

A Pharmacokinetic Bioequivalence Study of Plozasiran Administered Subcutaneously via Autoinjector Versus Prefilled Syringe in Healthy Adults

Jia Wen Chang,¹ Erick Leung,² Jennifer Hellawell,² Lalitha Aiyer,² Jack Shi²

¹PPD Development, LP, Austin, TX; ²Arrowhead Pharmaceuticals, Inc., Pasadena, CA

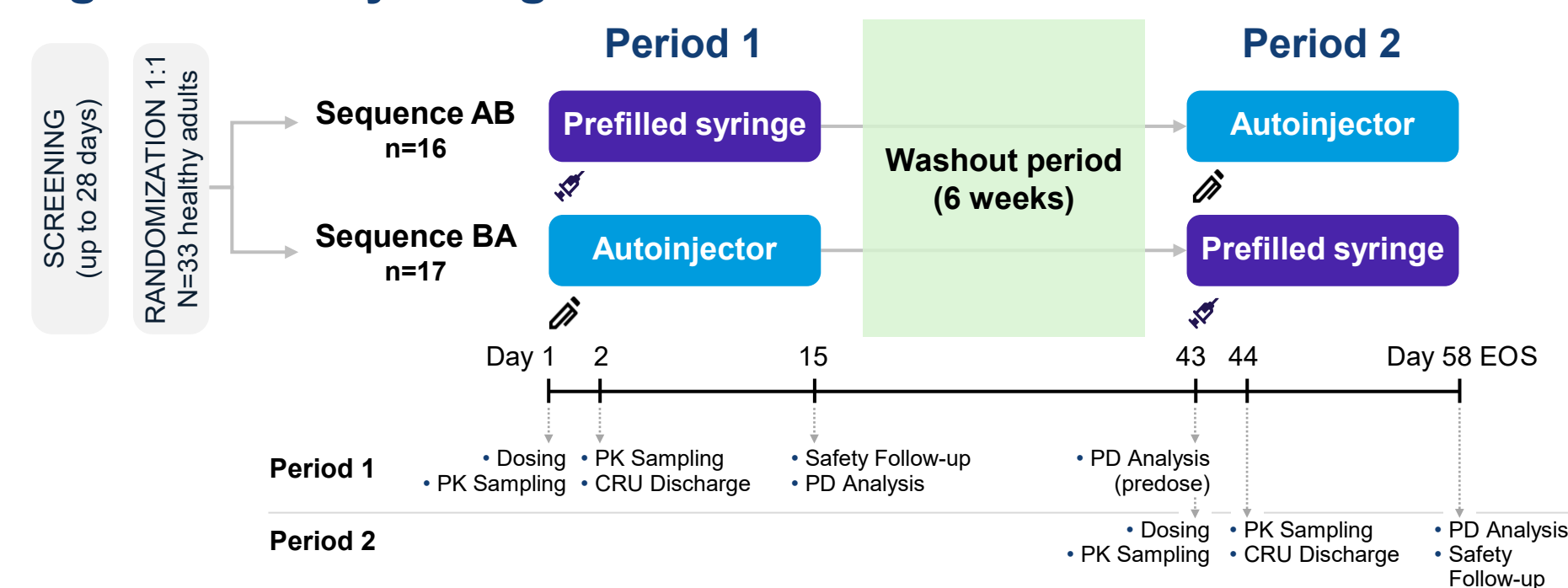
INTRODUCTION

- Plozasiran is a hepatocyte-targeted siRNA that silences *APOC3*, enhancing TG lipolysis and hepatic receptor-mediated clearance of TRL remnants and thereby reducing plasma TGs¹
- Plozasiran is approved in a number of regions as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS)^{2,3} and is in development for the treatment of severe hypertriglyceridemia (sHTG)⁴
- The approved presentation of plozasiran is a 25 mg/0.5 mL (50 mg/mL) solution supplied in a single-dose prefilled syringe³
- This study evaluated the relative bioavailability and bioequivalence, safety profiles, and pharmacodynamics of single doses of plozasiran 25 mg (50 mg/mL) administered subcutaneously via autoinjector (test presentation) versus prefilled syringe (reference presentation) in healthy adults

