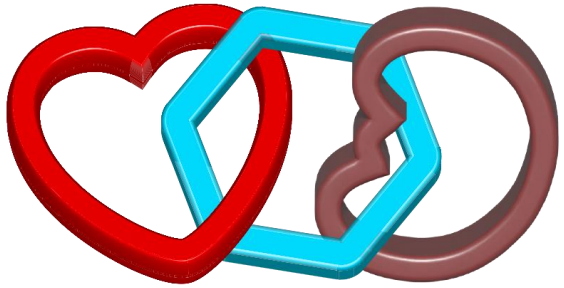


Nieuwe ontwikkelingen in lipidenverlagende behandelingen

Prof. dr. Wouter Jukema

Cardioloog, LUMC, Leiden

Disclosure potential conflicts of interest J.W. Jukema

Geen (potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties:	
Sponsoring/honorarium/vergoeding of onderzoeksgeld	JW Jukema/his department has received research grants from and/or was speaker (with or without lecture fees) on a.o.(CME accredited) meetings sponsored by Amgen, Athera, Astra-Zeneca, Biotronik, Boston Scientific, Dalcor, Daiichi Sankyo, Lilly, Medtronic, Merck-Schering-Plough, Pfizer, Roche, Sanofi Aventis, The Medicine Company, the Netherlands Heart Foundation, CardioVascular Research the Netherlands (CVON), the Netherlands Heart Institute and the European Community Framework KP7 Programme.

Nicolai Anitschkow (1885 – 1964)

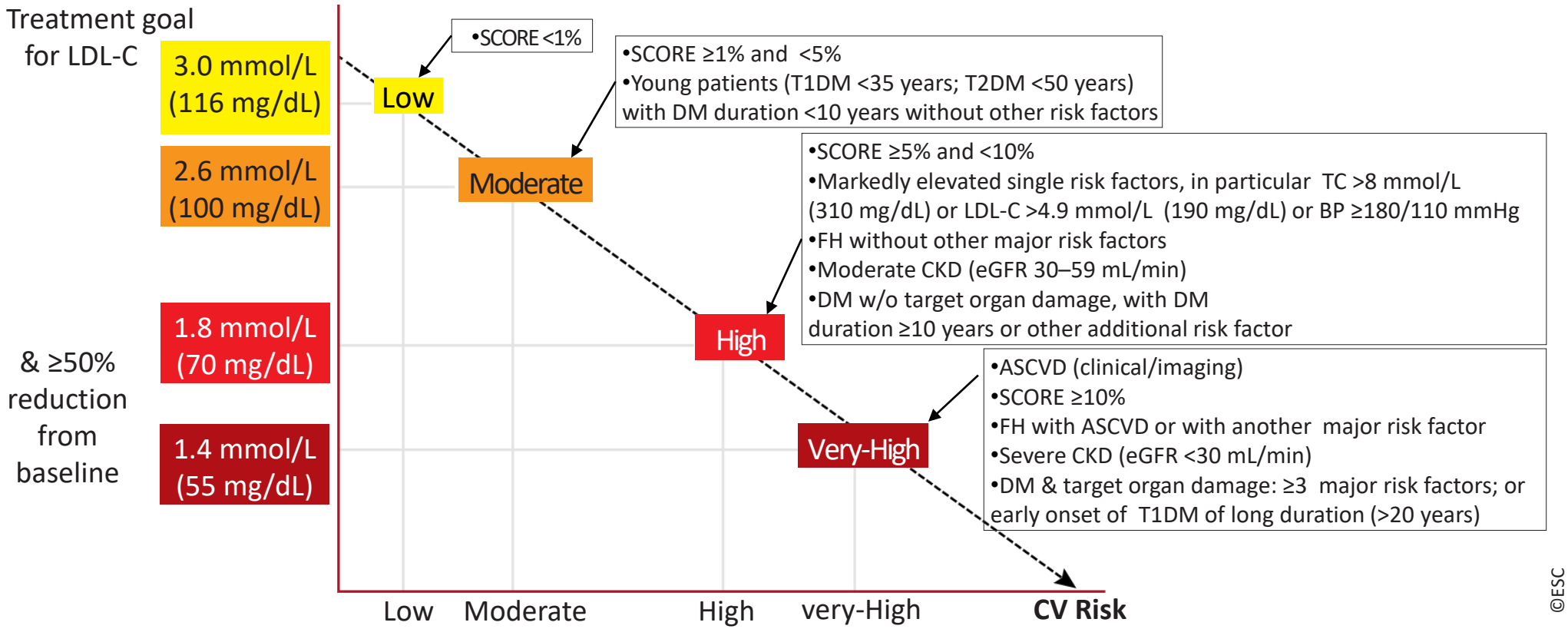
- Identified cell types involved in atherosclerosis
  - Smooth muscle cells
  - Macrophages
  - Lymphocytes

- “There is no atherosclerosis without cholesterol”

Anitschkow NN, Chatalov S (1913). "Über experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse". *Zentralbl Allg Pathol* 24: 1-9.

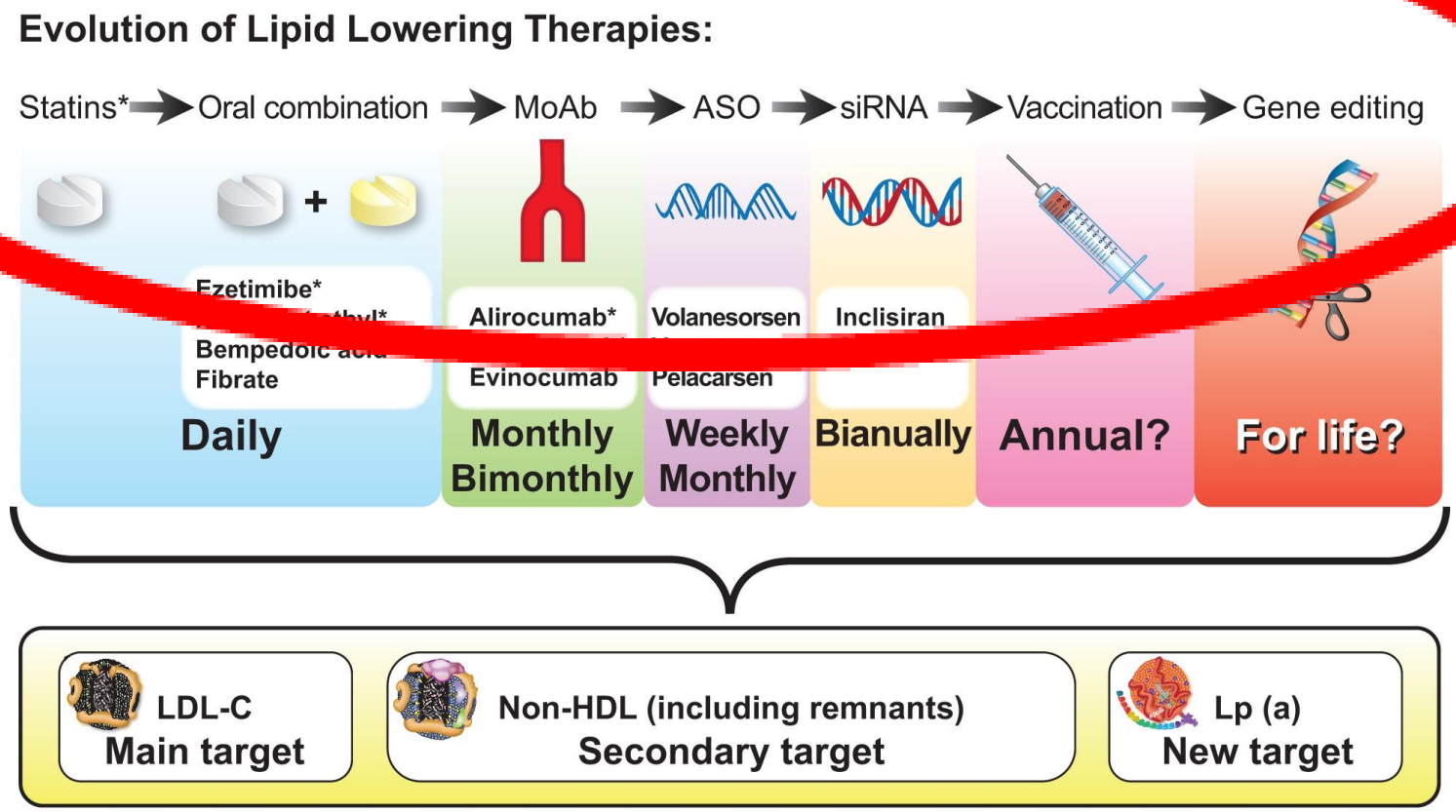
Anitschkow NN (1913). "Über die Veränderungen der Kaninchenaorta bei experimenteller Cholesterinsteatose". *Beitr Pathol Anat* 56: 379-404.

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk (with statins, ezetimibe, PCSK-9 inhibitors)



2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Graphical Abstract The future evolution of lipid-lowering therapies.
The quest for new lipid-lowering therapies enabling less ...



*Therapies shown to decrease CV events

Eur Heart J, Volume 43, Issue 34, 7 September 2022, Pages 3198–3208, https://doi.org/10.1093/eurheartj/ehab841

Graphical Abstract The future evolution of lipid-lowering therapies.
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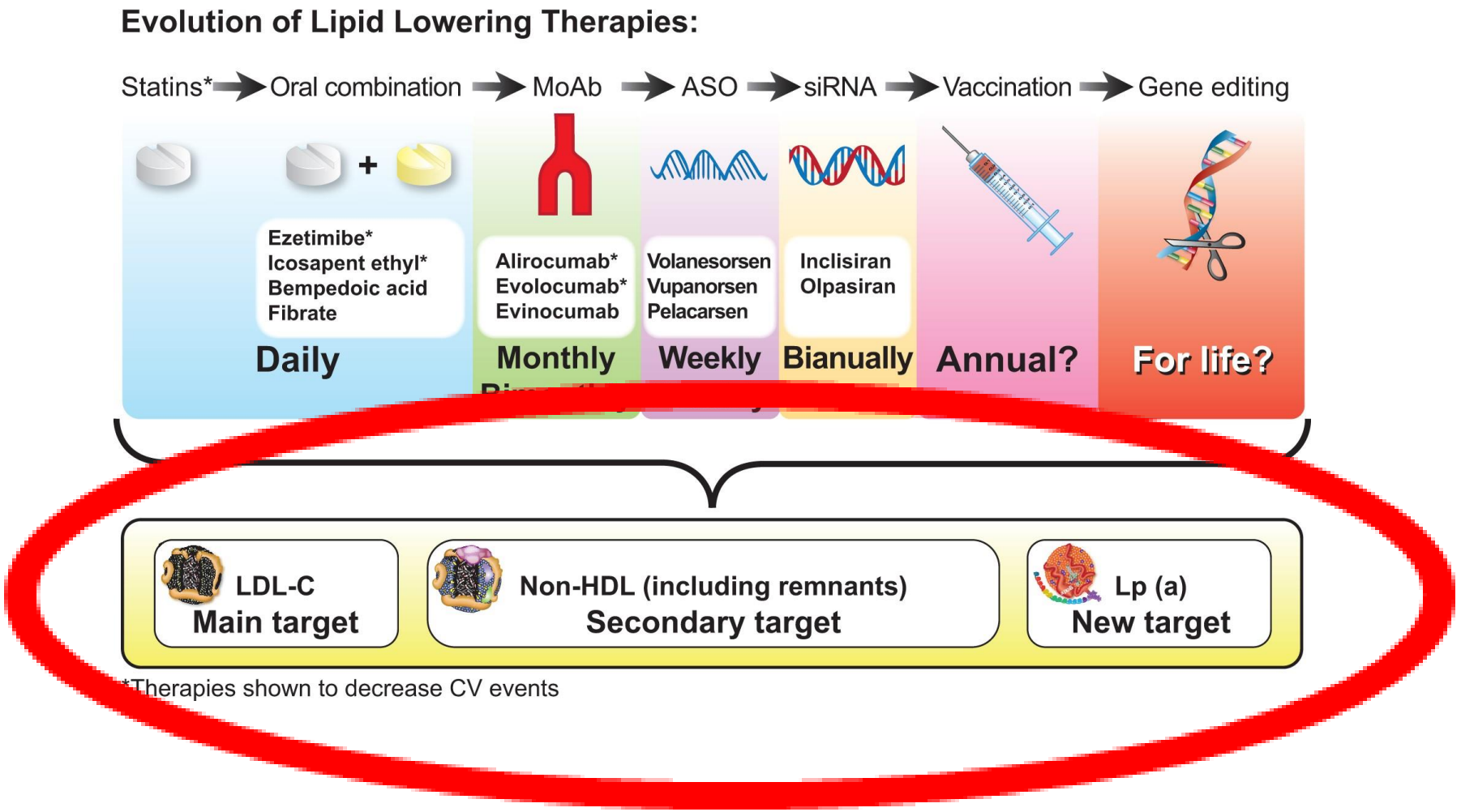

