Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

PCSK9 Inhibitors

Evidence Summary

PCSK9 inhibition offers cardiovascular benefit through the lowering of LDL-C. PCSK9 inhibitors are generally well-tolerated and can be safely used with other lipid-lowering therapies.

Neuroprotective Benefit: Most gene association studies for PCSK9 and clinical experience with PCSK9 inhibitors to date indicate that PCSK9 inhibition has a neutral effect on cognitive outcomes.

Aging and related health concerns: PCSK9 inhibition reduces LDL-C levels and protects against adverse cardiovascular outcomes. Inhibitors may also have utility as an adjunct to cancer immunotherapy.

Safety: PCSK9 inhibitors are generally well-tolerated, with injection site reactions as the most common adverse event, and muscle pain has also been reported. They can be safely used with statins and other lipid-lowering medications.

Availability: Rx (alirocumab, evolocumab, inclisiran); next generation inhibitors, including oral formulations, are in clinical trials	**Dose**: All currently FDA approved PCSK9 inhibitors are administered via subcutaneous injection. The recommended doses described below are for patients with atherosclerotic cardiovascular disease/ hyperlipidemia. Alirocumab: the recommended dose is 75 mg every two weeks (Q2W), with alternative less frequent dosing of 300 mg Q4W. For inadequate response, dosing can be increased to 150 mg Q2W. Evolocumab: the recommended dose is 140 mg Q2W, with an alternative less frequent dosing of 420 mg Q4W. Inclisiran: the recommended dose is a single injection of 284 mg, a second at 3 months, and then every 6 months.
Half-life: Alirocumab: 17-20 days Evolocumab: 11-17 days Inclisiran: ~9 hours Tafolecimab: 26 days (geometric mean) Ongericimab: 4.5-6.5 days Recaticimab: 18.6-27.4 days AZD780: ~40 hours (in plasma) MK-0616: 35-130 hours	**BBB**: Approved PCSK9 inhibitors are targeted to the liver.
Clinical trials: Alirocumab and Evolocumab have each been tested in over 50 clinical trials, while inclisiran has been tested in over 20 clinical trials, including several large Phase 3 RCTs with n's >500 participants with hypercholesterolemia. Tafolecimab has been tested for hypercholesterolemia in Phase 1, 2, and 3 trials, in over 1,000 participants overall,	**Observational studies**: Mendelian randomization studies of PCSK9 gene variants indicate that PCSK9 plays a causal role in LDL-C levels and cardiovascular outcomes. PCSK9 levels are also elevated in the CNS in the context of neurodegenerative disease.

in China. Recaticimab has been tested in Phase 1, 2, and 3 (n=703; n=698) trials for hypercholesterolemia in China. Ongericimab has been tested in Phase 1 and 1/2 trials (n=84; n=86) for hypercholesterolemia in China. AZD780 has been tested in Phase 1 trials (n=117 for trial with published results) in participants with elevated LDL-C. MK-0616 has been tested in Phase 1 and Phase 2b (n=380) for hypercholesterolemia.	

What is it?

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein that is primarily made and secreted by the liver [1]. To a lesser degree, PCSK9 is also produced in the brain, small intestine, and kidney. On average, we produce around 20 µg/kg of PCSK9 per day, such that plasma levels are normally around 200 ng/mL in adults [2]. Levels of PCSK9 can be influenced by metabolic status and hormones, such that low production of cholesterol, as occurs with the use of statins, can lead to an increase in PCSK9, whereas the hormone estrogen decreases PCSK9 [3].

In 2003, genetic variants were identified in PCSK9 that linked it with levels of low-density lipoprotein-cholesterol (LDL-C) levels. PCSK9 influences circulating LDL-C levels through the regulation of the receptor responsible for its uptake into cells, LDLR [1]. The binding of PCSK9 to LDLR prevents the recycling of the receptor to the cell surface, and instead targets it for degradation. Therefore, an increase in PCSK9 leads to a decrease in the amount of LDLR localized to the cell surface, which in turn limits the uptake of LDL-C, such that more of it remains in circulation. In addition to influencing LDL-C levels, genetic variants that reduce PCSK9 activity were also found to be associated with a lower risk for cardiovascular disease. These associations prompted the clinical development of PCSK9 inhibitors for cardiovascular disease, particularly in the context of hypercholesterolemia.

The first PCSK9 inhibitors to be developed were monoclonal antibodies (mAbs) designed to prevent the interaction between PCSK9 and LDLR. Subsequently, other types of PCSK9 inhibitors have been developed, including short interfering RNAs (siRNAs), antisense oligonucleotides (ASOs), and oral small molecule inhibitors. To date, only mAbs and siRNAs targeting PCSK9 have been approved for patient use. They are typically used in combination with statins to enhance LDL-C lowering in individuals unable to achieve target LDL-C levels through the use of statins alone.

PCSK9 inhibitors are administered as a second- or third-line treatment for hypercholesterolemia, and are not currently recommended as a first line therapy. Current guidelines from the National Institute for Health and Care Excellence (NICE) recommend PCSK9 inhibitors primarily for secondary prevention, and only recommend their use in individuals without cardiovascular disease when LDL-C levels exceed 135 mg/dL [4]. Guidelines from the American College of Cardiology and the National Lipid Association recommend the addition of PCSK9 inhibitors to maximally tolerated statins in patients with cardiovascular disease, at LDL-C levels ≥55 mg/dL in those at very high risk and at LDL-C levels ≥70 mg/dL in those at moderate risk [5]. They can also be considered in adults with primary hypercholesterolemia on statins with LDL-C levels ≥70 mg/dL, and in those without cardiovascular disease with high baseline LDL-C (≥190 mg/dL) that is not adequate controlled (≥100 mg/dL) by statins.

Approved PCSK9 inhibitors:

Alirocumab (Praluent®) is a mAb targeting PCSK9 marketed by Sanofi and Regeneron. It was approved by the FDA and EMA in 2015 for adults with hypercholesterolemia.

Evolocumab (Repatha®) is a mAb targeting PCSK9 marketed by Amgen. It was approved by the FDA and EMA in 2015 for adults with hypercholesterolemia, and in 2021, it was approved for use in pediatric patients (≥10 years old) with heterozygous or homozygous familial hypercholesterolemia.

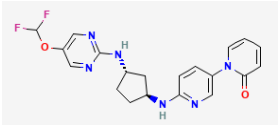
Inclisiran (Leqvio®) is a siRNA targeting PCSK9 marketed by Novartis. It was approved by the EMA in 2020 and by the FDA in 2021 for adults with hypercholesterolemia.

Tafolecimab (Sintbilo®) is a mAb targeting PCSK9 marketed by Innovent Biologics. It was approved for use in China by the National Medical Products Administration (NMPA) in 2003 for adults with hypercholesterolemia.

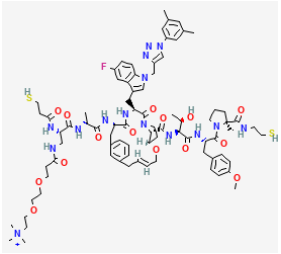
PCSK9 inhibitors in clinical development:

Ongericimab is a mAb targeting PCSK9 in clinical development in China by Junshi Biosciences. It has undergone testing in early Phase clinical trials.

Recaticimab is a mAb targeting PCSK9 in clinical development in China by Jiangsu Hengrui Pharmaceuticals. It has been tested in Phase 1, 2, and 3 clinical trials.



AZD780 is an oral small molecule inhibitor of PCSK9 currently in clinical development by AstraZeneca. It has been tested in a Phase 1 trial, and is currently being tested in additional Phase 1 and Phase 2 trials. (Formula: $C_{20}H_{20}F_2N_6O_2$; MW: 414.4 g/mol; Source: PubChem)



MK-0616 is an oral small molecule inhibitor of PCSK9 currently in clinical development by Merck. It has been tested in Phase 1 and 2 trials, and is currently being tested in large scale Phase 3 trials. (Formula: $C_{81}H_{109}FN_{15}O_{15}S_2$+; MW: 1616.0 g/mol; Source: PubChem)

Neuroprotective Benefit: Most gene association studies for PCSK9 and clinical experience with PCSK9 inhibitors to date indicate that PCSK9 inhibition has a neutral effect on cognitive outcomes.

Types of evidence:

- 1 meta-analysis of RCTs testing PCSK9 inhibitors assessing impact to cognition
- 1 clinical trial assessing cognitive outcomes with long term use of evolocumab
- 6 Mendelian randomization/gene association studies for PCSK9 and neurodegenerative disease
- 4 observational biomarker studies of PCSK9 levels in neurodegenerative disease
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Mendelian randomization studies assessing the impact of gene variants that affect PCSK9 expression and/or activity levels are mixed regarding the potential impact of PCSK9 on dementia risk and cognition, though the majority find that it has a neutral effect. These discrepancies may stem from slight differences in the downstream effects of the different variants across individuals depending on genetic makeup and other environmental/lifestyle factors. Additionally, these variants reflect differences in gene expression throughout the body over the lifetime of an individual. PCSK9 expression in the brain is most relevant during development, and appears to be less impactful during adulthood [6]. These early life differences in PCSK9 activity could then potentially impact brain health outcomes later in life. Consequently, these genetic analyses are not fully reflective of the effects of current PCSK9 inhibitors, which are administered later in life, and largely restricted to the liver.

The evidence to date suggests a neutral cognitive profile for available PCSK9 inhibitors.
A meta-analysis of individual participant data including 3,340 participants from 14 Phase 2 and 3 RCTs testing the PCSK9-targeting mAb, alirocumab (at a dose of 75 or 150 mg every two weeks), primarily on the background of maximally tolerated statin therapy, assessed neurocognitive adverse events [7]. The control groups received either placebo or ezetimibe. Overall, there was no significant difference in the rate of neurocognitive adverse events in patients treated with alirocumab relative to placebo (0.9% vs 0.7%; Hazard Ratio [HR]: 1.24, 95% confidence interval [CI] 0.57 to 2.68), or ezetimibe (1.2% vs 1.3%; HR: 0.81, 95% CI 0.32 to 2.08). Rates of neurocognitive adverse events were also not affected by the degree of LDL-C lowering (<25 mg/dL vs ≥25 mg/dL) achieved.
The impact of the PCSK9-targeting mAb, evolocumab, on cognitive function was assessed in the EBBINGHAUS study, a sub-study of the FOURIER trial. The primary outcome of the EBBINGHAUS study was the score on the spatial working memory strategy index of executive function, which is a principal component of the Cambridge Neuropsychological Test Automated Battery (CANTAB). There was no significant difference on this measure of executive function (evolocumab 0.21±2.62 vs placebo −0.29±2.81) in the 1,204 study participants over a median of 19 months [8]. There were also no significant differences observed in measures for working memory, episodic memory, or psychomotor speed. A subset of participants (n=473) continued to be followed for a median of 5.1 years during an open-label extension period [9]. Similar to the original findings, evolocumab use was not associated with differences in executive function during the follow-up period.

