



Sequential *in vivo* CRISPR base editing of the *PCSK9* and *ANGPTL3* genes in non-human primates

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CSO/CMO

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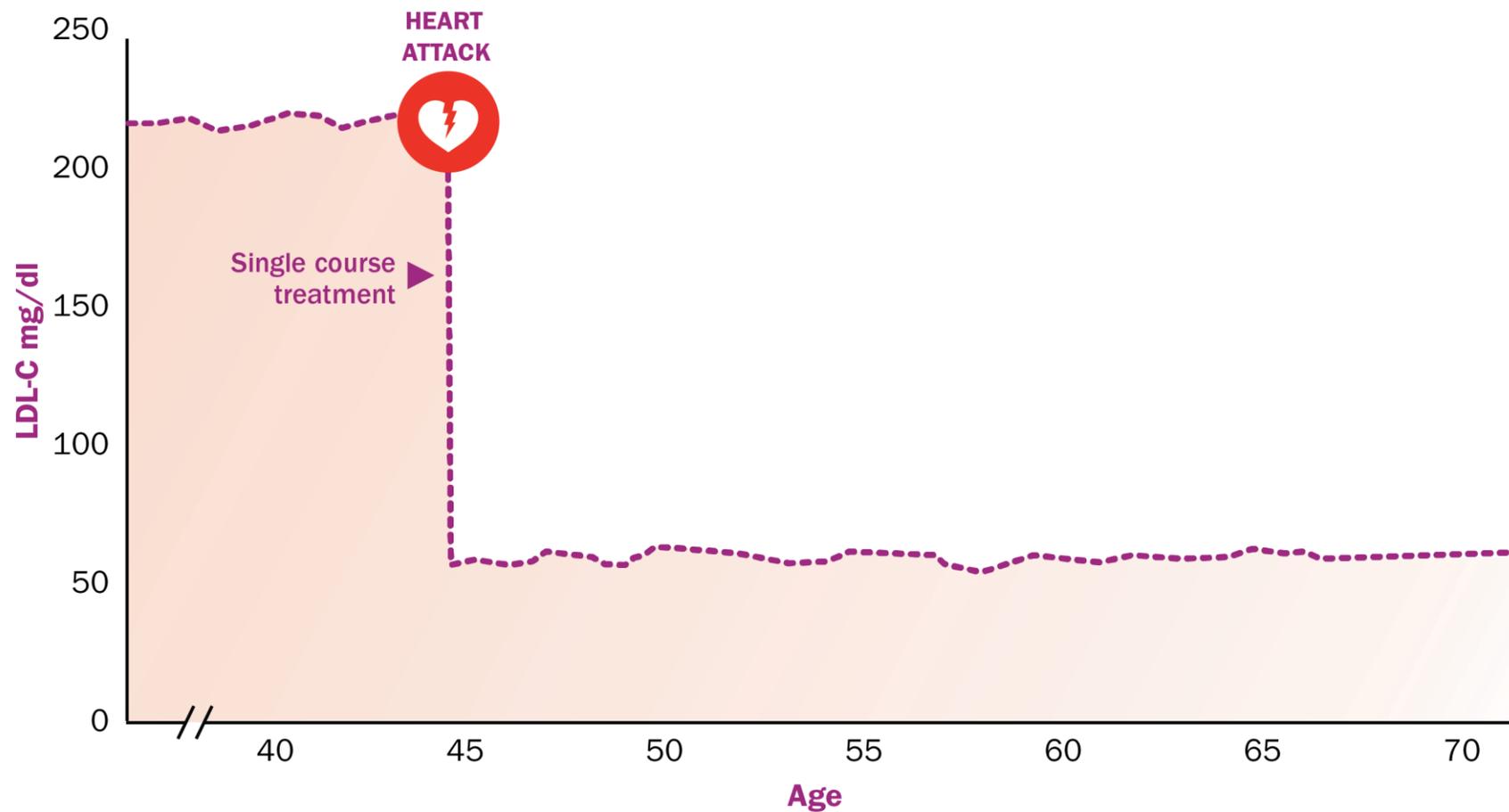
ACC22



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Single-course treatment for ASCVD could address key unmet need: getting LDL-C as low as possible for as long as possible



Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who was treated with a single-course treatment after suffering a heart attack at age 44

Advancing a pipeline of single-course *in vivo* gene editing programs to safely and durably lower LDL-C and treat ASCVD

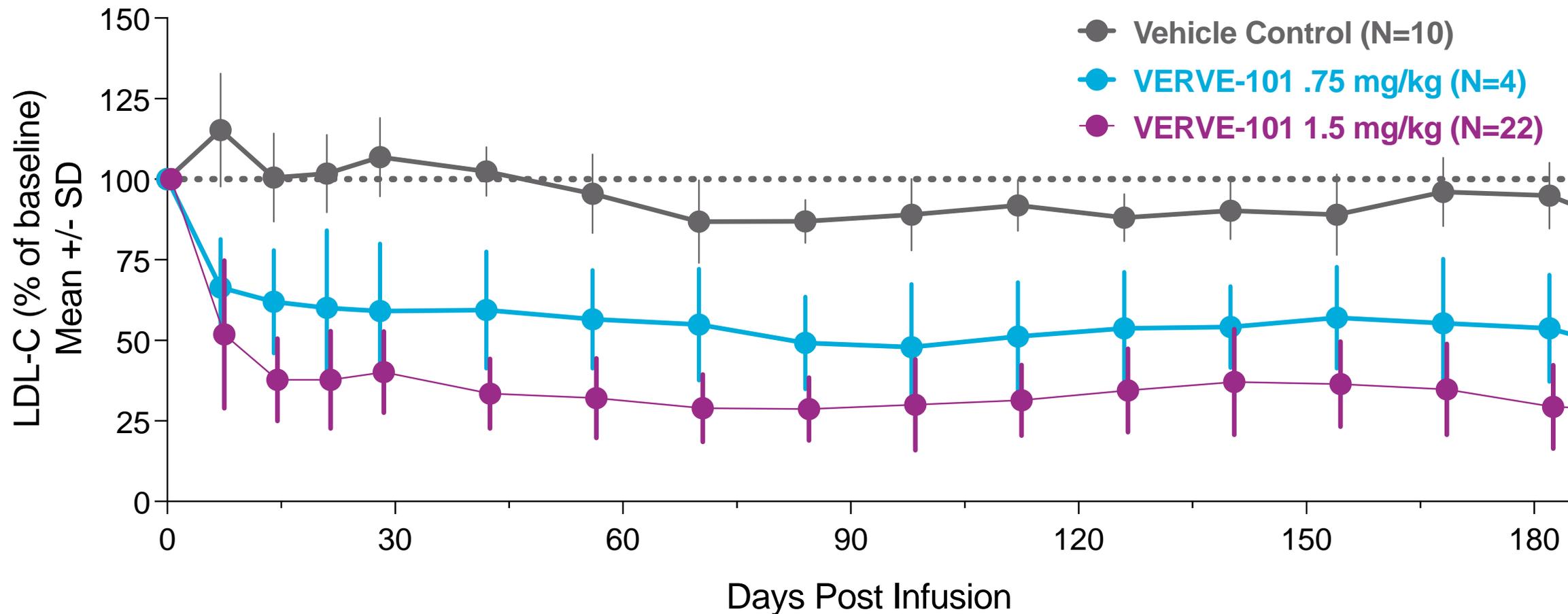


PROGRAM	INDICATIONS	DEVELOPMENT STATUS				
		Research/ Lead optimization	IND-Enabling	Phase 1	Phase 2	Phase 3
Low-density lipoprotein cholesterol (LDL-C)						
VERVE-101 PCSK9	Heterozygous familial hypercholesterolemia	●	●	●	●	●
	ASCVD not at LDL-C goal on oral therapy	●	●	●	●	●
LDL-C & Triglyceride-rich lipoprotein (TRL)						
ANGPTL3	Homozygous familial hypercholesterolemia	●	●	●	●	●
	ASCVD not at LDL-C goal on oral + PCSK9i	●	●	●	●	●