METHODS

- This was a single-center Phase 1 study, and written institutional review board approval was obtained from Advarra prior to study initiation
- The study comprised an open-label, randomized, 2-sequence, 2-period crossover design in healthy adults (18–55 years of age) (Figure 1)
- Each treatment period was preceded by an overnight fast of at least 10 hours

Figure 1. Study Design



RESULTS

- A total of 33 participants were randomized (Sequence AB, n=16; Sequence BA, n=17) and 32 participants were included in the PK population

Table 1. Baseline Characteristics

	Sequence AB (n=16)	Sequence BA (n=17)
Age (years), Mean (SD)	36.3 (7.4)	34.6 (11.0)
Race, n (%)		
Asian	0 (0.0)	1 (5.9)
Black or African American	5 (31.3)	7 (41.2)
White	11 (68.8)	9 (52.9)
Ethnicity, n (%)		
Hispanic or Latino	9 (56.3)	5 (29.4)
Not Hispanic or Latino	7 (43.8)	12 (70.6)
BMI (kg/m ²), Mean (SD)	27.3 (2.6)	26.9 (3.0)
Serum APOC3 (mg/dL), Mean (SD)	9.5 (1.2)	8.6 (1.8)
Serum Fasting TGs (mg/dL), Mean (SD)	95.1 (40)	76.4 (29)

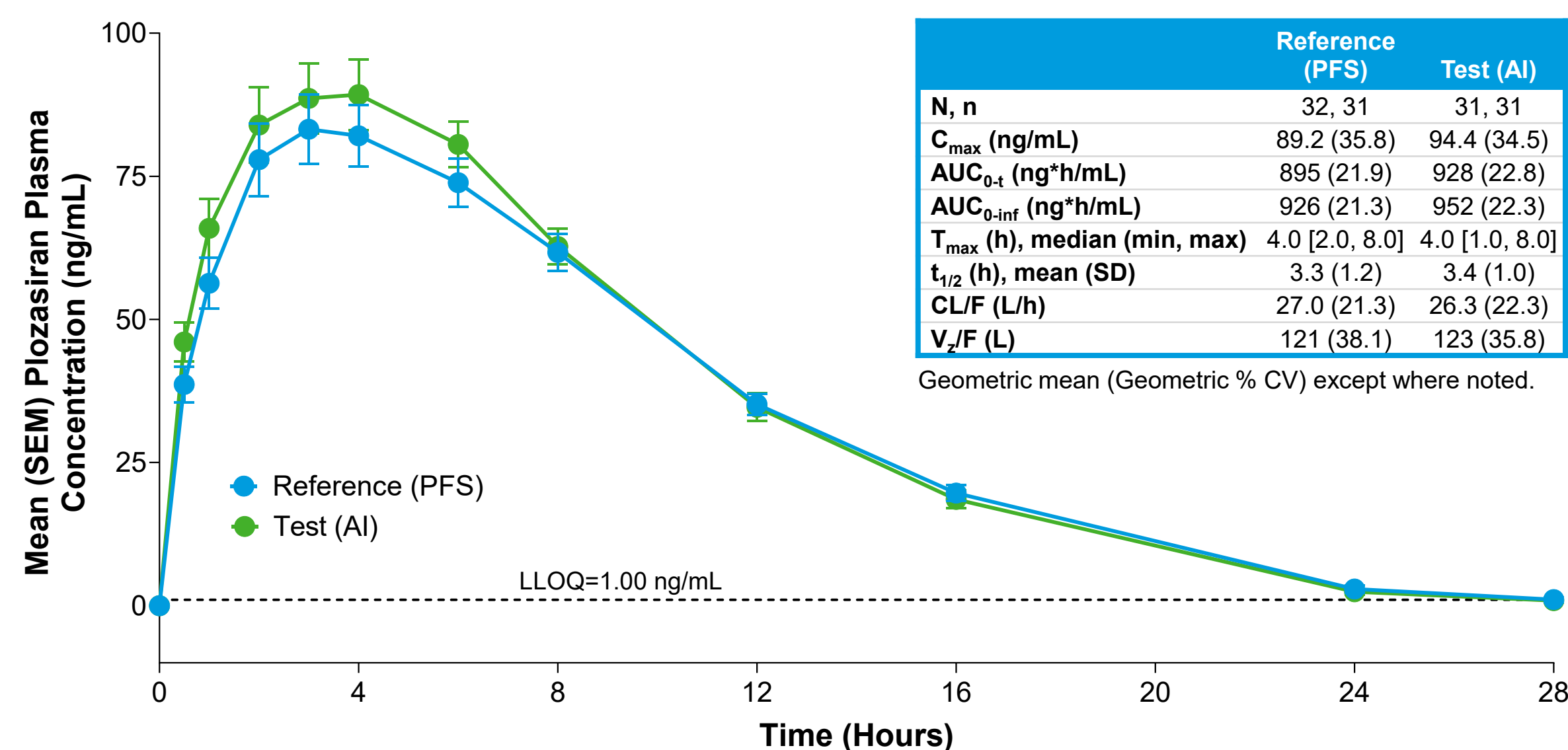
Note: Sequence AB received PFS in Period 1 and AI in Period 2; Sequence BA received AI in Period 1 and PFS in Period 2.



