
Roche

Roche Science Events: ACC 2008
Conference Call for Investors and Analysts

HDL raising as a new therapeutic intervention and Roche's CETP inhibitor R1658

Chicago, April 2, 2008

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Agenda

HDL raising and Roche's CETP inhibitor

- **Introduction**

  Dr. Karl Mahler, Head of Investor Relations, Roche

- **Metabolic Diseases Patterns and Market**

  Luke Miels, Strategic Marketing Head Metabolic Diseases and Anemia, Roche

- **HDL raising: The new target**

  Prof. Dr. Philip Barter, Director, Heart Research Institute, Sydney

- **Safety data for Roche's CETP inhibitor**

  Dr. Fouzia Laghrissi-Thode, Life Cycle Leader for R1658, Roche

- **Phase III Morbi-Mortality (M&M) study**

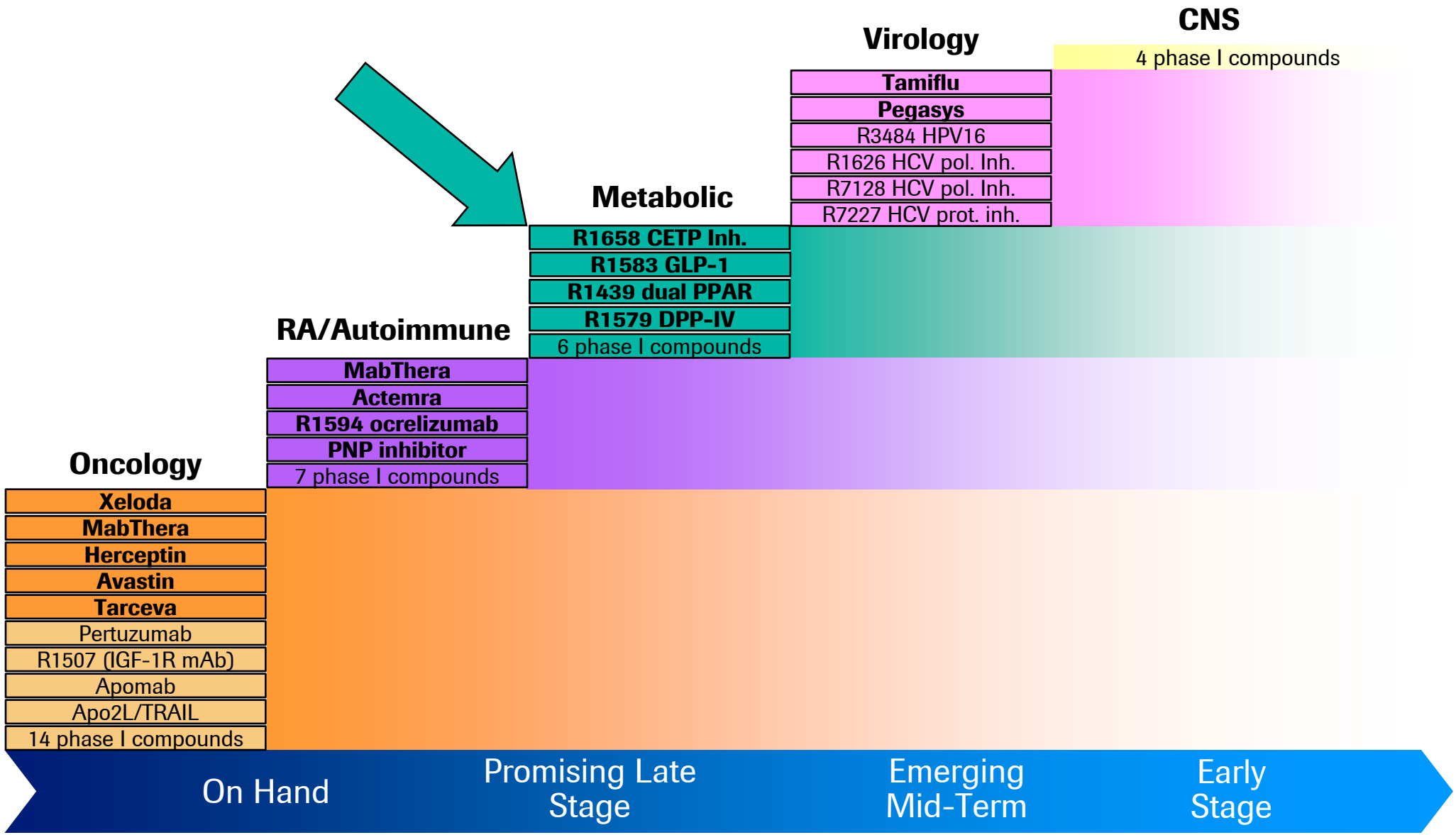
  Dr. Fouzia Laghrissi-Thode, Life Cycle Leader for R1658, Roche

- **Next steps**

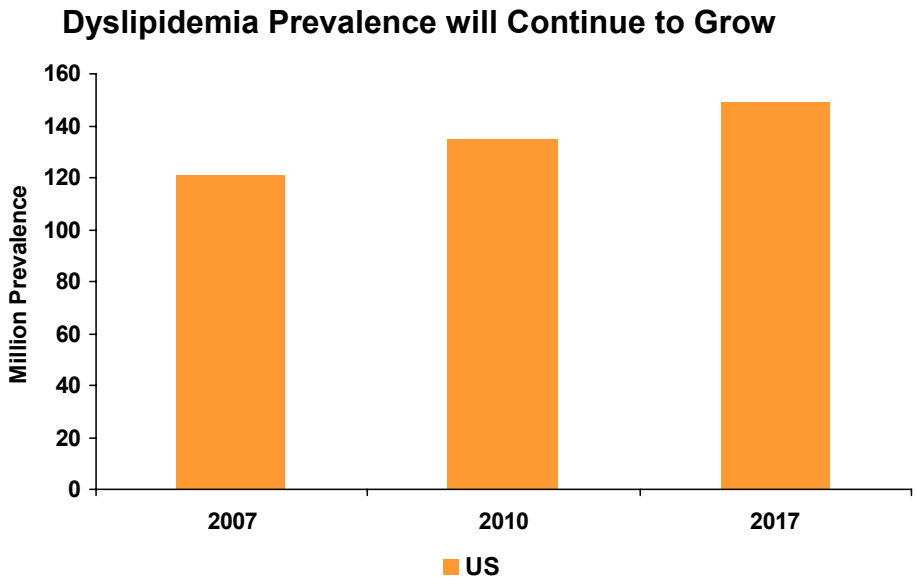
  Luke Miels, Strategic Marketing Head Metabolic Diseases and Anemia, Roche

