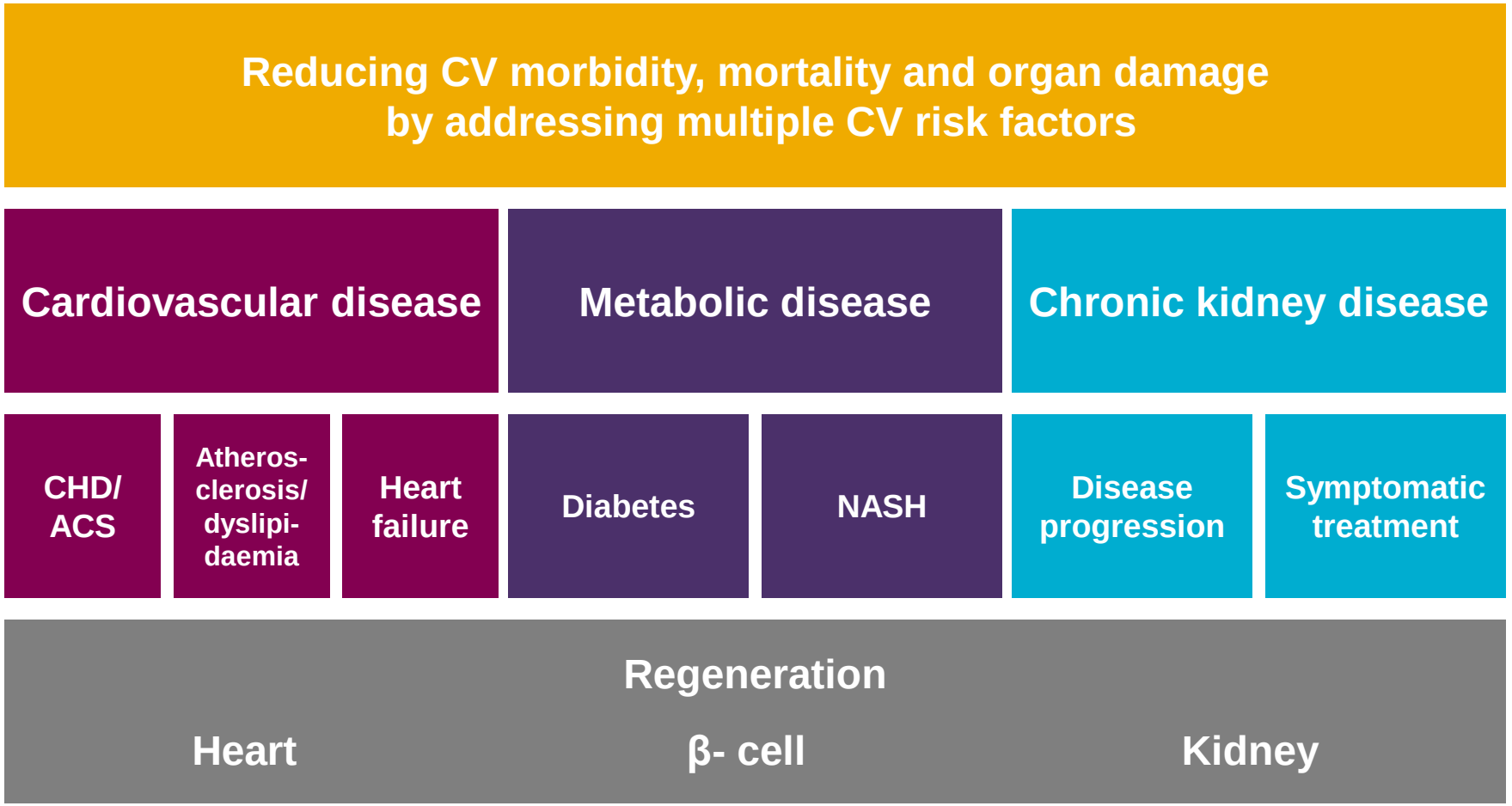
Pipeline: Cardiovascular & Metabolic Disease (CVMD)

Addressing the next frontier in cardiovascular medicine

Elisabeth Björk, Vice President, Head CVMD GMD

Cardiovascular & Metabolic Disease (CVMD): Strategy



CHD: Coronary heart disease
ACS: Acute coronary syndrome
NASH: Non-alcoholic steatohepatitis