Human research to suggest benefits to patients with dementia:

PCSK9 inhibitors have not yet been tested in dementia patients for potential impacts on cognition or disease progression.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

There is evidence to support a theoretical benefit for PCSK9 inhibition related to its roles in cholesterol regulation. However, genetic, clinical, and preclinical studies indicate that PCSK9 has a complex, context-dependent role in the CNS.
The dysregulation of lipids and cholesterol regulation is a prominent feature of the Alzheimer's disease (AD) brain [10]. Receptors involved in cholesterol homeostasis, such as LDLR and Lpr1, have also been implicated in the clearance of Aβ from the brain. Whether this dysregulation of cholesterol plays a casual role or is a consequence of other pathological processes is unclear, and may be a combination of

both. The 'lipid invasion model' posits that disruptions to the blood-brain-barrier (BBB) may result in the inappropriate exchange of peripheral cholesterol into the CNS [10]. Since PCSK9 plays an important role in levels of LDL-C in the periphery, it could theoretically play a role in this process.
PCSK9 is also expressed in the brain, where it plays distinct roles from its effects in the periphery [6]. It is primarily expressed during neurodevelopment, such that PCSK9 appears to play only a marginal role in the regulation of brain cholesterol in adulthood under normal conditions. But, there is some evidence to suggest that in pathological conditions, PCSK9 may have a more pronounced effect on cerebral lipid metabolism [6].
Since available PCSK9 inhibitors act peripherally, targeting liver PCSK9, their contributions to cognition and neuropathology would likely be related to the impact of LDL-C lowering on these processes, rather than the direct modulation of PCSK9 activity in the CNS.

Mendelian randomization/genomic studies: The impact of genetic variants related to LDL-C lowering generally, and PCSK9 reduction, specifically, has been mixed with respect to cognitive performance and dementia risk. Most studies find no significant relationships between genetic PCSK9 variants and risk profiles, suggesting a lack of either clear benefit or harm to cognitive function.

A Mendelian randomization study including approximately 740,000 participants assessed the relationships of long-term PCSK9 inhibition and statin use on neurocognitive outcomes as proxied by genetic variants associated with lower PCSK9 or HMGCR [11]. Genetic PCSK9 inhibition was not associated with significant effects on cognitive performance, memory performance, or cortical surface area. Additionally, genetic PCSK9 inhibition was not associated with changes to biomarkers associated with disease progression and risk for AD and Lewy body dementia.
A phenome-wide analysis compared genetic variation at the PCSK9 locus, based on gene score (comprised of four variants) derived from data from over 300,000 participants, with outcomes of pharmacological PCSK9 inhibition based on data from 17 RCTs including 79,578 participants [12]. No genetic associations were observed between PCSK9 and AD (Odds Ratio [OR]: 0.91, 95% CI 0.55 to 1.51) or cognitive performance, which is consistent with the cognitively neutral profile observed in PCSK9 inhibitor trials.
A Mendelian randomization study assessing 380 genetic variants associated with low LDL-C found that genetically low LDL-C was associated with reduced risk for AD [13]. However, PCSK9 variants were not significantly associated with AD risk in this study.

A case-control study including 468 AD cases and 410 controls from the Quebec Founder Population found that the presence of PCSK9 loss of function variants, R46L and InsLEU, did not significantly affect rates of AD prevalence or age of disease onset [13].
Additional support for a neutral effect on cognition comes from case reports of individuals with homozygous loss of function mutations in PCSK9 or compound heterozygous loss of function mutations in PCSK9 with normal cognition [13; 14; 15].

There are few studies suggesting that PCSK9-mediated LDL-C lowering could impact AD risk either positively or negatively, however, the relationships may be tied to specific genetic variants. One Mendelian randomization study including participants of European ancestry assessed the impact of variants in genes that serve as the target for LDL-C lowering therapies, including PCSK9 [16]. In this analysis, inhibition of PCSK9 was predicted to increase the risk for AD (OR per standard deviation lower LDL-C: 1.45, 95% CI 1.23 to 1.69), though the magnitude was less than the protection afforded on cardiovascular outcomes. Variants in other LDL-C associated genes, including HMGCR, APOB, and NPC1L1were not significantly associated with AD risk in this study. Meanwhile, a separate study identified an association between a variant associated with elevated PCSK9, rs4927193, and increased AD risk and AD-related biomarkers (e.g. tau) in females [17].

Observational biomarker studies: Elevations of PCSK9 in the brain and CSF have been observed in the context of neurodegenerative disease, particularly in concert with changes in lipids and other lipid-associated proteins. This suggests that changes to PCSK9 in the CNS may be part of a broader dysregulation of lipid homeostasis with neurodegeneration. However, it is unclear whether these changes are directly contributing to disease progression, or a consequence of ongoing pathological processes.

A study assessing CSF levels of PCSK9 found that PCSK9 levels were increased in AD patients (2.80 ng/mL; n=36) relative to individuals without neurogenerative disease (2.30 ng/mL; n=11), but that levels did not significantly differ between patients with AD and those with other types of neurodegenerative disease (2.83 ng/mL; n=20) [18].
Another study found that CSF PCSK9 levels were inversely associated with 27-hydroxycholesterol (27-HC) in AD patients, and that CSF PCSK9 was also inversely associated with 24-HC in ApoE4 carriers with AD [19]. Additionally, there was a positive correlation between CSF and serum PCSK9 in AD patients, suggesting that there may be some abnormal peripheral to central exchange of PCSK9. Notably, these

correlations were not observed in patients with an earlier stage of mild cognitive impairment (MCI), suggesting that they may be related to changes associated with disease progression.
PCSK9 levels were found to be elevated in disease-affected brain regions in AD patients, such as the frontal cortex, but not in unaffected regions, such as the cerebellum [17]. CSF PCSK9 levels were also positively associated with CSF tau levels in AD patients [17]. CSF levels of PCSK9 were elevated in AD patients, along with levels of the lipoproteins, ApoE, ApoJ, and ApoB. Notably, CSF PCSK9 protein levels were correlated with ApoE levels in a population of cognitively normal participants considered at risk for AD based on family history. The increase in ApoE likely stems from the PCSK9-mediated reduction in ApoE internalizing receptors, such as LDLR.

Preclinical studies: PCSK9 was originally identified as a gene associated with apoptosis in primary cerebellar neurons, suggesting that it may promote neuronal cell death [6]. PCSK9 may also impact lipid metabolism and the clearance of Aβ from the brain, through the regulation of receptors involved in these processes, such as LDLR, VLDLR, and ApoER2. Further studies suggest that its effects on both cell death and lipid homeostasis in the CNS are context dependent, resulting in contradictory results in *in vivo* studies.

A study in the 5XFAD mouse model found that PCSK9 plays a role in the Lpr1-mediated clearance of Aβ from the brain to the blood across the endothelium [20]. Treatment with anti-PCSK9 mAbs (alirocumab or evolocumab 1 μg/g i.p. weekly for 10 weeks) in female 5XFAD mice starting at 14 weeks of age led to a reduction in cerebral Aβ40 and Aβ42, as well as a preservation of hippocampal-dependent learning, based on contextual freezing behavior. Notably, the protective effects of the PCSK9 inhibitors on cerebral Aβ levels and cognition were abolished when Lrp1 was absent from the brain endothelium. This suggests that the neuroprotection afforded by PCSK9 inhibition stems from the increased presence and activity of cholesterol receptors associated with Aβ clearance in the membrane of the brain endothelium.
Similarly, another study found that the genetic loss of PCSK9 reduced the number of ThS+ amyloid plaques, by around 40%, in the dentate gyrus and neocortex of 5XFAD mice [21].
By modulating cholesterol levels, PCSK9 may influence the toxicity of Aβ [22]. The overexpression of PCSK9 was shown to reduce neuronal cholesterol content and increase the neurotoxicity of Aβ in cell culture. Thus, by preserving neuronal cholesterol levels, the inhibition of PCSK9 may limit the toxicity of Aβ fibrils.

However, some biomarker studies in humans have found associations between CSF levels of PCSK9 and tau, but not with Aβ, suggesting there are additional complexities to these relationships that may depend on disease stage and other factors [17].

Other neurological conditions:

Parkinson's disease: UNCLEAR
The relationship between lipid lowering and Parkinson's disease (PD) is complex. Some studies suggest that lipid lowering may increase the risk for PD, while other studies find no association, suggesting that the findings may stem from reverse causation due to changes in diet/lifestyle following the onset of disease.
A Mendelian randomization study assessing the impact of genetically proxied HMGCR inhibition and PCSK9 inhibition found that LDL-C lowering variants for both of these genes were associated with increased risk for PD (PCSK9 OR: 1.417, 95% CI 1.178 to 1.657; HMGCR OR: 1.907, 95%CI 1.502 to 2.312) [23].
A case-control study comparing lipid profiles between 31 patients with PD with 31 controls found that that there was a non-significant trend toward higher levels of PCSK9 in PD patients, but that PCSK9 levels were not related to PD severity or PD-associated lipid changes [24]. Notably, LDL-C levels were lower in PD patients, which would not be consistent with an elevation in PCSK9.
Another observational study also found that LDL-C levels were lower in PD patients, with LDL-C levels below 4 mmol/L associated with increased PD risk [25]. However, a related Mendelian randomization analysis did not find a significant association between LDL-C lowering variants and PD risk, suggesting that the reduction in LDL-C may be downstream of PD, rather than a causal factor.

