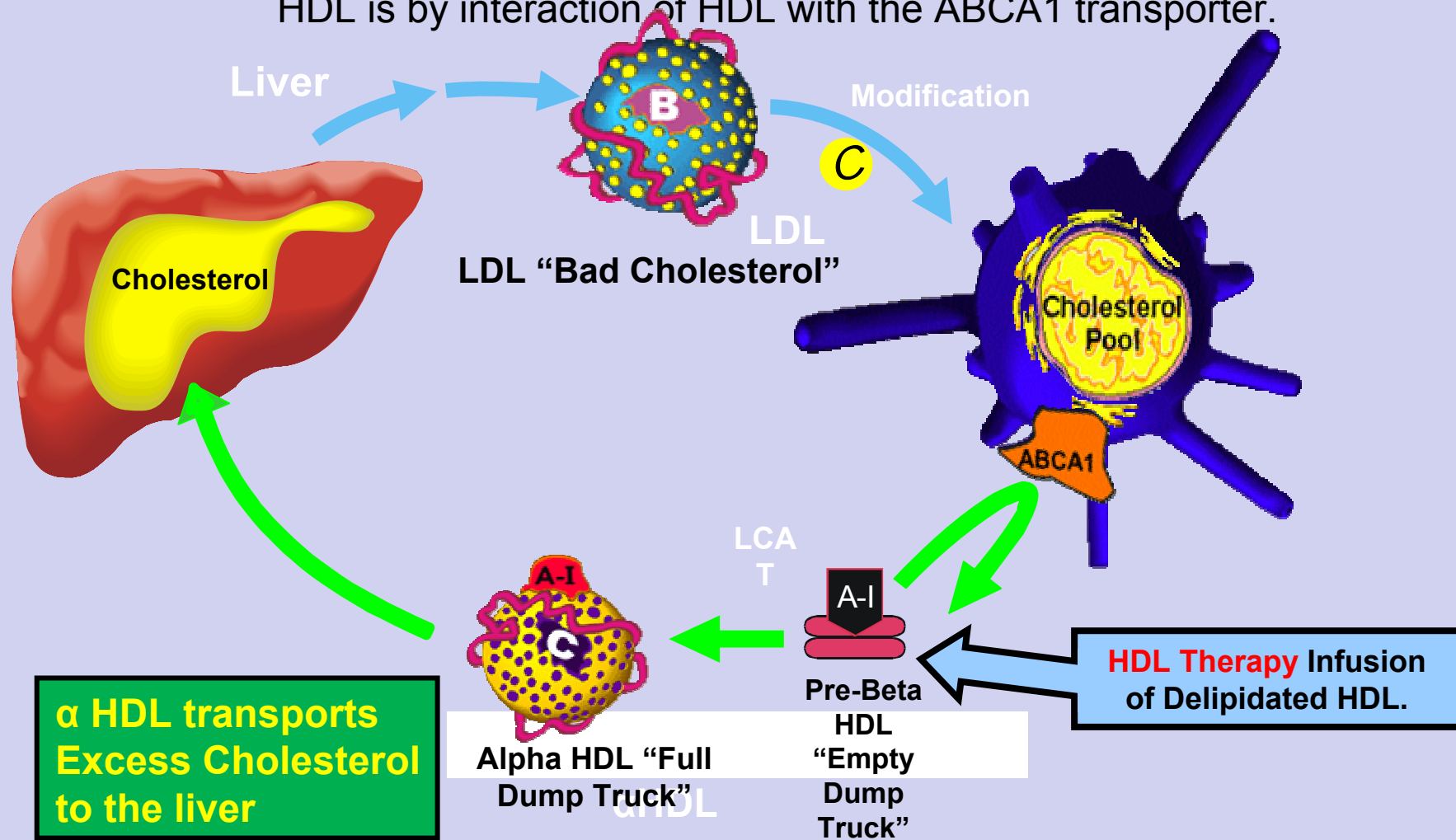# HDL Therapy Via Plasmapheresis
### A First-In-Man, Randomized, Placebo-Controlled Study to Evaluate the Safety and Feasibility of Autologous Delipidated HDL Plasma Infusions in Patients with Acute Coronary Syndrome

