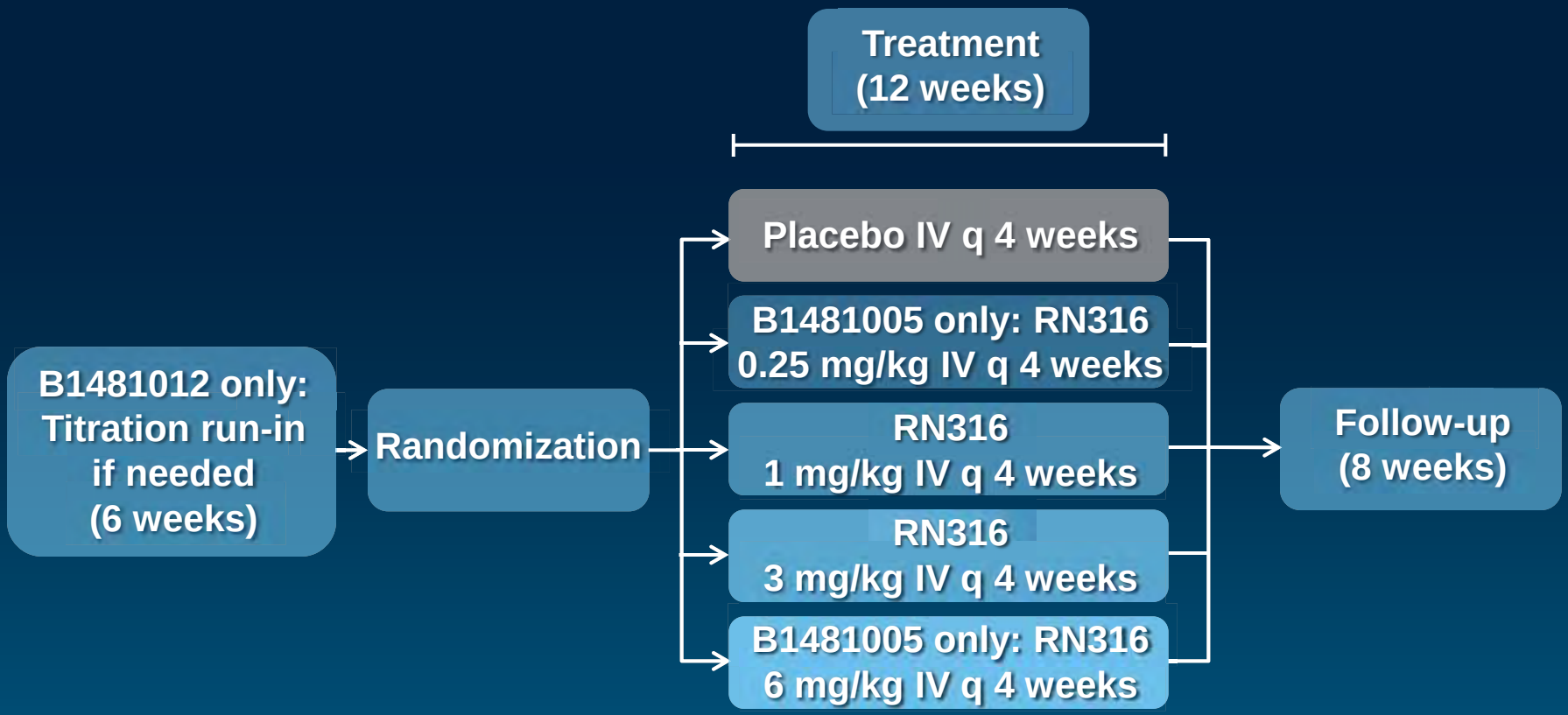
Objective

- Two Phase 2 studies were conducted to assess the effects of RN316 on LDL-C when added on to high-to-maximal doses of statins in subjects with primary hypercholesterolemia