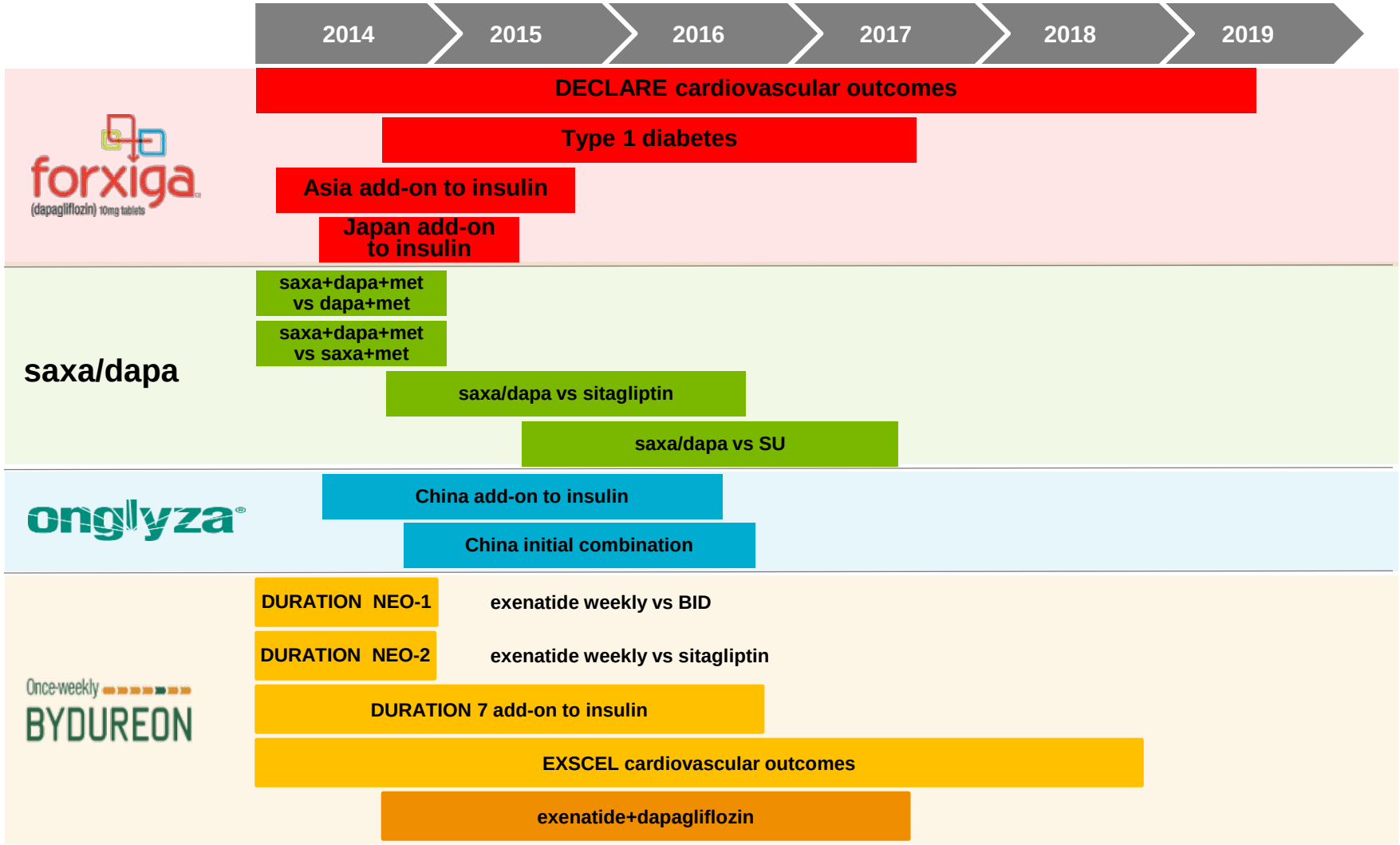
Diabetes:
Strategy to transform patient care

Shift treatment paradigm to early combination therapy and accelerate achievement of treatment goals

Develop a science-led life cycle management strategy

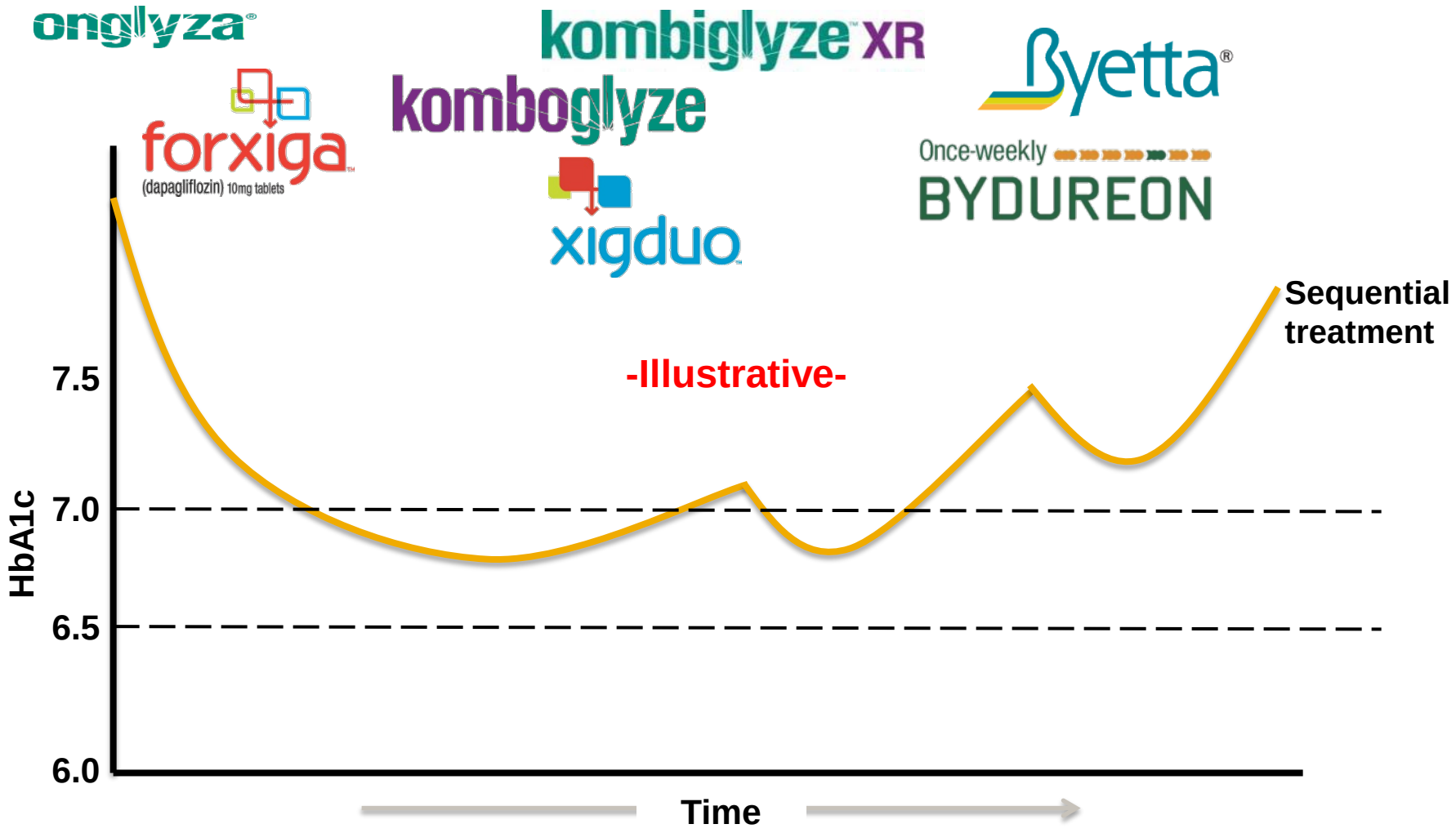
Expand into new areas of unmet need, including expansion into Type 1 diabetes with *Forxiga*

