AstraZeneca

at ACC 2025

AZD0780 (oPCSK9) Phase IIb PURSUIT

29-31 March 2025

Driving next-wave of innovation with novel mechanism to address dyslipidaemia

Dyslipidaemia at a glance

Elevated LDL-C is a key risk factor for cardiovascular disease and the occurrence of major cardiovascular events. Despite current treatment options, the global burden of dyslipidaemia continues to increase, and there remains a vast unmet need among high-risk patients for additional, efficacious treatment options.

In dyslipidaemia, PCSK9 causes LDL Receptor degradation, resulting in increased LDL-C levels. AZD0780, an oral PSCK9 inhibitor, binds to PCSK9 and, through its unique mechanism of action, allows the recycling of LDL Receptors back to a cell's surface which ultimately leads to increased LDL Receptor levels and lowered plasma LDL-C levels.

Our ambition

At AstraZeneca, our ambition is to eliminate LDL-C as a risk factor for cardiovascular disease.

c.2bn

suffering from dyslipidaemia globally[1]

4.4m

annual deaths caused by elevated LDL-C worldwide[2]

70%

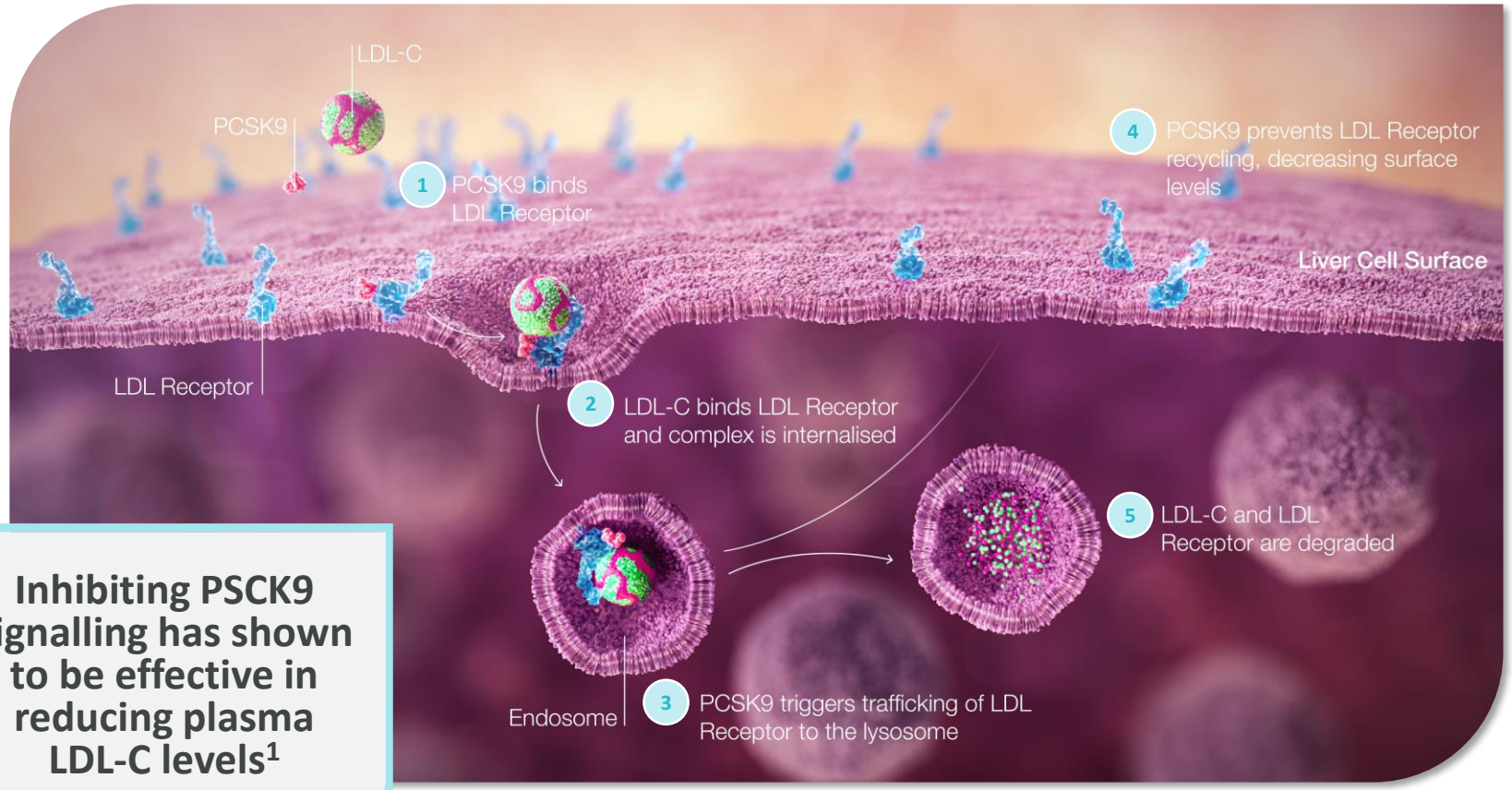
of patients with cardiovascular disease not at LDL-C target, despite high-intensity statins[3,4,5]