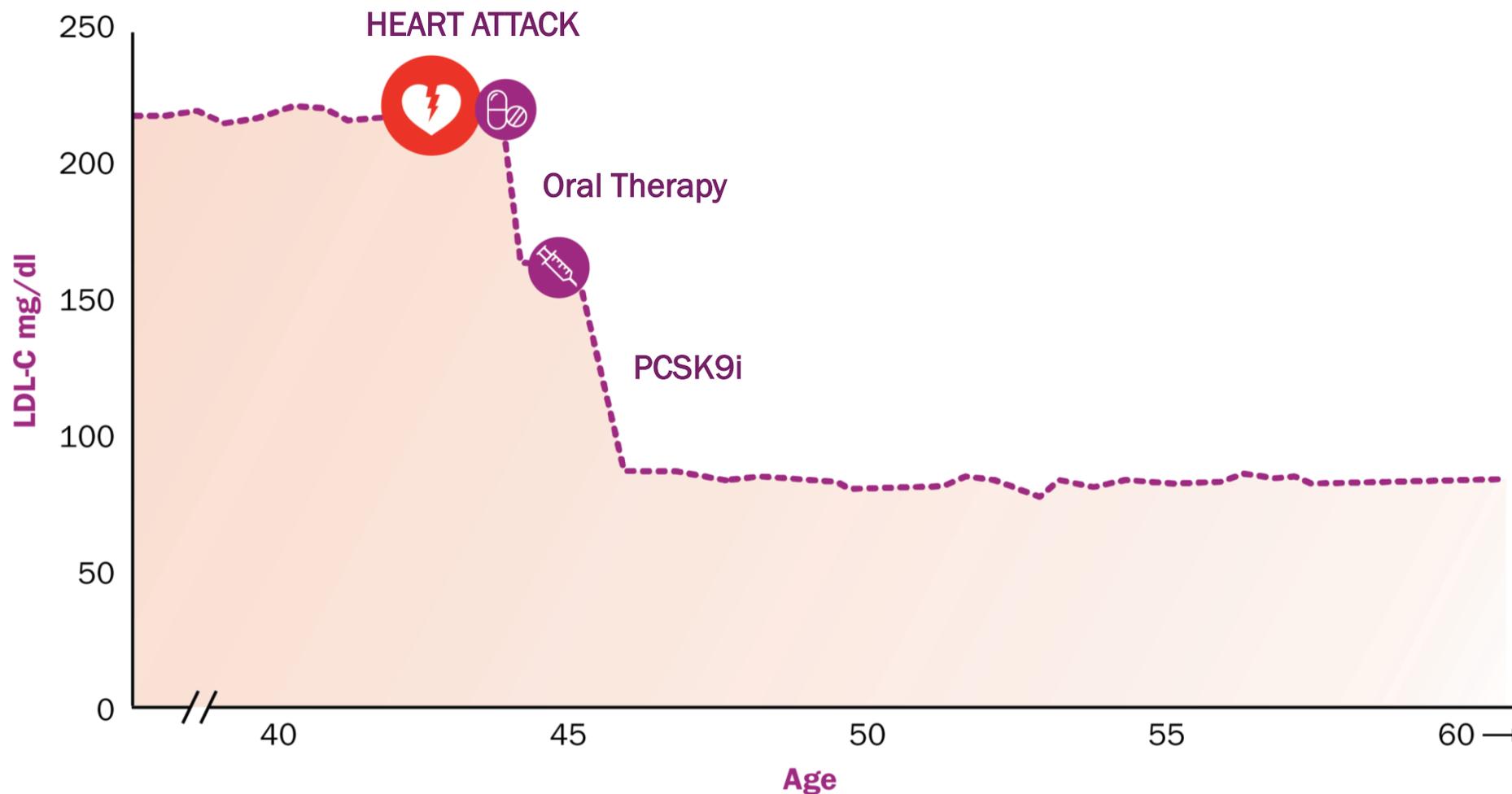
VERVE-101: one-time intravenous infusion in non-human primates, durable lowering of blood LDL-C by >60%



Phase 1 study initiation for VERVE-101 planned for 2nd half of 2022



Problem: some ASCVD patients start with very high LDL-C and still do not reach LDL-C goal despite oral standard-of-care (SOC) and PCSK9i



Illustrative graphic of a hypothetical patient with ASCVD and hypercholesterolemia treated with serial addition of lipid-lowering therapies to achieve goal LDL-C after suffering a heart attack at age 44.

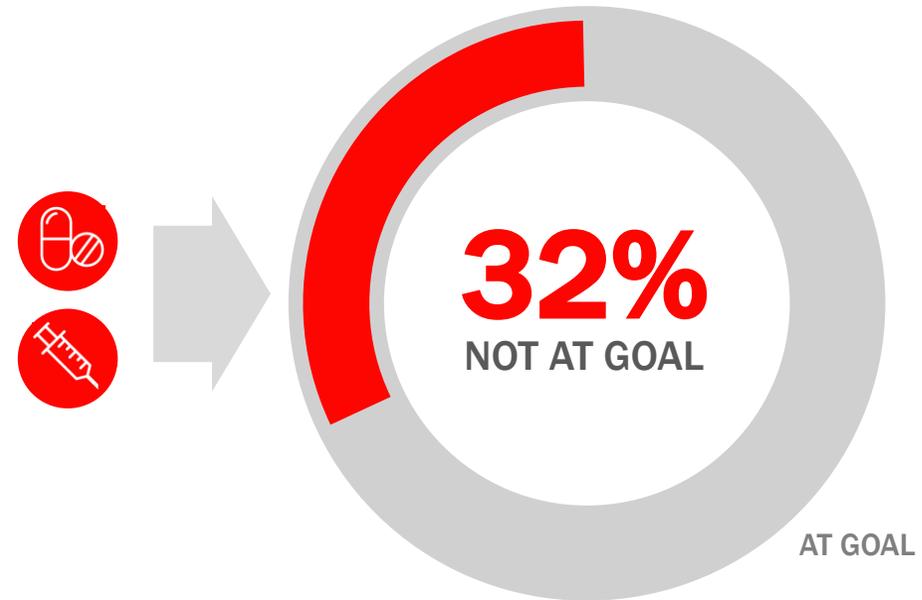
Two indications with high unmet need

Homozygous familial hypercholesterolemia



In a global registry of HoFH patients, 47% did not attain LDL-C goal even on 5 lipid-lowering therapies

Atherosclerotic CVD not at LDL-C goal on oral SOC + PCSK9i

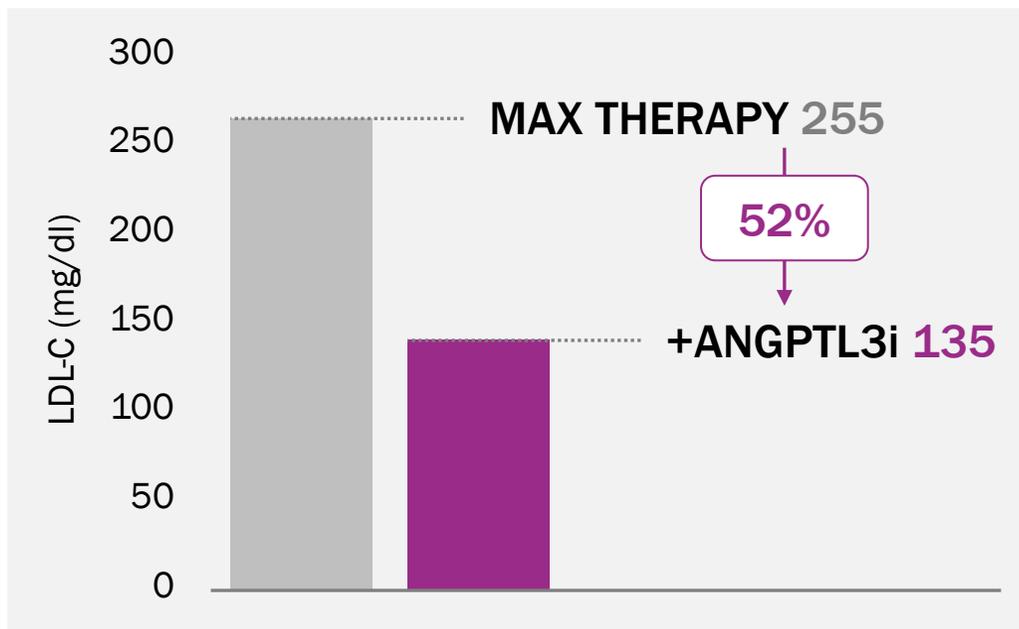


In the ORION-9, -10, and -11 clinical trials of inclisiran, 32% did not attain LDL-C < 70 mg/dl even on oral (statin) + PCSK9i (inclisiran) therapy

In these two indications, inhibition of the ANGPTL3 protein by a monoclonal antibody has been proven to work

