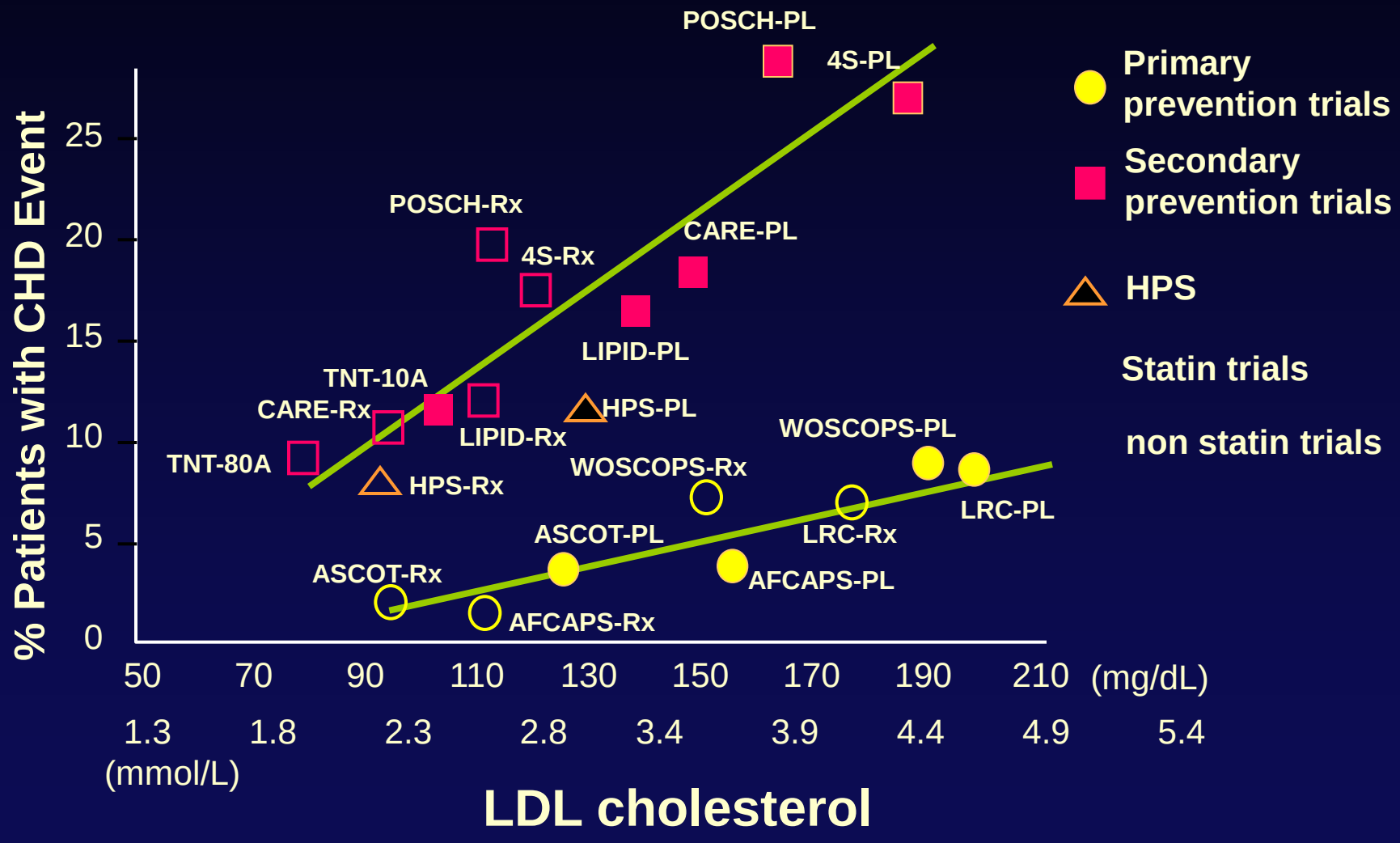
Will Future Therapies Help to Further Lower LDL Cholesterol?