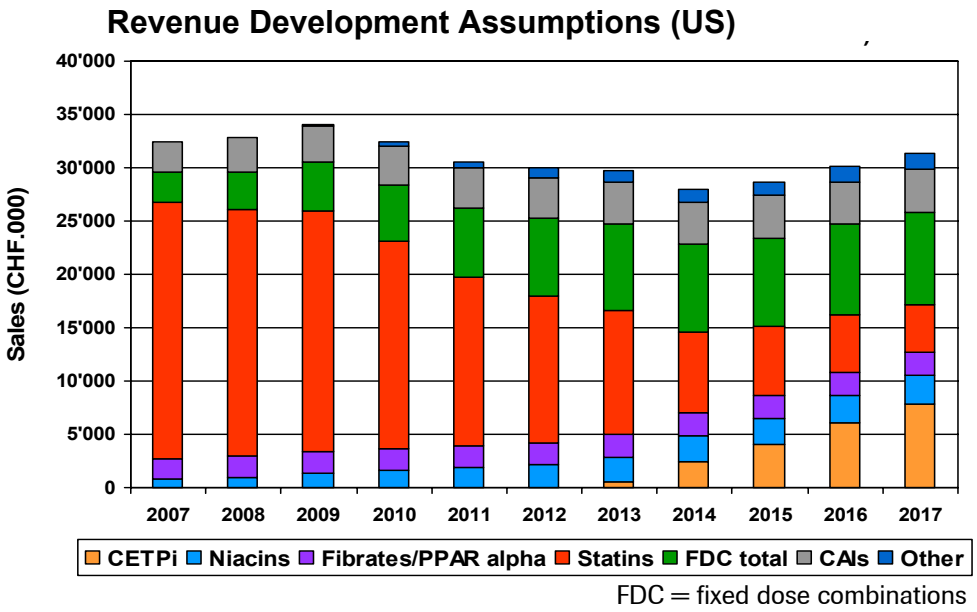
Roche key therapeutic areas

Current and future pillars of growth



Dyslipidemia: Future growth driven by HDL treatment





FDC = fixed dose combinations

CETP inhibitors and other HDL raising drugs will be responsible for the majority of market value

Sources: Wood MacKenzie, IMS therapy forecaster, Roche assumptions
Decision Resources, Cardium Study#4, 2007; Datamonitor Pipeline Insight dyslipidemia 2007

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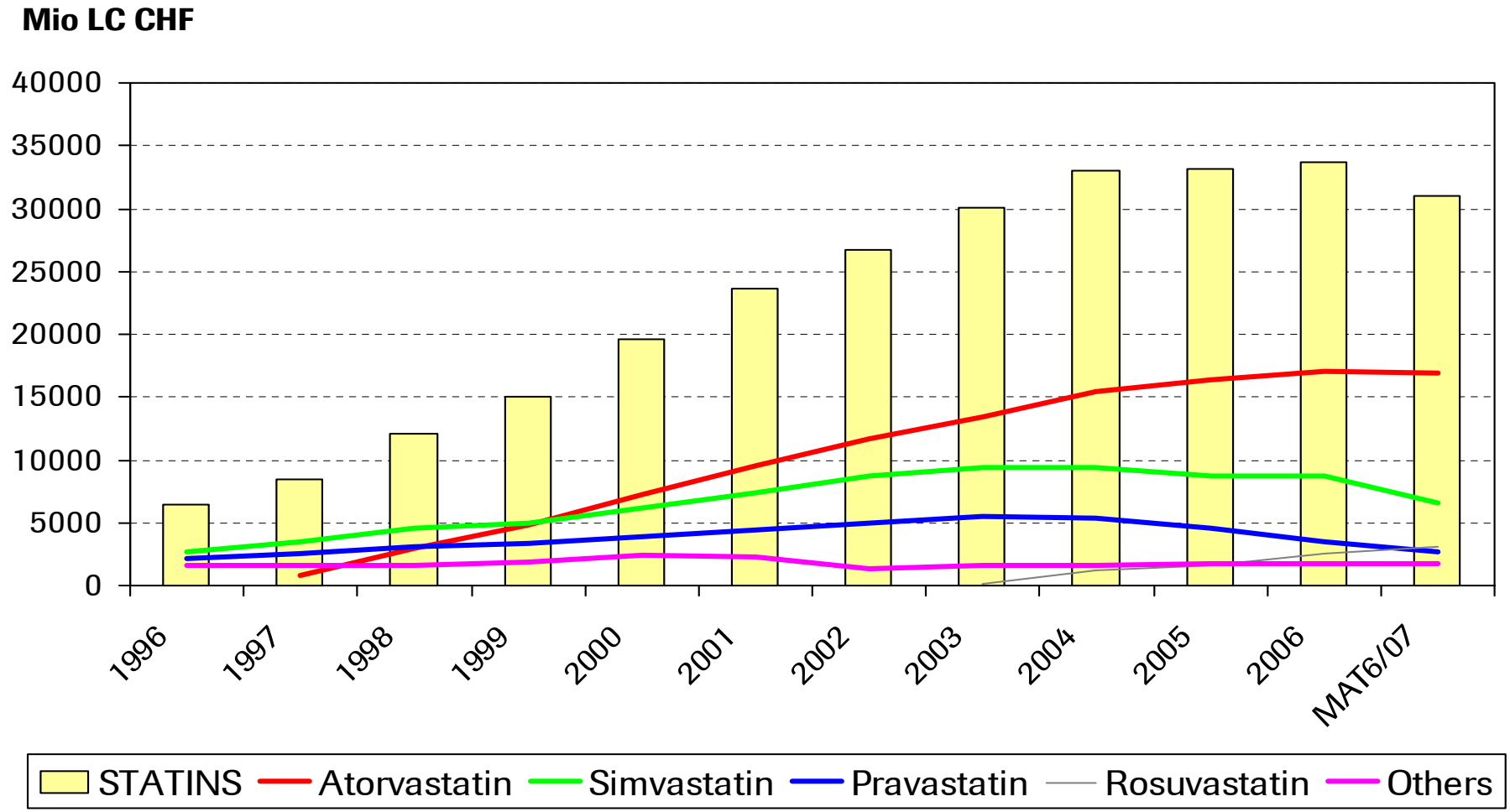
Next steps

