AstraZeneca
What science can do

Break-out session 1

New CVRM: emerging pipeline

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25 March 2021

Interactive event for investors and analysts. This webinar is being recorded.
https://astrazeneca.zoom.us/webinar/register/WN_geSO9qdvR1GP_ysnR79e8A

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Bold ambitions in four disease areas with prioritised medicines

Cardiovascular

Reverse atherosclerosis to halt morbidity and prolong life

17.9 million

deaths per year[1]

AZD8233 PCSK9[2] ASO[3] (secondary CV[4] prevention)

Heart failure

Eliminate hospitalisations and cure HFrEF[5]

64 million

people worldwide affected by HF[5,6]

AZD4831 MPO[7] inhibitor (HFpEF[8])
AZD9977 MCR[9] modulator +
***Farxiga* (HF, CKD[10])**

Renal

Eliminate dialysis

840 million

people worldwide affected by CKD[11]

zibotentan ERA[12] antagonist
***Farxiga* SGLT2[13] inhibitor (CKD)**

Metabolism Liver disease

Cure diabetes
Eliminate NASH[14]

530 million

people affected worldwide[15]

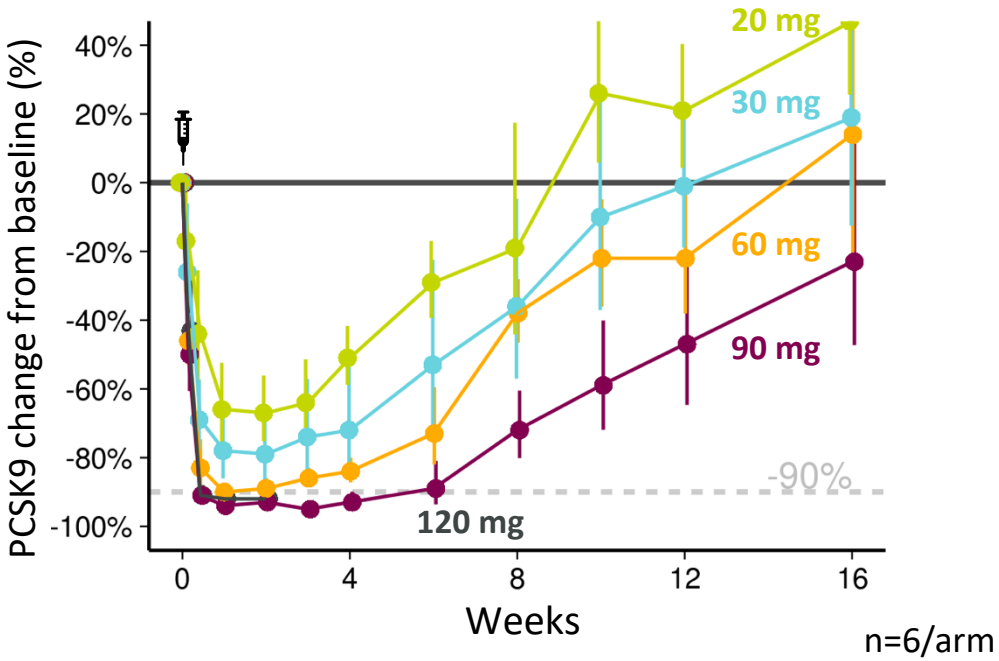
cotadutide GLP-1[16]/glucagon agonist (NASH, DKD[17])

1. WHO fact sheet 2016. www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) 2. Proprotein convertase subtilisin/kexin type 9 3. Anti-sense oligonucleotide 4. Cardiovascular 5. Heart failure with reduced ejection fraction 6. Heart failure 7. Myeloperoxidase 8. Heart failure with preserved ejection fraction 9. Mineralocorticoid receptor 10. Chronic kidney disease 11. Jager, et al. Nephrology Dialysis Transplantation 2019;34:1803-1805 12. Endothelin receptor antagonist 13. Sodium-glucose co-transporter-2 inhibitor 14. Non-alcoholic steatohepatitis 15. Younossi ZM, et al. Non-alcoholic fatty liver disease - a global public health perspective. J of Hepatology. 2019; 70(3):531-544 16. Glucagon-like peptide-1 17. Diabetic kidney disease.

