Lomitapide

For the treatment of homozygous familial hypercholesterolemia

Endocrinologic and Metabolic Drugs Advisory Committee

October 17, 2012

Aegerion® Pharmaceuticals

Introduction

Martha J. Carter

Chief Regulatory Officer & Senior Vice President
Aegerion Pharmaceuticals, Inc.

Proposed Indication

- Lomitapide is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B) and triglycerides (TG) in patients with homozygous familial hypercholesterolemia (HoFH)

Presentation Agenda

Introduction	***Martha J. Carter*** **Chief Regulatory Officer & Senior Vice President** **Aegerion Pharmaceuticals, Inc.**
Medical Landscape	***Daniel J. Rader, MD*** **Professor of Medicine and Pharmacology** **Chief, Division of Translational Medicine and Human Genetics** **Associate Director, Institute for Translational Medicine and Therapeutics** **Perelman School of Medicine at the University of Pennsylvania**
Summary of Efficacy and Safety	***Mark Sumeray, MD*** **Chief Medical Officer** **Aegerion Pharmaceuticals, Inc.**
Hepatic Steatosis: A Hepatologist's Perspective	***Naga Chalasani, MD, FACG*** **Professor of Medicine and Cellular & Integrative Physiology** **Director, Division of Gastroenterology And Hepatology** **Indiana University School Of Medicine**
Risk Management	***Martha J. Carter***
Benefit-Risk Assessment	***Robert A. Hegele, MD, FRCPC*** **Canada Research Chair in Human Genetics** **Distinguished University Professor of Medicine** **Robarts Research Institute** **The University of Western Ontario, London ON**

Medical Landscape

Daniel J. Rader, MD

Professor of Medicine and Pharmacology

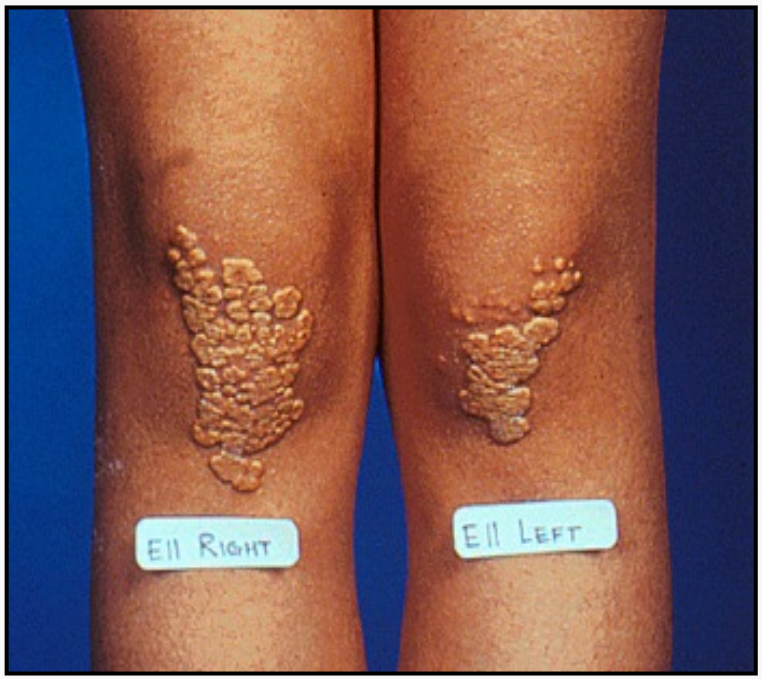
Chief, Division of Translational Medicine and Human Genetics

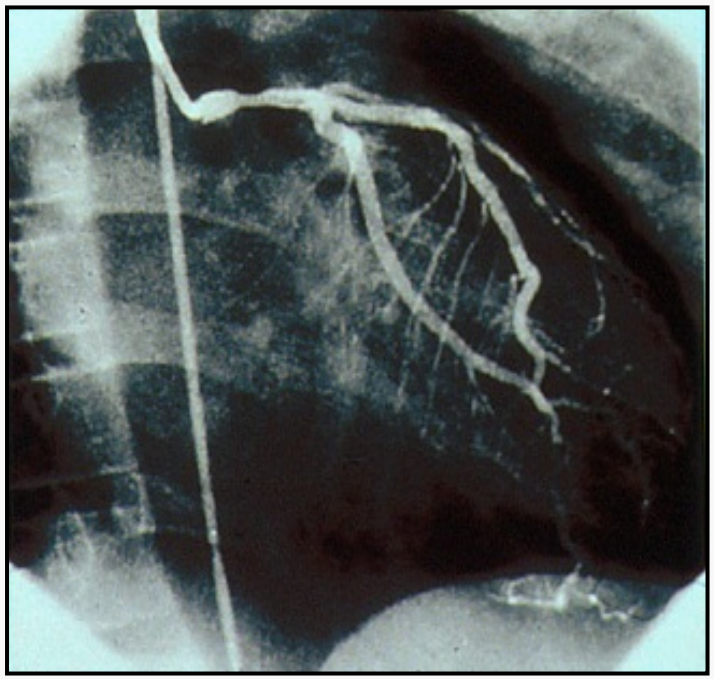
Associate Director, Institute for Translational Medicine and Therapeutics

Perelman School of Medicine at the University of Pennsylvania

Case: Homozygous Familial Hypercholesterolemia (HoFH)

28 year-old female
Cutaneous xanthomas beginning at age 3
Obstructive coronary artery disease and CABG at age 12
LDL cholesterol = 780 mg/dL



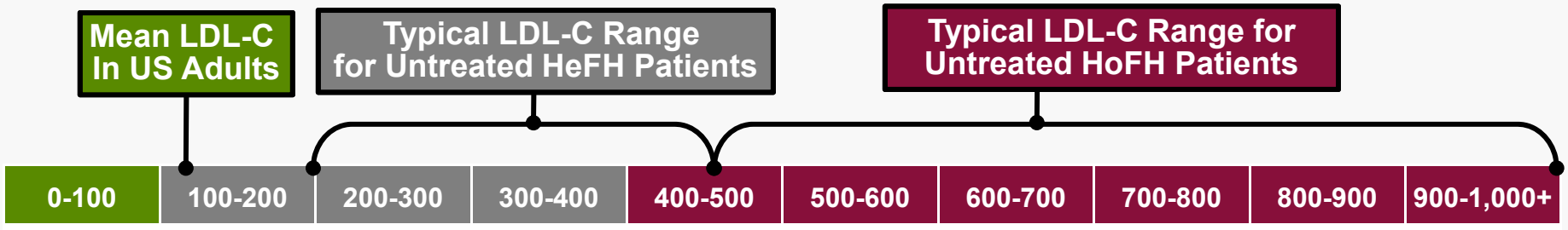


CM-006

Etiology of Homozygous FH (HoFH)

- Loss of function mutations in both LDL receptor alleles
- ~1600 mutations in the LDL receptor reported

The Spectrum of Familial Hypercholesterolemia

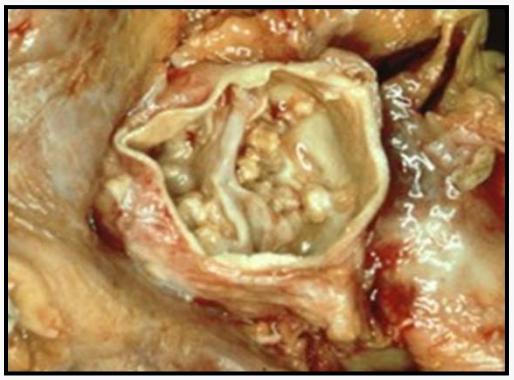


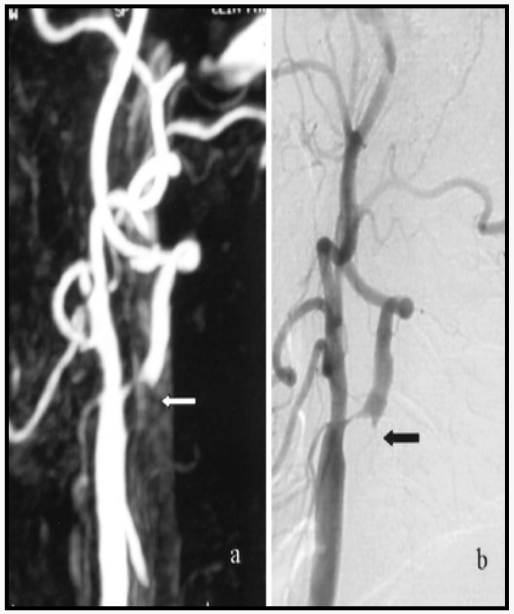
- Estimated Prevalence
  - Heterozygous FH: 1:500†
  - Homozygous FH: 1:1 million‡

† Goldstein, J. L., H. H. Hobbs, et al. (2001). *The Metabolic and Molecular Basis of Inherited Disease*.
‡ Moorjani, S., M. Roy, et al. (1993). *Lancet* 341(8856): 1303-1306.

Cardiovascular Consequences of Markedly Elevated LDL-C in HoFH

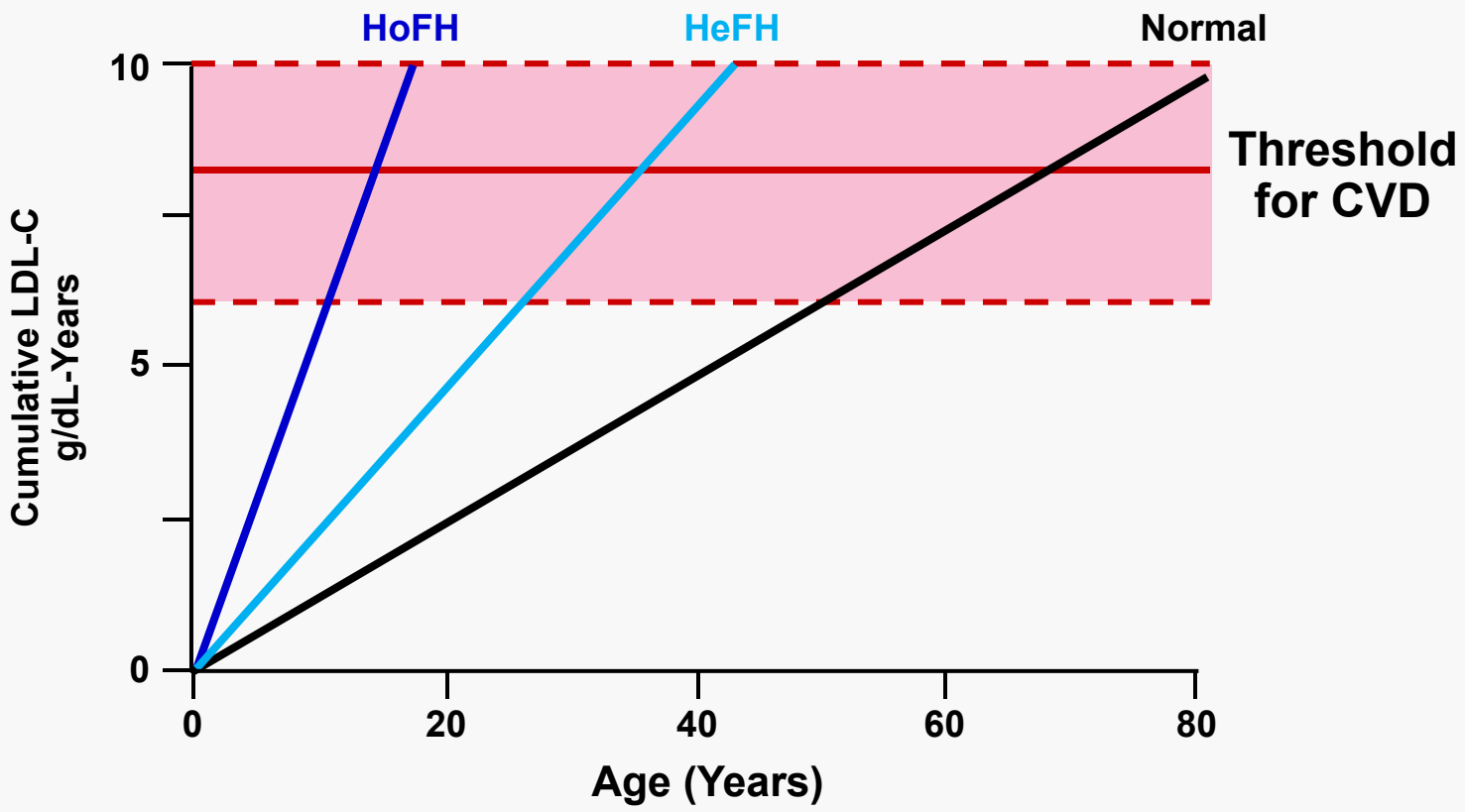
- Patients with HoFH typically develop cardiovascular disease before the age of 20[1]
  - Coronary artery disease
  - Myocardial infarction
  - Severe aortic stenosis
  - Heart failure
  - Stroke
  - Sudden death
- Even with currently existing therapies, the mean age of death is 33 years[2]





1. Goldstein, J. L., H. H. Hobbs, et al. (2001). *The Metabolic and Molecular Basis of Inherited Disease*.
2. Raal J, et al. *Circulation*. (2011).

Elevated LDL-C is the Cause of Cardiovascular Disease in HoFH



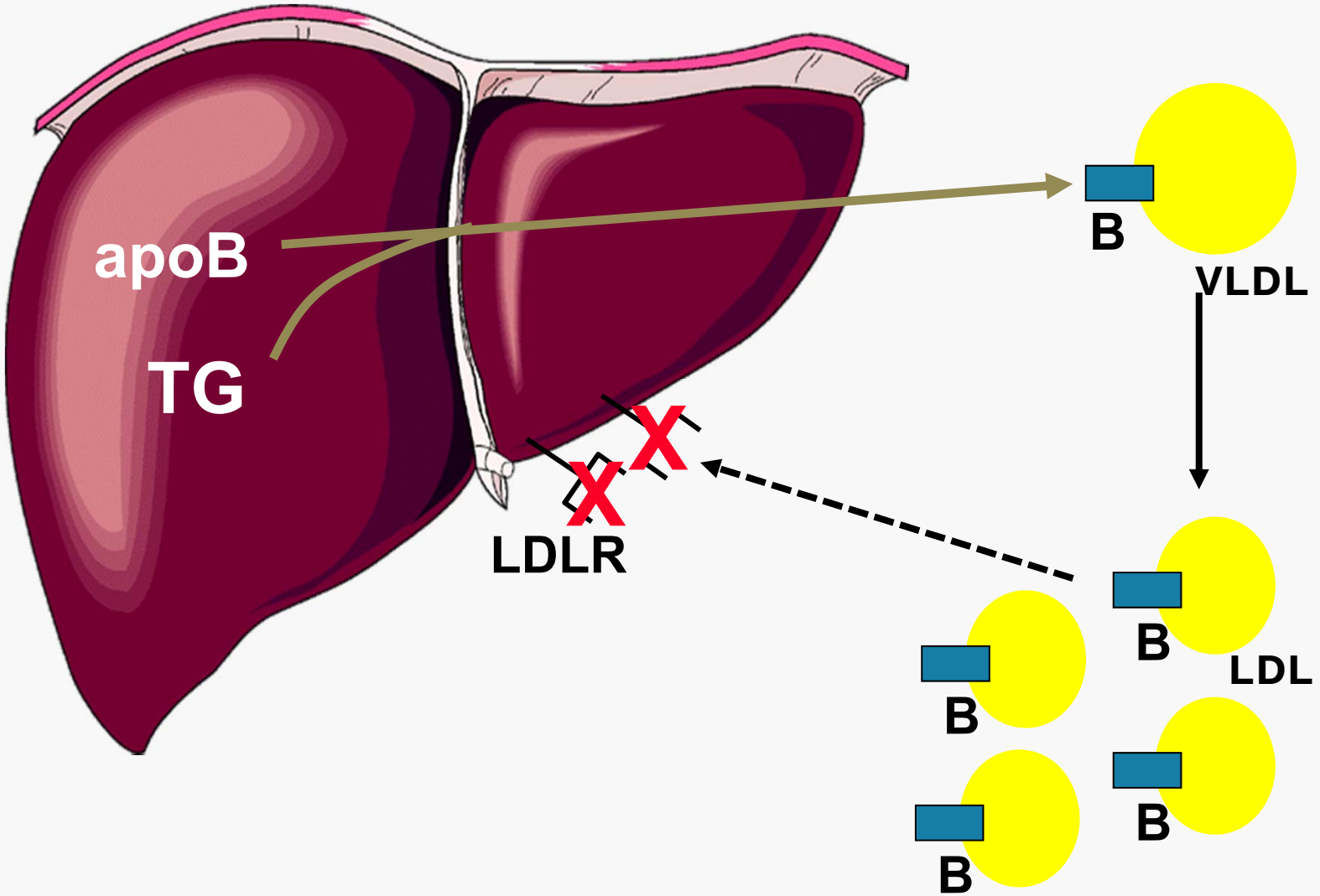
Adapted from Horton et al. *J Lipid Res*. 2009;50:S172-S177.

CM-010

Reduction in LDL-C Results in Reduced Cardiovascular Morbidity

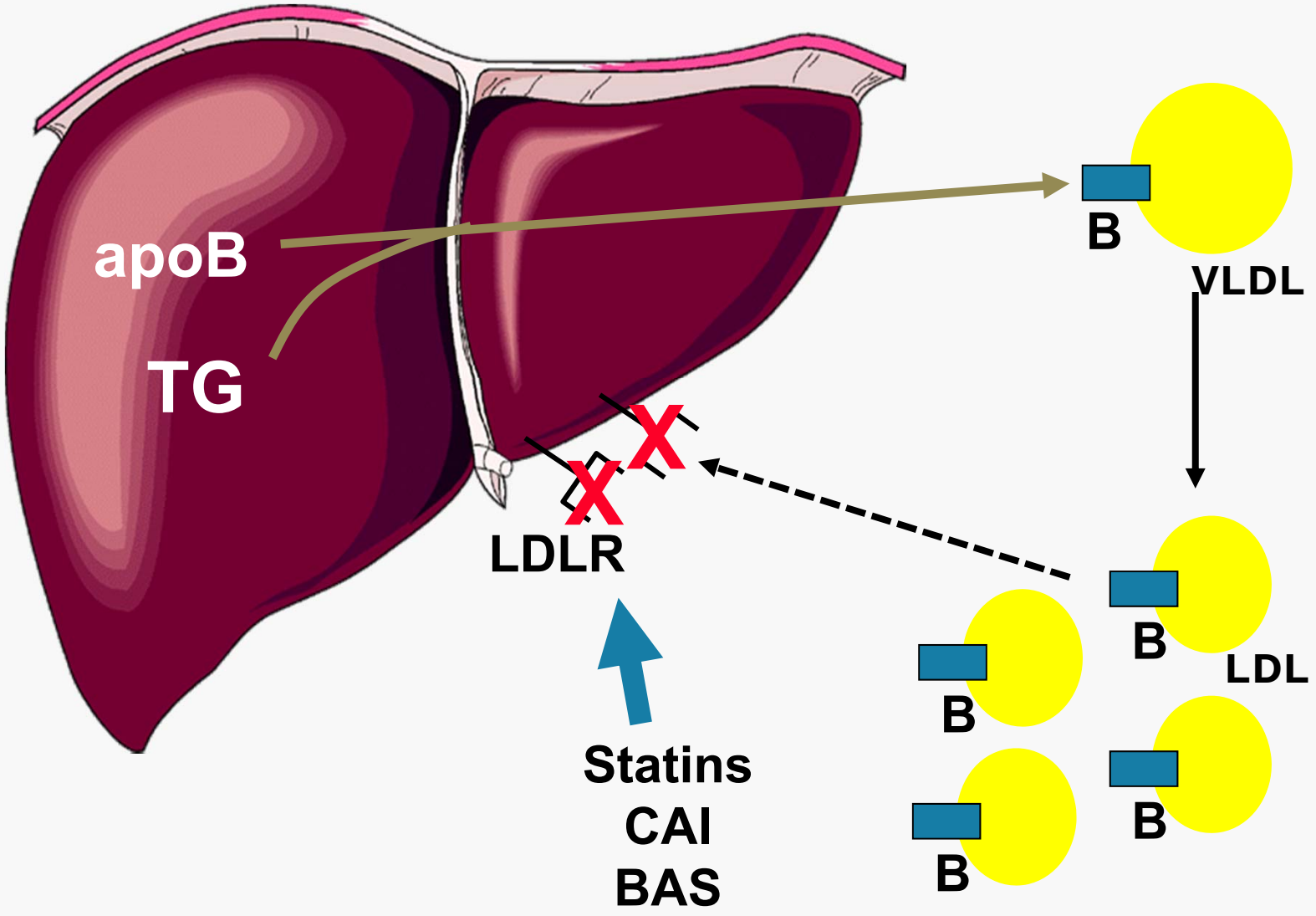
- **Interventional studies**
  - **Statins**: *(Baigent, 2005; Baigent, 2010)*
  - **Immediate–release niacin**: *(Canner, 1986)*
  - **Bile acid sequestrants** (cholestyramine): *(Lipid Research Clinics 1984a & b)*
  - **Partial ileal bypass**: *(Buchwald, 1990)*
  - **LDL-C apheresis**: *(Sachais / Rader, 2005; Winters, 2012 and Nishimura, 1999: Matsuzaki, 2002; Bambauer, 2003, Moga and Harstall, 2004; Koga, 2005; Ziajka, 2005; Thompsen and Thompson, 2006)*
- **LDL-C is a causal factor in the development of CVD and reduction of LDL reduces the risk of CVD**