Global Statin Market – CHF 31bn



IMS MIDAS (PADDS), Roche panels

The Market Today

HDL as an emerging target in dyslipidemia

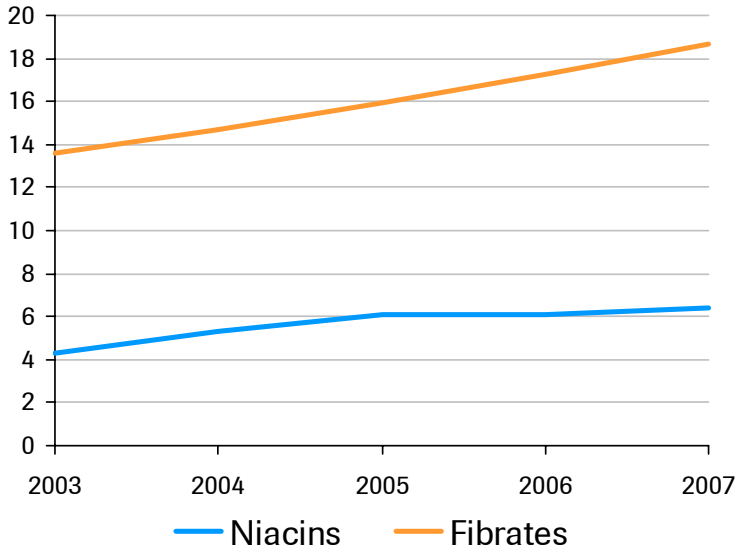
Short Term

- Currently 6 million TRx/year in the US
- Market growth will be driven by Niacin based combinations
  - Moderate to severe flushing occurs in more than 30% of patients

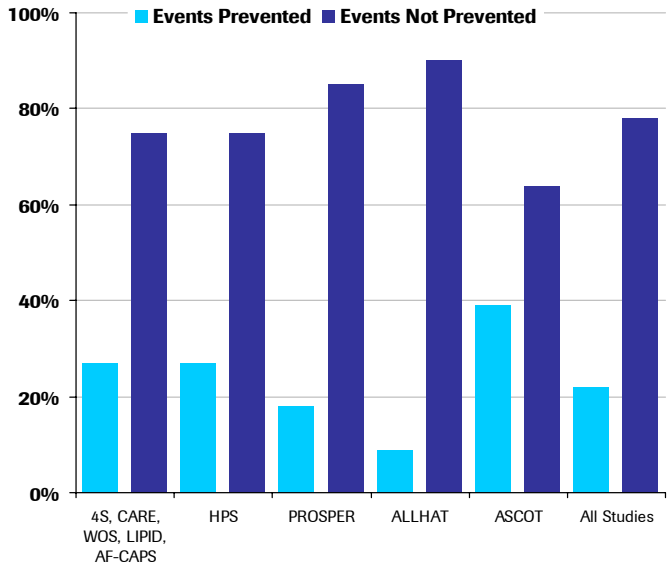
Medium Term

- Entry of the CETPi class
- CETPi class will launch with M&M data in high risk populations
- CETPi are expected to be prescribed on top of statins to treat cardiovascular residual risk

US Niacin and Fibrate Scripts (MM TRx)



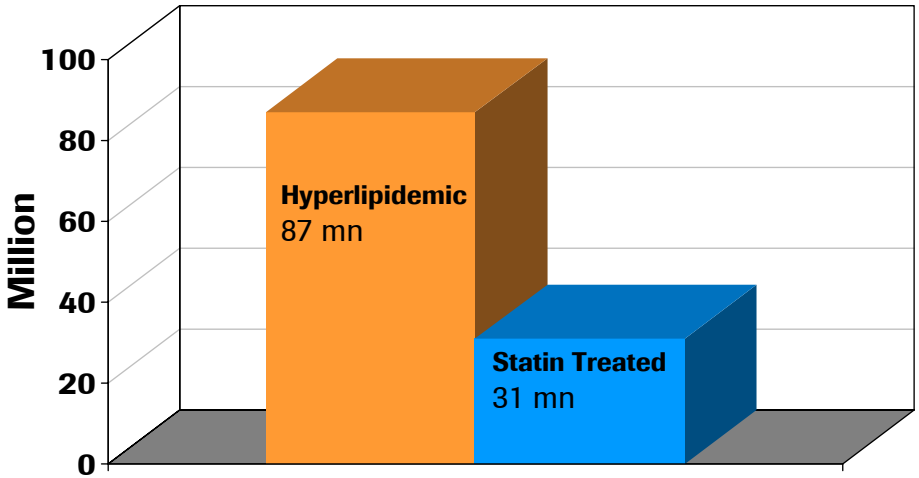
Percentage of Cardiovascular Events Prevented or Not Prevented in Major Clinical Studies



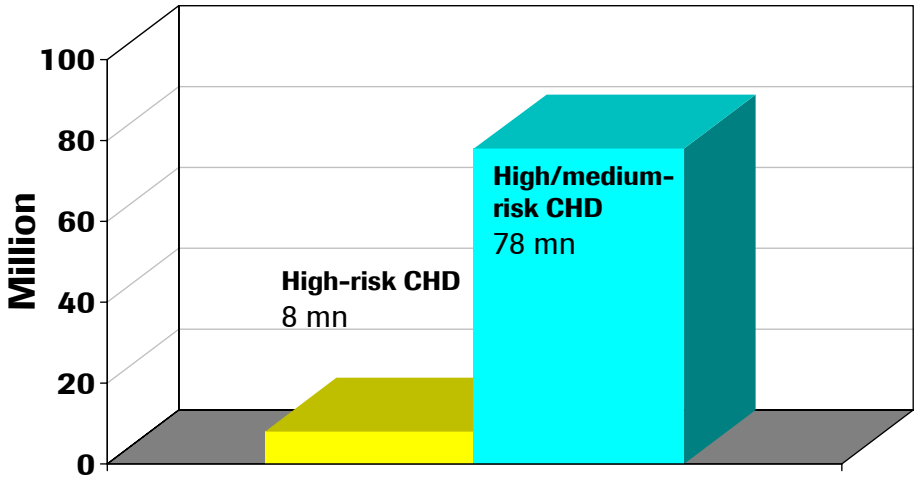
High / Medium-Risk CHD patients in US

Patients potentially benefiting from HDL raising

Hyperlipidemia



High/medium-risk CHD



Source: Decision Resources

The Dyslipidemic Market

Differences between LDL and HDL hypothesis

LDL

- Validated surrogate marker
- Established scientific understanding of the LDL particle
- M&M data is not a launch requirement for LDL compounds
- Mature market
- Generics (statins)