Diabetes: R&D commitment

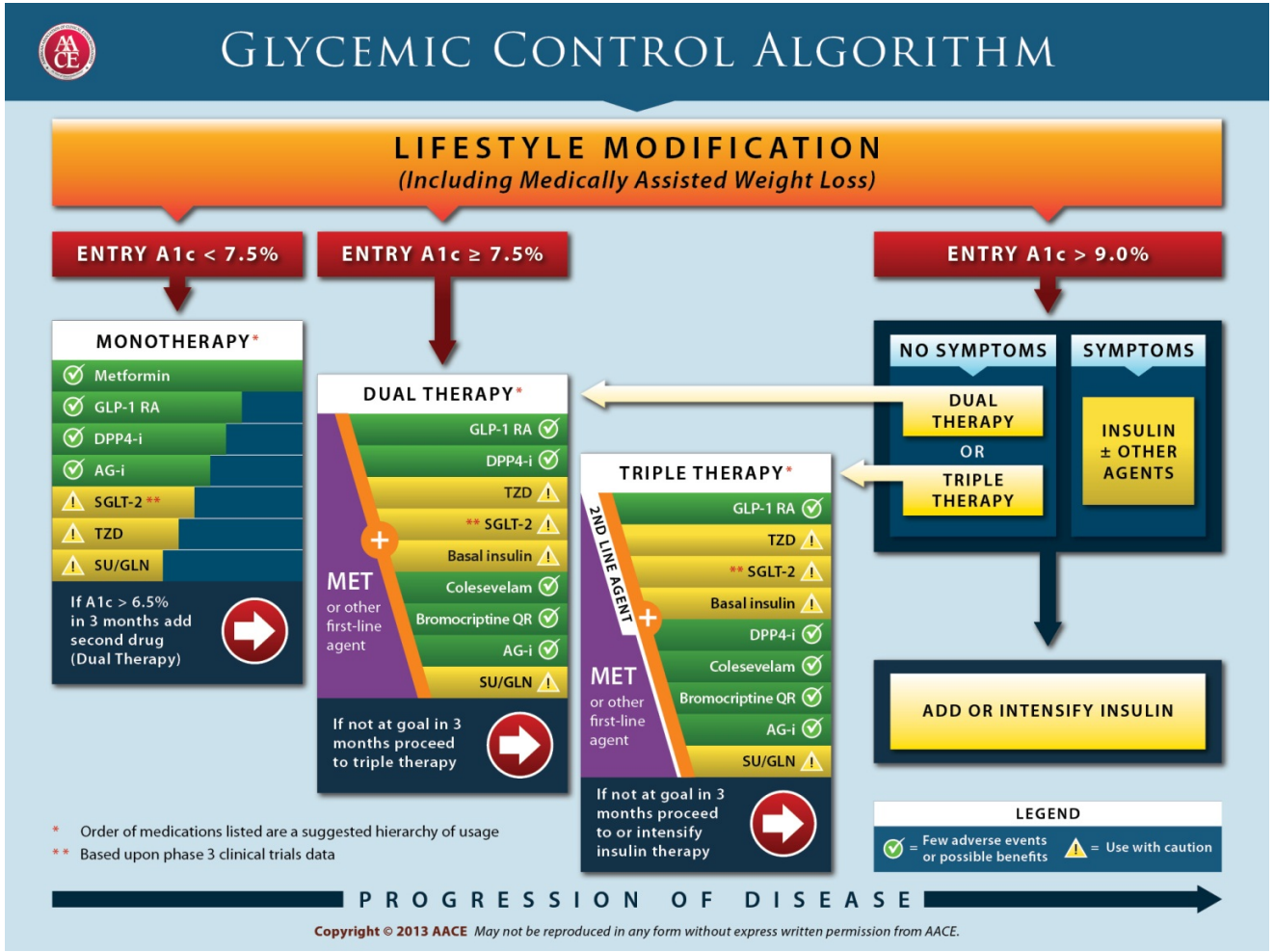


~40,000 patients in clinical trials world wide

Diabetes:
Helping patients along disease progression



Diabetes:
New guidelines more aggressive with earlier combinations



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

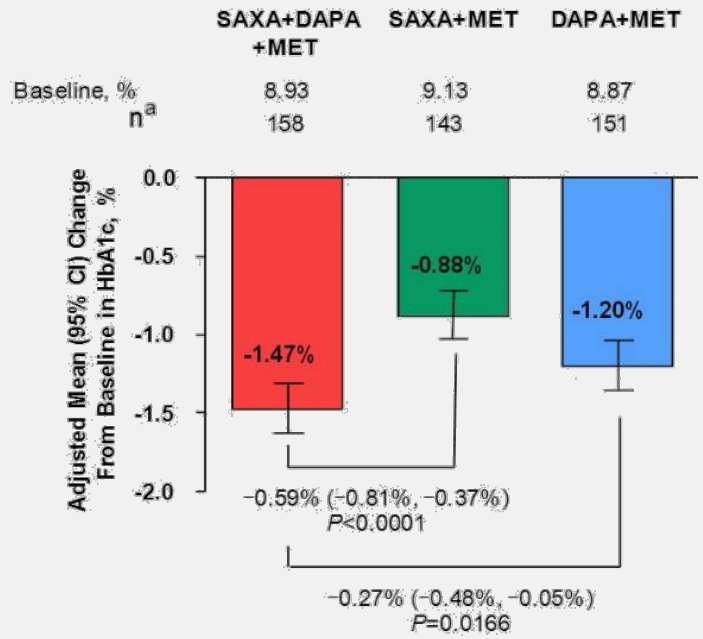
Oral combinations:
Saxa/dapa & saxa/dapa/metformin