Defective LDL Receptors in HoFH Leads to Impaired LDL Catabolism



CM-012

Patients With HoFH Respond Poorly to Currently Available Therapies



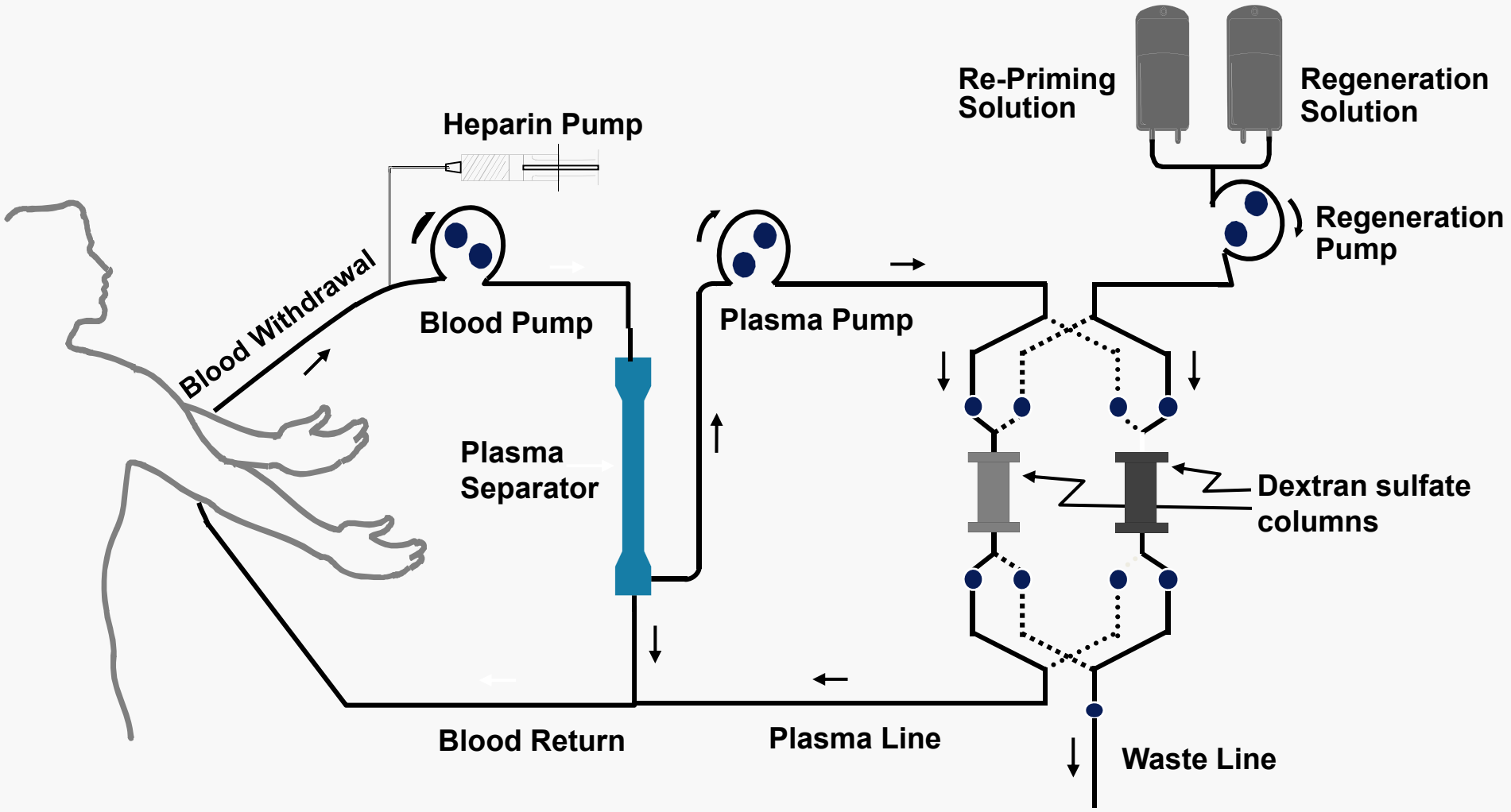
CM-013

Current Cholesterol-Lowering Drugs Are Insufficient in HoFH

Class	Major Effect	Typical LDL-C-Lowering Response
Statins (e.g. atorvastatin, rosuvastatin)	**↑ LDLR activity**	**<10 to 25%**
Bile acid sequestrants (e.g. cholestyamine, colestipol)	**↑ LDLR activity**	**<10%**
Cholesterol absorption inhibitors (e.g. ezetimibe)	**↑ LDLR activity**	**<10%**
Nicotinic acid (ie, niacin)	**Unknown**	**<10%**

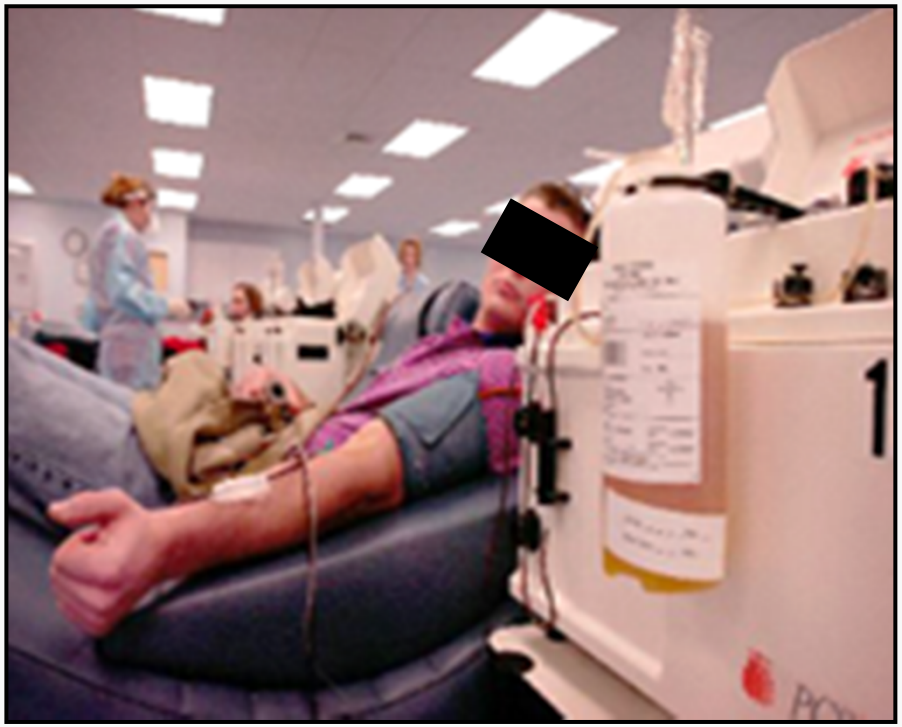
Rader DJ, et al. *J Clin Invest.* 2003;111:1796-1803.
Konrad RJ, et al. *Lipids Health Dis.* 2011;10:38.

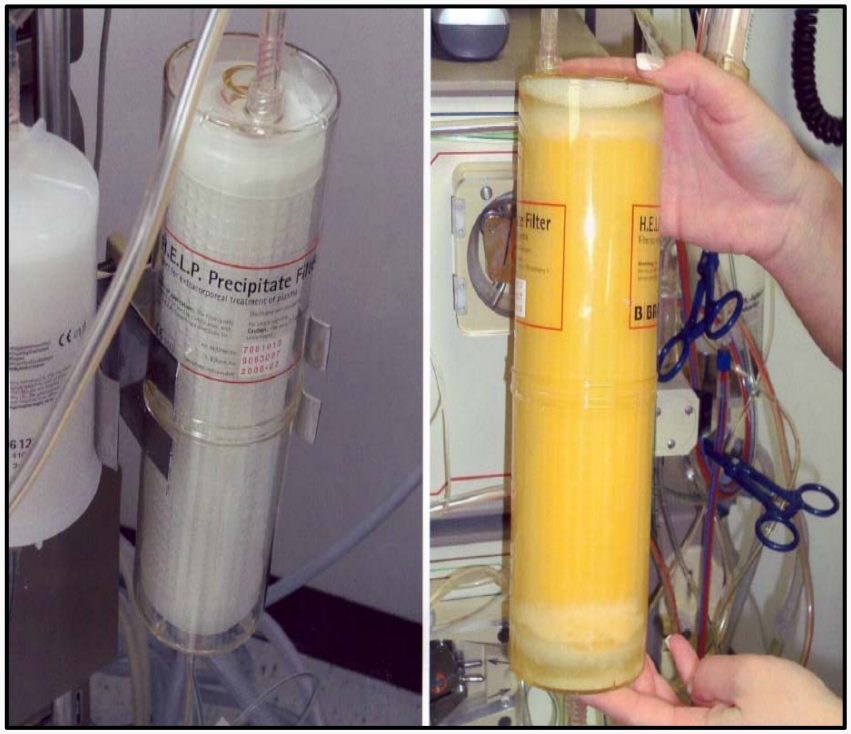
LDL Apheresis is Current Standard of Care for HoFH



CM-015

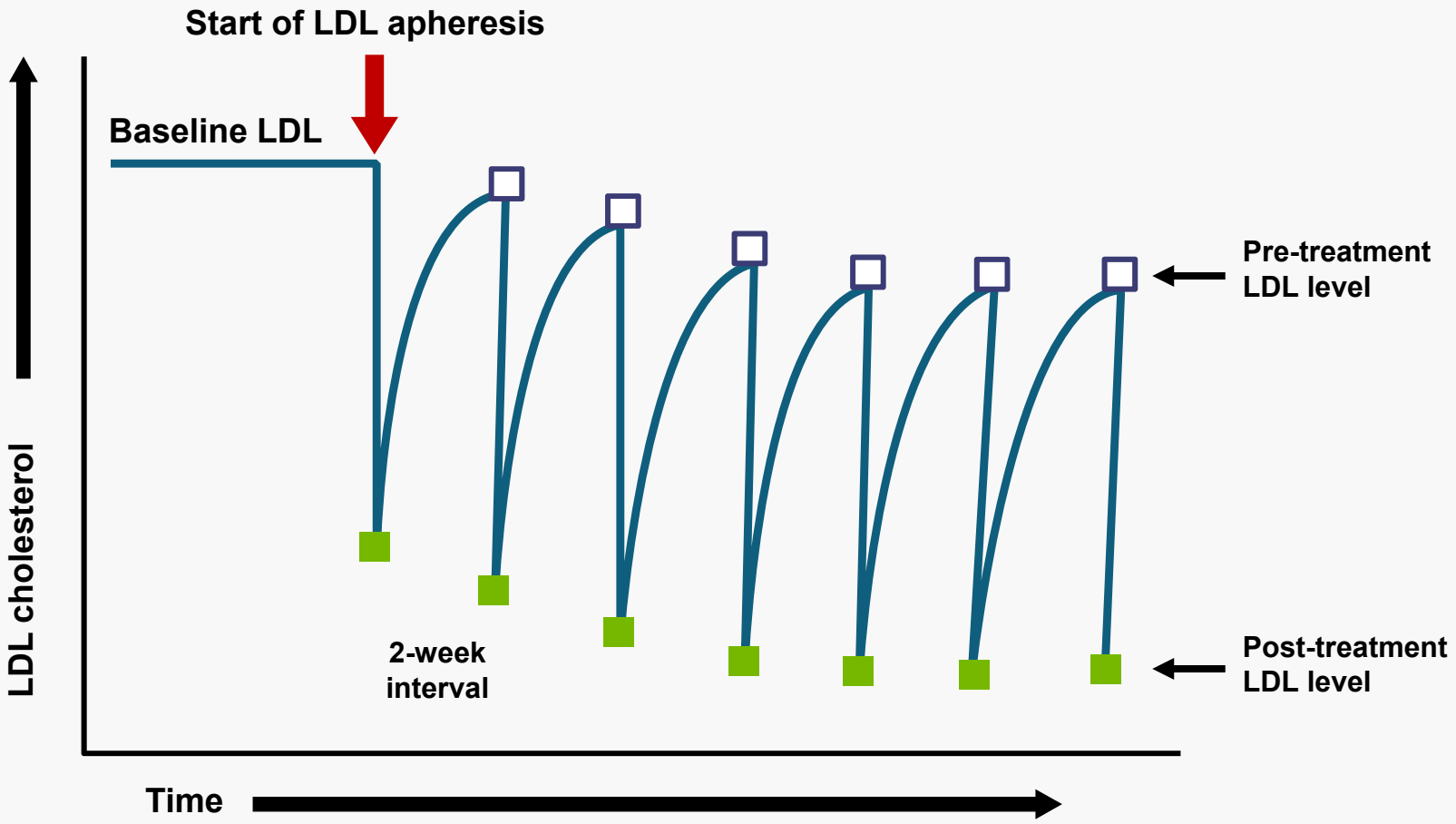
LDL Apheresis Purges the Blood of LDL Cholesterol





CM-016

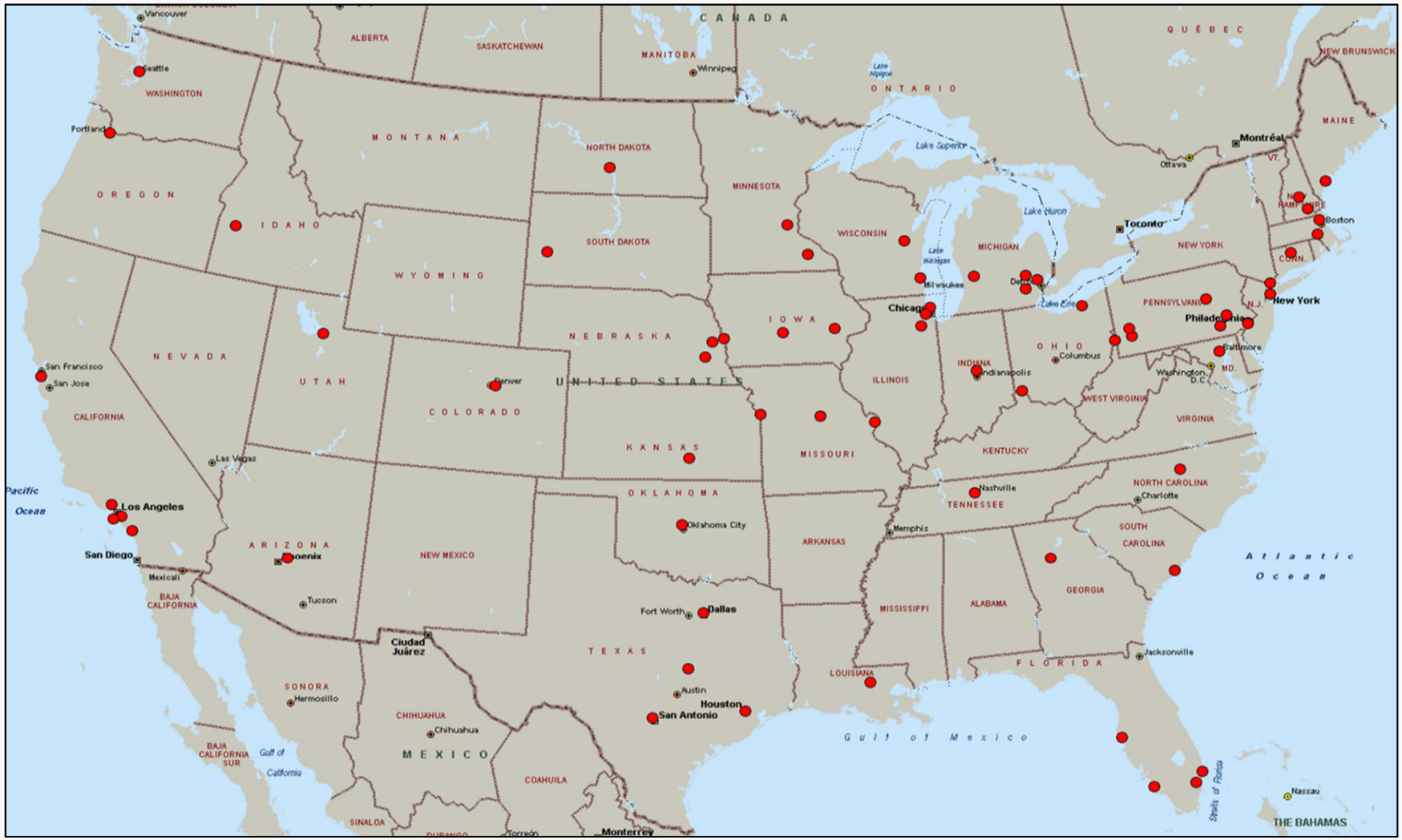
LDL-C Levels Acutely Decrease and then Rebound Following Apheresis



Thompsen J & Thompson PD. *Atherosclerosis*. 2006;189: 31-8.