Study Design: RN316 Phase 2 Clinical Trials

Design Element	High-Dose Statin (B1481005)	Maximal-Dose Statin (B1481012)
Overview	Randomized, double-blind, placebo-controlled, parallel design	
Background statins	Atorva 40 & 80 mg Rosuva 20 & 40 mg Simva 40 & 80 mg	Atorva 80 mg Rosuva 40 mg
N	90	45 (*Run-in: 13)
*6-week statin run-in/ titration/switch	No run-in/ titration/switch	Atorva 80 → no run-in Rosuva 40 → no run-in Atorva 40 → 80 mg Rosuva 20 → 40 mg Simva 40 → Atorva 80 mg Simva 80 → Atorva 80 mg
LDL-C inclusion criterion	≥100 mg/dL	≥80 mg/dL
RN316 treatment arms (IV infusion)	0.25 mg/kg 1.0 mg/kg 3.0 mg/kg 6.0 mg/kg Placebo	1.0 mg/kg 3.0 mg/kg Placebo
Dose interruption when LDL-C ≤25 mg/dL (resumed after ≥40 mg/dL)		

Combined Study Design: RN316 Phase 2 Clinical Trials



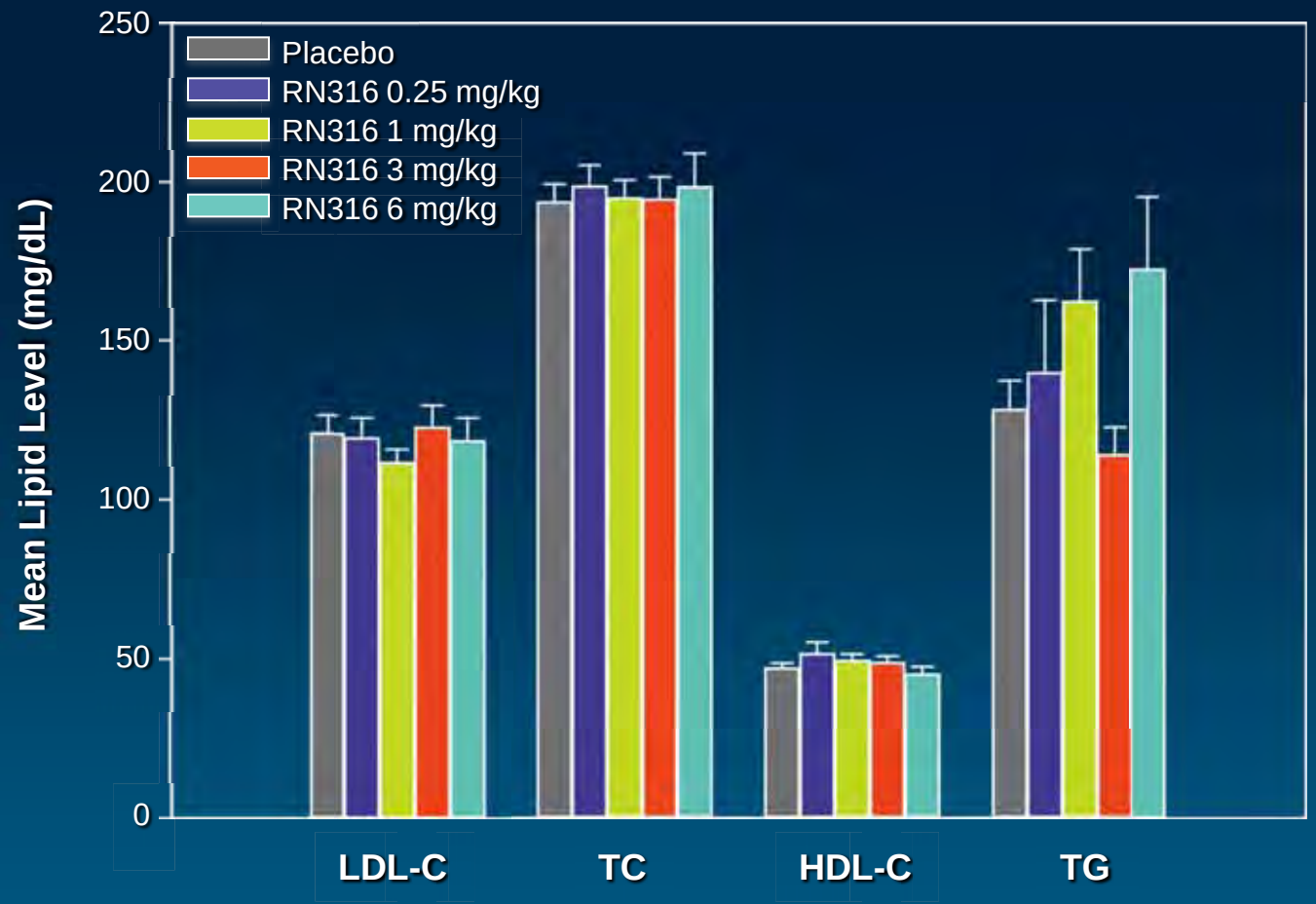
- Two Phase 2 trials (B1481005 & B1481012)
- All subjects self-administered statin
- Dose interruption when LDL-C ≤25 mg/dL; resumed after LDL-C ≥40 mg/dL