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

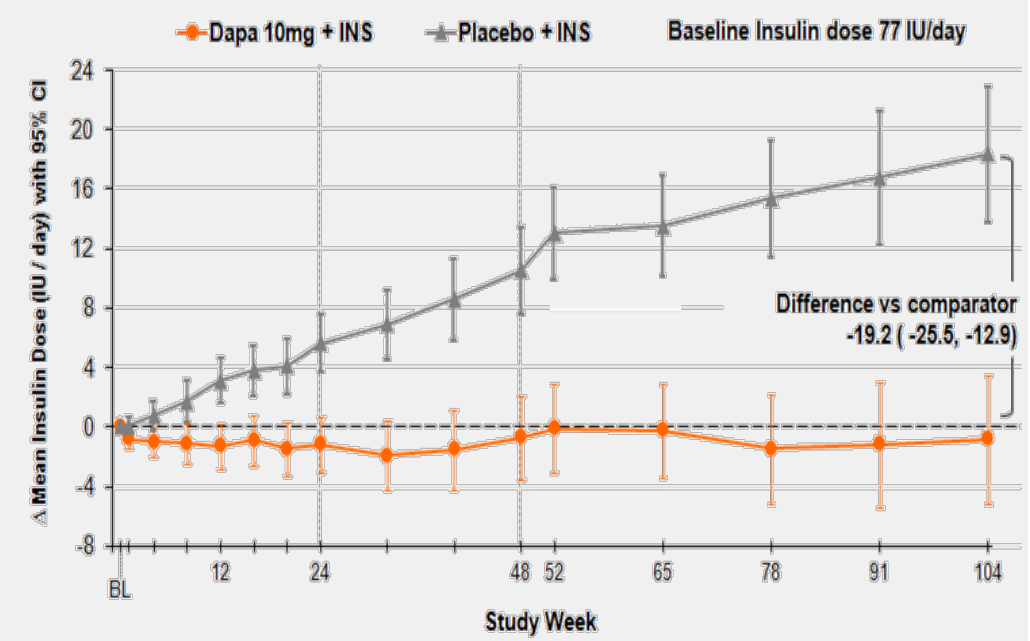


[a] Number of randomized patients with non-missing baseline values and Week 24 values.
CI, confidence interval.

Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, Iqbal N. Dual Add-On Therapy in Poorly Controlled Type 2 Diabetes on Metformin: Randomized Double-Blind Trial of Saxagliptin+Dapagliflozin vs Saxagliptin and Dapagliflozin Alone. 127-LB, American Diabetes Association, 2014.