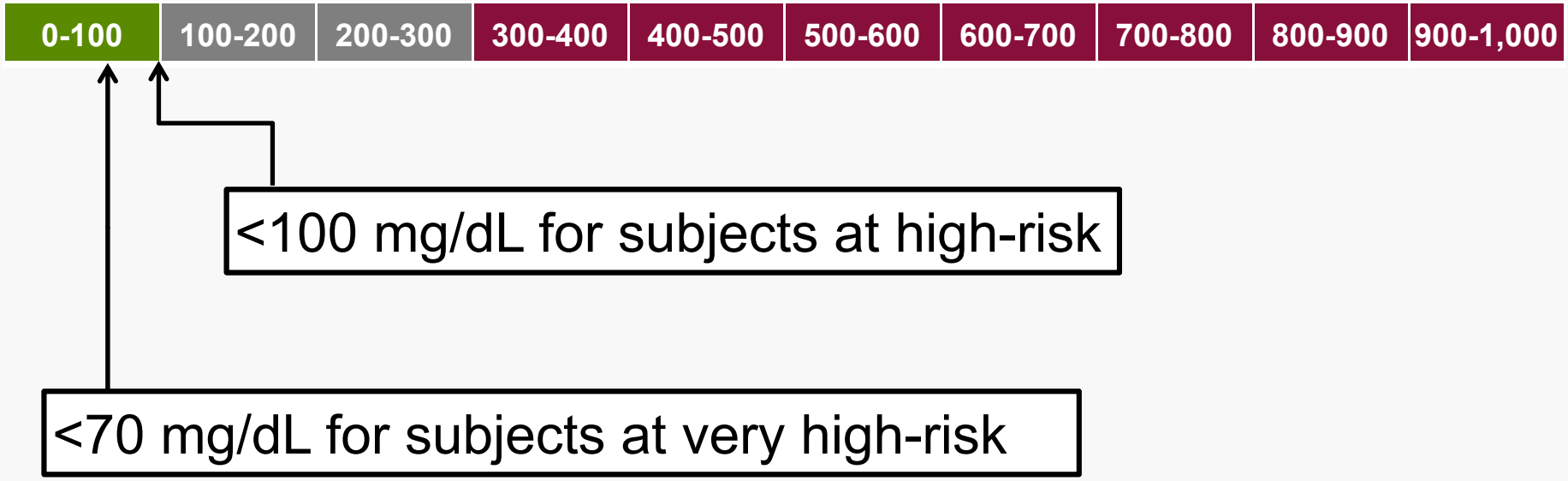
CM-017

LDL Apheresis Centers in the US: Limited Geographical Access

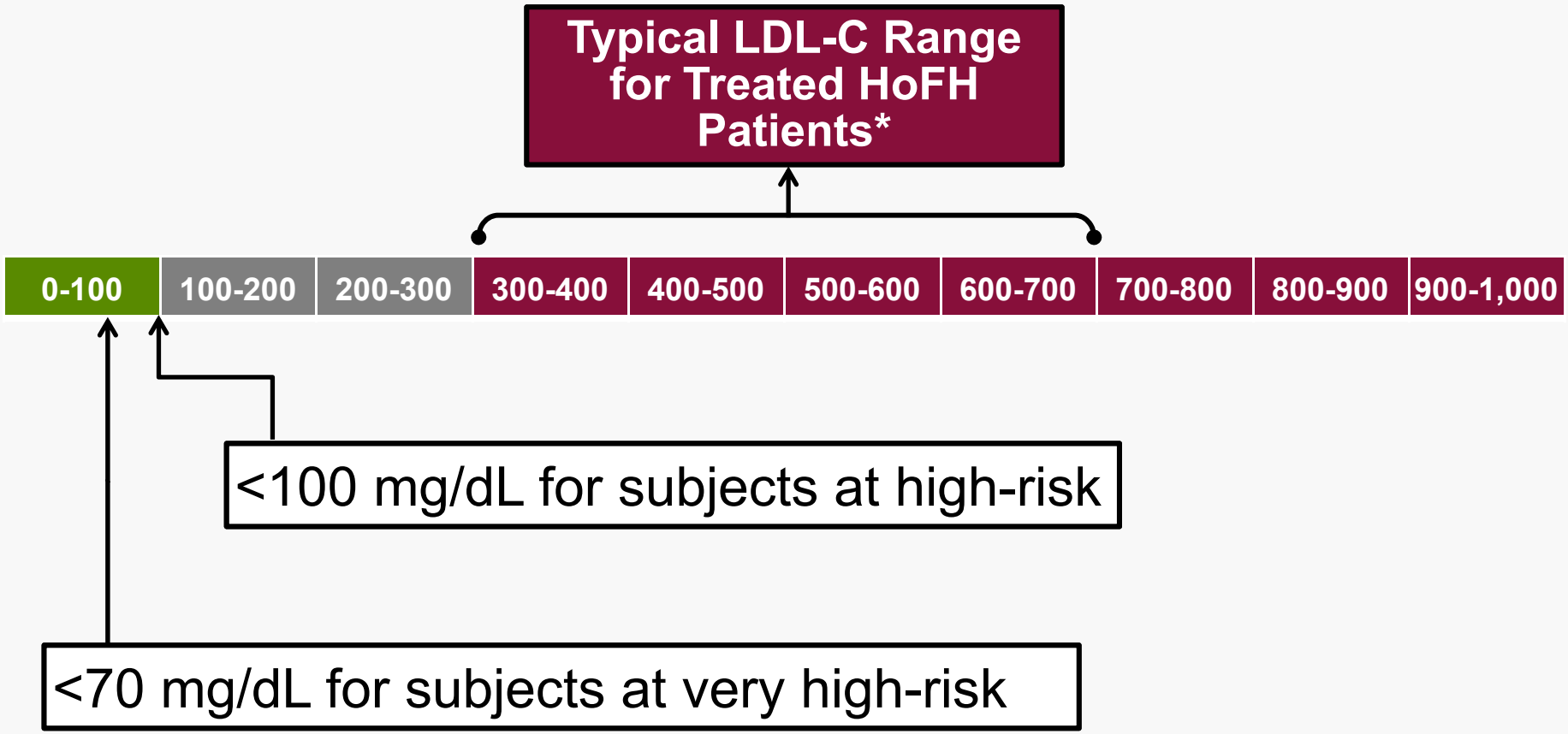


CM-018

LDL-C Target Treatment Goals



Treated HoFH Patients are Still Far from LDL-C Target Treatment Goals



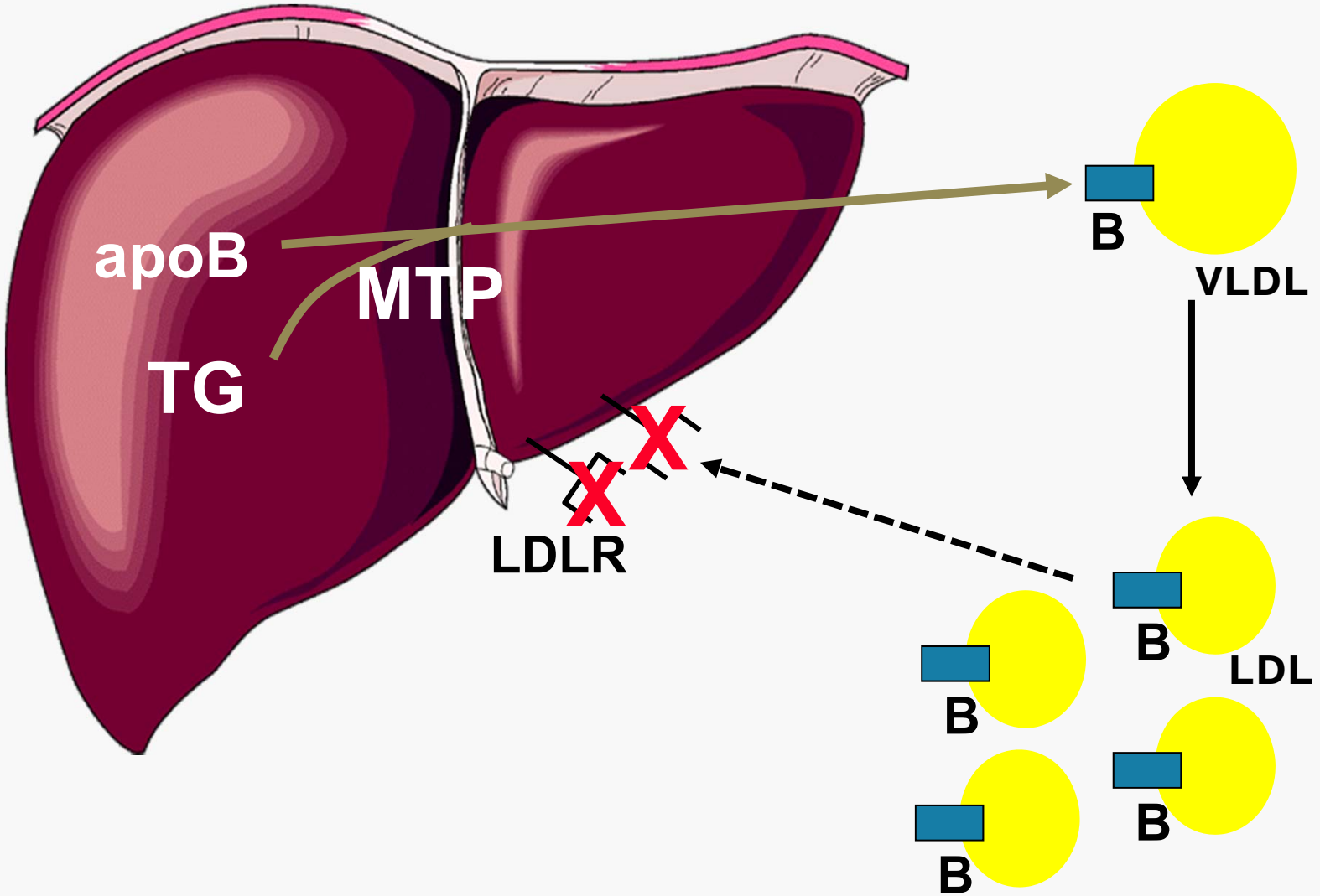
* Raal J, et al. *Circulation*. (2011).

CM-020

HoFH Represents a Major Unmet Medical Need

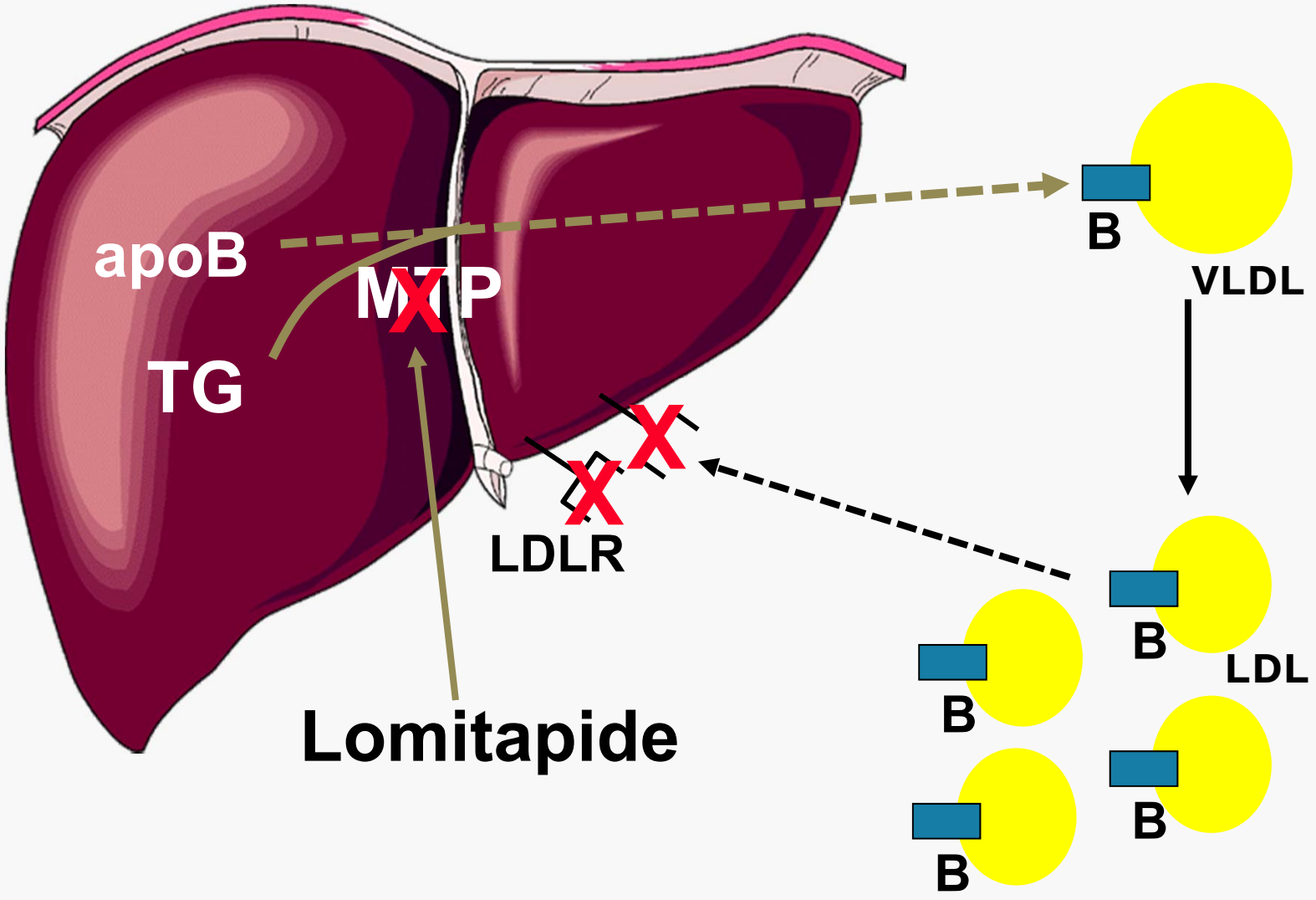
- HoFH patients have inadequate response to existing pharmacologic cholesterol-lowering therapies
- While LDL-apheresis provides some benefit, LDL-C reduction is not sustained, LDL-C is not optimally-controlled, and the procedure is not widely available
- New approaches to reducing LDL-C in patients with HoFH are needed

MTP is Required for Secretion of VLDL, the Precursor to LDL



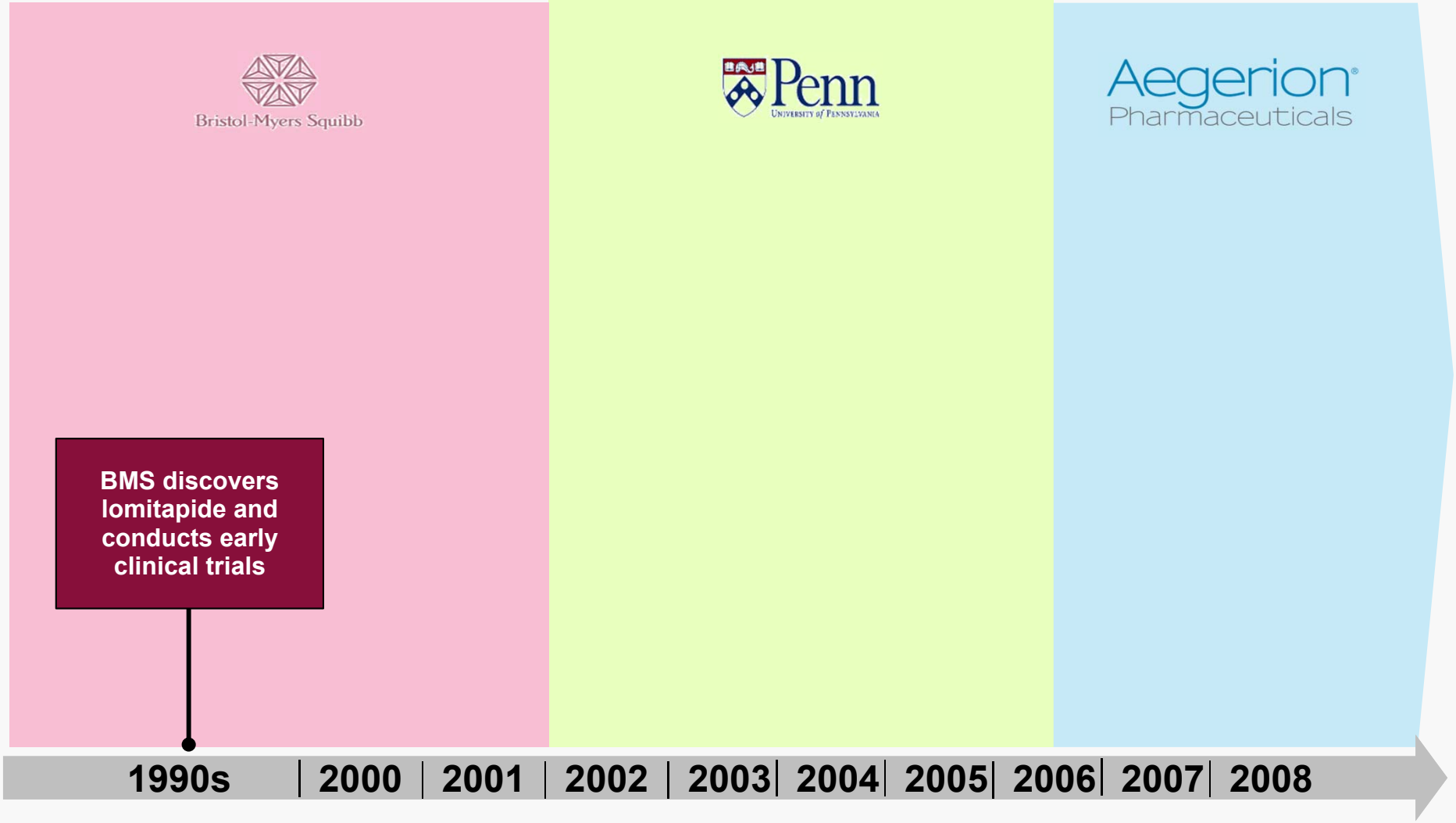
CM-022

Lomitapide is an Inhibitor of MTP and Reduces VLDL Production



CM-023

Lomitapide History of Development

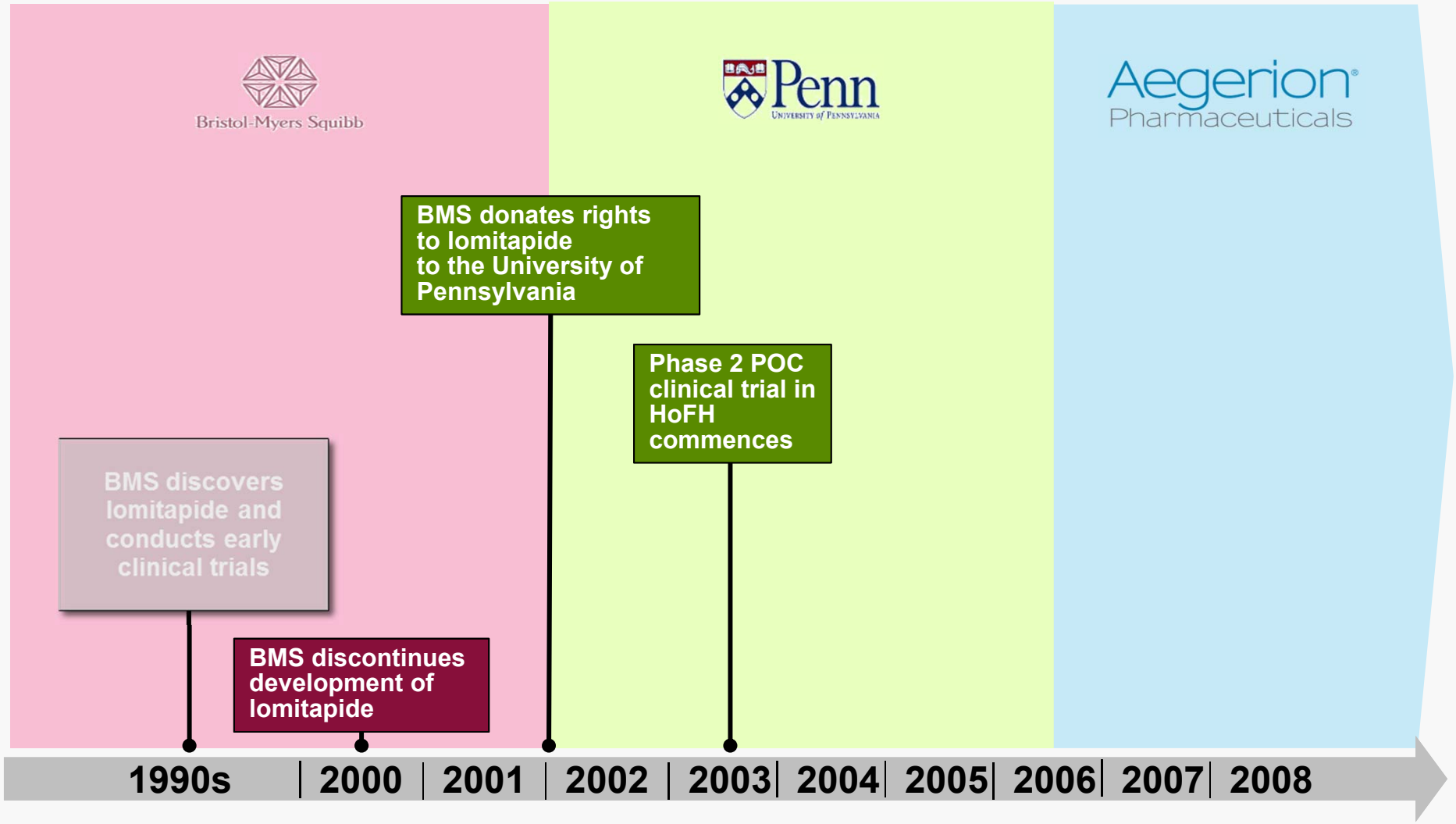


CM-024

BMS Phase 2 Study

- 76 subjects with LDL-C ≥160 mg/dL were randomized to a fixed dose of lomitapide 25 mg or placebo for 4 weeks, followed by a 6-week wash-out period
- Major results:
  - LDL-C was rapidly reduced by 64% in lomitapide group compared to no change in placebo
  - GI AEs were common, leading to discontinuation in 21% of lomitapide treated subjects
  - Hepatic fat increased at 4 weeks and returned to Baseline after 6-week wash-out

Lomitapide History of Development



CM-026

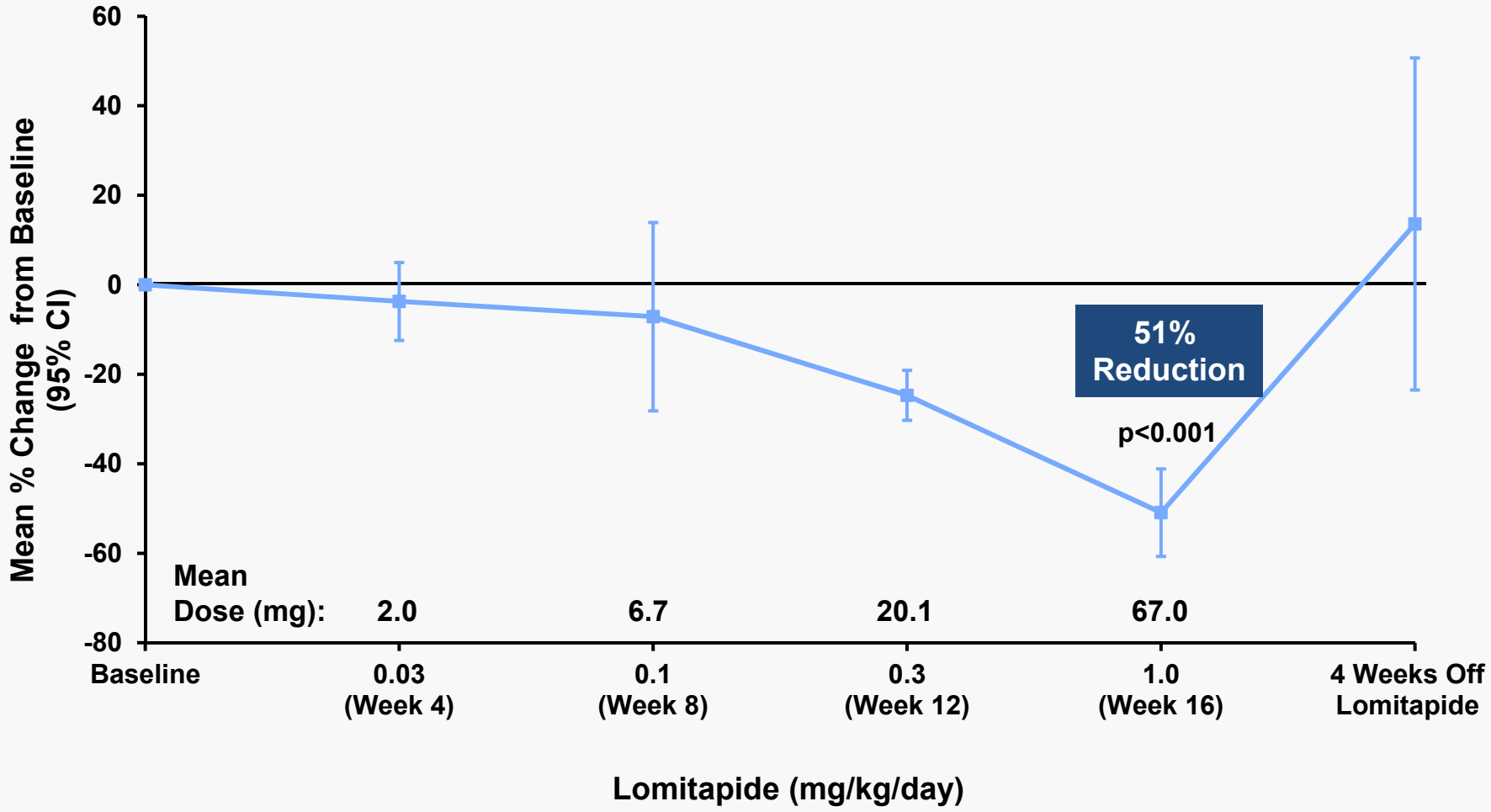
Lomitapide as Therapy for HoFH

- Will lomitapide reduce LDL-C effectively in patients with HoFH?
- Can steps be taken to reduce the GI side effects and hepatic fat?