ALS: UNCLEAR/POTENTIAL BENEFIT FOR GENETIC PCSK9 INHIBITION
A Mendelian randomization study assessing the impact of genetically proxied HMGCR inhibition and PCSK9 inhibition found that the inhibition of PCSK9 was associated with reduced risk for ALS (OR: 0.89, 95% CI 0.77 to 1.00) [23]. The authors speculate that this may stem from anti-apoptotic effects of inhibiting PCSK9 in motor neurons, suggesting benefit may be derived from a direct effect of PCSK9 in the CNS, independent of LDL-C lowering. In that case, peripherally targeted PCSK9 inhibitors that primarily modulate LDL-C would be unlikely to provide neuroprotective benefit.

Neuropsychiatric conditions: NO CLEAR HARM OR BENEFIT

A Mendelian randomization study including variants derived from European ancestry-based genome-wide association studies assessing the impact of genetically proxied PCSK9 inhibition with 12 neuropsychiatric endpoints, including measures of depression, anxiety, self-harm, and AD, did not find any significant relationships in men or women, after correcting for multiple comparisons [26].

APOE4 interactions: NO CLEAR ASSOCIATIONS TO DATE

PCSK9 levels in the CSF have been shown to be associated with levels of ApoE. Observational studies suggest that lipid and lipoprotein-related alterations in the CNS linked with changes in PCSK9 levels may be associated with ApoE subtype. However, to date, there is no evidence to indicate that the effects of available PCSK9 inhibitors on cognition depend on ApoE genotype.

One small observational biomarker study found that changes in levels of oxidative cholesterol metabolites (24-HC and 27-HC) in the CSF of ApoE4 carriers were associated with changes in PCSK9 levels [19]. Additionally, ApoE4 carriers were more likely to show correlations between levels of PCSK9 in the serum and CSF, suggestive of pathology-related lipid exchange between the peripheral and central compartments. These findings may be related to the increased prevalence of BBB breakdown in ApoE4 carriers, and it is unclear the degree to which PCSK9 itself may contribute to altered lipid profiles associated with ApoE4. A separate observational study found that CSF PCSK9 levels were highly correlated with ApoE levels, irrespective of ApoE genotype [17].
Participants in the EBBINGHAUS study, a sub-study of the FOURIER trial focused on cognitive outcomes in response to long-term evolocumab treatment as an add-on to statin therapy, provided self-reports of cognitive changes, and received objective cognitive testing using the CANTAB [27]. There were no significant relationships between ApoE genotype and memory, executive functioning, or self-reported cognition (Everyday Cognition Scale) in the evolocumab arm, indicating that cognitive performance in response to evolocumab was not significantly impacted by ApoE genotype.

Aging and related health concerns: PCSK9 inhibition reduces LDL-C levels and protects against adverse cardiovascular outcomes. Inhibitors may also have utility as an adjunct to cancer immunotherapy.

Types of evidence:

- 15 meta-analyses of trials for the effect of PCSK9 inhibitors on cardiovascular measures
- 1 meta-analysis of RCTs for the effect of PCSK9 inhibitors on bone health
- 2 clinical trials for ongericimab
- 3 clinical trials for recaticimab
- 2 clinical trials for AZD8233
- 1 clinical trial for AZD0780
- 2 clinical trials for MK-0616
- 1 clinical trial for NNC0385-0434
- 1 clinical trial for VERVE-101
- 2 Mendelian randomization studies for genetic PCSK9 inhibition and lifespan
- 1 Mendelian randomization study for genetic PCSK9 inhibition and osteoporosis
- Numerous laboratory studies

Lifespan: PCSK9 INHIBITION MAY REDUCE CARDIOVASCULAR-RELATED MORTALITY, BUT IT IS NOT ASSOCIATED WITH MAXIMUM LIFESPAN EXTENSION

Cardiovascular health is one of the major factors impacting life expectancy in older adults. Mendelian randomization studies suggest that levels of PCSK9 can impact life expectancy primarily through its protective effects on cardiovascular health.
A Mendelian randomization study using GWAS datasets including up to 500,193 individuals of European ancestry examined the effect of gene variants that mimic LDL-C lowering therapies on lifespan [28]. Genetic reduction in LDL-C was associated with increased lifespan in the discovery and validation datasets. In general, variants that increased LDL-C were associated with shorter lifespans, but the impact of most variants was modest. The expression of PCSK9, along with LPL, and APOB, was only associated with lifespan in the discovery dataset, and generally related to life expectancy rather than acting as causal factors for extreme longevity. The effects of LDL-C lowering on lifespan were largely driven by its effects on reducing coronary heart disease, which mediated 22.8% of the effect.
Similarly, a Mendelian randomization study including individuals of European ancestry from the UK Biobank assessed the impact of lipid-lowering gene variants in relation to genetic variants associated with lifespan based on attained parental ages of their maternal (n=412,937) or paternal (n=415,311)

lineages [29]. Genetic PCSK9 inhibition was associated with longer lifespan in men (2.39 years per standard deviation LDL-C, 95% CI 0.42 to 4.36 p=0.02). However, there was no significant association between PCSK9 inhibition and lifespan with women, and the sex-difference interaction was not significant. Since PCSK9's impact on lifespan appears to be primarily mediated by its effects on cardiovascular health, the preferential effect on men likely stems from the higher risk of cardiovascular-related mortality in men. Additionally, some studies suggest that due to sex differences in circulating PCSK9 levels, men may be more likely to achieve target LDL-C lowering with PCSK9 inhibition.
Overall, these studies suggest that PCSK9 inhibition may reduce the risk of cardiovascular-related mortality in individuals with elevated LDL-C, but is unlikely to extend lifespan in otherwise healthy individuals.

Osteoporosis: NO CLEAR HARM OR BENEFIT WITH PCSK9 INHIBITOR USE

Changes in lipid metabolism, such as what is observed in hyperlipidemia, have been associated with osteoporosis-like changes in bone, such as a loss of bone mineral density [30]. However, evidence to date does not indicate that PCSK9 inhibitors have a protective effect against osteoporosis.
A Mendelian randomization study including four GWAS datasets including a total of 1,475,880 individuals of European ancestry, found that there were significant associations between genetic PCSK9 inhibition and increased osteoporosis risk in three of the datasets (ORs: 1.0047, 1.0081, and 1.4188, respectively) [30]. The authors of the study speculate that it may be related to changes in estrogen, but the potential mechanism is unclear. Typically, estrogen reduces levels of PCSK9.
There has been no evidence to date to indicate that the clinical use of PCSK9 inhibitors impairs bone health. A meta-analysis of 30 RCTs testing PCSK9 inhibitors including 95,911 adults found that the use of PCSK9 inhibitors was not associated with osteoporosis-related measures [31]. The use of alirocumab (n=14 RCTs), evolocumab (n=7 RCTs), bococizumab (n=6 RCTs) or inclisiran (n=3 RCTs) for a period of six to 64 months showed no significant associations with the risks for major osteoporotic fracture (OR: 1.08, 95% CI 0.87 to 1.34, based on 24 trials; n=93,181), hip fracture (OR: 1.05, 95% CI 0.73 to 1.53, based on 15 trials; n= 87,845), osteoporotic non-vertebral fracture (OR: 1.03, 95% CI 0.80 to 1.32, based on 22 trials, n=92,329), or total fracture (OR: 1.03, 95% CI 0.88 to 1.19, based on 30 trials, n=95,911).

Cardiovascular disease

Hyperlipidemia: BENEFIT

The role for PCSK9 in the modulation of LDL-C was discovered when mutations in PCSK9 were identified as casual variants in autosomal dominant familial hypercholesterolemia in 2003 [32]. Since then, a variety of variants have been identified that modulate PCSK9 expression. Gene association and Mendelian randomization studies have linked these variants with LDL-C levels and cardiovascular outcomes. There is also some evidence to suggest that PCSK9 may impact cardiovascular health independent from its effects on LDL-C, though the mechanisms have not been well established. In observational studies, PCSK9 levels alone have not been a consistent predictor of cardiovascular outcomes [2].
A phenome-wide analysis of PCSK9 genetic variants impacting LDL-C levels based on participants from the China Kadoorie Biobank and UK Biobank developed a PCSK9 genetic score [33]. Genetic profiles of PCSK9 linked with LDL-C lowering were associated with reduced risks of carotid plaque (OR: 0.61 (95% CI 0.45 to 0.83; based on n=8,340), major occlusive vascular events (OR: 0.80, 95% CI 0.67 to 0.95; based on n= 15,752), and ischemic stroke (OR: 0.80, 95% CI 0.66 to 0.98; based on n=11,467).

LDL-C lowering: BENEFIT

The primary mechanism by which the reduction of PCSK9 protects against cardiovascular pathology is through the lowering of LDL-C. Many patients are unable to achieve target LDL-C levels on maximally tolerated statins alone. PCSK9 inhibitors lower LDL-C in a mechanistically different manner from statins (i.e. HMG-CoA reductase inhibitors), thus the combination can have additive effects. PCSK9 inhibitors have been shown to reduce LDL-C levels around 40 to 70% in clinical studies, usually on a background of maximally tolerated statins, allowing the majority of patients to achieve target LDL-C levels.