John J.P. Kastelein, MD PhD

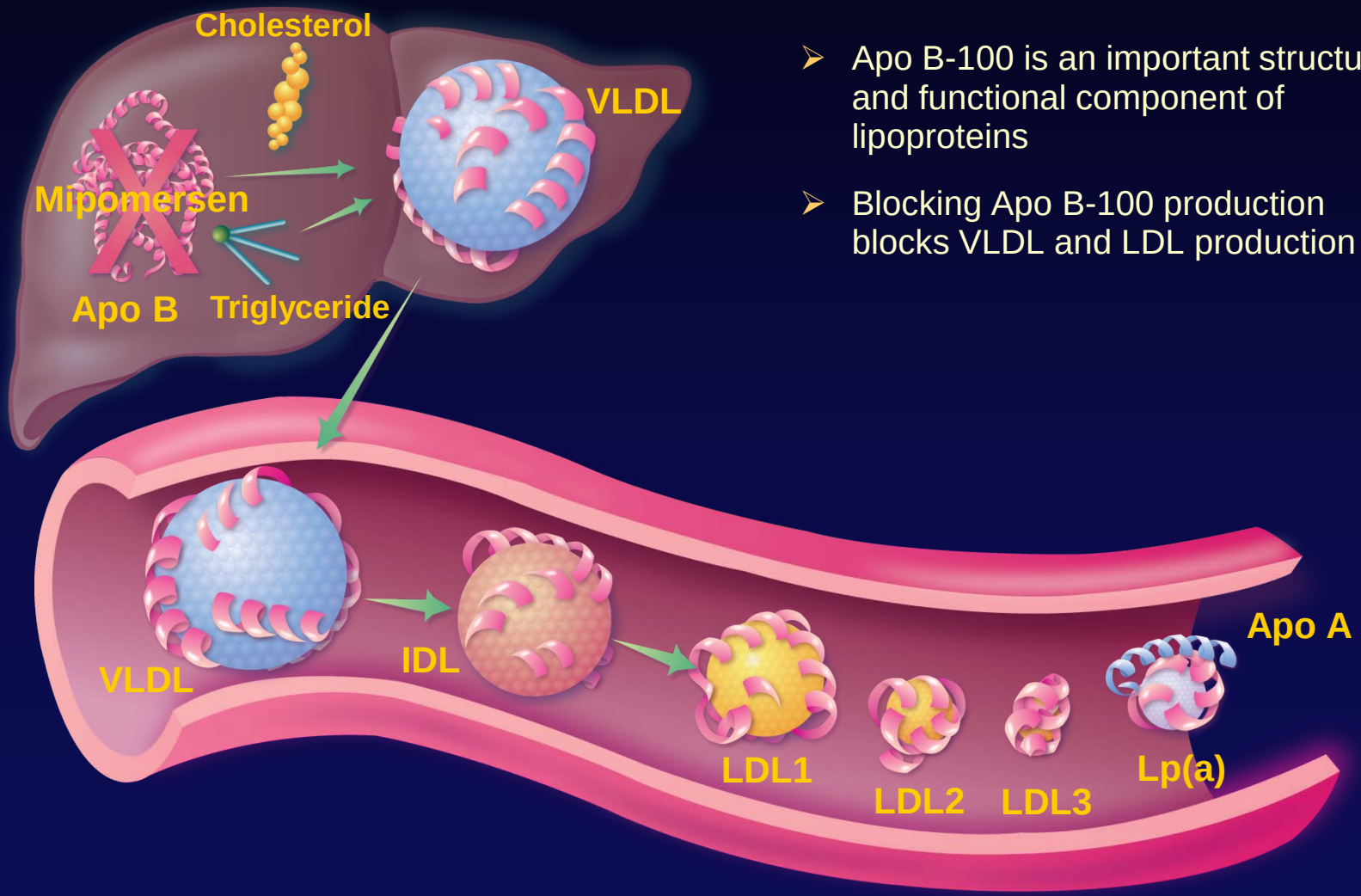
Academic Medical Center / University of Amsterdam