Phase 2 Proof-of-Concept Study in HoFH

- New dosing regimen: lomitapide started at a low dose and dose-escalated every four weeks
- Subjects were counseled on a low-fat diet (<10% energy from fat)
- Single arm, open label study, 6 subjects
- Background therapies were discontinued for duration of study
- Hepatic fat was assessed by MRI every four weeks

Phase 2 HoFH Study: 51% Reduction in LDL-C



Cuchel, M. et al. *NEJM* 2007; 356:148-56.

CM-029

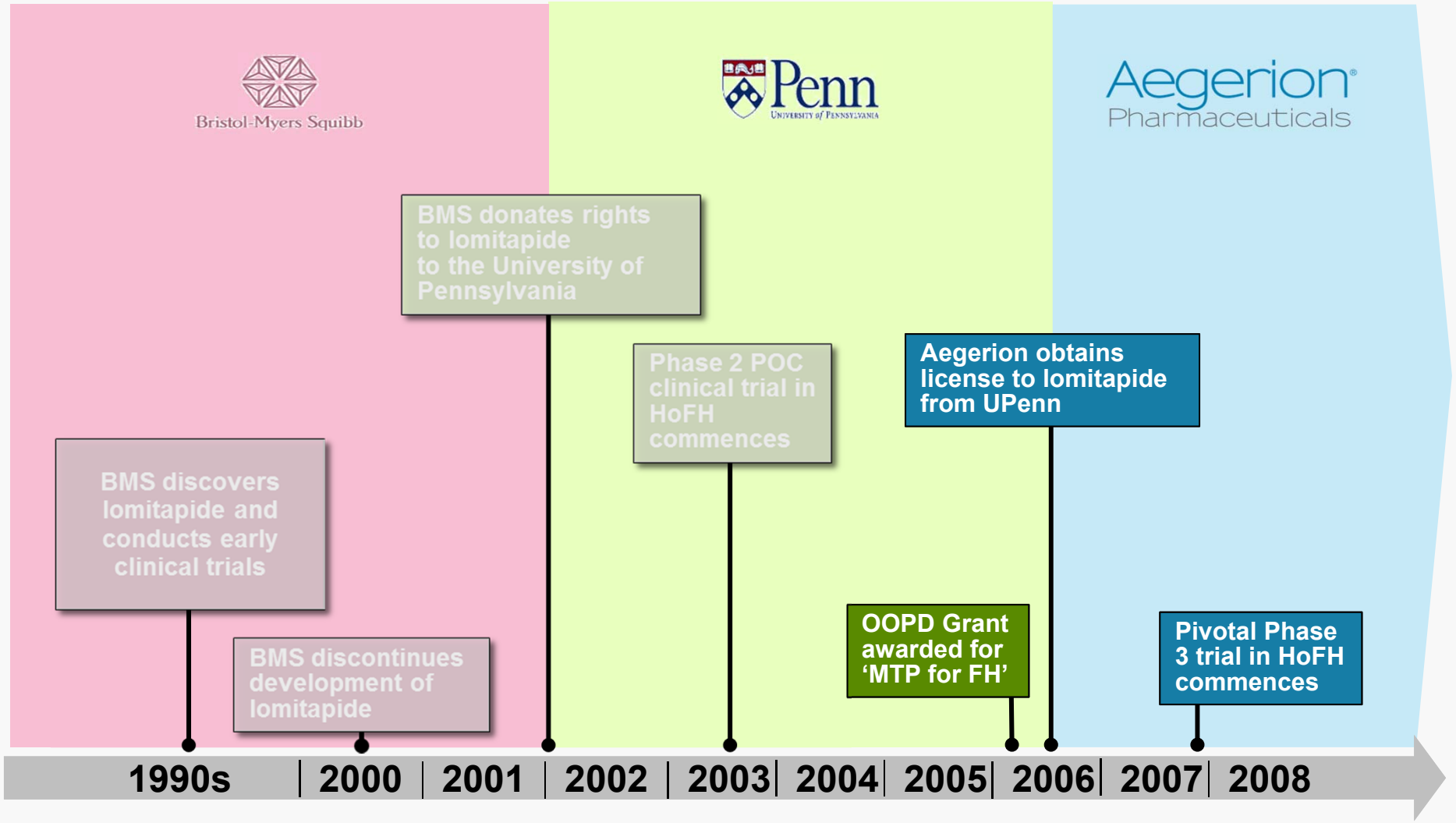
Phase 2 HoFH: Safety and Tolerability Findings (1)

- Improved GI AE profile compared with prior fixed-dose studies. Attributed to:
  - Dose escalation
  - Utilization of low fat diet (mean 17% energy from fat)
- Reductions in vitamin E observed which were proportional to the reduction in LDL-C:
  - Serum vitamin E in all subjects remained within or above normal limits
- Essential fatty acid levels decreased over time

Phase 2 HoFH: Safety and Tolerability Findings (2)

- Variable increases in ALT/AST
  - Dose-dependent
  - Returned to lower levels with dose reduction or continued therapy with same dose
  - Not associated with increases in bilirubin or alkaline phosphatase
- Increases in hepatic fat as measured by MRI
  - Dose-dependent
  - Highly variable from patient to patient
  - Returned to baseline within 4 week washout (except for subject consuming large amount of alcohol)

Lomitapide History of Development



CM-032

Summary

- HoFH is associated with markedly elevated LDL-C levels, leading to early cardiovascular disease and death
- Reduction in LDL-C proven to reduce cardiovascular risk and is a mainstay of therapy in HoFH
- Current treatment options are inadequate to reduce LDL-C levels in HoFH
- MTP inhibition with lomitapide provides a magnitude of cholesterol reduction in patients with HoFH that is expected to change the course of the disease and substantially delay cardiovascular events and mortality

Lomitapide in HoFH

Mark Sumeray, MD
Chief Medical Officer
Aegerion Pharmaceuticals, Inc

Overview of Clinical Studies in the Lomitapide Clinical Development Program

Study Type	Patient Population	Number of Subjects
15 Phase 1 Studies		
6 x Dose Finding/ PK	HV, elevated cholesterol	135
1 x Food Effect Study	Healthy volunteers	25
5 x Drug Drug Interaction	Healthy volunteers	216
2 x Special Population	Renal, hepatic impairment	46
1 x tQTc Study	Healthy volunteers	56
6 Phase 2 Studies		
5 x LDL-C	Elevated LDL-C	622
HoFH POC	HoFH	6
Phase 3 Study and Extension		
Pivotal HoFH	HoFH	29
Extension to Phase 3	HoFH	19
Total Subjects		1135

CE-035

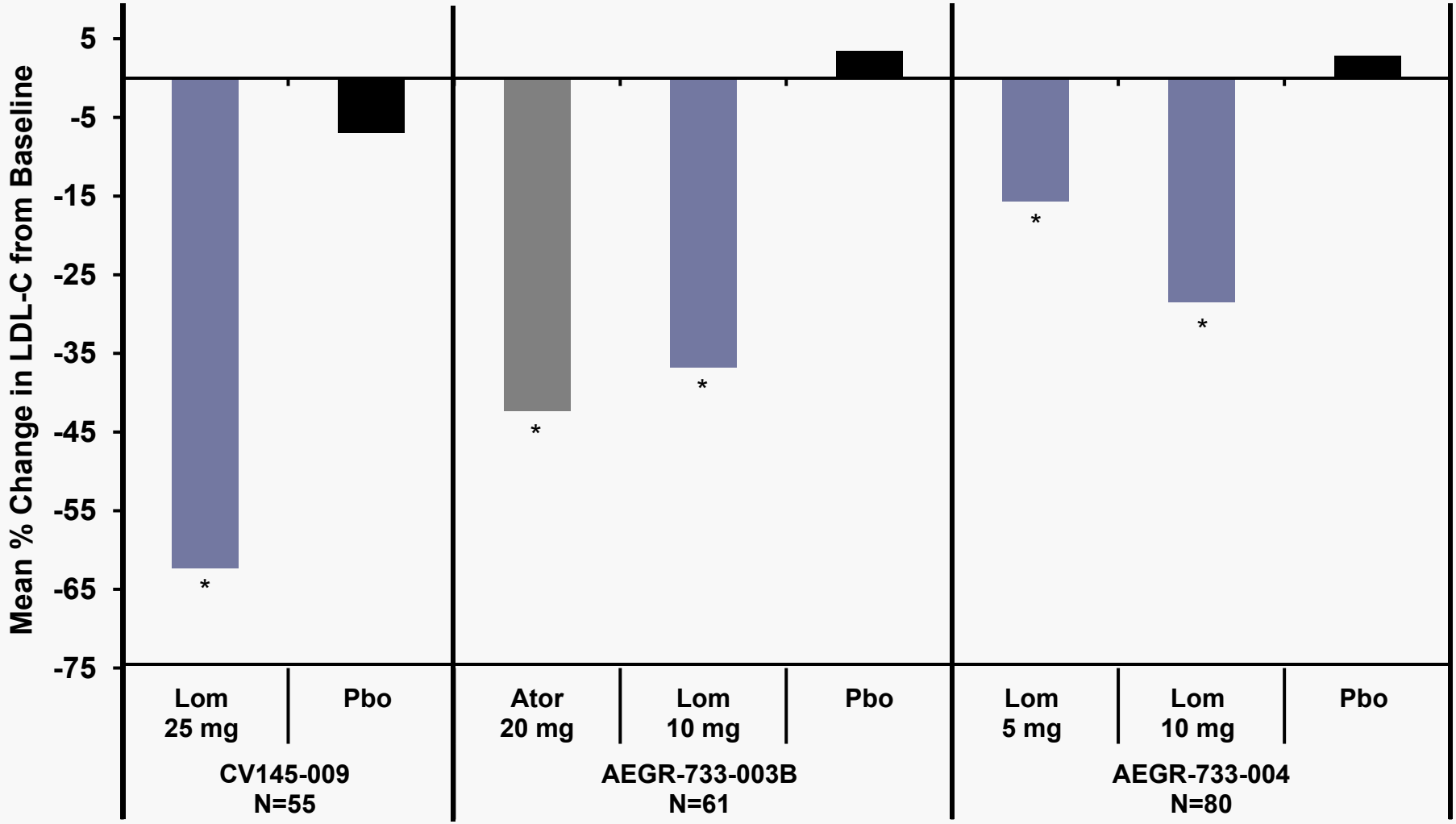
Clinical Pharmacology

- Lomitapide is a small molecule administered orally, once a day
- High solubility and permeability
- Delivered to site of action (small intestine and liver)
- At least 33% absorbed, but low systemic bioavailability (7%) likely due to a high first pass effect
- Extensively metabolized, predominantly by CYP 3A4
- Half-life approximately 34 hours

Phase 2 studies – Non-HoFH

- 5 controlled trials in subjects with hypercholesterolemia
- Significant LDL-C lowering observed in all studies
- 3 studies included a placebo arm (n=493)
  - 4-12 Weeks in duration

Efficacy Consistently Demonstrated in Phase 2 Studies of Non-HoFH Subjects



* p<0.05 compared to placebo

CE-038

Phase 3 Pivotal Trial of Lomitapide in Patients with HoFH

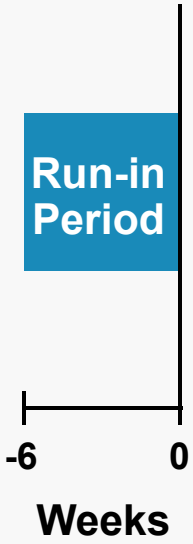
- Initial funding provided by FDA Office of Orphan Product Development
- Objective: To evaluate the long-term efficacy and safety of the MTP inhibitor lomitapide in patients with homozygous FH in order to support regulatory approval for this orphan indication
- Study powered to show 25% reduction in LDL-C from baseline after 26 weeks of treatment (N=20)

Phase 3 Study in HoFH Patients

Multinational study conducted at 11 sites in 4 countries

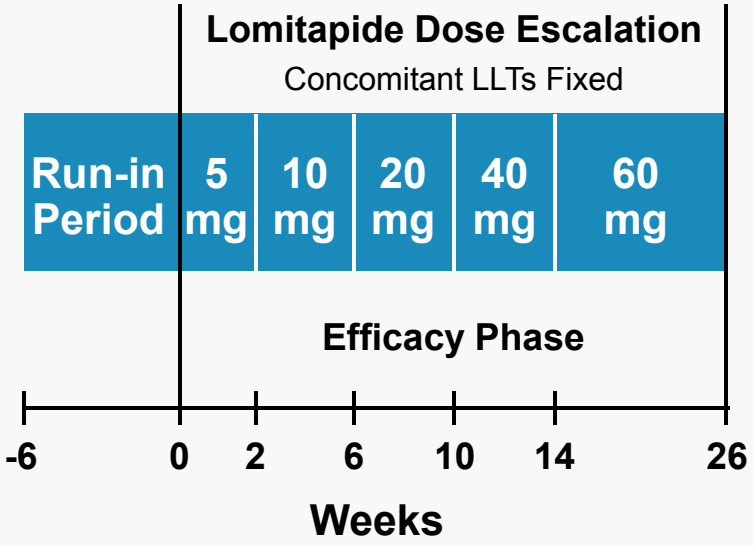
Country	Sites N	Patients N (%)
United States	2	7 (24)
South Africa	3	11 (38)
Italy	4	6 (21)
Canada	2	5 (17)

Phase 3 Study Design



- Minimum 6-week run-in period
  - Low fat diet (<20% energy from fat)
  - Background lipid lowering therapies (LLTs) stabilized
  - From screening to end of run-in period LDL-C change was -1.2%

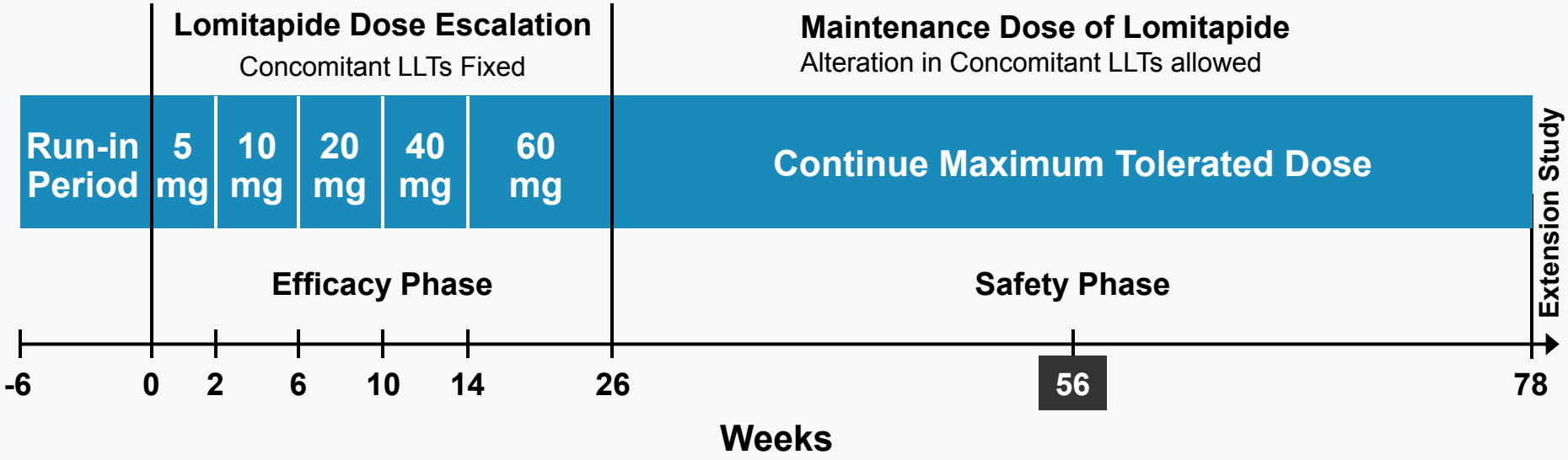
Phase 3 Study Design



- Efficacy phase: Weeks 0-26
  - Dose of lomitapide escalated to an individually determined maximum tolerated dose based on LFT criteria and GI tolerability
  - Background LLTs fixed
  - Primary efficacy endpoint: Percent change in LDL-C at Week 26

CE-042

Phase 3 Study Design



- Safety phase: From week 26-78
  - Continued maximum tolerated dose
  - Changes in concomitant LLTs allowed
  - Week 56 data submitted in NDA
- Extension study for patients who successfully completed the phase 3 study
- 4 Month Safety Report through week 78 and the extension study

CE-043

Diagnostic Entry Criteria in Phase 3

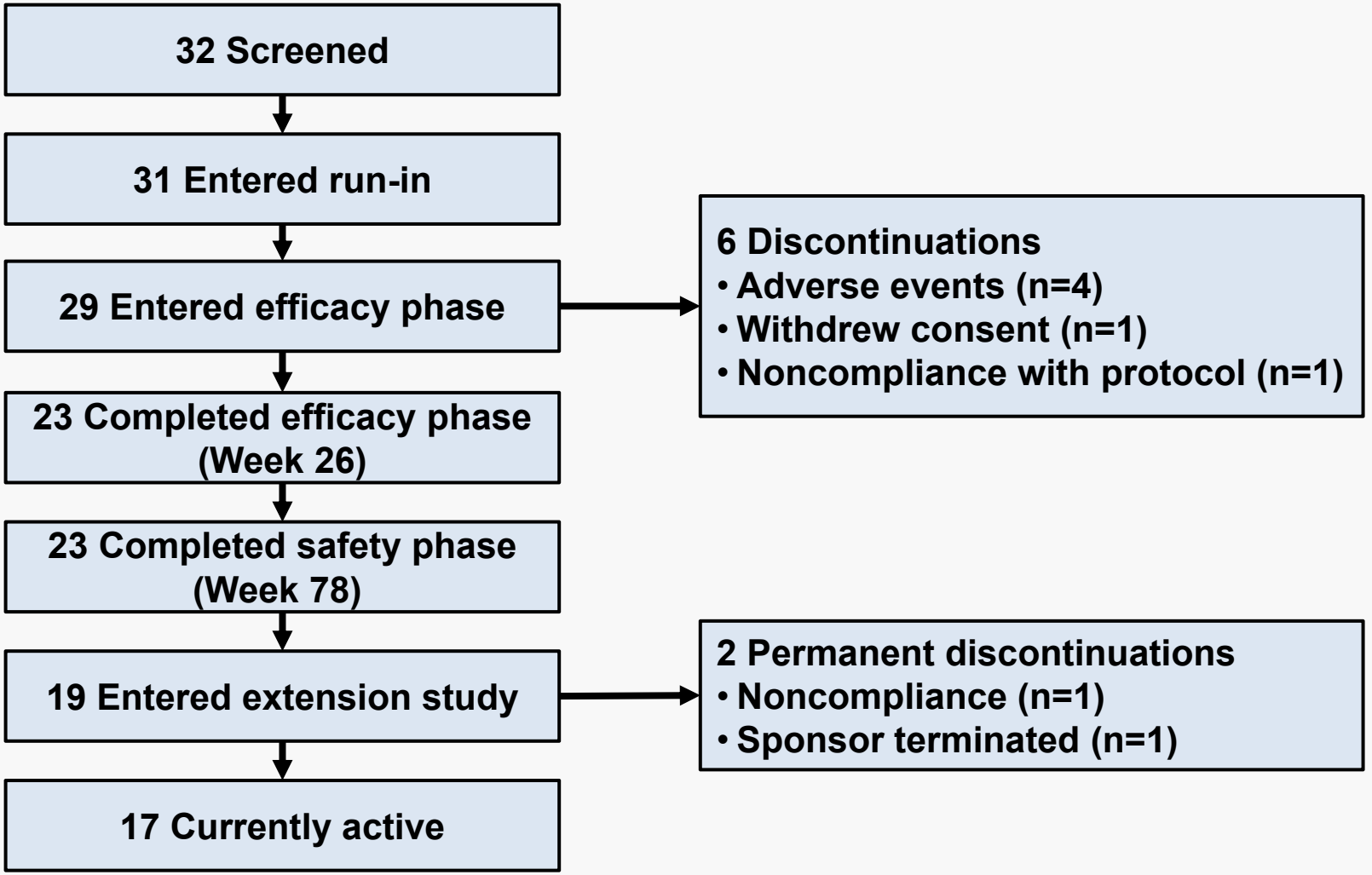
- Patients must have been diagnosed as having functional HoFH defined by at least one of the following criteria:

  1. Documented functional mutation(s) in both LDL receptor alleles or alleles of other genes known to affect LDL receptor functionality

  2. Skin fibroblast LDL receptor activity <20% normal

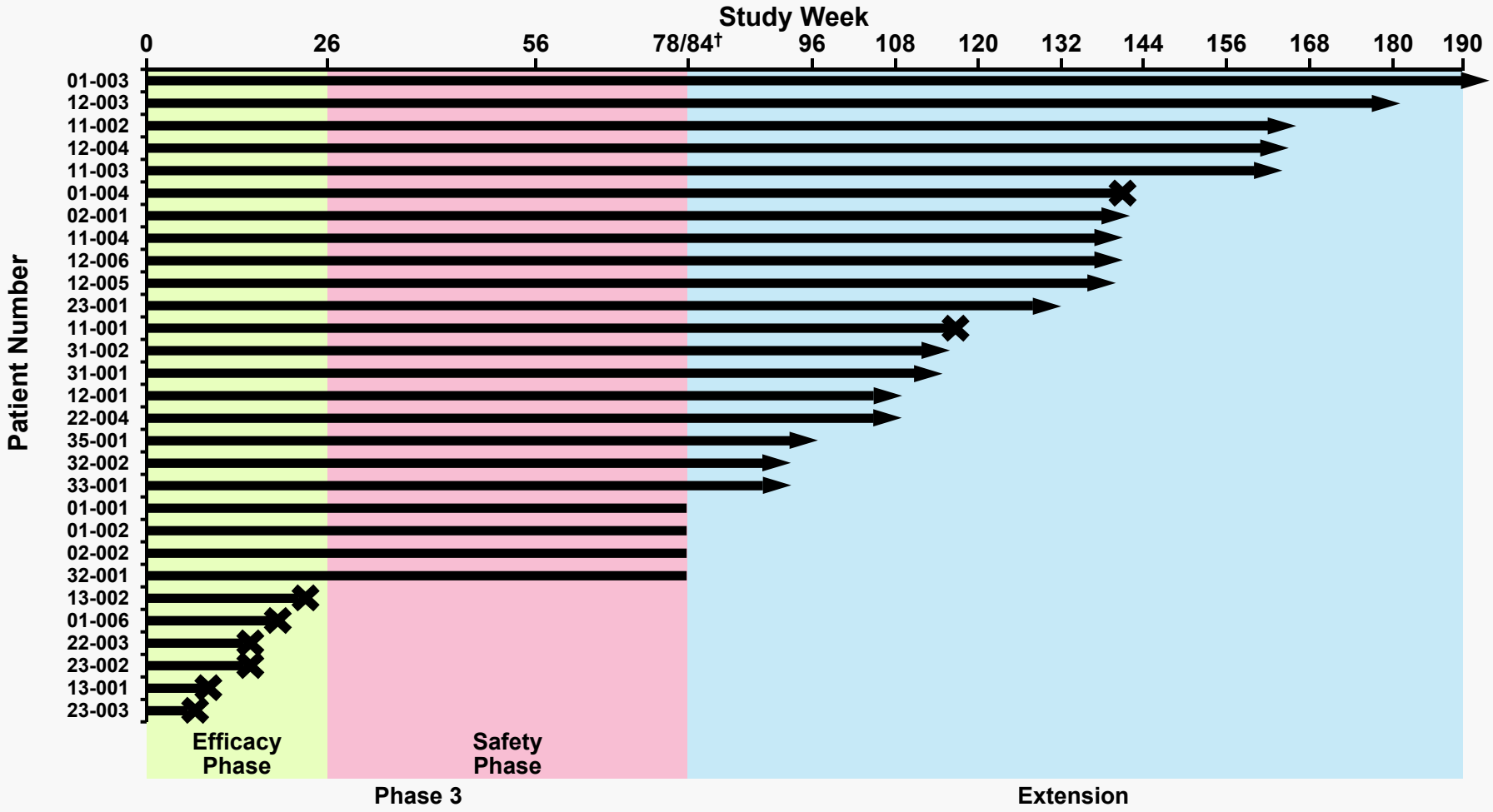
  3. Untreated TC >500 mg/dL AND TG <300 mg/dL AND both parents have documented TC >250 mg/dL

Patient Disposition in Phase 3



CE-045

Individual Patient Time Course in Phase 3 and Extension Study



† The week 84 was only for subjects that did not enroll in the extension study.

CE-046

Patient Demographic and Baseline Characteristics in Phase 3

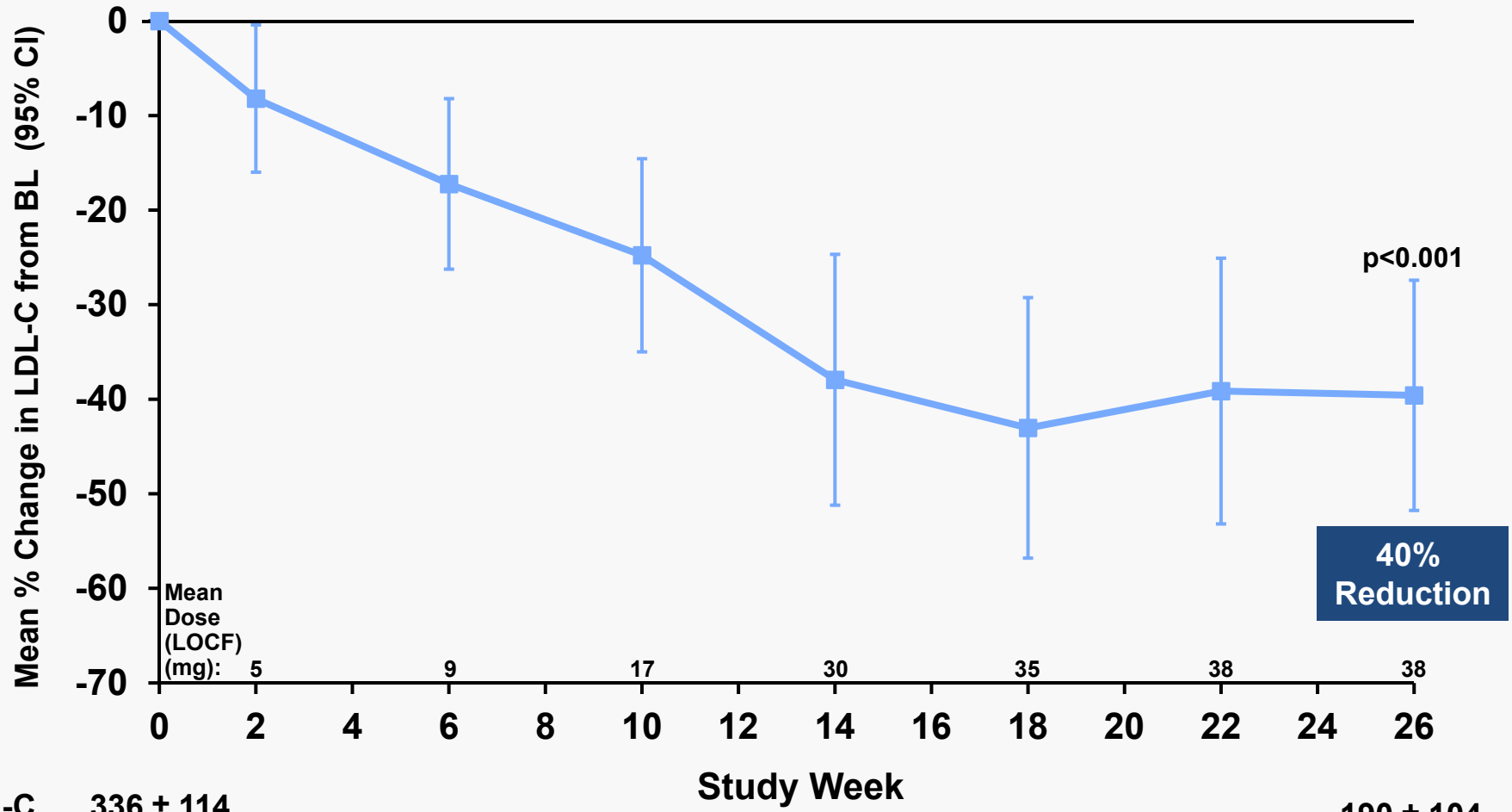
Parameter	Value	Min, Max
Mean Age (years)	30.7± 10.6	18.0, 55.0
Gender (M/F)	16/13	
Race (Caucasian/Asian/Black/Other)	25/2/1/1	
Mean (SD) BMI (kg/m^2)	25.8 ± 5.4	19.3, 41.3
Mean (SD) baseline LDL-C (mg/dL)	336 ± 114	152, 564
Receiving apheresis, n (%)	18 (62%)	
Receiving lipid lowering drugs (LLDs), n (%) Statins Ezetimibe (all in combination with statins)	27 (93%) 27 (93%) 22 (76%)	
Genetic diagnosis	29 (100%)	

CE-047

Cardiovascular History of Patients in Phase 3

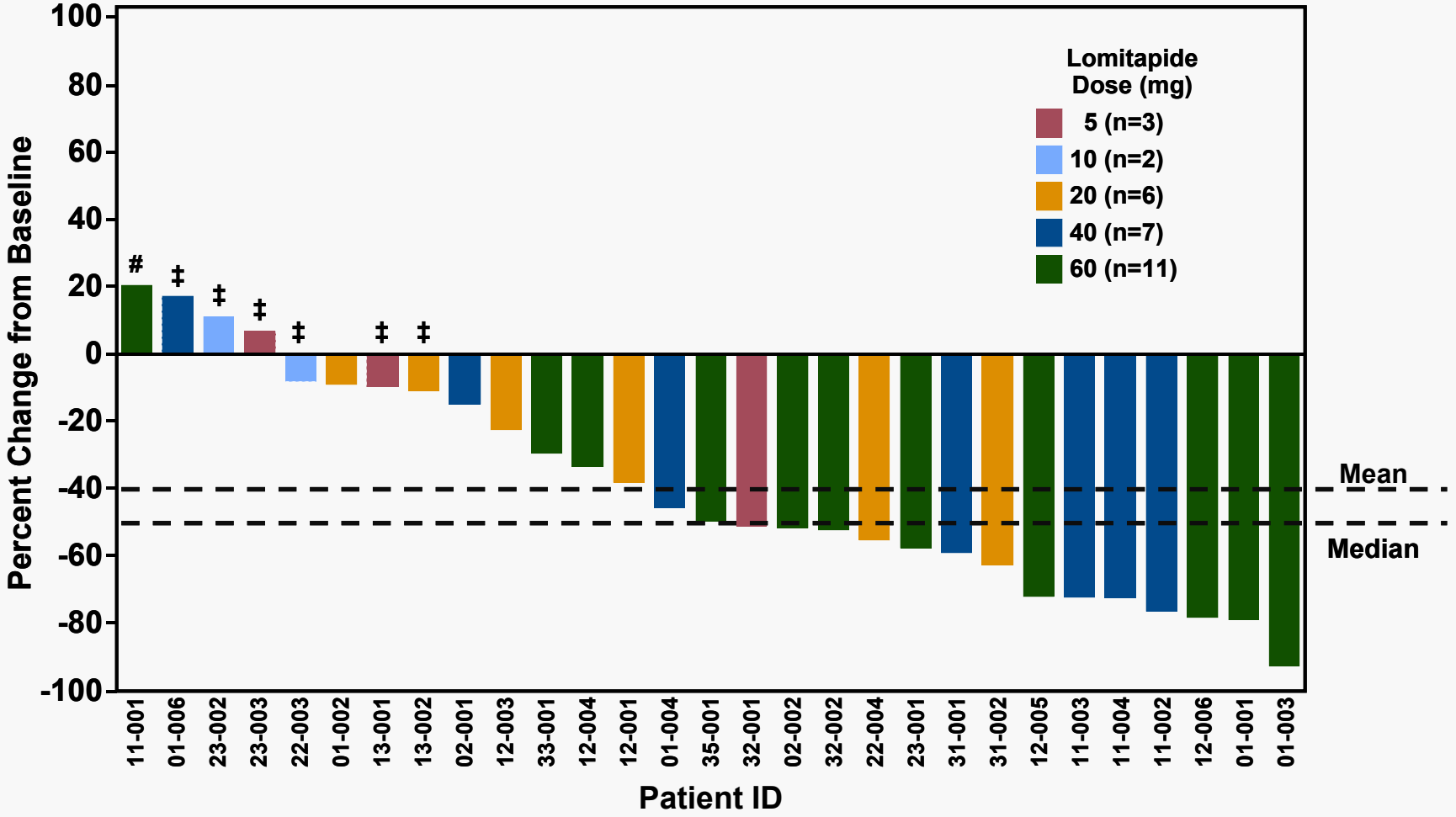
- 27/29 patients had a history of CVD at baseline
- 10 (35%) of 29 patients had undergone CABG surgery
  - 5 of these patients were ≤21 years of age
  - 3 patients under the age of 8 at the time of open-heart surgery
  - 3 patients had undergone multiple CABG procedures
- Coronary angioplasty was performed in 3 patients (10%)
- Aortic valve replacement in 3 patients (10%)
- Mitral valve replacement or repair in 3 patients (10%)

LDL-C Reduced by 40% at Week 26 in Phase 3
(ITT with LOCF, N=29)



CE-049

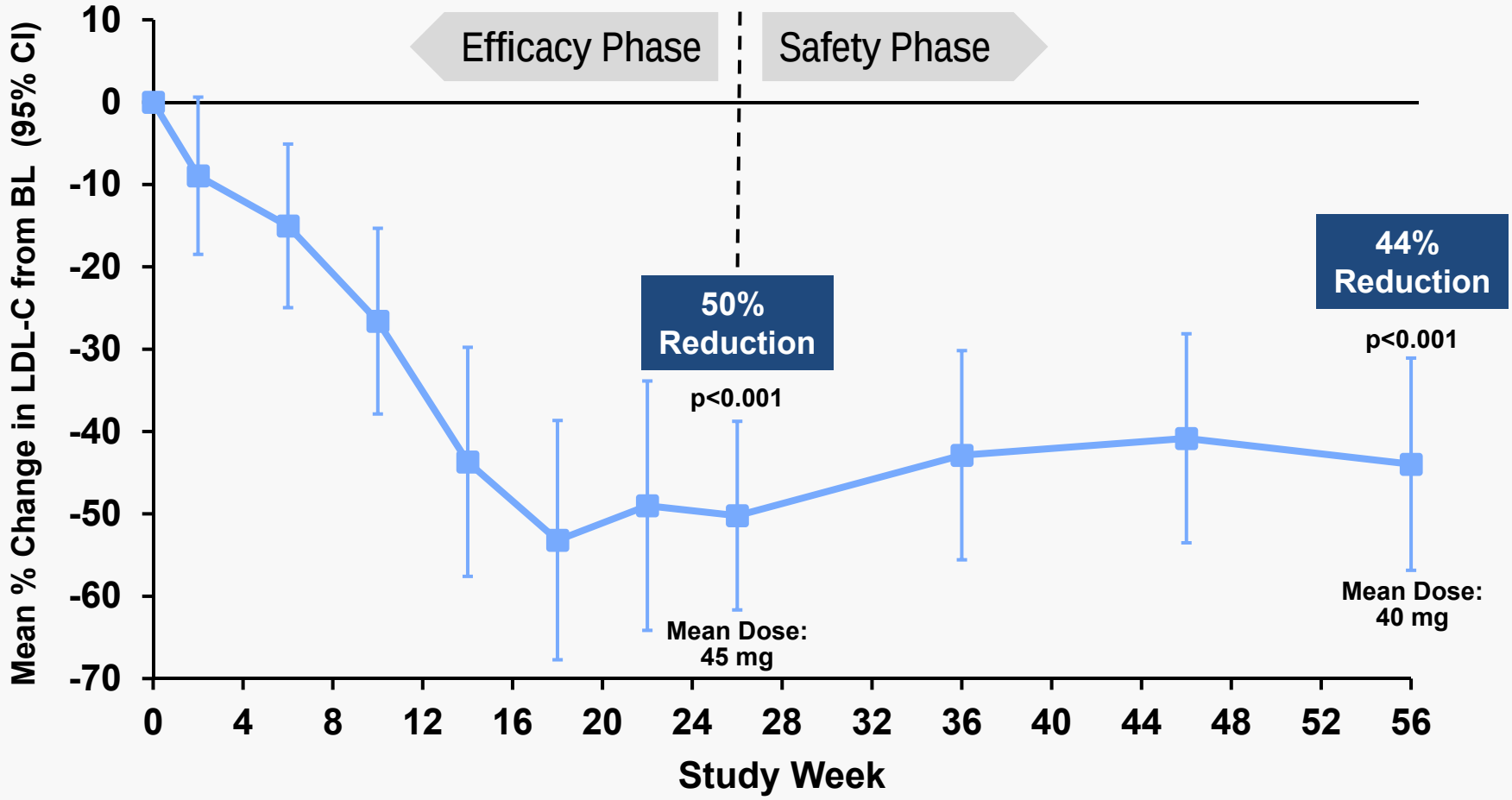
Percent Change in LDL-C at Week 26 by Patient in Phase 3
(ITT with LOCF, N=29)



Patient was a responder at later time points during the study.
‡ Patients discontinued from the study.