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

Ann Intern Med. 2012;156(6):405-415
Study 006 Clinical Study Report, Figure4, Table 11.2.6.1.1
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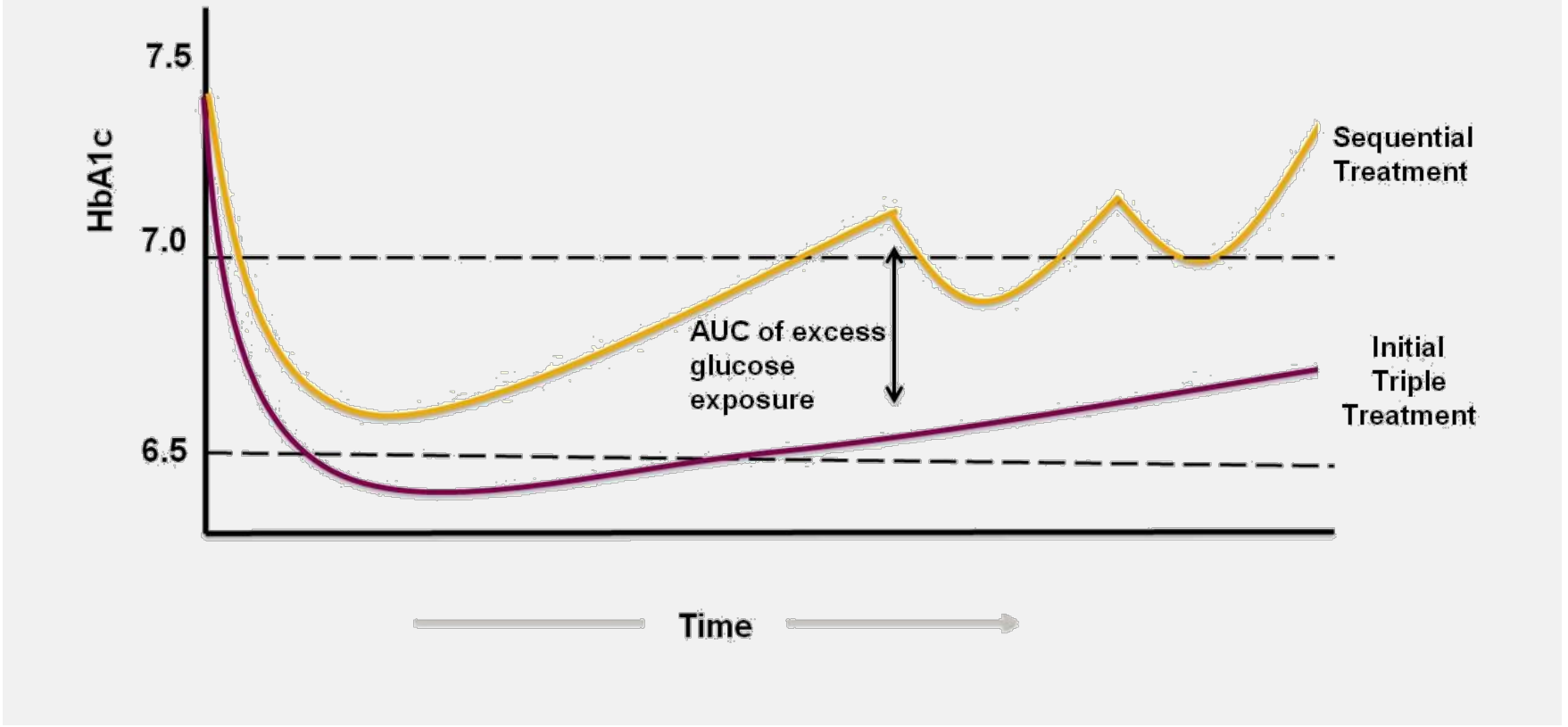
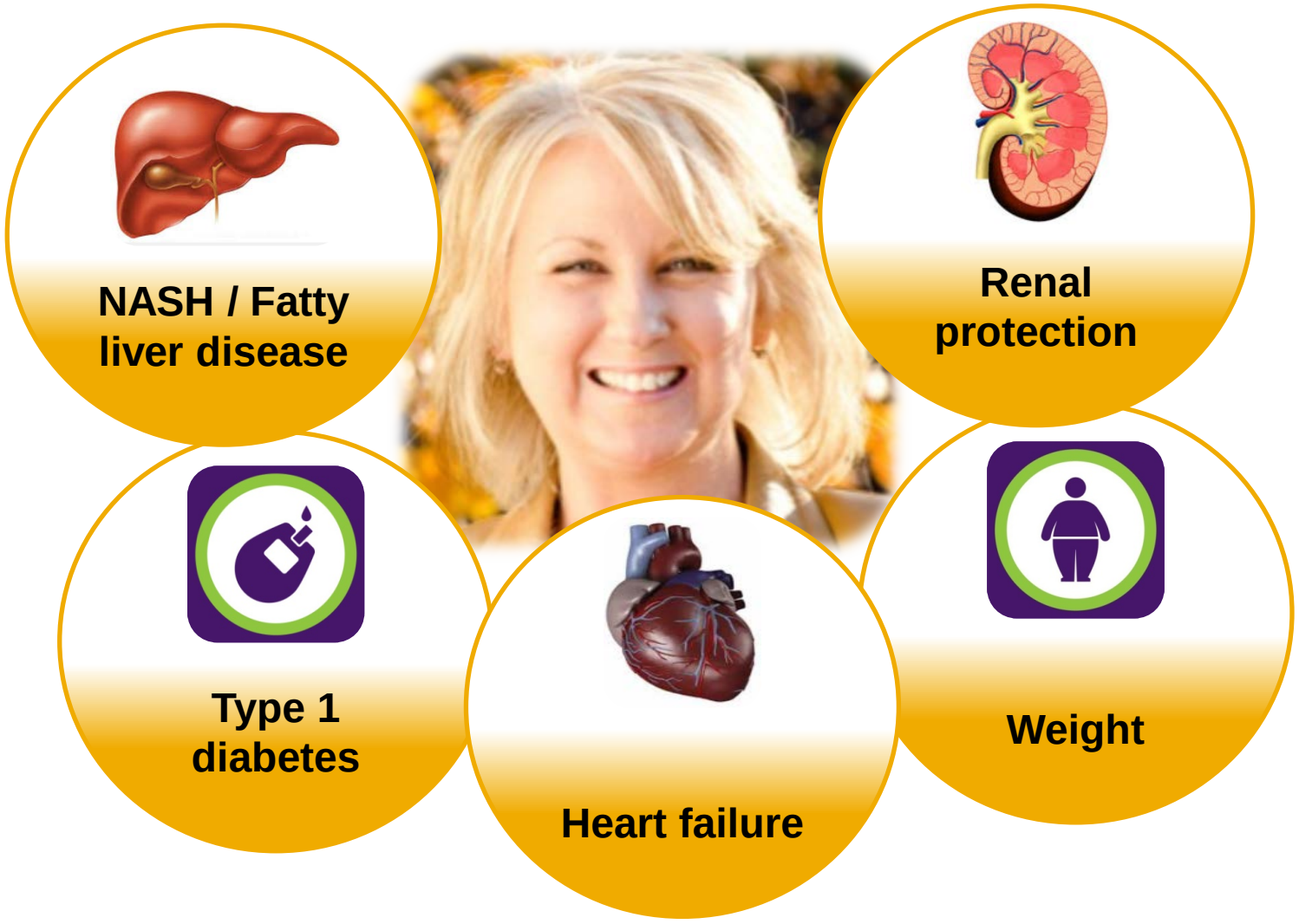
Diabetes:
Potential of early combinations to slow disease progression

Illustrative

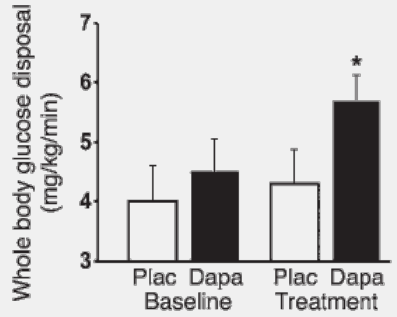


CVMD:
Science-driven innovation into new areas of unmet need

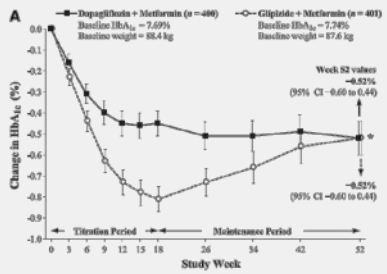


CVMD:
Visualising diabetes impact via differentiated technology

Functional data



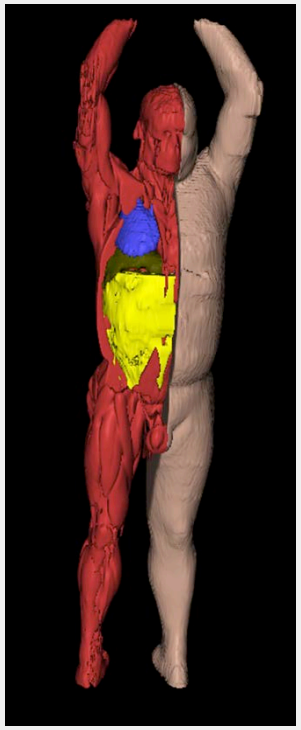
Source: Merovci et.al JCI 2014



Source: Nauck et.al Diabetes Care 2011

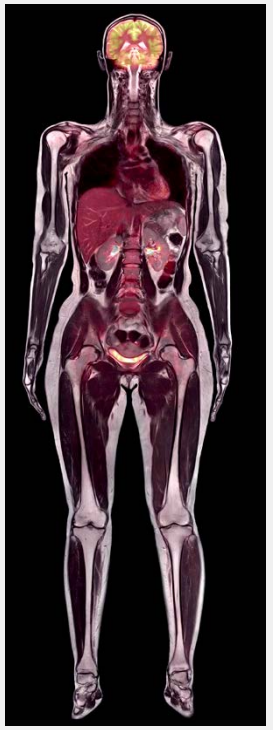
Glucose disposal and HbA1c

Body composition and ectopic lipids



Automated body composition analysis (DAPA-12)