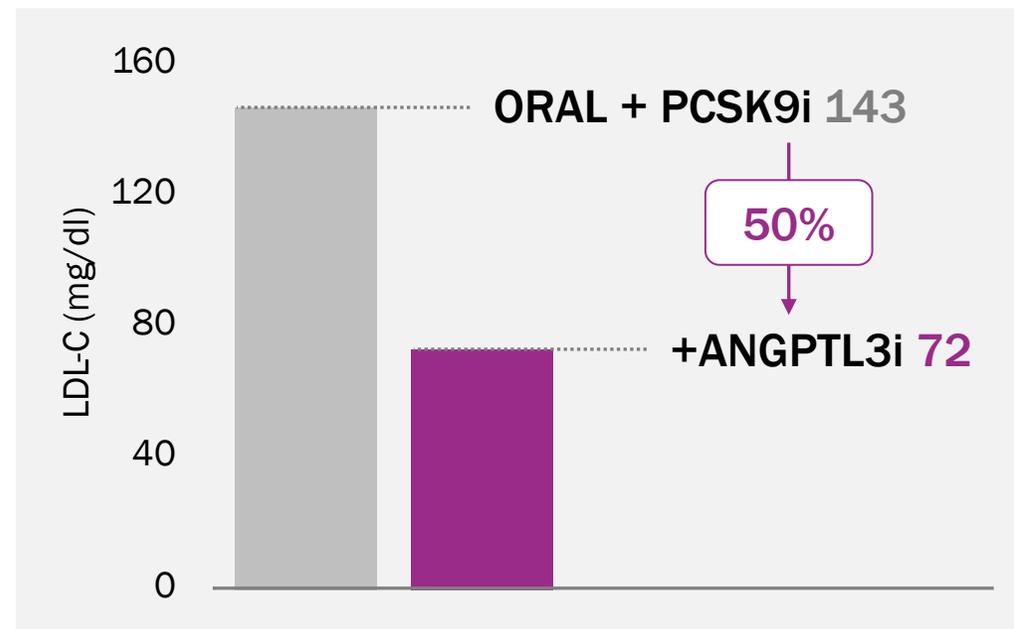


Homozygous familial hypercholesterolemia



registration trial of evinacumab (Evkeeza) in homozygous FH patients on maximum lipid-lowering therapy ANGPTL3 inhibition ↓ LDL-C by 47%

Atherosclerotic CVD not at LDL-C goal on oral SOC + PCSK9i



trial of evinacumab (Evkeeza) in ASCVD patients with LDL-C ≥ 70 on oral + PCSK9i therapy ANGPTL3 inhibition ↓ LDL-C by 51%

Inactivation of ANGPTL3 is a compelling target to lower LDL-C: validated by human genetics of ANGPTL3 deficiency

Lower LDL-C and ASCVD

Heterozygous deficiency
lower lipids in population
resistant to ASCVD

Homozygous deficiency
'Human knockout'
LDL-C: 37 mg/dL

Rare Gene Mutations Inspire New Heart Drugs

By Gina Kolata

May 24, 2017

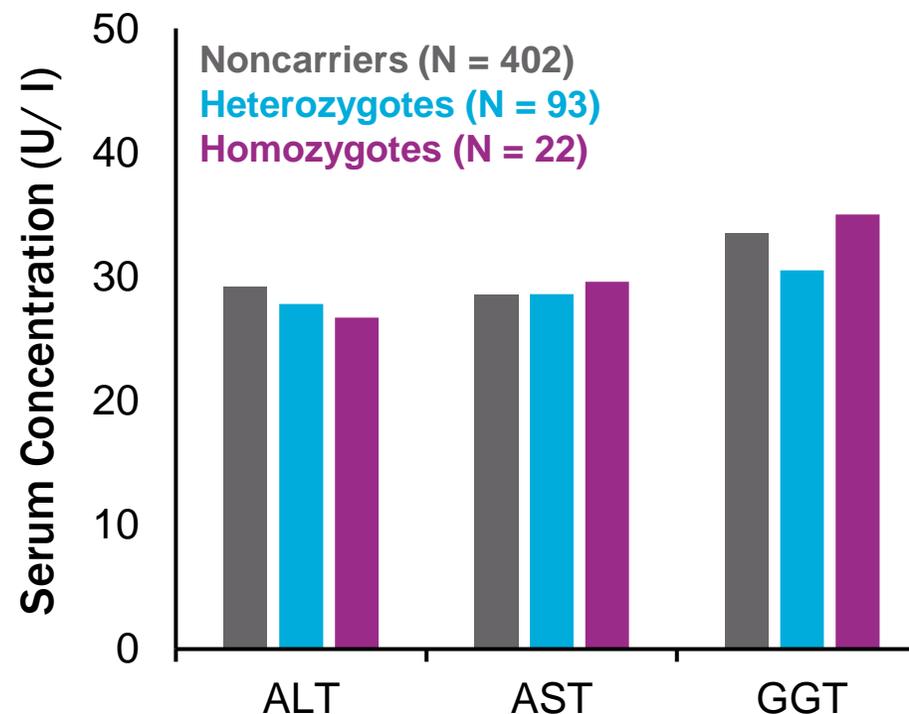
Anna Feurer learned she had unusually low triglyceride levels after having bloodwork at a corporate health fair. The discovery prompted researchers to recruit her and her family for a research study of their genetic makeup.



Credit. Jess T. Dugan for The New York Times

No adverse effects

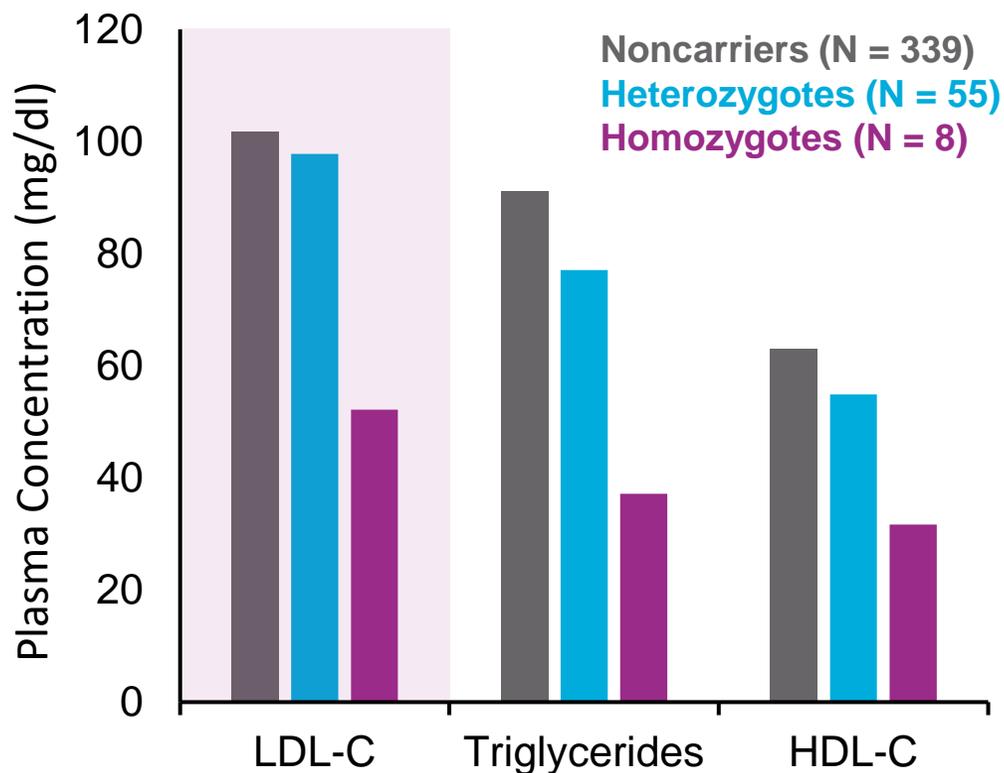
No increase in markers of liver injury or prevalence of liver steatosis in heterozygous or homozygous deficiency



Human genetic and pharmacologic data indicate >90% blood ANGPTL3 reduction required to lower LDL-C