CE-050

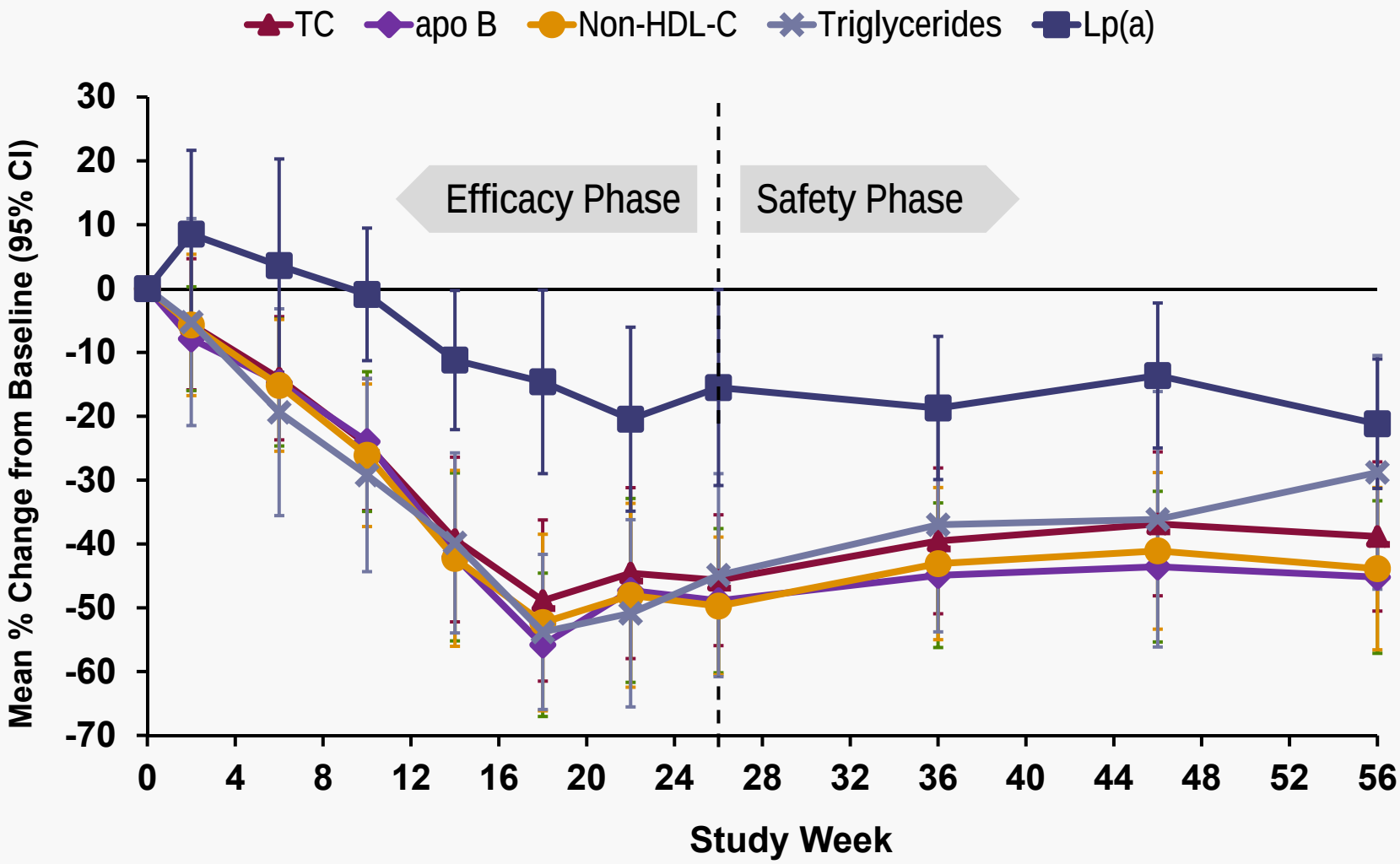
Efficacy Was Durable in Phase 3
(Completer Population, N=23)



LDL-C (mg/dL):	352 ± 116 Baseline	168 ± 96 Week 26	199 ± 123 Week 56

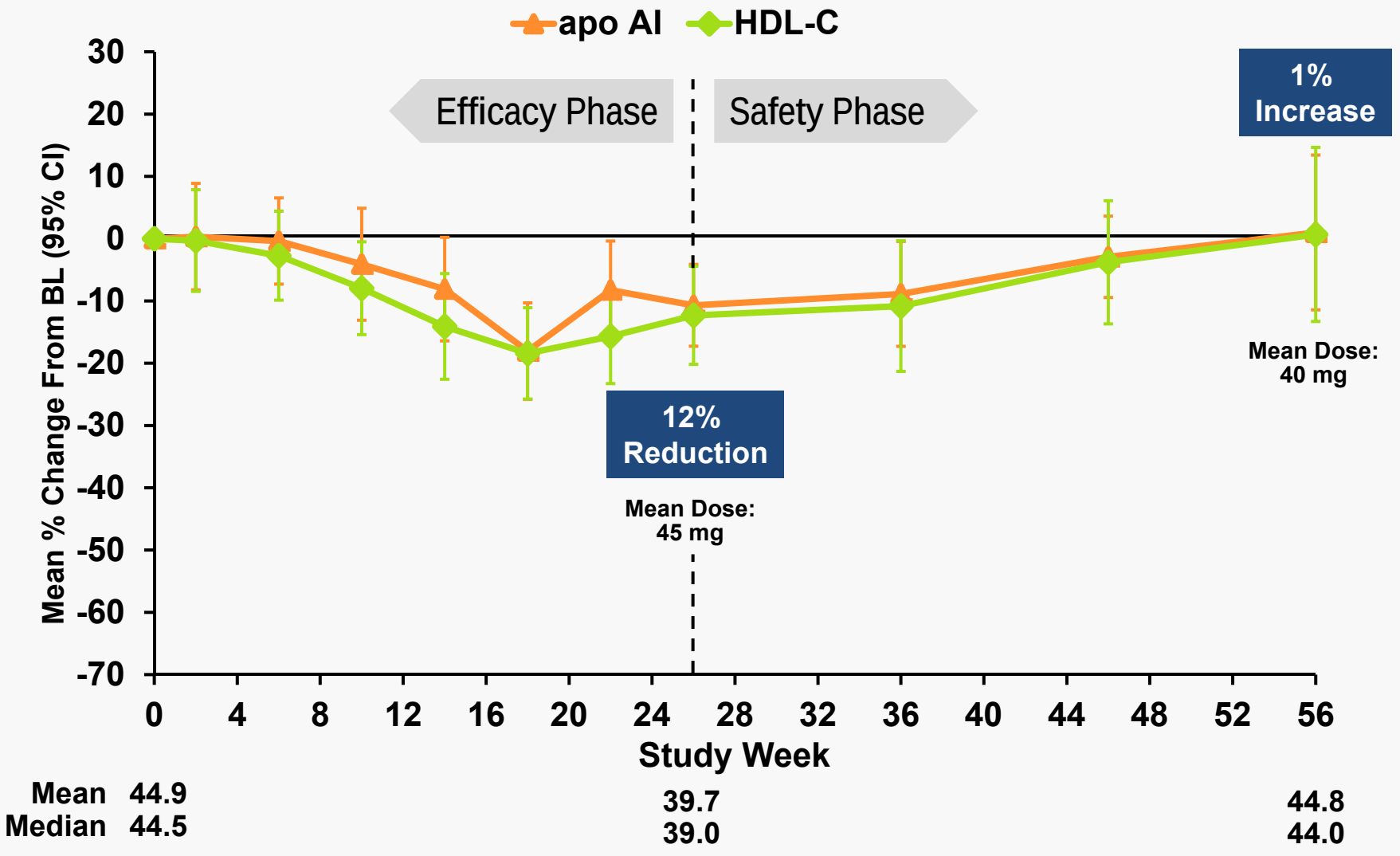
CE-051

Secondary Lipid Parameters Declined Through Week 56 in Phase 3
(Completer Population, N=23)



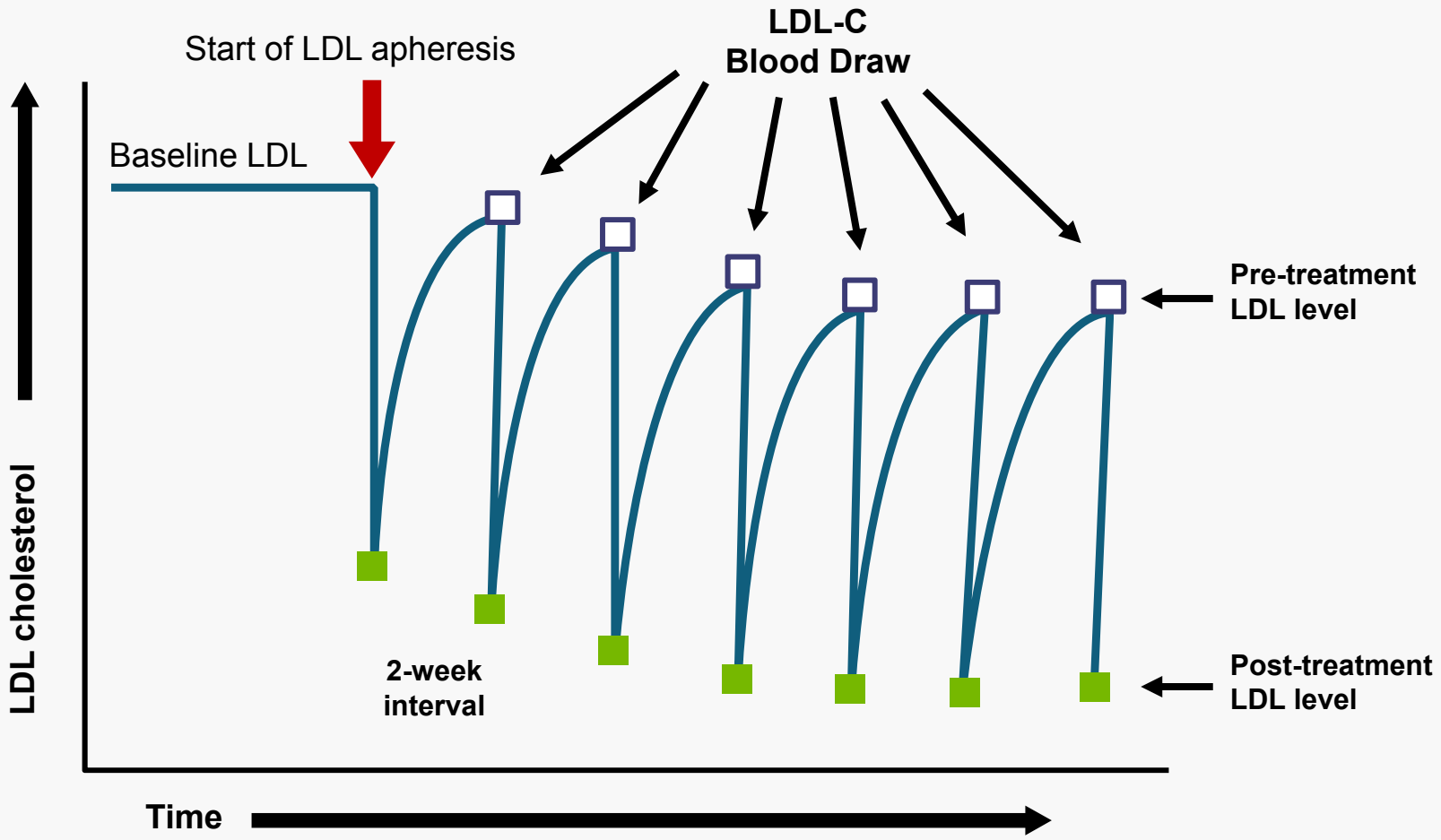
CE-052

Pharmacologic MTP Inhibition Did Not Permanently Affect HDL-C Levels in Phase 3
(Completer Population, N=23)



CE-053

LDL-C Was Assessed at the Peak of the Rebound Curve in Phase 3



Thompsen J & Thompson PD. *Atherosclerosis*. 2006;189: 31-8.

CE-054

Apheresis Did Not Impact Efficacy of Lomitapide in Phase 3

Lipid Parameter	Did not Receive Apheresis N=11 LSM (SE)	Received Apheresis N=18 LSM (SE)	Estimated Difference (SE) (Apheresis vs. No Apheresis)	p-value
LDL-C	-55.09 (8.94)	-47.99 (7.51)	7.10 (11.70)	0.5448
Total cholesterol	-49.81 (8.15)	-43.81 (6.86)	6.00 (10.68)	0.5753
apo B	-53.20 (8.22)	-47.88 (6.92)	5.31 (10.83)	0.6246
Non-HDL-C	-54.16 (8.89)	-48.25 (7.47)	5.90 (11.65)	0.6132

Results from a mixed-model repeated-measures analysis.

LDL-C Treatment Goal Attainment in Phase 3

Time Point	LDL-C	
	<100 mg/dL	<70 mg/dL
Baseline (N=29)	0 (0%)	0 (0%)
At any time on treatment with lomitapide (N=29)	16 (55%)	9 (31%)

- ACC AHA Treatment Guidelines for patients:
  - At high risk: <100 mg/dL
  - At very high risk: <70 mg/dL

CE-056

Alterations in Apheresis Treatment During the Safety Phase of Phase 3

- 13 (57%) patients were receiving apheresis at the start of the safety phase
- 6 patients had changes to their apheresis regimen

	Patients Reducing Frequency of Apheresis Treatments	Patients Stopping Apheresis
Safety phase (from Week 26 to Week 56 [NDA submission])	**1**	**3**
From Week 56-78	**2**	**0**

Phase 3 Efficacy Conclusions

- Patients with HoFH demonstrated a mean percent reduction in LDL-C from baseline of 40% (ITT) and 50% (completers) at Week 26 on maximum background therapy
- Reduction in LDL-C was maintained over 56 weeks
- Treatment with lomitapide produced significant reductions in apo B, total cholesterol, and non-HDL cholesterol that were maintained over 56 weeks
- At any time on treatment with lomitapide 16 (55%) had LDL-C <100 mg/dL and 9 (31%) <70 mg/dL

Evidence of Substantial LDL-C Lowering with Lomitapide

- Study design elements control potential confounders (diet, LLTs)
- Evidence of stable LDL-C during run-in phase
- LDL-C is an objective endpoint (no assessment bias)
- Magnitude and time course of observed effect
- Evidence from Phase 2 HoFH Study - return to baseline after D/C of lomitapide
- Supportive efficacy from Phase 2 / Phase 1

Lomitapide Safety

Patient Exposure During Lomitapide Clinical Development Program

- 1135 subjects treated across the lomitapide program
  - 915 received oral lomitapide
- Lomitapide administered 1 mg to 200 mg
- The majority of subjects (844 of 1135) were enrolled in placebo and/or active-controlled trials
- Duration:
  - Phase 1 and 2 brief exposure (up to 12 weeks)
  - 23 patients with HoFH: 1.5 years
    - 19 patients (active extension study): up to 4 years

Adverse Events in ≥5% Subjects in the Elevated LDL-C and Other CV Risk Factors Study Pool (Safety Population, N=598)

MedDRA Body System	Lomitapide Dose Group: Escalated (5-10 mg) N=77 n (%)	Lomitapide Dose Group: Mid-Dose (2.5-10 mg) N=343 n (%)	Lomitapide Dose Group: High Dose (25-100 mg) N=62 n (%)	Total Lomitapide N=482 n (%)	Placebo N=116 n (%)
Gastrointestinal	40 (51.9)	251 (73.2)	51 (82.3)	342 (71.0)	34 (29.3)
Investigations	25 (32.5)	54 (15.7)	8 (12.9)	87 (18.0)	4 (3.4)
Infections	11 (14.3)	59 (17.2)	4 (6.5)	74 (15.4)	19 (16.4)
General disorders	4 (5.2)	47 (13.7)	12 (19.4)	63 (13.1)	5 (4.3)
Nervous system	4 (5.2)	43 (12.5)	10 (16.1)	57 (11.8)	19 (16.4)
Musculoskeletal	5 (6.5)	40 (11.7)	9 (14.5)	54 (11.2)	12 (10.3)
Respiratory	3 (3.9)	27 (7.9)	2 (3.2)	32 (6.6)	5 (4.3)

Adverse Events in >15% of HoFH Patients in Phase 3
(Safety Population, N=29)

MedDRA Body System	Total Patients (N=29) n (%)
Gastrointestinal	27 (93.1)
Infections	17 (58.6)
Investigations	15 (51.7)
General disorders	12 (41.4)
Injuries	10 (34.5)
Musculoskeletal	11 (37.9)
Cardiac	7 (24.1)
Nervous system	7 (24.1)
Respiratory	7 (24.1)
Metabolism and nutrition	6 (20.7)
Psychiatric	5 (17.2)

CS-063

Patient 11-004: SAE “Hepatotoxicity”

- 55 year old Caucasian male with HoFH
- Elevated ALT/AST at baseline (prior to lomitapide)
- Liver biopsy – mild steatosis only
- Enrolled in Phase 3 Feb 2009, completed and enrolled in the extension study in Oct 2010
- Lomitapide (MTD=40 mg) administered for 2.5 years with maximum ALT to 4.2x ULN
- 2.5 years on lomitapide – ALT 24x ULN (asymptomatic)
- Recently prescribed clarithromycin and agomelatine

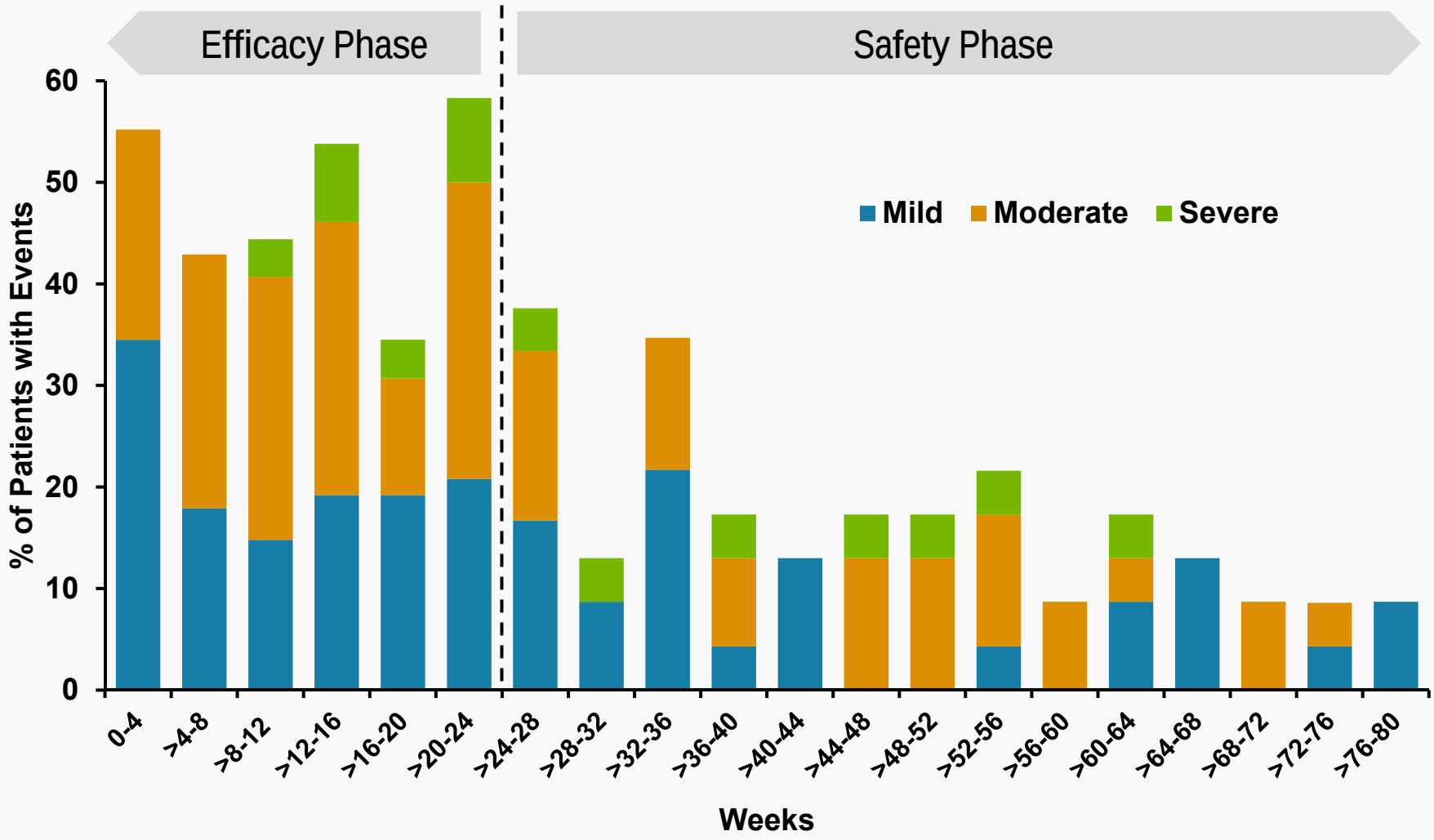
Patient 11-004: SAE "Hepatotoxicity"

- All drugs and lomitapide discontinued
- ALT 2.4x ULN and AST normal after 2 weeks
- 2nd liver biopsy
  - Mild steatosis (increased from last report) with no inflammatory activity or fibrosis
- Restarted lomitapide in Mar 2012 without complications
  - ALT ≤ 2x ULN, AST & bilirubin normal

Gastrointestinal Effects in Phase 3

- Gastrointestinal related adverse events
- Fat soluble nutrients
- Weight loss

Gastrointestinal Adverse Events in Phase 3
(Safety Population, N=29)