AZD8233: PCSK9 ASO

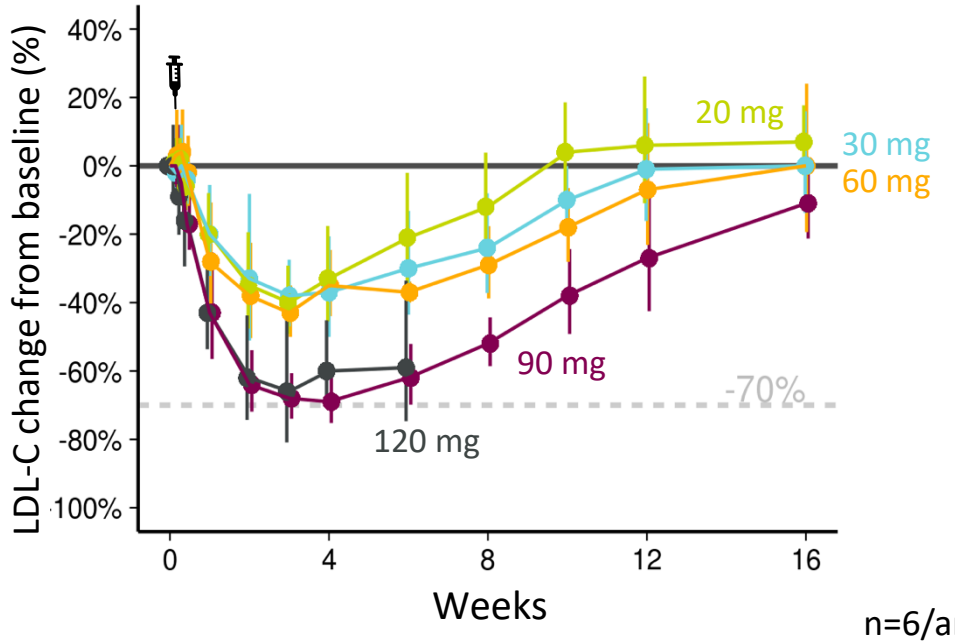
Potential for improved efficacy with convenient at-home administration

Up to 90% PCSK9 inhibition for six weeks in Phase I SAD[1]



n=6/arm

Up to 70% reduction of LDL[2] cholesterol in Phase I SAD



n=6/arm

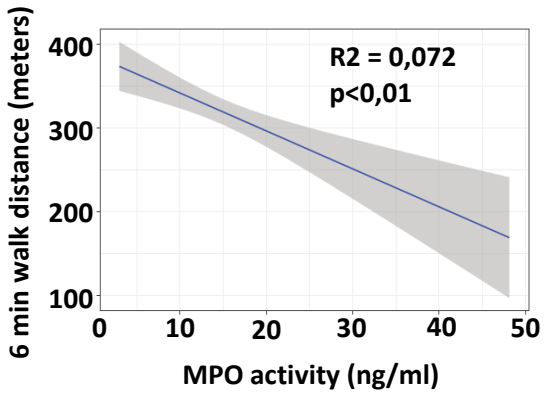
Potent and durable reduction of PCSK9 and LDL cholesterol
Phase IIb data in H2 2021

1. Single-ascending dose trial 2. Low-density lipoprotein.
Source: American Heart Association 2020, C Nilsson et. al. Data is geomean ± sd.

AZD4831: small-molecule MPO inhibitor

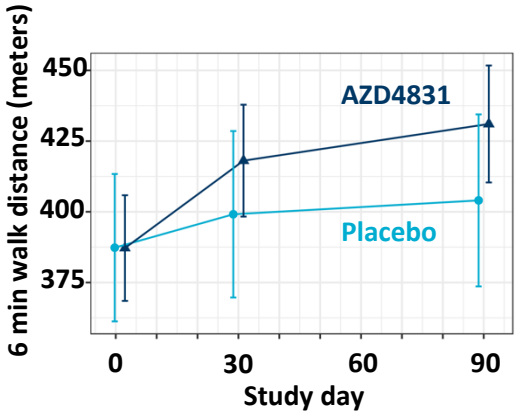
Targeting blood vessels inflammation and fibrosis