HDL

- Non-validated surrogate marker
- Evolving scientific understanding of the HDL particle
- M&M data is a launch requirement for CETP class
- Emerging market
- Few compounds to raise HDL in phase III clinical development

Metabolic diseases patterns and market

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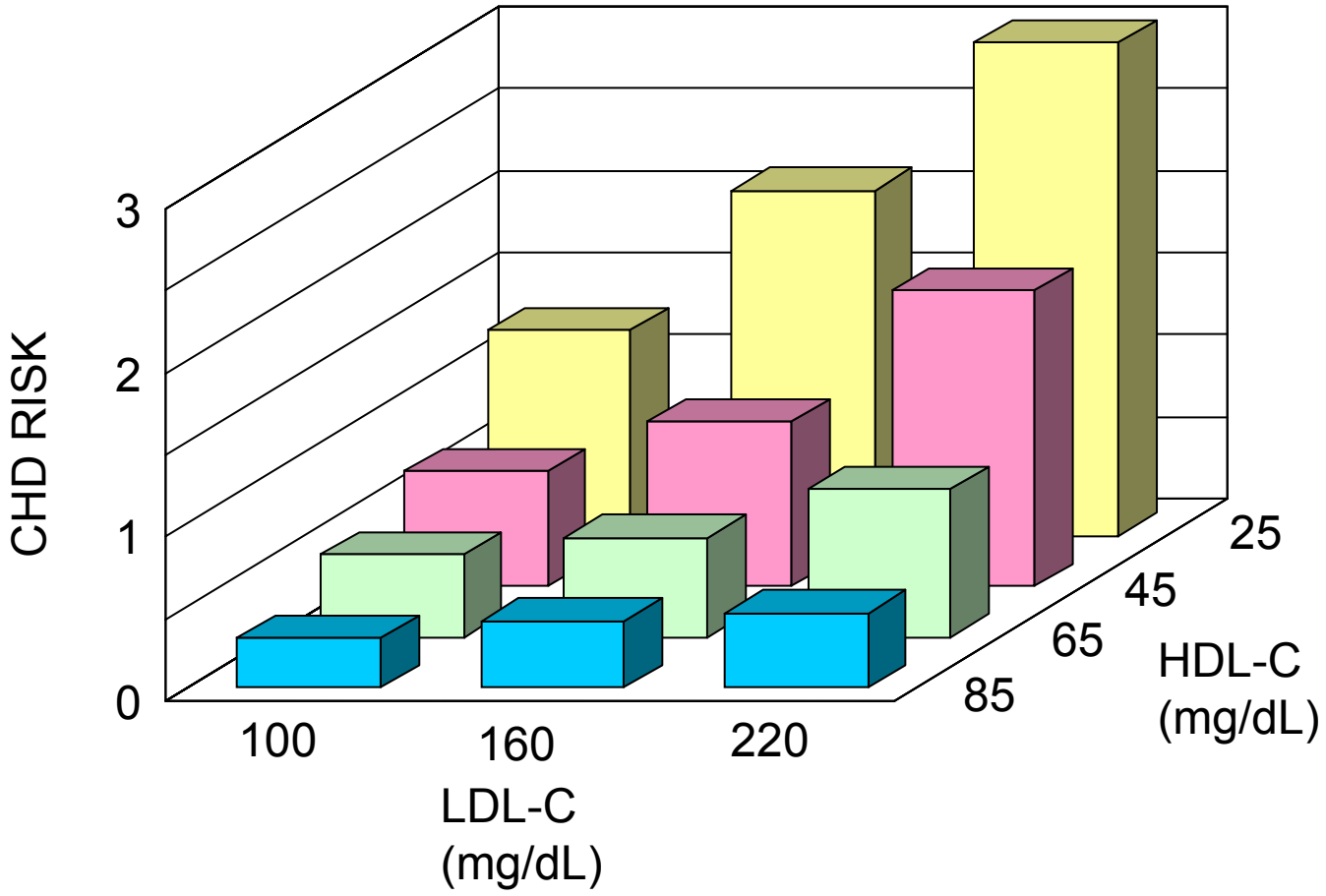
Phase III Morbi-Mortality (M&M) study

Next steps

FRAMINGHAM: Low HDL-C is an independent factor of CHD risk even when LDL-C is low

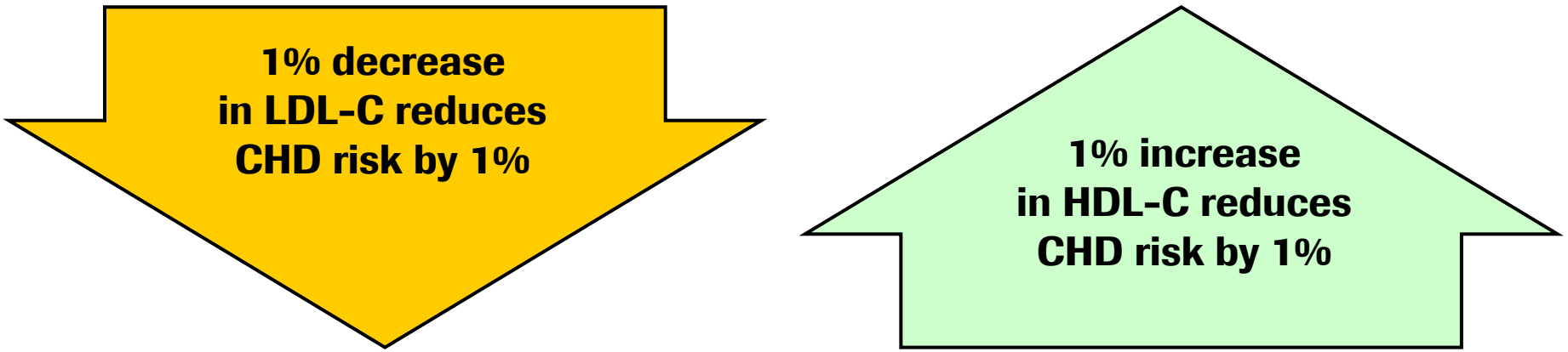


A highly significant correlation in more than 10'000 individuals, across two generations.

