VSA003 (Zodasiran), a GalNac siRNA Targeting ANGPTL3, Demonstrated Substantial Reductions in LDL-Cholesterol and Multiple Atherogenic Lipoproteins in Chinese Patients with HoFH

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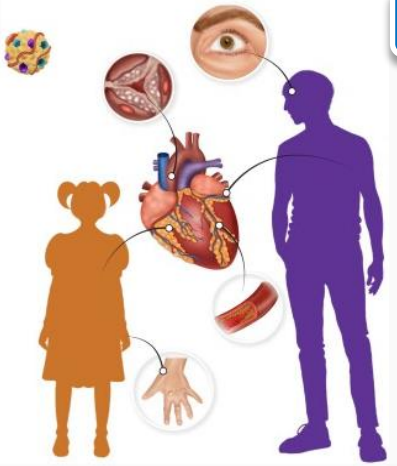
Homozygous Familial Hypercholesterolemia: Rare Disease with High Unmet Medical Needs

HoFH is a Rare But Serious Disease

- Prevalence[1]:
  1/300,000 to 1/170,000 worldwide;
- Extremely high LDL-C concentrations;
- Very high risk of coronary and aortic stenosis and even death in childhood or adolescence if untreated[2].



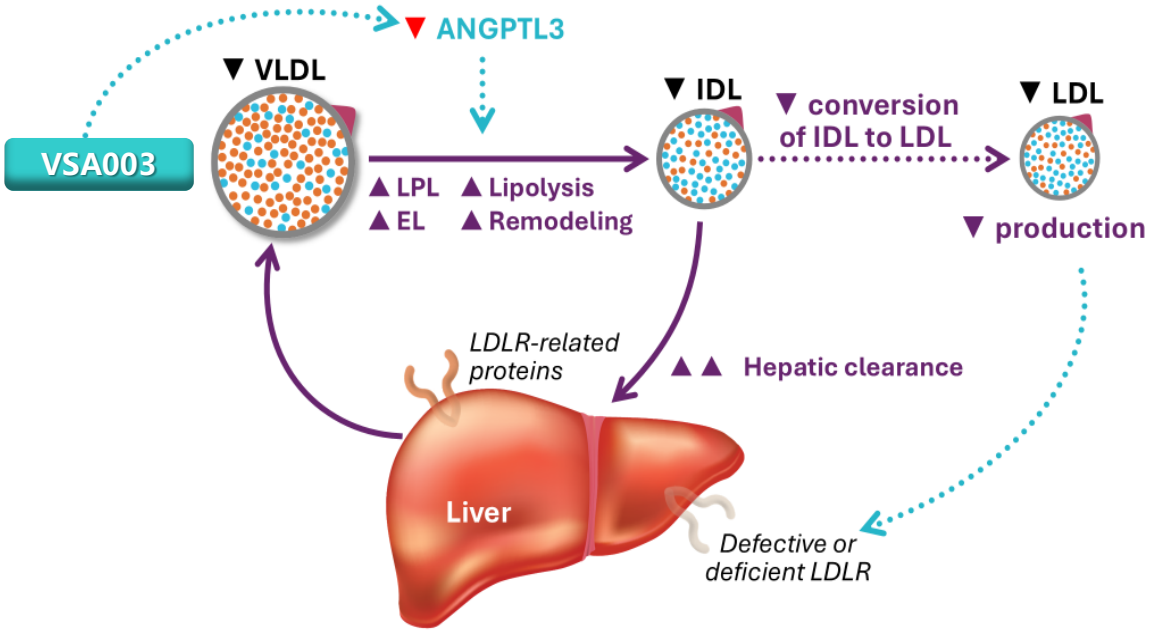
HoFH Patients have High Unmet Medical Needs[3]

- Underdiagnosis and undertreatment;
- Suboptimal response to conventional lipid-lowering therapies due to dysfunctional LDL receptor pathways.