PROMIS observational trial in HFpEF patients



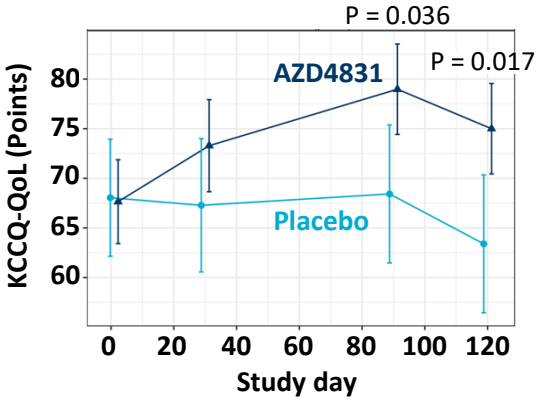
n=240

Trend towards 6MWD improvement



n=27

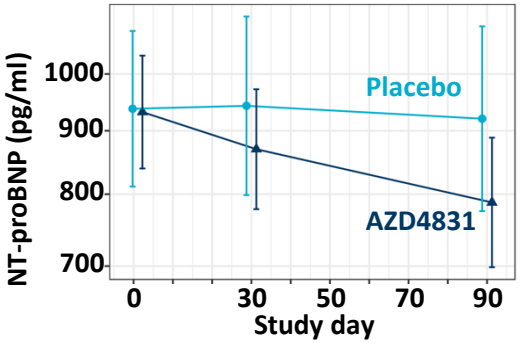
Improved quality of life at day 90



Similar trends on improvement versus placebo in all KCCQ[2] domains

n=27

Reduced NT-proBNP[3]



n=27

MPO correlated with 6MWD[1] and clinical outcome

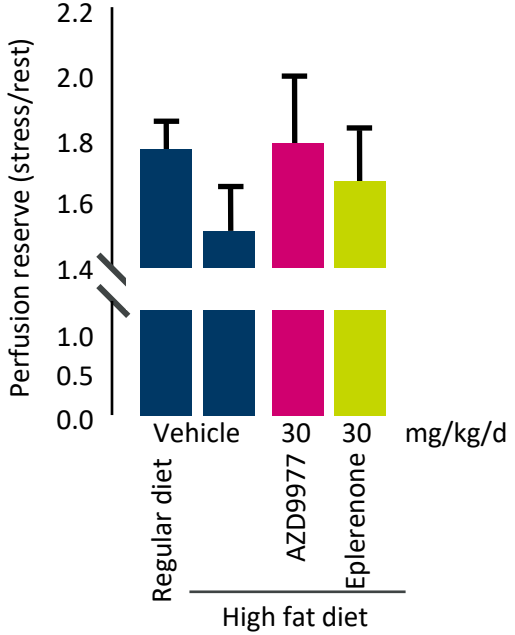
SATELLITE Phase IIa: improved symptomatic and biomarker endpoints
Phase IIb start in H1 2021

1. Six-minute walk distance 2. The Kansas City Cardiomyopathy Questionnaire 3. N-terminal pro-B-type natriuretic peptide, an established biomarker for heart failure.
Source: AstraZeneca data on file.

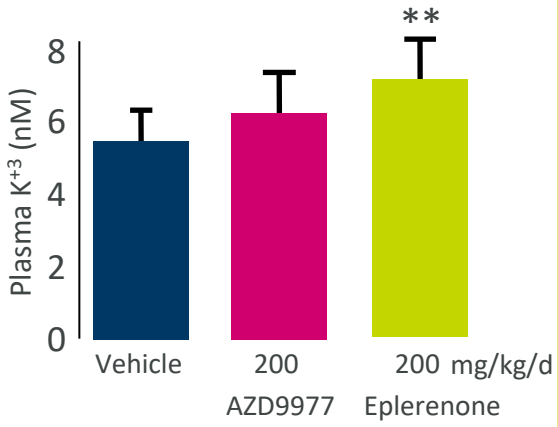
Farxiga: novel, fixed-dose combinations

AZD9977 and zibotentan combos with opportunity to enhance efficacy

Rodent model: AZD9977 improved cardiac function similar to MRAs[1]



