The role of Phase I in the quest for “good”cholesterol
- failure of the CETP modulator dalcetrapib

Joint Conference 2013 of CPI | AGAH | BAPU | AHPPI
Nice, 11 April 2013, Michael Derks

Outline Presentation

- MOA of CETPi: Roles of CETP Inhibition in Atherosclerosis and HDL-C in CV risk reduction
- Background of dalcetrapib
- Clinical Pharmacology program:
  - SAD/MAD
  - DDI
  - Formulation; Food effect;
  - ADME
  - TQT
  - Special populations
  - M&S
- Lessons Learned

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., Anders G. Olsson, M.D., Ph.D., Markus Abt, Ph.D.,

N Engl J Med 2012; 367:2089-2099

CONCLUSIONS

In patients who had had a recent acute coronary syndrome, dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent cardiovascular events.

- no association between HDL cholesterol levels and cardiovascular risk – no effect under optimal standard of care?
- altered physiologic functions of HDLs, including reverse cholesterol transport?
- mean increase of 0.6 mm Hg in systolic blood pressure
- 18% increase in the median CRP
- HDL too low / LDL not decreased?

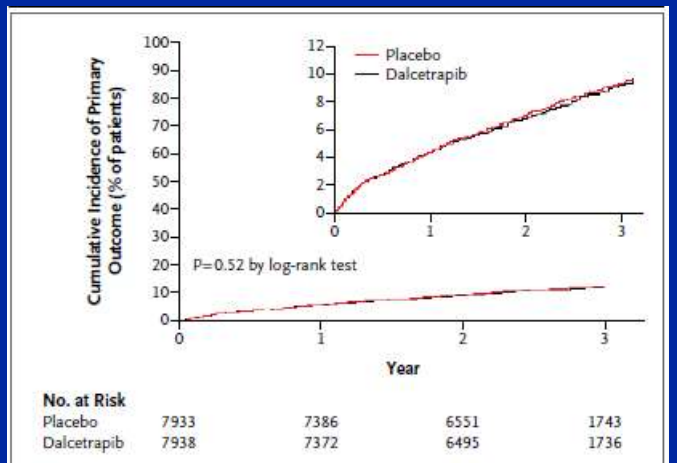

Figure 2. Incidence of the Primary Efficacy End Point.
Shown is the cumulative incidence in the two study groups of the composite primary end point of death from coronary heart disease, a major nonfatal coronary event (myocardial infarction, hospitalization for unstable angina with objective evidence of acute myocardial ischemia, or resuscitation after cardiac arrest), or stroke of presumed atherothrombotic cause. The inset shows the same data on an enlarged y axis.

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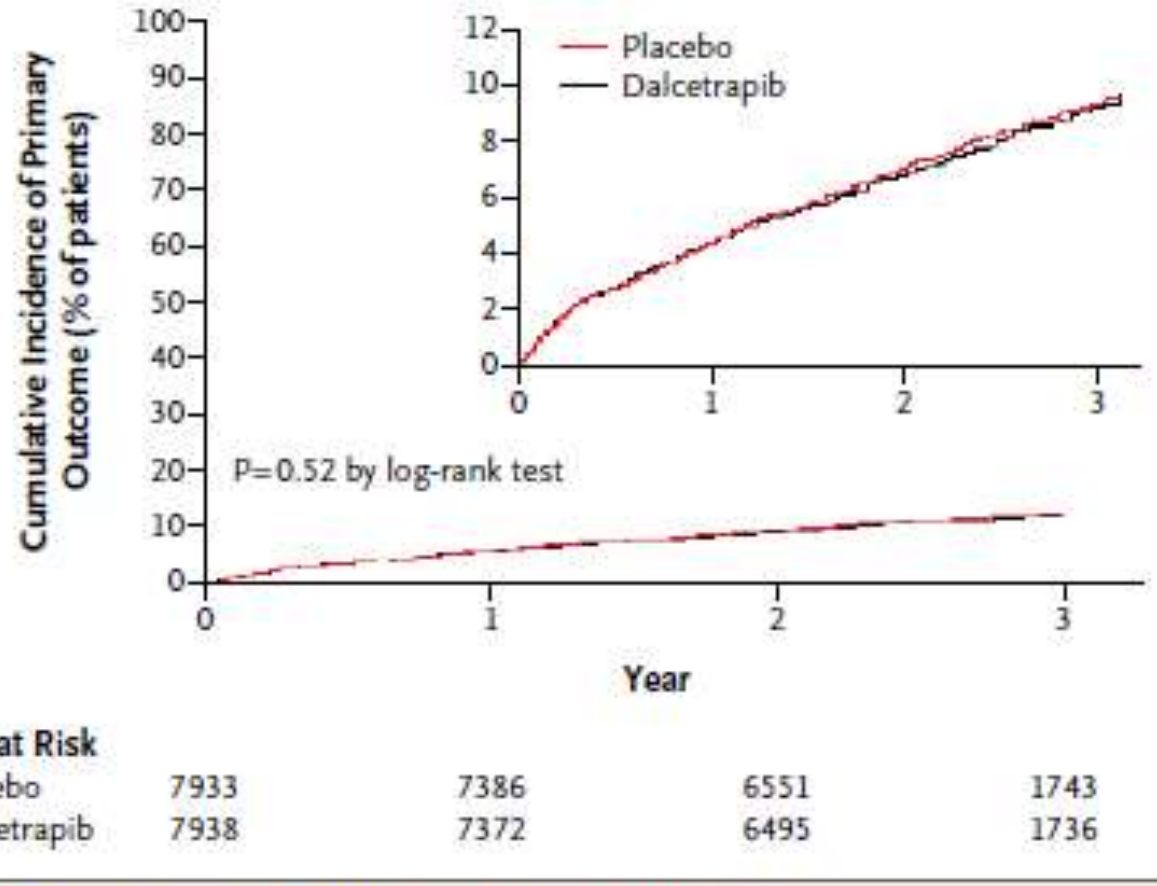