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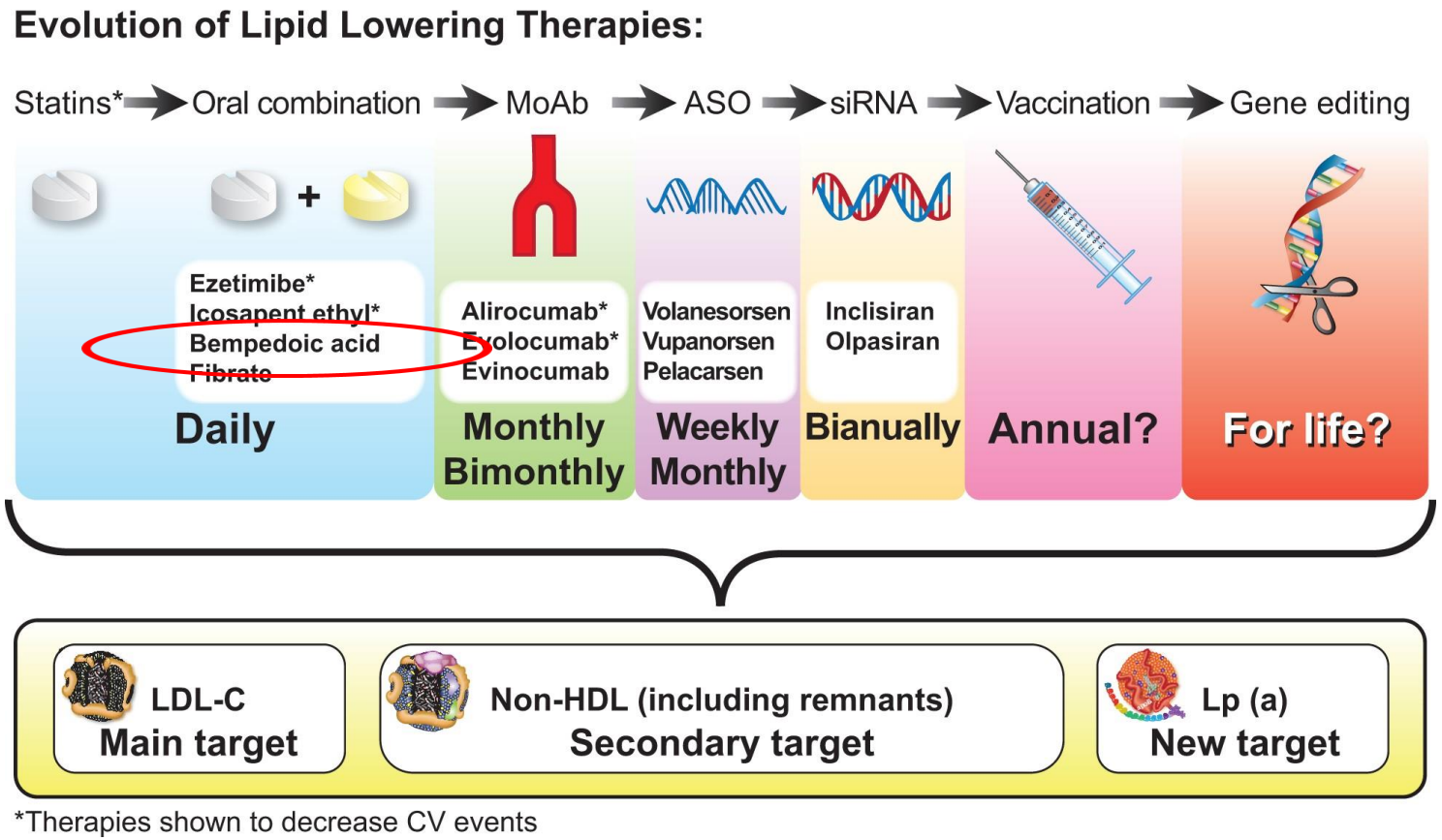
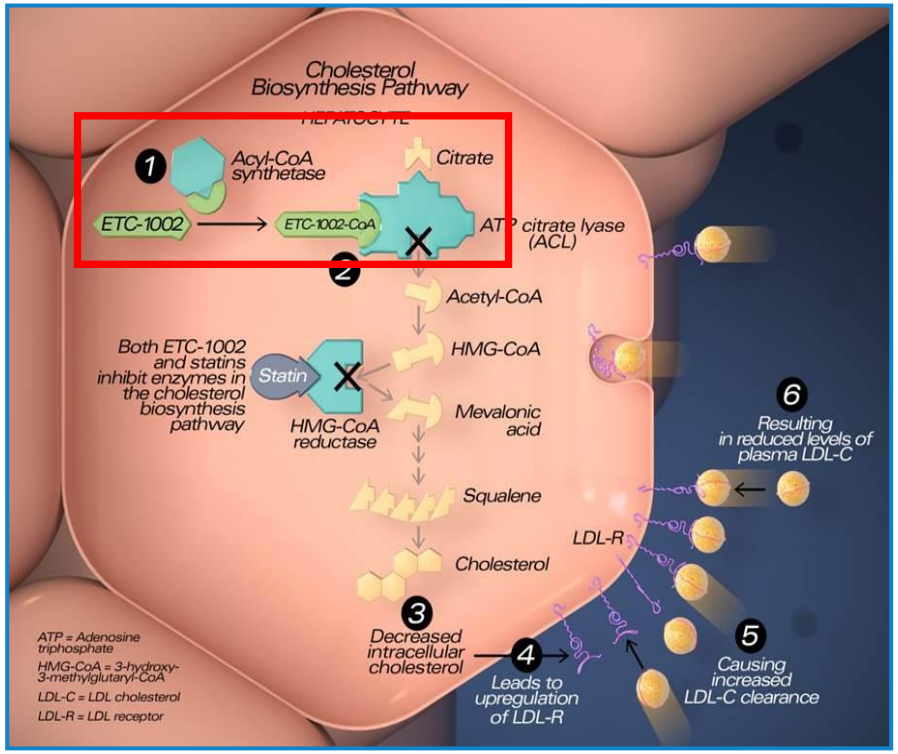


Eur Heart J, Volume 43, Issue 34, 7 September 2022, Pages 3198–3208, https://doi.org/10.1093/eurheartj/ehab841

Bempedoic acid - Mechanism of action

Converted to ETC-1002-CoA, the active form, in the liver

Liver targeted, muscle-sparing drug



- Bempedoic acid (BA) acts in the same cholesterol biosynthesis pathway as statins
- Bempedoic acid targets **ATP-Citrate Lyase,** an enzyme upstream of HMG-CoA reductase
- Upregulates LDL receptors and lowers LDL-C
- BA is a prodrug; the specific isozyme (ACSVL1) which converts BA into an active CoA form is not present in skeletal muscle

Pinkosky, S. L., et al. (2016). Nature Communications, 7, 13457 doi:10.1038/ncomms13457

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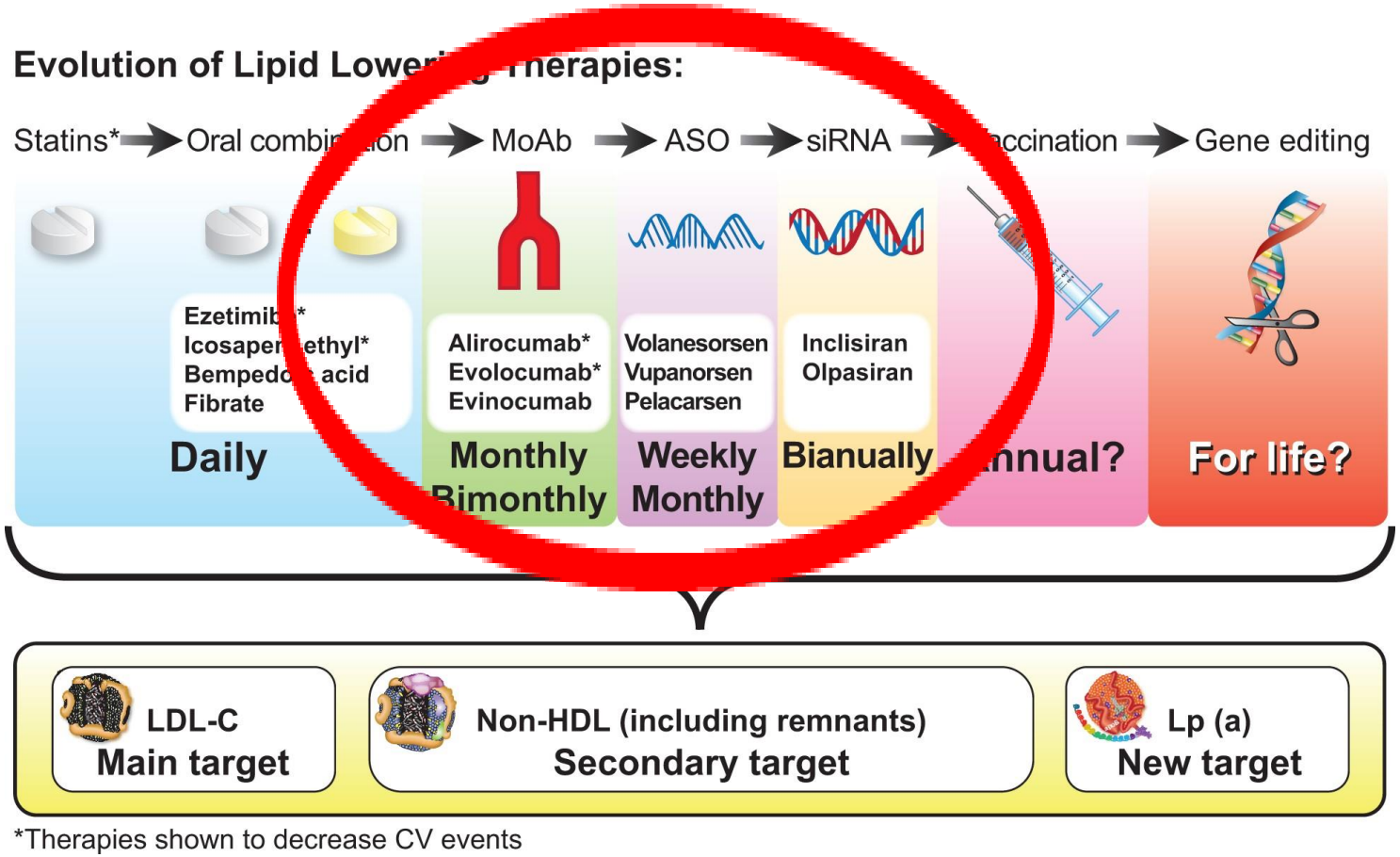

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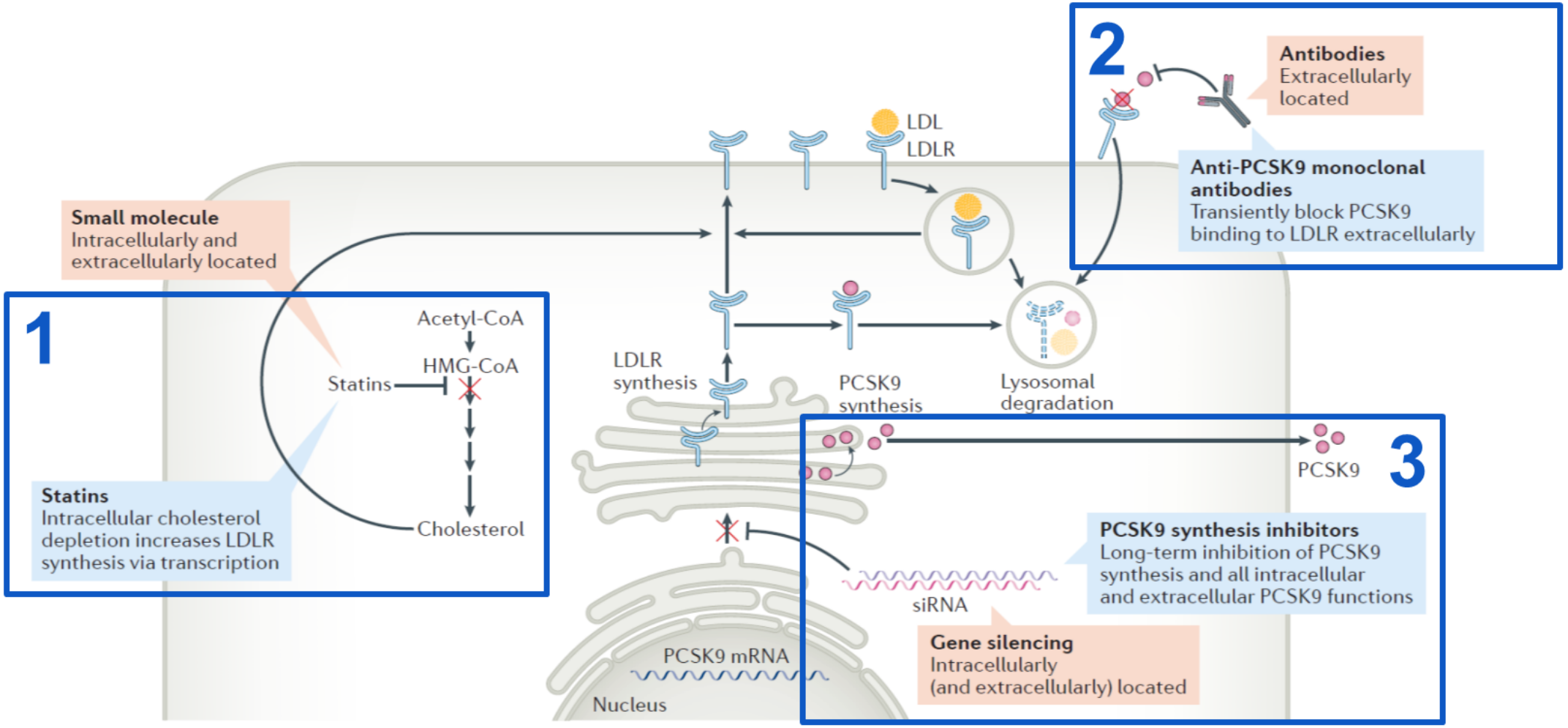
Novel platforms

From antibodies to RNA-based therapies



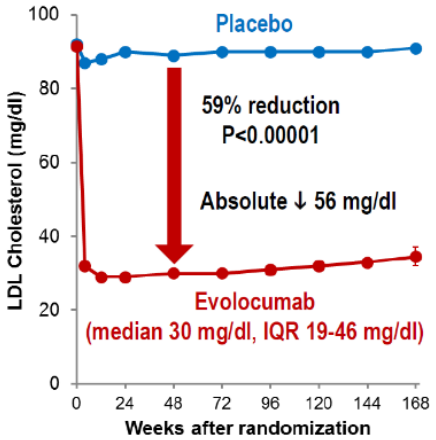
The NEW ENGLAND JOURNAL of MEDICINE

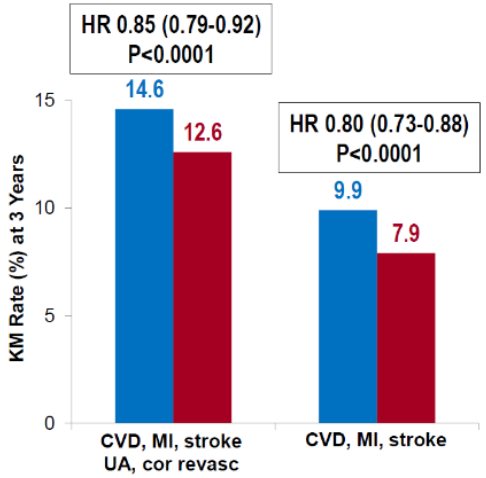
ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated



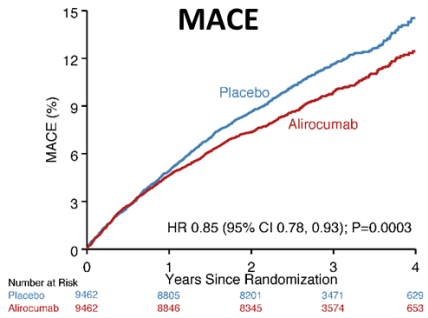


Sabatine MS et al. NEJM 2017;376:1713-22

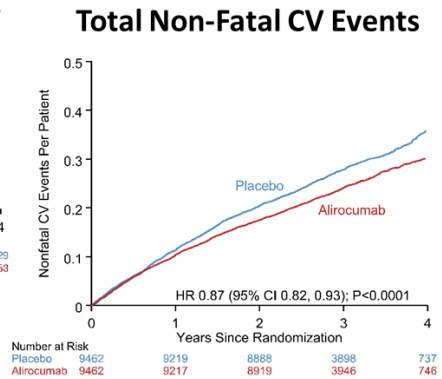
ORIGINAL ARTICLE

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

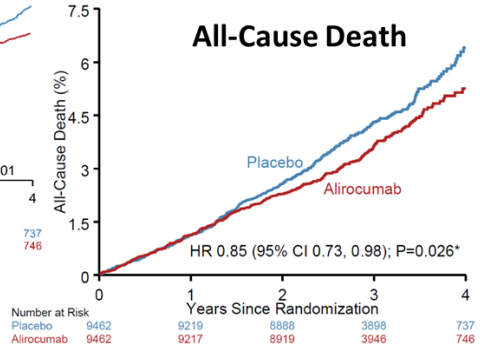
G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*