Demographics: RN316 Phase 2 Clinical Trial Subjects Pooled Data

Characteristic	Placebo	RN316 Dose			
		0.25 mg/kg	1 mg/kg	3 mg/kg	6 mg/kg
N	33	17	33	35	17
Age (y)	57 ± 17	58 ± 10	55 ± 14	55 ± 14	61 ± 6
Gender (M/F)	21/12	8/9	15/18	15/20	9/8
Weight (kg)	88 ± 23	83 ± 15	87 ± 25	83 ± 23	82 ± 15
BMI (kg/m^2)	31 ± 7	30 ± 6	30 ± 8	30 ± 7	29 ± 6
Statin (n)					
Atorva	14	6	14	14	6
Rosuva	12	5	13	14	5
Simva	7	6	6	7	6

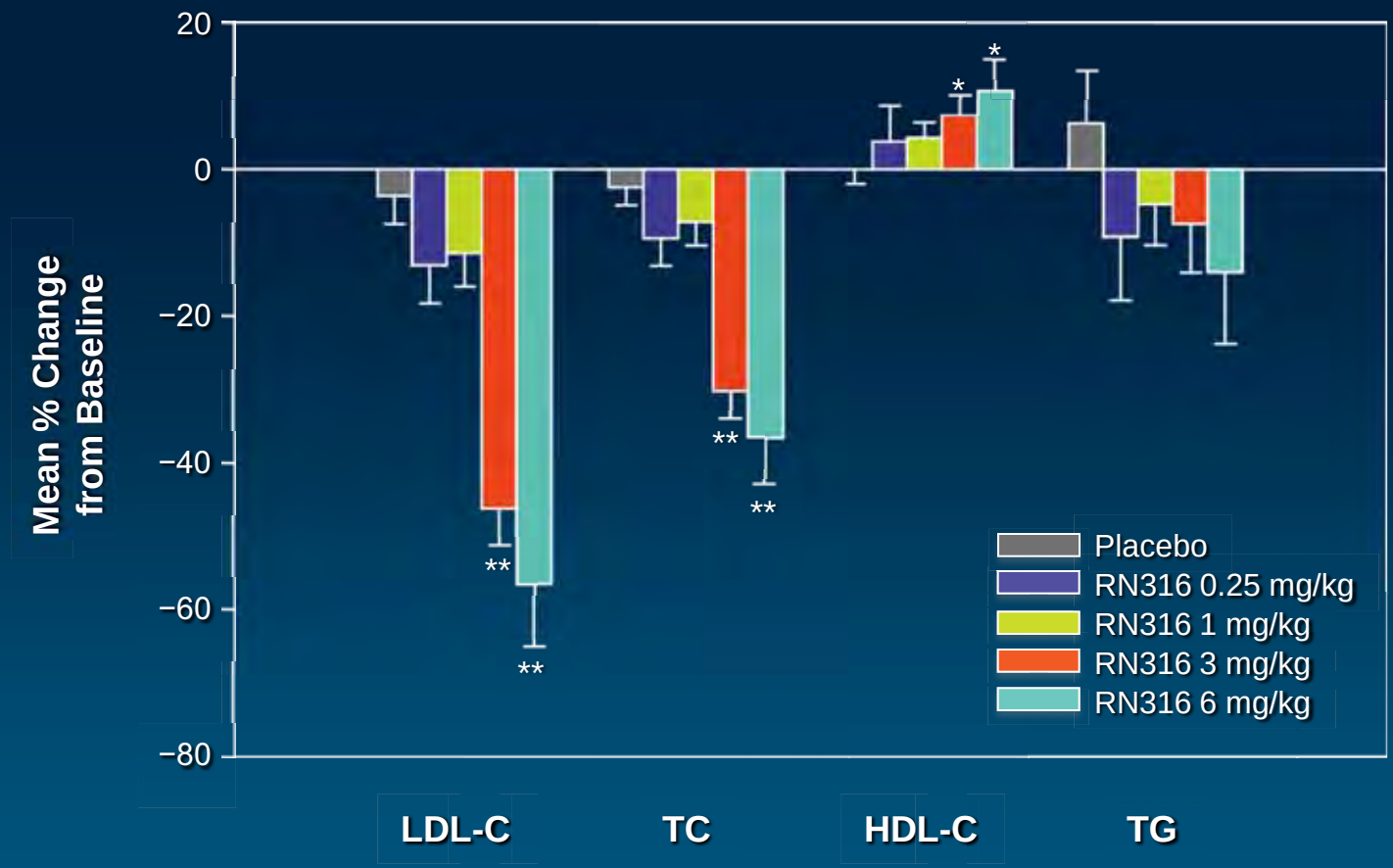
Values are mean ± SD
B1481005 and B1481012 data combined