Ron Waksman, MD; Kenneth Kent, MD, PhD; Augusto Pichard, MD; William Suddath, MD; Lowell Satler, MD; Dianne Martin, RN; Timothy Perlman; Dale Richardson, MBA; Jo-Ann Maltais, PhD; Patricia Landry, MBA; Rebecca Torguson, MPH; Neil J. Weissman, MD; Peter Fitzgerald, MD; H. Bryan Brewer, MD
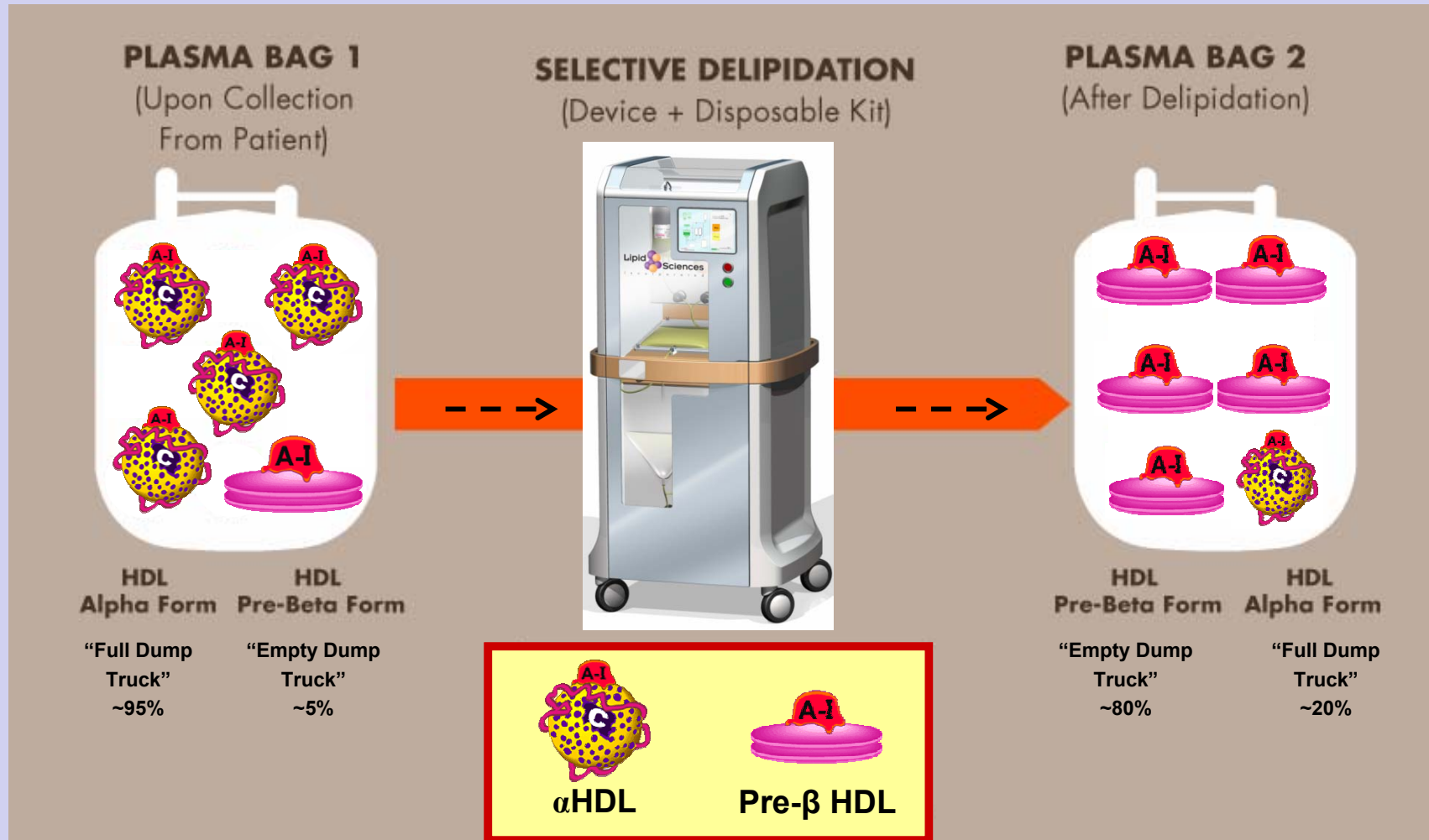
# How Does HDL Therapy Work?
# Delipidated HDL Enhances
# Reverse Cholesterol Transport

The major pathway for cholesterol efflux from macrophages to HDL is by interaction of HDL with the ABCA1 transporter.

Liver

Cholesterol

B

Modification

C

LDL

LDL "Bad Cholesterol"

Cholesterol Pool

ABCA1

LCAT

A-I

A-I

C

Pre-Beta HDL "Empty Dump Truck"

Alpha HDL "Full Dump Truck"

αHDL

HDL Therapy Infusion of Delipidated HDL.