Schwartz GG, et al *NEJM* 2018;379:2097



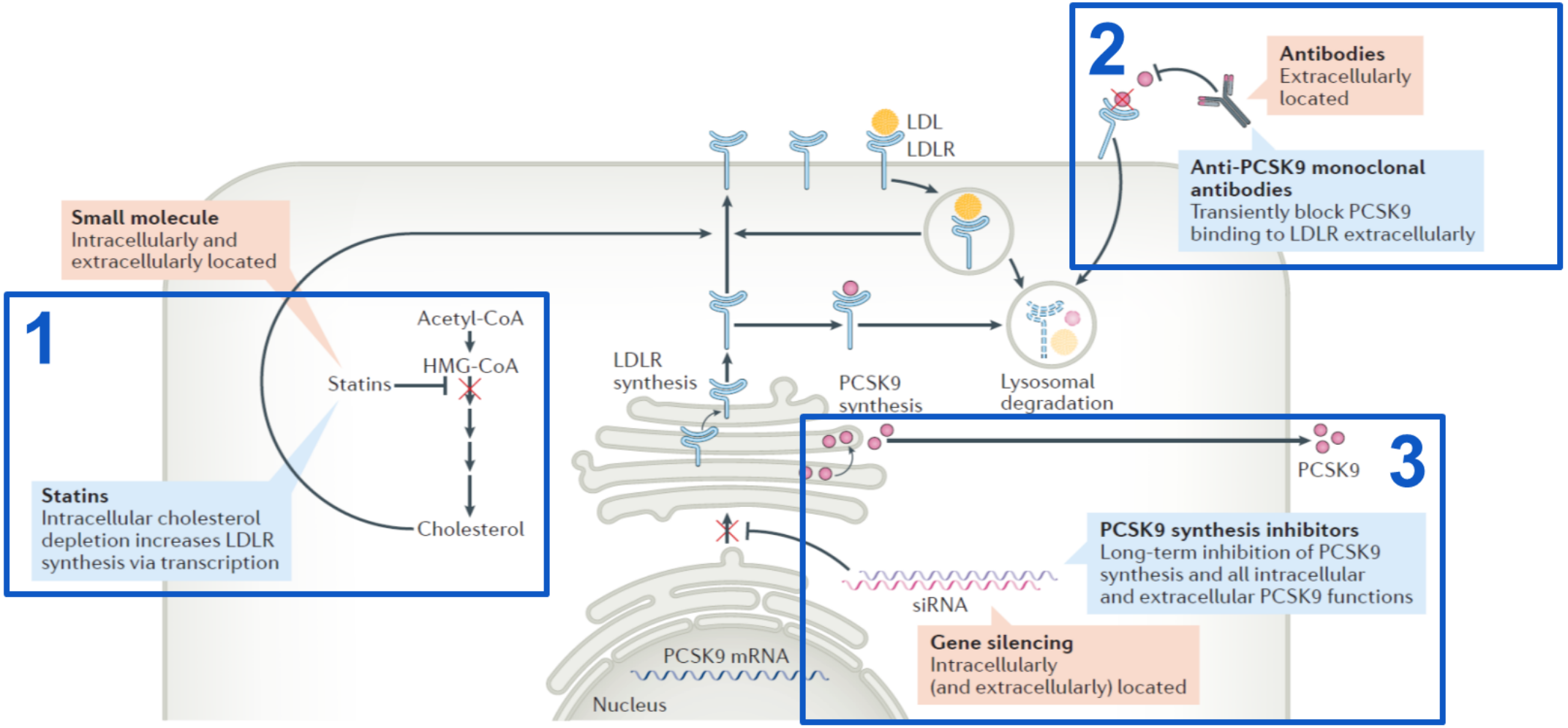
Szarek M et al. *JACC* 2019;73:387



Schwartz GG, et al *NEJM* 2018;379:2097
* Nominal p-value

Novel platforms

From antibodies to RNA-based therapies



Inclisiran – ORION trial programme

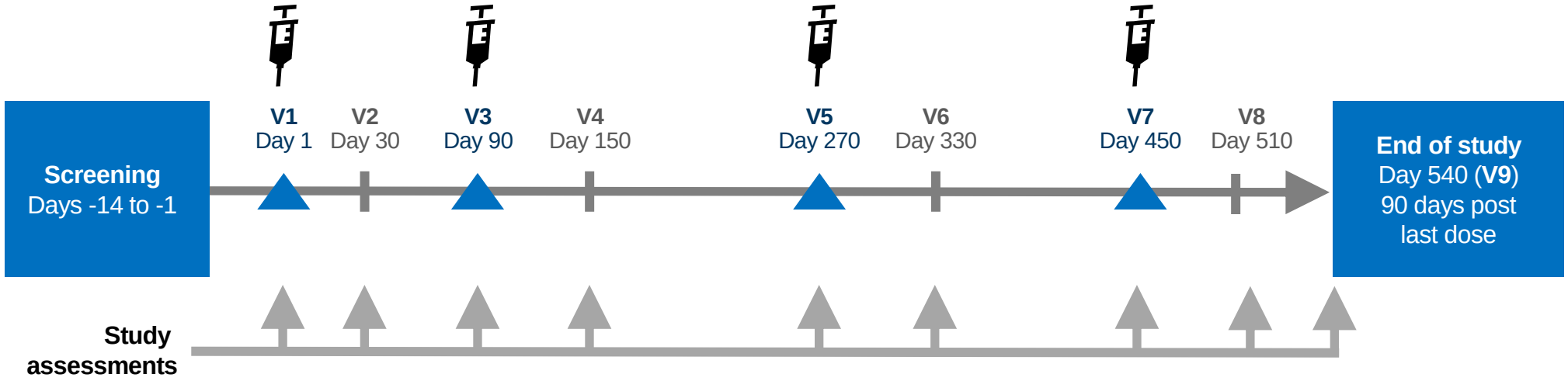
- Inclisiran, a synthetic si RNA molecule, inhibits PCSK9 synthesis in the liver[1]
- In phase I, 300 mg inclisiran lowered LDL-C 50 - 60% for 84 days (n=69)[2]
- Objective of ORION-1: evaluate optimal dosing regimens in patients with elevated LDL-C and high CV risk

1. Fitzgerald et al. Lancet 2014; 383: 60-8
2. Fitzgerald et al. N Engl J Med 2017; 376: 41-51

ORION-9, -10, -11: Study design and assessment schedule

18-month study medication was given to participants on maximally tolerated background statin therapy*[1,2]

Randomized 1:1 to receive 300 mg inclisiran sodium (equivalent to 284 mg inclisiran) or placebo

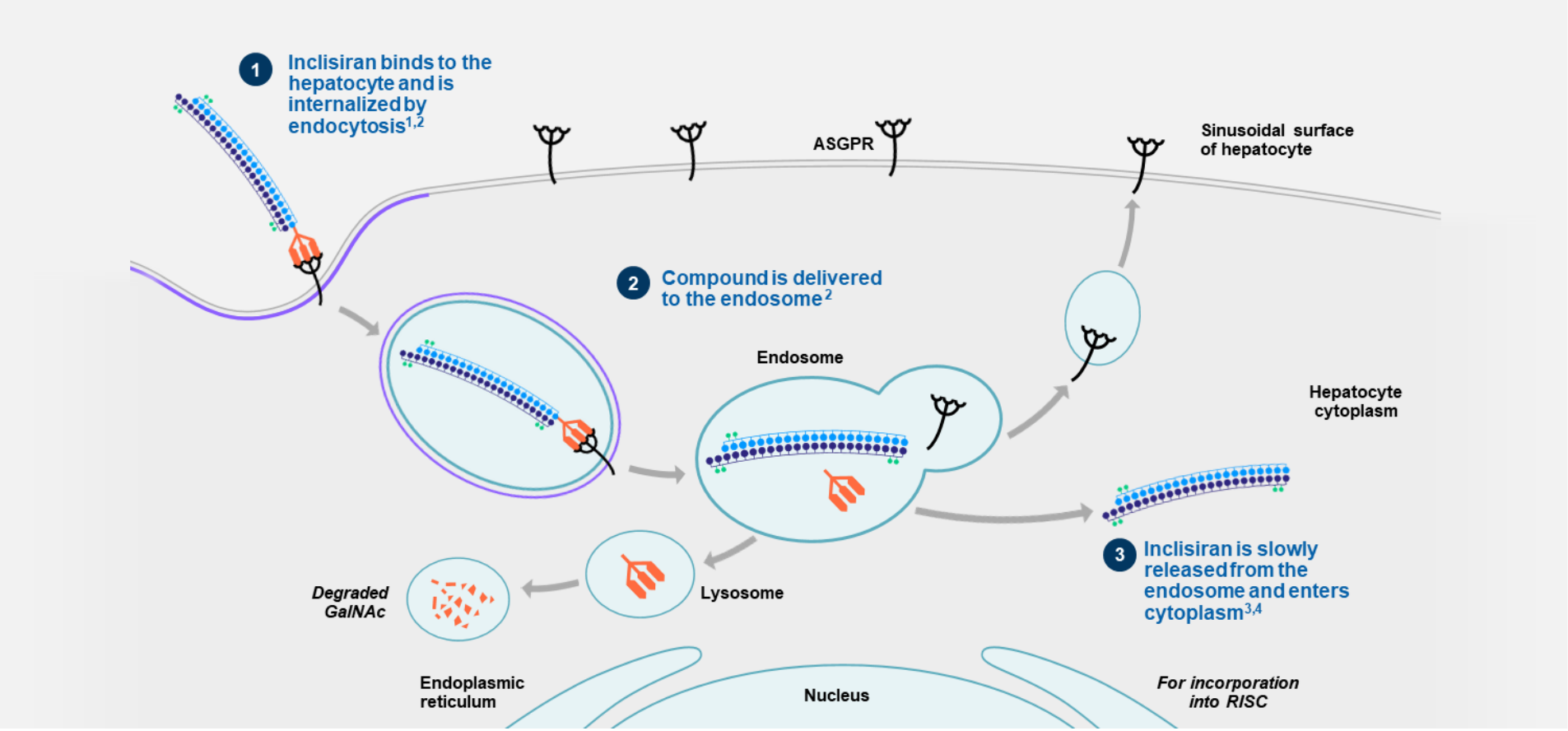


*>90% of patients included were on background statin therapy

1. Raal FJ, et al. *N Engl J Med.* 2020; 382:1520–1530
2. Ray KK, et al. *N Engl J Med*. 2020; 382:1507–1519

GalNAc binds specifcally to liver cells

Using a body endogenous mechanism for protein recycling

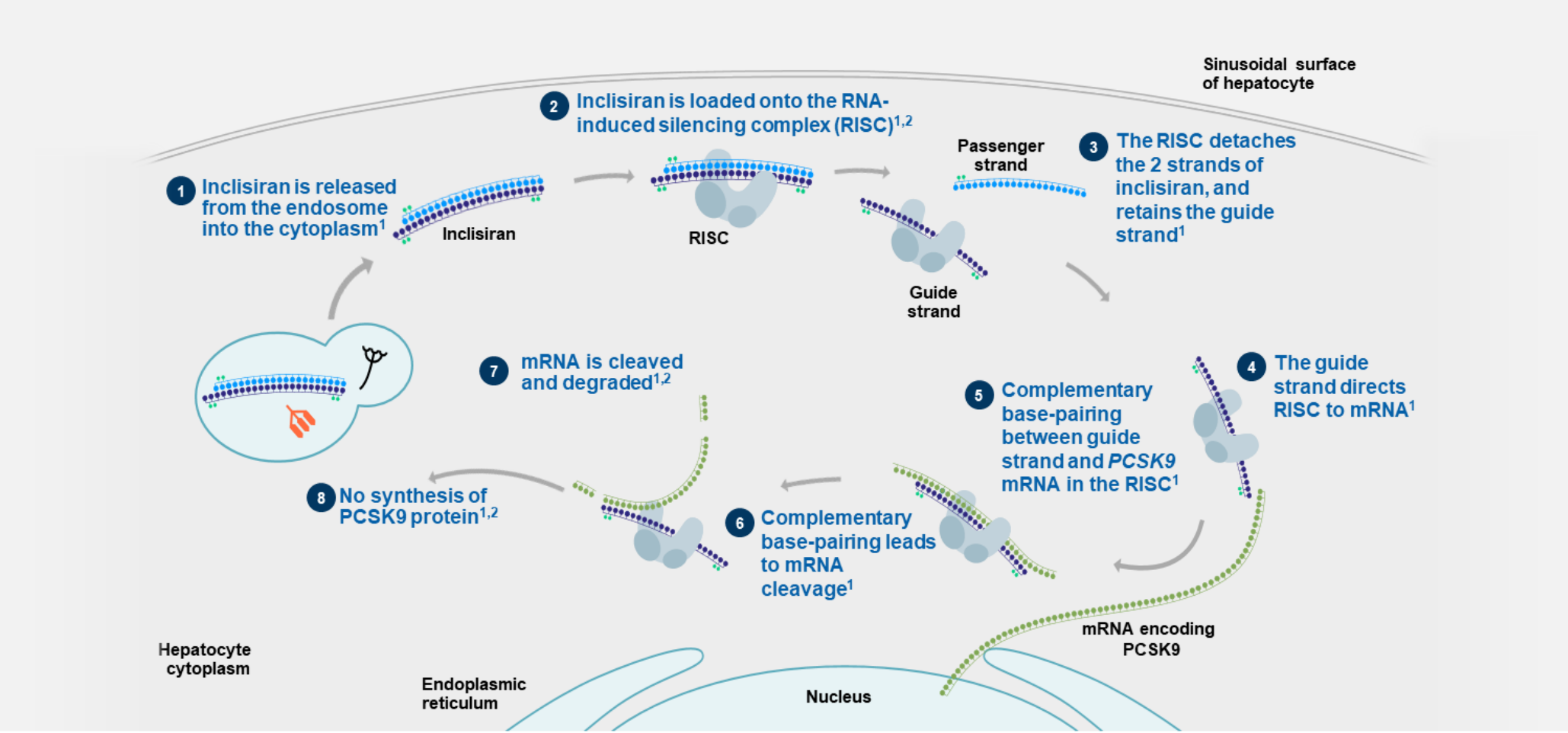


ASGPR = Asialoglycoprotein receptor, RISC = RNA-induced silencing complex, GalNAc = N-Acetylgalactosamine

1. Wang N, et al. *Circ Res*. 2017;120:1063-1065. 2. Springer AD, et al. *Nucleic Acid Ther*. 2018;28:109-118.
3. Khvorova A, et al. *N Engl J Med*. 2017;376:4-7. 4. Tsouka AN, et al. *Curr Pharm Des*. 2018;24:3622-363.

siRNA induces break down of target mRNA

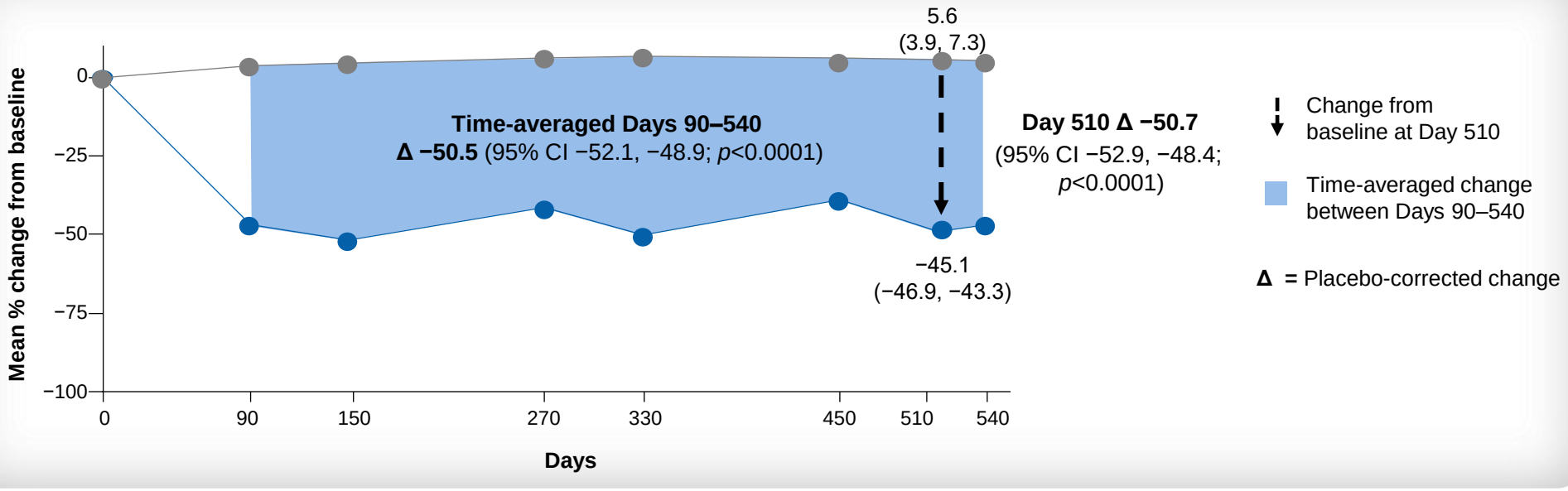
By using the natural RNA interference mechanism