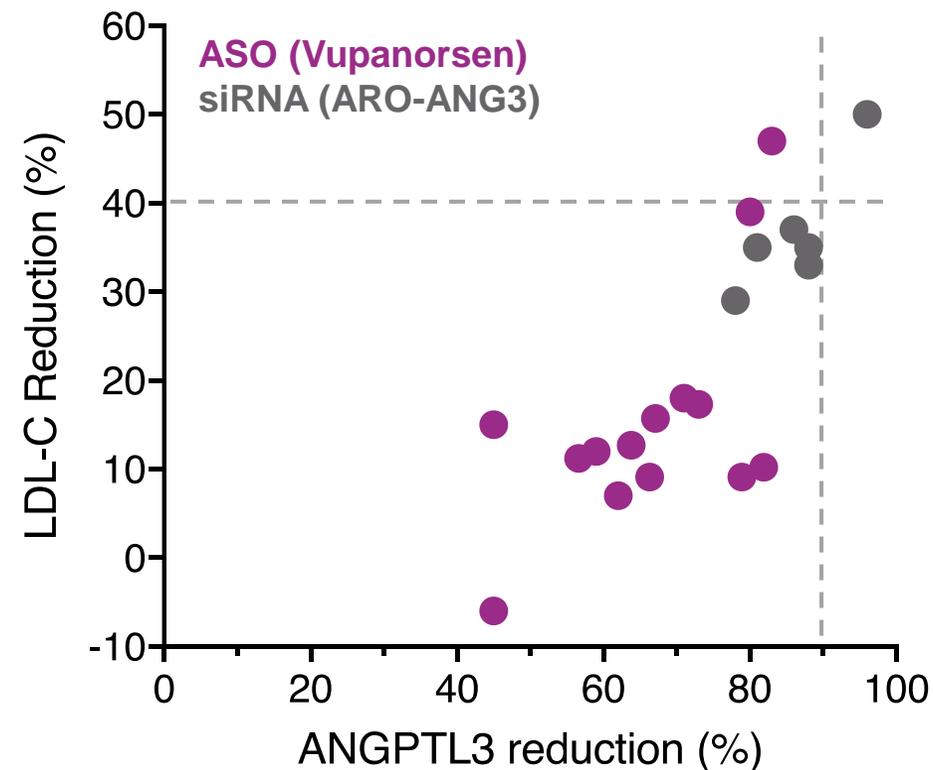
Human genetics

LDL-C ↓ by 49% in homozygote loss-of function 'human knockout' versus noncarriers

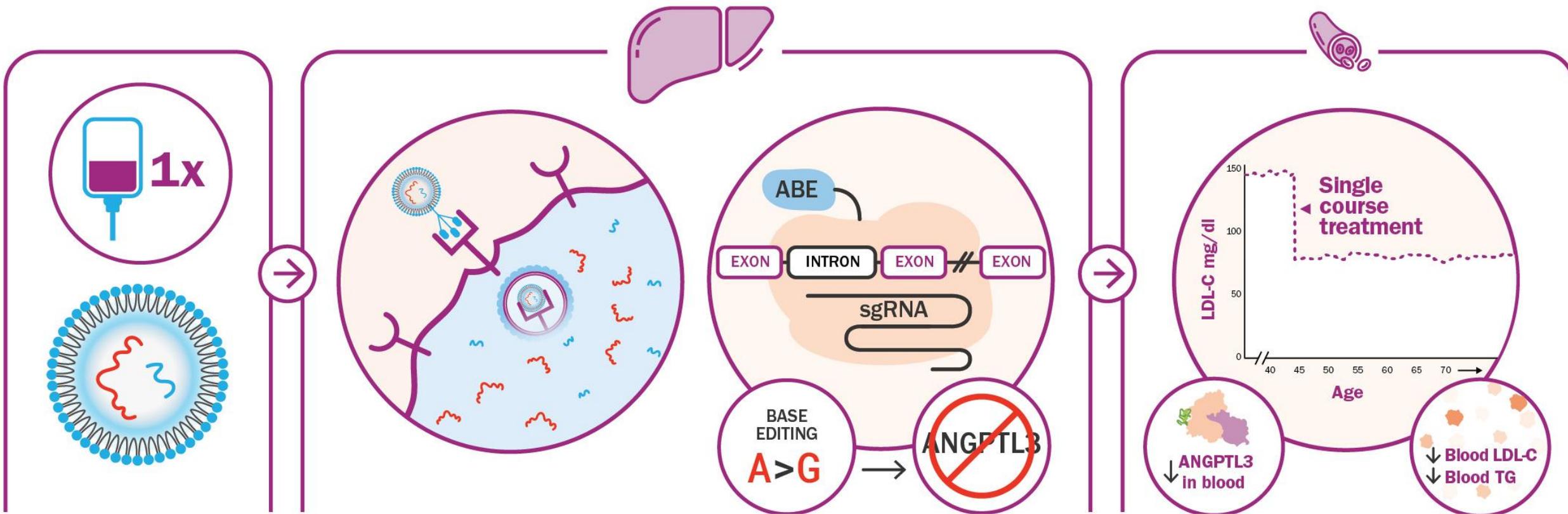


Human pharmacology

ANGPTL3 reduction of ~90% has lowered LDL-C ~40%

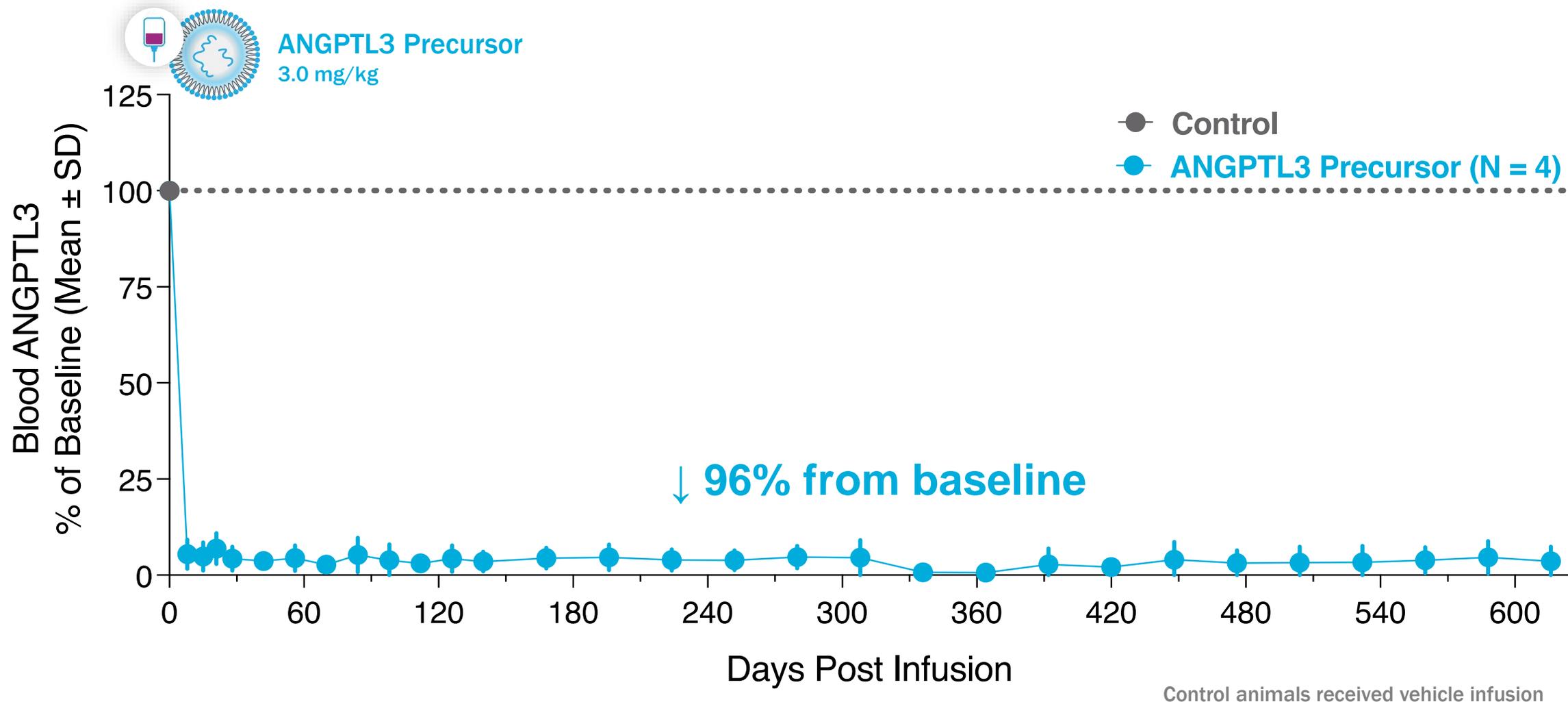


Goal of ANGPTL3 program: turn off gene (permanently) in liver with base editing to lower LDL-C and treat ASCVD