Baseline Lipids: RN316 Phase 2 Clinical Trial Subjects Pooled Data



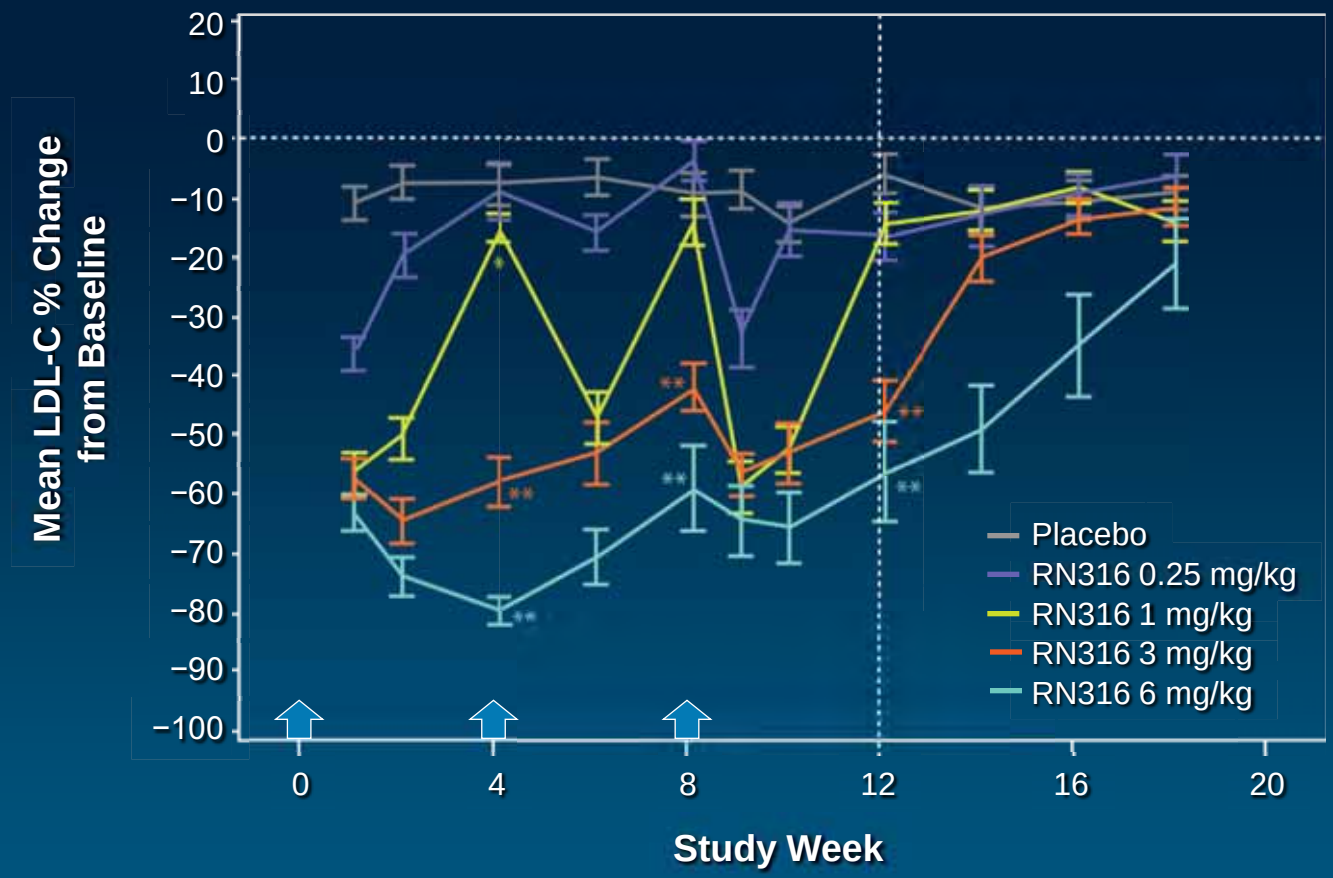
Values are mean ± SE
B1481005 and B1481012 data combined