1. Tsouka AN, et al. *Curr Pharm Des*. 2018;24:3622-3633.
2. Khvorova A, et al. *N Engl J Med*. 2017;376:4-7.

Inclisiran achieved a mean >50% reduction in LDL-C levels from baseline

LDL-C percentage change from baseline



No. of patients	Day 0	Day 90	Day 150	Day 270	Day 330	Day 450	Day 510	Day 540
Inclisiran	1833	1788	1792	1755	1741	1726	1646	1679
Placebo	1827	1796	1768	1733	1721	1695	1634	1651

Wright, R.S. et al. *J Am Coll Cardiol*. 2021;77(9):1182-93

Trials with inclisiran

Implications
Inclisiran has moved into Phase III

LDL-C lowering trials underway

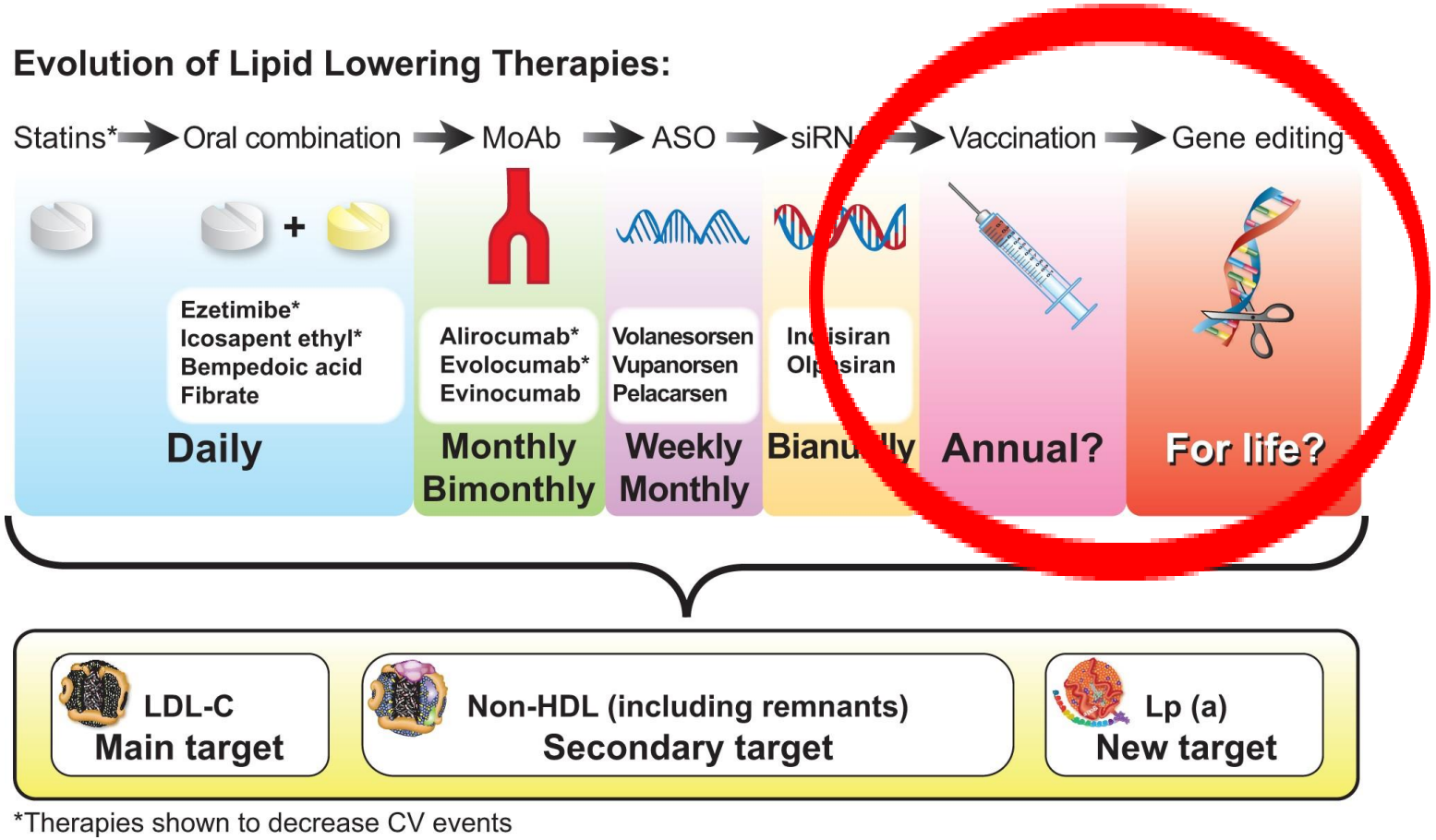
- 3,000 subjects with ASCVD/ risk equivalents (ORION-10, -11)
- 400 subjects with HeFH (ORION-9)
- 60 subjects with HoFH (ORION-5)

Parallel cardiovascular outcomes trial in preparation

- 15,000 subjects with high risk ASCVD (ORION-4)

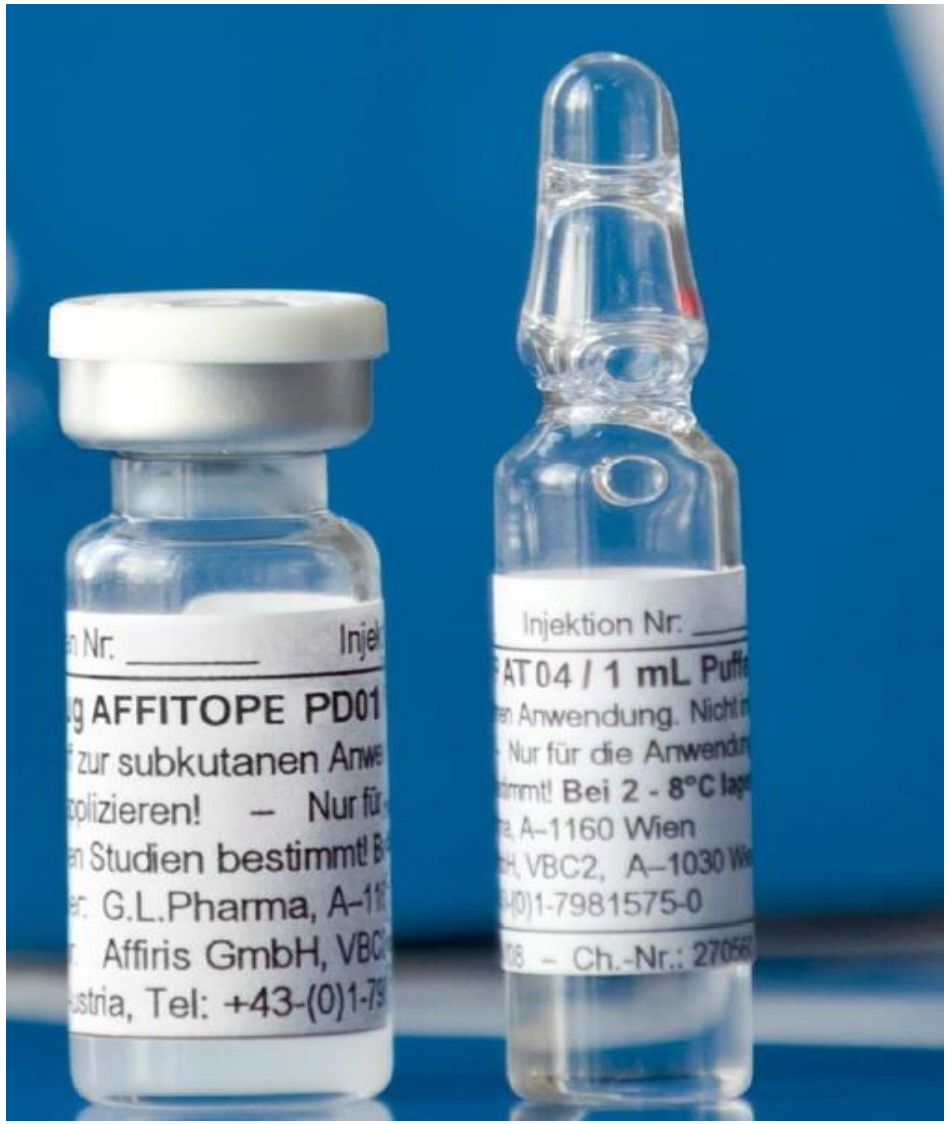
VICTORION-2 PREVENT: A randomized double-blind, placebo controlled, multicenter trial, assessing the impact of inclisiran on major adverse cardiovascular events in participants with established cardiovascular disease

Graphical Abstract The future evolution of lipid-lowering therapies.
The quest for new lipid-lowering therapies enabling less ...



Eur Heart J, Volume 43, Issue 34, 7 September 2022, Pages 3198–3208, https://doi.org/10.1093/eurheartj/ehab841

Bringing vaccines to chronic disease



European Heart Journal (2017) **38**, 2499–250
doi:10.1093/eurheartj/ehx260

BASIC SCIENCE

The AT04A vaccine against proprotein convertase subtilisin/kexin type 9 reduces total cholesterol, vascular inflammation, and atherosclerosis in APOE*3Leiden.CETP mice

Christine Landlinger[1†], Marianne G. Pouwer[2,3†], Claudia Juno[1], José W.A. van der Hoorn[3], Elsbet J. Pieterman[3], J. Wouter Jukema[2], Guenther Staffler[1*], Hans M.G. Princen[3†], and Gergana Galabova[1†]

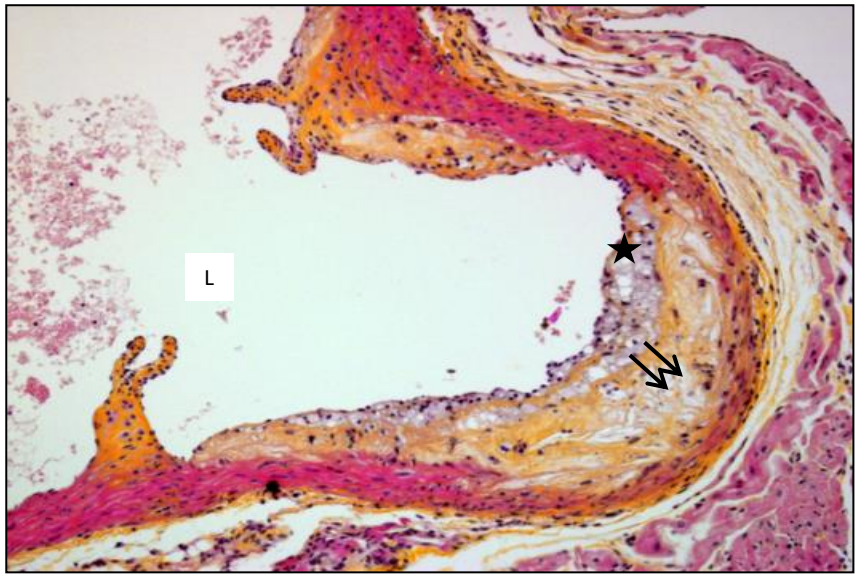
[1]AFFiRiS AG, Karl-Farkas-Gasse 22, Vienna 1030, Austria; [2]Department of Cardiology, LUMC, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; and [3]The Netherlands Organization of Applied Scientific Research (TNO)—Metabolic Health Research, Gaubius Laboratory, Zernikedreef 9, 2333 CK, PO Box 2215, 2301CE, Leiden, The Netherlands

Received 18 October 2016; revised 16 March 2017; editorial decision 27 April 2017; accepted 9 May 2017; online publish-ahead-of-print 19 June 2017

See page 2508 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx302)

Preclinical evidence of atherosclerosis prevention

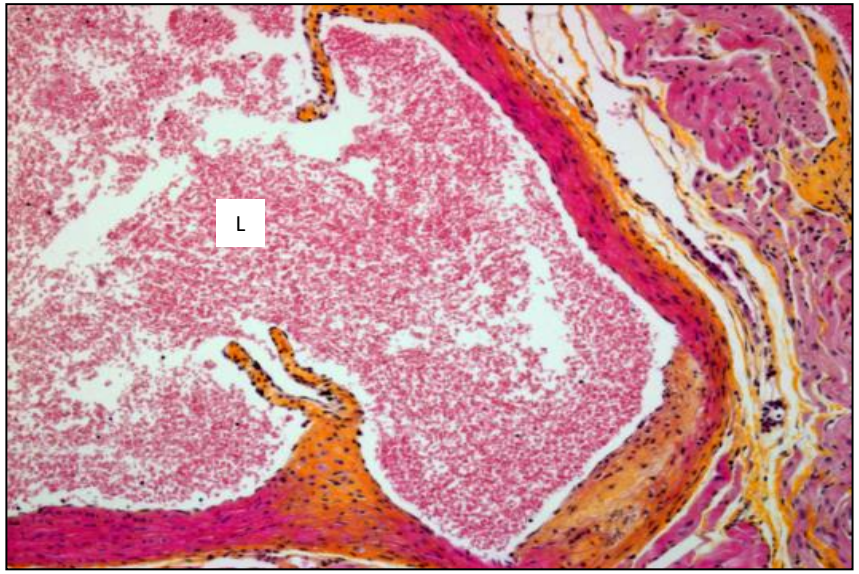
Control



Severe plaque: the media is severely damaged, elastic lamina are broken. Often visible: cholesterol clefts/crystals, mineralization (calcium) and necrosis.