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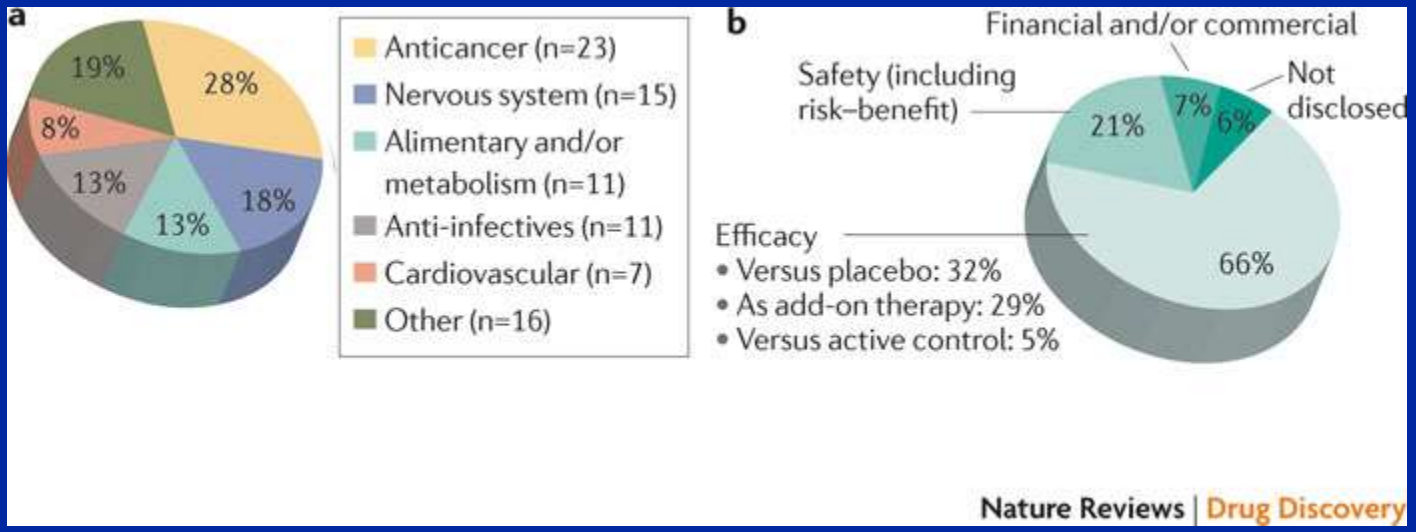
Phase III and Submission Failures: 2007 – 2010
combined success rate at Phase III and submission ~50%

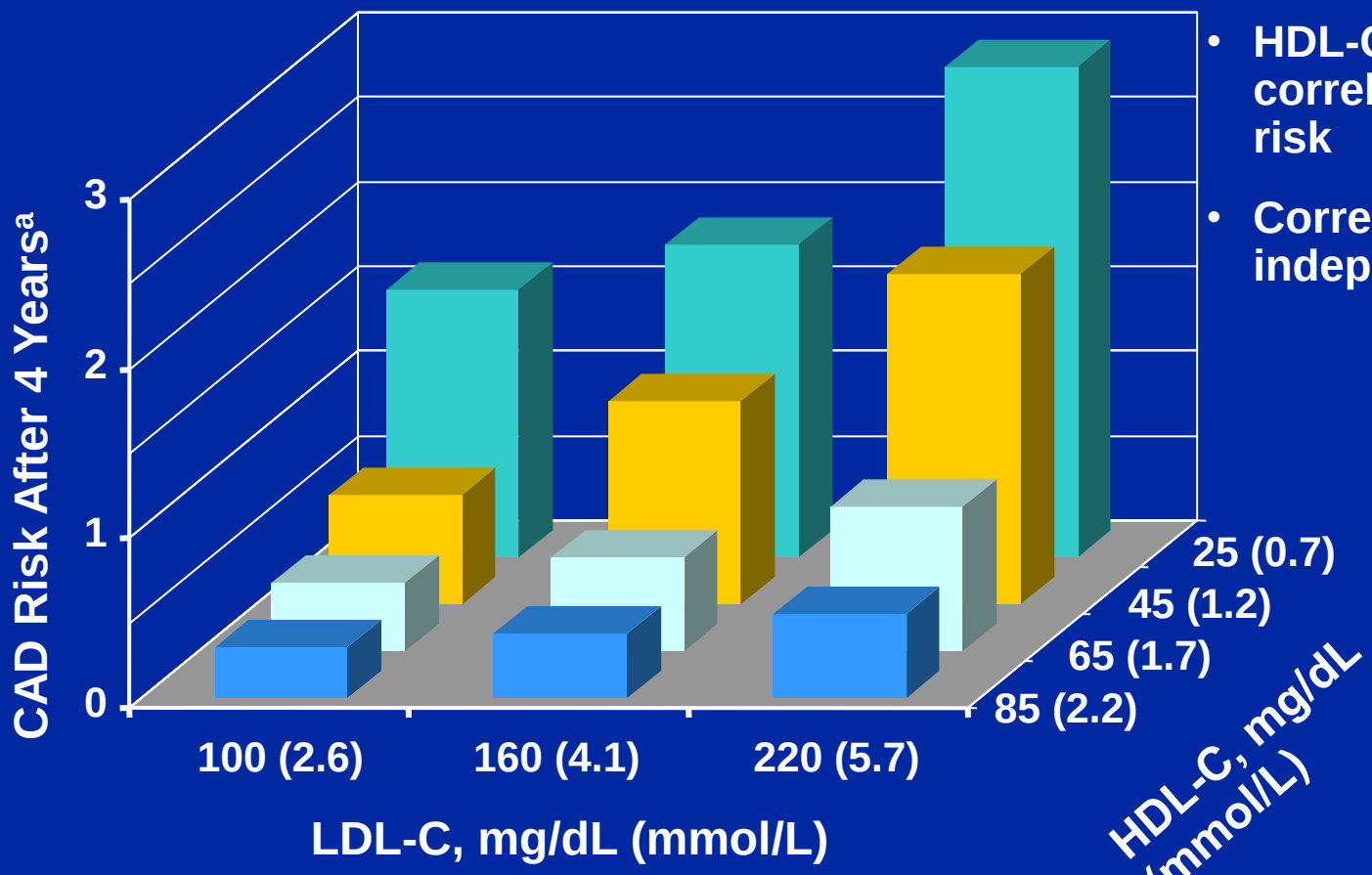


- Novel mechanisms of action in areas of high unmet medical need
- Progression into Phase III trials with limited proof of efficacy in Phase II POC
- Assumption that success in one disease will translate into success in a different disea