α HDL transports Excess Cholesterol to the liver

# HDL Selective Delipidation
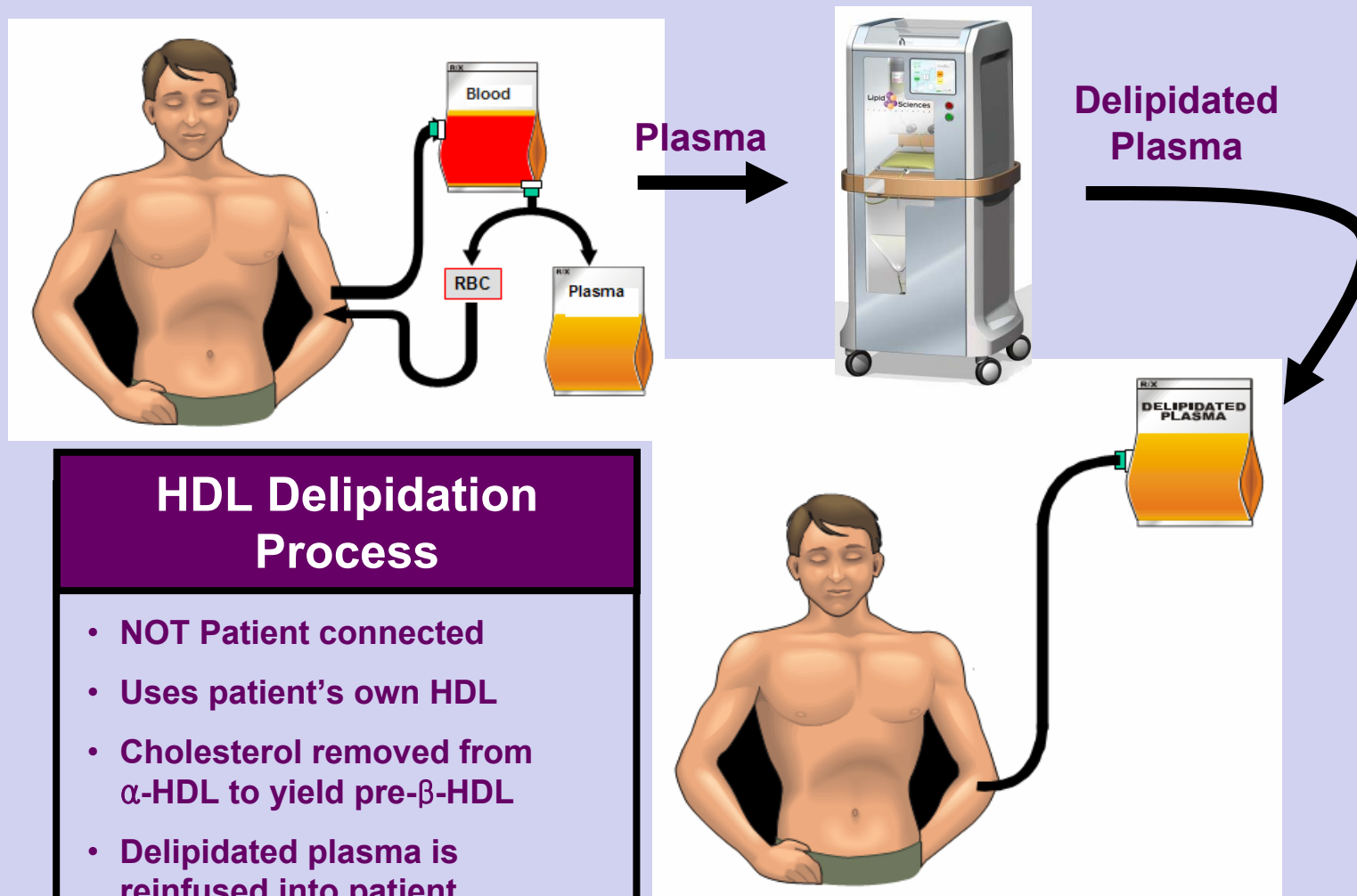## "Energized HDL"

# Objectives

- The primary aim of this study was to test the safety and feasibility of autologous delipidated HDL infusions in acute coronary syndrome (ACS) patients.