Lesions severity

AT04A



L – Aortic Lumen

↘ Cholesterol clefts

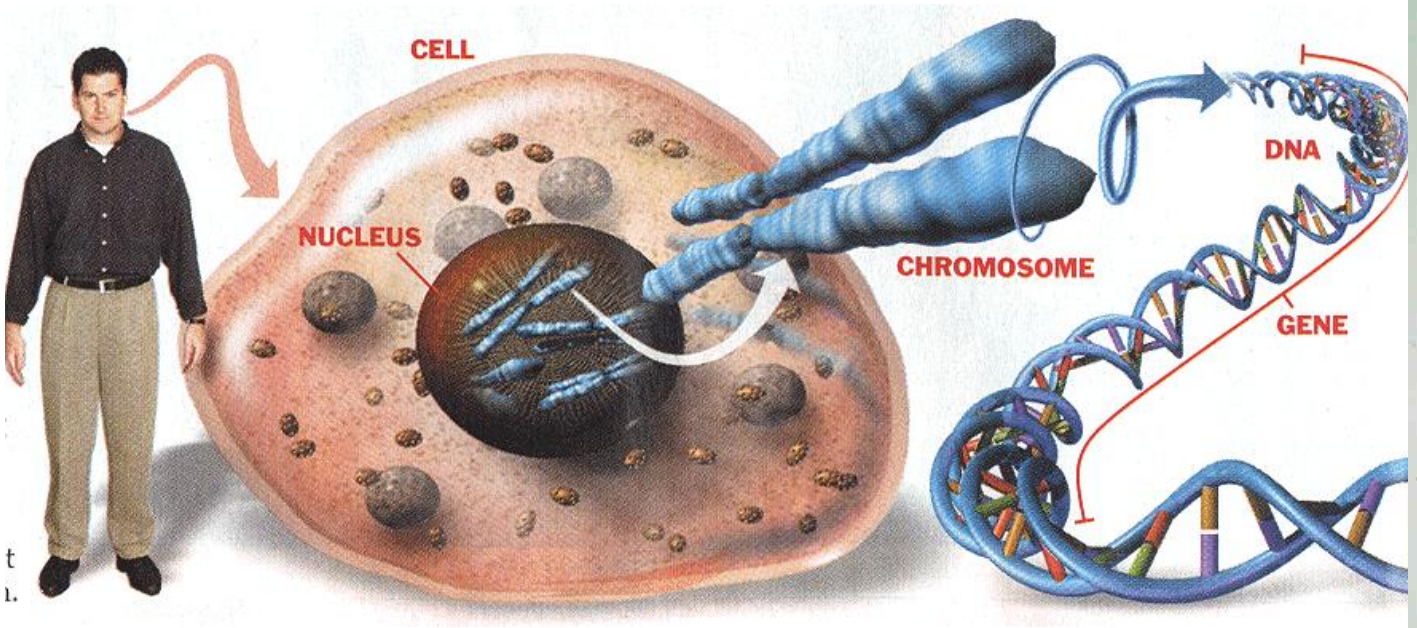
★ Foam Cells

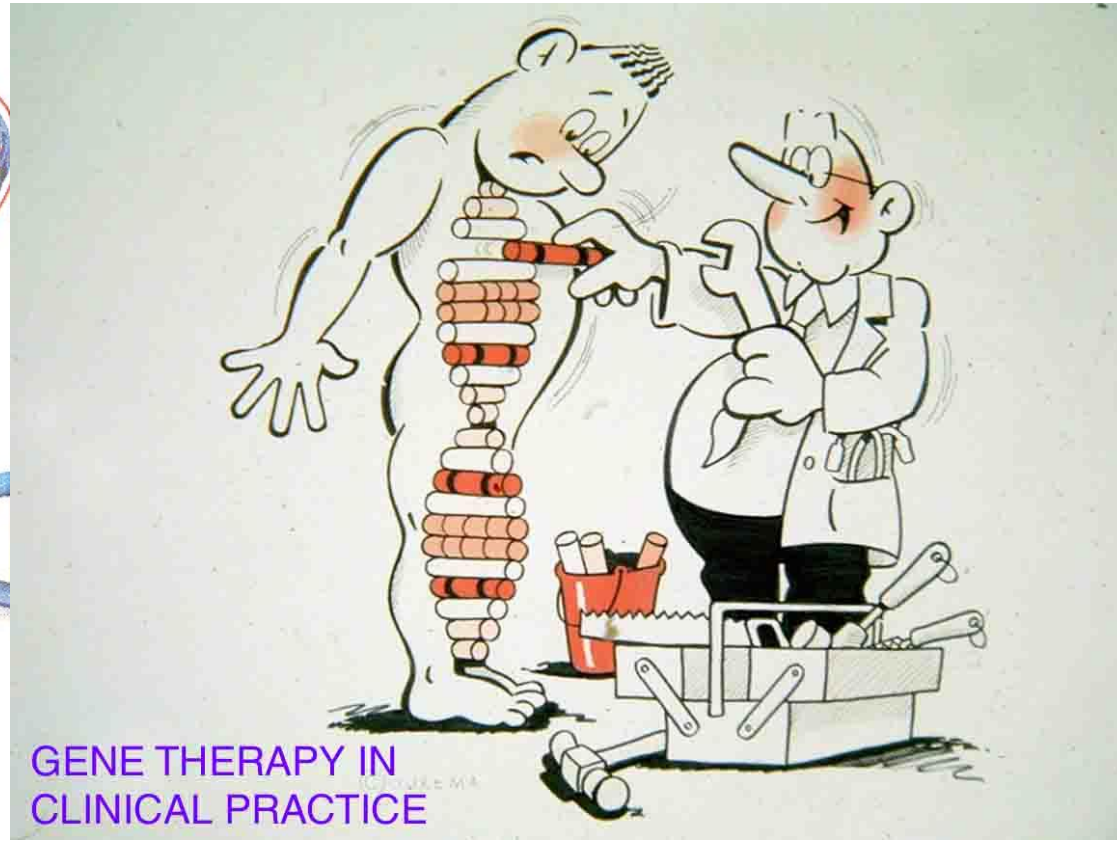
..... Dotted lines mark the boundaries between the plaques and normal tissue

n=15

Gene-editing therapy: Verve 101

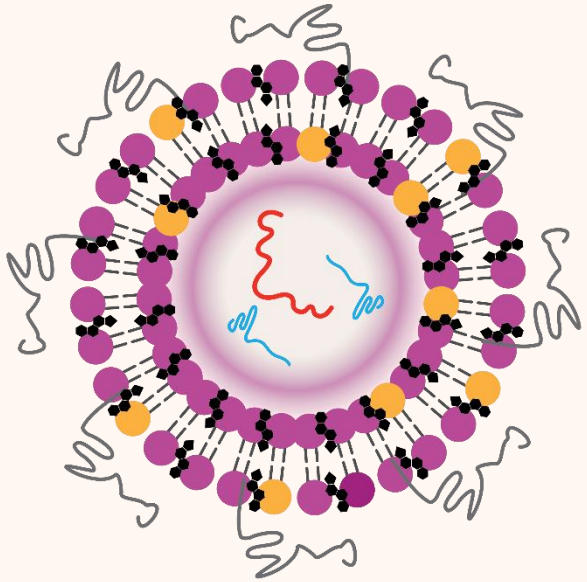
single-course treatments designed to permanently turn off the *PCSK9* gene in the liver to reduce disease-driving LDL-C.





VERVE-101: novel CRISPR base editing medicine

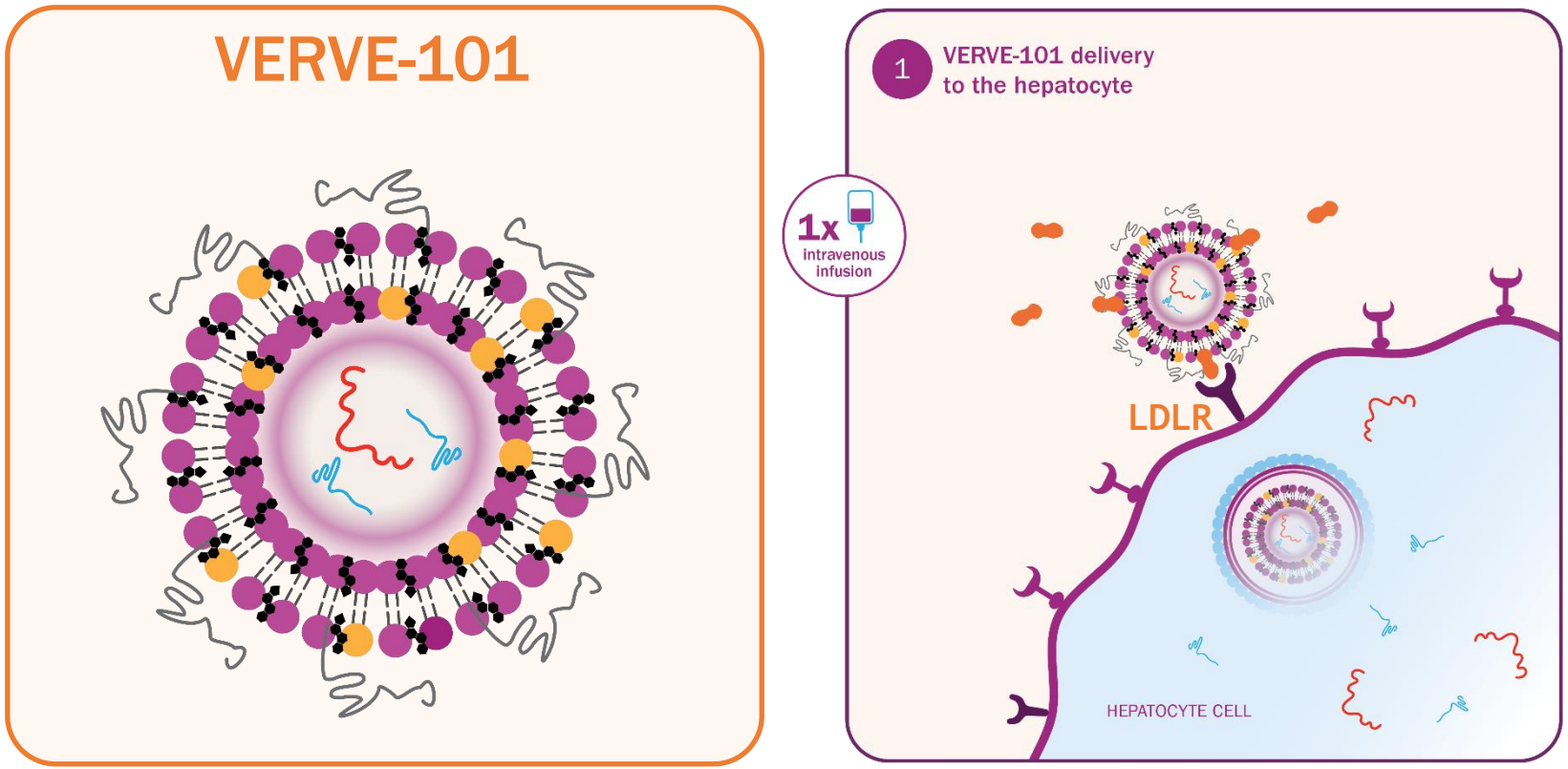
VERVE-101



Lipid nanoparticle
Ionizable amino lipid
DSPC
LDL receptor (LDLR)
apoE
mRNA
gRNA
PEG Lipid
Cholesterol

DSPC, distearoyl-sn-glycerol-3-phosphocholine; gRNA, guide RNA; LNP, lipid nanoparticle; mRNA, messenger RNA; RNA, ribonucleic acid

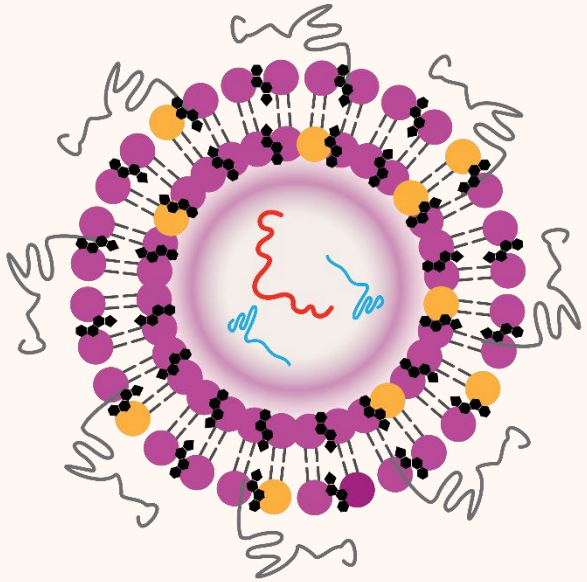
VERVE-101: novel CRISPR base editing



DSPC, distearoyl-sn-glycerol-3-phosphocholine; gRNA, guide RNA; LNP, lipid nanoparticle; mRNA, messenger RNA; RNA, ribonucleic acid