Download a copy of this poster at:
<https://www.arrowheadmedicalaffairs.com/CMHC2026/AI%20PFS/>

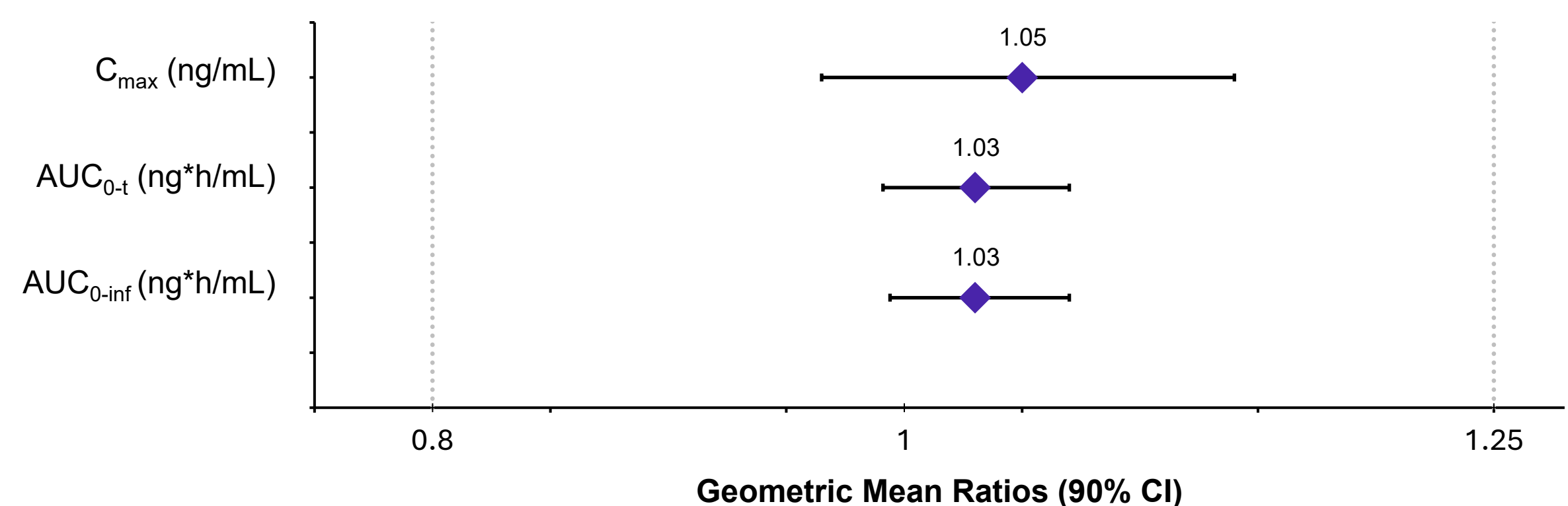
RESULTS (CONTINUED)