The Netherlands

Clear Cardiovascular Benefits of Intensive Lipid-Lowering Therapy



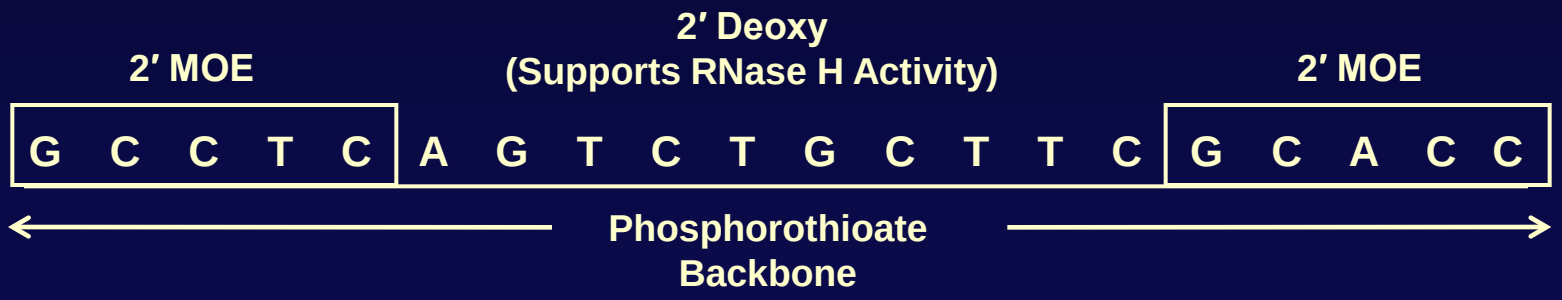
Mipomersen: Apo B-100 as a Target



- Apo B-100 is an important structural and functional component of lipoproteins
- Blocking Apo B-100 production blocks VLDL and LDL production

Overview of Mipomersen

- **A 20-mer phosphorothioate antisense oligonucleotide that is complementary in sequence to a segment of the human Apo B mRNA**