* Men aged 50-70

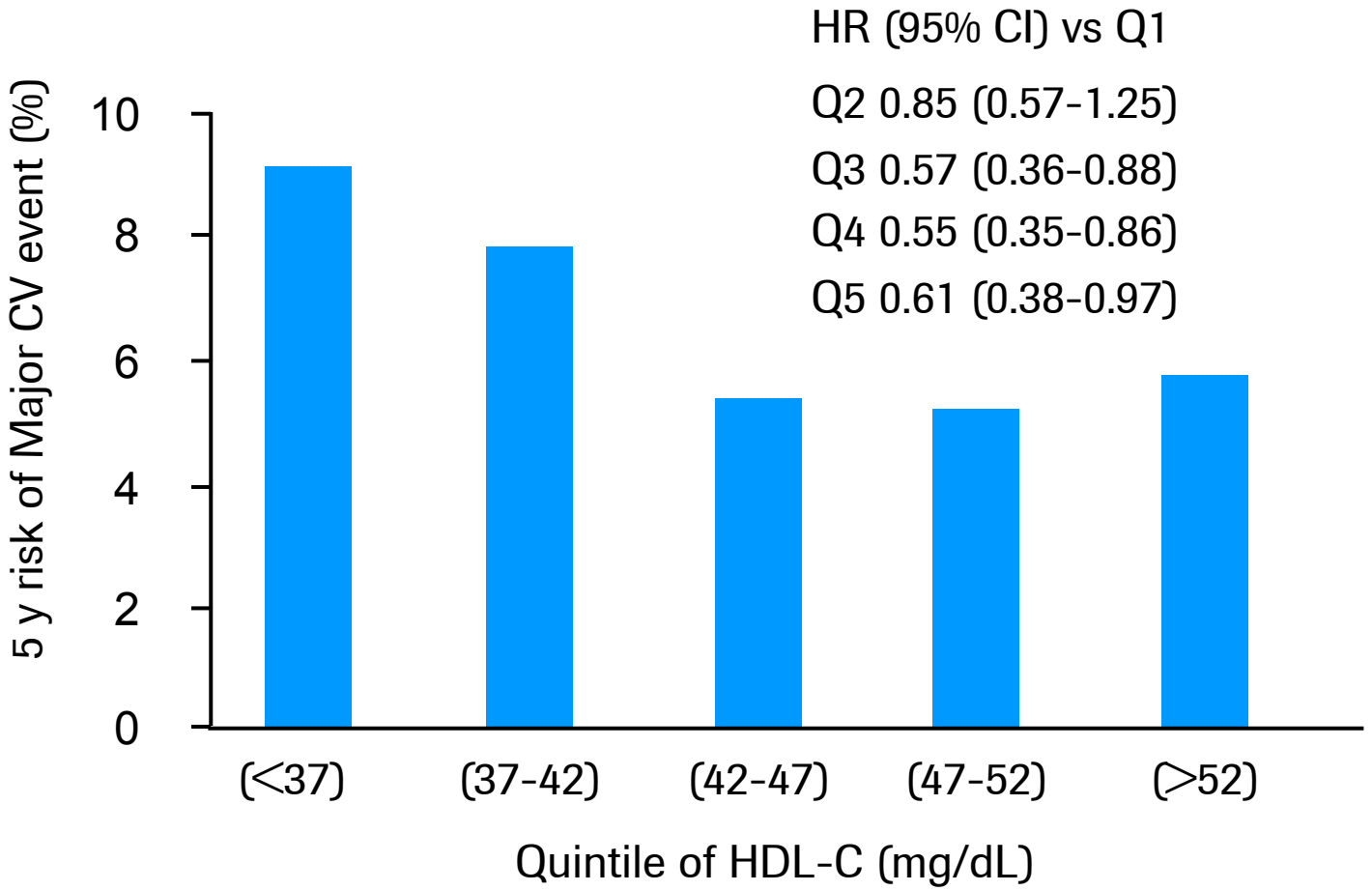
Gordon, Castelli et al. Am J Med 1977;62:707–714

Relationship Between Changes in LDL-C and HDL-C Levels and CHD Risk



Third Report of the NCEP Expert Panel. NIH Publication No. 01-3670 2001.

TNT Trial: Major Cardiovascular Event Frequency by HDL level in group with LDL-C < 70 mg/dL



No of Events	57	50	34	34	35
No of Patients	473	525	550	569	544

Barter et al, NEJM 2007, 357; 13, 1301-1310

Benefits of raising HDL

Animal studies

- Raising HDL-C either by infusing HDL or by increasing the synthesis of apoA-I by genetic manipulation greatly inhibits the development of atherosclerosis in both mice and rabbits

