ION775, a long-acting siRNA targeting *APOC3*: Single-dose, 12-month results in participants with moderate hypertriglyceridemia

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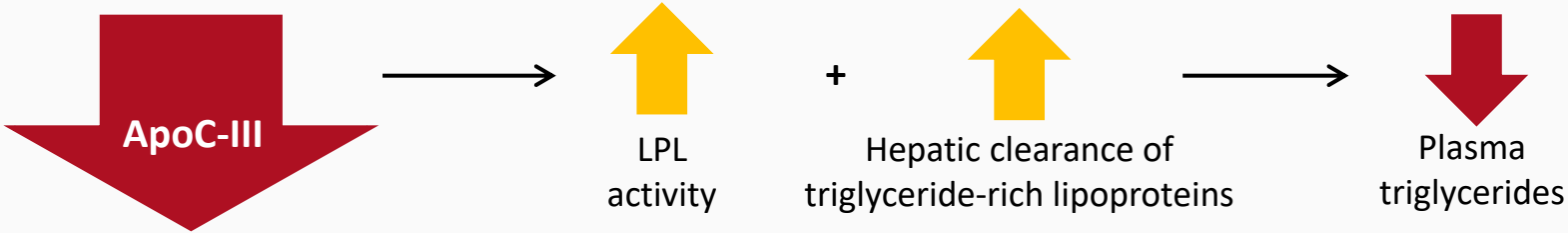
Background

- ApoC-III is a central regulator of triglyceride metabolism[1]



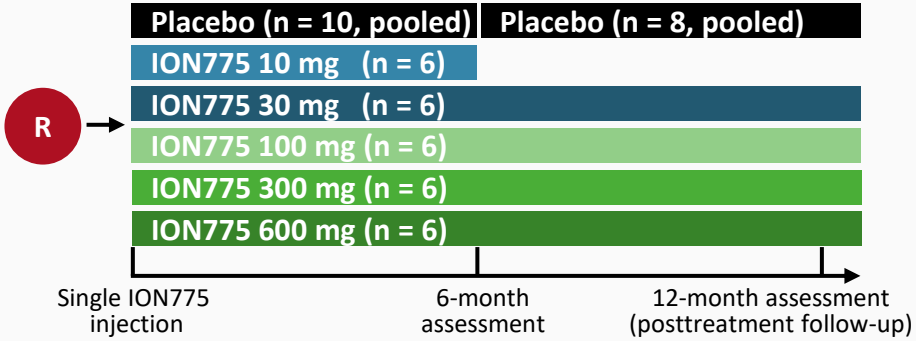
- Although effective therapies exist,[2,3] there is potential for more potent and durable inhibition of ApoC-III for sustained reduction in triglyceride-rich lipoproteins
- ION775 is an investigational GalNAc-conjugated siRNA targeting *APOC3* mRNA in hepatocytes, leading to mRNA degradation and reduced hepatic production of ApoC-III

APOC3/ApoC-III, apolipoprotein C3/C-III; GalNAc, triantennary N-acetylgalactosamine; LPL, lipoprotein lipase; mRNA, messenger RNA; siRNA, small interfering RNA.

1. Hegele RA. *Eur Heart J*. 2022;43:1413-5. 2. Tryngolza (olezarsen). Package insert. Ionis Pharmaceuticals, Inc.; 2026. 3. Redemplo (plozasiran). Package insert. Arrowhead Pharmaceuticals, Inc.; 2025.

Study design and population

- Phase 1 randomized, double-blind, placebo-controlled, single ascending dose study in adults with moderate hypertriglyceridemia



Key inclusion criteria

- Fasting triglyceride level ≥150 mg/dL and ≤500 mg/dL
- Age 18–65 years
- BMI ≤35.0 kg/m^2

Endpoints

- Primary: Incidence of TEAEs
- Pharmacodynamic: Percent change from baseline in ApoC-III, triglycerides, and other lipids at month 6 (vs pooled placebo); durability through month 12; proportion achieving a triglyceride level <150 mg/dL