Lipid Results: Week 12 Mean % Change from Baseline Pooled Data



Values are mean ± SE
B1481005 and B1481012 data combined; modified ITT results
Results include subjects who had dosing interrupted for LDL-C ≤25 mg/dL
*P<0.05; **P<0.001

Lipid Results: Mean LDL-C % Change from Baseline Pooled Data



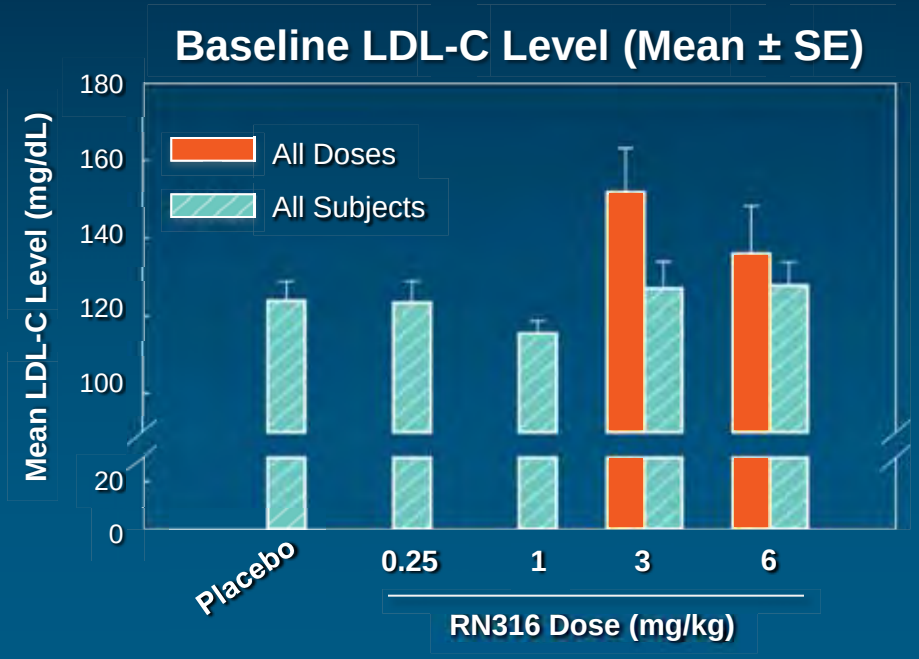
Values are mean ± SE; ⇧ indicates dosing
B1481005 and B1481012 data combined
Results include subjects who had dosing interrupted for LDL-C ≤25 mg/dL
*P<0.05; **P<0.001