Rodent model: AZD9977 had a predicted reduced hyperkalemia risk

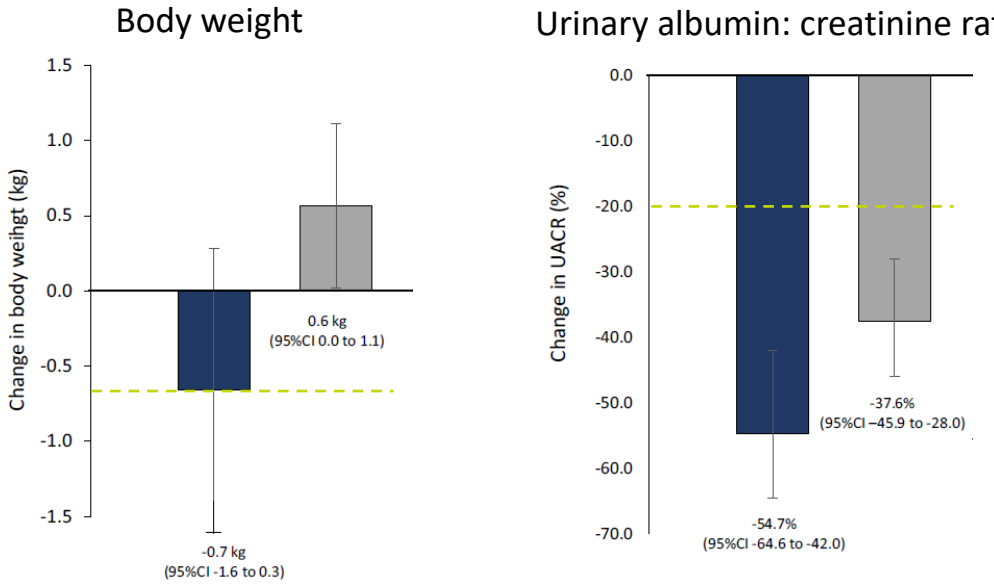


** p<0.01

Complimentary efficacy and safety profiles with opportunity for AZD9977 + *Farxiga* FDC[2] in HF patients with CKD

SONAR[3] *post hoc* sub-analysis

DELIGHT trial data: *Farxiga* effect on BW (left) and uACR (right)



n=14, n=57 respectively

Adding SGLT2 inhibitor to ERA[4] mitigated fluid retention and reduced albuminuria compared to ERA alone

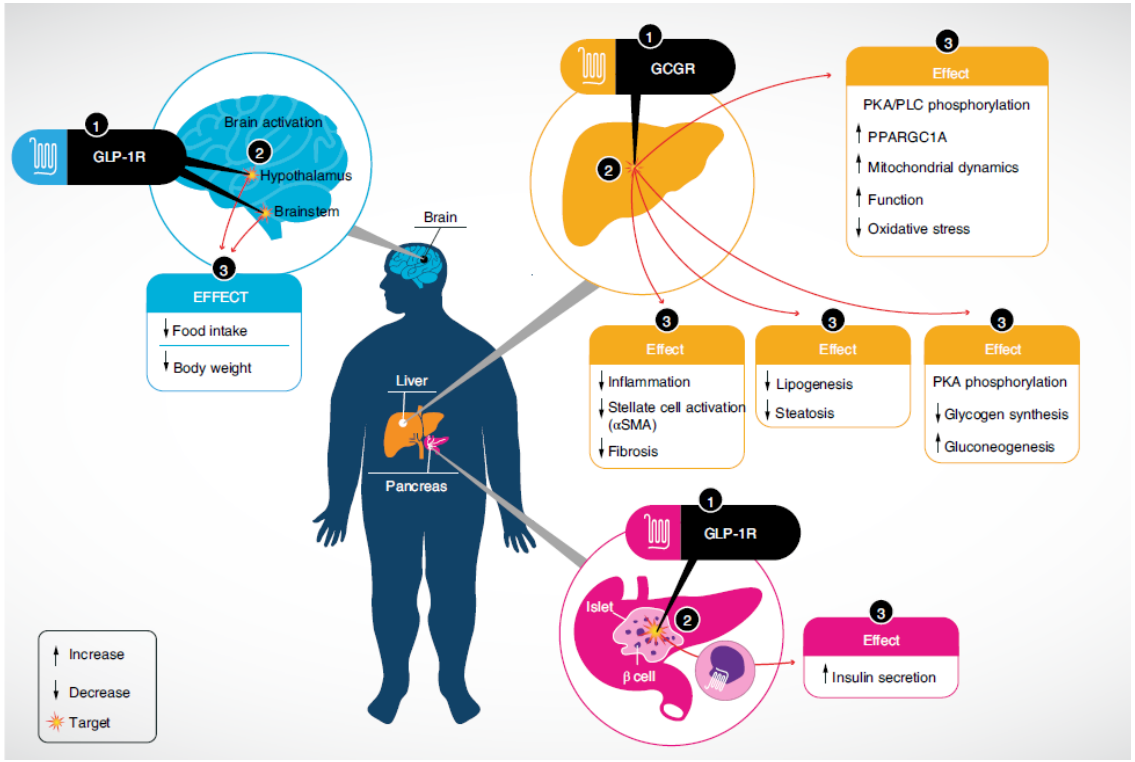
1. Mineralocorticoid receptor antagonists 2. Fixed dose combination. Source: AstraZeneca data on file.