Sharon Barr
EVP, BioPharmaceuticals R&D

"Our work in dyslipidaemia builds on our strong heritage in cardiovascular, renal and metabolic diseases, where we are advancing novel therapies, alone or in combination with other molecules in our extensive portfolio, that could redefine treatment standards and patient outcomes."

1. WHO – Global Health Observatory Raised Cholesterol. 2. World Heart Federation. Cholesterol. 3. Krahenbuhl S, et al. Unmet Needs in LDL-C Lowering: When Statins Won't Do! Drugs. 2016;76(12):1175-90. 4. Ray KK, et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. Eur J Prev Cardiol. 2021;28(11):1279-89. 5. Ridker PM, et al. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. Eur Heart J. 2016;37(17):1373-9. LDL-C = low-density lipoprotein cholesterol; PCSK9 = protein convertase subtilisin/kexin type 9.

PCSK9, a well-known and validated target in LDL-C metabolism



Inhibiting PSCK9 signalling has shown to be effective in reducing plasma LDL-C levels[1]

1. **PCSK9 binds LDL Receptor**
2. **LDL-C binds LDL Receptor and complex is internalised**
3. **PCSK9 triggers trafficking of LDL Receptor to the lysosome**
4. **PCSK9 prevents LDL Receptor recycling, decreasing surface levels**
5. **LDL-C and LDL Receptor are degraded**

1. Koren MJ, Vega RB, Agrawal N, Xu Y, Barbour AM, Yu H, et al. An oral, small molecule PCSK9 inhibitor for treatment of hypercholesterolemia: The PURSUIT randomized trial. J Am Coll Cardiol. 2025; https://www.jacc.org/doi/10.1016/j.jacc.2025.03.499. LDL-C = low-density lipoprotein cholesterol; PCSK9 = protein convertase subtilisin/kexin type 9.

AZD0780, a potential best-in-class oral PCSK9 inhibitor and simple add-on to standard-of-care

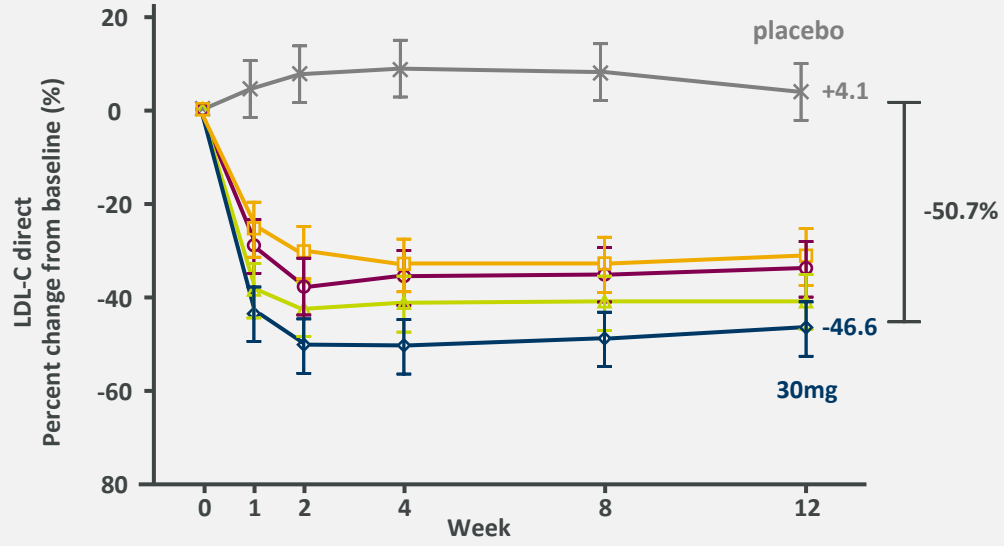
Differentiated profile
with high bioavailability, no observed food effect or fasting requirement and no permeability enhancer required