- ✓ **HoFH is a rare condiction, listed in the First Catalogue of Rare Diseases;**
- ✓ **There are approximately 5,000 Chinese HoFH patients, with only 4.2% receiving LLT[4];**
- ✓ **<5% HoFH patients reached LDL-C goals with currently approved drugs in China.**

1. Mi Tang, et al. Front Public Health. 2025 Aug 27:13:1642895; **2**. Marina C, et al. European Heart Journal. 2023; 44: 2277-91; **3**. Tromp TR, et al. Lancet. 2022; 399: 719-28; **4**. MN Huang et al. Lipids in Health and Disease. 2024; 23:423-40. **HoFH**, Homozygous Familial Hypercholesterolemia; **LDL-C**, low-density lipoprotein cholesterol; **LLT**, lipid-lowering therapy

ANGPTL3: a Key Regulator of Lipoprotein Disposition



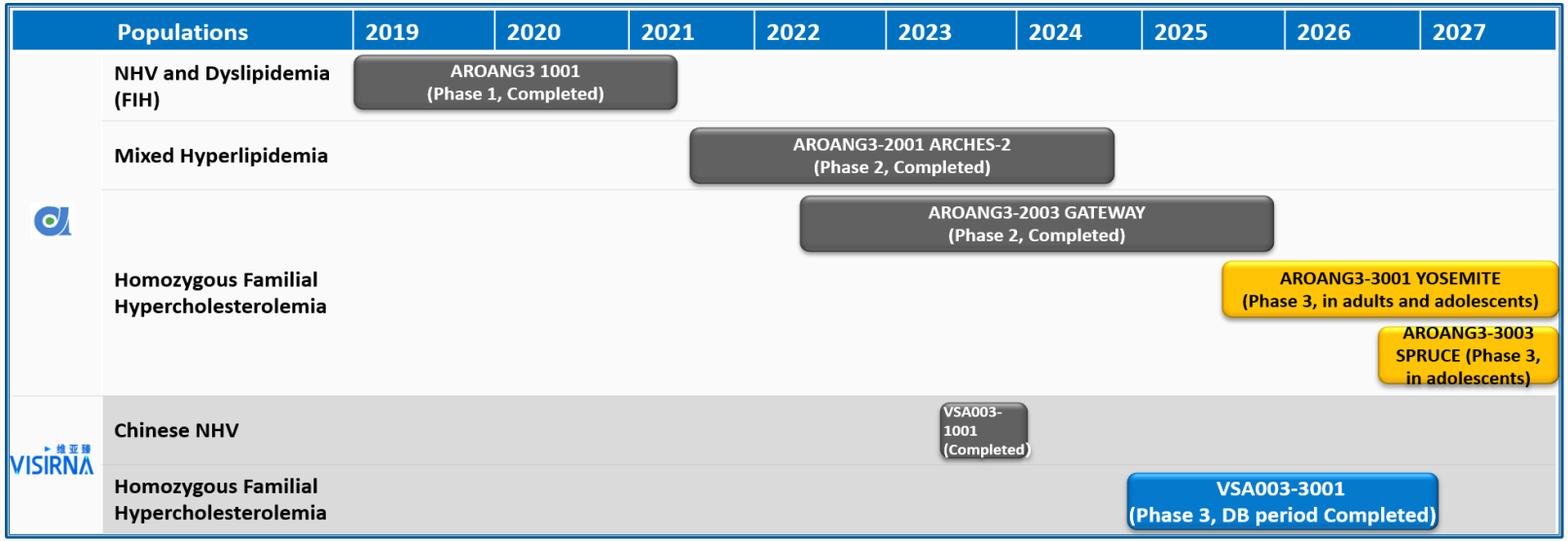
- *ANGPTL3* is a hepatocyte expressed regulator of lipid and lipoprotein metabolism with multiple potential modes of action, including inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL)[1,2]
- *ANGPTL3* loss-of-function variants lead to enhanced LPL and EL activity, resulting in:
  - ▼ LDL-C, TG, VLDL-C/ remnant-C, and HDL-C[3-5]
  - ▼ Risk of ASCVD[3,4,6]
- No known adverse phenotype is associated with genetic deficiency in *ANGPTL3*[3,4]

Figure adapted from the presentation of GATEWAY study in 2025 EAS Congress.

