Ongoing clinical trials and cardiovascular drugs in the pipeline - is there a shortage of innovation?

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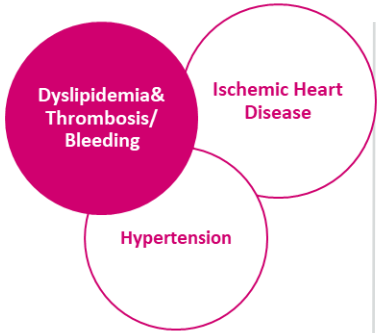
ESC European Society of Cardiology

Some compounds illustrated from AstraZeneca may refer to selected pipeline products still under investigation and development. AstraZeneca pipeline products are investigational products and as such, are not approved by the US Food & Drug Administration (FDA), the European Medicines Agency (EMA) or any other regulatory agency for the uses under investigation. Information regarding these investigational products should under no circumstances be regarded as a recommendation for their use or of their safety or efficacy.

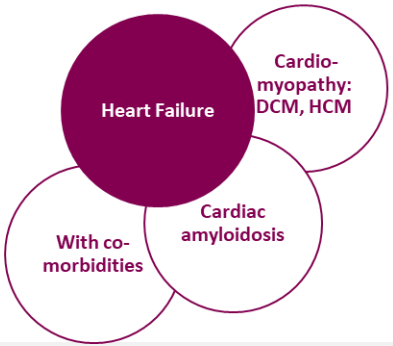
We have a strong and diverse pipeline of next-wave innovations[1-4]

Cardiovascular



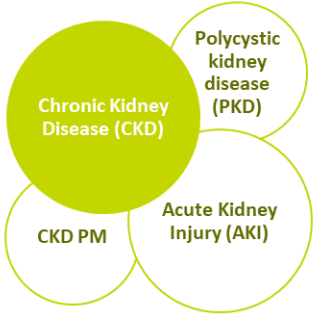
- Brilinta/Brilique
- Andexxa/Ondexxya
- baxdrostat
- AZD0780 oPCSK9

Heart Failure



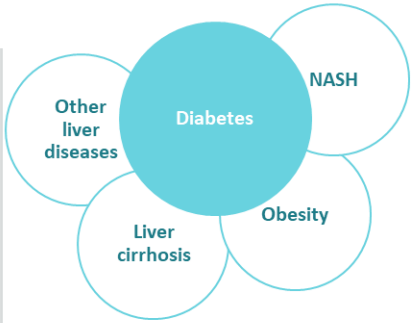
- Forxiga
- eplontersen
- mitiperstat
- balcinerone/dapagliflozin
- AZD3427 relaxin
- AZD5462 RXFP1

Renal Disease



- Forxiga
- Lokelma
- zibotentan/dapagliflozin
- AZD2373 APOL1

Metabolism



- Forxiga
- zibotentan/dapagliflozin
- mitiperstat
- AZD2693 PNPLA3
- AZD7503 HSD17B13
- AZD9550 GLP-1/GCG
- AZD5004 oGLP-1

Clinical Pipeline | Inline

1. AstraZeneca. Our therapy areas: CVRM. Accessed: October 2023. Available at: Pipeline – AstraZeneca. 2. ION532. Accessed: October 2023. Available at: https://www.ionispharma.com/medicines/ionis-az5-2-5/. **3.** AZD2693. Accessed: October 2023. Available at: https://openinnovation.astrazeneca.com/clinical-research/clinical-molecules/azd2693.html. **4**. Knockdown of HSD17B13 mRNA, Pharmacokinetics, Safety, and Tolerability, of AZD7503 in Non-Alcoholic Fatty Liver Disease. NCT05560607. Clinical.Trials.gov. Accessed: October 2023. Available at: https://clinicaltrials.gov/study/NCT05560607.

Baxdrostat for the treatment of resistant and uncontrolled hypertension

Pre-clinical | Phase I | **Phase II** | Phase III | LCM

Unmet Need

~50%

do not achieve SBP control through anti-hypertensive medications[1]

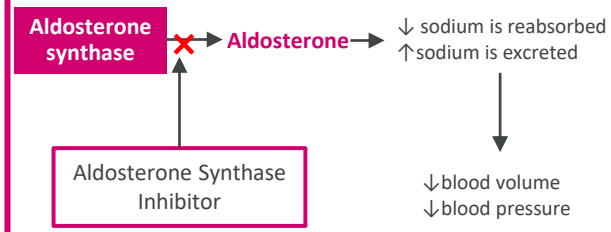
>10%

remain uncontrolled with residually high SBP, despite being on 3+ anti-hypertensive medications[2]