A meta-analysis of 54 RCTs testing PCSK9 inhibitors (alirocumab, evolocumab, or inclisiran) including a total of 87,669 participants assessed their LDL-C lowering efficacy over a median period of 24 months [34]. Evolocumab reduced LDL-C by -61.09% (95% CI -64.81% to -57.38%) while alirocumab reduced LDL-C by -46.35% (95% CI -51.75% to -41.13%). At a dose of 284 mg, inclisiran reduced LDL-C by -54.83% (95% CI -59.04% to -50.62%) and at a dose of 300 mg, it reduced LDL-C by -43.11% (95% CI -52.42% to -33.80%).
A comparative analysis including 10 studies assessed the LDL-C lowering capacity of PCSK9 inhibitors (alirocumab, evolocumab, or inclisiran) [35]. Alirocumab reduced LDL-C and apolipoprotein-B (apoB) by 39.6% to 72.4% and 27.3% to 57.9%, respectively, with maximum reductions achieved at a dose of 150 mg Q4W. Evolocumab reduced LDL-C and apoB by 42.7% to 64.7% and 31.9% to 53.9%, respectively, with the maximum reductions achieved at a dose of 140 mg Q2W. Inclisiran reduced LDL-C and apoB by

40.1% to 51.3% and 38.2% to 44.8%, respectively, with the maximum reductions achieved with a dose of 284 mg inclisiran, administered via a 1.5-ml subcutaneous injection on days 1, 90, 270, and 450.
A network meta-analysis of 26 Phase 3 RCTs including a total of 16,510 hyperlipidemic patients on maximally tolerated statin therapy assessed the LDL-C lowering efficacy of PCSK9 inhibitors (alirocumab, evolocumab, tafolecimab, or inclisiran) in comparison with ezetimibe or placebo [36]. Evolocumab, at a dose of 140 mg Q2W, showed the greatest LDL-C lowering capacity (−69.13%, 95% CI −74.55% to −63.72%), followed by tafolecimab at a dose of 450 mg QM (−63.94%, 95% CI −71.36% to −56.51%).

Sex effect: PCSK9 levels are negatively regulated by estrogen, thus women experience fluctuations in PCSK9 levels over the course of the menstrual cycle [37]. Additionally, PCSK9 levels increase after menopause, due to the loss of estrogen. As such, circulating PCSK9 levels tend to be higher in postmenopausal women, relative to men. This suggests that postmenopausal women may need to achieve more aggressive PCSK9 inhibition to attain meaningful LDL-C lowering.
A meta-analysis of 16 trials including 54,996 participants assessed the impact of PCSK9 inhibitors on LDL-C lowering stratified by sex [38]. The analysis found that while both men and women achieved significant LDL-C lowering with PCSK9 inhibitors, the effect was significantly stronger in men relative to women at both 12 weeks (MD: -4.55%, 95% CI -7.34% to -1.75%) and 24 weeks (MD: -7.11%, 95% CI -9.99% to -4.23%). Similarly, a genome wide association study found that there was sexual dimorphism in PCSK9 genetic variants with a stronger effect in men [39]. These studies suggest that sex-specific dosing adjustments may be warranted.

PCSK9 mAbs

Alirocumab (Praluent®) is fully human recombinant immunoglobulin G1 (IgG1) mAb that inhibits the binding of PCSK9 to LDLR.
Evolocumab (Repatha®) is a fully human recombinant IgG2 mAb that inhibits the binding of PCSK9 with LDLR.
These mAbs are the first-in-class approved PCSK9 inhibitors, and the majority of information regarding the utility of PCSK9 inhibitors to protect against cardiovascular events is based on the clinical use of these two drugs.

Tafolecimab (IBI306, SINTBILO®) is a novel recombinant fully human IgG2 mAb that inhibits the binding of PCSK9 to LDLR developed by Innovent Biologics, Inc [40]. It has a higher affinity for PCSK9 and exerts more durable LDL-C lowering, which allows for less frequent administration (i.e. every four to six weeks),

relative to alirocumab and evolocumab (i.e. every two to four weeks). It was approved by China's National Medical Products Administration (NMPA) for the treatment of adult patients with primary hypercholesterolemia and mixed dyslipidemia in 2023 (Press release). It is approved for use at the three subcutaneous dosing regimens that demonstrated significant LDL-C lowering in clinical trials, 150 mg Q2W, 450 mg Q4W, and 600 mg Q6W.

A meta-analysis of three trials testing tafolecimab at dose of 450 mg Q4W conducted in China including 686 patients with hyperlipidemia found that tafolecimab was associated with significant reductions in LDL-C relative to placebo at week 12 (-63.78%, 95% CI - 65.88% to - 61.68%) [41]. A study assessing the pharmacokinetic exposure-response relationship of tafolecimab found that the greatest degree of LDL-C lowering was achieved when concentrations of tafolecimab reached 5 µg/mL, and that increasing exposure was unlikely to result in further lowering of LDL-C levels [42].

PCSK9 siRNA

Inclisiran (LEQVIO®) is a siRNA targeting PCSK9. In contrast to the PCSK9-targeting mAbs, which bind to PCSK9 to block its interaction with LDLR, as an siRNA, inclisiran inhibits the synthesis of PCSK9 in the liver [43]. The siRNA is directed to the liver through the conjugation to the GalNaC moiety, which allows it to be taken up into hepatocytes via the asialoglycoprotein receptor (ASGPR). PCSK9 produced in the liver serves as the main source of circulating PCSK9, however, there are also extrahepatic sources of PCSK9, such as in the brain, heart, and kidneys. Preservation of these extrahepatic sources may allow for the maintenance of potentially beneficial physiological functions of PCSK9 while blocking its potentially deleterious effects on LDL-C levels. While it has a short half-life in circulation (~9 hours), its effects are long-lasting, lasting around six months, such that it is administered only twice per year [43]. Inclisiran was only approved in 2021, so there is less information regarding long-term cardiovascular outcomes, relative to the PCSK9-targeting mAbs, which have been around for around a decade. The less frequent dosing may make inclisiran a more attractive therapeutic option relative to the biweekly dosing of PCSK9-targeting mAbs, however, whether it offers greater long-term therapeutic benefit has not been established. To date, it shows relatively similar efficacy in terms of lipid lowering.

A meta-analysis of eight RCTs including 4,947 patients testing inclisiran found that inclisiran was associated with PCSK9 lowering of -70.80 % (95 % CI -76.52% to -65.08%), LDL-C lowering of -46.95 % (95% CI -53.26% to -40.46%) [44]. Inclisiran treatment was also associated with significant reductions in serum total cholesterol (-29.47 %, 95% CI -32.56% to -26.39%), ApoB (-36.77 %, 95% CI -40.94% to -32.61%), and Lp(a) (-20.04 %, 95 % CI -24.2% to -15.87%) $P < 0.05$), as well as increases to HDL-C (+6.09 %, 95% CI 3.63% to 8.55%).

A separate network meta-analysis including 33 studies testing PCSK9 inhibitors involving 23,375 participants compared the LDL-C lowering capacity of inclisiran, PCSK9-targeting mAbs, and statins plus ezetimibe therapy [45]. Surface under the cumulative ranking (SUCRA)-based probabilities indicated that inclisiran was more likely to be the most effective at LDL-C lowering (26% vs 11% vs 7.4%, respectively), however, in paired meta-analysis, there were no statistically significant differences in the degree of LDL-C lowering achieved amongst the three therapeutic interventions.

Lp(a): LOWERING BELOW THE THRESHOLD OF CLINICAL MEANINGFULNESS

In contrast to statins, which are associated with increases in levels of Lp(a), PCSK9 inhibitors have been shown to reduce levels of Lp(a). However, the degree of reduction is generally below the level that would be considered clinically meaningful, and there is some evidence to suggest that those with the highest baseline Lp(a) levels benefit the least [46]. Although they do not appear to meaningfully reduce the risk associated with elevated Lp(a), PCSK9 inhibitors provide a mechanism to reduce the risk associated with elevated LDL-C, without further exacerbating Lp(a)-related risk.

A network meta-analysis of 41 RCTs testing PCSK9 inhibitors, including a total of 17,601 participants found that PCSK9 inhibitors were associated with reductions in Lp(a) up to 25.1%, and that evolocumab (140 mg Q2W) had the highest efficacy for Lp(a) lowering [47]. However, the authors noted that the use of a PCSK9 inhibitor alone was insufficient to a degree of Lp(a) considered clinically meaningful.
Similarly, a more recent network meta-analysis of 26 Phase 3 trials (n= 16,510 participants) also found that evolocumab was associated with the highest efficacy in lowering Lp(a) (−36.04%, 95% CI −42.04% to −30.04%), with tafolecimab exhibiting a similar degree of lowering (-36.00%, 95% CI −48.24% to −23.76%) [36].
A meta-analysis of 47 studies including 67,057 participants testing PCSK9 inhibitors found that, on average, PCSK9 inhibitors were associated with a reduction in Lp(a) levels of -27% (95% CI -29.8% to -24.1%) [48]. The degree of reduction was stronger in trials less than or equal to 12 weeks relative to trials longer than 12 weeks, which could stem from the development of treatment resistance over time. The degree of Lp(a) lowering was associated with the degree of LDL-C and ApoB lowering.

Atherosclerosis: POTENTIAL BENEFIT FOR REDUCING PLAQUES

There is evidence to suggest that the lipid related changes stemming from PCSK9 inhibition impact atherosclerotic processes in vessels.

A meta-analysis of 12 studies assessed the impact of adding PCSK9-targeting mAbs (alirocumab or evolocumab) to statin therapy on plaque phenotypes, compared to the use of statins alone [49]. The use of PCSK9 inhibitors was associated with reductions in percent atheroma volume (Mean Difference [MD]: - 0.99, 95% CI -1.83 to - 0.16), reductions in total atheroma volume (MD: -8.13, 95% CI -14.32 to -1.95), improvements to fibrous cap thickness (MD: 23.60, 95% CI 16.27 to 30.93), decreases to lipid arc based on OCT measures (MD: -24.77, 95% CI -29.61 to -19.93), improvements to the quantitative flow ratio based on 3D angiography data (MD: 0.01, 95% CI 0.01 to 0.02), and decreases to the percent diameter of stenosis based on 3D angiography data (MD: -4.04, 95% CI - 6.23 to -1.86).
A separate meta-analysis of five studies including 158 participants found that the addition of PCSK9 inhibitors significantly reduced arterial stiffness, as measured by pulse wave velocity (MD: -2.61 m/s, 95% C: -3.70 to -1.52 (pooled effect size: -1.62, 95% CI -2.53 to -0.71) [50].

Major adverse cardiovascular events: BENEFIT FOR REDUCING MACE

The rationale for lowering LDL-C stems from the relationship between elevated LDL-C and increased risk for adverse cardiovascular events. Consequently, the key efficacy endpoints for PCSK9 inhibitors relate to their ability to prevent major adverse cardiovascular events (MACE). The events that fall within the composite endpoint of MACE can vary between studies, but commonly include some combination of nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, hospitalization due to heart failure, and cardiovascular mortality.