Nature Reviews Drug Discovery 10, 87 (February 2011)

HDL-C Predicts Risk for CAD Independent of LDL-C

Framingham Heart Study



- HDL-C is inversely correlated with CAD risk
- Correlation is independent of LDL-C

[a]Men aged 50–70

Castelli. *Can J Cardiol*. 1988;4(suppl A):5A–10A.

Benefits of Raising HDL-C

Animal Studies

- Raising HDL-C either by infusing HDL-C or by increasing the synthesis of apo-A1 by genetic manipulation greatly inhibits the development of atherosclerosis in both mice and rabbits

Human Studies

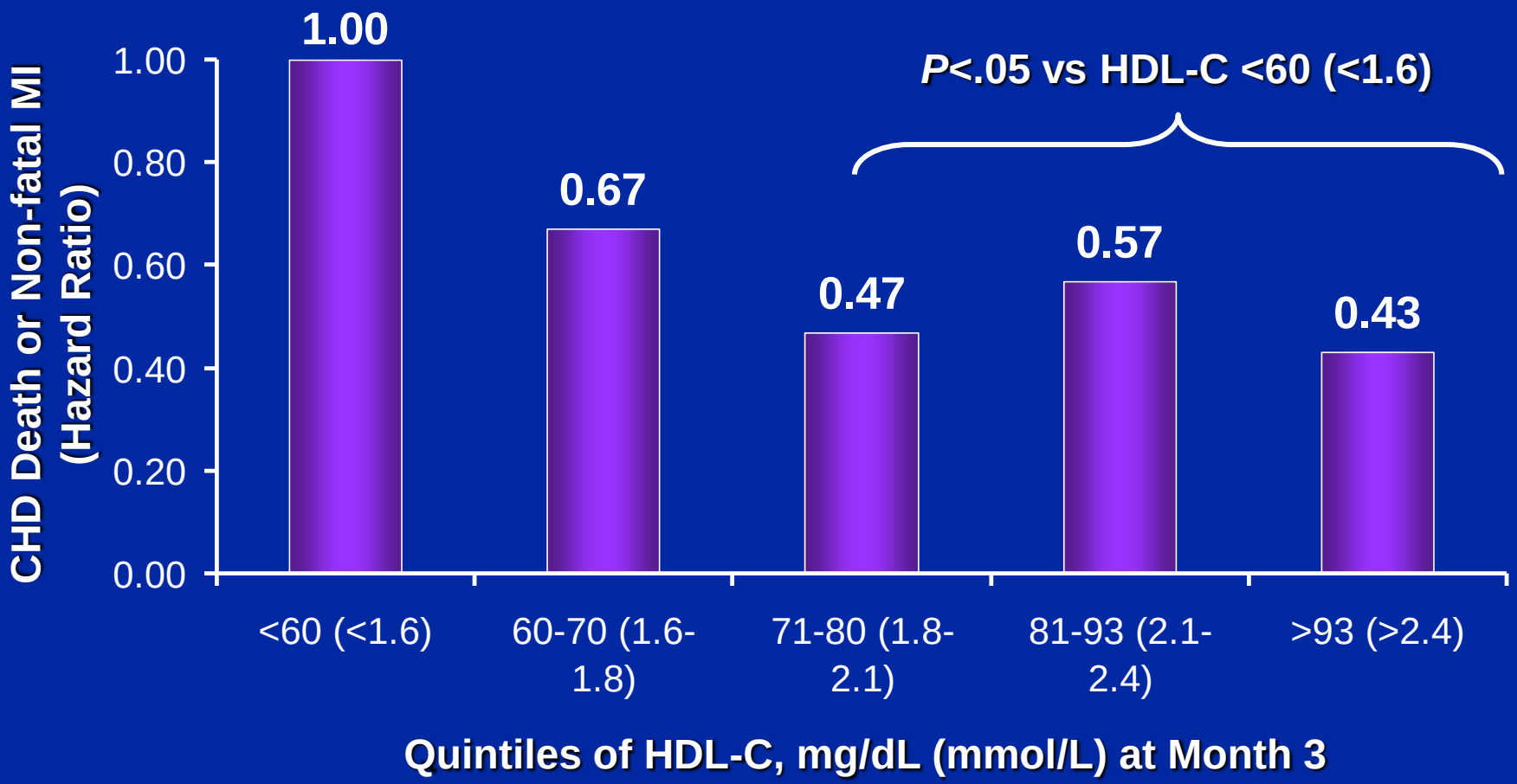
- Raising HDL-C by treatment with either niacin or fibrates in intervention trials is associated with a slowing of progression of CHD and a reduction in CV events
- Infusion of reconstituted HDL-C reduces the atherosclerosis burden as assessed by IVUS

Barter. *Eur Heart J Suppl*. 2004;6(suppl A):A19-A22

Barter. *Arterioscler Thromb Vasc Biol*. 2005;25(7):1305-1306

ILLUMINATE Trial: Higher Achieved HDL-C in Torcetrapib Treated Patients, Lower Event Rate[a]