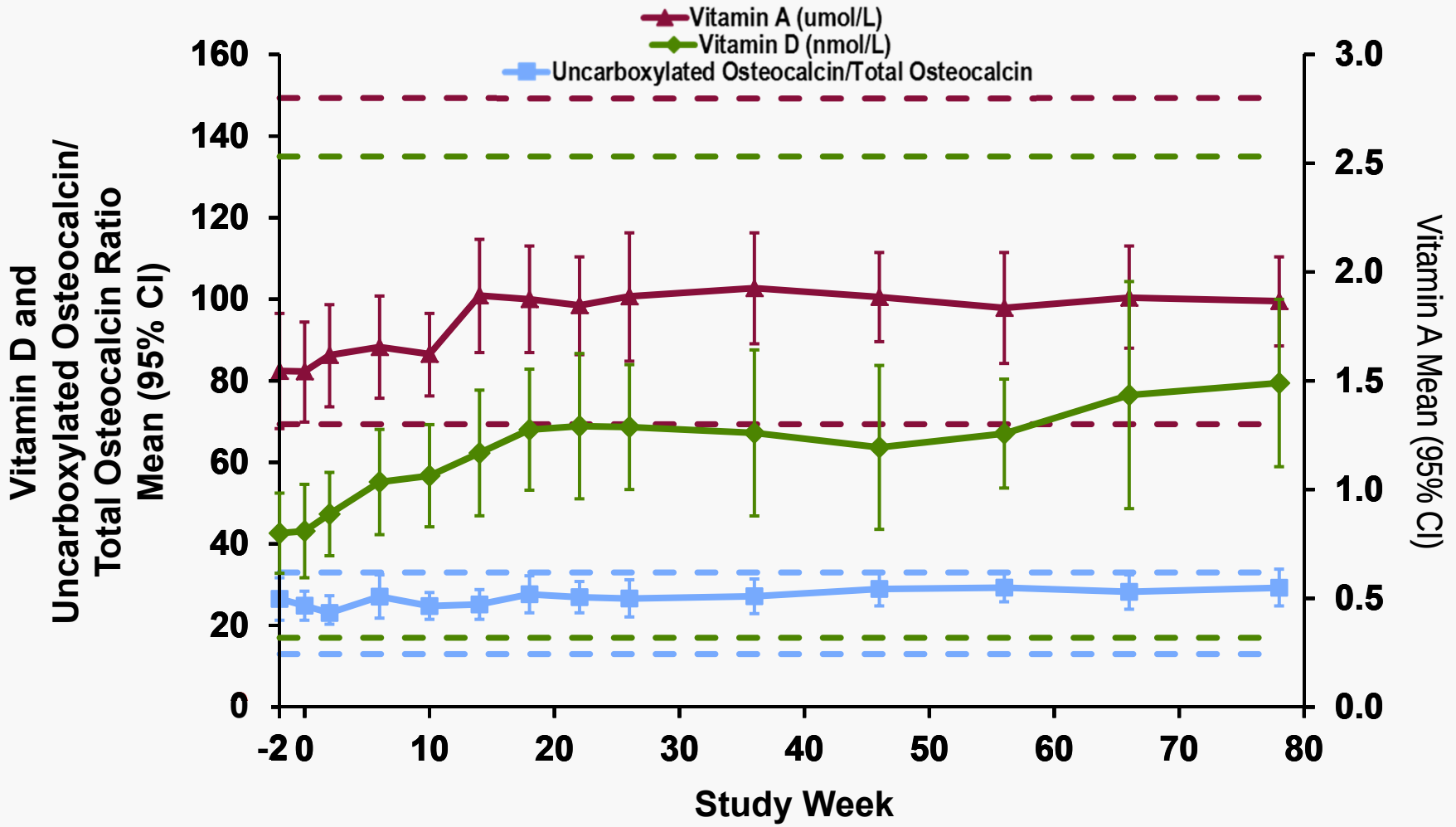


CS-067

Absorption of Fat Soluble Nutrients

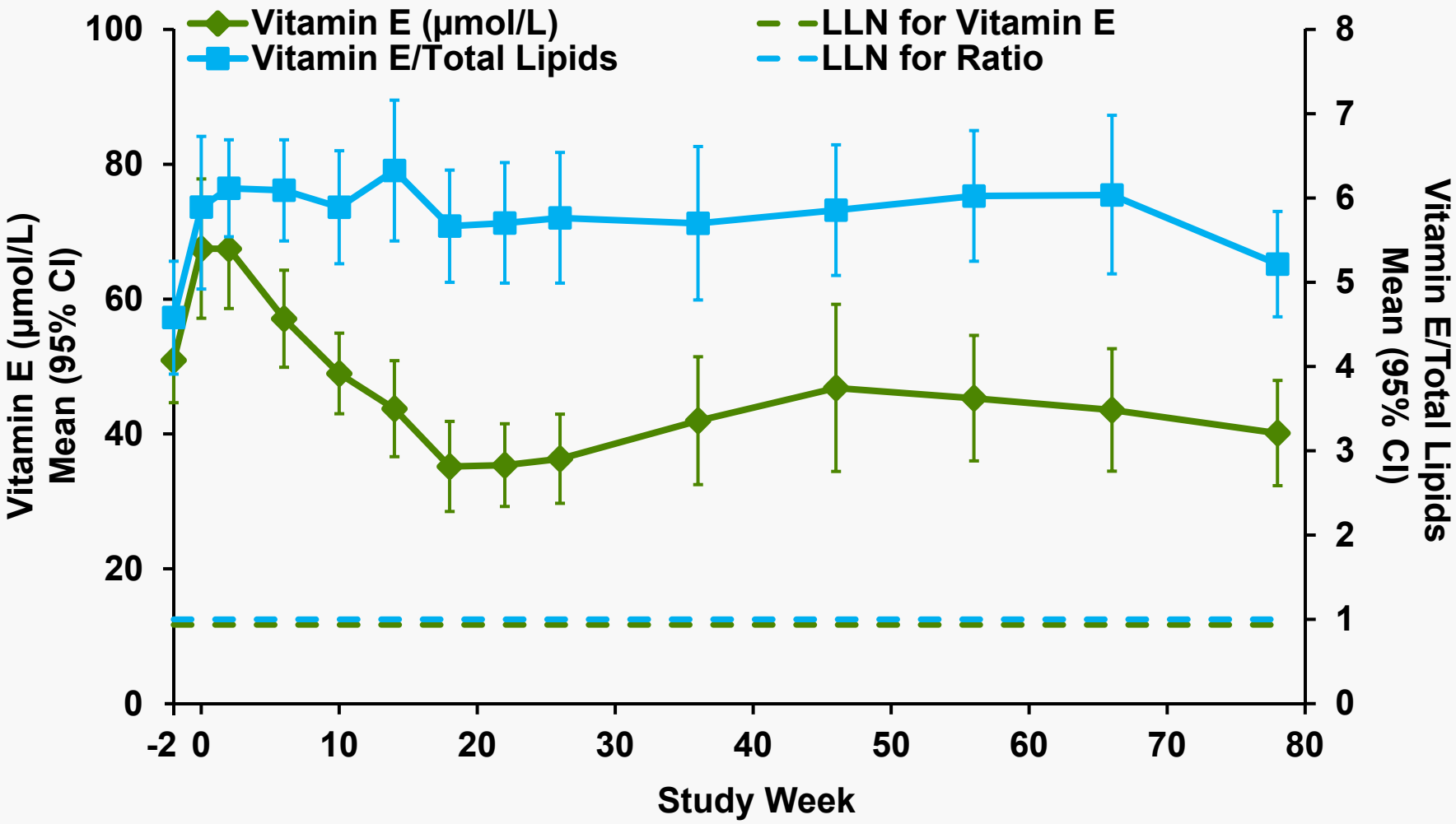
- Patients instructed to supplement diet with vitamin E & essential fatty acids (linoleic acid, EPA, ALA and DHA) based on Phase 2 HoFH study
- No evidence of net malabsorption of fat soluble nutrients

Vitamins A and D Increased and Vitamin K Stable in Phase 3
(Safety Population, N=29)



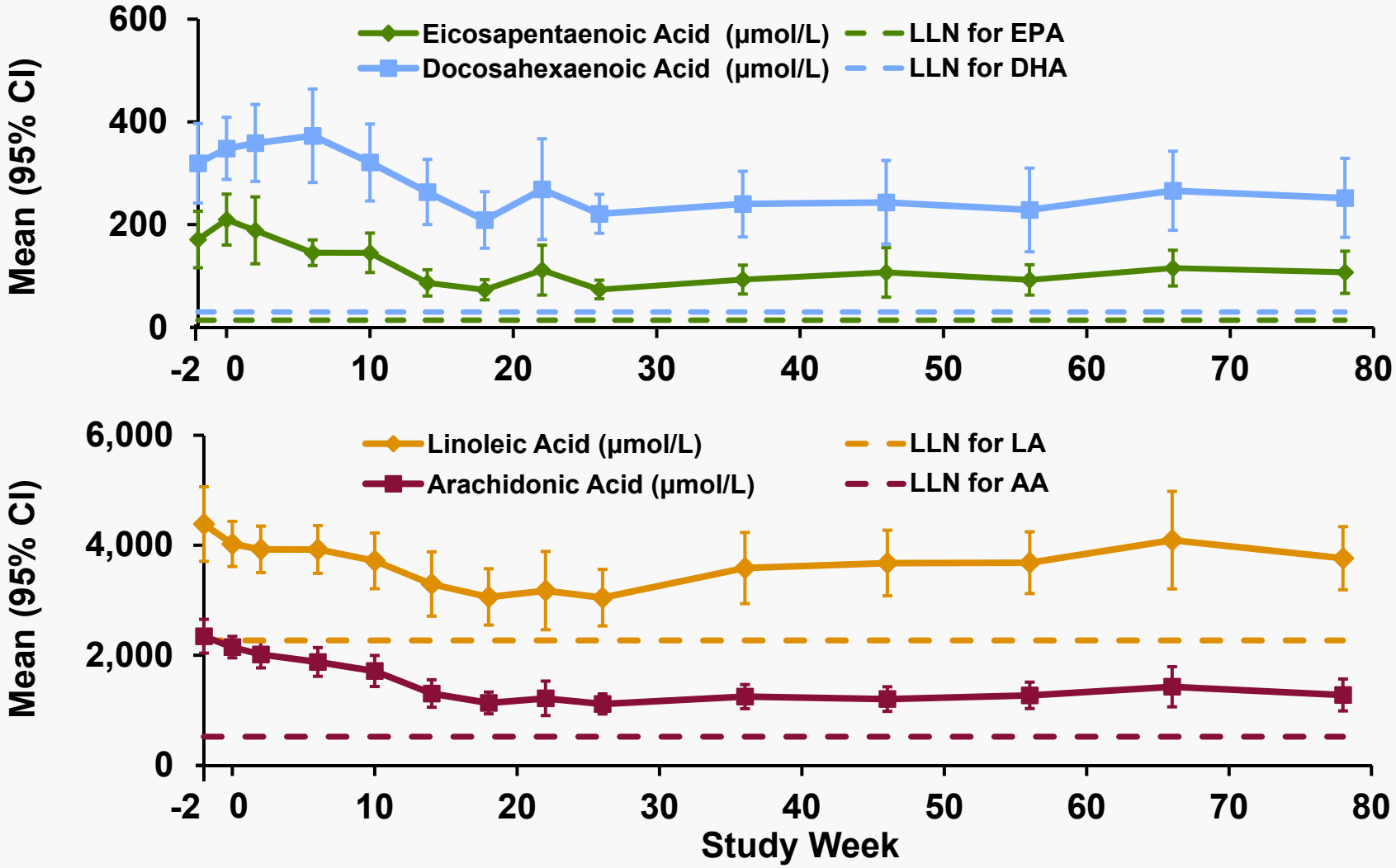
CS-069

Mean Vitamin E Levels in Phase 3
(Safety Population, N=29)



CS-070

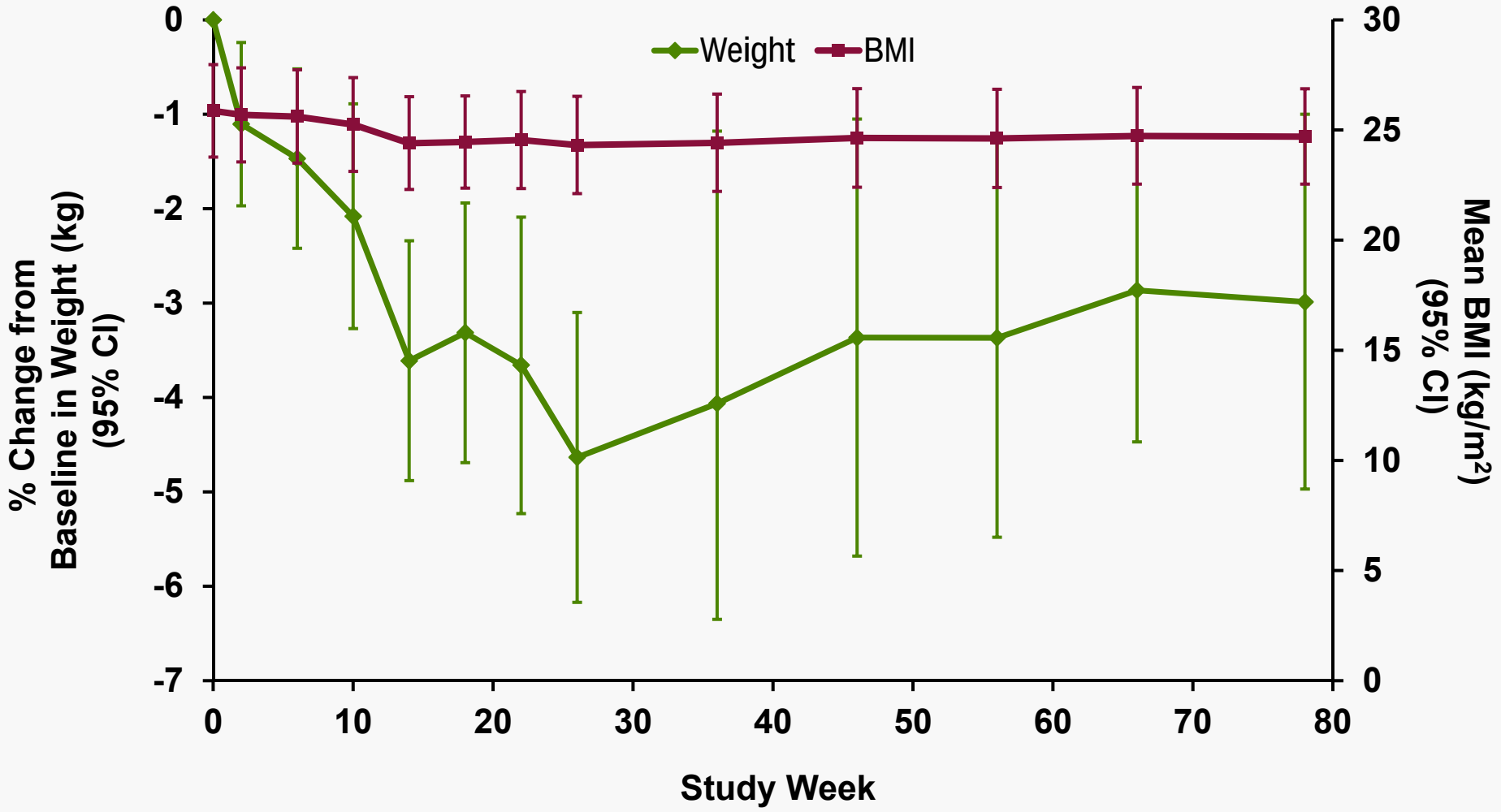
Mean Essential Fatty Acids in Phase 3
(Safety Population, N=29)



CS-071

Mean % Change in Weight and Mean Absolute BMI in Phase 3

(Safety Population, N=29)



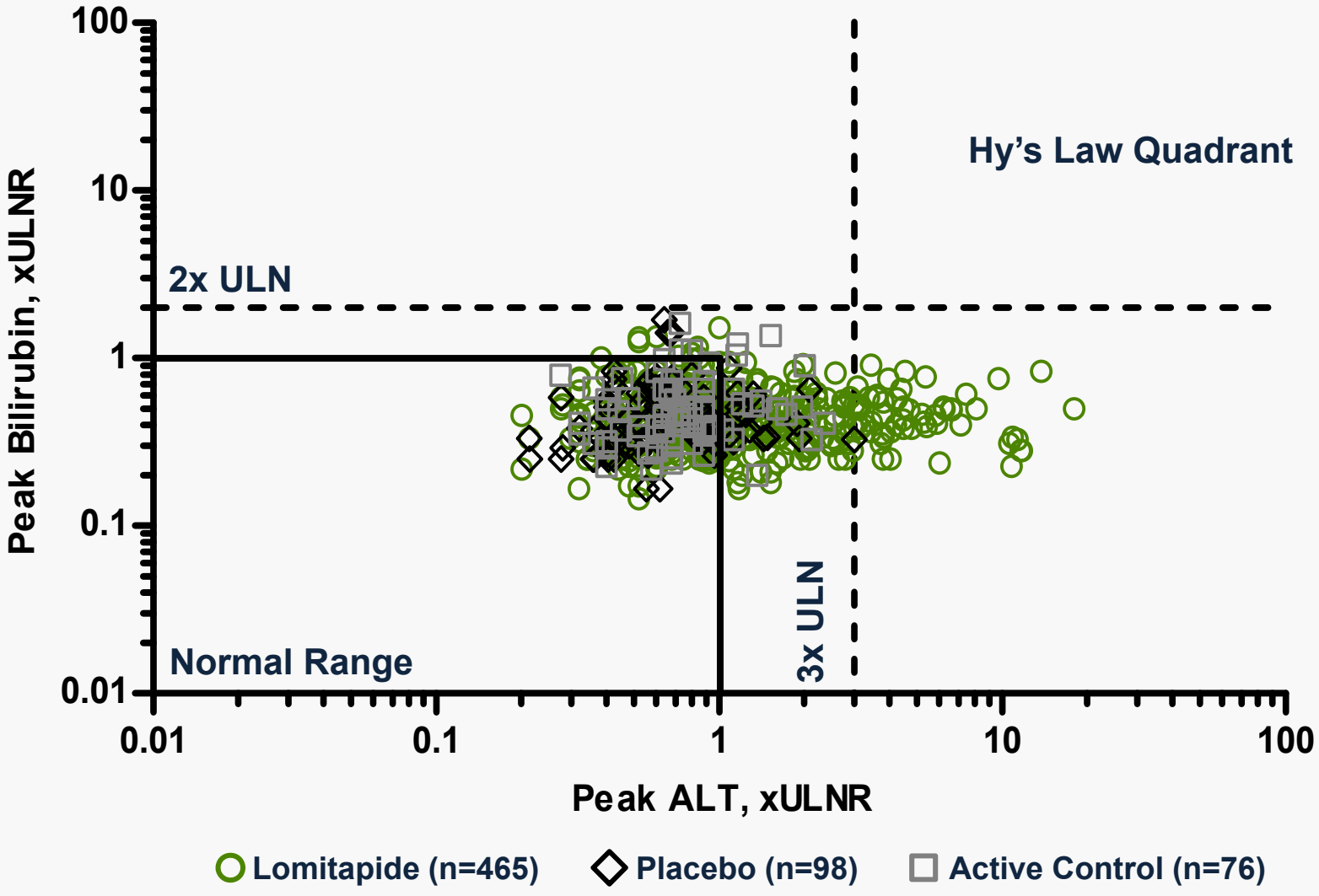
CS-072

Hepatic Aminotransferases

- In phase 1 & 2 studies:
  - ALT and/or AST elevations >3x ULN were observed
  - No concomitant significant elevations in bilirubin

Peak ALT Value with Corresponding Bilirubin

Elevated LDL Cholesterol and Other Risk Factors Pool (Safety Population, N=639)