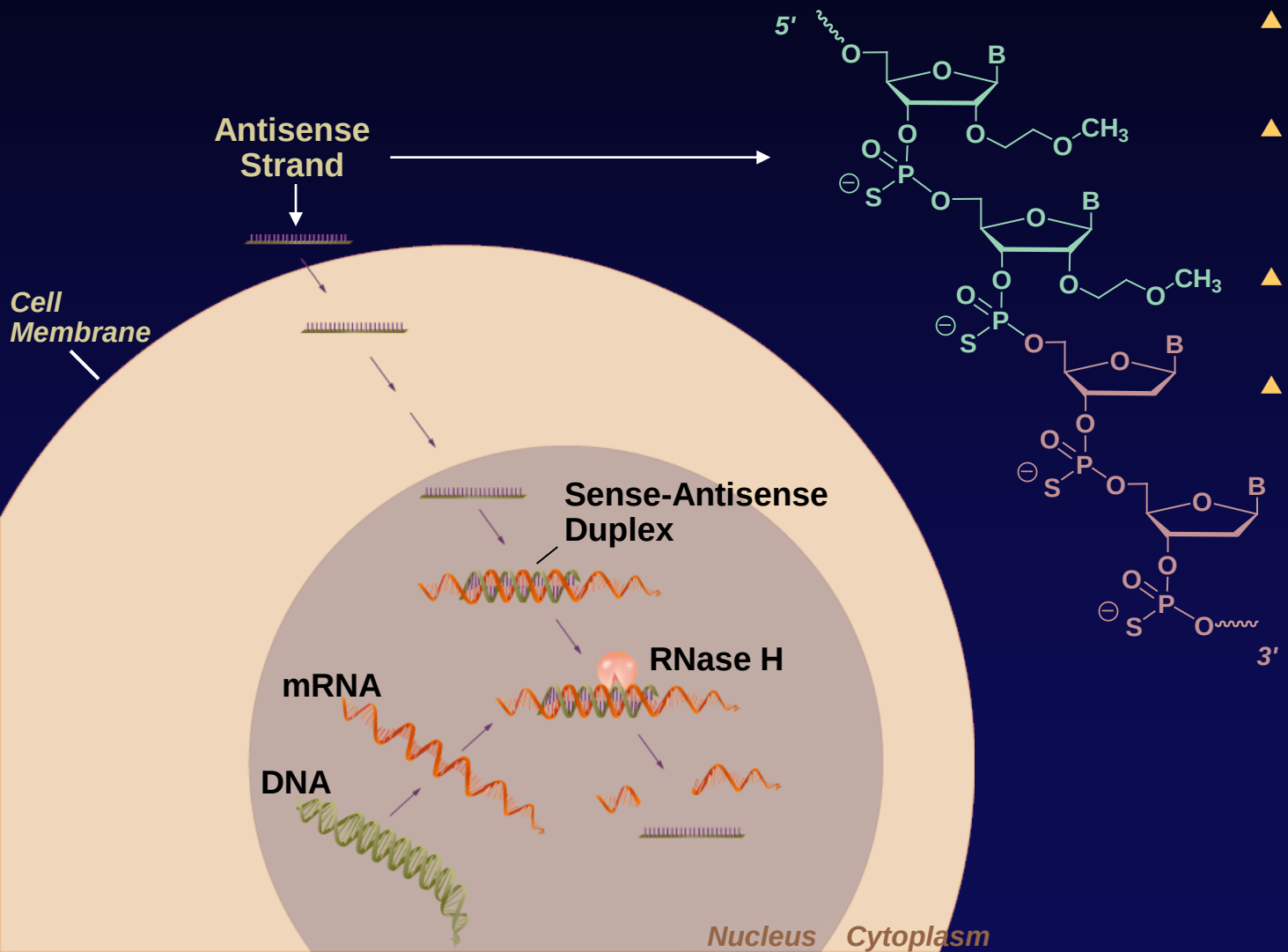


Kastelein JJ, et al. *Circulation*. 2006;114(16):1729-1735.

Antisense: A Novel Approach to Drug Discovery by Inhibition of Translation of a Specific Targeted Protein

RNase H Dependent Mechanism of Action

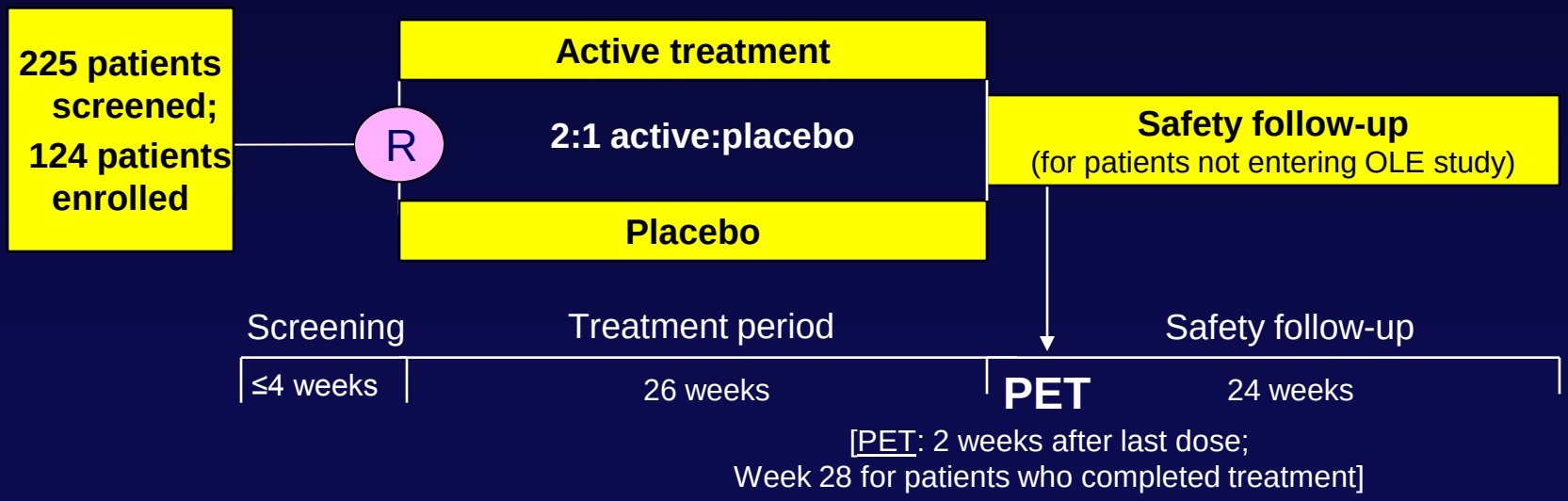
2nd Generation Antisense Drugs



- ~20X more potent
- 1X/week to 1X/quarter dosing
- Better tolerated
- Lower cost of therapy