Figure 2. Mean PK Profiles Were Highly Comparable Between PFS and AI Presentations of Plozasiran 25 mg



N, number of participants in the treatment group; n, number of participants with t_{1/2}, AUC_{0-t}, CL/F, and V_d/F values used in calculation of summary statistics. Notes: One participant from Sequence AB (PFS->AI) discontinued the study prior to the Period 2 dose due to a positive drug screen; plasma samples collected from Period 1 dosing were included in the PK analysis. One participant from Sequence BA (AI->PFS) withdrew prior to the Period 2 dose due to a car accident; plasma samples collected from Period 1 dosing were not analyzed and the participant was excluded from the PK Population. One of the PFS PK profiles did not support accurate estimation of AUC_{0-inf}.

Figure 3. Geometric Mean Ratios (AI/PFS) and Corresponding 90% CI Values Were Within Prespecified Bioequivalence Limits



For each comparison, only participants with estimable PK exposure parameters during both dosing occasions were retained for the bioequivalence analysis. Adjusted geometric means are the least squared geometric means of exposures determined from an ANOVA for a crossover design with fixed effects of sequence, period, and treatment (presentation), and participant within sequence as a random effect, following logarithm transformation of PK exposure parameters.

ABBREVIATIONS

AI, autoinjector; ALT, alanine aminotransferase; APOC3, apolipoprotein C3; AST, aspartate aminotransferase; AUC_{0-inf}, area under the plasma concentration versus time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; BMI, body mass index; CI, confidence interval; CL/F, apparent clearance in plasma compartment; C_{max}, maximum observed plasma concentration; CRU, clinical research unit; LLOQ, lower limit of quantification; PD, pharmacodynamic; PFS, prefilled syringe; PK, pharmacokinetic; SAE, serious TEAE; SD, standard deviation; SEM, standard error of the mean; t_{1/2}, terminal elimination half-life; TEAE, treatment-emergent adverse event; TG, triglyceride; TRL, triglyceride-rich lipoprotein; T_{max}, time to C_{max}; ULN, upper limit of normal; V_d/F, apparent terminal-phase volume of distribution.

REFERENCES

- Ballantyne CM, et al. *New Engl J Med*. 2021;384(12):1177-1187.
- Watts GF, et al. *New Engl J Med*. 2025;392(2):127-137.
- 2024;391: 899-912.
- REDEMPLO. Prescribing Information. Arrowhead Pharmaceuticals; 2025.
- Watts GF, et al. *Eur Heart J*. 2025; 46(Supplement_1).

ACKNOWLEDGEMENTS

This study was sponsored by Arrowhead Pharmaceuticals, Inc., Pasadena, California. Arrowhead and the authors would like to thank Allison Saviano and Heather Hartley-Thorne of Sephirus Communications Inc. for graphical support and poster design. Michelle Po and Nathalie Kertesz of Arrowhead contributed to writing and review.

DISCLOSURES

J Chang is an employee of PPD, which received funding from Arrowhead Pharmaceuticals to conduct this study. E Leung, J Hellawell, L Aiyer, and J Shi are current employees of Arrowhead Pharmaceuticals.

Figures 4 and 5. Comparable Serum APOC3 and TG Reductions with PFS and AI Presentations