1. Adam, et al. *J Lipid Res*. 2020;61(9): 1271-86. **2.** Rosenson. *J Lipid Res.* 2021:62:100060. **3.** Dewey, et al. *N Engl J Med*. 2017;377 (3):211-21. **4.** Minicocci, et al. *J Lipid Res.* 2013;54(12): 3481-90. **5.** Musunuru, et al. *N Engl J Med*. 2010; 363(23):2220-7. **6.** Stitziel, et al. *J Am Coll Cardiol*. 2017; 69(16):2054-63. ▼=Reductions in; **ANGPTL3**, angiopoietin-like protein 3**; ASCVD,** atherosclerotic cardiovascular disease**; EL**, endothelial lipase; **IDL**, intermediate-density lipoprotein; **LDL**, low-density lipoprotein; **LDL-C**, low-density lipoprotein cholesterol; **LDLR**, low-density lipoprotein receptor; **LPL**, lipoprotein lipase; **remnant-C,** remnant cholesterol; **VLDL**, very low-density lipoprotein

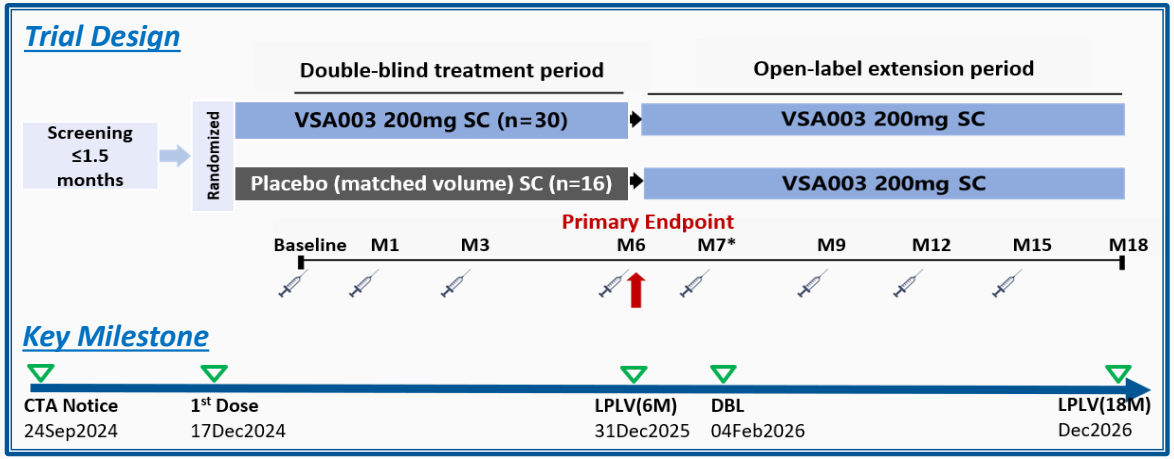
Overview of VSA003 and Development Program

VSA003, a synthetic double-stranded, liver-targeted NAG-conjugated small RNA interference therapeutic designed to target mRNA transcripts from ANGPTL3 gene, inhibits ANGPTL3 expression and reduces atherogenic lipoproteins through mechanisms independent of the LDLR.



NAG, N acetyl galactosamine; **mRNA**, messenger RNA; **ANGPTL3**, angiopoietin-like protein 3; **NHV**, normal healthy volunteers; **FIH**, first-in-human; **LDL-C**, low density lipoprotein cholesterol; **TG**, triglyceride; **HoFH**, Homozygous Familial Hypercholesterolemia; **DB**, double-blind

A Phase 3 Trial to Evaluate the Efficacy and Safety of VSA003 in Chinese Adolescents and Adults with HoFH



Population

- Aged ≥12 years with genetically or clinically confirmed HoFH
- Fasting LDL-C ≥2.6 mmol/L
- On stable low-fat diet and local SoC LLT

Endpoints

- **Primary Efficacy Endpoint:** percent change from baseline to M6 in fasting LDL-C vs. placebo
- **Key Secondary Efficacy Endpoints:** percent & absolute change from baseline to M6 in ANGPTL3, LDL-C, ApoB, non-HDL-C, VLDL-C, TC, TG, proportion of patients achieving LDL-C reduction ≥30% or ≥50%
- **Safety**