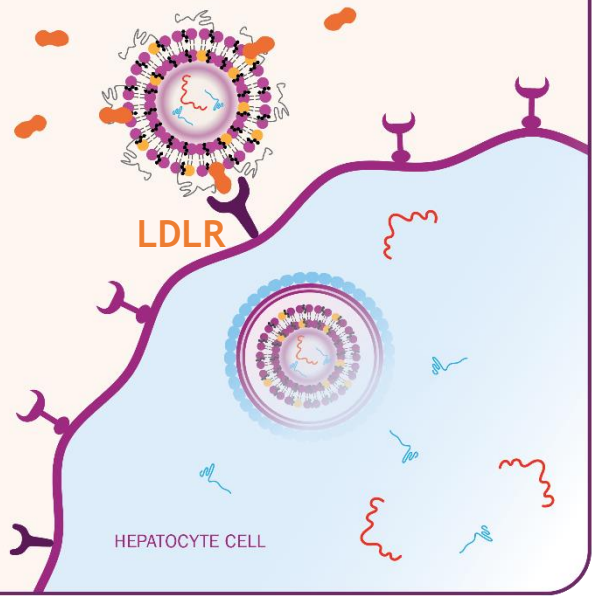
VERVE-101: novel CRISPR base editing

VERVE-101



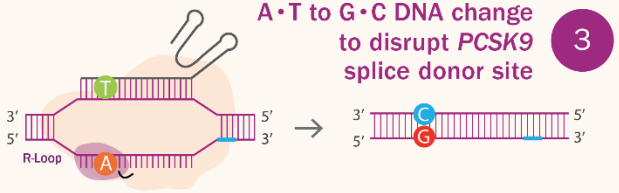
1 VERVE-101 delivery to the hepatocyte

1x intravenous infusion

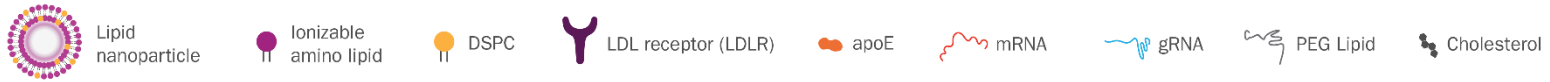


2 Localization to *PCSK9* gene

A•T to G•C DNA change to disrupt *PCSK9* splice donor site 3

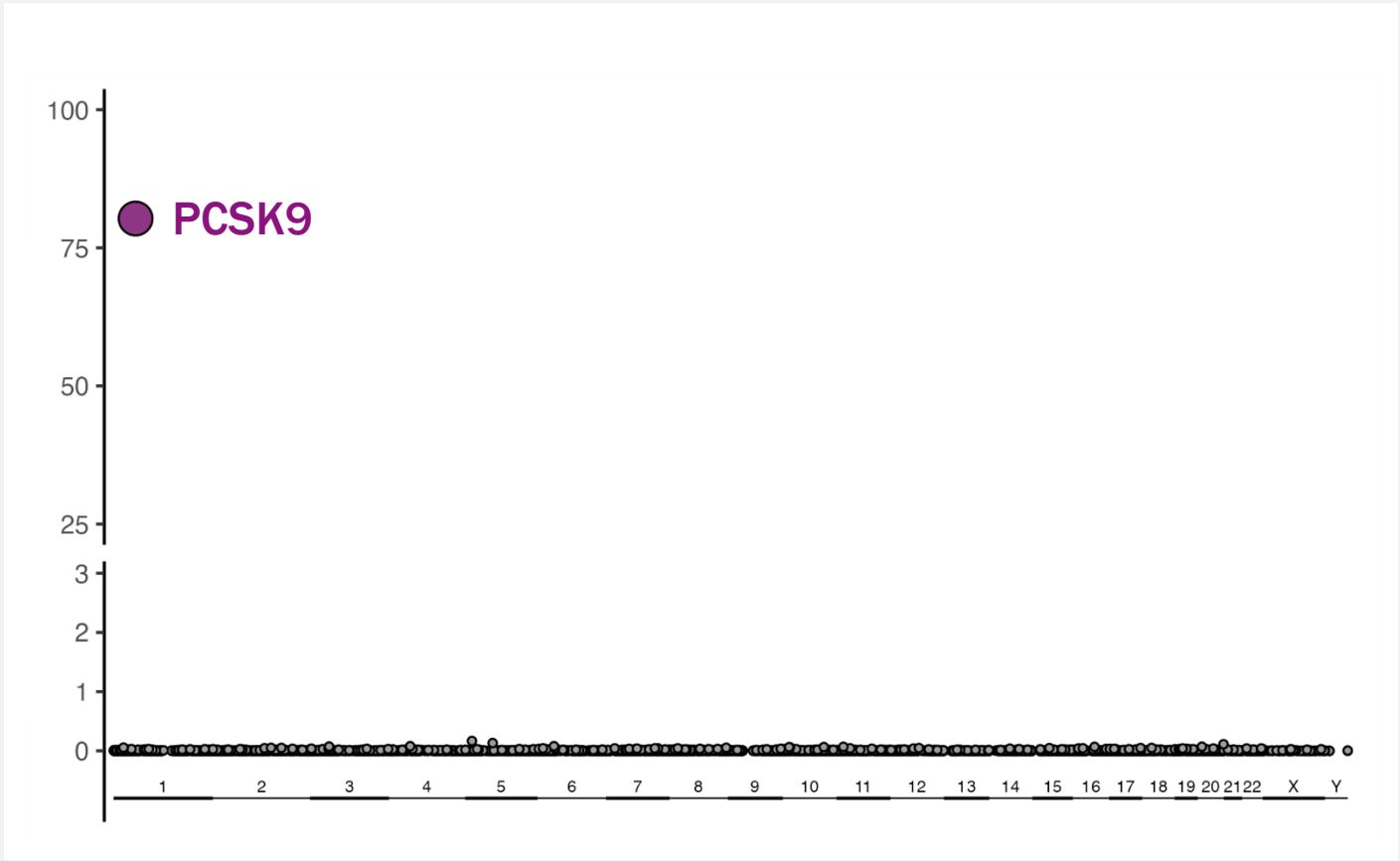


A to G "spelling" change in DNA to turn off gene



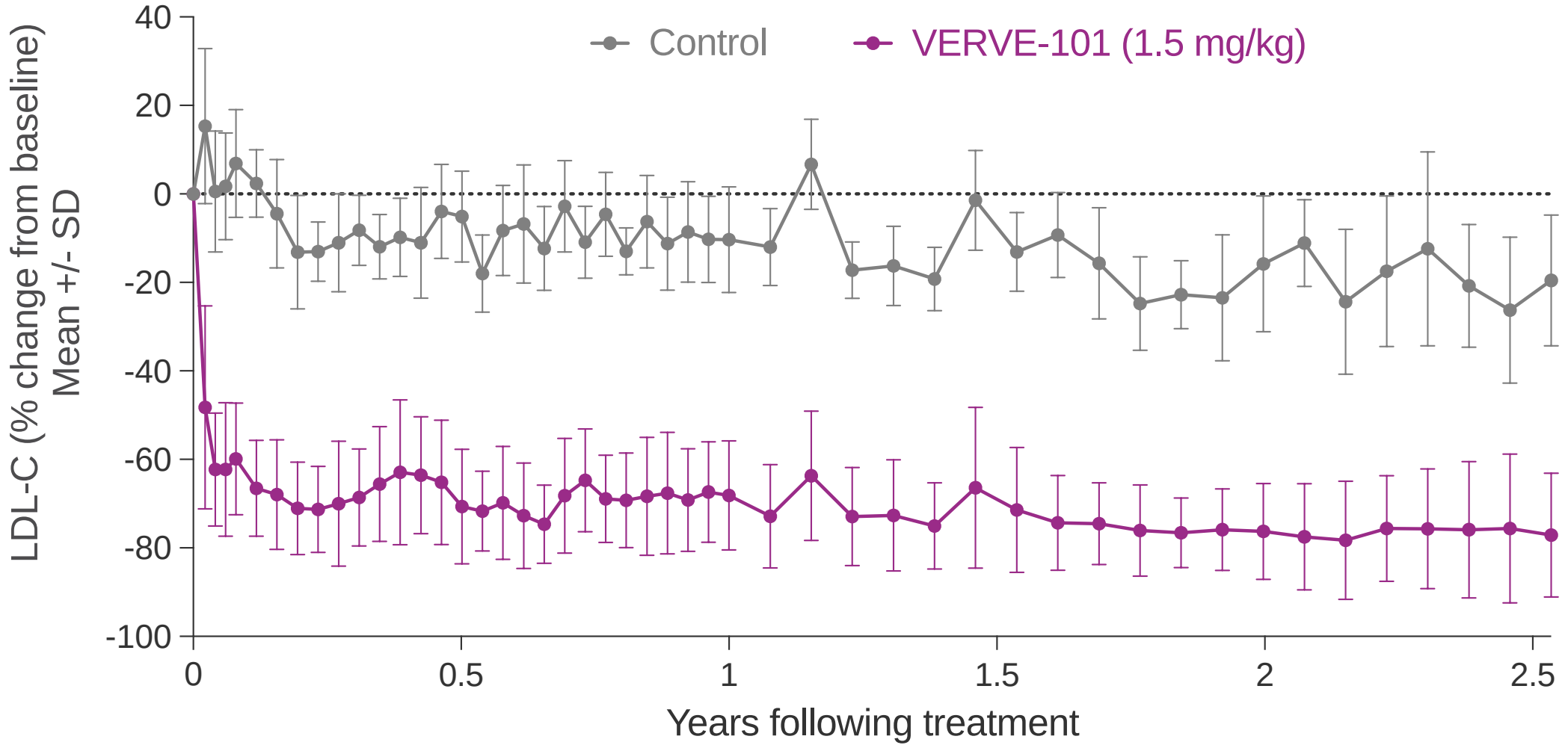
DSPC, distearoyl-sn-glycerol-3-phosphocholine; gRNA, guide RNA; LNP, lipid nanoparticle; mRNA, messenger RNA; RNA, ribonucleic acid

In human liver cells treated with VERVE-101, no evidence for off-target editing



- Donor primary human hepatocytes treated with saturating dose of VERVE-101 LNPs
- ‘Manhattan-style’ plot of ~6000 candidate sites
- No candidate sites show statistically significant net editing

In non-human primates, blood LDL-C observed to be durably lowered for 2.5 years following single infusion of VERVE-101



Data represents mean +/- SD for cohorts which included N=10 in control and N=22 in VERVE-101 at the earliest time points and N=7 and N=16, respectively, at the last time point.

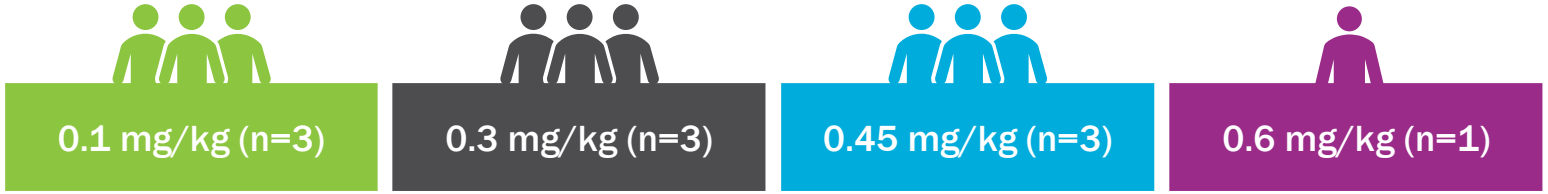
heart-1 is a first-in-human phase 1b trial designed to evaluate the safety and tolerability of VERVE-101

heart-1

First-in-human, open-label, single ascending dose study in patients with HeFH and high risk for cardiovascular events

Interim update:
10 participants treated across 4 dose cohorts[5]

Data cut-off date October 16, 2023



STUDY POPULATION SUMMARY

- Males and females[1] (age 18 to 75)
- HeFH
- Established ASCVD
- Uncontrolled hypercholesterolemia[2]
- On maximally-tolerated oral lipid-lowering therapy[3]

DRUG ADMINISTRATION

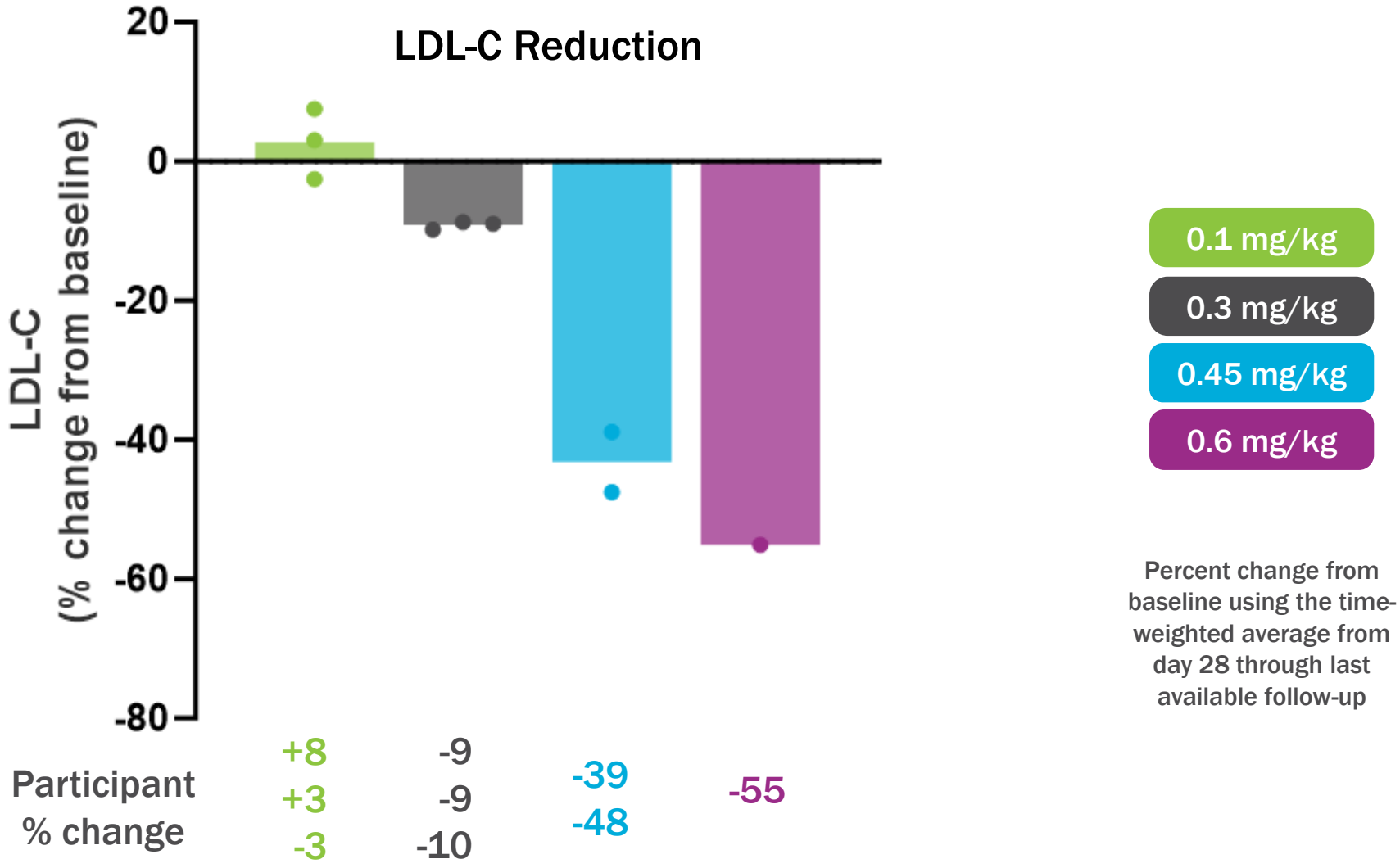
- Pre-medication with dexamethasone and antihistamines
- VERVE-101 delivered as single infusion via a peripheral intravenous[4]

TRIAL ENDPOINTS

- Primary: Safety and tolerability
- Additional endpoints:
  - Pharmacokinetics of VERVE-101
  - Blood PCSK9 and LDL-C, quantified as percent change from baseline, time averaged from day 28 onward
- Study duration 1 year with long-term follow-up required by FDA for another 14 years

Clinical trial registration: NCT05398029; 1. Women of childbearing potential are excluded from the study; 2. LDL-C threshold for inclusion value varies by country-specific protocol; 3. maximum tolerated statin and/or ezetimibe (statin intolerant allowed). 4. dosing based on weight for participants ≤ 100 kg; participants > 100 kg are dosed on an assumed 100 kg weight; 5. 10 participants included in the safety analysis, but only 9 participants included in the pharmacodynamic analyses as the 10th participant had not reached the 28-day follow-up as of the data cut-off date. Single participant dosed at 0.6 mg/kg prior to initiation of 0.45 mg/kg cohort.

Reductions in blood LDL-C of 39%, 48% and 55% observed in the two higher dose cohorts following VERVE-101 administration



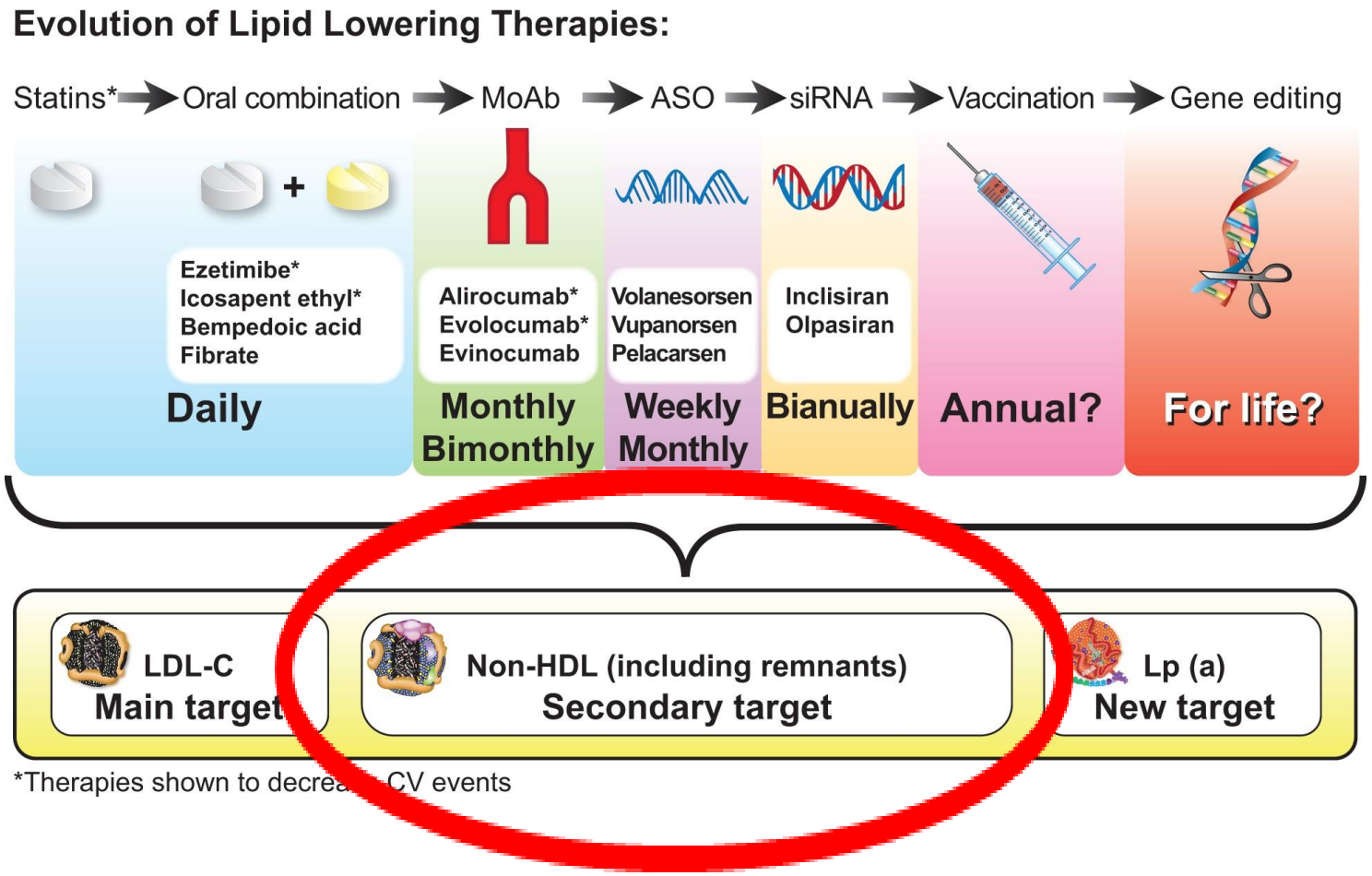
As of October 16, 2023. Data are from an ongoing study with an open database and have not been fully cleaned
Day 28 value was used for time-weighted average in participants where day 28 was latest timepoint. One participant who has not reached day 28 excluded from analysis. Observations in 2 participants in 0.1 mg/kg cohort censored from analysis after changes in lipid lowering treatment (both >90 days after VERVE-101 infusion).

Gene-editing therapy: Verve 101

Single-course treatments designed to permanently turn off the *PCSK9* gene in the liver to reduce disease-driving LDL-C.