Clinical Vision

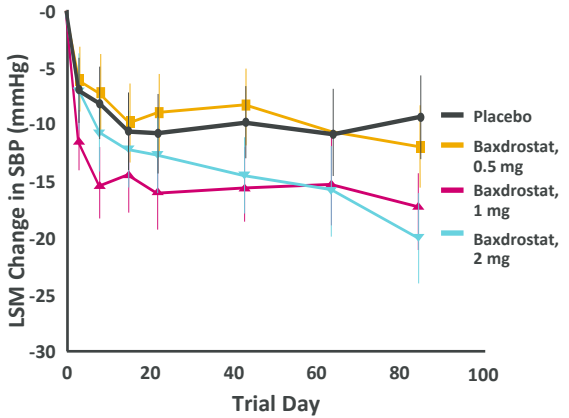
A **once-daily oral, highly potent** and **selective aldosterone synthase inhibitor** that is reliable for a **full 24 hours** and aims to achieve **significant systolic blood pressure reduction** as an add-on therapy for the treatment of **difficult-to-treat hypertension**[3,4]

Mode of Action



Scientific Evidence

BrigHTN: Patients with treatment-resistant hypertension who received baxdrostat had significant dose-related reductions in blood pressure[3]



1. NCD Risk Factor Collaboration (NCD-RisC). *Lancet*. 2021;398(10304):957-980. **2.** Noubiap JJ, et al. *Heart*. 2019;105(2):98-105. **3.** Freeman MW, et al. *N Engl J Med*. 2023;388(5):395-405. **4.** Freeman MW, et al. *Hypertens Res*. 2023;46(1):108-118.

AZD0780 (oPCSK9) to manage dyslipidaemia in patients with high CV risk

Pre-clinical | **Phase I** | Phase II | Phase III | LCM

Unmet Need

Hyperlipidemia a key risk factor for cardiovascular disease, the **#1** cause of death in the world[1]

Only ~ **50%**
of patients are at goal for LDL-C[2]

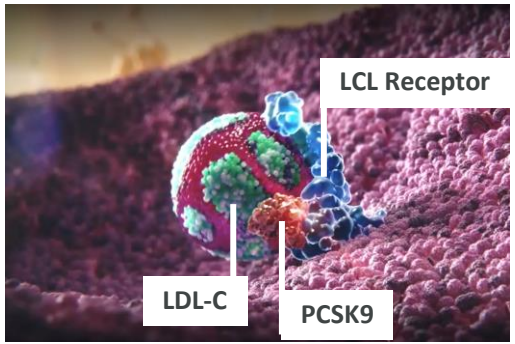
Clinical Vision

Transform the management of dyslipidaemia in patients with **high CV risk with a best-in-class, oral small molecule** that will **not have limitations of food effect**

Mode of Action

LDL receptors on the surface of liver hepatocytes are the primary mechanism that regulate serum LDL-C levels.[3]

PCSK9 **reduces the capacity** of liver cells to **uptake circulating LDL**[3]



Scientific Evidence

- PCSK9 is a recognised regulator of serum LDL-C.[3]
- There are currently no oral PCSK9 inhibitors available to patients.
- AZD0780 binds directly to a novel binding pocket in PCSK9.[4]
- Robust pre-clinical programme that demonstrated AZD0780 cholesterol lowering and safety potential.[4]

LDL-C: Low-density lipoprotein cholesterol

1. World Health Organization. 2023. Accessed: September 2023. Available at: https://www.who.int/health-topics/cardiovascular-diseases. **2.** Ray KK, et al. *Eur J Prev Cardiol*. 2021;28(11):1279-1289. **3.** Roth EM, et al. *Rev Cardiovasc Med*. 2018;19(S1):S31-S46. **4.** Dogma Therapeutics. Press release. Accessed: September 2023. Available at: https://www.prnewswire.com/news-releases/dogma-therapeutics-announces-global-acquisition-of-oral-pcsk9-inhibitor-program-by-astrazeneca-301132698.html.

Eplontersen for Transthyretin Amyloid Cardiomyopathy (ATTR)

Pre-clinical | Phase I | Phase II | **Phase III** | LCM

Unmet Need

~300-500K patients with ATTR-CM resulting in death within **3-5 yrs** from disease onset[1]

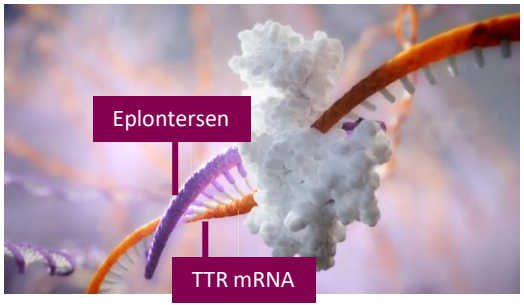
ATTR-CM is present in **~5-15%** of **patients with HFpEF**[2,3]

Clinical Vision

A potential **best-in-class ligand-conjugated antisense oligonucleotide** (ASO) that aims to be the **standard of care** for all ATTR patients with neuropathic symptoms

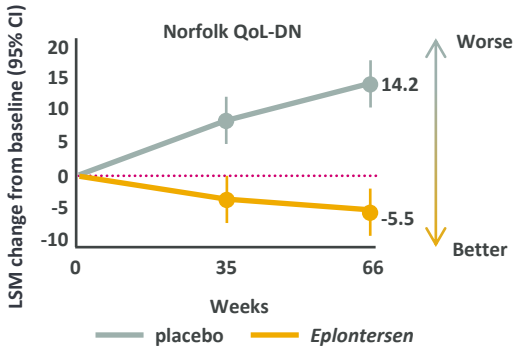
Mode of Action

A silencer that **precisely binds to and cleaves TTR mRNA**, substantially reducing the amount available for translation and misfolding[4-7]