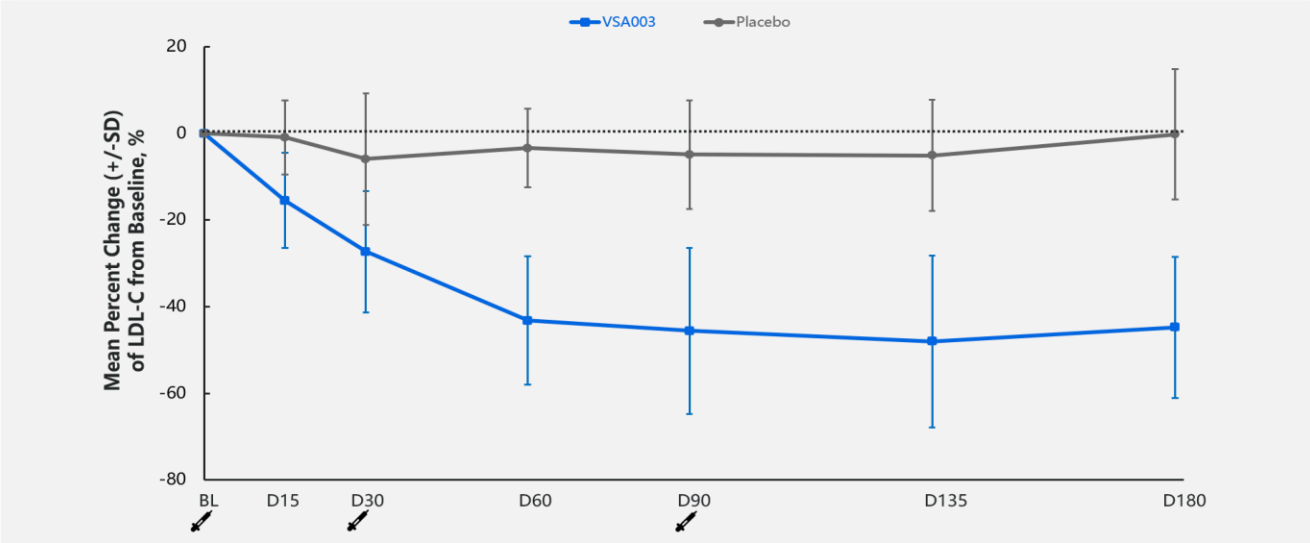
HoFH, Homozygous Familial Hypercholesterolemia; **ANGPTL3**, angiopoietin-like protein 3; **ApoB,** apolipoprotein B; **LDL-C**, low-density lipoprotein cholesterol; **non-HDL-C**, non-high-density lipoprotein cholesterol; **SC**, subcutaneous; **TG**, triglyceride; **TC**, total cholesterol; **VLDL-C**, very low-density lipoprotein cholesterol; **SoC**, standard-of-care; **LLT**, lipid-lowering therapy; **CT**, clinical trial; **LPLV**, last patient last visit; **DBL**, database lock

Baseline Characteristics

Baseline Characteristics Enrolled		Placebo (N=16)	VSA003 (N=30)
Age (years), mean (SD)		31.6 (13.5)	36.0 (11.8)
Age group, n(%)	12-17 yrs	2 (12.5)	2 (6.7)
	≥18 yrs	14 (87.5)	28 (93.3)
Female, n(%)		10 (62.5)	21 (70.0)
Body Mass Index (kg/m^2), mean (SD)		23.1 (4.0)	22.6 (3.6)
LDL-C (mmol/L), mean (SD)		10.4 (2.9)	9.9 (2.8)
Apo B (g/L), mean (SD)		2.7 (0.8)	2.6 (0.6)
Non-HDL-C (mmol/L), mean (SD)		11.9 (3.5)	11.1 (3.0)
HDL-C (mmol/L), mean (SD)		0.7 (0.3)	0.8 (0.3)
VLDL-C (mmol/L), mean (SD)		1.1 (1.0)	1.0 (0.5)
TC (mmol/L), mean (SD)		12.6 (3.4)	11.9 (2.9)
TG (mmol/L), mean (SD)		1.3 (0.7)	1.2 (0.6)
Lipoprotein(a) (nmol/L), mean (SD)		148.8 (119.2)	116.5 (100.0)
ANGPTL3 (ng/mL), mean (SD)		77.1 (41.8)	84.6 (55.1)
Hemoglobin A1c (%), mean (SD)		5.4 (0.4)	5.5 (0.6)
Genetically confirmed HoFH, n(%)		6 (37.5)	15 (50.0)
Clinically confirmed HoFH, n(%)		12 (75.0)	19 (63.3)
Genetically and Clinically confirmed HoFH, n(%)		2 (12.5)	4 (13.3)
Concomitant PCSK9 inhibitors use, n(%)		10 (62.5)	20 (66.7)

Over 43.9% Reduction in LDL-C versus placebo by Month 6

LDL-C change over time (Primary Endpoint)