- Baseline characteristics were broadly similar among dose groups

Characteristic	Placebo (n = 10)	Total ION775 (n = 30)
Age, mean, years	41.3	50.5
Sex, n		
Male	10	22
Female	0	8
BMI, mean, kg/m²	26.8	28.9
Lipid parameters, mean (SD)		
ApoC-III, mg/dL	12.1 (3.7)	12.9 (3.3)
Triglycerides, mg/dL	230.6 (116.2)	211.2 (51.5)
ApoB, mg/dL	110.0 (19.4)	112.5 (30.8)
HDL-C, mg/dL	38.8 (8.7)	43.9 (9.9)
Non-HDL-C, mg/dL	172.4 (29.2)	170.4 (46.7)
LDL-C, mg/dL	133.3 (35.7)	132.6 (44.6)
VLDL-C/remnant C, mg/dL	39.1 (16.1)	37.8 (11.6)
Lp(a), nmol/L	67.8 (69.6)	45.9 (74.2)

ApoB, apolipoprotein B; ApoC-III, apolipoprotein C-III; BMI, body mass index; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein a; R, randomization; SD, standard deviation; TEAE, treatment-emergent adverse event; VLDL, very-low-density lipoprotein.

ION775 was well tolerated in this study

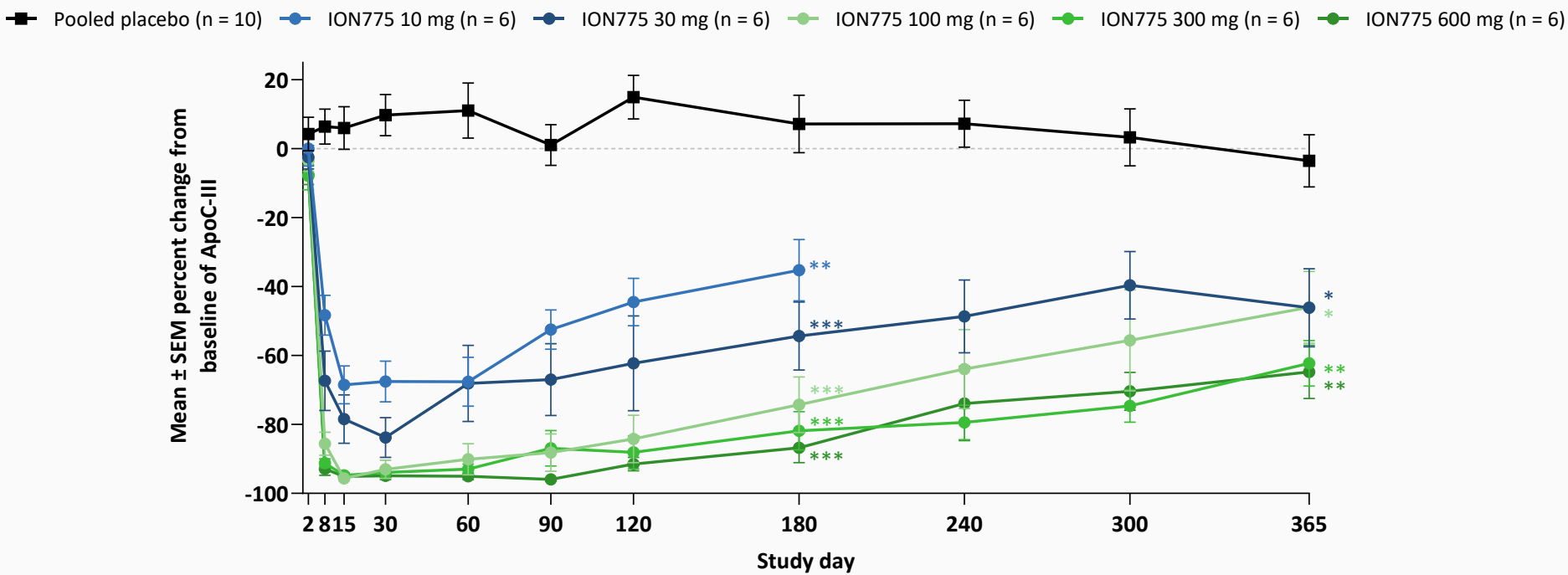
- No serious TEAEs, severe TEAEs, or injection-site reactions in any group
- No ALT or AST elevations ≥5 × ULN or total bilirubin elevations ≥2 × ULN