Human Studies

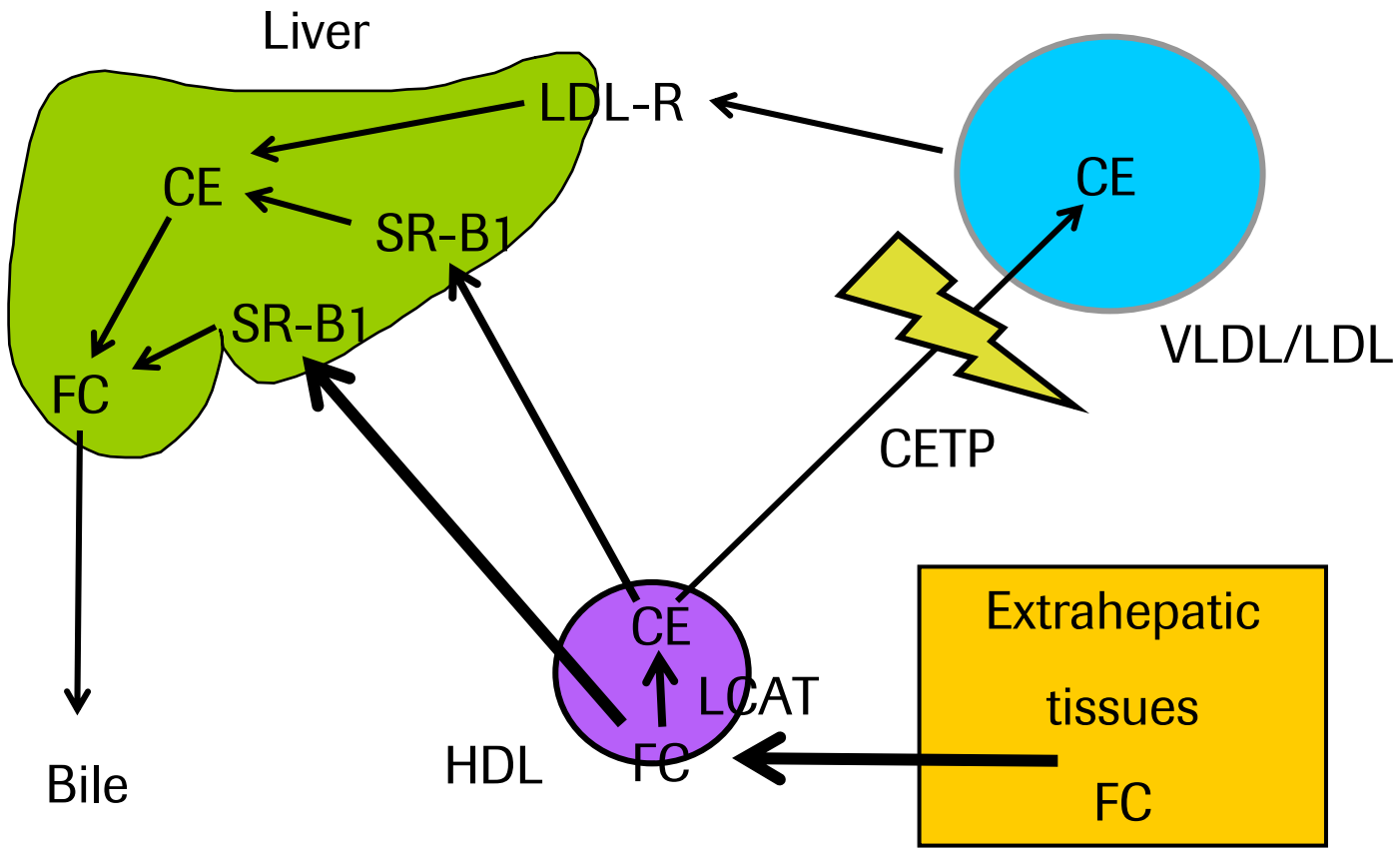
- Raising HDL-C by treatment with either niacin or fibrates in intervention trials is associated with a slowing of progression of CAD and a reduction in CV events.
- Infusion of reconstituted HDL reduces the atherosclerosis burden as assessed by IVUS.

Vascular protective properties of HDL

Promote cholesterol efflux from macrophages

- Anti-oxidant properties
- Anti-thrombotic properties
- Anti-inflammatory properties
- Improve endothelial function
- Promote endothelial repair
- Other

Effect of CETP inhibition on plasma cholesterol transport



Relationship between CETP and atherosclerosis

Animal studies (Rodents)

- Rodents naturally deficient in CETP
- Rodents naturally resistant to development of atherosclerosis
- Expression of CETP in transgenic mice and rats increases atherosclerosis in most (but not all) models

Animal studies (Rabbits)

- Rabbits have high level of activity of CETP
- Rabbits naturally highly susceptible to the development of atherosclerosis
- Inhibition of CETP in rabbits decreases atherosclerosis in all models

Relationship between CETP and atherosclerosis

Human studies

- Torcetrapib inhibits CETP in humans and raises HDL-C by about 60% and lowers LDL-C by more than 20%
- In human studies torcetrapib had no effect on atherosclerosis in three imaging trials
- In human studies torcetrapib increased both mortality and major cardiovascular events in a large end-point trial

Off-target pharmacological effects of torcetrapib unrelated to CETP inhibition

In patients receiving torcetrapib in the ILLUMINATE trial there was a significant:

- Increase in blood pressure
- Decrease in serum potassium
- Increase in serum bicarbonate
- Increase in serum sodium
- Increase in serum aldosterone

The adverse outcome in the ILLUMINATE trial may thus have been the consequence of an off-target pharmacology of torcetrapib unrelated to CETP inhibition.

Barter et al, NEJM 2007;357:1301-1310

The changes in potassium and bicarbonate predicted adverse outcome in the ILLUMINATE trial

Deaths by changes in K+ and HCO3- from baseline to month 1

Decrease in serum potassium

	Decrease ≥ Median (≥ 0.1 mmol/L)	Decrease < Median (< 0.1 mmol/L)	N/C*
Sample size	**3709**	**3629**	**195**
Deaths (%)	**54 (1.46)**	**35 (0.96)**	**4 (2.05)**