A meta-analysis of 60 RCTs (n= 408,959 participants) for lipid-lowering therapies, including seven trials testing PCSK9 inhibitors, found that, overall, the mean reduction in major vascular events per 1 mmol/L LDL-C reduction was 22% (HR: 0.78, 95 % CI 0.75 to 0.81) [51]. This is attenuated with age for primary prevention, such that at age 60 the reduction in major vascular events per 1 mmol/L LDL-C reduction is around 33% (HR: 0.60, 95 % CI 0.58 to 0.77), but this drops down to around 12% (HR: 0.88, 95% CI 0.75 to 1.04) by age 75.
A meta-analysis of 54 RCTs testing PCSK9 inhibitors (alirocumab, evolocumab, or inclisiran) including 87,669 participants found that over a median of eight months, evolocumab reduced the risk of myocardial infarction (OR: 0.72, 95% CI 0.64 to 0.81), coronary revascularization (OR: 0.77, 95% CI 0.70 to 0.84), stroke (OR: 0.79, 95% CI 0.66 to 0.94) and overall MACE (OR: 0.85, 95% CI 0.80 to 0.89, based on 42,637 participants) [34]. Alirocumab reduced the risk for myocardial infarction (OR: 0.57, 95% CI 0.38 to 0.86), cardiovascular mortality (OR: 0.35, 95% CI 0.16 to 0.77), all-cause mortality (OR: 0.60. 95% CI 0.43 to 0.84), and overall MACE (OR: 0.35, 95% CI 0.16 to 0.77, based on 15,760 participants).

Inclisiran was not associated with a reduced risk of MACE in this analysis, however, it was based on a more limited clinical sample (n=2 RCTs; n=3,174 participants).
A meta-analysis of 20 studies including 48,621 participants found that the addition of PCSK9 inhibitors (alirocumab or evolocumab) to statin therapy was associated with a reduction in the incidence of MACE (Relative Risk [RR]: 0.87, 95% CI 0.83 to 0.9) [52]. PCSK9 inhibitors reduced the incidence of myocardial infarction (RR: 0.80, 95% CI 0.74 to 0.86, based on 10 studies), and the incidence of angina (RR: 0.90, 95% CI 0.83 to 0.97, based on 6 studies), but was not associated with a significant reduction in the incidence of cardiac death in this analysis (RR: 0.92, 95% CI 0.83 to 1.03, based on 7 studies).
While sex-stratified analysis suggests that men achieve a greater degree of LDL-C lowering with PCSK9 inhibitors relative to women, a meta-analysis of 16 trials including 54,996 participants found that PCSK9 inhibitor use was associated with the reduced risk for MACE in both men (HR: 0.85, 95% CI 0.79 to 0.91) and women (HR: 0.86, 95% CI 0.74 to 0.97) [38].

Stroke: POTENTIAL BENEFIT FOR RISK REDUCTION

A meta-analysis of 20 RCTs including 93,093 participants found that the use of PCSK9 inhibitors was associated with a significant reduction in the risk for stroke (RR: 0.75, 95 % CI 0.66 to 0.86), but that this effect was not associated with the magnitude of LDL-C lowering with this class of drugs [53].
Similarly, a meta-analysis including 25 studies testing the PCSK9-targeting mAbs, alirocumab or evolocumab, found that the use of these PCSK9 inhibitors was associated with significant reductions for relative stroke risk in the context of both primary prevention (RR: 0.733; 95% CI 0.618 to 0.870) in those without pre-existing cardiovascular disease, as well as for secondary prevention (RR: 0.703, 95% CI 0.562 to 0.880), in those with cardiovascular disease [54]. Meanwhile, the relative risk for hemorrhagic stroke was not significantly affected by the use of the PCSK9-targeting mAbs.
A protective effect for inclisiran with respect to stroke was not observed in a meta-analysis of three RCTs including 3,660 participants (RR: 0.92, 95% CI 0.54 to 1.58), however, it is not clear if the PCSK9-targeted siRNA is less effective at reducing vascular events relative to the mAbs, or an effect for inclisiran cannot be detected due to limited sample size [55].

PCSK9i in clinical development

PCSK9 mAbs: In addition to tafolecimab, which was approved in China in 2023, there are several other companies in China developing PCSK9-targeting mAbs designed to be dosed less frequently than currently available PCSK9-targeting mAbs.

Ongericimab (JS 002) is a novel 145.6 kDa, recombinant human monoclonal immunoglobulin G4-kappa antibody targeting PCSK9 [56]. It is in clinical development by Junshi Biosciences Co., Ltd. It has non-linear kinetics, with a decrease in clearance at higher doses, and in clinical trials has shown a terminal elimination half-life ranging from 4.5 to 6.5 days. It exerts a long-acting LDL-C lowering effect that is dose-dependent, such that reductions were sustained for less time at lower doses (i.e. 14 to 21 days at a single dose of 150 mg), relative to higher doses (i.e. 35 to 42 days at a single dose of 450 mg). Ongericimab is administered subcutaneously, and to date has been tested in a Phase 1 trial in healthy volunteers (n=84), and a Phase 1/2 trial in patients with hypercholesterolemia (n=86). In healthy volunteers, single doses led to reductions of LDL-C from 30% to 73%, and through repeated dosing in patients with hypercholesterolemia, reductions ranged from 67% to 80% [56].

Recaticimab (SHR-1209) is a novel humanized monoclonal antibody targeting PCSK9 that has been tested in Phase 1, 2, and 3 trials in China. It is in clinical development by Jiangsu Hengrui Pharmaceuticals. It has a longer half-life (18.6–27.4 days) relative to the FDA approved PCSK9-targeted mAbs (range from 11-20 days), which may allow for less frequent dosing [57]. In a placebo-controlled Phase 1b/2 trial (NCT039441090) in 110 patients with hypercholesterolemia on a statin background, dosing ranged from 75 mg Q4W for 16 weeks to 450 mg Q12W for 24 weeks [57]. Reductions in LDL-C ranged from -43.93% (95% CI -55.10% to -32.77%) for the 300 mg Q12W group to -55.06% (95% CI -62.96% to -47.17%) for the 150 mg Q4W group.
In the Phase 3 REMAIN-1 trial, recaticimab was tested as a monotherapy in 703 patients with elevated LDL-C (≥100 mg/dL and <190 mg/dL) at low-to-moderate risk for atherosclerotic cardiovascular disease [58]. Relative to placebo, LDL-C was reduced by -49.6% (95% CI -54.9% to -44.2%) at 12 weeks at a dose of 150 mg Q4W, -52.8% (95% CI -57.2% to -48.3%) at 12 weeks at a dose of 300 mg Q8W, and -45.0% (95% CI -49.0% to -41.0%) at 16 weeks at a dose of 450 mg Q12W.
In the Phase 3 REMAIN-2 trial, recaticimab was tested on the background of statin therapy in 689 patients with hypercholesterolemia for 48 weeks [59]. At 24 weeks, recaticimab reduced LDL-C by -62.2% (95% CI -67.0% to -57.4%) at a dose of 150 mg Q4W, -59.7% (95% CI -65.0% to -54.4%) at a dose of 300 mg Q8W, and -53.4% (95% CI -58.7% to -48.2%) at a dose of 450 mg Q12W, with reduction sustained out to 48 weeks.

PCSK9 Antisense oligonucleotides (ASOs): To date, only one ASO targeting PCSK9 has been clinically tested, but its development has been discontinued due to lower efficacy (and possibly safety) relative to approved PCSK9 inhibitors.

AZD8233 (also known as ION449) is an antisense oligonucleotide (ASO) targeting PCSK9 that was previously in clinical development for hypercholesterolemia by AstraZeneca and Ionis Pharmaceuticals. In Phase 2 trials, it was administered monthly via subcutaneous injection. In the Phase 2b ETESIAN trial (NCT04641299) including 119 patients with dyslipidemia on statin therapy, AZD8233 was administered at doses of 15 mg, 50 mg, or 90 mg per month for 12 weeks [60]. The study met its primary endpoint at the higher doses of LDL-C lowering in relation to placebo, with changes from baseline to 12 weeks of -72% (95% CI -78% to -65%) and -79% (-83% to -74%), for the 50 mg and 90 mg doses, respectively. It also met the secondary endpoint of PCSK9 lowering, with reductions of -88% (95% CI -91% to -84%) and -93% (95% CI -95% to -91%), for the 50 mg and 90 mg doses, respectively. However, the Phase 2b SOLANO trial (NCT04964557) testing AZD8233 at a dose of 60 mg per month for 28 weeks in 411 patients with primary hypercholesterolemia on statin therapy did not meet its prespecified endpoint criteria (Press release). The study met its primary endpoint, achieving a significant lowering of LDL-C by 62.3%, but this was less than had been achieved in the ETESIAN trial at the 50 mg dose. Based on the lower-than-expected efficacy, and a potential safety signal of moderate treatment-emergent liver enzyme elevations, clinical development of AZD8233 was discontinued.

PCSK9 small molecule inhibitors: There are several small molecule inhibitors of PCSK9 in clinical development. They are relatively early stages, and have shown promising efficacy to date, with LDL-C lowering rates similar to what is observed with approved PCSK9 inhibitors (mAbs and siRNA).

AZD0780 is an oral small molecule modulator of PCSK9 in clinical development by AstraZeneca. It was tested in treatment naïve adults with LDL-C levels ≥70 mg/dL and ≤190 mg/dL in a Phase 1 trial [61]. In the single ascending dose study, it was tested as a monotherapy in 36 participants at single oral doses of 30 mg, 60 mg, 120 mg (fed and fasted), and 200 mg. The multiple dosing study included 45 participants, randomized to 30 mg, 60 mg, or placebo daily for four weeks. AZD0780 reduced LDL-C by 30% (95% CI -41% to -18%) and 38% (95% CI -48% to -30%) at the 30 mg and 60 mg doses, respectively. Drug exposure increased by around 30% in the fed state, relative to fasting. Additionally, 35 patients with hypercholesterolemia (LDL-C >100 mg/dL to 190 mg/dL) were treated with 20 mg rosuvastatin for three weeks followed by AZD0780 30 mg or placebo for four weeks. The addition of AZD0780 led to a reduction in LDL-C of 52% (95% CI -57% to -45%), resulting in a total reduction up to 78% from baseline. Modeling suggests that the combination had a synergistic effect on LDL-C lowering.