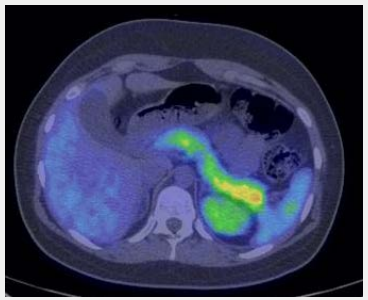
Tissue-specific insulin sensitivity



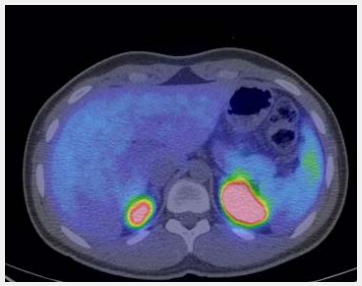
FDG (fluor-dioxyglucose) uptake during insulin clamp

Beta cell mass

Healthy control



T1D patient

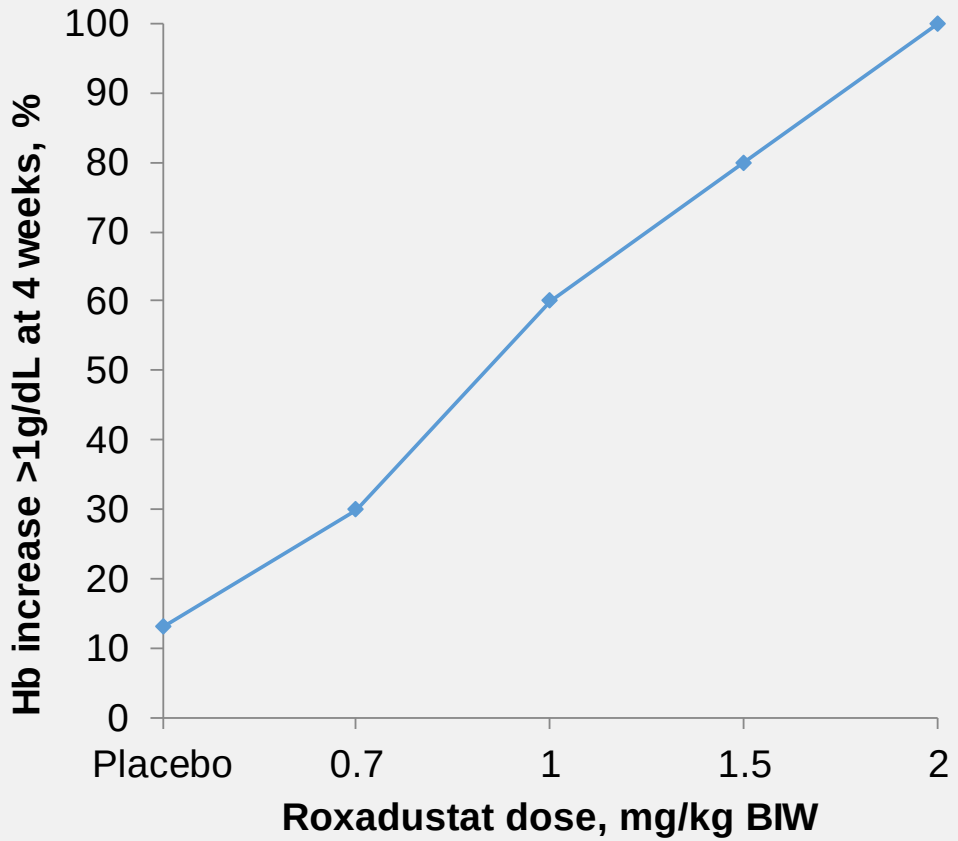


^{11}C-5-HTP or ^{68}Ga-Exendin-4

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

Hb correction in pre-dialysis CKD patients

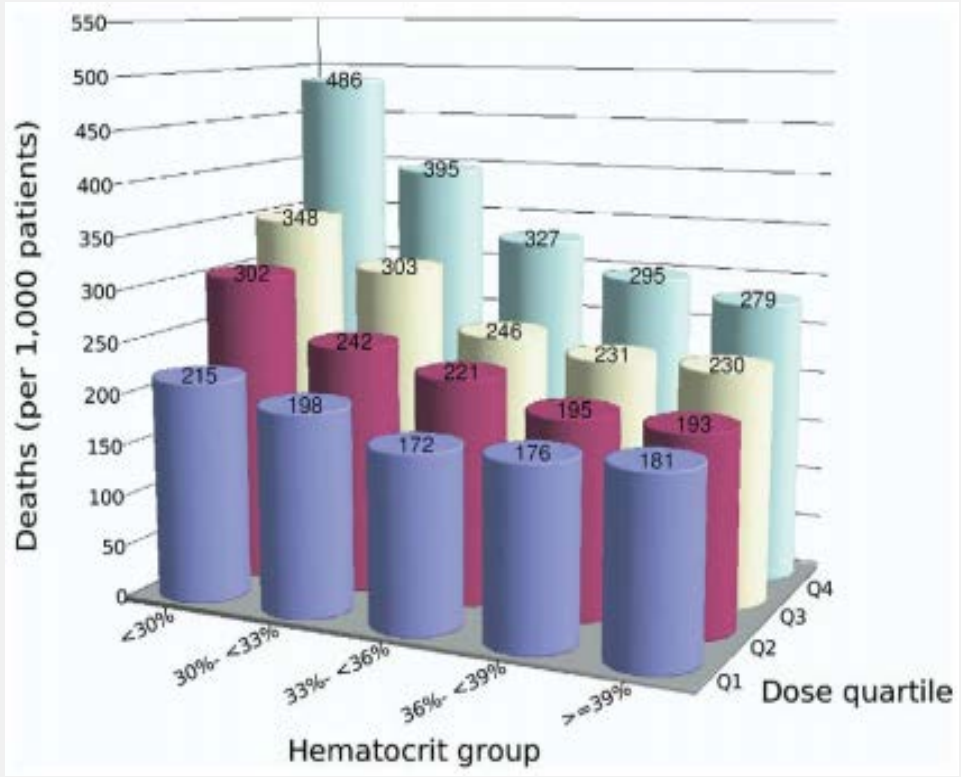


Source: FibroGen Registration Statement