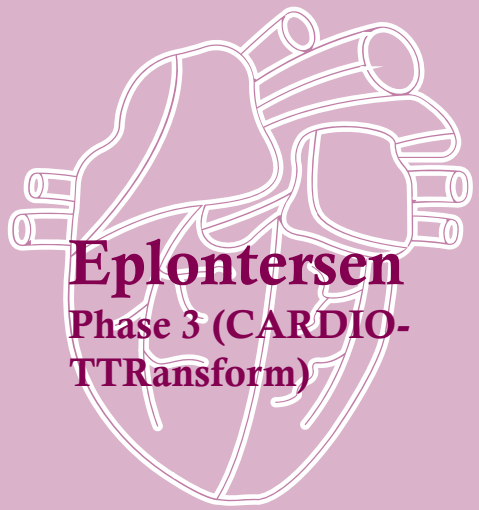


Scientific Evidence

First precision medicine with **sustained reduction in serum TTR** through 66 weeks in ATTR-PN and **halted progression of neuropathic impairment** with **improved quality of life**[5-8]

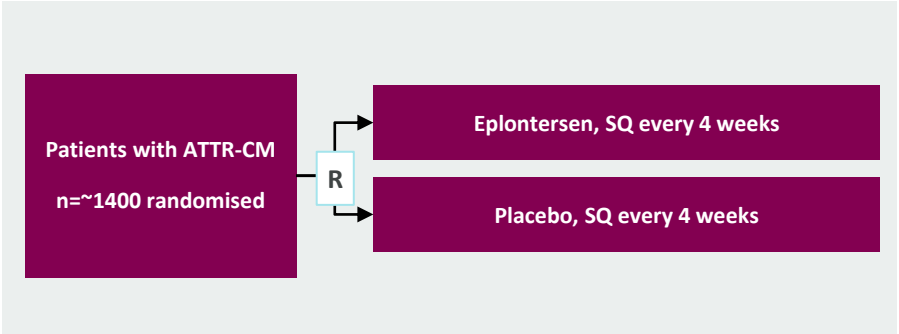


1. Ionis Pharmaceuticals. Annual Report 2022. Accessed September 2023. Available at: https://ir.ionispharma.com/static-files/db9dff5d-8683-485a-a517-15e264fe7532. **2.** Nativi-Nicolau JN, et al. *Heart Fail Rev*. 2022;27(3):785-793**. 3**. Mohammed SF, et al. *JACC Heart Fail*. 2014;2(2):113-122, **4.** Ioannou A, et al. *BioDrugs*. 2023;37(2):127-142. doi:10.1007/s40259-023-00577-7. **5**. AstraZeneca. Eplontersen demonstrated sustained benefit in Phase III trial for hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN) through 66 weeks. Accessed: September 2023. Available at: https://www.astrazeneca.com/media-centre/press-releases/2023/eplontersen-demonstrated-sustained-benefit-in-phase-iii-trial.html. **6.** Khella S et al. American Academy of Neurology 2023 Annual Meeting, 22-27 April 2023, Boston. **7.** Ionis, AstraZeneca claim success for competitor to Alnylam rare disease drug. Accessed: September 2023. Available at: https://www.biopharmadive.com/news/ionis-astrazeneca-eplontersen-ttr-study-results/625751/. **8.** Eplontersen May Soon Provide Another Safe, Effective Treatment for People Diagnosed with ATTR**.** Accessed: September 2023. Available at: https://www.oligotherapeutics.org/eplontersen-may-soon-provide-another-safe-effective-treatment-for-people-diagnosed-with-attr/



Eplontersen Phase 3 (CARDIO-TTRansform)[1]

Eplontersen Phase 3 CARDIO-TTRansform: study design[1]



Primary endpoint
Composite outcome of CV mortality and recurrent CV clinical events up to week 140

Secondary endpoints
Change from baseline in the 6-minute Walk Test (week 121), KCCQ scores (week 121), CV clinical events (week 140), CV mortality (week 140), all cause mortality (week 140)

Key Points:

- To evaluate the efficacy of eplontersen compared to placebo in participants with ATTR-CM receiving available standard of care (SoC)
- Primary endpoint: Composite outcome of CV mortality and recurrent CV clinical events up to week 140
- Secondary endpoints: Change from baseline in the 6-minute Walk Test (week 121), KCCQ scores (week 121), CV clinical events (week 140), CV mortality (week 140), all cause mortality (week 140)

Status: Active, not recruiting

1. CARDIO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR CM). NCT04136171. ClinicalTrials.gov. Accessed: September 2023. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04136171.