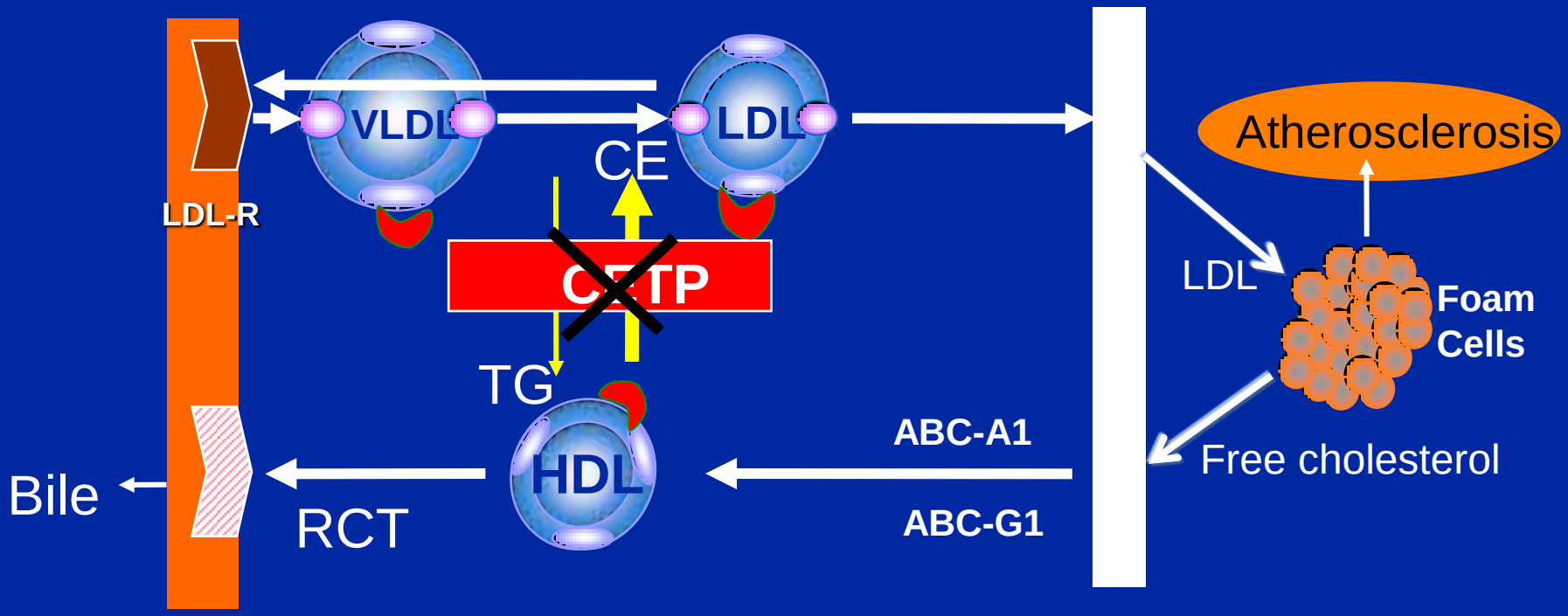
Hazard Ratios for CHD Death or Non-fatal MI by Quintile of On-Trial HDL-C (Referent Group Is HDL-C <60 mg/dL [1.55 mmol/L] Stratum)



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

Barter et al. Presented at: American Heart Association Scientific Sessions. Nov 4-7, 2007; Orlando, Florida

Role of CETP Inhibition in Atherosclerosis



- Human CETP deficiency is associated with marked increase in HDL-C[1]
- CETP activity is inversely correlated with plasma HDL-C[1]
- Reduction in CETP activity is associated with a marked reduction in the cholesterol burden in TG-rich particles in both fasting and postprandial phases[2,3]
- Decreasing CETP activity has consistently inhibited atherosclerosis in animal models[1]

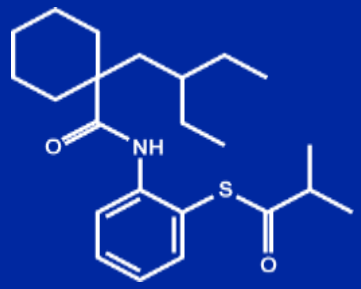
[1]Barter et al. *Arterioscler Thromb Vasc Biol*. 2003;23:160–167; [2]Contacos et al. *Atherosclerosis.* 1998;141:87–98;
[3]Guerin et al. *Arterioscler Thromb Vasc Biol*. 2008;28:148–154.

Background of dalcetrapib

- Dalcetrapib is a cholesteryl ester transfer protein (CETP) inhibitor
- Discovered by Japan Tobacco who performed initial Entry in Man and Ph2a studies
- Roche took over clinical development in beginning in 2005
- By 2010 extensive program of clinical studies had been developed
  - 33 completed healthy volunteer studies and 10 completed Phase 2a patient studies