- An exploratory aim of this study was to assess the impact on plaque volume assessed by IVUS measurements.
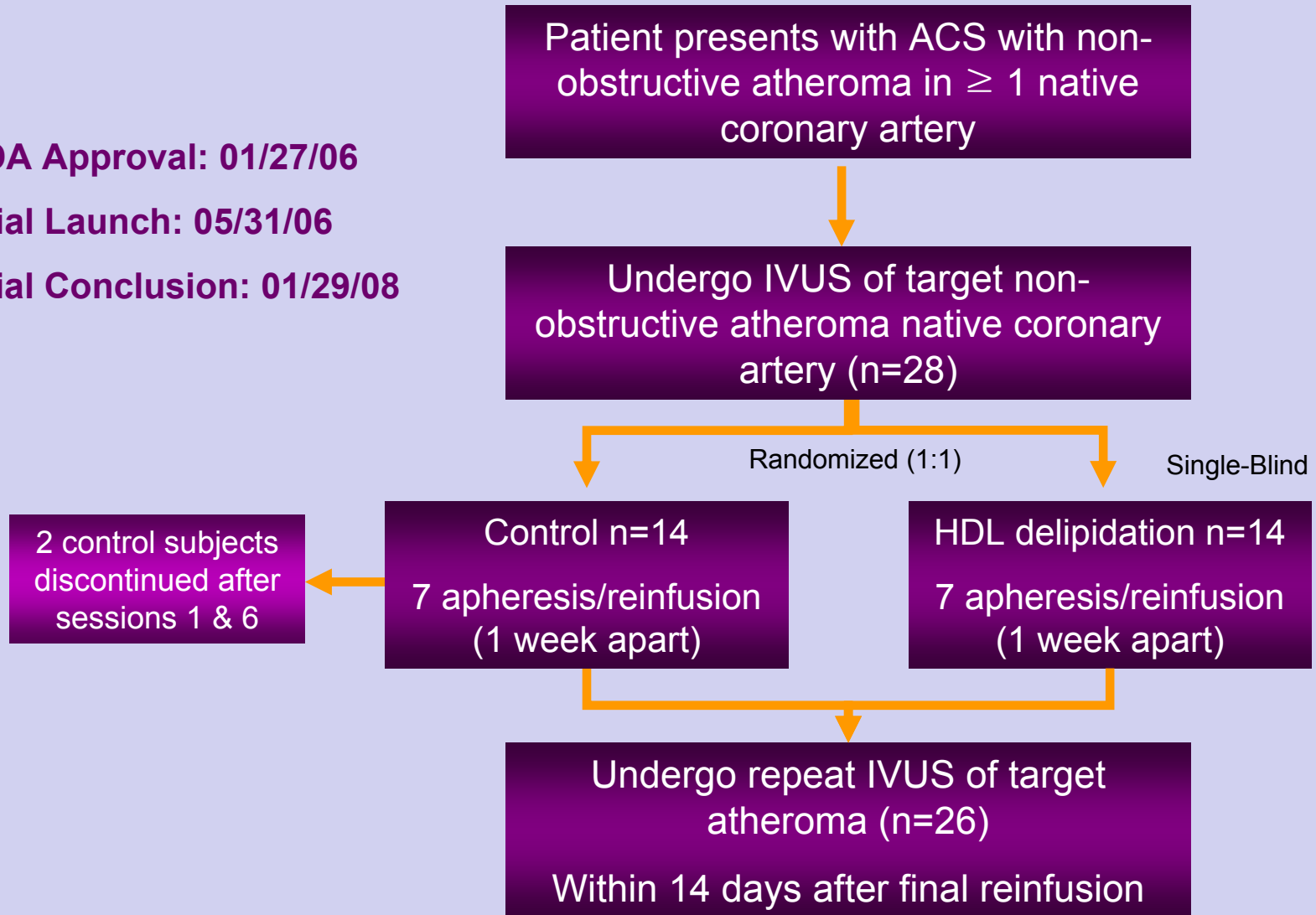
# HDL Selective Delipidation Trial Design
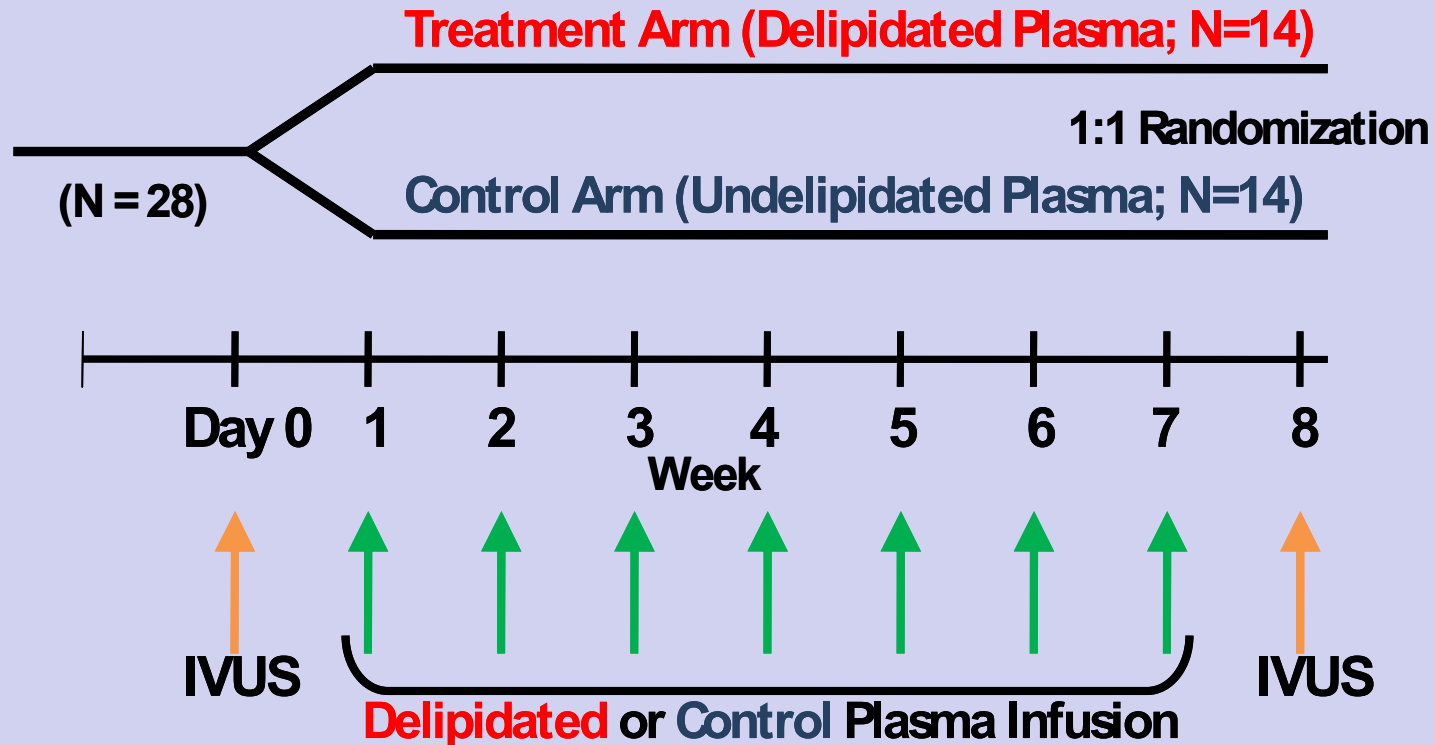