Increase in serum bicarbonate

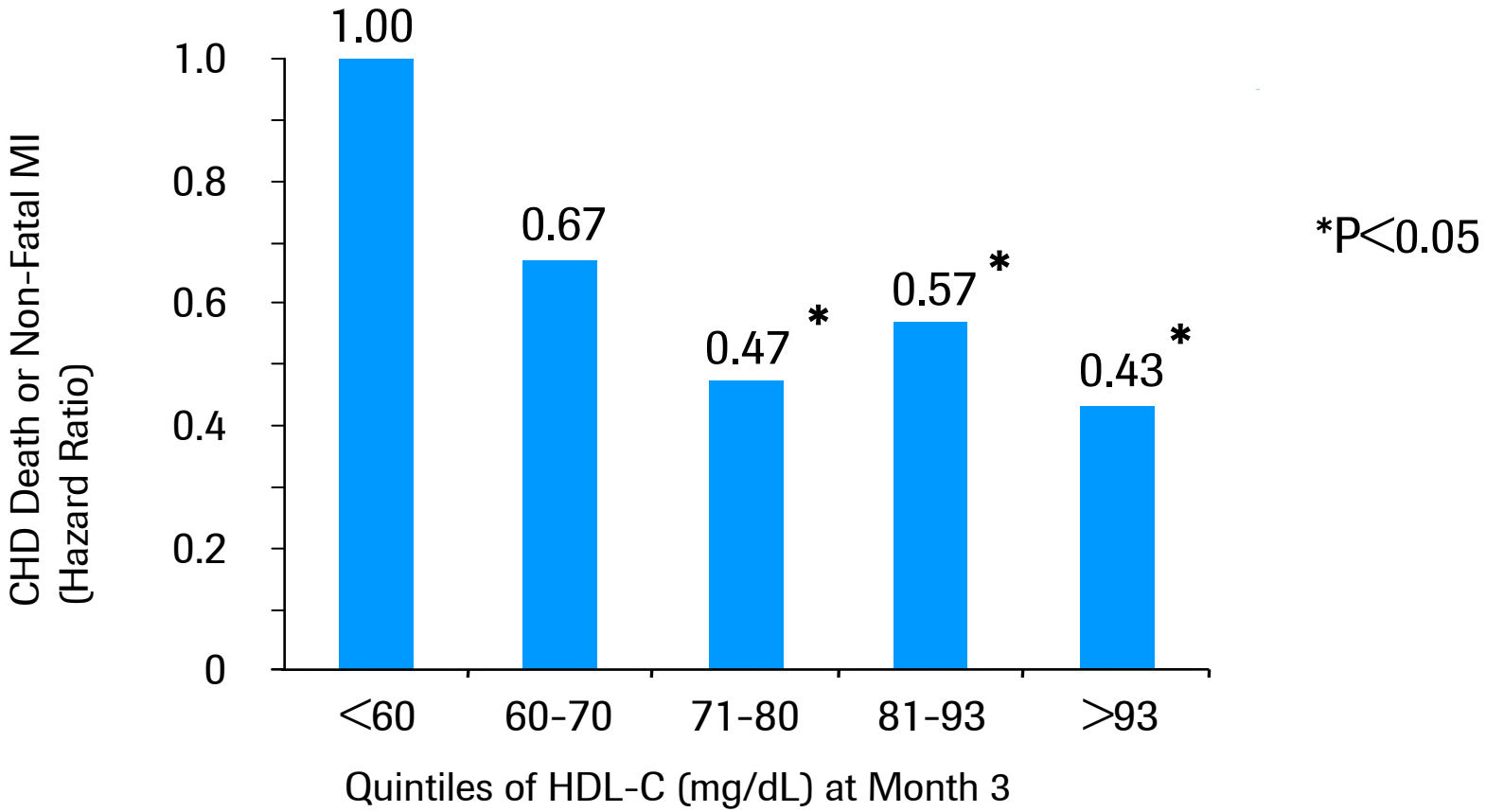
	Increase > Median (> 0.7 mmol/L)	Increase ≤ Median (≤ 0.7 mmol/L)	N/C*
Sample size	**3669**	**3695**	**169**
Deaths (%)	**54 (1.47)**	**35 (0.95)**	**4 (2.37)**

N/C = not classified due to missing value

Barter et al, NEJM 2007;357:1301-1310

ILLUMINATE trial:
The higher the achieved HDL-C in the torcetrapib treated patients, the lower the event rate

Hazard ratios for CHD Death or Non-Fatal MI by quintile of on-trial HDL-C (referent group is HDL-C < 60 mg/dL stratum)



Cox proportional hazard model adjusted for age, gender and baseline HDL-C.
Excludes 265 patients with missing month 3 HDL-C.

Barter. AHA 2007

What is the future of CETP inhibition as an anti-atherogenic strategy in humans?

Given:

- the powerful evidence in animal studies that inhibiting CETP is anti-atherogenic and
- that off-target effects of torcetrapib unrelated to CETP inhibition may have been responsible for the adverse outcome in the ILLUMINATE trial

There is a compelling case for further testing of the hypothesis that inhibiting CETP will be anti-atherogenic in humans so long as the hypothesis is tested with a CETP inhibitor that does not share the off-target pharmacology of torcetrapib.

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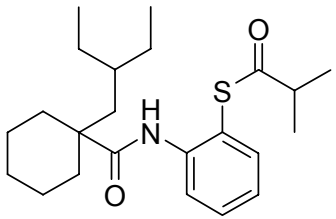
CETP Inhibitors

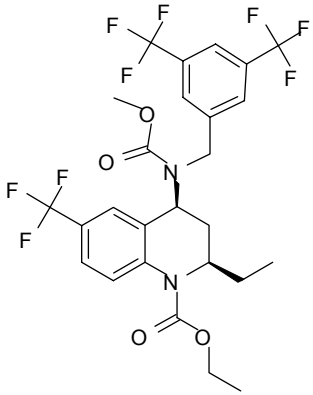
R1658 is a unique CETPi

- In contrast to the majority of other CETPi, R1658 has a different chemical backbone to Torcetrapib
- In patients treated with R1658, HDL is of normal composition
- In pre-clinical models and in clinical trials up to phase II, data showed that R1658 at therapeutic doses had a similar safety profile to placebo, including effects on blood pressure and RAAS activation

R1658



Torcetrapib



Blood pressure and renin–angiotensin system genes

Stroes ESG et al, poster number 1021-204 presented at ACC 08

- Rat model to investigate the off-target toxicity of two CETP inhibitors
- Investigators reported
  - Torcetrapib dose-dependently increased blood pressure and the expression of renin-angiotensin-aldosterone system (RAAS) genes involved in regulating blood pressure
  - R1658 did not change blood pressure, heart rate or RAAS gene expression

- In contrast to torcetrapib, R1658 was not associated with the off-target toxicity on RAAS gene expression
- In this model, R1658, unlike torcetrapib, did not change blood pressure

General safety profile of R1658

Stein EA et al, poster number 1028-167 presented at ACC 08

- The safety profile of the CETPi R1658 was evaluated
  - data from five Phase 2 clinical trials
  - 561 patients received R1658; 277 received placebo
  - Treatment period of up to 12 weeks in duration