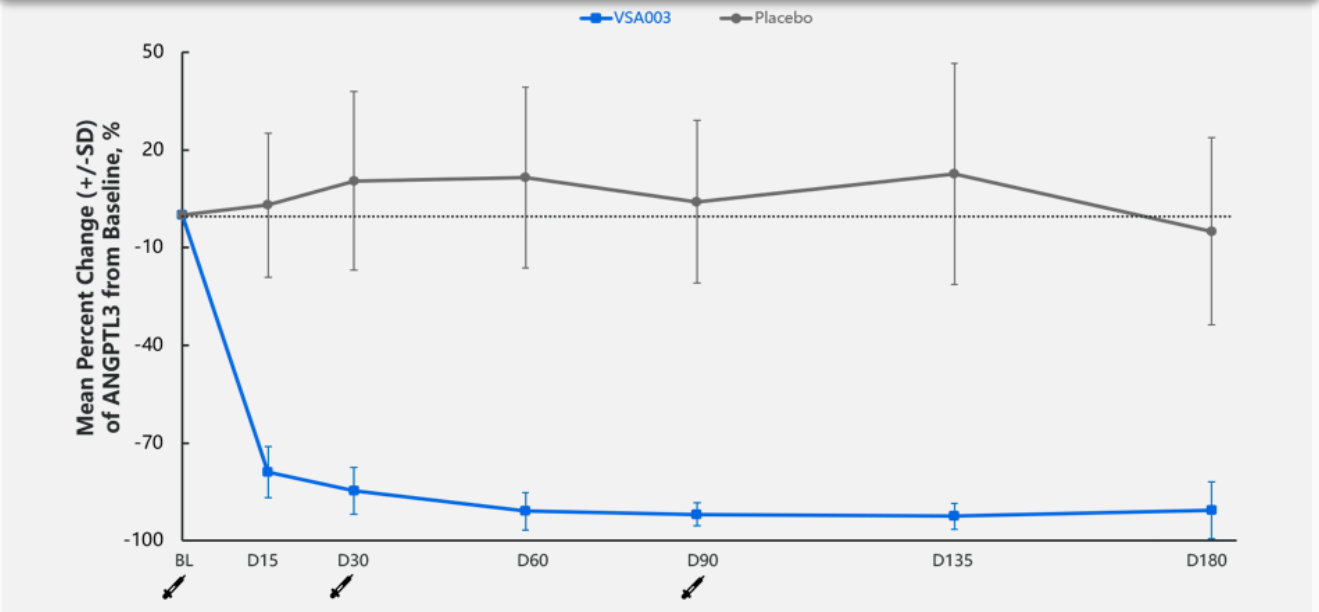


Statistics	Placebo	VSA003	LS Mean Difference (SE) vs. Placebo, *P value*
LS Mean (SE) Percent Change from BL at M6 (MI), %	-0.9 (4.3)	**-44.8 (3.2)**	**-43.9 (5.2), *P<0.0001***
LS Mean (SE) Change from BL at M6 (MI), mmol/L	-0.2 (0.4)	**-4.6 (0.3)**	**-4.4 (0.5), *P<0.0001***

LDL-C, low-density lipoprotein cholesterol; **SD**, standard deviation; **SE**, standard error; **LS**, least squares; **BL**, baseline

Rapid and Substantial Reduction in ANGPTL3

ANGPTL3 change over time (Target)

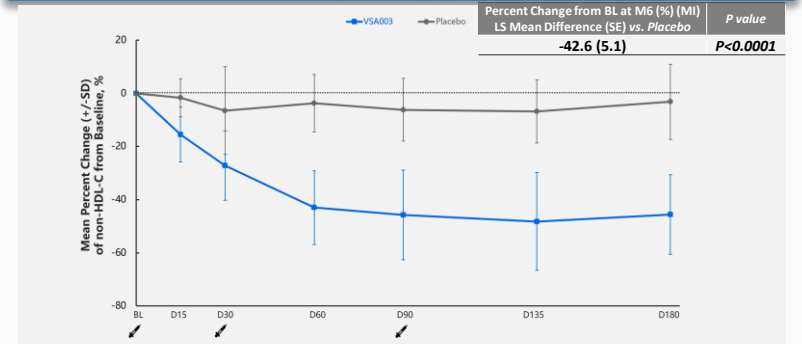


	Placebo	VSA003	LS Mean Difference (SE) vs. Placebo, *P value*
LS Mean (SE) Percent Change from BL at M6 (MI), %	-3.2 (5.3)	**-89.4 (4.2)**	**-86.2 (6.6), *P<0.0001***