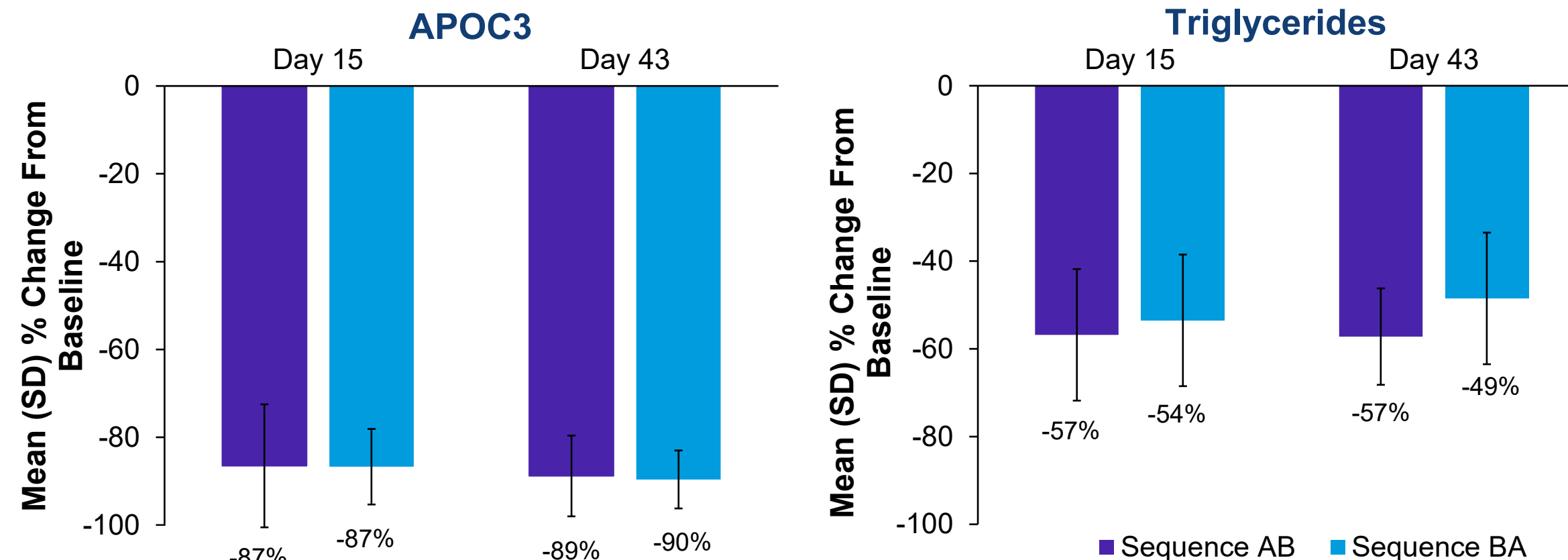


Table 2. Plozasiran Delivered by PFS and AI was Well-Tolerated, with No SAEs or TEAEs Leading to Drug Discontinuation

n (%)	PFS (n=33)	AI (n=33)	Total (N=33)
Number of Participants with at Least One:			
All TEAEs	6 (18.2)	5 (15.2)	11 (33.3)
Serious TEAEs	0	0	0
TEAEs Leading to Drug Discontinuation	0	0	0
Injection Site Reactions ^a	1 (3.0)	0	1 (3.0)
ALT Increased	2 (6.1)	1 (3.0)	3 (9.1)
Headache	1 (3.0)	2 (6.1)	3 (9.1)
Allergic Rhinitis	1 (3.0)	0	1 (3.0)
AST Increased	0	1 (3.0)	1 (3.0)
Breast Pain	1 (3.0)	0	1 (3.0)
Dysmenorrhea	1 (3.0)	0	1 (3.0)
Ecchymosis	0	1 (3.0)	1 (3.0)
Gamma-glutamyl transferase Increased	0	1 (3.0)	1 (3.0)
Muscle Spasms	0	1 (3.0)	1 (3.0)
Nausea	1 (3.0)	0	1 (3.0)
Puncture Site Bruise ^b	1 (3.0)	0	1 (3.0)
Pyrexia	0	1 (3.0)	1 (3.0)

^aOne participant reported injection site erythema and injection site pain. Both were mild and resolved by Day 3. ^bNot related to study drug.

- Both drug presentations were generally well tolerated, with no notable difference in the safety profile between presentations
- No unanticipated adverse device effects (UADEs) were reported
- No clinically meaningful changes in hepatic or renal function, vital signs, or ECG parameters were observed, and no Hy's Law cases were identified

CONCLUSIONS

- The 25 mg plozasiran dose administered subcutaneously by the autoinjector and prefilled syringe demonstrated comparable bioavailability, meeting predefined bioequivalence criteria
- Consistent with bioequivalence, the two presentations had comparable pharmacodynamic effects with respect to APOC3 and TG reduction
- Both presentations were safe and generally well tolerated
- Together, these findings support the autoinjector as an alternative delivery option for future clinical use of plozasiran