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

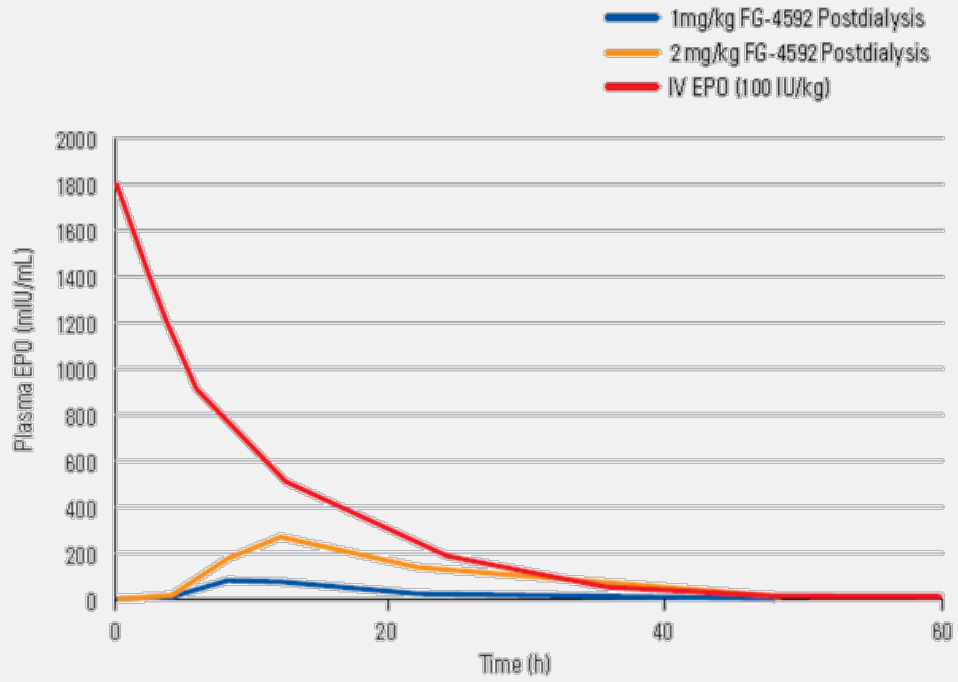


Zhang et al. Am J Kidney Dis 2004;44:866-87

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

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



Source: FibroGen Registration Statement

* 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)

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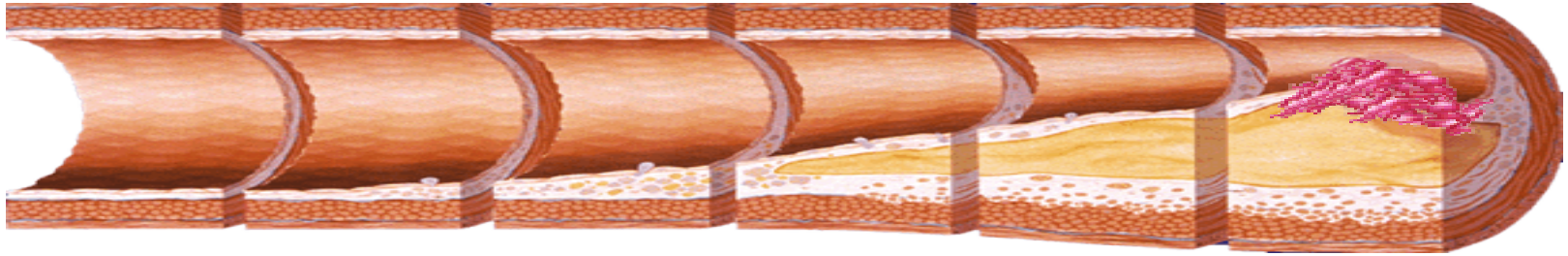
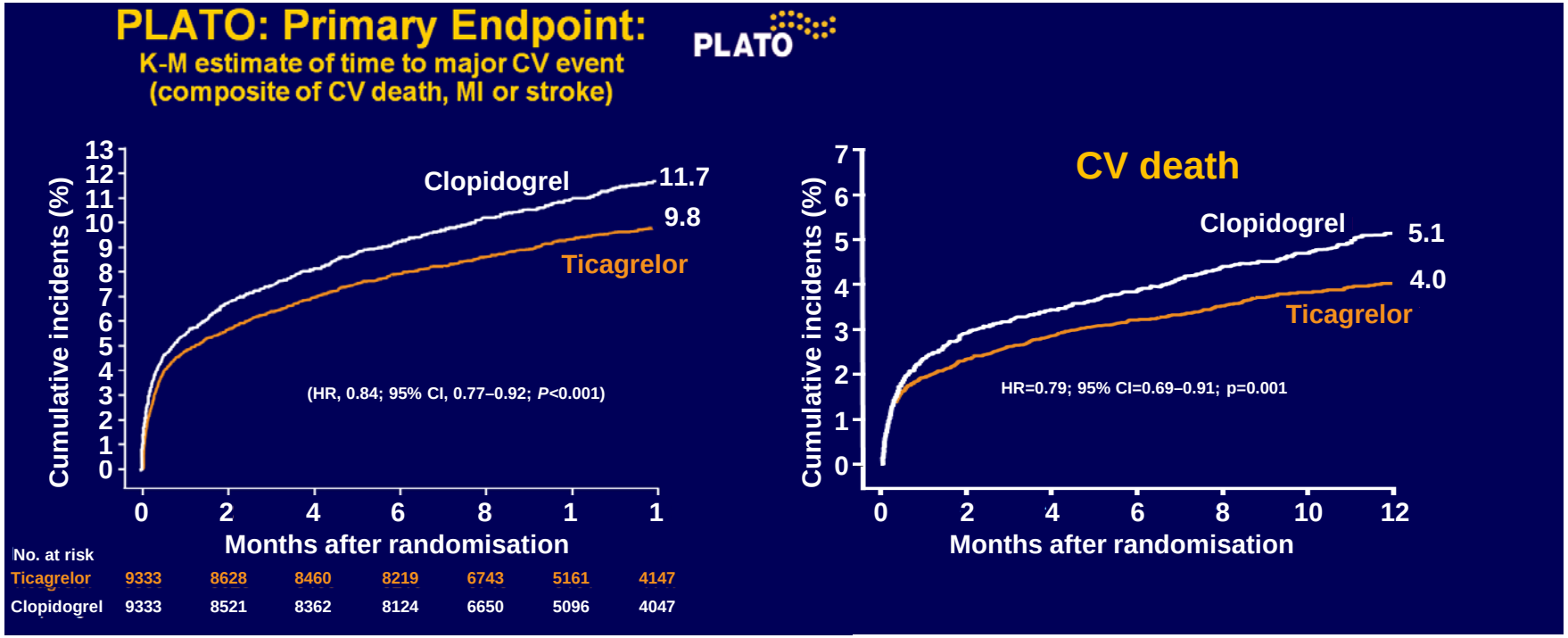
ticagrelor tablets