Patients with ACS scheduled for cardiac cath with non obstructive atheroma were randomized to HDL delipidation or control and subjected to apheresis/ reinfusion. Patients had 7 sessions each 1 week apart. IVUS performed up to 14 days from last procedure to assess atheroma volume indices.

# Schematic Overview of the Methodology for the Selective Delipidation of HDL in Plasma



**Plasma**

**Delipidated Plasma**

Blood

RBC

Plasma

DELIPIDATED PLASMA

## HDL Delipidation Process

- **NOT Patient connected**
- **Uses patient's own HDL**
- **Cholesterol removed from $\alpha$-HDL to yield pre-$\beta$-HDL**
- **Delipidated plasma is reinfused into patient**

# Study Design

- **FDA Approval: 01/27/06**
- **Trial Launch: 05/31/06**
- **Trial Conclusion: 01/29/08**

Patient presents with ACS with non-obstructive atheroma in $\geq$ 1 native coronary artery

Undergo IVUS of target non-obstructive atheroma native coronary artery (n=28)

Randomized (1:1)

Single-Blind

Control n=14

7 apheresis/reinfusion (1 week apart)

2 control subjects discontinued after sessions 1 & 6

HDL delipidation n=14

7 apheresis/reinfusion (1 week apart)

Undergo repeat IVUS of target atheroma (n=26)

Within 14 days after final reinfusion

# Major Adverse Cardiac Events

| Variable, n (%) - ITT | Delipidation Group n=14 | Control Group n=14 |
|---|---|---|
| Death | 0 | 0 |
| Re-infarction | 0 | 0 |
| Target Lesion Revascularization | 0 | 0 |
| Non-Target Lesion Revascularization | 1 (7.2) | 2 (11.8) |
| Unanticipated Adverse Device Effects | 0 | 0 |

# Quantitative 2-D Gel Electrophoresis & Pre-β HDL (ELISA) Following Delipidation

| HDL Subfraction | Undelipidated | *Delipidated* |
|---|---|---|
| preβ HDL | 5.6% | *79.1%* |
| αHDL | 92.8% | *20.9%* |