Impact of Dose Interruption (LDL-C ≤25 mg/dL): Baseline LDL-C Level

Number (%) of subjects with dose interruption

		RN316 Dose			
	Placebo	0.25 mg/kg	1 mg/kg	3 mg/kg	6 mg/kg
N (all subjects)	30	16	33	32	17
Week 4 only	0	0	0	10 (31%)	5 (29%)
Week 8 only	0	0	0	7 (22%)	5 (29%)
Week 4 & 8	0	0	0	2 (6%)	2 (12%)

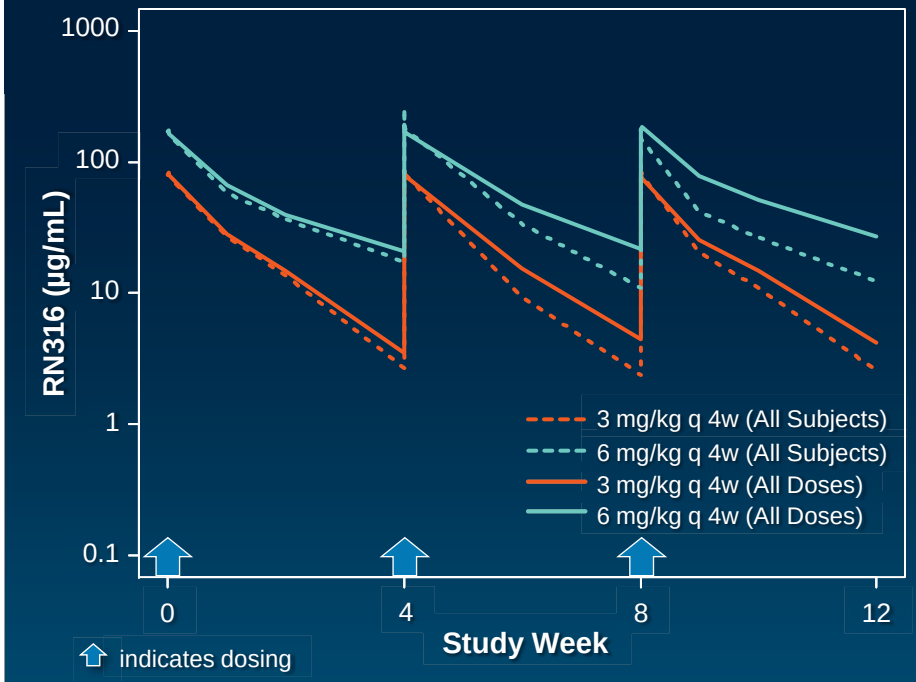
B1481005 and B1481012 data combined



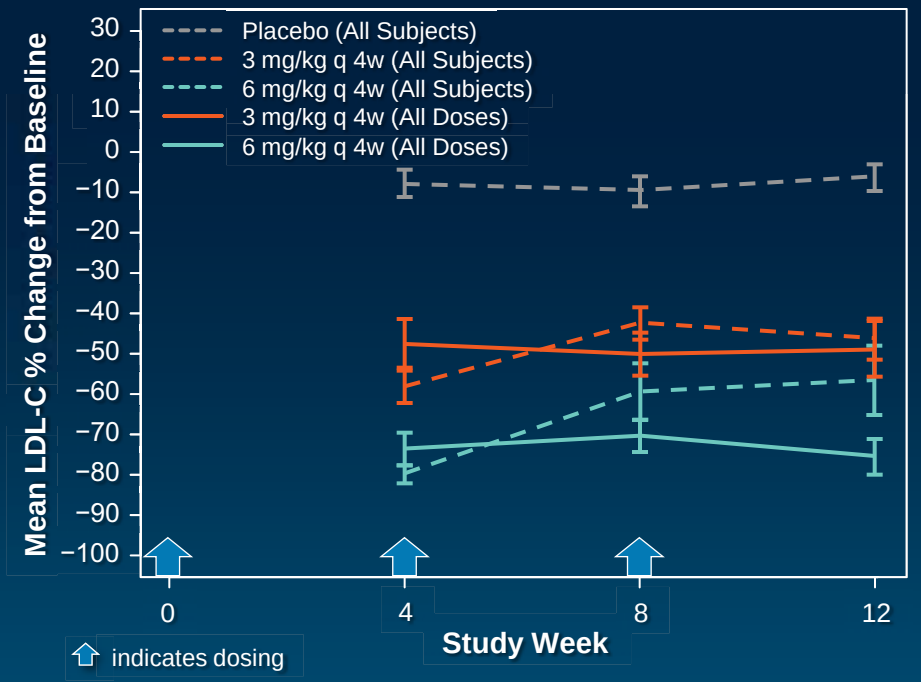
The mean baseline LDL-C level in the subgroup who received all 3 doses (i.e. no dose interruption) was higher than the mean baseline LDL-C level for all subjects in the study