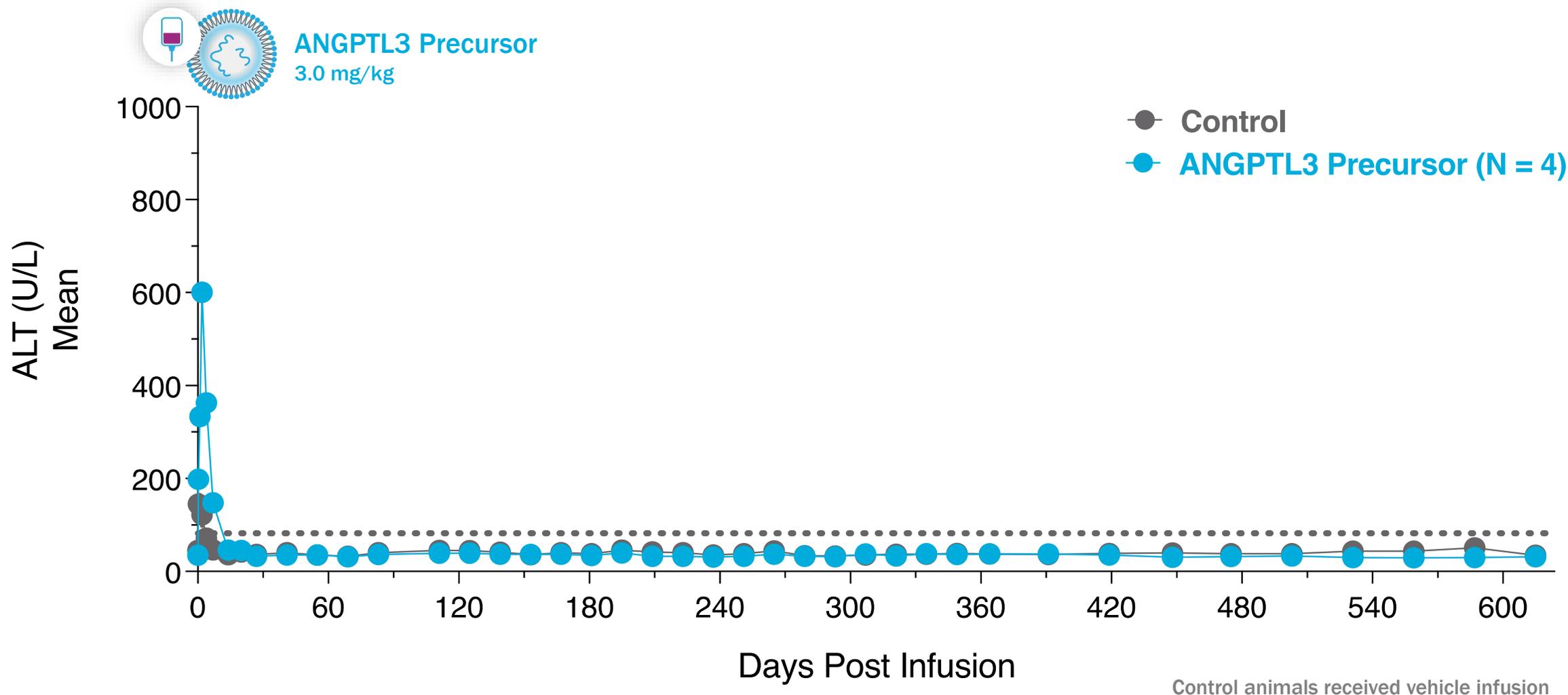


mRNA gRNA GalNAc

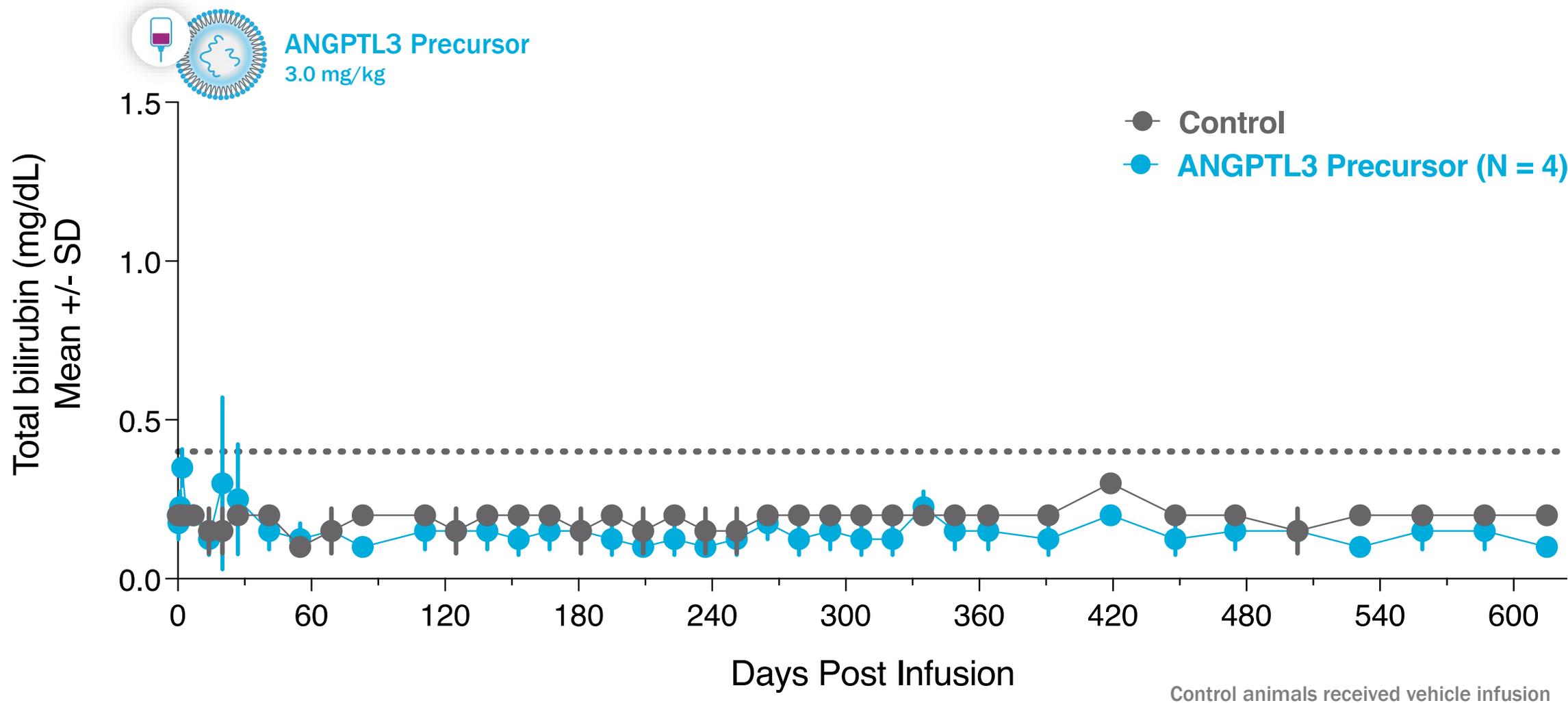
Verve ANGPTL3 precursor given to non-human primates: 616 days following infusion, **durable >90%** reduction in blood ANGPTL3



Verve ANGPTL3 precursor given to non-human primates demonstrates no long-term impact on alanine aminotransferase (ALT)



Verve ANGPTL3 precursor given to non-human primates demonstrates no long-term impact on total bilirubin