Preβ HDL In Post-Delipidated Plasma Increases An Average of *28 X* Vs. Preβ HDL In Pre-Delipidated Plasma
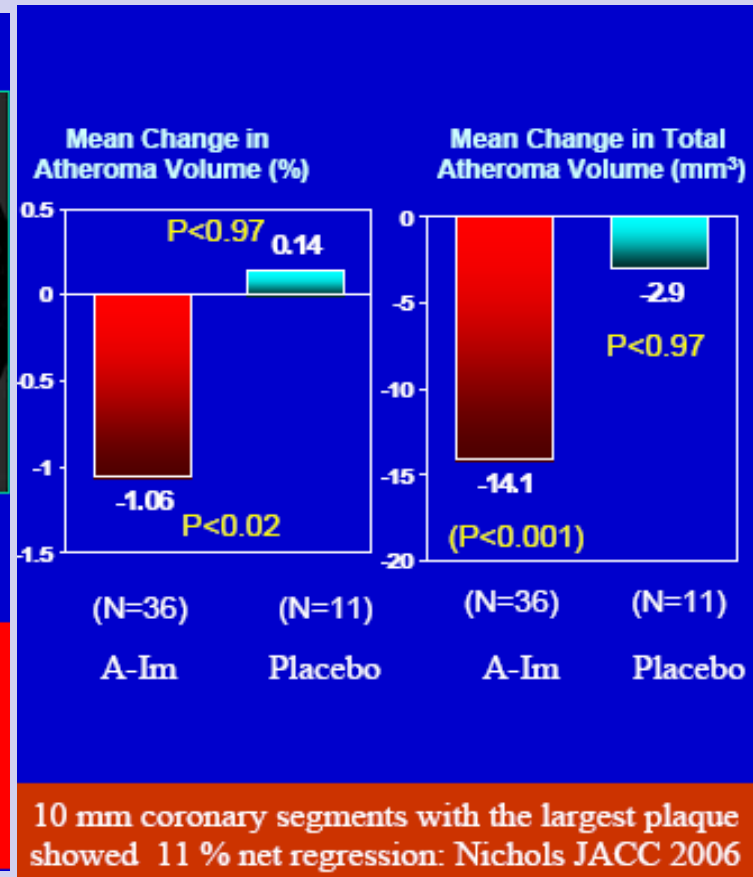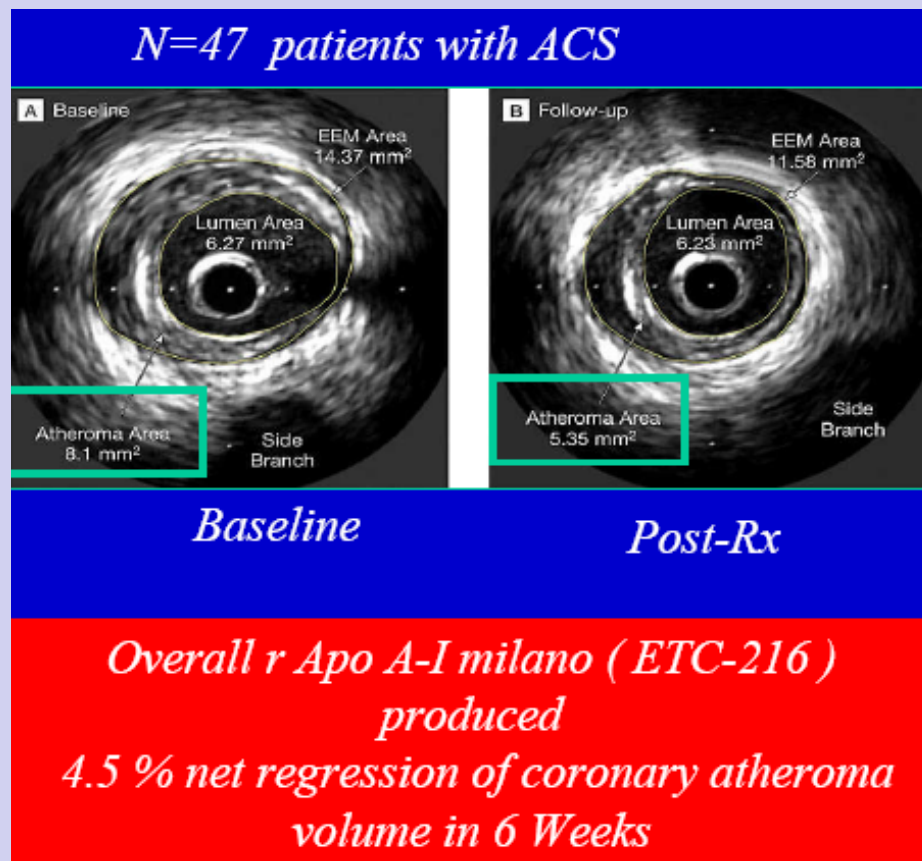