≥50% LDL-C reduction
in addition to standard-of-care statins

~80% LDL-C reduction
from untreated baseline

Oral small molecule
enabling combinations with other oral small molecules across portfolio

Phase IIb PURSUIT: AZD0780 demonstrated statistically significant LDL-C reduction when administered on top of standard-of-care statins vs. placebo[1]



placebo		n=86	79	78	76	77	77
AZD0780	1mg	n=86	80	84	85	77	74
AZD0780	3mg	n=85	82	77	80	77	74
AZD0780	10mg	n=84	81	82	81	80	80
AZD0780	30mg	n=85	83	82	82	80	76

Robust efficacy and favourable tolerability profile:

- 50.7% LDL-C reduction at 12 weeks[3,4]
- Similar efficacy observed regardless of moderate- or high-dose statin
- Well-tolerated following once-daily administration without any fasting or food requirements

84% of patients met AHA/ACC guideline-recommended LDL-C target (<70 mg/dL)[1,2]

1. Koren M, Agrawal N, Vega RB, Xu Y, Barbour AM, Rosenmeier JB. Efficacy and safety of AZD0780, an oral small molecule PCSK9 inhibitor for treatment of hypercholesterolemia: Results from a Ph2b randomized placebo-controlled clinical trial. Presented at: American College of Cardiology Annual Scientific Session (ACC 2025); 2025 Mar 29-31; Chicago, IL. 2. Koren MJ, Vega RB, Agrawal N, Xu Y, Barbour AM, Yu H, et al. An oral, small molecule PCSK9 inhibitor for treatment of hypercholesterolemia: The PURSUIT randomized trial. J Am Coll Cardiol. 2025; https://www.jacc.org/doi/10.1016/j.jacc.2025.03.499. 3. With once-daily AZD0780 (30mg) taken in addition to standard-of-care statins. 4. 95% CI: -59.0%, -42.4%, p<0.001. PCSK9 = protein convertase subtilisin/kexin type 9; LDL-C = low-density lipoprotein cholesterol; AHA = American Heart Association; ACC = American College of Cardiology.

$5bn+ potential with oral AZD0780 add-on and combination opportunities

Addressing c.70% of dyslipidaemia patients not reaching LDL-C goals

Maximising cardiovascular benefit with complimentary lipid-lowering combinations

Potential to reduce residual cardiovascular risk with novel combinations

oPCSK9 add-on
AZD0780 + statin

Proven broad efficacy
with 50.7% LDL-C reduction regardless of statin dose (~80% reduction from untreated baseline) which can eliminate LDC-C as a risk factor for cardiovascular disease in the vast majority of patients via once-daily oral tablet with no food effect

oPCSK9 combination
AZD0780 + lipid-lowering therapy

Revolutionising standard-of-care
with potential to achieve best-in-class efficacy with simplified treatment regime

oPCSK9 + oLp(a)
AZD0780 + pre-clinical asset[1]

Novel mechanism
with potential lipid-lowering benefit in a range of cardiovascular indications

oPCSK9 + oGLP-1 RA
AZD0780 + AZD5004

Potential to reduce cardiovascular disease
by addressing modifiable risk factors of LDL-C, T2D and overweight/obesity

Future potential combination opportunities

1. Following exclusive license agreement with CSPC Pharmaceutical Group Ltd for YS2302018, a pre-clinical candidate small molecule. Peak Year Revenue, non-risk adjusted; includes combination opportunities. LDL-C = low-density lipoprotein cholesterol; oPCSK9 = oral protein convertase subtilisin/kexin type 9; oLp(a) = oral lipoprotein(a); oGLP-1 RA = oral glucagon-like receptor peptide-1 receptor agonist; T2D = type 2 diabetes.