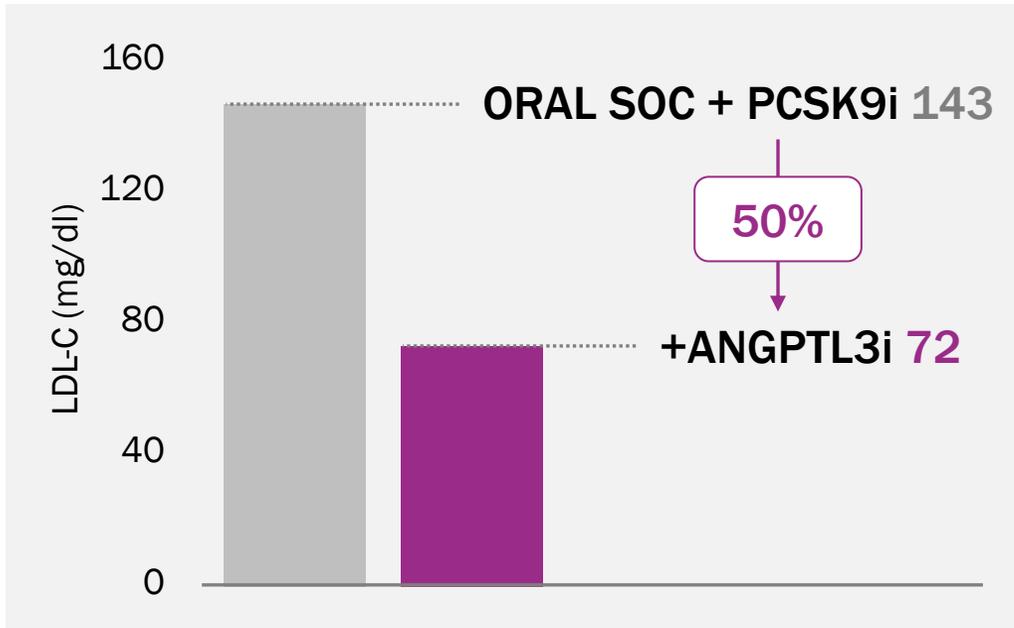




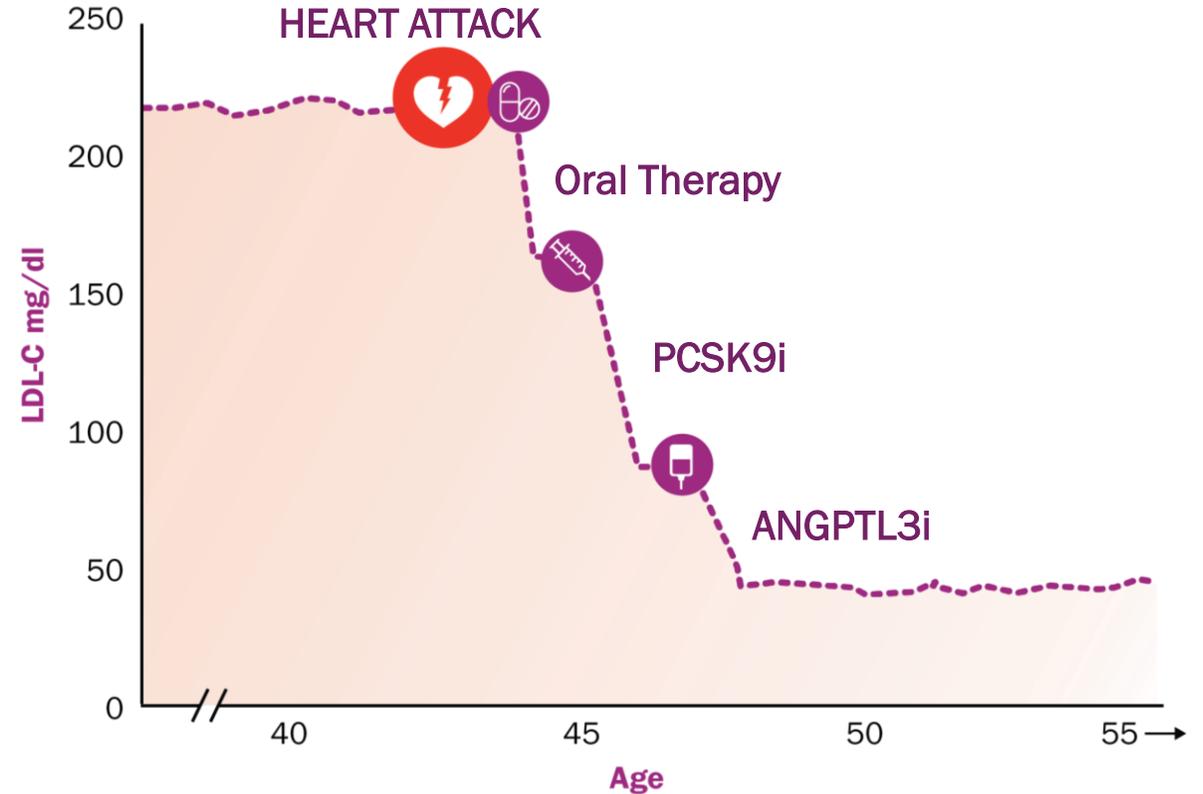
**Sequential editing
of PCSK9 followed
by ANGPTL3
in vivo in NHP**

ANGPTL3 inactivation has been proven to lower LDL-C in ASCVD patients not at goal on oral SOC + PCSK9i therapy

Atherosclerotic CVD not at LDL-C goal

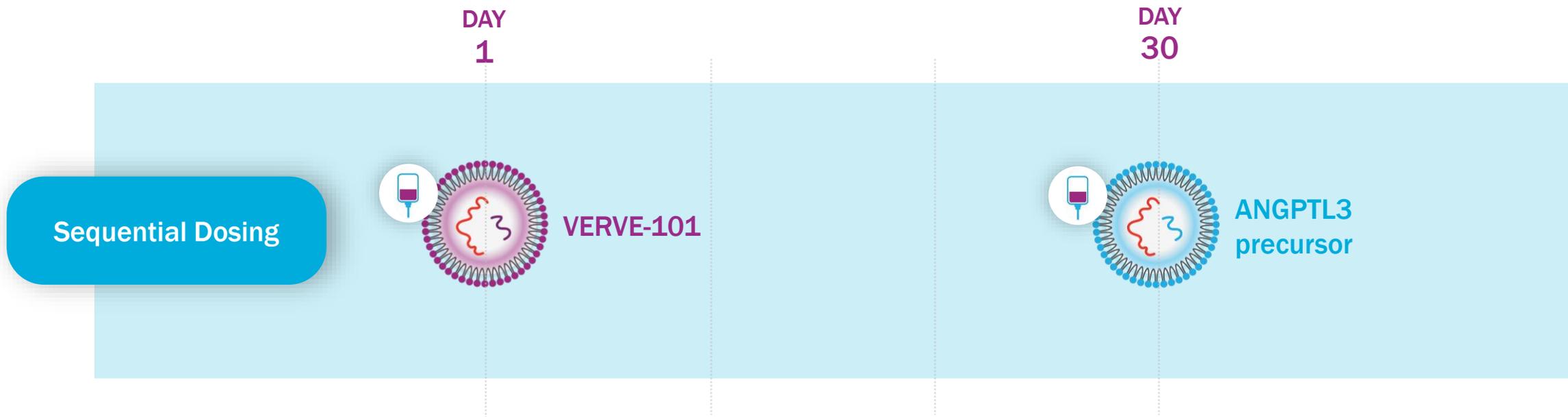


trial of evinacumab (Evkeeza) in ASCVD patients with LDL-C \geq 70 on oral SOC + PCSK9i therapy
ANGPTL3 inhibition \downarrow LDL-C by 51%

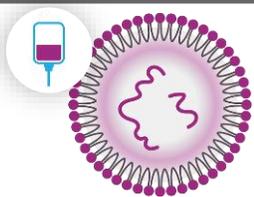


Illustrative graphic of a hypothetical patient with ASCVD and hypercholesterolemia treated with serial addition of lipid-lowering therapies to achieve goal LDL-C after suffering a heart attack at age 44.

Can ANGPTL3 base editor be sequentially dosed after VERVE-101 to target two independent CV risk pathways?