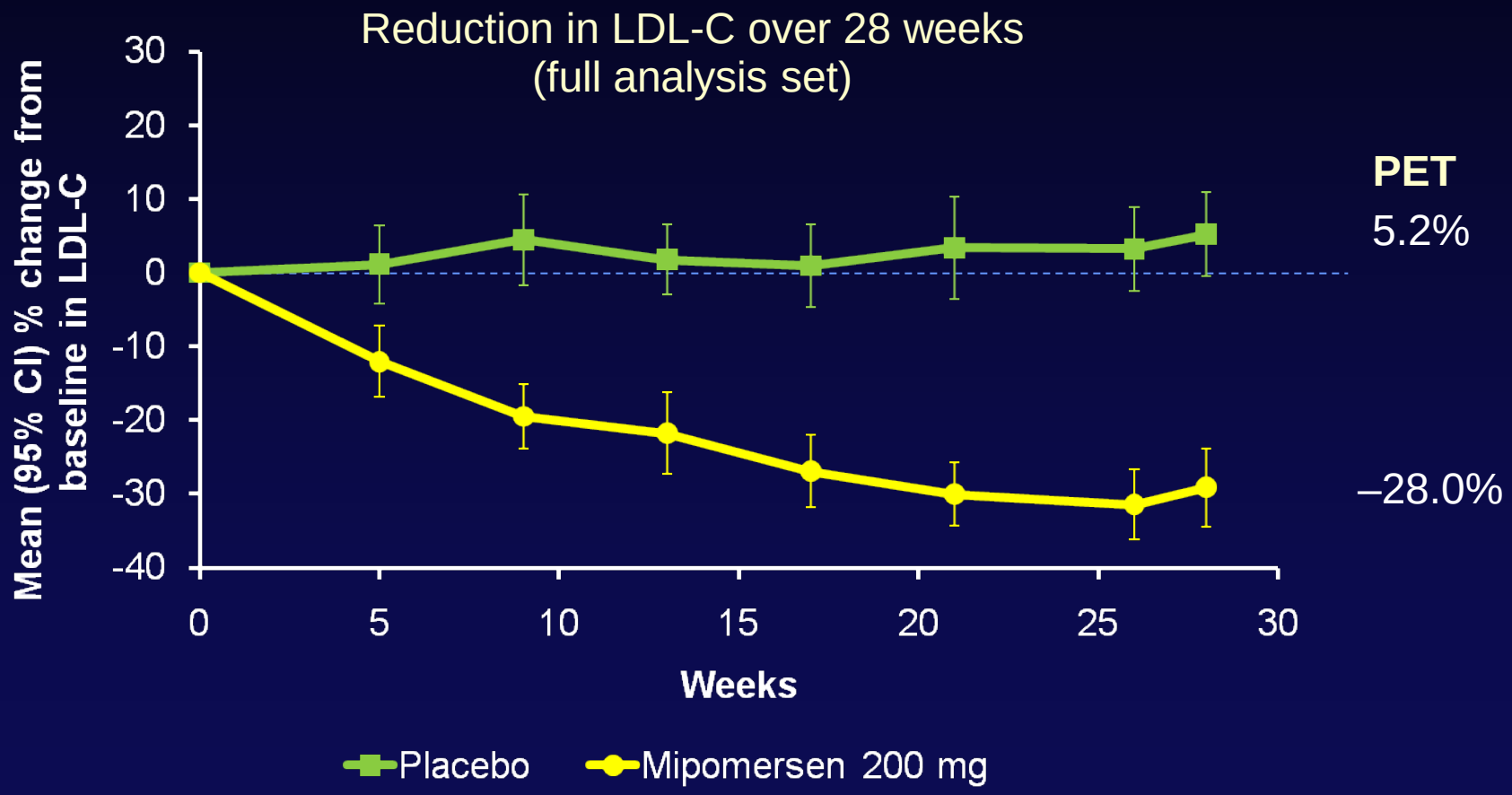
Heterozygous Familial Hypercholesterolemia Study Design

- Patients were randomized 2:1 to receive weekly subcutaneous injections of mipomersen 200 mg or placebo for 26 weeks