Impact of Dose Interruption (LDL-C ≤25 mg/dL): PK Profile and LDL-C % Change from Baseline

Mean RN316 PK Profiles



Mean LDL-C % Change from Baseline (± SE)



Subjects receiving all 3 doses had greater drug exposure than those in whom dosing was interrupted; minimal to no accumulation of RN316 occurred when dosed 3 and 6 mg/kg q 4 weeks

Week 12 LDL-C lowering was comparable to Week 4 LDL-C lowering in subjects receiving all 3 doses

Without dose interruption, overall LDL-C lowering at Week 12 would have been similar to maximal LDL-C lowering observed at Week 4

Safety: Key Adverse Events and Lab Analyses Pooled Data

Treatment-Emergent AEs (Treatment-Related)	Placebo	RN316 Dose			
		0.25 mg/kg	1 mg/kg	3 mg/kg	6 mg/kg
General					
N (all subjects)	33	17	33	35	17
AEs	23 (5)	23 (4)	25 (5)	20 (6)	10 (3)
SAEs	0	1 (0)	2 (0)	0	0
Discontinuation due to AE	1 (0)	0	0	0	1 (0)
AEs of potential clinical interest					
Arthralgia	1 (0)	0	2 (0)	3 (1)	3 (2)
Myalgia	2 (0)	2 (0)	1 (1)	1 (1)	1 (1)
ALT/Dir Bili/Alk Phos	0	0	1 (0)	0	0
CPK	0	1 (0)	0	0	0
Key lab analyses					
ALT, AST >3x ULN	0	0	0	0	0
CPK >10x ULN	0	1	0	0	0
Anti-drug antibodies (non-neutralizing)	N/A	0	3	1	1

B1481005 and B1481012 data combined

Safety: Serious Adverse Events and Discontinuations Due to Adverse Events

Type	Event	RN316 Dose (mg/kg)	Tx-Related	Description
SAE	Depression	0.25	No	Worsening depression Hospitalized 69 days after last dose
SAE	Abdominal pain	1	No	Worsening menstrual cramps Onset after Week 8 infusion Hospitalized 1 day
SAE	Non-cardiac chest pain	1	No	3 hospitalizations Cardiac evaluation negative
Discon	Neuralgic amyotrophy	Placebo	No	Pre-randomization left shoulder pain & weakness Dx on Day 11
Discon	↑ GGT	6	No	Baseline / Day 70 (peak) GGT (10–61 U/L): 223 / 431 ALT (6–43 U/L): 40 / 97 AST (11–36 U/L): 20 / 42 No clinical hepatobiliary dysfunction Lost to follow-up

Summary

- In two Phase 2 trials, when IV RN316 at 3 and 6 mg/kg is administered every 4 weeks and added to high/maximal-dose statins:
  - LDL-C and total cholesterol are significantly lowered and HDL-C is significantly increased
  - Significant LDL-C lowering persists for 4 weeks
  - Interrupting dosing when LDL-C ≤25 mg/dL attenuated mean LDL-C lowering by ~15–20%
  - AEs were infrequent (5% receiving RN316), almost all were not considered related to study drug, were mild in nature, and resolved without intervention
  - Anti-drug antibodies were infrequent and none were associated with hypersensitivity reactions
  - Few SAEs occurred and none were considered related to study drug
  - Few significant lab abnormalities occurred

Conclusions

- RN316 significantly lowered LDL-C in hypercholesterolemic subjects on high-to-maximal doses of statins
- RN316 was generally safe and well tolerated in these studies