WHC Delipidations ± SEM (n=6)
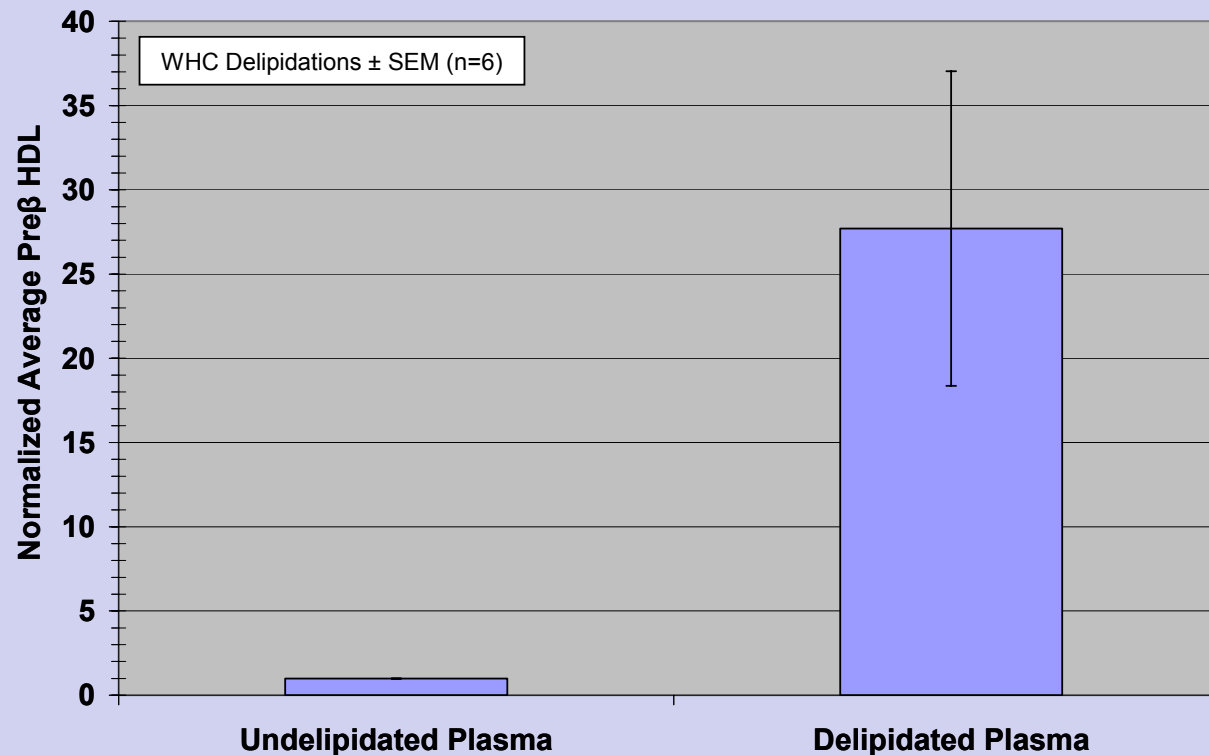
# Change in IVUS parameters, post delipidation treatments minus baseline ACS presentation

| Variable (mean $\pm$ SD) | Delipidated Group n=14 | Control Group n=12 |
|---|---|---|
| Change in Total Atheroma Volume ($mm^3$) | -12.18 $\pm$ 36.75 | 2.80 $\pm$ 21.25 |
| Change in Plaque Burden (%) | -1.0 $\pm$ 4.0 | 0.0 $\pm$ 4.0 |
| Change in 10 mm Most Diseased Subsegment – Atheroma Volume ($mm^3$) | -6.24 $\pm$ 17.94 | -1.73 $\pm$ 11.21 |
| Change in 10 mm Least Diseased Subsegment – Atheroma Volume ($mm^3$) | -1.10 $\pm$ 11.35 | 1.53 $\pm$ 11.70 |
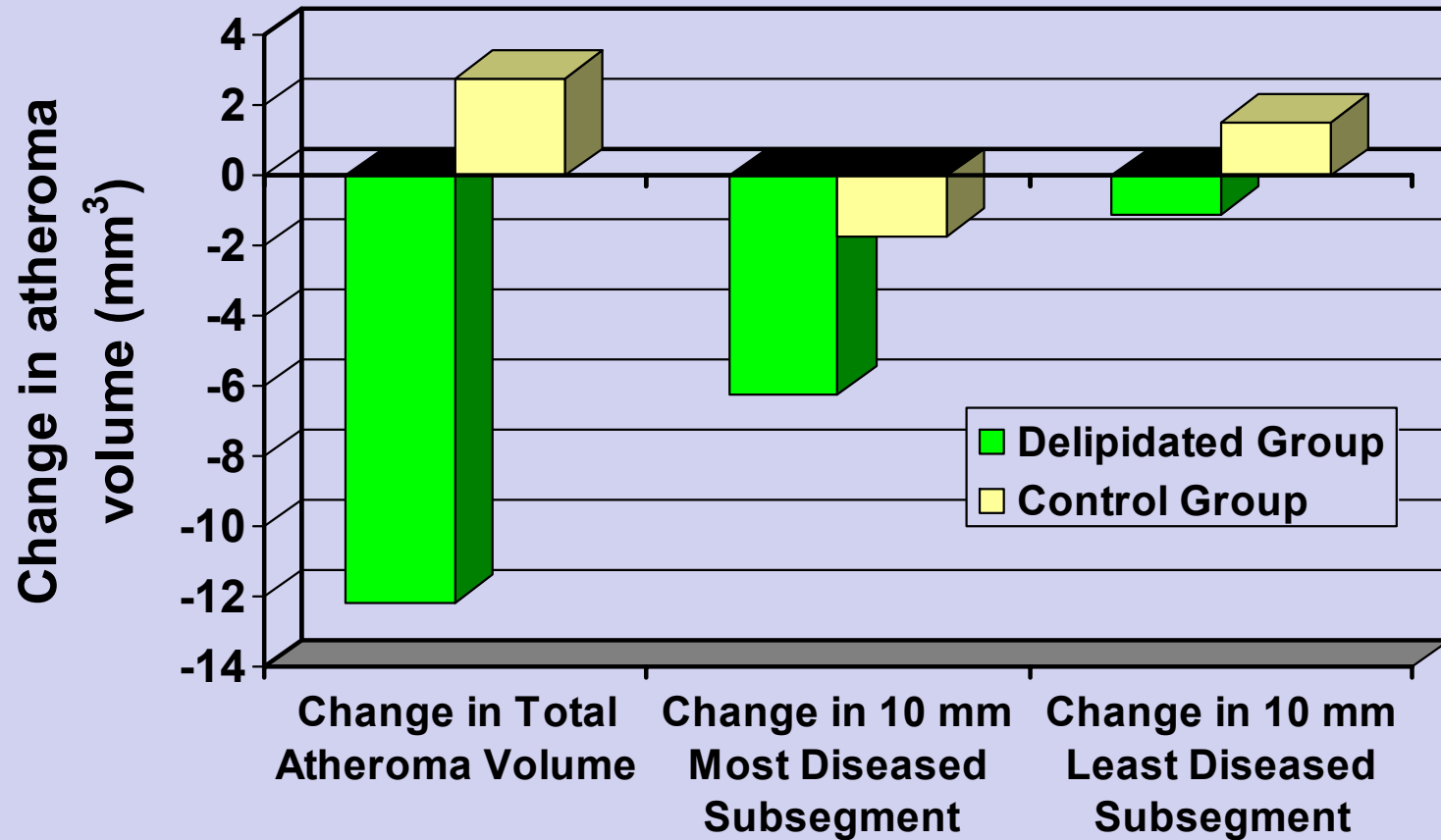
# Rapid Regression of Human Coronary Plaque after 5 Weekly Intravenous Injections of Recombinant rApo A-I*milano (ETC-216)*