Mitiperstat for heart failure

Pre-clinical | Phase I | **Phase II** | Phase III | LCM

Unmet Need

~64M people currently living with HF[1]

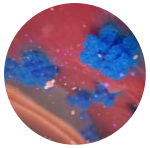
Leading **cause of hospitalisation** for those over the age of 65[2]

Clinical Vision

A first in class MPO inhibitor which aims to eradicate the residual unmet medical need in HFpEF by reducing **microvascular inflammation, preventing cardiac fibrosis, and improving overall quality of life and survival**

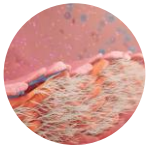
Mode of Action

Mitiperstat potentially breaks the cycle of microvascular dysfunction, fibrosis and remodelling[3,4]



Myeloperoxidase (MPO) is a **pro-inflammatory enzyme** that produces damaging free radical.[5]

If MPO gets into blood vessel walls it indirectly **leads to microvascular dysfunction.[3,6]**

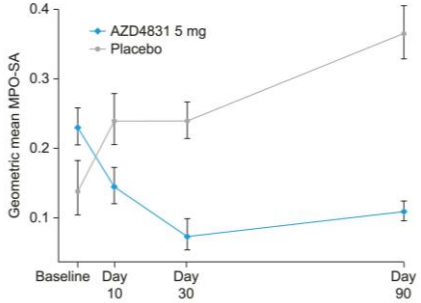


Free radicals also drive collagen secretion from cells in the **extracellular matrix causing fibrosis.[5,6]**

Scientific Evidence

Phase IIa data from SATELLITE[7]:
Showed target engagement, trends of efficacy in NT-proBNP, and good safety and tolerability

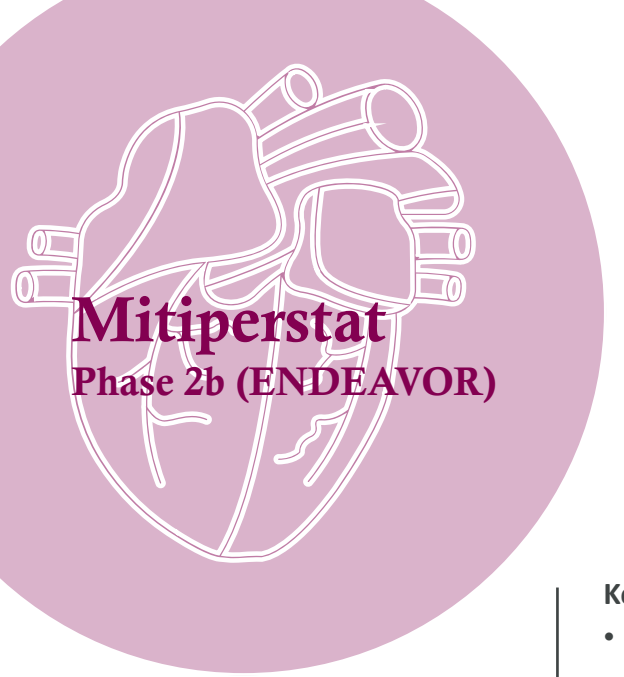
Relative change in myeloperoxidase activity from baseline



Also in clinical development for **NASH[4]** and **COPD[8]**

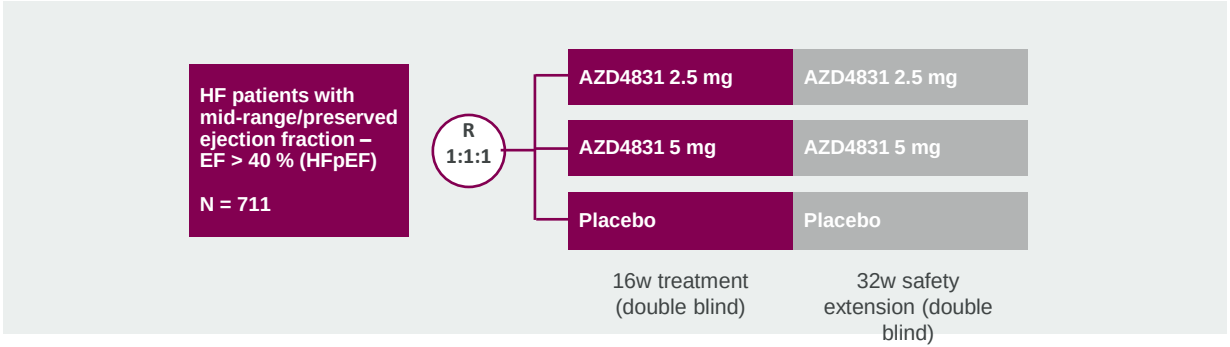
1. Savarese G, et al. *Cardiovasc Res*. 2023;118(17):3272-3287. **2.** Azad N, Lemay G. *J Geriatr Cardiol*. 2014;11(4):329-337. **3.** Michaëlsson E, et al. *JACC Heart Fail*. 2023;11(7):775-787. **4.** Mitiperstat by AstraZeneca for Non-Alcoholic Steatohepatitis (NASH): Likelihood of Approval. Accessed: September 2023. Available at https://www.pharmaceutical-technology.com/data-insights/mitiperstat-what-is-the-likelihood-that-drug-will-be-approved/.