Event or measure	Placebo	ION775 10 mg	ION775 30 mg	ION775 100 mg	ION775 300 mg	ION775 600 mg
Adverse events, n (%)						
Any TEAEs	6 (60.0)	4 (66.7)	3 (50.0)	5 (83.3)	1 (16.7)	5 (83.3)
Any serious TEAEs	0	0	0	0	0	0
Severe TEAEs	0	0	0	0	0	0
Injection-site reactions	0	0	0	0	0	0
Laboratory measures, n/total n (%)						
Hepatic measures						
ALT or AST ≥3 × ULN	0/10 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)	1/6 (16.7)
ALT or AST ≥5 × ULN	0/10 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)
Total bilirubin ≥2 × ULN	0/10 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Rapid, sustained, and dose-dependent reductions in ApoC-III levels with ION775

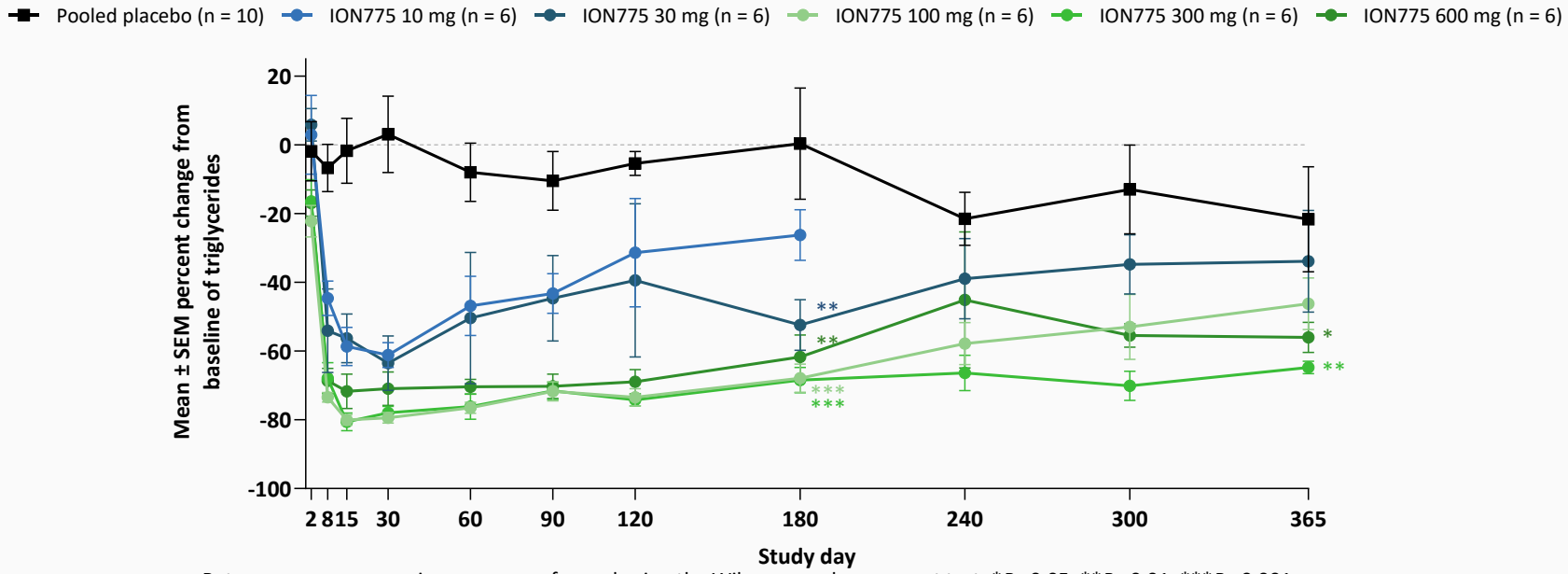
- At month 6, ION775 reduced ApoC-III by 35.3% to 86.8% from baseline (vs +7.2% for pooled placebo)



Between-group comparisons were performed using the Wilcoxon rank-sum exact test. *P <0.05, **P <0.01, ***P <0.001.
ApoC-III, apolipoprotein C-III; SEM, standard error of the mean.