Brilinta: PARTHENON potentially transforms atherosclerosis treatment



	2014		2015		2016		2017		2018		2019	
	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2
Prior MI	▲ Data		▲ Submission		US/EMEA		Japan	China				
Stroke/TIA				▲ Data	▲ Submission		EMEA US	Japan	China			
Peripheral Arterial Disease						▲ Data	▲ Submission		EMEA US	Japan	China	
Diabetes							▲ Data	▲ Submission		EMEA US	Japan	China
OAP market access *(% current volume)*	*20%*		*20%*		*31%*		*68%*		*83%*		*84%+*	

Brilinta:
PLATO results displayed unique clinical profile

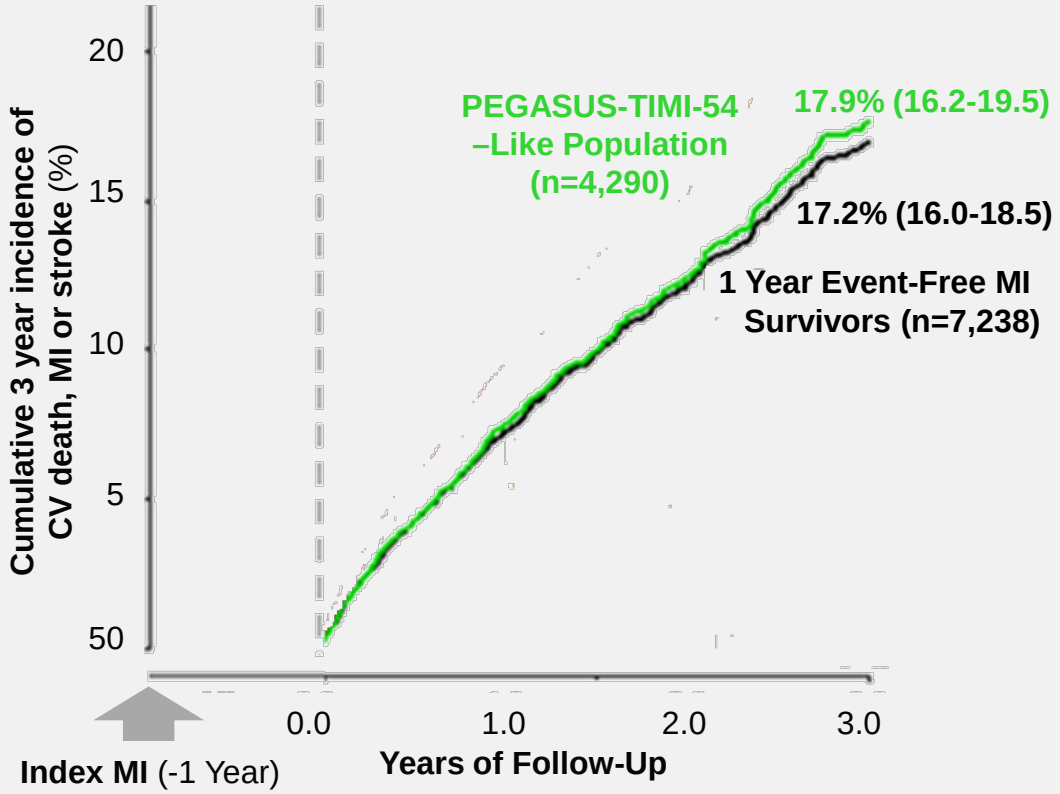


- Continuous benefit for one year
- Mortality benefit
- Potential unique benefit beyond P2Y12 inhibition driven by ENT1

K-M, Kaplan-Meier
Wallentin L, et al. N Engl J Med. 2009;361:1045-1057

Brilinta:
APOLLO UK proved unmet need in PEGASUS-like patients

APOLLO UK analysis



~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

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

Q&A



James Ward-Lilley, *moderator*
Bing Yao
Elisabeth Björk
Chuck Bramlage
Maarten Kraan
Fouzia Laghrissi Thode
Tom Keith-Roach