3. The Study of Diabetic Nephropathy with Atrasentan (SONAR). 4. Endothelin receptor antagonist.
Source: Heerspink H. JL *Kidney International* (2021) 99, 346-347, Heerspink H. et. al., *Lancet Diabetes Endocrinol* 2019; 7: 429-41.

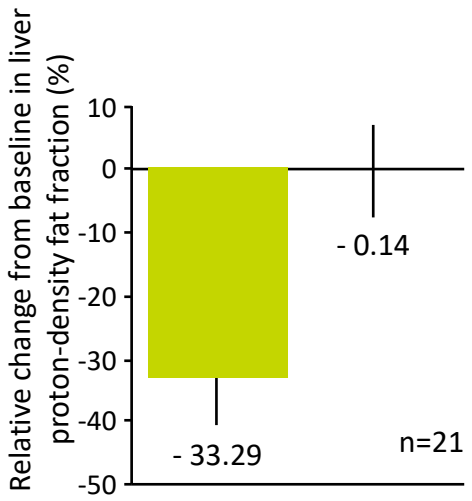
Cotadutide: dual glucagon and GLP-1 receptor agonist

Promising efficacy in overweight T2D[1] patients with fatty liver

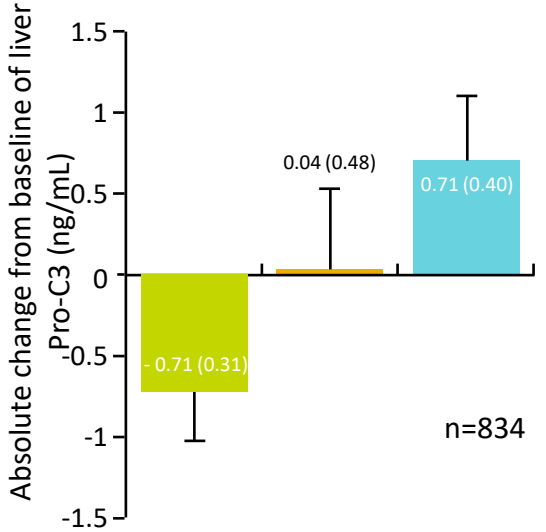
Mechanism of action at target organs



Reduced liver fat after four weeks



Reduced liver fibrosis after 54 weeks



Potential in NASH, with beneficial impact on liver health and cardiometabolic risk
Phase IIb data in H2 2021

1. Type-2 diabetes.

Source: Boland ML, Laker RC, Mather K, et al. Resolution of NASH and hepatic fibrosis by the GLP-1R/GcgR dual-agonist cotadutide via modulating mitochondrial function and lipogenesis. *Nat Metab*. 2020;2(5):413-431.

Source: Phase IIa glycogen imaging trial presented at European Association for the Study of Diabetes 2019, ADA 2020 Parker V. et. al.

Source: Phase IIb T2D trial, presented at European Association for the Study of Liver, the International Liver Congress 2020 Ambry P et. al.

Full pipeline and news flow

Upcoming milestones and expanding pipeline

New CVRM: emerging pipeline

Phase I	Phase II	
AZD2373 (APOL-1[1]) podocyte health nephropathy	**AZD4831** (MPO) HFpEF	**MEDI6012** (LCAT[8]) CV disease
AZD2693 (PNPLA3[2]) NASH	**AZ5718** (FLAP[5]) coronary artery disease / CKD	**MEDI6570** (LOX-1[9]) CV disease
AZD3366 (CD39L3[3]) CV disease	**AZD8233** (PCSK9) hypercholesterolemia	**verinurad** (URAT-1[10]) CKD / HFpEF
AZD3427 (relaxin ThP) CV disease	**AZD8601**[6] (VEGF-A[7]) CV disease	**AZD9977 + *Farxiga*** (MCR + SGLT2) HF with CKD
AZD9977 (MCR) CV disease	**cotadutide** (GLP-1/glucagon) NASH, DKD	**zibotentan + *Farxiga*** (ETR + SGLT2) CKD
MEDI8367 (avb8[4]) CKD	**MEDI3506** (IL33) DKD	**MEDI5884**[11] (cholesterol modulator) CV disease

Upcoming milestones
Phase IIa/b data readouts

H1 2021
- AZD5718 - CAD[12]

H2 2021
- cotadutide - NASH
- AZD8233 - hypercholesterolemia

2022
- MEDI6570 - CV disease
- AZD5718 - CKD
- cotadutide - DKD

Highlighted in presentation Other pipeline medicines

Status as of 25 March 2021. 1. Apolipoprotein L1 2. Patatin-like phospholipase domain-containing protein 3 3. Ectonucleoside triphosphate diphosphohydrolase-3 4. Alpha v beta 8 5. 5-Lipoxygenase-activating protein 6. Partnered with Moderna, Inc. 7. Vascular endothelial growth factor A 8. Lecithin-cholesterol acyltransferase 9. Lectin-like oxidized low-density lipoprotein receptor-1 10. Urate transporter 1 11. In collaboration 12. Coronary artery disease.

