Break-out session 1

New CVRM: emerging pipeline

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Lori Kreamer, Vice President, CVRM, BioPharmaceuticals Business Unit

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

**Heart failure**
- Eliminate hospitalisations and cure HFrEF
- **64 million** people worldwide affected by HF

**Renal**
- Eliminate dialysis
- **840 million** people worldwide affected by CKD

**Metabolism Liver disease**
- Cure diabetes
  - Eliminate NASH
- **530 million** people affected worldwide

### Medicines

**Cardiovascular**
- AZD8233 PCSK9
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- ASO
- (secondary CV prevention)

**Heart failure**
- AZD4831 MPO inhibitor (HFpEF)
- AZD9977 MCR modulator + Farxiga (HF, CKD)

**Renal**
- zibotentan ERA antagonist
- Rotigotine SGLT2 inhibitor (CKD)

**Metabolism Liver disease**
- cotadutide GLP-1/glucagon agonist (NASH, DKD)

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AZD8233: PCSK9 ASO
Potential for improved efficacy with convenient at-home administration

Up to 90% PCSK9 inhibition for six weeks in Phase I SAD\textsuperscript{1}

n=6/arm

Up to 70% reduction of LDL\textsuperscript{2} cholesterol in Phase I SAD

n=6/arm

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

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

Trend towards 6MWD improvement

Improved quality of life at day 90

Reduced NT-proBNP\(^3\)

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

**SONAR\(^3\)** *post hoc* sub-analysis
- DELIGHT trial data: *Farxiga* effect on BW (left) and uACR (right)

**Complimentary efficacy and safety profiles with opportunity for AZD9977 + *Farxiga* FDC\(^2\)** in HF patients with CKD

**Adding SGLT2 inhibitor to ERA\(^4\)** mitigated fluid retention and reduced albuminuria compared to ERA alone

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\(^1\) Mineralocorticoid receptor antagonists  
\(^3\) The Study of Diabetic Nephropathy with Atrasentan (SONAR).  
\(^4\) Endothelin receptor antagonist.  

**P** p<0.01
Cotadutide: dual glucagon and GLP-1 receptor agonist
Promising efficacy in overweight T2D 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: 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.
# Upcoming milestones and expanding pipeline

## Full pipeline and news flow

### New CVRM: emerging pipeline

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Other pipeline medicines</th>
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<tbody>
<tr>
<td><strong>AZD2373</strong> (APOL-1&lt;sup&gt;1&lt;/sup&gt;) podocyte health nephropathy</td>
<td><strong>AZD4831</strong> (MPO) HfPEF</td>
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<tr>
<td><strong>AZD2693</strong> (PNPLA3&lt;sup&gt;2&lt;/sup&gt;) NASH</td>
<td><strong>AZ5718</strong> (FLAP&lt;sup&gt;3&lt;/sup&gt;) coronary artery disease / CKD</td>
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<td><strong>AZD3366</strong> (CD39L3&lt;sup&gt;3&lt;/sup&gt;) CV disease</td>
<td><strong>AZD8233</strong> (PCSK9) hypercholesterolemia</td>
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<tr>
<td><strong>AZD3427</strong> (relaxin ThP) CV disease</td>
<td><strong>AZD8601</strong> (VEGF-A&lt;sup&gt;3&lt;/sup&gt;) CV disease</td>
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<td><strong>AZD9977</strong> (MCR) CV disease</td>
<td><strong>cotadutide</strong> (GLP-1/glucagon) NASH, DKD</td>
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<tr>
<td><strong>MEDI8367</strong> (avb8&lt;sup&gt;4&lt;/sup&gt;) CKD</td>
<td><strong>MEDI3506</strong> (IL33) DKD</td>
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### Upcoming milestones

#### Phase IIa/b data readouts

**H1 2021**
- AZD5718 - CAD<sup>12</sup>

**H2 2021**
- cotadutide - NASH
- AZD8233 - hypercholesterolemia

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

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Questions & Answers

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

### Cotadutide

<table>
<thead>
<tr>
<th>Trial</th>
<th>Journal</th>
<th>Title</th>
<th>Author</th>
<th>Citation</th>
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<tbody>
<tr>
<td>Phase II</td>
<td>The Lancet</td>
<td>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</td>
<td>Ambery, P et al.</td>
<td>Lancet 2018; 391: 2607-18</td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>Nature Metabolism</td>
<td>Resolution of NASH and hepatic fibrosis by the GLP-1R and GCGR dual-agonist cotadutide via modulating mitochondrial function and Lipogenesis</td>
<td>Boland, M.L et al.</td>
<td>Nature Metabolism 2020; V.2 413-431</td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>Molecular Metabolism</td>
<td>Pnpla3 silencing with antisense oligonucleotides ameliorates nonalcoholic steatohepatitis and fibrosis in Pnpla3 I148M knock-in mice</td>
<td>Linden, D et al.</td>
<td>Molecular Metabolism 2019; V. 22, 49-61.</td>
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### 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

<p>| 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     | Prostaglandins 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 &amp; Other Lipid Mediators; 2020, V. 150, 106463. |</p>
<table>
<thead>
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<th>Trial</th>
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<td><strong>AZD5718, continued</strong></td>
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<td><strong>AZD4831</strong></td>
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<tr>
<td>Pre-clinical</td>
<td><em>Clinical Translational Science</em></td>
<td><strong>Early clinical experience with AZD4831, a novel myeloperoxidase</strong>&lt;br&gt;inhibitor, developed for patients with heart failure with preserved&lt;br&gt;ejection fraction</td>
<td>Nelander, K et al.</td>
<td><a href="https://doi.org/10.1111/cts.12859">https://doi.org/10.1111/cts.12859</a></td>
</tr>
<tr>
<td>Pre-clinical</td>
<td><em>Hepatology Communications</em></td>
<td><strong>Therapeutic Targeting of Myeloperoxidase Attenuates NASH in Mice</strong></td>
<td>Koop AC et al.</td>
<td><em>Hepatology Communications</em> 2020, 4, 1441-1458.</td>
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