N=47 patients with ACS

A Baseline — EEM Area 14.37 mm², Lumen Area 6.27 mm², Atheroma Area 8.1 mm², Side Branch

B Follow-up — EEM Area 11.58 mm², Lumen Area 6.23 mm², Atheroma Area 5.35 mm², Side Branch

Baseline — Post-Rx

Overall r Apo A-I milano (ETC-216) produced 4.5 % net regression of coronary atheroma volume in 6 Weeks

Mean Change in Atheroma Volume (%)
P<0.97 0.14
-1.06 P<0.02
(N=36) A-Im — (N=11) Placebo

Mean Change in Total Atheroma Volume (mm³)
-2.9 P<0.97
-14.1 (P<0.001)
(N=36) A-Im — (N=11) Placebo

10 mm coronary segments with the largest plaque showed 11 % net regression: Nichols JACC 2006

Nissen et al.: JAMA, 2003

# Comparison of the Changes in IVUS Parameters in Lipid Sciences Selective Delipidation Trial and ApoA-I Milano Trial

| Variable (mean $\pm$ SD) | LS-001 Trial N=14 | ApoA-I Milano Trial N=36* |
|---|---|---|
| Change in Total Atheroma Volume (mm$^3$) | -12.18 $\pm$ 36.75 | -14.10 $\pm$ 39.50 |
| Change in % Atheroma Volume (Plaque Burden) | -1.0% $\pm$ 4.0% | -1.1% $\pm$ 3.2% |
| Change in Most Diseased 10 mm Subsegment, Atheroma Volume (mm$^3$) | -6.24 $\pm$ 17.94 | -7.20 $\pm$ 12.60 |

*Nissen et al JAMA 2003: 290, 2292-300

# Summary

- Pre-clinical studies have demonstrated that pre-$\beta$ HDL is a key component in reverse cholesterol transport

- Safety and feasibility of delipidation were demonstrated

- Infusions are well tolerated by patients

- Patient compliance is excellent

- The PDS-2 consistently, reliably, and dramatically converts $\alpha$HDL to pre-$\beta$ HDL

- IVUS data demonstrates a numeric trend towards reduction in atheroma volumes

# Conclusions

- In patients with ACS, serial autologous infusions of HDL delipidated plasma are well tolerated by patients, and are clinically feasible and safe.

- This therapy may offer a novel adjunct treatment for patients presenting with ACS, and may ultimately stabilize and regress atherosclerotic plaques.

*Thank You*