5. Hawkins CL, et al. *Free Radic Biol Med*. 2021;172:633-651. **6**. Gan LM, et al. *Br J Clin Pharmacol*. 2019;85(4):762-770. **7.** Lam CSP, et al. *J Card Fail*. 2023:S1071-9164(23)00142-2. **8.** Mitiperstat by AstraZeneca for Chronic Obstructive Pulmonary Disease (COPD): Likelihood of Approval. Accessed: September 2023. Available at https://www.pharmaceutical-technology.com/data-insights/mitiperstat-what-is-the-likelihood-that-drug-will-be-approved-3/#:~:text=patient%20data%20sharing-,Mitiperstat%20by%20AstraZeneca%20for%20Chronic%20Obstructive%20Pulmonary,COPD)%3A%20Likelihood%20of%20Approval&text=Mitiperstat%20is%20under%20clinical%20development,Obstructive%20Pulmonary%20Disease%20(COPD).



Mitiperstat
Phase 2b (ENDEAVOR)

Mitiperstat Phase IIB ENDEAVOR: study design[1,2]



Key Points:

- Randomised, double-blind, placebo-controlled, multi-centre, dose finding studies to evaluate the efficacy and safety of mitiperstat (formerly AZD4831) in HFpEF patients,16 weeks treatment followed by 32 weeks safety extension, 2 doses + placebo
- Primary endpoints: The change from baseline to 16 weeks in KCCQ-TSS and 6MWD
- Secondary endpoints: NT- proBNP reduction
- Selection of surrogate outcomes remains a key challenge in the design of clinical trials in patients with HFpEF/HFmrEF

Status: Active, Completed Recruitment

1. Study to Evaluate the Efficacy and Safety of AZD4831 in Participants With Heart Failure With Left Ventricular Ejection Fraction > 40% (ENDEAVOR). NCT04986202. ClinicalTrials.gov. Accessed: August 2023. Available at: https://clinicaltrials.gov/study/NCT04986202. **2.** Lund LH, et al. *Eur J Heart Fail.* 2023;10.1002/ejhf.2977.

AZD3427 (relaxin agonist) for HF patients with pulmonary hypertension

Pre-clinical | Phase I | **Phase II** | Phase III | LCM

Unmet Need

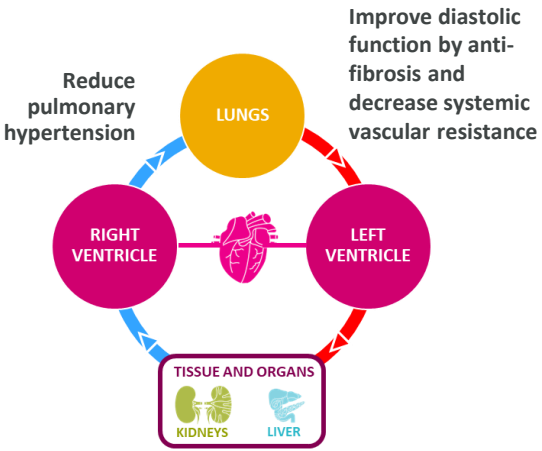
Pulmonary hypertension is a key driver for chronic right ventricular failure (RVF)[1,2]

Median two-year mortality up to ~45% in RVF and high hospitalisation rate[1]

Clinical Vision

AZD3427 addresses the key drivers of RVF and **uniquely improves right** (and left) **ventricle function**

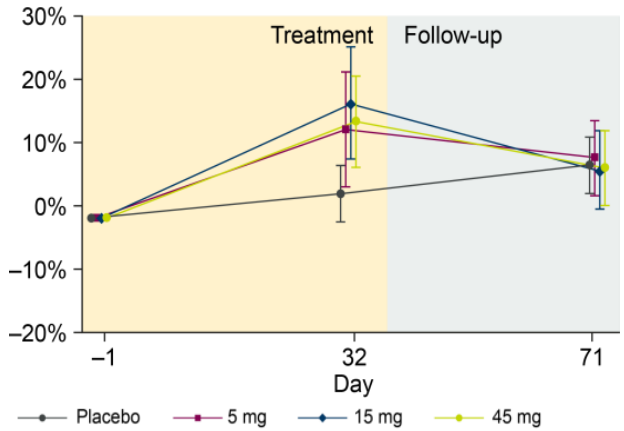
Mode of Action[3-8]



Adapted from: England E, et al. Sci Rep. 2023;13(1):9825

Scientific Evidence

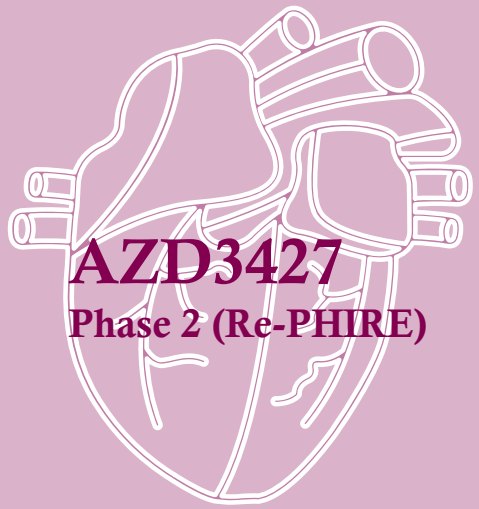
AZD3427 tended to **increase stroke volume** in Phase 1 MAD[8]