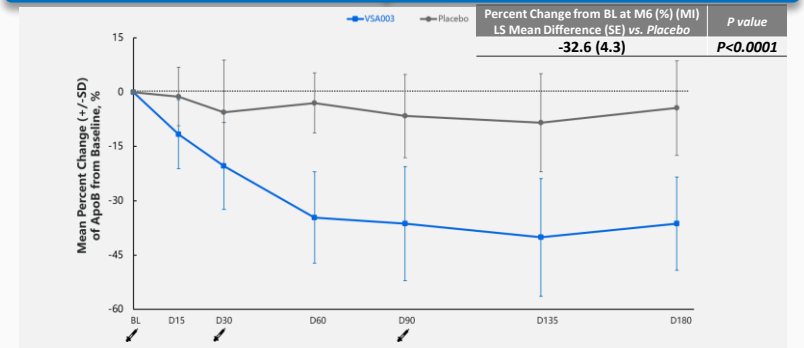
ANGPTL3, angiopoietin-like protein 3

Significantly Reduced Atherogenic Lipid and Lipoproteins

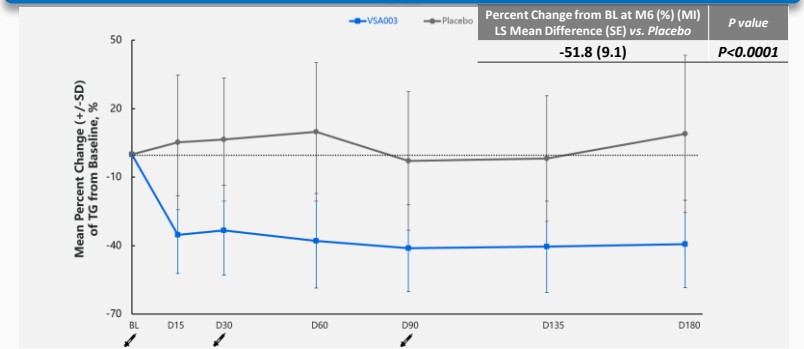
non-HDL-C



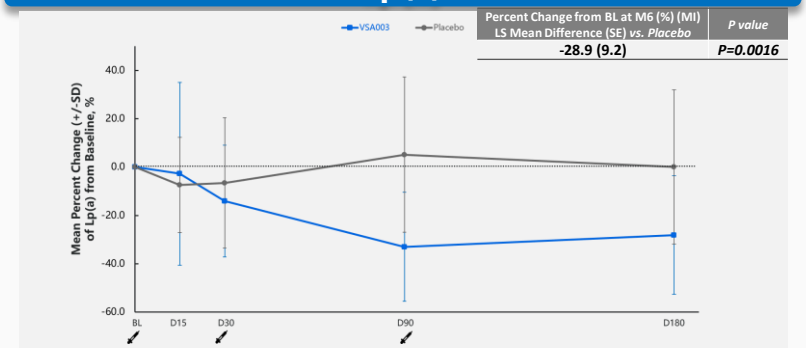
ApoB



TG

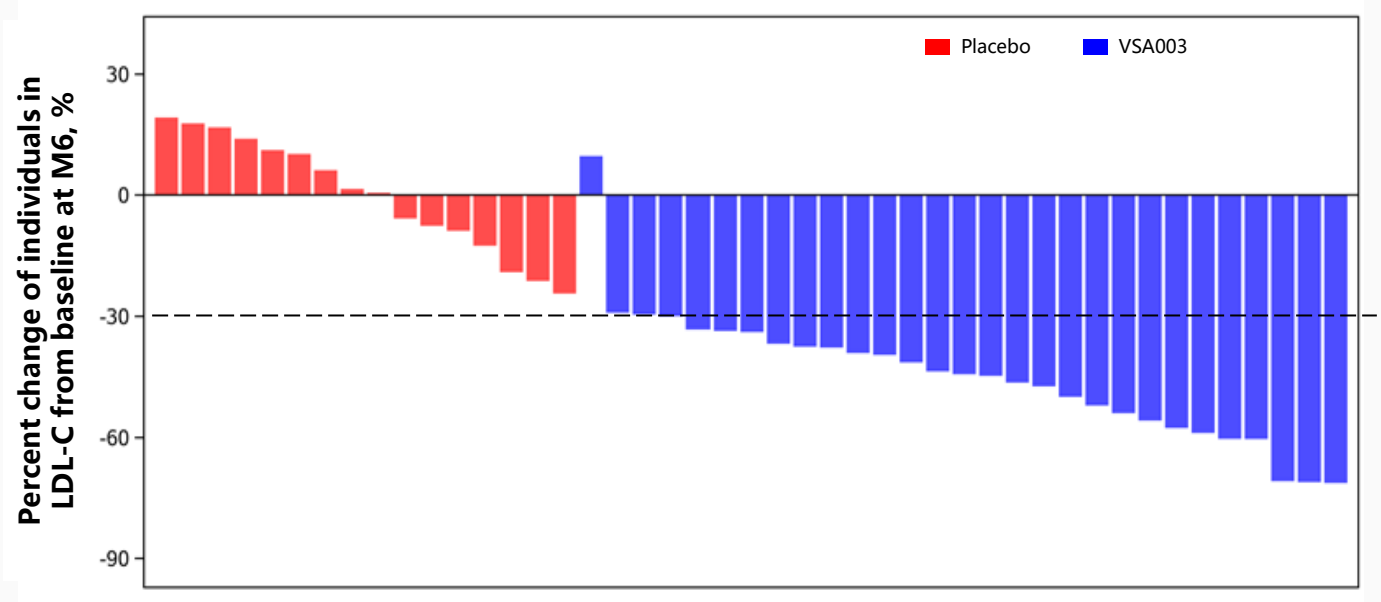


Lp(a)