- VERVE-101 was well-tolerated in the two lower dose cohorts, with no treatment-related adverse events observed.
- In the two higher dose cohorts, treatment-related adverse events were observed, including transient, mild or moderate infusion reactions and transient, asymptomatic increases in liver transaminases with mean bilirubin levels below the upper limit of normal.
- Two patients experienced serious adverse events, which were each cardiovascular events in the context of severe underlying ASCVD.
- All safety events were reviewed with the independent data and safety monitoring board who recommended continuation of study enrollment with no protocol changes required.

Graphical Abstract The future evolution of lipid-lowering therapies.
The quest for new lipid-lowering therapies enabling less ...



Eur Heart J, Volume 43, Issue 34, 7 September 2022, Pages 3198–3208, https://doi.org/10.1093/eurheartj/ehab841

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD,

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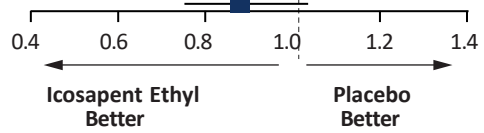
Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD,

Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, Christie M. Ballantyne, MD, on Behalf of the REDUCE-IT Investigators

REDUCE-IT: Pre-specified hierarchical testing of endpoints

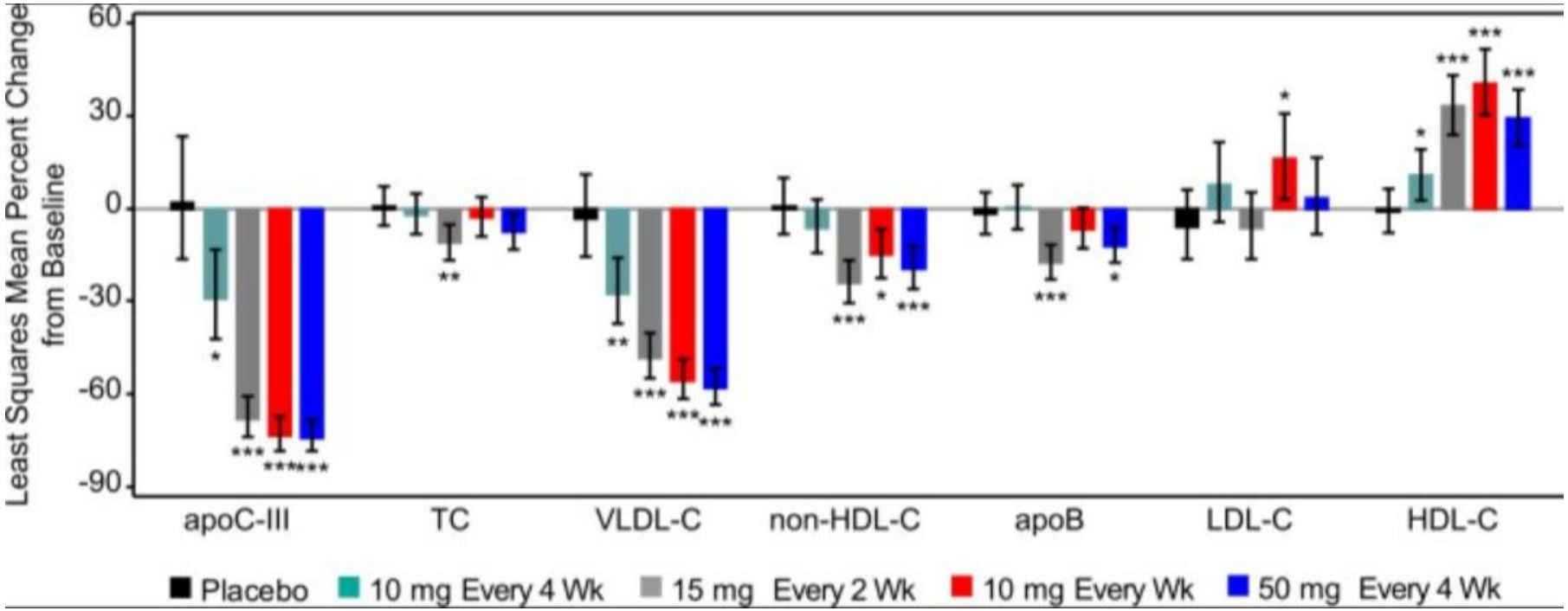
Endpoint	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	RRR	*P*-Value
	No. of Patients With Event (%)				
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	25%	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	26%	<0.001
Cardiovascular death or non-fatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	25%	<0.001
Fatal or non-fatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	31%	<0.001
Urgent or emergency revascularisation	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	35%	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	20%	0.03
Hospitalisation for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	32%	0.002
Fatal or non-fatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	28%	0.01
Death from any cause, non-fatal myocardial infarction or non-fatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	23%	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	13%	—



The rates of all end points up to death from any cause were significantly lower in the icosapent ethyl group than in the placebo group.

Bhatt DL, et al. *N Engl J Med*. 2019;380(1).

- Olezarsen (Apo CIII inhibitor – antisense nucleotide) significantly reduced apoC-III, triglycerides, and atherogenic lipoproteins
- in patients with moderate hypertriglyceridaemia and at high risk for or with established cardiovascular disease.



Tardif J-C et al. Eur Heart J . 2022 Apr 6;43:1401-1412.

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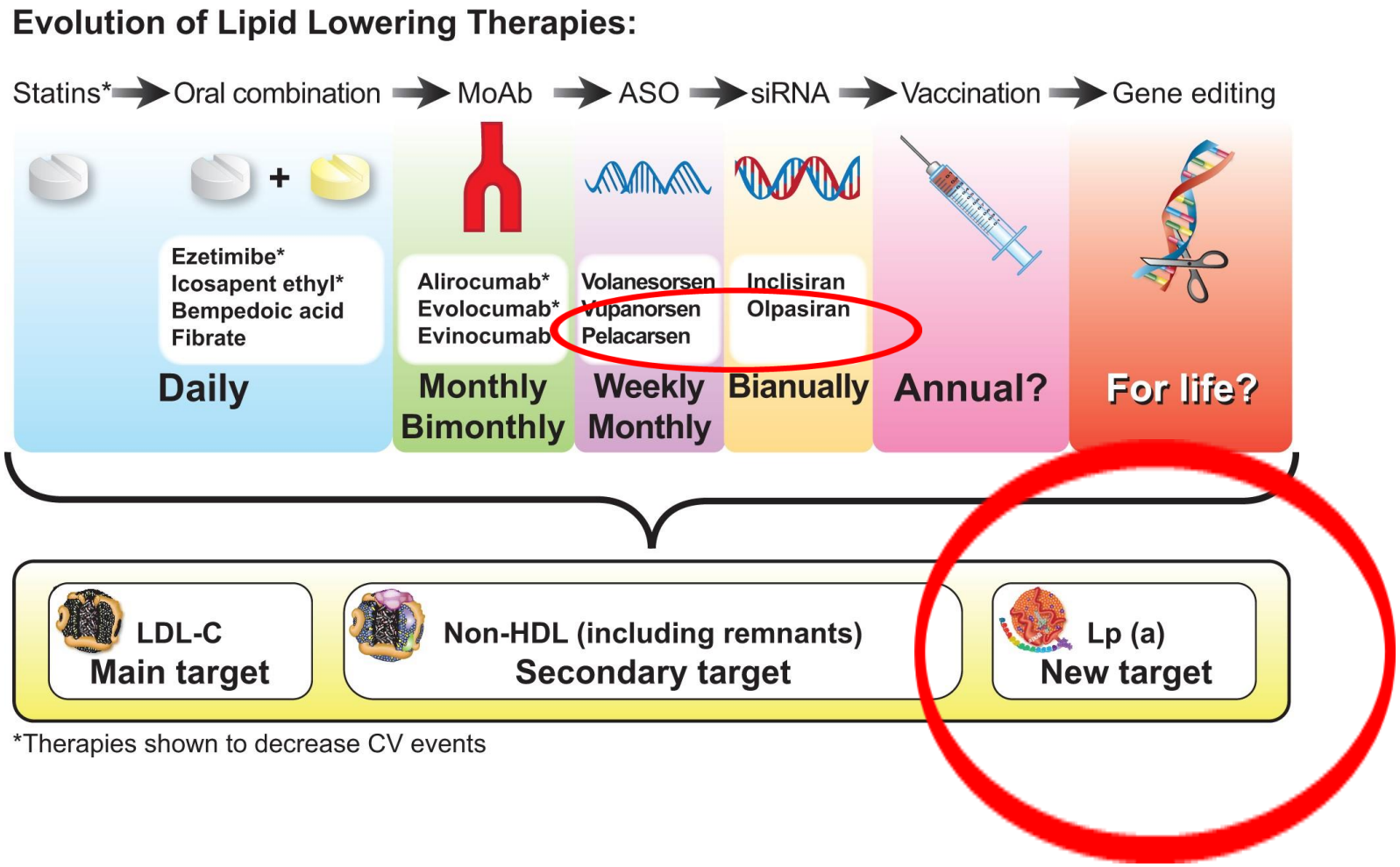

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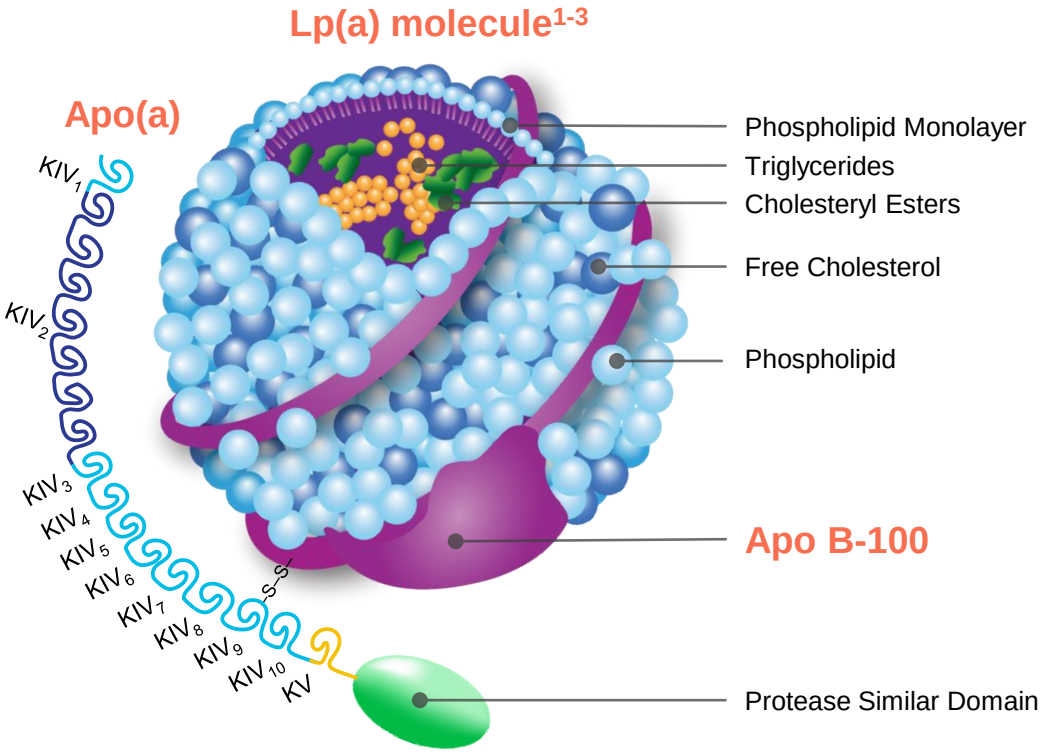
Lp(a) is Atherogenic, Prothrombotic and Proinflammatory[1,2]



- Lp(a) is produced in the liver and has two main components joined by a covalent disulfide bond[1,2]
  - A lipid core moiety that is an LDL-like particle containing apolipoprotein B-100, which is proatherosclerotic[1,2]

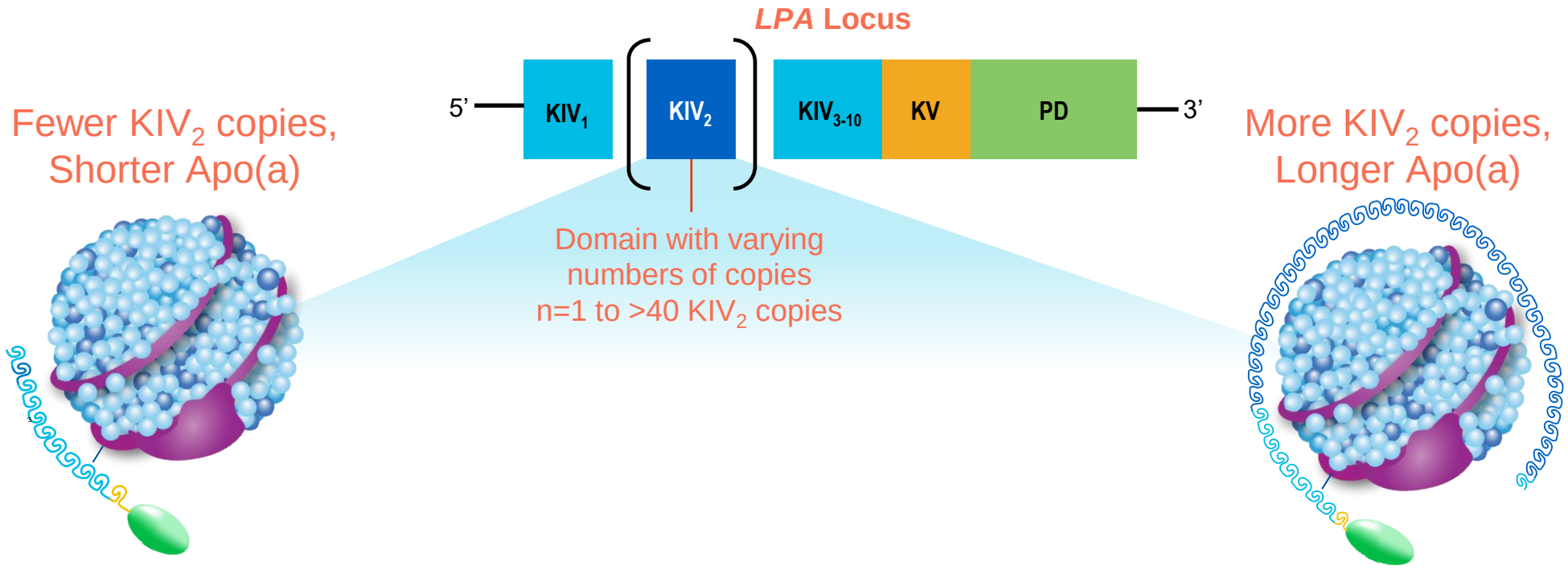
    and
  - A single molecule of apolipoprotein(a)[1-3]

Lp(a) differs from LDL in that Lp(a) contains a molecule of apo(a)[1,2]

Apo, apoprotein; KI, kringle type I; KII, kringle type II; KIII, kringle type III; KIV, kringle type IV; KV, kringle type V; Lp(a), lipoprotein (a).

1. Cai A, et al. *Dis Markers*. 2013;35(5):551-559. 2. Tsimikas S. *J Am Coll Cardiol*. 2017;69:692-711. 3. Jawi MM, et al. *J Lipids*.2020:1-26. doi.org /10.1155/2020/3491764.