Sequential dosing of VERVE-101



Biopsy
Day 15
PCSK9 editing

VERVE-101
1.0 mg/kg

NHP 1

70%

NHP 2

67%

NHP 3

79%

NHP 4

69%*

mean +/- SD

71 ± 5%

NHP 1

0.1%

NHP 2

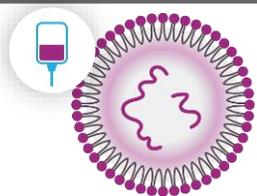
0.3%

NHP 3

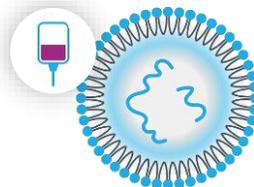
0.2%

* biopsy error, initial biopsy 16%, repeat 69%

Sequential dosing of VERVE-101, followed by dosing with a Verve ANGPTL3 precursor on day 30 in NHPs



Biopsy
Day 15
PCSK9 editing



Biopsy
Day 45
ANGPTL3 editing

Treatment

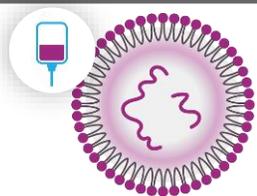
	VERVE-101 1.0 mg/kg	ANGPTL3 1.0 mg/kg
NHP 1	70%	59%
NHP 2	67%	50%
NHP 3	79%	54%
NHP 4	69%*	44%
mean +/- SD	71 ± 5%	52 ± 6%

Control

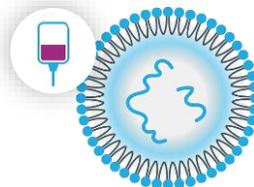
NHP 1	0.1%	0.2%
NHP 2	0.3%	0.2%
NHP 3	0.2%	0.2%

* biopsy error, initial biopsy 16%, repeat 69%

On necropsy at day 90, high efficiency liver editing of both PCSK9 (69%) and ANGPTL3 (63%) genes



Biopsy
Day 15
PCSK9 editing



Biopsy
Day 45
ANGPTL3 editing

Necropsy
Day 90

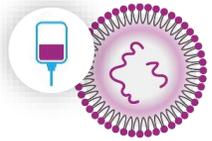
Treatment

Control

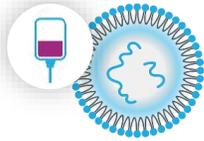
	VERVE-101 1.0 mg/kg	70%	ANGPTL3 1.0 mg/kg	59%	68% PCSK9 63% ANGPTL3
NHP 1		70%		59%	68% PCSK9 63% ANGPTL3
NHP 2		67%		50%	69% PCSK9 62% ANGPTL3
NHP 3		79%		54%	70% PCSK9 62% ANGPTL3
NHP 4		69%*		44%	70% PCSK9 63% ANGPTL3
mean +/- SD		71 ± 5%		52 ± 6%	69 ± 1% PCSK9 63 ± 1% ANGPTL3
NHP 1		0.1%		0.2%	0.1% PCSK9 0.1% ANGPTL3
NHP 2		0.3%		0.2%	0.1% PCSK9 0.2% ANGPTL3
NHP 3		0.2%		0.2%	0.1% PCSK9 0.2% ANGPTL3

* biopsy error, initial biopsy 16%, repeat 69%

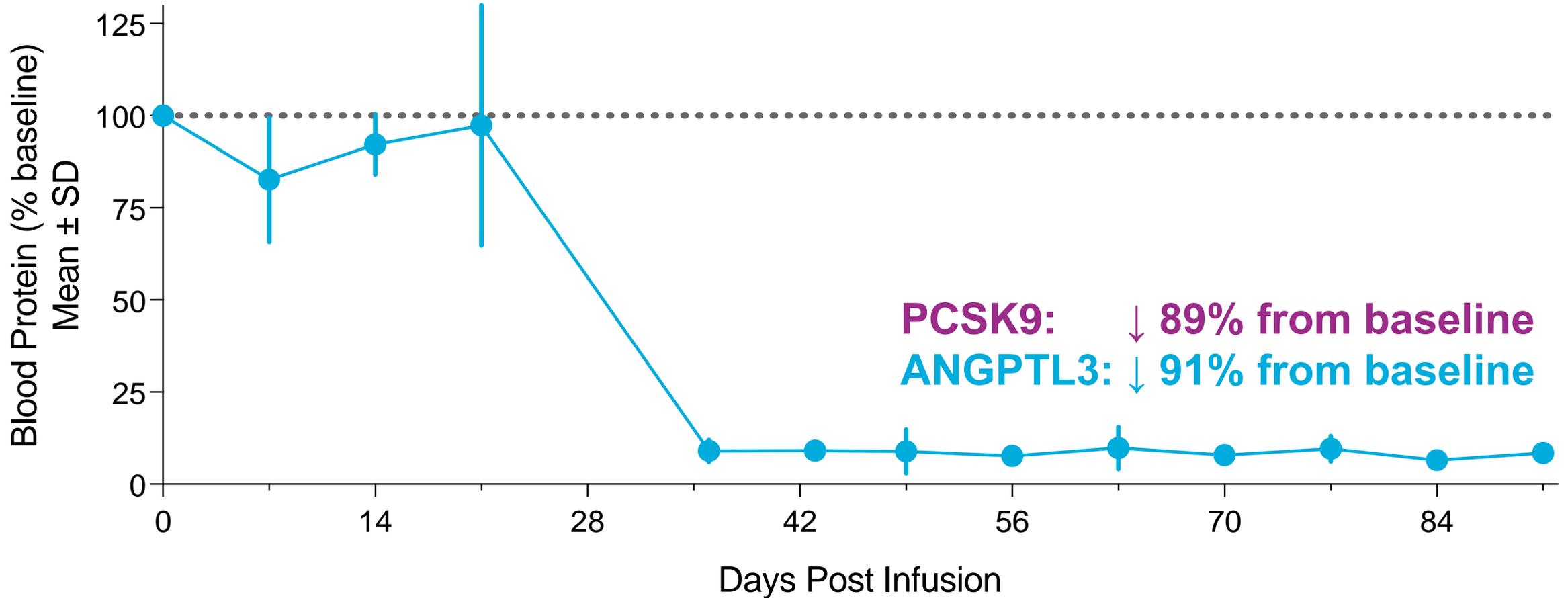
Sequential dosing in NHPs: 89% reduction of blood PCSK9 protein and 91% reduction of blood ANGPTL3 protein



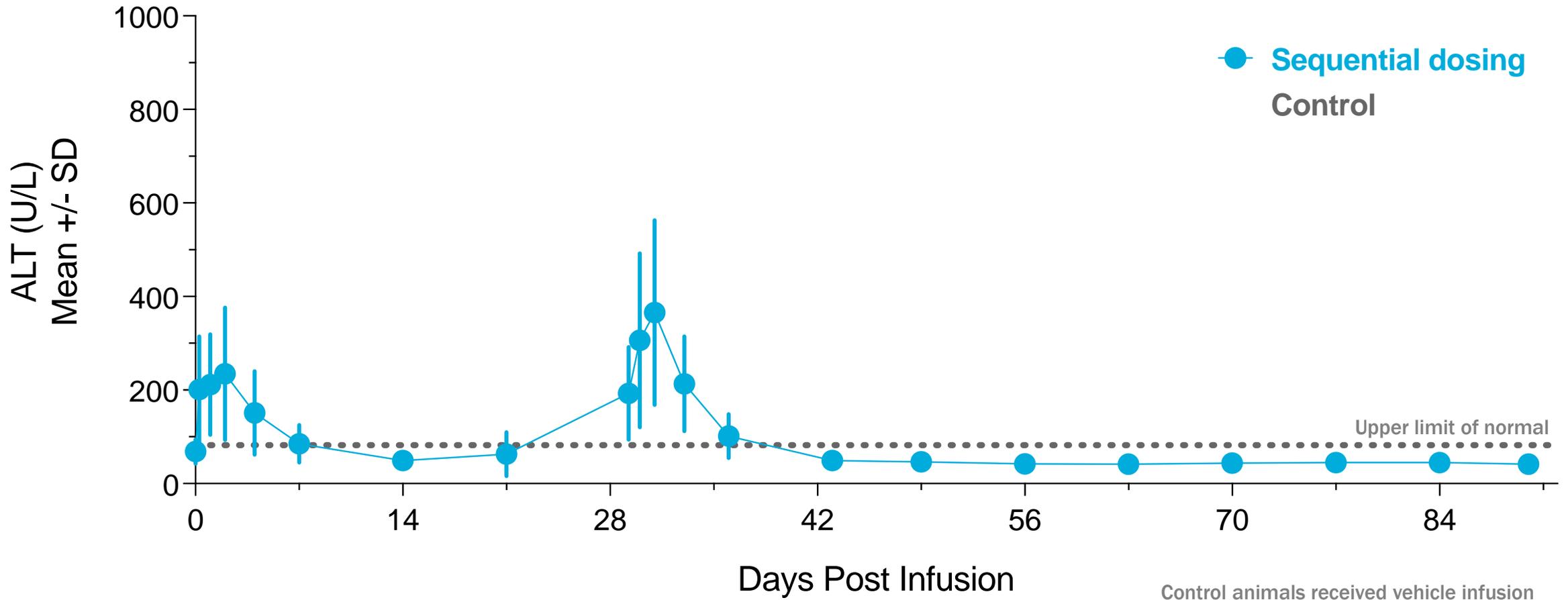
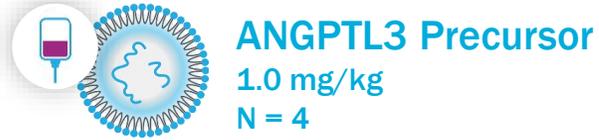
VERVE-101
1.0 mg/kg
N = 4