Questions & Answers

<u>To ask a question</u>
Webinar
Click 'Raise Hand' (preferred):

or type your question into the Q&A box (alternative)

Phone
*6 - Toggle mute/unmute
*9 - Raise hand

Appendix

Publications

Trial	Journal	Title	Author	Citation
Cotadutide				
Phase II	*The Lancet*	MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study	Ambery, P et al.	*Lancet* 2018; 391: 2607-18
Phase II	*The Journal of Clinical Endocrinology and Metabolism*	Efficacy, Safety, and Mechanistic Insights of Cotadutide, a Dual Receptor Glucagon-Like Peptide-1 and Glucagon Agonist	Parker, V.E.R et al.	*The Journal of Clinical Endocrinology & Metabolism* 2020; V.105, Issue 3:803-820
Pre-clinical	*Nature Metabolism*	Resolution of NASH and hepatic fibrosis by the GLP-1R and GCGR dual-agonist cotadutide via modulating mitochondrial function and Lipogenesis	Boland, M.L et al.	*Nature Metabolism* 2020; V.2 413-431
	Alimentary Pharmacology & Therapeutics	The emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis	Carlsson, B et al.	*Aliment Pharmacol Ther*. 2020; 51: 1305-1320.
AZD2693				
Pre-clinical	*Molecular Metabolism*	Pnpla3 silencing with antisense oligonucleotides ameliorates nonalcoholic steatohepatitis and fibrosis in Pnpla3 I148M knock-in mice	Linden, D et al.	*Molecular Metabolism* 2019; V. 22, 49-61.
AZD5718				
Phase II	*Contemporary Clinical Trials Communications*	Design and rationale of FLAVOUR: A phase IIa efficacy study of the 5-lipoxygenase activating protein antagonist AZD5718 in patients with recent myocardial infarction	Prescott, E et al.	*Contemporary Clinical Trials Communications* 2019; V. 19, 100629.
Phase I	*Prostagladins and Other Lipid Mediators*	Development of a highly sensitive liquid chromatography-mass spectrometry method to quantify plasma leukotriene E4 and demonstrate pharmacological suppression of endogenous 5-LO pathway activity in man	Lofgren, L et al.	*Prostaglandins & Other Lipid Mediators*; 2020, V. 150, 106463.
Pre-clinical	*Organic Process Research and Development*	Diethanolamine Boronic Esters: Development of a simple and standard process for boronic ester synthesis	Inglesby, P et al.	*Org. Process Res. Dev.* 2020, 24, 9, 1683-1689
Pre-clinical	*Journal of Medicinal Chemistry*	Discovery and early clinical development of an Inhibitor of 5-Lipoxygenase activating protein (AZD5718) for treatment of coronary artery disease	Pettersen D et al.	*J. Med. Chem.* 2019, 62, 9, 4312-4324

Publications, continued

AZD5718, continued				
Trial	**Journal**	**Title**	**Author**	**Citation**
	Journal of Medicinal Chemistry	Novel chemical series of 5-Lipoxygenase-activating protein inhibitors for treatment of coronary artery disease	Lemurell M et al.	*J. Med. Chem.* 2019, 62, 9, 4325-4349.
AZD4831				
Phase I	*Br J Clin Pharmacol*	Safety, tolerability, pharmacokinetics and effect on serum uric acid of the myeloperoxidase inhibitor AZD4831 in a randomized, placebo-controlled, phase I study in healthy volunteers	Gan, L-M et al.	Br J Clin Pharmacol. 2019, 85, 762-770.
Pre-clinical	*Clinical Translational Science*	Early clinical experience with AZD4831, a novel myeloperoxidase inhibitor, developed for patients with heart failure with preserved ejection fraction	Nelander, K et al.	https://doi.org/10.1111/cts.12859
Pre-clinical	*Hepatology Communications*	Therapeutic Targeting of Myeloperoxidase Attenuates NASH in Mice	Koop AC et al.	Hepatology Communications 2020, 4, 1441-1458.

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