MK-0616 (also known as enlicitide decanoate) is an oral small molecule inhibitor of PCSK9 in clinical development by Merck. It is a macrocyclic peptide that is expected to bind to the LDLR binding domain of PCSK9 [62]. In human plasma it inhibits PCSK9 with an IC_{50} of 2.5 ± 0.1 nM, which is in the range of physiological levels. It must be formulated with an absorption enhancer, such as PE Labrasol or sodium caprate, to allow for adequate oral bioavailability, since it is not cell permeable [62]. Once delivered, the lack of passive permeability could potentially boost the safety and efficacy of the parent compound *in vivo*.

In a Phase 1 multiple ascending dose study in 40 statin-treated participants with LDL-C between 70 and 160 mg/dL, oral doses of 10 mg and 20 mg per day in a fasted state for 14 days led to LDL-C reductions of 58.2% (95% CI 41.1% to 82.6%) and 60.5% (95% CI 42.9% to 85.3%), respectively [62]. The Cmax was reduced under fed conditions, and negatively impacted drug efficacy, such that LDL-C reductions at the 10 mg dose only reached 11.6% (95% CI 7.5% to 17.8%) when it was administered 30 minutes after a standard meal.

MK-0616 was tested in a randomized, double-blind, placebo-controlled Phase 2b trial including 380 participants with hypercholesterolemia and varying atherosclerotic cardiovascular disease risk, with 38.6% having clinical ASCVD, 56.4% at intermediate/high risk for ASCVD, and 4.7% at borderline risk [63]. The use of background statin therapy also varied, with 39.4%, 34.6%, and 26.0% of participants not taking statins, taking low- to moderate-intensity therapy, or taking high-intensity therapy, respectively. MK-0616 was tested at daily oral doses (in a fasted state) of 6, 12, 18, or 30 mg for eight weeks, and participants achieved placebo-adjusted LDL-C lowering of -41.2%, -55.7%, -59.1%, and -60.9% for each of these doses, respectively. Significant reductions were also observed on levels of ApoB (up to 52%) and non-HDL-C (up to 56%).

NNC0385-0434 is a small molecule inhibitor of PCSK9 that was previously in clinical development for hypercholesterolemia by Novo Nordisk. In a Phase 2 trial in 267 patients with or at risk for atherosclerotic cardiovascular disease and elevated LDL-C (≥1.8 mmol/L) on statin therapy, participants were randomized to oral doses of NNC0385-0434 co-formulated with the oral absorption enhancer sodium N-[8-(2-hydroxybenzoyl)amino] caprylate at 15 mg, 40 mg, or 100 mg per day in comparison to placebo or open-label evolocumab (140 mg Q2W s.c.) for 12 weeks [64]. The placebo-corrected degree of LDL-C reduction at week 12 was 32%, 44.9%, and 61.8% for the 15 mg, 40 mg, and 100 mg doses, respectively. The degree of LDL-C lowering from baseline was similar for the 100 mg dose (56.2%, SE 4.0%) compared to evolocumab (59.6%, SE 4.1%). Clinical development of NNC0385-0434 has been discontinued by the study sponsor due to portfolio considerations.

PCSK9 CRISPR: Verve Therapeutics has several CRISPR-based gene editing programs aimed at protecting against atherosclerotic cardiovascular disease. Their most advanced program targets PCSK9, for which they have developed two gene editor constructs, VERVE-101 and VERVE-102. These are single-course base editing therapies aimed at inactivating PCSK9 in the liver.

VERVE-101 inactivates PCSK9 by inducing an A/T to G/C base change leading to the disruption of a donor splice site, without introducing double-strand breaks. It is targeted to the liver using a lipid nanoparticle delivery system (ionizable lipid: ALC-0307, PEG lipid: ALC-0159), with uptake in hepatocytes via endocytosis through LDLR (Company Presentation). In non-human primates, a single dose of VERVE-101 (1.5 mg/kg) administered intravenously led to a durable reduction in LDL-C, around 70%, for at least 3 years. VERVE-101 was tested in the Phase 1 proof-of-concept, open-label, heart-1 trial in 13 adult patients with heterozygous familial hypercholesterolemia (HeFH). This single-ascending dose study tested VERVE-101 at intravenously administered doses of 0.1 mg/kg, 0.3 mg/kg, 0.45 mg/kg, and 0.6 mg/kg. Participants were pre-treated with dexamethasone and antihistamines. VERVE-101 treatment led to dose-dependent reductions in PCSK9 blood protein levels, with reductions over 60% for the higher dose cohorts. LDL-C reductions were also dose-dependent and sustained at the higher doses. The mean reduction in LDL-C for those treated at the 0.45 mg/kg dose (n=6) was 42% at six months, and was sustained for at least 12 months. A single participant dosed at the 0.6 mg/kg (effective dose ~0.5 mg/kg) dose showed a mean reduction of 57% at six months, that was sustained for at least 18 months. However, study enrollment was paused due to laboratory abnormalities, including transient increases in liver enzymes at higher doses. The investigators believe that these are related to the lipid nanoparticles, and are conducting further nonclinical studies.

VERVE-102 uses the same guide RNA and base editor as VERVE-101, to inactivate PCSK9. However, it uses a different lipid nanoparticle delivery system (ionizable lipid: LP000001, PEG lipid: DMG-PEG_{2000}), along with the addition of the hepatocyte-targeting moiety GalNAc, which will allow for liver targeting via ASGPR or LDLR (Company Presentation). The GalNAc moiety has been successfully used to target other therapeutics to hepatocytes, such as inclisiran, and Lp(a)-targeting siRNAs and ASOs. Additionally, these lipid carriers (ionizable and PEG) have been shown to be well-tolerated in other clinical trials. VERVE-102 is being tested in the first-in-human open-label Phase 1b heart-2 trial in patients with HeFH and/or premature coronary artery disease (NCT06164730). This single-ascending dose study is designed to test four intravenous doses of VERVE-102, with three to nine participants per dose cohort.

Cancer: PCSK9 INHIBITION MAY AUGMENT RESPONSES TO IMMUNOTHERAPY

PCSK9 has been found to be elevated in a variety of cancers, and associated with poor prognosis [65]. PCSK9 may impact cancer progression through a variety of mechanisms [65]. Cholesterol is known to play a role in the development and progression of cancer, thus it may impact cancer metabolism through the regulation of circulating cholesterol levels. Preclinical studies suggest that PCSK9 may also selectively impact tumor cell survival, such that PCSK9 inhibition may promote the apoptosis of cancer cells, while preserving the integrity of the host tissue. Additionally, there are studies to suggest that PCSK9 may play a context-dependent role in immune regulation, such that PCSK9 inhibition may enhance anti-cancer immune responses.
Based on these findings, PCSK9 inhibitors are currently being tested in clinical trials for their ability to augment the anti-cancer capacity of cancer immunotherapy, primarily in combination with anti-PD-1 mAbs.

Safety: PCSK9 inhibitors are generally well-tolerated, with injection site reactions as the most common adverse event, and muscle pain has also been reported. They can be safely used with statins and other lipid-lowering medications.

Types of evidence:

- 8 meta-analyses of RCTs for PCSK9 inhibitors and safety outcomes
- 2 real-world evidence safety reports
- 2 clinical trials for ongericimab
- 3 clinical trials for recaticimab
- 2 clinical trials for AZD8233
- 1 clinical trial for AZD0780
- 2 clinical trials for MK-0616
- 1 clinical trial for NNC0385-0434
- 1 clinical trial for VERVE-101
- Numerous laboratory studies

PCSK9 inhibitors have generally been found to be safe and well-tolerated in clinical trials and in clinical practice when used as monotherapy or in combination with statins. The currently approved PCSK9 inhibitors are all administered via subcutaneous injection, and the primary adverse event associated

with their use is injection site reactions. In some cases, the addition of a PCSK9 inhibitor is associated with improved safety due to their efficacy in reducing serious cardiovascular-related adverse events.

Comparative safety analyses:

A network meta-analysis of 33 RCTs involving 23,375 patients with hyperlipidemia compared the efficacy and safety of PCSK9-targeted mAbs (alirocumab and evolocumab) with inclisiran and statins plus ezetimibe [45]. The safety profiles were found to be comparable.

A network meta-analysis of 26 Phase 3 RCTs including 16,510 patients with hyperlipidemia on a statin background assessing the safety and efficacy of PCSK9 inhibitors alirocumab, evolocumab, tafolecimab, or inclisiran) in comparison to ezetimibe or placebo found that the PCSK9 inhibitors generally did not increase the risk for adverse events, or serious adverse events [36]. They exhibited a favorable safety profile overall, with injection-site reactions as the primary adverse event.

Muscle symptoms are one of the primary adverse events that limit the tolerability of statins. A network meta-analysis of 28 RCTs including 100,193 patients, assessed the impact of PCSK9 inhibitor therapies (bococizumab, alirocumab, evolocumab, or inclisiran) on muscle-related symptoms [66]. In all of the comparisons, the confidence intervals included 1.0, indicating that the risk for muscle symptoms was not significantly elevated. Of the three mAbs, evolocumab was associated with the lowest risk for new onset muscle symptoms. Inclisiran was associated with a higher risk for creatine kinase levels >3x the upper limit of normal, relative to alirocumab or evolocumab.

A comparative analysis of the real-world safety profiles for inclisiran relative to the PCSK9-targeting mAbs alirocumab and evolocumab based on the FDA Adverse Event Reporting System (FAERS) found that inclisiran was associated with a higher incidence of adverse events classified as gastrointestinal disorders (reporting odds ratio [ROR]: 1.55, 95% CI 1.4 to 1.69), infections and infestations (ROR: 1.39, 95% CI 1.23 to 1.57), musculoskeletal and connective tissue disorders (ROR: 1.70, 95% CI 1.60 to 1.82), as well as renal and urinary disorders (ROR: 1.61, 95% CI 1.33 to 1.95) [67]. But, inclisiran was associated with lower rates of events related to eye disorders (ROR = 0.39, 95% CI 0.30 to 0.52), general disorders and administration site conditions (ROR: 0.59, 95% CI 0.55 to 0.62), injury, poisoning and procedural complications (ROR: 0.70, 95% CI 0.57 to 0.86), neoplasms benign, malignant and unspecified (inclcysts and polyps) (ROR: 0.71, 95% CI 0.53 to 0.96), as well as skin and subcutaneous tissue disorders (ROR: 0.73, 95% CI 0.65 to 0.83).