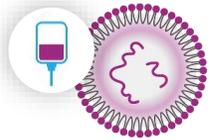
ANGPTL3 Precursor
1.0 mg/kg
N = 4



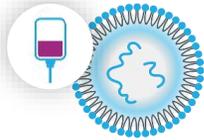
Sequential dosing in NHPs of VERVE-101 followed by ANGPTL3 precursor: no sustained impact on alanine aminotransferase (ALT)



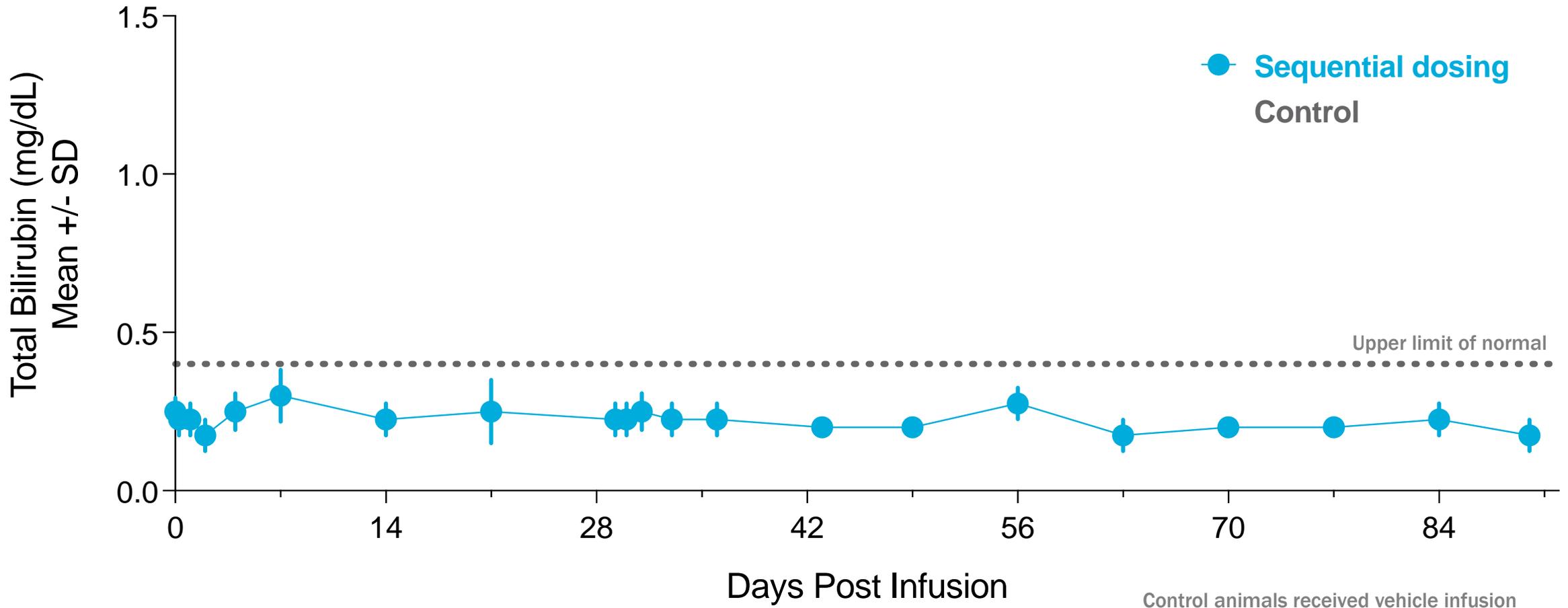
Sequential dosing in NHPs of VERVE-101 followed by ANGPTL3 precursor: no impact on total bilirubin



VERVE-101
1.0 mg/kg
N = 4



ANGPTL3 Precursor
1.0 mg/kg
N = 4

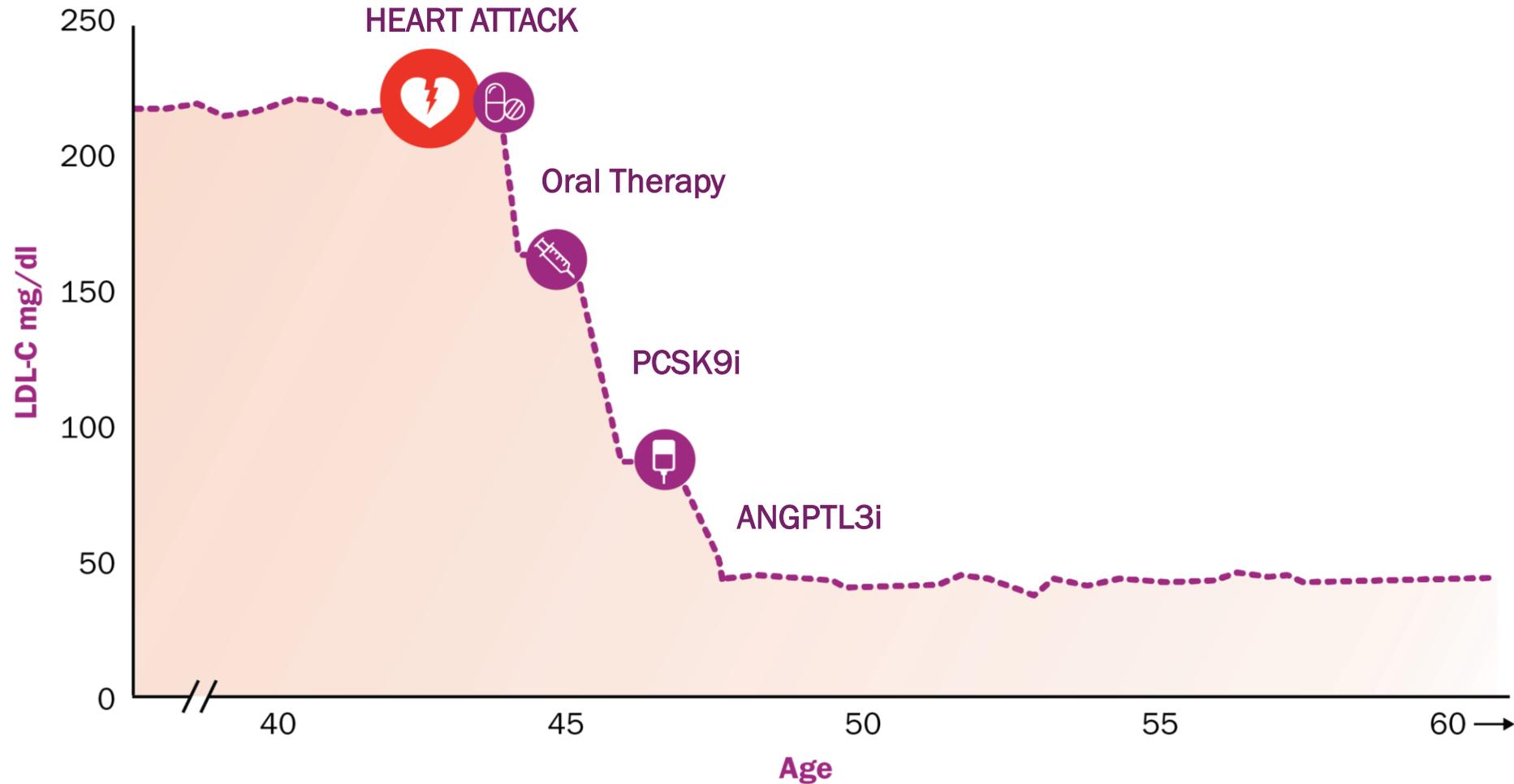


Conclusion: single course gene editing medicines demonstrate the potential to durably lower LDL-C and treat ASCVD



-  **Goal:** lower LDL-C as much as possible for as long as possible
-  The majority of patients do not attain LDL-C goal in current chronic care model
-  Specific patient populations require different treatments
-  Gene editing has the potential to potently and durably lower LDL-C
-  Suite of complementary single course gene editing medicines to lower LDL-C and treat ASCVD by targeting distinct pathways

Inactivation of ANGPTL3 with a single-course treatment to lower LDL-C has potential to address unmet need in ASCVD



Illustrative graphic of a hypothetical patient with ASCVD and hypercholesterolemia treated with serial addition of lipid-lowering therapies to achieve goal LDL-C after suffering a heart attack at age 44.