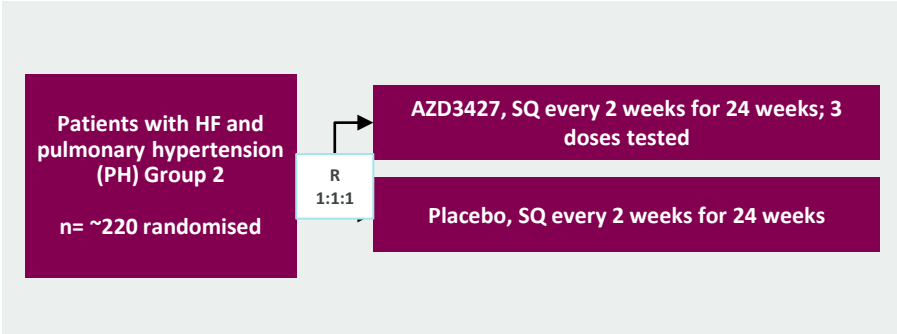
Stroke volume, percentage change from baseline. Mean ± SE
This is in patients with HF with EF ≥ 41%

1. Melenovsky V, et al. Eur Heart J. 2014 ;35(48):3452-62. **2.** Houston BA, et al. *N Engl J Med*. 2023;388(12):1111-1125. **3.** Bennett RG. Targeting the RelaxinPathway for Liver Disease Treatment. EurMed J Hepatol. 2018 May;6(1):80-87. **4.** Chen TY, et al. *Mol Genet Genomic Med*. 2020 Apr;8(4):e1194. **5.** NCT05737940. ClinicalTrials.gov. Accessed August 2023. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05737940, **6**. Magder S. Crit Care. 2018;22(1):257. **7**. Rosenkranz S, et al. EurHeart J. 2016;37(12):942-54, **8.** Ufnal M. et al. *Heart Failure* 2023, Prague, Czech.

AZD3427 Phase II Re-PHIRE: study design[1]



AZD3427
Phase 2 (Re-PHIRE)



Primary endpoint
Change from baseline in Pulmonary Vascular Resistance (PVR)

Key secondary endpoints
Change from baseline in mPAP, PAWP, cardiac output, KCCQ TSS, 6MWD

Status: Recruiting

Key Points:

- This study is a randomised, placebo-controlled, multi-centre, dose-ranging study of AZD3427 in participants with heart failure and pulmonary hypertension due to left heart disease
- This study is intended to assess the ability of AZD3427 to reduce pulmonary vascular resistance (PVR) after 24 weeks of treatment in participants with heart failure (HF) and pulmonary hypertension (PH) Group 2
- Primary endpoints: Change from baseline in Pulmonary Vascular Resistance (PVR)

1. A Study of AZD3427 in Participants With Heart Failure and Pulmonary Hypertension Group 2 (Re-PHIRE). NCT05737940. ClinicalTrials.gov. 2023. Available at: https://clinicaltrials.gov/study/NCT05737940. Last accessed August 2023.

Balcinrenone/dapagliflozin to reduce the risk of CV death and HF events in adults with symptomatic chronic HF with impaired kidney function

Pre-clinical | Phase I | **Phase IIb MIRACLE** | Phase III | LCM

Unmet Need

~50% HF patients have co-morbid CKD[1]

↓ eGFR of 15 mL/min approximately **doubled** the odds of hyperkalaemia[2]

Clinical Vision

Balcinrenone/dapagliflozin aims to deliver next generation **cardiorenal protection,** setting new standards for extending and improving the lives of people with heart failure and CKD

Mode of Action

Balcinrenone is **a selective MR modulator** that:

Deliver organ-protective effects[3,6]

Reduced effect on urinary electrolyte excretion in contrast to MR antagonists[3,6]

Dapagliflozin is **a sodium-glucose cotransporter 2 (SGLT2) inhibitor** that:[4,5,7]

Slows renal function decline

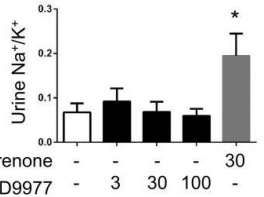
Provides cardiovascular benefits

Decreases albuminuria

improves diuresis to combat fluid retention

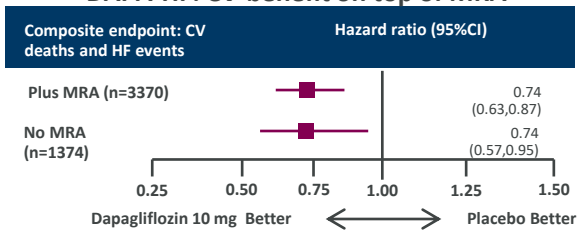
Scientific Evidence

Balcinrenone **did not affect urinary electrolyte excretion**, while MRA increased the urinary electrolyte excretion[6]