- There were no deaths in any of the studies
- Incidence of adverse events was similar in placebo and R1658 treatment groups
- Gastrointestinal side effects occur more frequently in R1658 treatment groups
- Incidence of adverse events did not increase with increasing dose
- Blood pressure remained stable over the study period
- R1658 was generally well tolerated in Phase 2 studies

Cardiovascular (CV) safety profile of R1658

Steiner G et al, poster number 1028-166 presented at ACC 08

- Specific CV safety and tolerability were assessed in a detailed analysis
  - data from five phase 2 clinical trials
  - 561 patients received R1658; 277 received placebo
  - Treatment period of up to 12 weeks in duration

- CV adverse events occurred at a similar low frequency in placebo and R1658 groups
- Severity and causality of CV adverse events were not related to R1658 dose
- No clinically relevant changes in blood pressure was observed.
- R1658 was generally well tolerated in phase 2 trials

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Next steps

M & M Study
Rationale

- Mortality and morbidity data: only true evaluation of the CV benefits of raising HDL-C by CETPi
- R1658 is being investigated to reduce CV risk on top of current recommended standard of care for CV risk factors
- Currently the only route to approval of CETPi

M&M Study

Patient population

- Roche trial will focus on high-risk CHD patients, after a recent event
- M&M study population
  - Selected after thorough consultation with medical/scientific experts and health authorities
  - Have the highest likelihood to benefit from treatment with CETPi
  - Will be closely monitored to detect, as early as possible, clinically meaningful differences between treated and controlled groups

M&M Study Design

Trial in high-risk CHD patients, after a recent event

- Approx 15’600 patients considered to have stable disease after a recent event
- Randomized to active treatment or placebo
- Optimized background therapy to assess “real” effect of raising HDL-C
- Study to run until final adjudicated event occurs

Metabolic diseases patterns and market

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Phase III M+M study

Next steps

CETPi – Development Plan

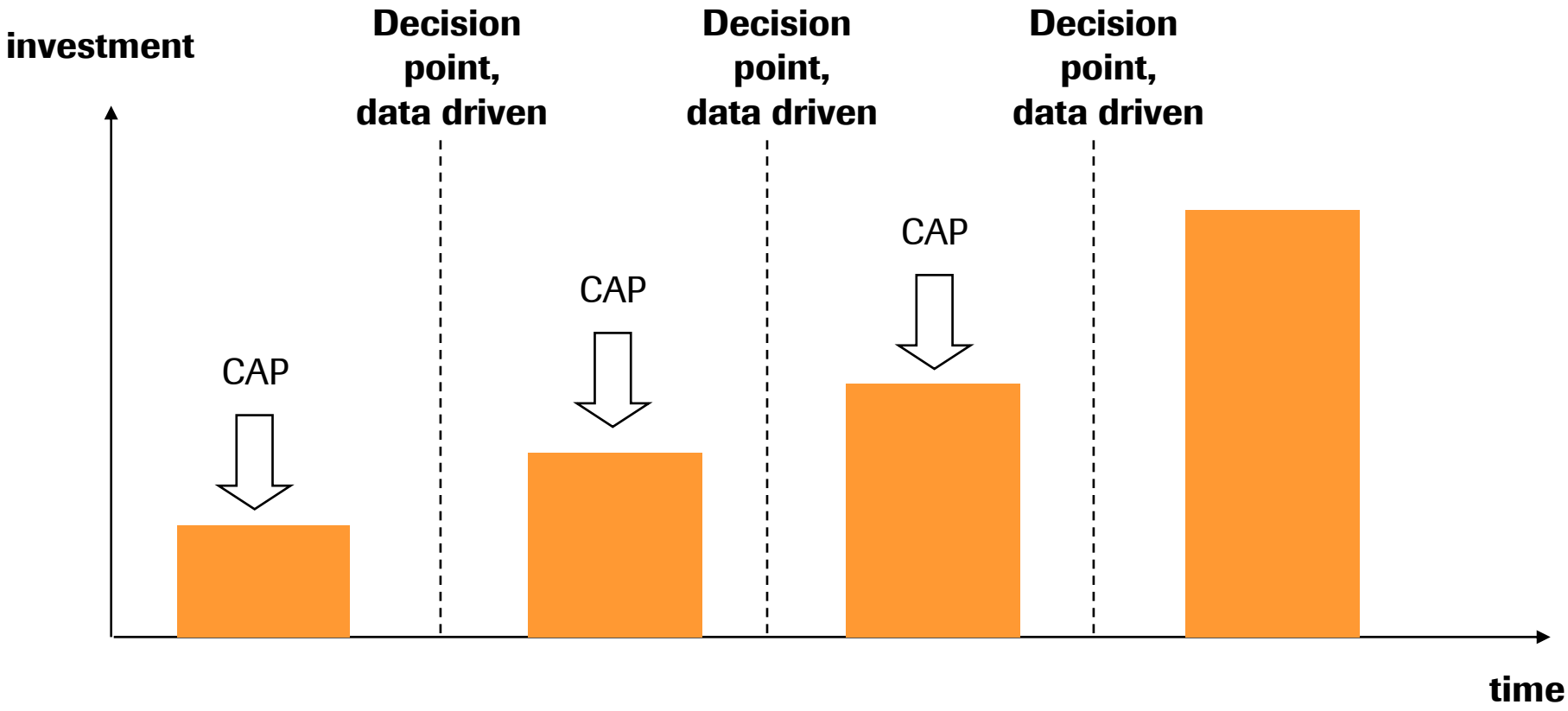
Step-wise investment – several key decision points

- Thorough, structured and step-wise phase III clinical programme implemented
- Strict safety monitoring through independent DSMB*: rapid assessment of findings in all studies throughout the phase III programme
- Key decision points incorporated to determine clinical trials progression
- Ongoing investment decisions matched to key decision points

* Data Safety Monitoring Board

CETPi – Development Plan

Step-wise investment – several decision points



Metabolic Portfolio

Promising Late-Stage Assets

- CETPi first phase III entry
- Compounds approaching phase III
  - GLP-1
  - DPP-IV
  - aleglitazar
- Update on Diabetes portfolio at ADA, June 2008

We Innovate Healthcare