A retrospective disproportionality analysis based on 15,236 individual case safety reports from the EudraVigilance Database for inclisiran (563 cases), alirocumab (5,016 cases), or evolocumab (9,562 cases) found that both classes of PCSK9 inhibitors showed a similar trend in increasing case reports over

the first five post-marketing semesters [68]. Relative to the PCSK9-targeting mAbs, inclisiran was associated with increased cases of myalgia (ROR: 2.43, 95% CL 1.83 to 3.10) and 'drug ineffective' (ROR: 6.74, 95% CI 4.14 to 10.99). Other commonly reported events were related to the injection site, including pain, erythema, pruritus and reactions.

Alirocumab: The FDA prescribing label indicates that the most common adverse events (≥5%) in clinical trials associated with alirocumab are nasopharyngitis, injection site reactions, and influenza. It is contraindicated in anyone with a prior hypersensitivity reaction to it. Anti-drug antibodies were detected in 4.8% of patients treated with alirocumab (vs 0.6% in the control group) for a pool of ten RCTs testing alirocumab, and 1.2% of patients developed neutralizing antibodies. The presence of anti-drug antibodies was associated with a higher incidence of injection site reactions.

Evolocumab: According to the FDA prescribing label, the most common adverse events (>5%) associated with evolocumab in trials including patients with primary hyperlipidemia were nasopharyngitis, upper respiratory tract infections, influenza, back pain, and injection site reactions. In trials including patients with established cardiovascular disease, the most common adverse events occurring at a higher rate with evolocumab relative to placebo were diabetes mellitus, nasopharyngitis and upper respiratory tract infection. It is contraindicated in individuals with a hypersensitivity to it or any of its excipients. The immunogenicity of evolocumab is low, as only 0.3% (48 out of 17,992 adult patients) participants treated with evolocumab in a cohort of pooled trials developed anti-drug antibodies, and none tested positive for neutralizing antibodies. Anti-drug antibodies were not detected in pediatric patients treated with evolocumab in clinical trials.

Airocumab and Evolocumab: A meta-analysis of 56 studies including 85,123 adult participants assessing the safety profiles of alirocumab and evolocumab found that they were not associated with adverse events leading to death (OR: 0.94, 95% CI 0.84 to 1.04), but were associated with a reduction in non-fatal serious adverse events (OR: 0.93, 95% CI 0.89 to 0.98) [69]. The primary treatment-related adverse event associated with the PCSK9-targeted mAbs is local injection site reactions (OR: 1.54, 95% CI 1.37 to 1.73). The mAbs had no significant effects on cognitive function, liver enzymes, or creatine kinase. Evolocumab was associated with a worsening of diabetes in studies less than 24 weeks (OR: 2.3), but was associated with reduced odds of worsening in studies over 24 weeks (OR: 0.89).
A meta-analysis of seven RCTs testing alirocumab or evolocumab, including 2,948 statin-treated patients following acute coronary syndrome found that treatment with the PCSK9-targeted mAbs did not significantly affect the incidence of non-serious side effects, but was associated with a reduction in the

risk for serious adverse events (RR: 0.77, 95% CI 0.60 to 0.99), such as myocardial infarction and death, in this population [49].

Tafolecimab: No exposure dependency was observed in a safety analysis of six clinical trials including a total of 1,388 participants testing tafolecimab [42]. It was generally found to have a favorable safety profile, comparable to other PCSK9-targeted mAbs, with tafolecimab-treated participants showing a lower incidence of adverse events. The most commonly reported treatment-emergent adverse events in clinical trials were upper respiratory tract infection, increased blood creatine phosphokinase, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and hypertension [40]. Reported serious adverse events were assessed as unlikely to be related to the study drug.

Ongericimab: In Phase 1a and 1b/2 trials, ongericimab was generally found to be well-tolerated. There were no serious adverse events or adverse events leading to discontinuation, and reported severe adverse events were deemed unrelated to the study drug [56]. The most common treatment-emergent adverse events were respiratory infections and hyperglycemia in the Phase 1a and 1b/2 trials, respectively. Injection site reactions were primarily of mild severity, and all adverse events resolved during the follow-up period.

Recaticimab: Recaticimab has shown a good safety profile in clinical trials, thus far. Incidences of adverse events have generally been similar between recaticimab and placebo arms [59]. In a Phase 1b/2 trial, the most common treatment-emergent adverse events were upper respiratory tract infection (recaticimab: 19.8% vs placebo:15.8%), increased ALT (9.9% vs10.5%), increased blood glucose (8.8% vs 0), and increased gamma-glutamyltransferase (GGT) (6.6% vs 0) [57]. In one recaticimab-treated participant, the increase in GGT was deemed a severe treatment-emergent adverse event. 26.4% of recaticimab-treated participants developed anti-drug antibodies, but their occurrence was not related to serum exposure, and only 1.1% developed neutralizing antibodies.
In the Phase 3 REMAIN-1 trial, adverse rates were generally low (14.1% vs 11.1% at 12 weeks) [58]. Injection site reactions were the most common treatment-emergent adverse events.

Inclisiran: In clinical trials, rates of treatment-emergent events were generally similar between participants in inclisiran and placebo-treated groups. In both clinical trials and real-world studies, the most common adverse event associated with inclisiran is injection site reactions. According to the FDA prescribing label, the most common adverse events (≥ 3%) associated with inclisiran in clinical trials were injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity,

and dyspnea. In a cohort of 1,830 participants treated with inclisiran in clinical trials tested for anti-drug antibodies, only 1.7% had evidence of newly onset anti-drug antibodies.
Pooled safety data from the ORION -8, -9, -10, and -11 trials found that the only treatment-emergent adverse events occurring at a higher rate with inclisiran, relative to placebo, were mild to moderate bronchitis (4.3% vs 2.7%) and injection site reactions (5% vs 0.7%) [43].
A meta-analysis of seven RCTs testing inclisiran including 4,790 patients with dyslipidemia assessing safety outcomes found that inclisiran was associated with an increased risk for injection site reactions (RR: 6.50, 95% CI 3.20 to 13.20; based on n=4,658), but was not significantly associated with risk for major adverse cardiovascular events (RR: 0.98; 95% CI, 0.82 to 1.17; based on n=4,105), nasopharyngitis (RR: 1.1, 95% CI 0.83 to 1.45; based on n=2,165), or type 2 diabetes (RR: 1.02, 95% CI 0.85 to 1.21; based on n=3,624) [70].

AZD8233: A Phase 1 study found that the ASO, AZD8233, was not associated with QT prolongation [71], however, transient, moderate elevations in liver enzymes occurred in some participants in Phase 2 trials (Press release).

AZD0780: In a Phase 1 ascending dose trial in participants with elevated LDL-C, AZD780 was found to be generally safe and well-tolerated at single oral doses up to 120 mg and multiple oral doses up to 60 mg per day [61]. AZD0780 exposure increased around 30% under fed relative to fasting conditions, but this was within the range to allow for dosing with or without food. It also showed a good safety profile when used in combination with rosuvastatin.

MK-0616: The oral PCSK9 inhibitor MK-0616 has generally been found to be safe and well-tolerated in clinical trials to date. In a Phase 1 trial, there were no serious adverse events, dose-limiting toxicities, or clinically meaningful changes on laboratory measures or ECG [62]. Drug-related adverse events included gastroesophageal reflux disease and dry mouth, dyspepsia, hunger, dizziness, insomnia, and flushing, of mild to moderate intensity, each occurring in only one or two participants. Drug concentrations are reduced when administered in a fed state, thus dosing is recommended under fasting conditions. In a Phase 2b trial testing doses up to 30 mg/day (under fasting conditions), adverse event rates were comparable across study groups (~33%), and there were no study-related serious adverse events [63]. The most common adverse event across groups was Covid-19 infection, while other common adverse events included diarrhea, dyspepsia, fatigue, nausea, and arthralgia. There were no dose-dependent effects on any adverse event class.

NNC0385-0434: The oral PCSK9 inhibitor, NNC0385-0434, was generally well-tolerated in Phase 1 and 2 trials, with gastrointestinal disorders, as the most common treatment-related adverse event [64].

VERVE-101: Laboratory test abnormalities, namely transient elevations in liver enzymes (ALT) were observed at higher doses (0.45 mg/kg and 0.6 mg/kg) were observed in the pilot heart-1 trial testing first in class CRISPR-based therapeutic targeting PCSK9, VERVE-101, in patients with HeFH (Company Presentation). Some mild elevations were also observed for bilirubin, but in all cases, levels remained below the upper limit of normal. One participant experienced a serious adverse event of Grade 3 drug-induced thrombocytopenia coupled with an increase in liver enzymes. Enrollment in the study was paused in response to these safety concerns. Based on nonclinical studies, the adverse effects appear to stem from the lipid nanoparticle system rather than the CRISPR activity. As a result, a different lipid nanoparticle system is being used for Verve's other CRISPR-base therapeutic targeting PCSK9, VERVE-102. The ionizable and PEG lipids used for VERVE-102 have been safely used in other clinical programs.

Drug interactions:

Alirocumab: There are interactions with two drugs used to treat myasthenia gravis, efgartigimod alfa (Vygart) and rozanolixizumab (Rystiggo) because they can reduce the blood levels and efficacy of alirocumab (Drugs.com).

Evolocumab: : There are interactions with two drugs used to treat myasthenia gravis, efgartigimod alfa (Vygart) and rozanolixizumab (Rystiggo) because they can reduce the blood levels and efficacy of evolocumab (Drugs.com).

Inclisiran: There are no established or expected drug interactions with inclisiran (Rxlist).