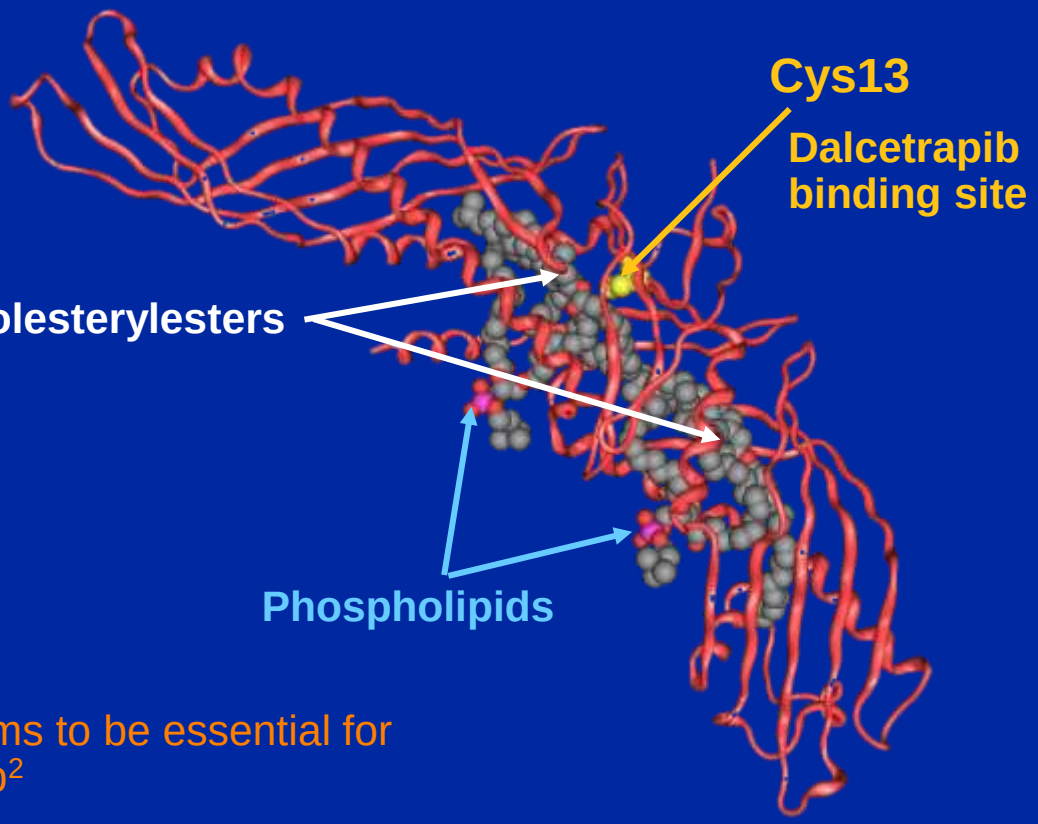
Dalcetrapib

Dalcetrapib[1]



Molecular weight: 389.60
Lipophilicity: cLogP ~7

CETP[3]



- The cysteine at residue 13 of CETP seems to be essential for decreased CETP activity with dalcetrapib[2]
- Dalcetrapib binding to CETP appears to induce a conformational change in the CETP molecule[2]

Prodrug and highly lipophylic → in vitro DMPK experiments of limited value

Primary route of metabolism through glucuronidation and methylation

PK concentration based on derivitization of circulating thiol

[1]http://www.ama-assn.org/ama1/pub/upload/mm/365/dalcetrapib.doc;
[2]Okamoto et al. *Nature.* 2000;406:203–207; [3]Qiu et al. *Nat Struct Mol Biol.*

Clinical Pharmacology contributes across the whole value chain

- Disease models for target identification and validation

- Design first in man studies
- CTA/IND

- Dose justification for confirmatory studies and regulatory submission
- Simulate confirmatory trials to assist in design optimisation
- Optimise drug label
- Investigate response variability and dose-adjustments to maximise efficacy and safety
- Investigate/confirm mechanism of action
- Confirm effects on important safety issues (eg QTc)
- NDA/MAA and regulatory questions

- Assess molecule for “drugability”
- Identify suitable biomarkers
- Create phase I plan

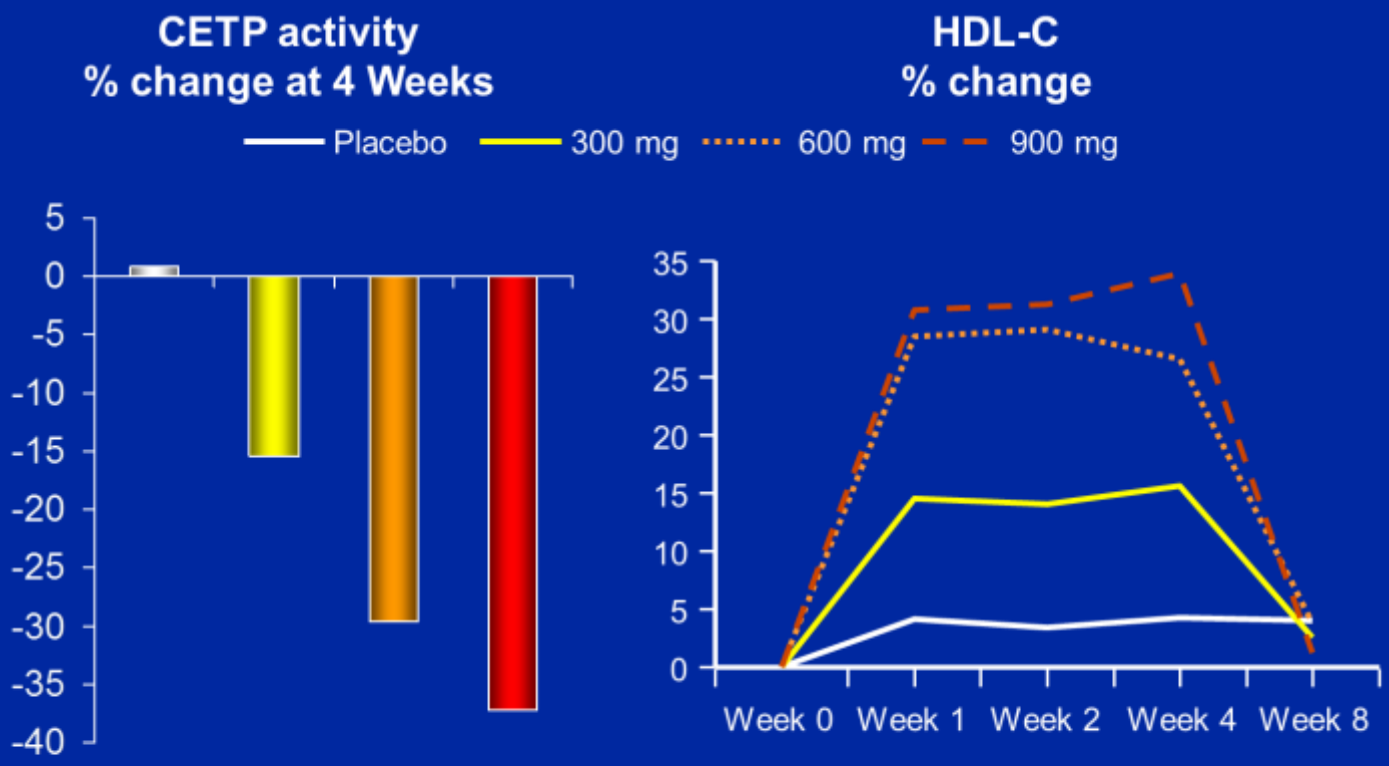
- Define dose-exposure-effect for pharmacology and tolerability
- Identify significant causes of PK/PD variability
- Confirm dose for PoC study
- Simulate PoC (and other) studies to assist in design optimisation
- Characterise significant “developability” questions
- Paediatric investigation plan