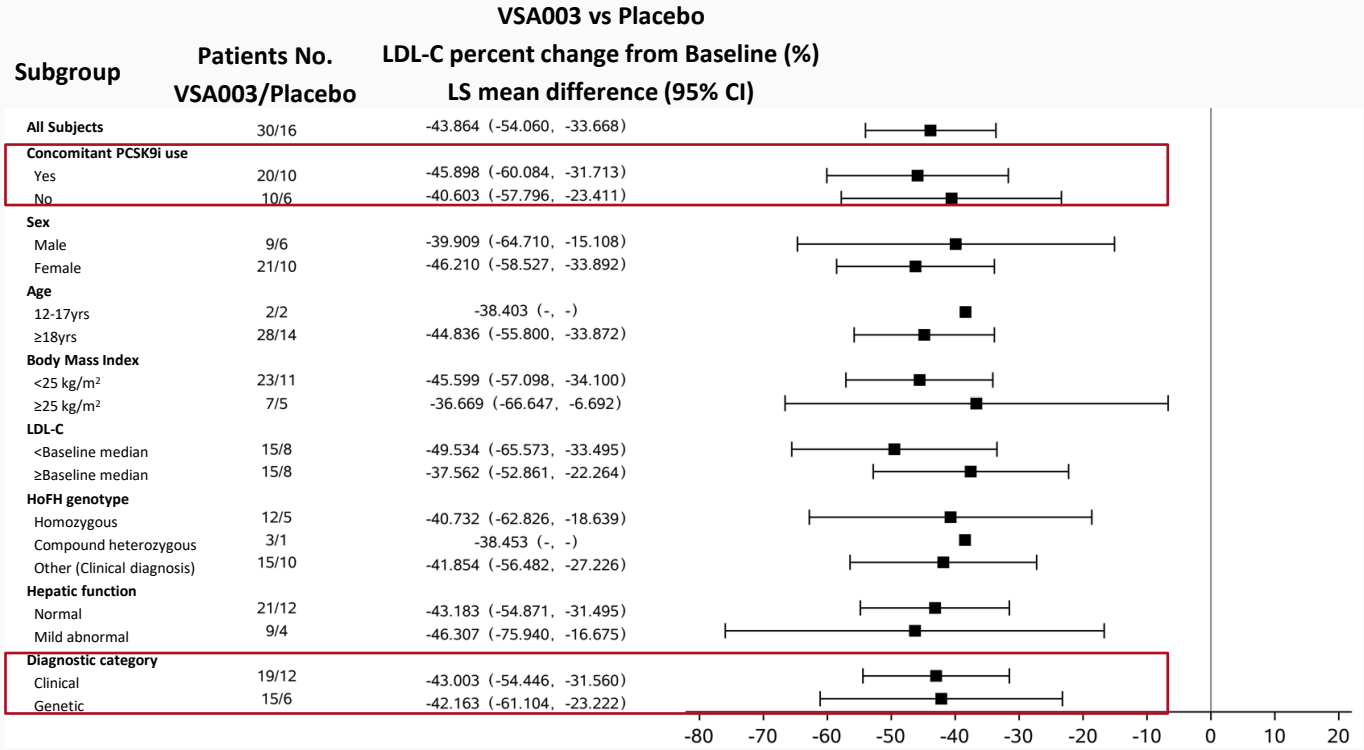


ApoB, apolipoprotein B; **non-HDL-C**, non-high-density lipoprotein cholesterol; **TG**, triglyceride; **Lp(a)**, lipoprotein(a); **SE**, standard error; **LS**, least squares; **BL**, baseline; **MI**, Multiple Imputation

83.3% of Patients Treated With VSA003 Achieved LDL-C Reduction ≥30% by Month 6



Consistent LDL-C Reductions Across Prespecified Subgroups



Subgroup analyses were exploratory and not powered to detect within-subgroup differences; no interaction testing adjustment was applied. **LS**, least squares; **CI**, confidence interval

Well-Tolerated and Favorable Safety Profile

- Treatment-emergent adverse events (TEAEs) were comparable between two groups;
- Study drug-related TEAEs were predominantly mild in severity, mainly injection site reactions and liver findings;
- No study drug-related serious AEs.

	Placebo (N = 16) n(%) [events]	VSA003 (N = 30) n(%) [events]
Number of patients with at least 1 TEAE	**12 (75.0) [38]**	**23 (76.7) [69]**
Study drug-related TEAEs	**3 (18.8) [7]**	**11 (36.7) [25]**
Mild	3 (18.8) [7]	9 (30.0) [23]
Moderate	0	2 (6.7) [2]
Severe	0	0
Serious adverse events (SAEs)	1 (6.3) [1]	3 (10.0) [3]
Study drug-related SAEs	**0**	**0**
Adverse events of special interest (AESI)	**2 (12.5) [2]**	**6 (20.0) [10]**
Injection site reactions	2 (12.5) [2]	4 (13.3) [7]
Liver findings*	**0**	**3 (10.0) [3]**
Poor glycemic control in diabetic patients	0	0
Study drug-related AESI	**2 (12.5) [2]**	**5 (16.7) [9]**
TEAE leading to death	0	1 (3.3) [1]
TEAE leading to treatment interruption	1 (6.3) [6]	0

*Liver findings included the following MedDRA Preferred Terms: abnormal or elevated ALT/AST, abnormal liver enzymes, increased blood bilirubin, liver fibrosis, hepatic steatosis, hepatic injury, liver failure, liver disease etc.