*p<0.05 compared to vehicle

DAPA-HF: CV-benefit on top of MRA[3]



Patients were included with HFrEF

1. Damman K. et al. *Eur Heart J.* 2014;35(7):455-469. **2.** Hunter R, Bailey MA, et al. *Nephrology Dialysis Transplantation*. 2019; 34(3):iii2–iii11, **3.** AstraZeneca. Full year and Q4 2022 results presentation. Accessed: September 2023. Available at: https://www.astrazeneca.com/content/dam/az/PDF/2022/fy/Full-year-and-Q4-2022-results-presentation.pdf. **4.** Lytvyn Y et al. *Circulation*. 2017:136:1643-1658. **5.** Veenit V, et al. *Nephrol Dial Transplant*. 2023 Apr 26:gfad078. **6.** Bamberg K, et al. PLoS One. 2018;13(2):e0193380. **7.** Jaikumkao K, Pongchaidecha A, et al. *Diabetes Obes Metab*. 2018;20(11):2617-2626.

Zibotentan/dapagliflozin to treat CKD

Pre-clinical | Phase I | **Phase II** | Phase III | LCM

Unmet Need

Elevated levels of proteinuria associated with an increased risk of progressive renal function loss over time[1]

Clinical Vision

Zibotentan/dapagliflozin **aims to slow progression of CKD** vs SGLT2i in patients with persistent high proteinuria.

Mode of Action

Zibotentan is a ET_A receptor antagonist that:

Improves renal and systemic haemodynamic[2]

Reduces albuminuria[2]

Reduces inflammation and fibrosis[2]

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor with proven benefits across multiple indications:

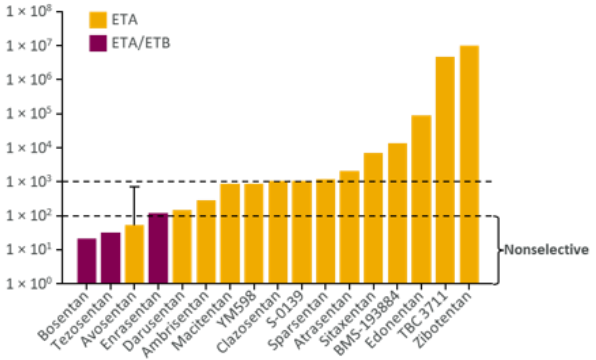
Slows renal function decline[2,4]

Decreases albuminuria[2]

Improves diuresis to potentially combat fluid retention[2]

Scientific Evidence

Zibotentan is the **most potent** and **selective endothelin receptor**[3]



Phase IIb ZENITH-CKD results were presented and published 3 November 2023

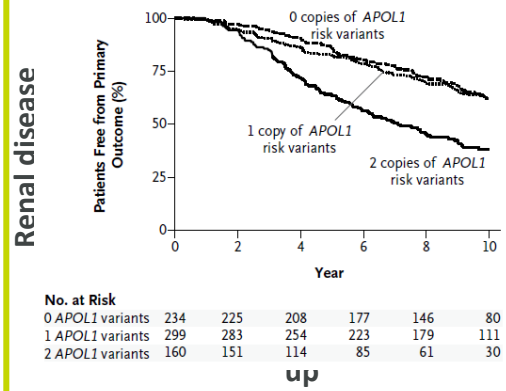
1. Heerspink HJ and Gansevoort RT, et. al. *Clin J Am Soc Nephrol*. 2015;10(6):1079-1088. 2. Veenit V, et al. *Nephrol Dial Transplant*. 2023 Apr 26:gfad078, 3. Davenport AP, et al. *Pharmacol Rev*. 2016 Apr;68(2):357-418. 4. Jaikumkao K, Pongchaidecha A, et al. *Diabetes Obes Metab*. 2018;20(11):2617-2626.

AZD2373 (APOL1) for the treatment of APOL1 nephropathy

Pre-clinical | **Phase I** | **Phase II** | Phase III | LCM

Unmet Need

CKD patients with two APOL1 mutant alleles **progress faster to end stage renal disease and death**[1]



Clinical Vision

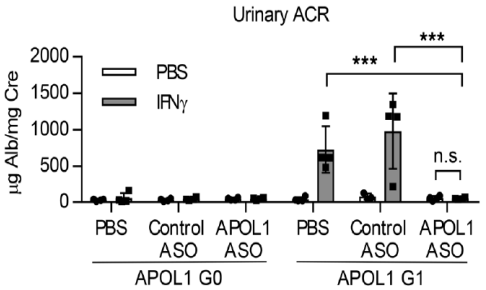
AZD2373 aims to deliver **the first precision medicine in CKD** for people with two APOL1 risk alleles to prevent disease progression.

