Pipeline: Cardiovascular & Metabolic Disease (CVMD)
Addressing the next frontier in cardiovascular medicine
Elisabeth Björk, Vice President, Head CVMD GMD
## Cardiovascular & Metabolic Disease (CVMD): Strategy

Reduction of CV morbidity, mortality, and organ damage by addressing multiple CV risk factors.

### Disease Focus

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<tr>
<th>Cardiovascular disease</th>
<th>Metabolic disease</th>
<th>Chronic kidney disease</th>
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<td>CHD/ACS</td>
<td>Diabetes</td>
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<td>Atherosclerosis/dyslipidaemia</td>
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### Regeneration

- Heart
- β-cell
- Kidney

**Abbreviations:**
- CHD: Coronary heart disease
- ACS: Acute coronary syndrome
- NASH: Non-alcoholic steatohepatitis
Diabetes:
Strategy to transform patient care

- Shift treatment paradigm to early combination therapy and accelerate achievement of treatment goals
- Develop a science-led life cycle management strategy
- Expand into new areas of unmet need, including expansion into Type 1 diabetes with Forxiga
**Diabetes: R&D commitment**

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<td>DECLARE cardiovascular outcomes</td>
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**Type 1 diabetes**

*Asia add-on to insulin*

*Japan add-on to insulin*

**saxa/dapa**

- saxa+dapa+met vs dapa+met
- saxa+dapa+met vs saxa+met
- saxa/dapa vs sitagliptin
- saxa/dapa vs SU

**China add-on to insulin**

**China initial combination**

**onglyza**

**DURATION NEO-1**

exenatide weekly vs BID

**DURATION NEO-2**

exenatide weekly vs sitagliptin

**DURATION 7 add-on to insulin**

**EXSCEL cardiovascular outcomes**

exenatide+dapagliflozin

~40,000 patients in clinical trials world wide
Diabetes: Helping patients along disease progression

-Illustrative-

Sequential treatment

HbA1c

Time

Pipeline: Cardiovascular & Metabolic Disease (CVMD)
Diabetes:
New guidelines more aggressive with earlier combinations

Note: AACE guidelines were published March 2013, SGLT-2 recommendation was based on Ph3 data.

6 – Pipeline: Cardiovascular & Metabolic Disease (CVMD)
Oral combinations: Saxa/dapa & saxa/dapa/metformin

Portfolio well-positioned to enable early combination treatment

- Saxa/dapa added to metformin in poorly controlled T2DM
  - HbA1c reduction 1.47%
  - HbA1c <7% in 41% of patients
- Regulatory submission for saxa/dapa FDC targeted for 2015
- Saxa/dapa/met FDC development ongoing. Regulatory submission expected post 2016

Significant reduction in HbA1c with low rates of hypoglycaemia

Adjusted mean change from baseline in HbA1c at 24 weeks

Forxiga / Xigduo: Insulin doses remained stable over 2 years

- Dapagliflozin showed sustained reductions in HbA1c in when used in combination with insulin
- Patients on dapa + insulin lost weight - 3kg vs insulin alone
- Insulin doses remained stable over the study period

Forxiga + insulin maintained HbA1c and induced weight loss vs insulin alone

Study 006 Clinical Study Report, Figure4, Table 11.2.6.1.1
Diabetes:
Potential of early combinations to slow disease progression
CVMD:
Science-driven innovation into new areas of unmet need

- NASH / Fatty liver disease
- Renal protection
- Type 1 diabetes
- Weight
- Heart failure
CVMD: Visualising diabetes impact via differentiated technology

Functional data
- Glucose disposal and HbA1c
  - Source: Merovci et al. JCI 2014

Body composition and ectopic lipids
- Automated body composition analysis (DAPA-12)
  - Source: Nauck et al. Diabetes Care 2011

Tissue-specific insulin sensitivity
- FDG (fluor-dioxyglucose) uptake during insulin clamp

Beta cell mass
- Healthy control
- T1D patient
- $^{11}$C-5-HTP or $^{68}$Ga-Exendin-4
Roxadustat (CKD): Potential to be first oral erythropoietic anaemia treatment

• Oral HIF-prolyl hydroxylase inhibitor
• Favourable efficacy and safety profile in Phase II
• >7,000 patient Phase III ALPINE programme designed to demonstrate CV safety in patients with dialysis and non-dialysis dependent chronic kidney disease (CKD)
• Top-line data post-2016

source: FibroGen Registration Statement
Roxadustat (CKD): Potential for reduced cardiovascular risk vs. rEPO

- Higher doses of rEPO predict mortality regardless of hematocrit
- Mechanism for increased CV risk with rEPO is uncertain, but may involve
  - supra-physiologic EPO levels
  - rapid rate of Hb rise
  - high Hb targets
  - effects on blood pressure
- Phase III programme designed to avoid these concerns through the novel mechanism of action and intermittent dosing

USRDS: Unadjusted 1-year mortality by epoetin dose & hematocrit

Roxadustat (CKD): Stimulates erythropoiesis similar to the body’s normal coordinated response to hypoxia

- rEPO infusion produces supra-physiological EPO concentrations, whereas roxadustat induces endogenous EPO concentrations within physiological range
- In addition, roxadustat induces expression of the EPO receptor as well as proteins that promote iron absorption and recycling

Source: FibroGen Registration Statement

Median plasma EPO concentration at two oral doses of roxadustat postdialysis compared with reported EPO levels following IV administration of rhEPO [100 IU/kg]*

* Data from IV EPO taken from Figure 1 in MacDougall, et al. J Am Soc Nephrol 1999;10(11):2392–95.
Provenzano et al. Nat. Kidney Foundation Conf 2011 (Poster #189)
**Brilinta:**
**PARTHENON potentially transforms atherosclerosis treatment**

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**OAP market access (% current volume)**
- 2014: 20%
- 2015: 20%
- 2016: 31%
- 2017: 68%
- 2018: 83%
- 2019: 84%+
Brilinta: PLATO results displayed unique clinical profile

- Continuous benefit for one year
- Mortality benefit
- Potential unique benefit beyond P2Y12 inhibition driven by ENT1

K-M, Kaplan-Meier
Brilinta:
APOLLO UK proved unmet need in PEGASUS-like patients

APOLLO UK analysis

PEGASUS-TIMI-54-Like Population (n=4,290)
17.9% (16.2-19.5)

1 Year Event-Free MI Survivors (n=7,238)
17.2% (16.0-18.5)

~1 in 5 PEGASUS-like patients, event-free for 1 year post-MI, will suffer a MI, stroke or CV death within 3 years

MI, myocardial infarction.
Rapsomaniki E, et al. ESC poster 2014: In press
*All patients were event free for the first year post MI. The PEGASUS-TIMI-54-like cohort also had at least 1 additional risk factor; age >65, diabetes, >1 prior MI or renal disease, with no history of stroke, dialysis or use of oral anti-coagulants and absence of age <50

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Summary

- Strategy of reducing morbidity, mortality and organ damage
- Diabetes growth from combo treatment and science-led LCM
- Opportunity to change the lives of CKD patients
- Transform atherosclerosis through Brilinta PARTHENON trials
James Ward-Lilley, moderator
Bing Yao
Elisabeth Björk
Chuck Bramlage
Maarten Kraan
Fouzia Laghrissi Thode
Tom Keith-Roach