Sources and dosing:

FDA approved PCSK9 inhibitors:
Alirocumab is marketed by Regeneron and Sanofi under the brand name Praluent®. It is approved as an adjunct for diet and maximally tolerated statins in adult patients with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. The recommended dosing for patients with atherosclerotic cardiovascular disease is 75 mg

Q2W, or an alternative less frequent dosing schedule of 150 mg Q4W administered via subcutaneous injection. For individuals with inadequate responses, the dosage can be increased to 150 mg Q2W.

Evolocumab is marketed by Amgen under the brand name Repatha®. It is approved for use in adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and coronary revascularization; as an adjunct to diet, or in combination with other LDL-C-lowering therapies, such as statins, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia. It is also approved for use in pediatric patients aged 10 years and older with heterozygous or homozygous familial hypercholesterolemia as an adjunct to diet and other LDL-C-lowering therapies to reduce LDL-C. It is administered via subcutaneous injection. The recommended dose in adults with cardiovascular disease/primary hyperlipidemia or pediatric patients with familial hypercholesterolemia is 140 mg Q2W, with an alternative less frequent dosing of 420 mg Q4W. In adult patients with homozygous familial hypercholesterolemia, the recommended dose is 420 mg Q4W, which can be increased to 420 mg Q2W in the case of an inadequate response.

Inclisiran is marketed by Novartis under the brand name Leqvio®. It is approved for use as an adjunct to diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, in need of additional lowering of LDL-C. The recommended dose is a single subcutaneous injection of 284 mg, followed by a second injection at three months, and then every six months afterwards.

<u>PCSK9 inhibitor approved in China</u>:
Tafolecimab is marketed for use in China by Innovent Biologics, Inc. under the brand name Sintbilo®. It is approved for use in China by the National Medical Products Administration (NMPA) for adult patients with primary hypercholesterolemia (heterozygous familial and non-familial hypercholesterolemia) and mixed dyslipidemia. It has three approved dosing regimens by subcutaneous administration, 150 mg Q2W, 450 mg Q4W, and 600 mg Q6W.

<u>PCSK9 inhibitors not yet approved and currently in clinical development</u>:
Recaticimab is currently in clinical development in China by Jiangsu Hengrui Pharmaceuticals for hypercholesterolemia. In Phase 3 trials, it was tested at doses of 150 mg Q4W, 300 mg Q8W, or 450 mg Q12W via subcutaneous injection.

Ongericimab is currently in clinical development in China by Junshi Biosciences for hypercholesterolemia. In Phase 1 trials, it was tested at doses of 150 mg Q2W, 300 mg Q4W, or 450 mg Q4W, administered via subcutaneous injection.
AZD780 is currently in clinical development by AstraZeneca for hypercholesterolemia. In a Phase 1 trial, it was tested at oral doses up to 60 mg per day.
MK-0616 is currently in clinical development by Merck. In a Phase 2b trial, it was tested at oral doses ranging from 6 mg to 30 mg per day, under fasting conditions. It is currently being tested at an oral dose of 20 mg per day in a large Phase 3 trials in adult patients with hypercholesterolemia.

Research underway:

PCSK9 inhibitors are in clinical trials for several categories of indications.

Currently, PCSK9 inhibitors are approved for hypercholesterolemia, and there are numerous ongoing clinical trials testing approved inhibitors for other **cardiovascular-related conditions**.

Alirocumab is being tested in trials for neo-atherosclerosis (NCT03533959), acute ischemic stroke associated with atherosclerosis (NCT06083961), acute stroke and symptomatic intracranial atherosclerosis (NCT05001984), symptomatic intracranial atherosclerotic stenosis (NCT06052020), asymptomatic intracranial atherosclerotic stenosis (NCT06080256), in heart transplant patients to prevent cardiac allograft vasculopathy (NCT03537742) (NCT04193306), cardiovascular risk in treated HIV infection (NCT03207945), after acute myocardium infarction (NCT05292404) (NCT04731155), in combination with bempedoic acid and ezetimibe in statin-intolerant patients (NCT06381947), and calcific aortic valve stenosis (NCT04968509). (Clinicaltrials.gov)

Evolocumab is being tested in trials for ST-segment elevation myocardial infarction (STEMI) (NCT06081803), for its effects on Lp(a) in combination with obiceptrapib (NCT06496243), subclinical atherosclerosis in patients with familial hypercholesterolemia (NCT04313270), very early after myocardial infarction (NCT05284747), symptomatic intracranial atherosclerotic stenosis (NCT05741086), in patients with high cardiovascular risk (NCT03872401), abdominal aortic aneurysm (NCT06081153), acute ischemic stroke (NCT06134635) (NCT06696820), acute coronary syndrome patients who underwent/undergoing percutaneous coronary intervention (NCT04719221) (NCT05661552), in patients with chronic total occlusions after successful percutaneous coronary intervention (NCT05623995), multivessel coronary disease after acute myocardial infarction (NCT06740552), LDL lowering after acute

myocardial infarction (NCT04951856), left ventricular remodeling in patients with anterior STEMI undergoing primary percutaneous coronary intervention (NCT05613426), effects on retinal microvessels in patients with coronary heart disease (NCT05802108), established atherosclerotic cardiovascular disease (NCT06295679), in combination with bempedoic acid and ezetimibe in statin-intolerant patients (NCT06381947), and calcific aortic stenosis (NCT04968509). (Clinicaltrials.gov)

Inclisiran is being tested in trials for its effects on carotid plaques as assessed by carotid ultrasound (NCT06586684), atherosclerotic cardiovascular disease (NCT06249165), primary hypercholesterolemia or mixed dyslipidemia (NCT06386419) (NCT05399992), long-term safety in patients with familial hypercholesterolemia (NCT05682378), to reduce the risk for atherosclerotic plaque rupture (NCT06791031), prevention of coronary artery disease (NCT06494501), pediatric patients with familial hypercholesterolemia (NCT06597019) (NCT06597006), to assess the effects on the morphology of coronary vulnerable plaques (NCT06338293), in combination with bempedoic acid in patients with atherosclerotic cardiovascular disease (NCT06431763), hypercholesterolemia (NCT05192941) (NCT04765657), in combination with pelacarsen (NCT06813911), the effect on plaques in patients with acute myocardial infarction (NCT06372925) (NCT05360446), and for the prevention of cardiovascular events in high-risk primary prevention patients (NCT05739383). (Clinicaltrials.gov)

Tafolecimab is being tested in trials for patients in China with acute coronary syndrome undergoing percutaneous coronary intervention (NCT06096909), prior to percutaneous intervention in patients with acute myocardial infraction (NCT06683131), and in calcific aortic stenosis (NCT04968509). (Clinicaltrials.gov)

PCSK9 inhibitors are also being tested in the context of cancer, particularly for non-small cell lung cancer, for their ability to potentiate the anti-cancer activity of other therapeutics, particularly **with cancer immunotherapy**.

Alirocumab is being tested in combination with PD-1 inhibitor therapy in patients with metastatic non-small cell lung cancer that were refractory to prior anti-PD-1 therapy (NCT05553834), and as a neoadjuvant to chemotherapy in non-small cell lung cancer (NCT06385262).
Evolocumab is being tested in combination with immunotherapy in metastatic non-small cell lung cancer (NCT03337698), in combination with nivolumab/ipilimumab in treatment-naïve patients with metastatic non-small cell lung cancer (NCT05144529), and in combination with nivolumab in patients with metastatic renal cell carcinoma (NCT06284564).

Tafolecimab is being tested in combination with chemotherapy in patients with advanced or metastatic driver gene-negative non-small cell lung cancer after failure of first-line immunotherapy (NCT06421298). ***Recaticimab*** is being tested in combination with adebrelimab (anti-PD-1) and chemotherapy and for perioperative treatment of resectable non-small cell lung cancer (NCT06467617).

Novel, **orally administered PCSK9 inhibitors** are continuing to undergo clinical development for hypercholesterolemia

AZD780 is being tested in a Phase 1 trial in combination with itraconazole and carbamazepine in healthy participants (NCT06671405), a Phase 1 trial in combination with ezetimibe in healthy adults with elevated LDL-C (NCT06742853), a Phase 2 trial assessing the effects on systolic blood pressure (NCT06692764), and a Phase 2/3 trial in patients with dyslipidemia (NCT06834932). (Clinicaltrials.gov)

MK-0616 is being tested in a Phase 1 trial in patients with severe renal impairment (NCT06643377), a Phase 1 trial in patients with liver function problems (NCT06575959), a Phase 3 trial in adults with hypercholesterolemia (NCT05952856) and associated open-label extension study (NCT06492291), a Phase 3 trial in adults with high cardiovascular risk (NCT06008756), a Phase 3 trial in adults with heterozygous familial hypercholesterolemia (NCT05952869), and a Phase 3 study in comparison with ezetimibe or bempedoic acid or ezetimibe and bempedoic acid in adults with hypercholesterolemia (NCT06450366). (Clinicaltrials.gov)

Novel **CRISPR-based PCSK9 inhibitors** are also in Phase 1 trials.

VERVE-102 is being tested in a pilot open-label SAD Phase 1 trial in patients with heterozygous familial hypercholesterolemia (HeFH) or premature coronary artery disease who require additional lowering of LDL-C (NCT06164730).

Search terms:

Pubmed, Google: PCSK9, alirocumab, evolocumab, tafolecimab, recaticimab, inclisiran, AZD8233, AZD780, NNC0385-0434, MK-0616, VERVE-101

- Alzheimer's disease, neurodegeneration, cognition, aging, lifespan, cardiovascular, cancer, safety, clinical trials, systematic review, meta-analysis

Websites visited for PCSK9 inhibitors

- Clinicaltrials.gov (alirocumab, evolocumab, inclisiran, tafolecimab, recaticimab, ongericimab, AZD0780, MK-0616, NNC0385-0434, VERVE-101
- Drugs.com (alirocumab, evolocumab, inclisiran)
- WebMD.com (alirocumab, evolocumab, inclisiran)
- PubChem (AZD0780, MK-0616)
- DrugBank.ca (alirocumab, evolocumab, inclisiran, tafolecimab, recaticimab, ongericimab)
- Cafepharma (alirocumab, evolocumab, inclisiran)

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