Lp(a) Isoform Varies by Length of Apo(a)[1,2]

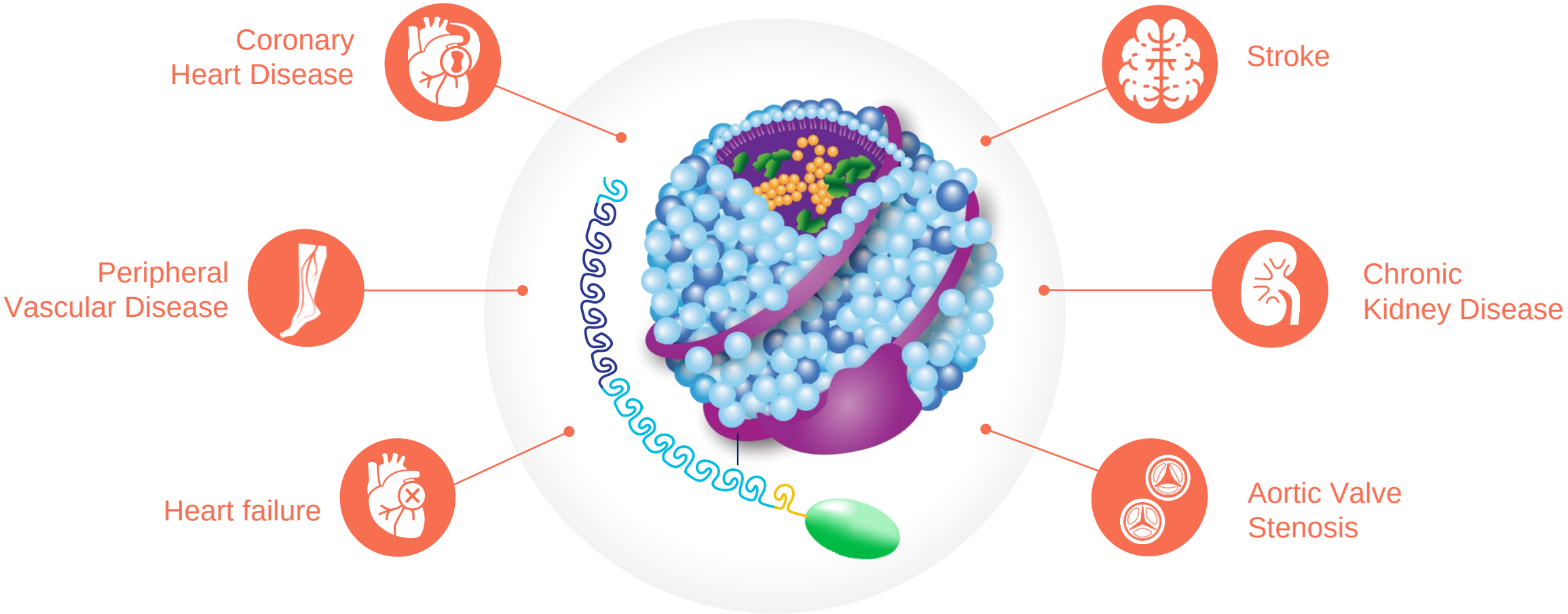


Lp(a) isoforms vary by length of Apo(a),
which is genetically determined by number of KIV_2 repeats[1]

Apo(a), apolipoprotein(a); IV-1, IV-2… kringle 4 types; K, kringle; Lp(a), lipoprotein(a), PD, protease domain.

1. Schmidt K, et al. *J Lipid Res*. 2016;56:1339-1359. 2. Paré G, et al. *Circulation*. 2019;139:1472-1482.

Elevated Lp(a) is Associated with Various Disease States



Disease associations were determined using logistic regression data from UK Biobank, adjusted for age, sex, and 10 other key components, with the exception of chronic kidney disease, which was determined using statistics from CKDGen.

Lp(a), lipoprotein(a).

Emdin CA, et al. *J Am Coll Cardiol*. 2016;68:2761-2772.

Emerging Specific Lp(a)-Lowering Therapies Targeting Lp(a) Production

Pelacarsen:

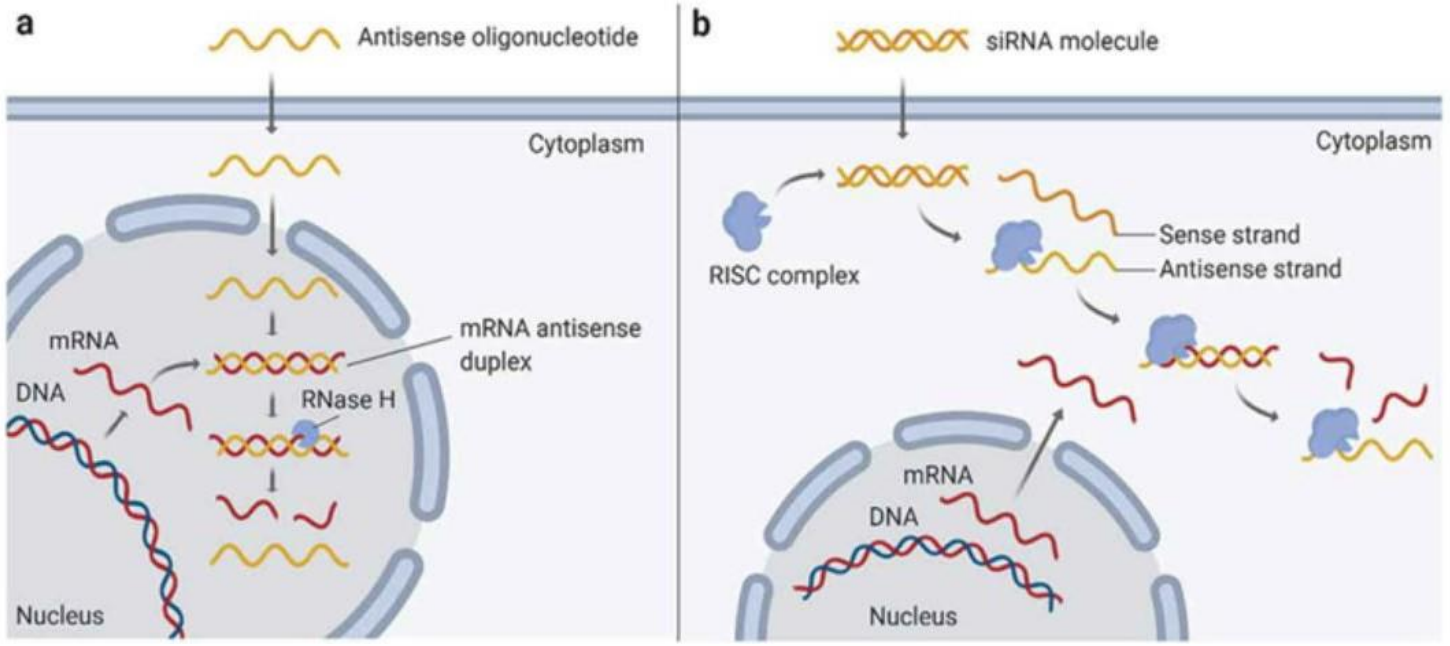
- Antisense oligonucleotide therapy (ASO): monthly dosing
- Outcome results from phase 3 are expected in 2025

Olpasiran

- siRNA technology: longer acting
- Dose finding study finished

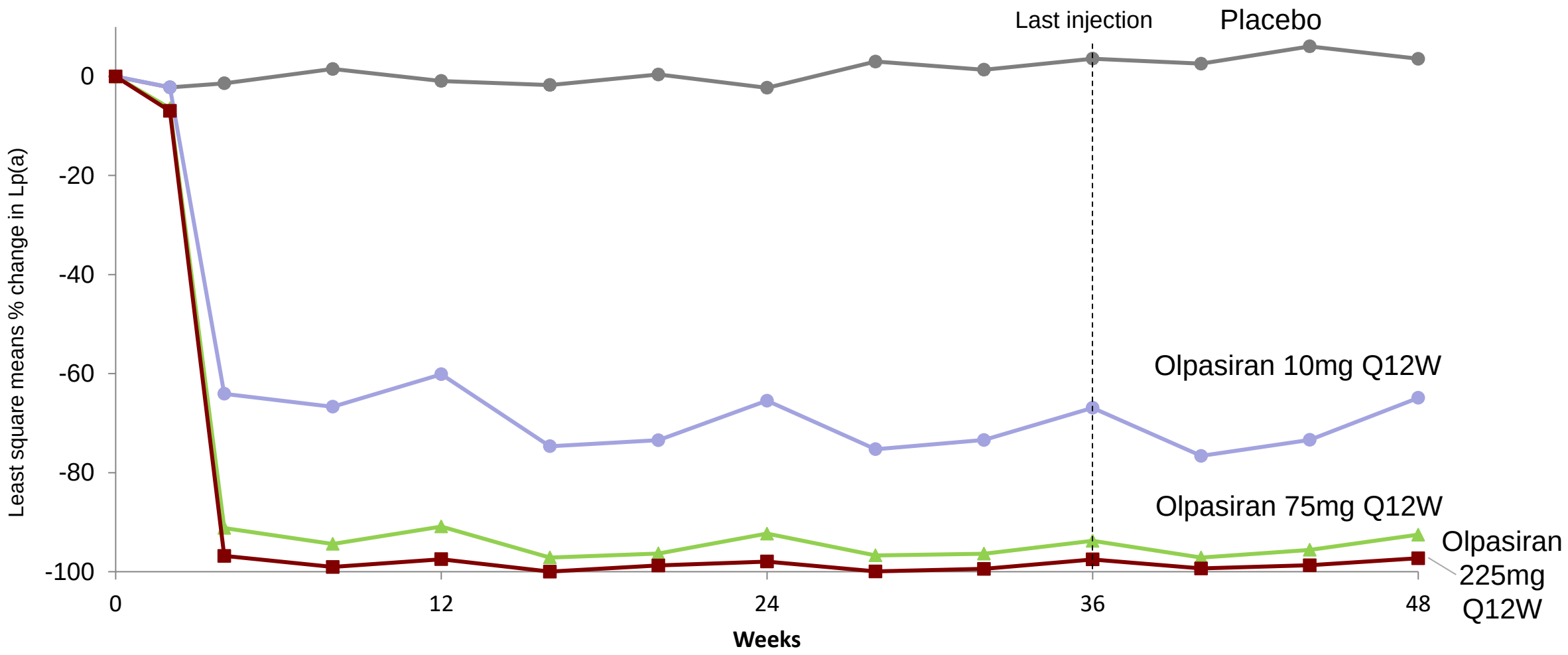
SLN360

- siRNA technology: longer acting
- Phase 1 finished



Tromp TR, et al. *Expert Opin Investig Drugs*. 2020; 29:483-93, Kronenberg F, et al. *Eu Heart J*. 2022; 43:3925-46

Changes in Lp(a) Through Follow-Up

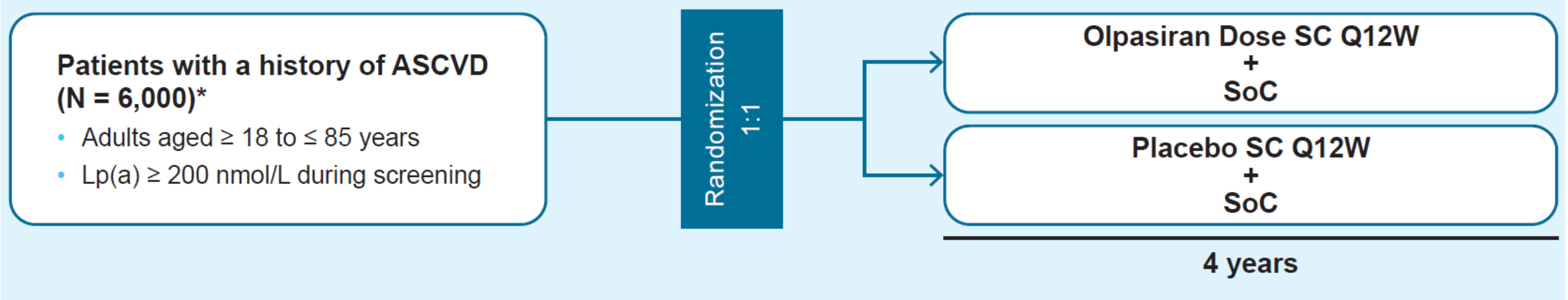


O'Donoghue ML, et al. Presentation at American Heart Association Scientific Sessions 2022; November 5-7 2022, Chicago, IL, O'Donogue ML, et al. New Eng J Med. 2022;387:1855-64.

OCEAN(a)-Outcomes Trial: Olpasiran Trials of Cardiovascular Events And LipoproteiN(a) Reduction – Outcomes Trial

A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Assessing the Impact of Olpasiran on Major CV Events in Participants With ASCVD and Elevated Lp(a)

Phase 3 Study Design:

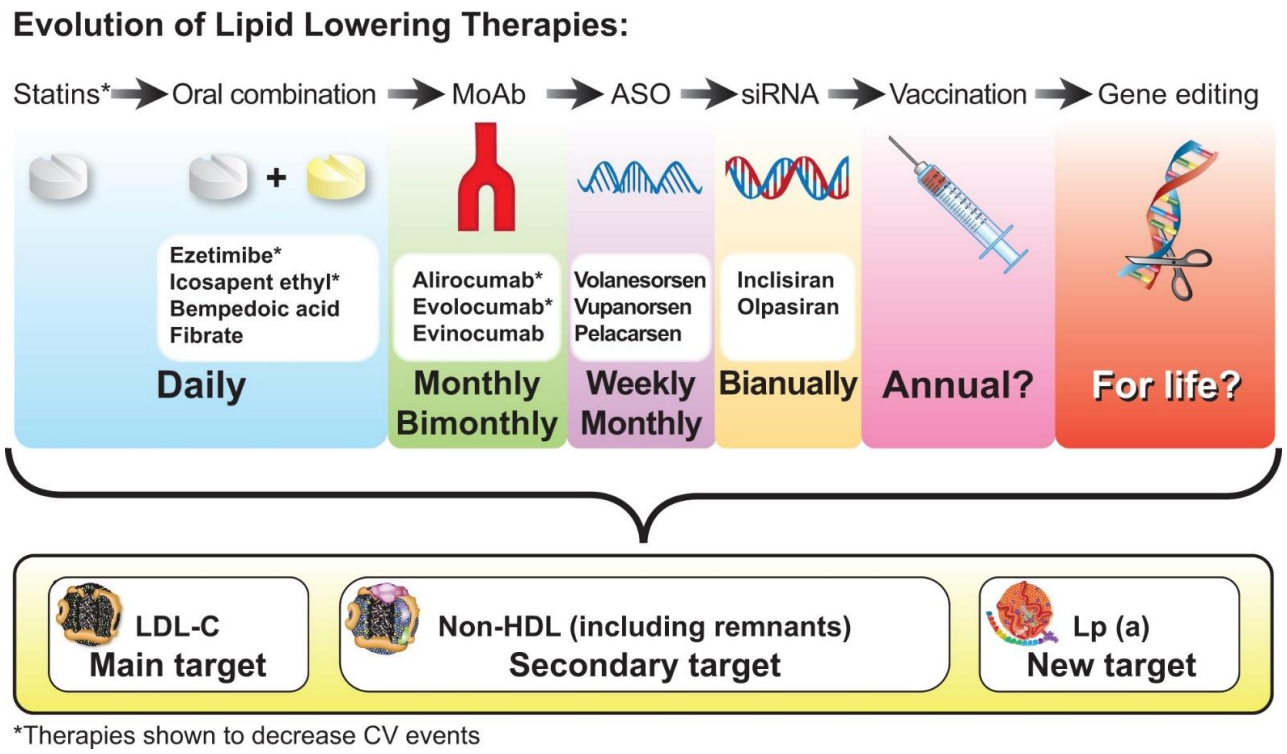


STUDY PURPOSE: To compare the effect of treatment with olpasiran to that of placebo on the risk of CHD death, MI, or urgent coronary revascularization inparticipants with ASCVD and elevated Lp(a)

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; Lp(a), lipoprotein(a); MI, myocardial infarction; Q12W, every 12 weeks; SC, subcutaneous; SoC, standard of care

https://www.clinicaltrials.gov/ct2/show/NCT05581303?term=olpasiran&draw=2&rank=4

The future evolution of lipid-lowering therapies.
The quest for new lipid-lowering therapies …



They are on the road!!