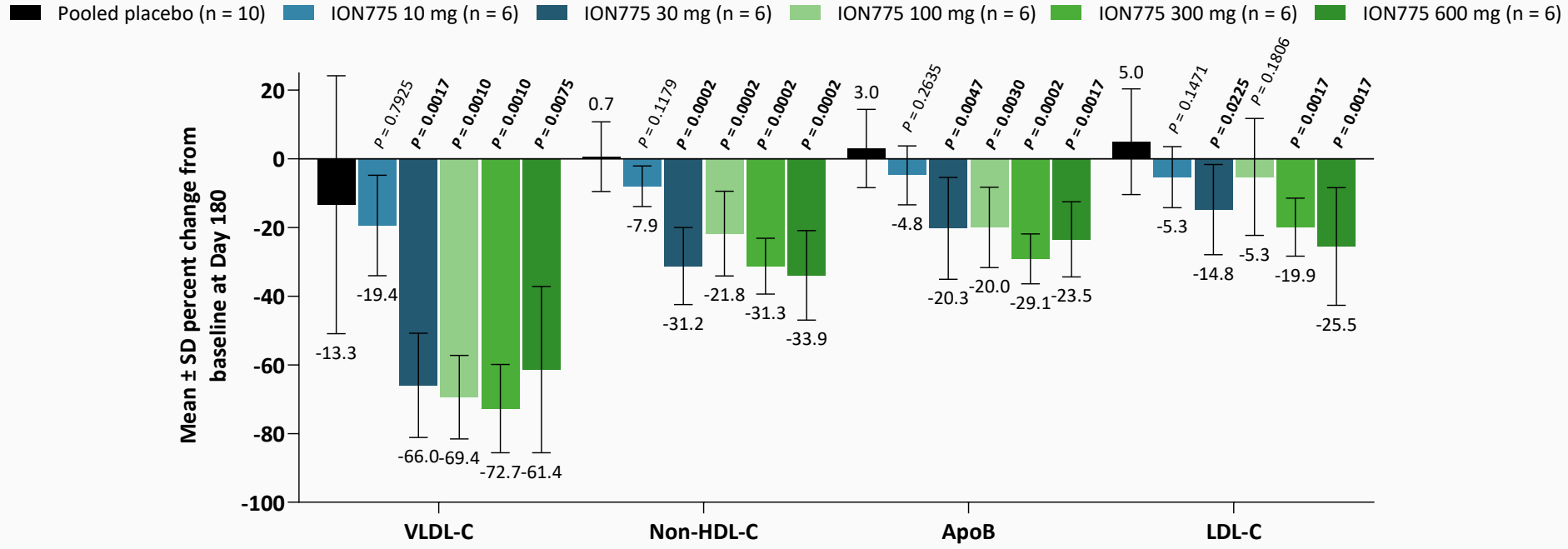
Rapid, sustained, and dose-dependent reductions in triglyceride levels with ION775

- At month 6, ION775 reduced triglycerides by 26.2% to 68.4% from baseline (vs +0.4% for pooled placebo), with effects sustained through month 12
- 100% of participants in the 100–600 mg dose levels achieved triglyceride levels <150 mg/dL



Between-group comparisons were performed using the Wilcoxon rank-sum exact test. *P <0.05, **P <0.01, ***P <0.001.
SEM, standard error of the mean.

Effect of ION775 on markers of atherogenic risk



P-values are from comparisons between each ION775 dose group and pooled placebo using the Wilcoxon rank-sum test; bold indicates $P < 0.05$.
ApoB, apolipoprotein B; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; VLDL, very-low-density lipoprotein.

Conclusions

- ION775 demonstrated an acceptable safety and tolerability profile after a single dose administered subcutaneously in adults with moderate hypertriglyceridemia across all dose levels tested
- Treatment with ION775 resulted in substantial, dose-dependent, and durable reductions in ApoC-III and triglyceride levels after a single dose
  - ION775 also reduced levels of atherogenic risk markers
- **These findings support *APOC3* silencing with ION775 as a promising approach to achieve durable reductions in triglyceride levels for up to 12 months**

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APOC3/ApoC-III, apolipoprotein C3/C-III.