- Bridging strategies for new populations and formulations
- Line extensions
- New indications

Basic pharmacokinetic or pharmacodynamic studies

- SAD and MAD studies in healthy volunteers
  - SAD (JT, MAD (JT), MAD (JT), MAD, SAD/MAD
  - Single doses up to 4500 mg, short-term repeated dosing up to 3900 mg/day; moderately variable PK; approximately dose linear
- Mass balance study
  - **Extensive and complex metabolism, no human-specific metabolites identified**
- Thorough QT study
  - No clinically relevant effect on QT interval duration
- Special population studies
  - Exposure modestly higher in moderate and severe renal impairment
  - No effect of moderate hepatic impairment

Dalcetrapib Phase IIa dose ranging



de Grooth et al. *Circulation*. 2002;105(18):2159-2165.

Biopharmaceutics study

- Food effect and food timing studies (3X)
  - **~2-fold higher in exposure fed vs. fasted state**
  - **Size of food effect depends on size and fat content of the meal**
- Rel. bio./bioequivalence studies (4X)
  - Bioequivalence linkage between JT and Roche tablet formulations
  - Exposure inversely related to particle size
- 2nd generation formulation studies (4X)
  - Modified release formulations
  - Nanoparticle capsule
  - Nanoparticle suspension

Drug-drug interaction studies

- Statins
  - Atorvastatin x 2, simvastatin, pravastatin, rosuvastatin
  - Dalcetrapib exposure reduced in combination with statin, extent dependent on size of LDL change (e.g. 8% with pravastatin, 35% with rosuvastatin)
  - No apparent effect on CETP inhibition or HDL effects of dalcetrapib
  - No clinically relevant effect on statin exposure
- Cholesterol absorption inhibitor (ezetimibe)
  - No clinically relevant interaction
- Thiazolinedione (rosiglitazone)
  - No clinically relevant interaction
- Lipase inhibitor (orlistat)
  - **Dalcetrapib exposure markedly reduced by clinical doses of orlistat**

Drug-drug interaction studies (cont.)

- CYP3A4 inhibitor (ketoconazole)
  - No clinically relevant effect on dalcetrapib pharmacokinetics
- ‘Cooperstown+1’ cocktail
  - No clinically relevant effect of dalcetrapib on cytochrome P450 activity
- Narrow therapeutic window (digoxin)
  - No clinically relevant interaction
- Oral contraceptives (Microgynon)
  - No clinically relevant interaction

Coadministration of Dalcetrapib With Pravastatin, Rosuvastatin, or Simvastatin : No Clinically Relevant Drug –Drug Interactions

Michael Derks, Markus Abt, Mary Phelan, Lynn Turnbull, Georgina Meneses-Lorente, Nuria Bech, Anne-Marie White and Graeme Parr