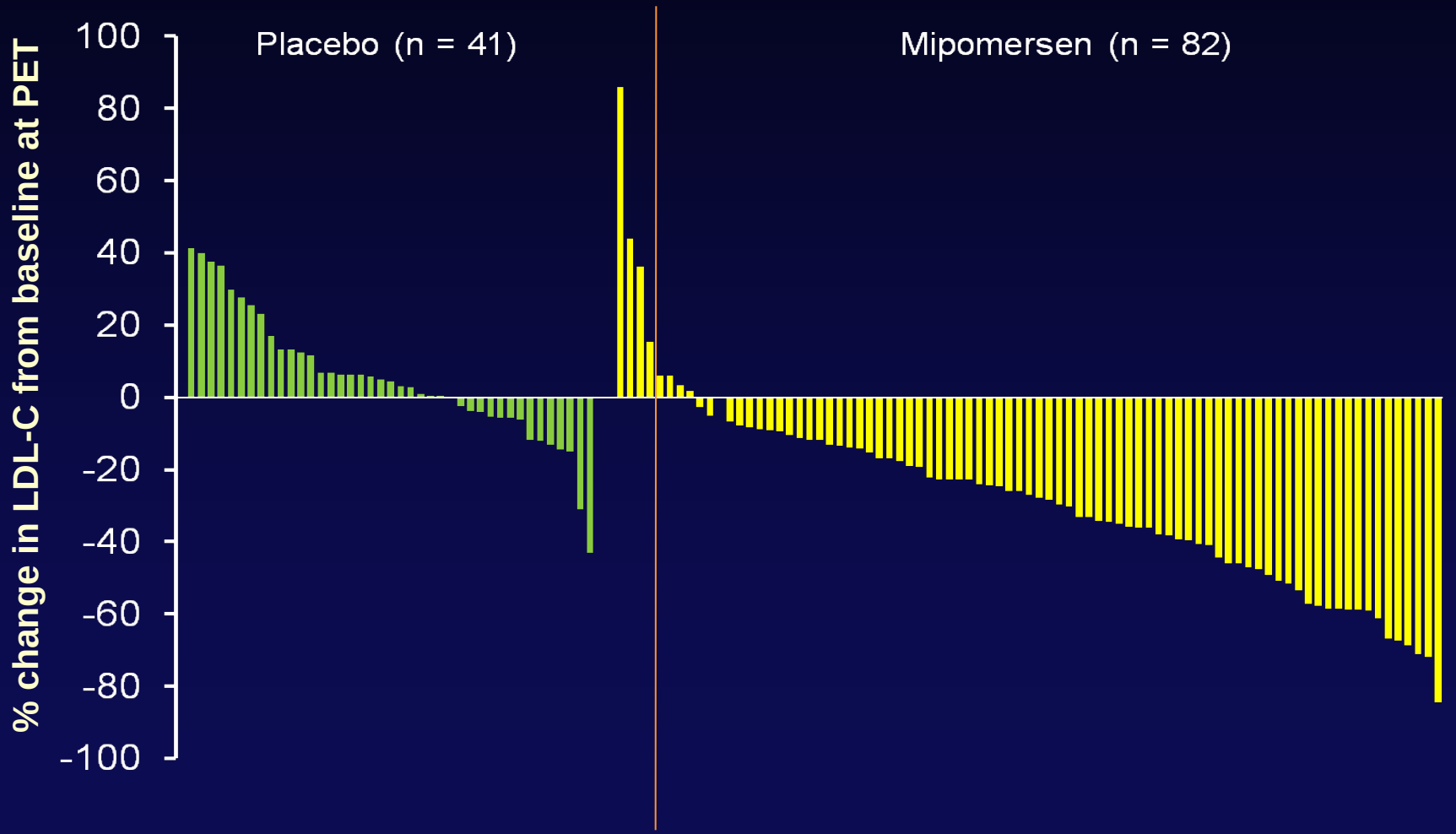
Cromwell W, et all, [poster]. American Heart Association Scientific Sessions; Nov 14-18; Orlando, FL; 2009

Mipomersen Significantly Reduced LDL-C



Data on file.