Mode of Action

AZD2373 is an antisense oligonucleotide that inhibits APOL1. Risk alleles (G1 and G2) of **APOL1 are associated with nondiabetic CKD** and increased rate of progression towards kidney failure.[2] These two variants are more frequently found in individuals of West-African ancestry.[2,4,5]

Scientific Evidence

Protection against proteinuria in nephropathy mouse model[3]



***P < 0.001

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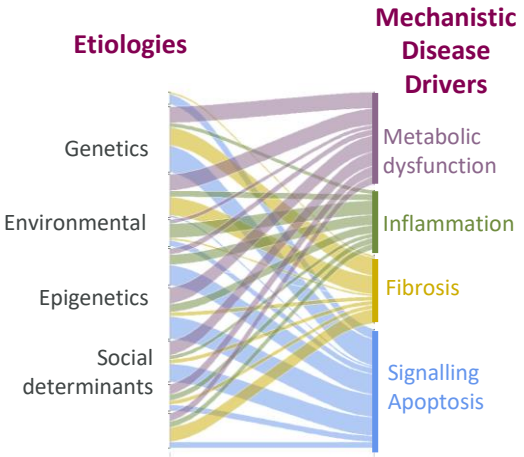
1. Parsa A, et al. "APOL1 risk variants, race, and progression of chronic kidney disease." The New England journal of medicine vol. 369,23 (2013): 2183-96. doi:10.1056/NEJMoa1310345, **2**. Ross MJ, et al. *Kidney Int Rep*. 2019;29;4(7):908-910, **3.** Aghajan M, et al. "Antisense oligonucleotide treatment ameliorates IFN-γ-induced proteinuria in APOL1-transgenic mice." JCI insight vol. 4,12 e126124. 20 Jun. 2019, doi:10.1172/jci.insight.126124. **4.** Does the APOL1 gene increase the risk of kidney disease in African Americans with diabetes?. Accessed: September 2023. Available at: https://www.medicalnewstoday.com/articles/apol1-gene-kidney-disease-risk. **5.** Limou S. et al. Adv Chronic Kidney Dis. 2014;21(5):426-433.

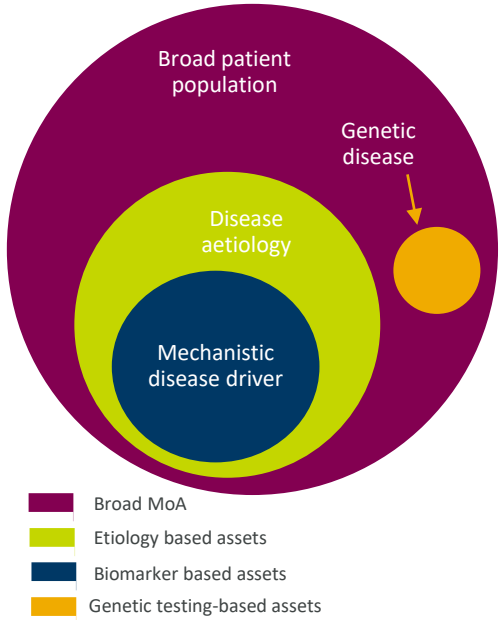
Shifting the treatment paradigm towards precision medicine

Stratifying patients based on disease drivers



Molecular re-classification of disease etiologies identify patient sub-clusters linked to mechanisms

Selecting the right medicines for the right patients



The potential of precision medicine

- Science: disease understanding, tailored therapy
- Patients: reduced trial and error
- Physicians: patient benefit with improved outcomes
- Payer: higher value for targeted treatment
- Regulators: efficacy and safety

We are focusing on new endpoints and driving trial efficiencies and recruitment

Novel endpoints

Change from baseline EGFR in dapa FDCs to reduce time to launch

AI-based event identification & submission

Balci/dapa in HF with CKD to drive earlier database lock and submission

Strengthening site engagements / relationships

Multiple new patient pre-identification approaches to frontload recruitment into our trials

Disease-specific pre-screening studies at top sites

ALIGN pre-screening study to drive recruitment across NASH programs

~1 in 5

CKD patients develop HF[2]

50%

HF patients die within 5 years[4] with poor quality of life[5]

NASH

projected to increase by 63% by 2030[7]

US:

~120M

hypertensives

~50% not controlled[1]

~50%

of CV patients with prior CV events >100mg/DL LDL-C[3]*

~300,000 – 500,000 affected by both the genetic and wild-type ATTR[6]

*Data from the U.S.

1. Centers for Disease Control and Prevention. Facts About Hypertension. Accessed: September 2023. Available at: https://www.cdc.gov/bloodpressure/facts.htm. **2.** House AA, et al.. *Kidney Int*. 2019;95(6):1304-1317. **2**. Data of file: REF-199486 **3.** Writing Group Members, et al. *Circulation*. 2016;133(4):e38-e360. **4.** Kosiborod MN, et al. *Circulation*. 2020 Jan;141(2):90-99. **5.** Ionis Pharmaceuticals, Inc., [Internet]. Annual Report, 2022 [cited 27 October 2022]. Accessed at: September 2023. Available at: https://ir.ionispharma.com/static-files/285deeed-625c-4d5b-beff-8490f93622ce. **6.** Estes C, et al. *Hepatology*. 2018;67(1):123-133.