J Clin Pharmacol 2010;50:1188-1201

- Relationship between dalcetrapib plasma concentrations and LDL-C levels

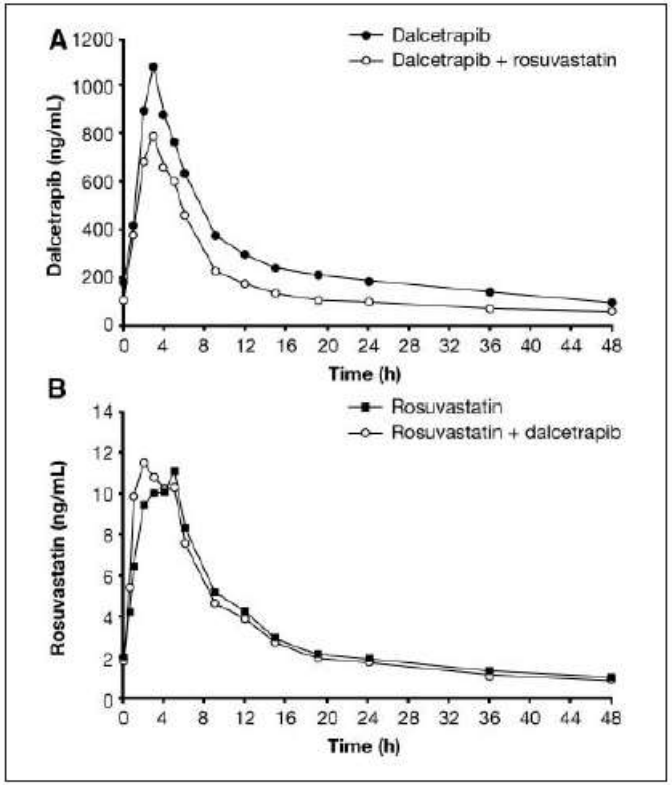
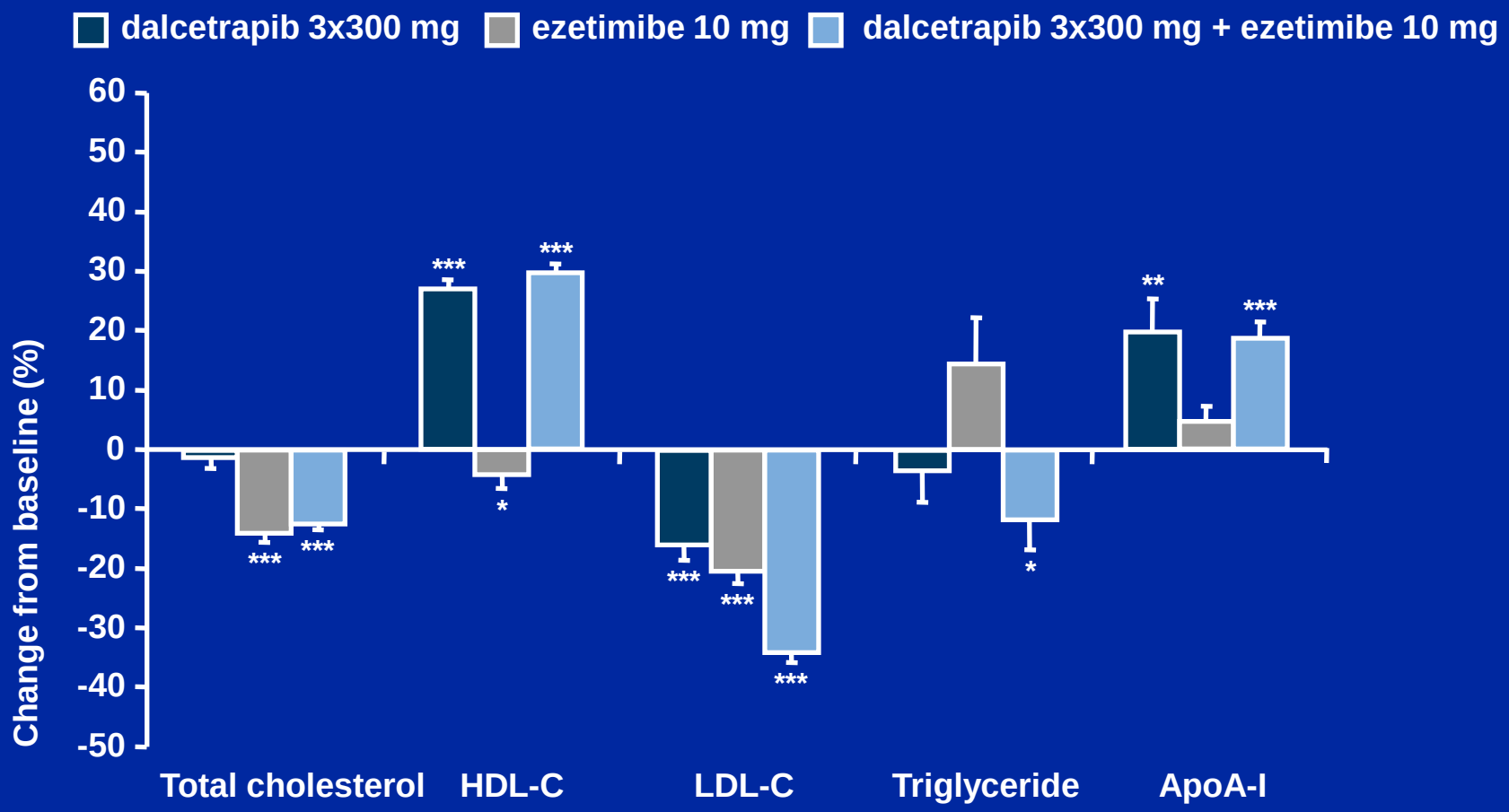


Figure 3. (A) Median dalcetrapib plasma concentrations following administration alone or in combination with rosuvastatin. (B) Median rosuvastatin plasma concentrations following administration alone or in combination with dalcetrapib.

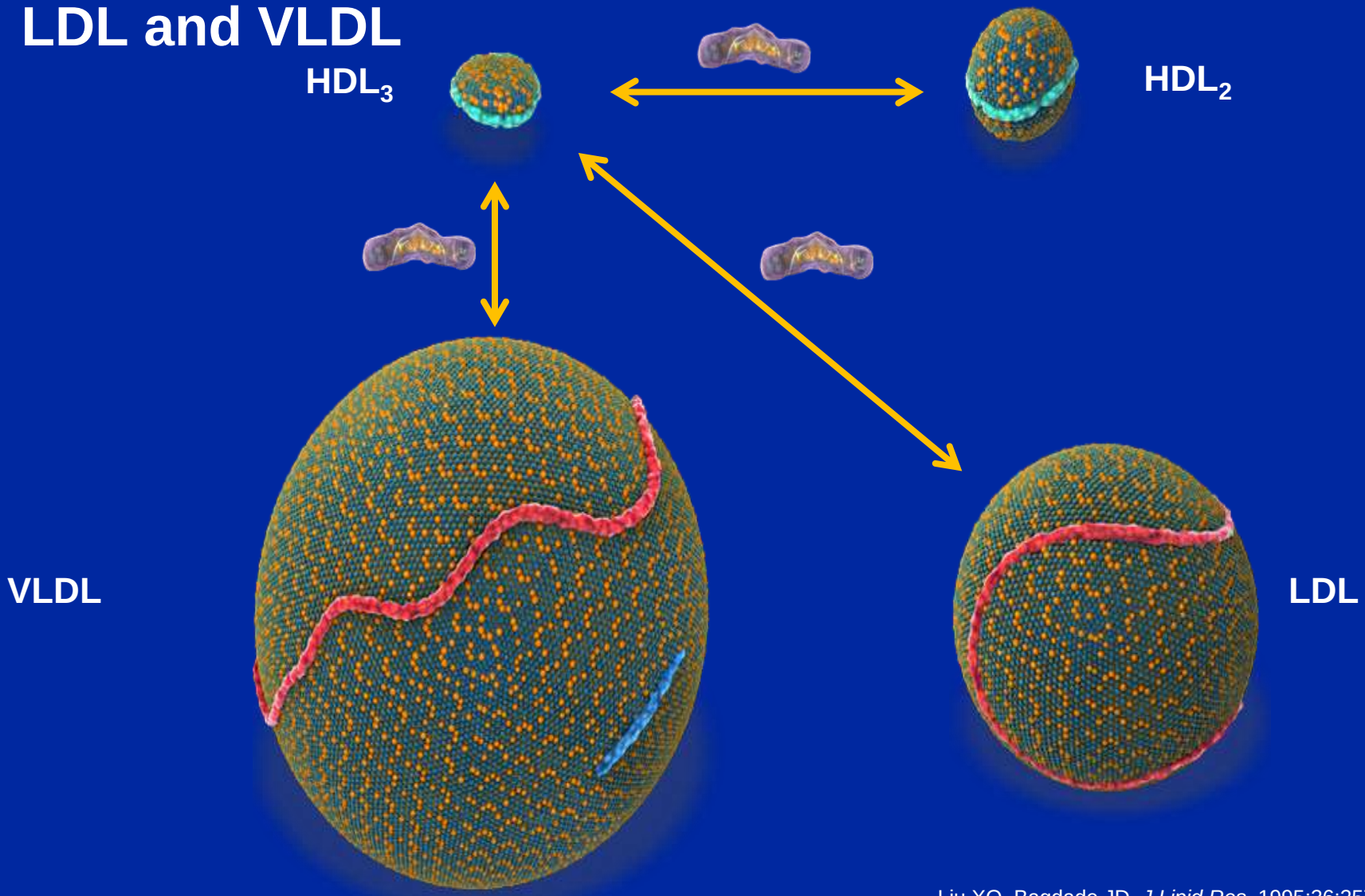
Changes in plasma lipids in 22 dalcetrapib-treated subjects with or without ezetimibe