Distribution of LDL-C % Change From Baseline



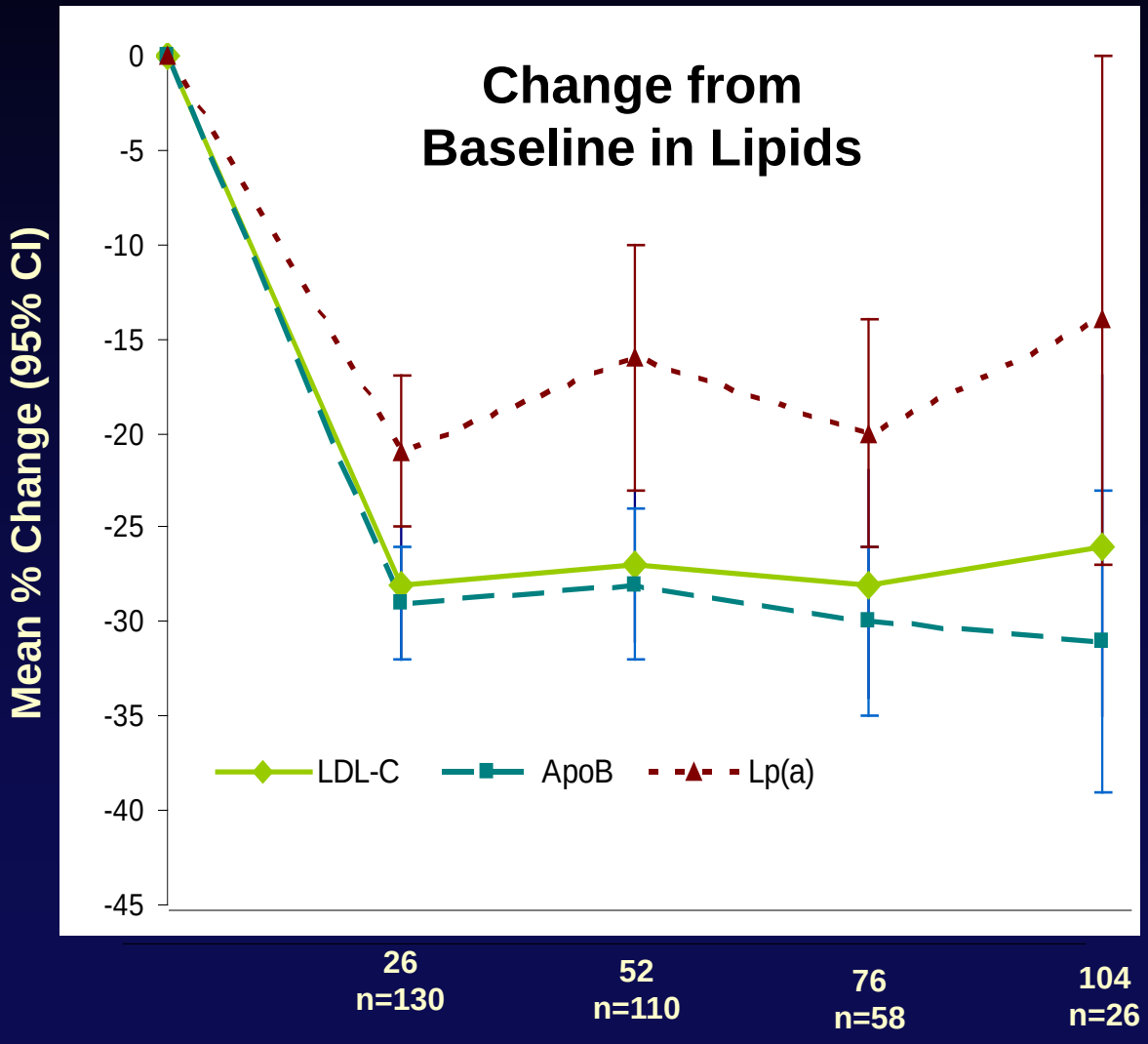
PET, primary efficacy time point, 2 weeks after final dose.

Data on file.

Long-term effects of Mipomersen in Extension Study Interim Data Analysis – March 2011

- 141 patients were enrolled in the open label extension study
  - From three Phase 3 studies (HoFH, HeFH and Severe HeFH)
- 17 patients completed the treatment
- 69 patients discontinued treatment
- 55 patients are currently continuing treatment

Long-term effects of Mipomersen in Extension Study Interim Data Analysis – March 2011



Source: Table 14.2.1a; Table 14.3.6

Percent Change from Baseline in Liver Fat

Week	n	Median (IQR)
26	60	5 (1, 17)
52	30	12 (2, 22)
76	37	6 (2, 13)
104	22	5 (3, 14)

Safety profile remains consistent with all phase 3 studies

***Dallas Heart Study General Population: 5.6% liver fat median**

Interim Summary Conclusions

- Continued robust lipid lowering activity with long-term treatment
  - All atherogenic lipids remained reduced with continued treatment including apoB, LDL-C, Lp(a), Tg, and non-HDL
  - No loss of activity observed over 2 years of treatment
- Preclinical observations of liver adaptation to reduced lipid transport apparent in long-term clinical experience
  - Liver fat, if increased, stabilized or decreased with continued dosing
  - Increases occurred in patients with fastest and greatest apoB/LDL-C changes

11