- **3 AESI of liver findings** were 2 mild (AST elevation >3-5xULN) and 1 moderate (AST elevation >5xULN) in severity, all with TBIL <2xULN and resolved within 0.5-1.5 months; the moderate case was assessed as probably not related to study drug by the investigator.
- **2 moderate study drug-related TEAEs** occurred in subjects with abnormal baseline liver enzymes and ALT/AST elevations >1.5-2-fold from baseline, both events were unresolved at DBL.
- **1 death** occurred due to sudden cardiac death in a 61-years-old female with multiple medical risk factors, which was assessed as not related to study drug by the investigator.

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **ULN**, upper limit of normal; **TBIL**, total bilirubin; **DBL**, database lock

Conclusion

- VSA003 demonstrated a significant reduction in LDL-C by 43.9% (5.2) *vs.* placebo in Chinese patients with HoFH;
- VSA003 substantially reduced other atherogenic lipids and lipoproteins, including ApoB, non-HDL-C, TG, and Lp(a);
- VSA003 was well tolerated and demonstrated a favorable safety profile;
- The findings were consistent with the global phase 2 efficacy and safety results, supporting VSA003 as a promising treatment for patients with HoFH.

Acknowledgements

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No	Principal Investigator	Site
1	**Zhuang Tian** **Shuyang Zhang***	Peking Union Medical College Hospital, Beijing
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5	**Yong Peng**	West China Hospital, Sichuan University, Chengdu
6	**Peng Dong**	Affiliated Hospital of Hangzhou Normal University, Hangzhou
7	**Daowen Wang**	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan
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9	**Jianping Li**	Peking University First Hospital, Beijing
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