Mean ± SEM; n = 22. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Niesor EJ, et al. *Atherosclerosis.* 2011;219:761-767

CETP has multiple activities: transfer of cholesteryl ester between HDL3 and HDL2, LDL and VLDL

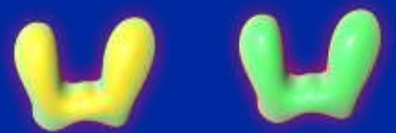


Liu XQ, Bagdade JD. *J Lipid Res*. 1995;36:2574-2579

CETP inhibitors vs. CETP Modulators

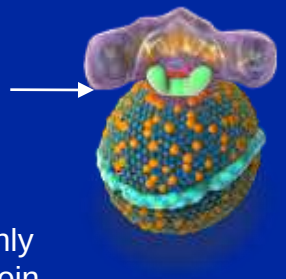
Changes in conformation of CETP will modulate activity

INHIBITORS

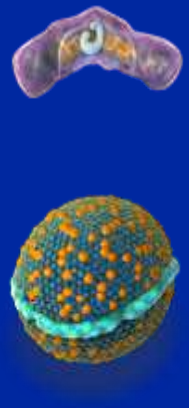


anacetrapib **torcetrapib**

- Inhibitor binds to CETP and HDL forming a triple complex
- CETP does not dissociate efficienly from any lipoprotein and CETP activity is fully inhibited



MODULATOR



- Dalcetrapib binds in the tunnel of CETP inducing a fixed conformational change
- This change in ‘shape’ means it is unable to interact with lipoproteins of large diameter such as LDL and VLDL
- CETP is still able to transfer cholesterol between HDL sub particles

THE LANCET

Volume 380, Issue 9841, 11–17 August 2012, Pages 572–580

Articles

Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

What else could have been done

1. **Quantitative assessment of drug distribution into lipid subfractions following oral dosing in a clinical study**
   - Quantitative drug distribution into different lipid fractions in vivo has not been established; hypothesised that changes in lipid profiles (e.g. in response to food, renal impairment, with lipid-modifying con meds) will change distribution, ‘free fraction’ and clearance

2. **Pharmacokinetic modeling of existing active form and metabolite data from preclinical and clinical studies**
   - Hepatic extraction of thiol changes over dosing interval; possibility of metabolite inhibition of thiol metabolism (i.e. auto-inhibition)

3. **A clinical study to characterize effects on postprandial lipaemia**
   - No clinical data on the acute effect on postprandial lipid profiles; clinical data available on torcetrapib, niacin, fibrates, statins

4. **A clinical relative bioavailability study employing an oral solution formulation**
   - Absolute bioavailability unknown and influence of dissolution on absorption not understood; an IV formulation is technically unfeasible

What else could have been done

5. **A preclinical study to investigate lymphatic transport using a cannulated animal model**
   - Contribution of lymphatic transport in absorption phase is unknown

6. **Additional GastroPlus modeling of drug absorption using existing data**
   - Absorption processes not understood; molecular species absorbed after oral dosing is unknown (thioester? thiol?)

7. **A clinical study to compare the pharmacodynamic effects of different dosing regimens**
   - Applicability of empirical PK/PD model to different clinical dosing regimens not proven; unproven which exposure parameter best predicts pharmacological response

8. **Measure faecal sterol excretion in clinical study**
   - Effects on reverse cholesterol transport in humans have not been proven

Lessons learned

- Even good science does not make a compound work
- Most markers are not surrogate and almost none are validated – nevertheless, sometimes it may be worth to take the risk to run large Phase III studies; would RCT / Entelos / genetic studies etc have stopped the development of dalcetrapib? Should a PoC in higher risk patients have been done?
- Compounds with unfavourable physico-chemical properties should be deslected preclinically, but that does not mean they cannot be developed successfully
- Dose selection should start to be addressed as early as possible (prior to PoC) and popPK should be done in Phase II (and III)
- Formulation optimization should be done in a strategic way
- Small signals should be explored as they can lead to useful insights
- Continuously learn from competitors
- Big projects with high (time) pressure: consult with Clin Pharm colleagues often and reevaluate the strategy so that opportunities or risks are not

Doing now what patients need next