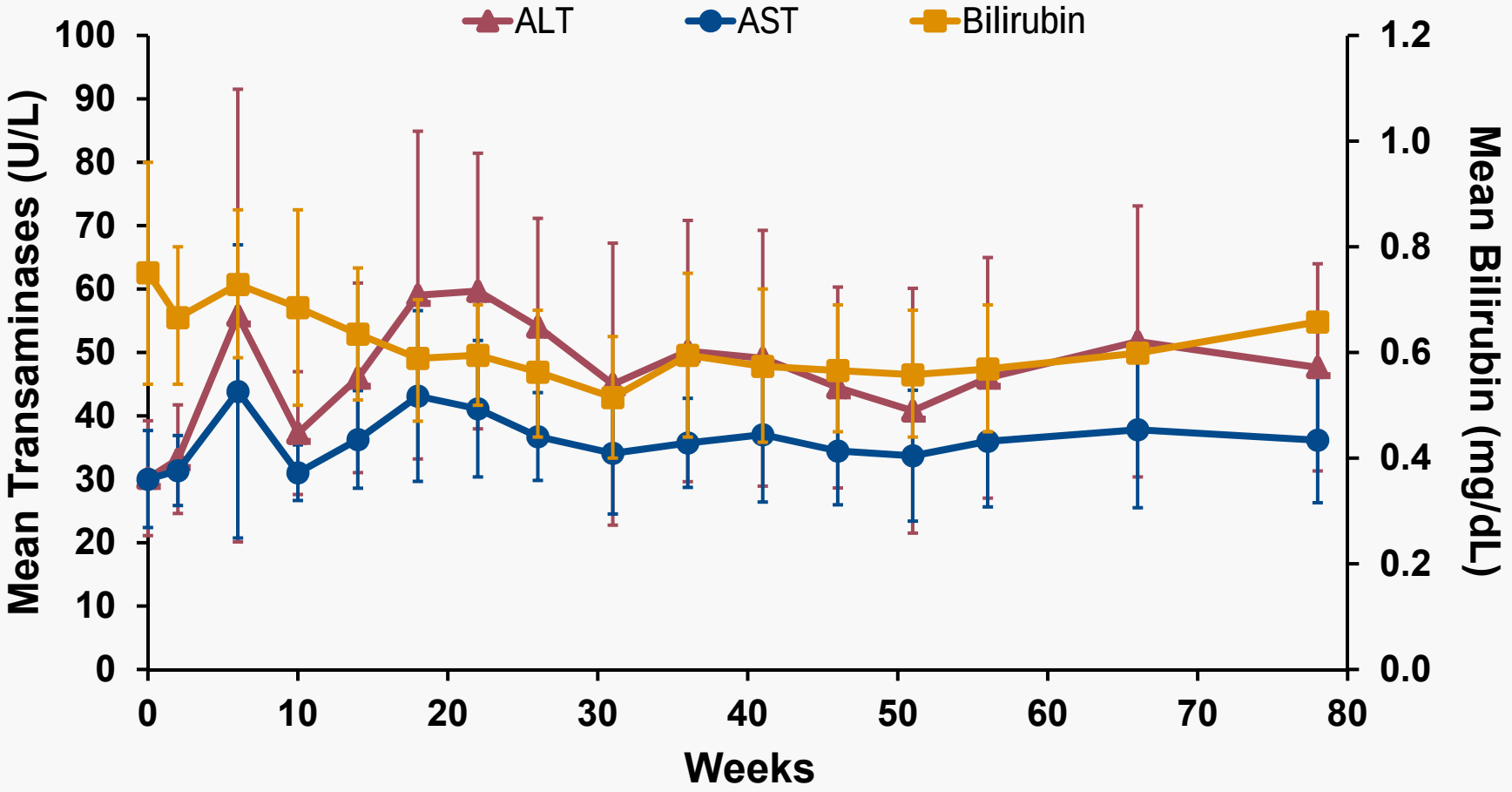


CS-074

Hepatic Safety in Phase 3

- Investigated the effects of lomitapide on aminotransferase levels in long term exposure
- Employed an algorithm for dose alteration based on LFT criteria (dose reduce when ALT/AST >5x- <10x ULN, treatment discontinuation ALT/AST ≥10xULN)
- DSMB was formed and reviewed all hepatic events during the trial
  - The committee did not recommend permanent discontinuation of lomitapide in any patient

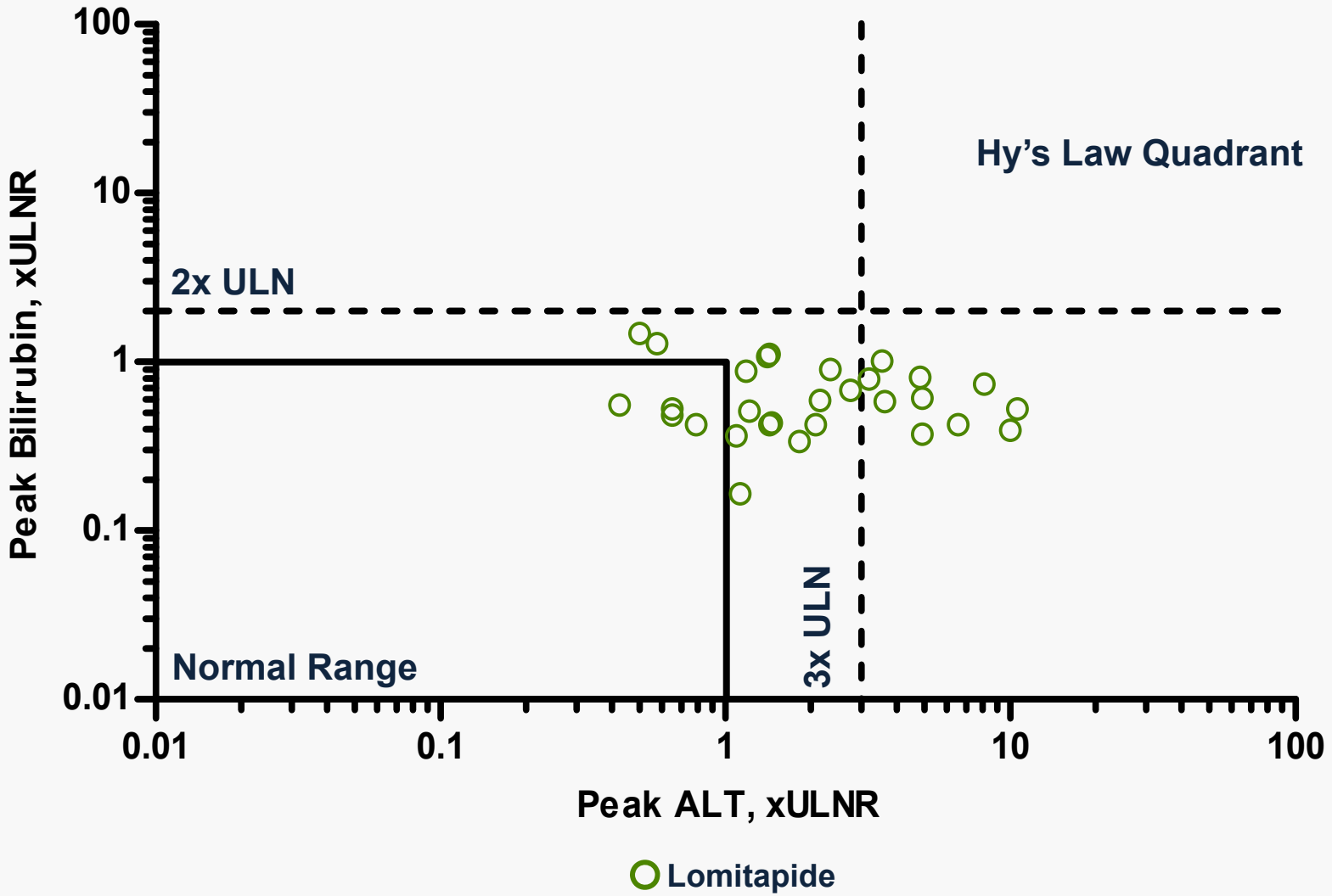
Mean Aminotransferase and Bilirubin Levels in Phase 3
(Safety Population, N=29)



ULN for ALT: females is 33 and males is 40 U/L.
ULN for AST: females is 36 and males is 43 U/L.
ULN for bilirubin (all patients) is 1.1 mg/dL.

CS-076

Peak ALT Value with Corresponding Bilirubin in Phase 3
(Safety Population, N=29)



CS-077

Peak Aminotransferase Levels in Phase 3
(Safety Population, N=29)

ALT and/or AST Levels†	Anytime During Lomitapide Treatment N=29	Efficacy Phase 0-26 Weeks N=29	Safety Phase From 26-56 Weeks N=23	Safety Phase From 56-78 Weeks N=23
≤2x ULN	15 (52%)	17 (59%)	16 (70%)	16 (70%)
>2x ULN - ≤3 x ULN	4 (14%)	4 (14%)	3 (13%)	5 (22%)
>3x ULN - ≤5 x ULN	6 (21%)	4 (14%)	2 (9%)	2 (9%)
>5x ULN - ≤10 x ULN	3 (10%)	3 (10%)	2 (9%)	0
>10x ULN - ≤20 x ULN	1 (3%)	1 (3%)	0	0

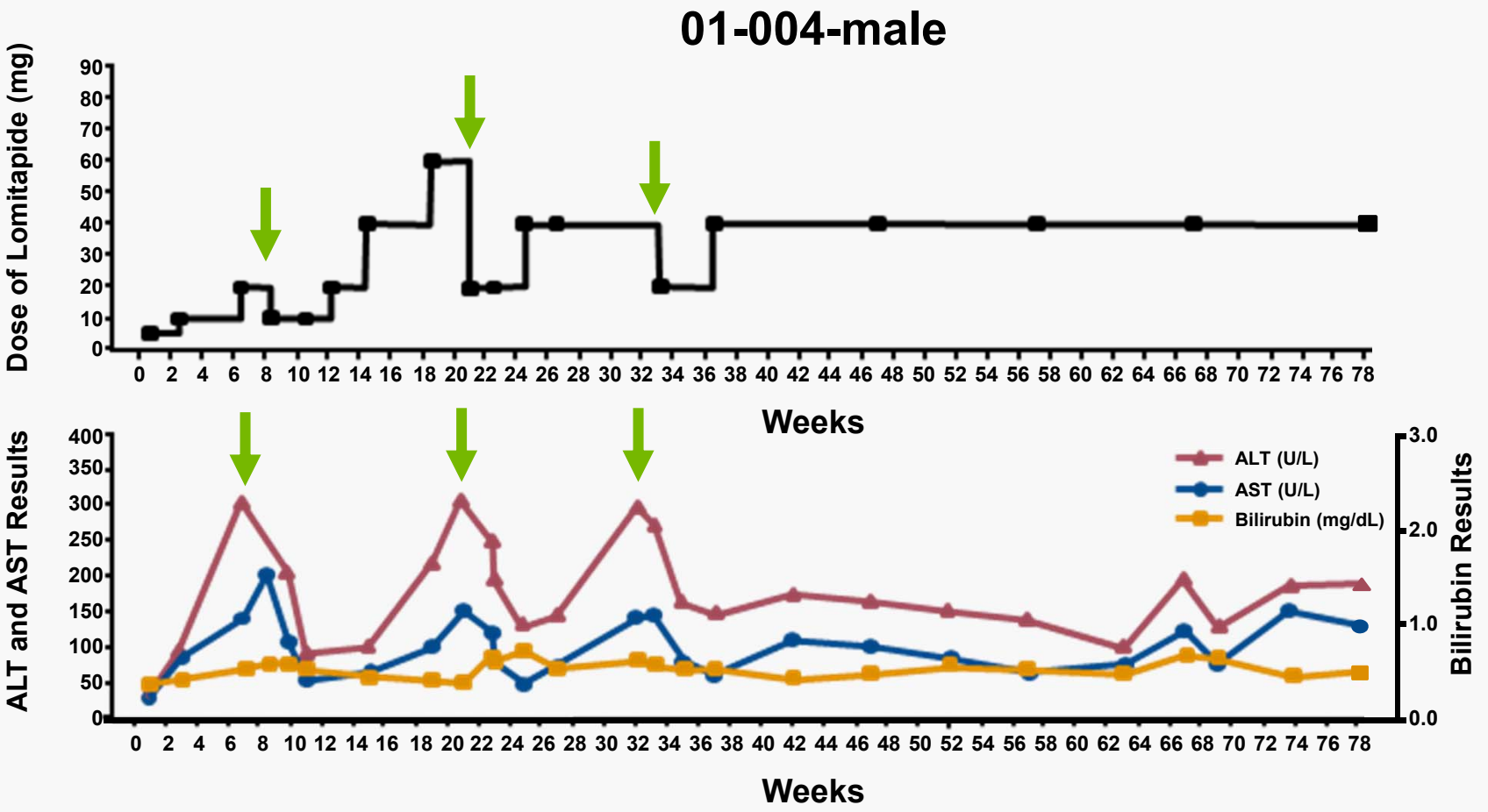
† ULN for ALT: 33 U/L (females); 40 U/L (males); ULN for AST: 36 U/L (females); 43 U/L (males).

CS-078

4 Patients with ALT/AST >5× ULN in Phase 3

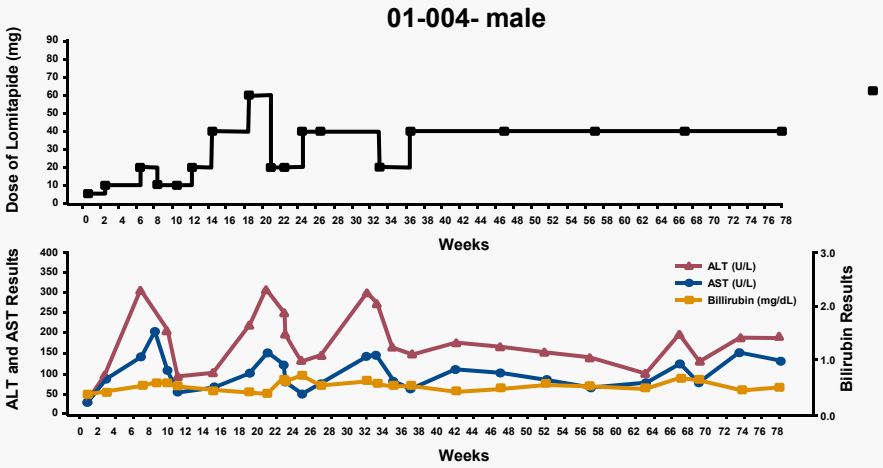
- Dose interruption or reduction used per protocol algorithm to achieve aminotransferase levels <5x ULN
- ALT/AST decreases occurred rapidly (7-28 days) following dose reduction/interruption
- 3 of 4 patients re-challenged successfully at dose associated with first ALT/AST elevation
- The fourth patient had lomitapide reduced to a lower dose
- Alcohol intake was reported outside of protocol in 3 of 4 of these patients

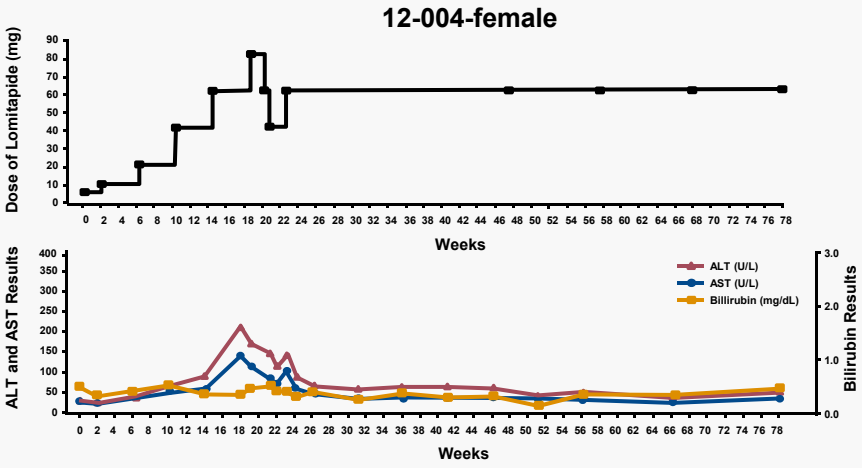
LFT Elevations Are Dose Responsive

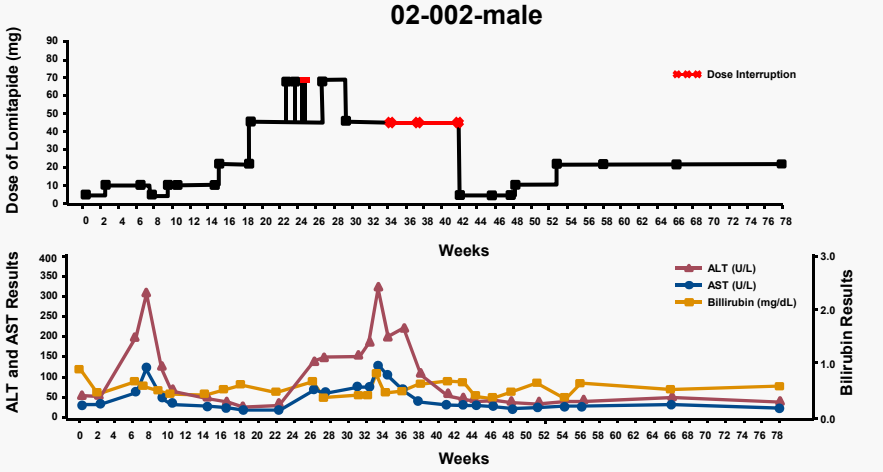


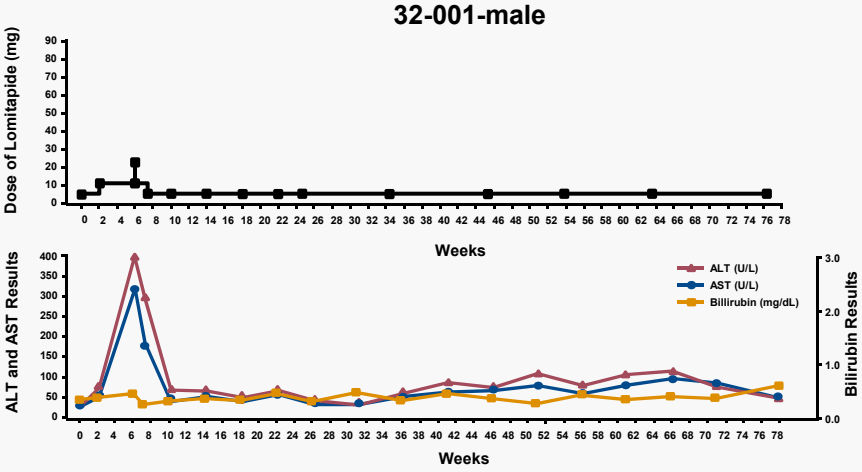
CS-080

LFT Elevations Are Dose Responsive





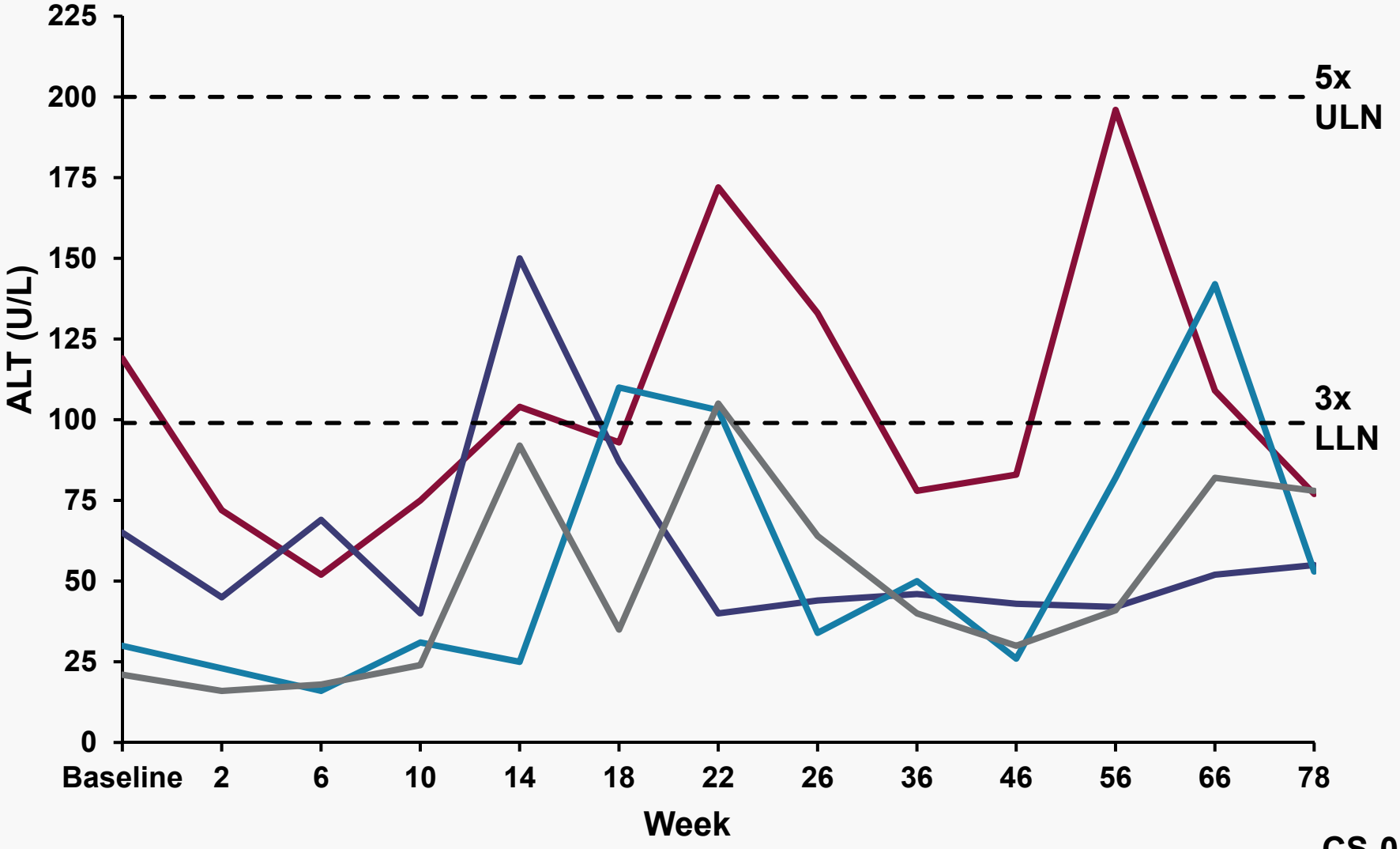




ULN for bilirubin (all patients) is 1.1 mg/dL; ULN for ALT: females is 33 and males is 40 U/L; ULN for AST: females is 36 and males is 43 U/L

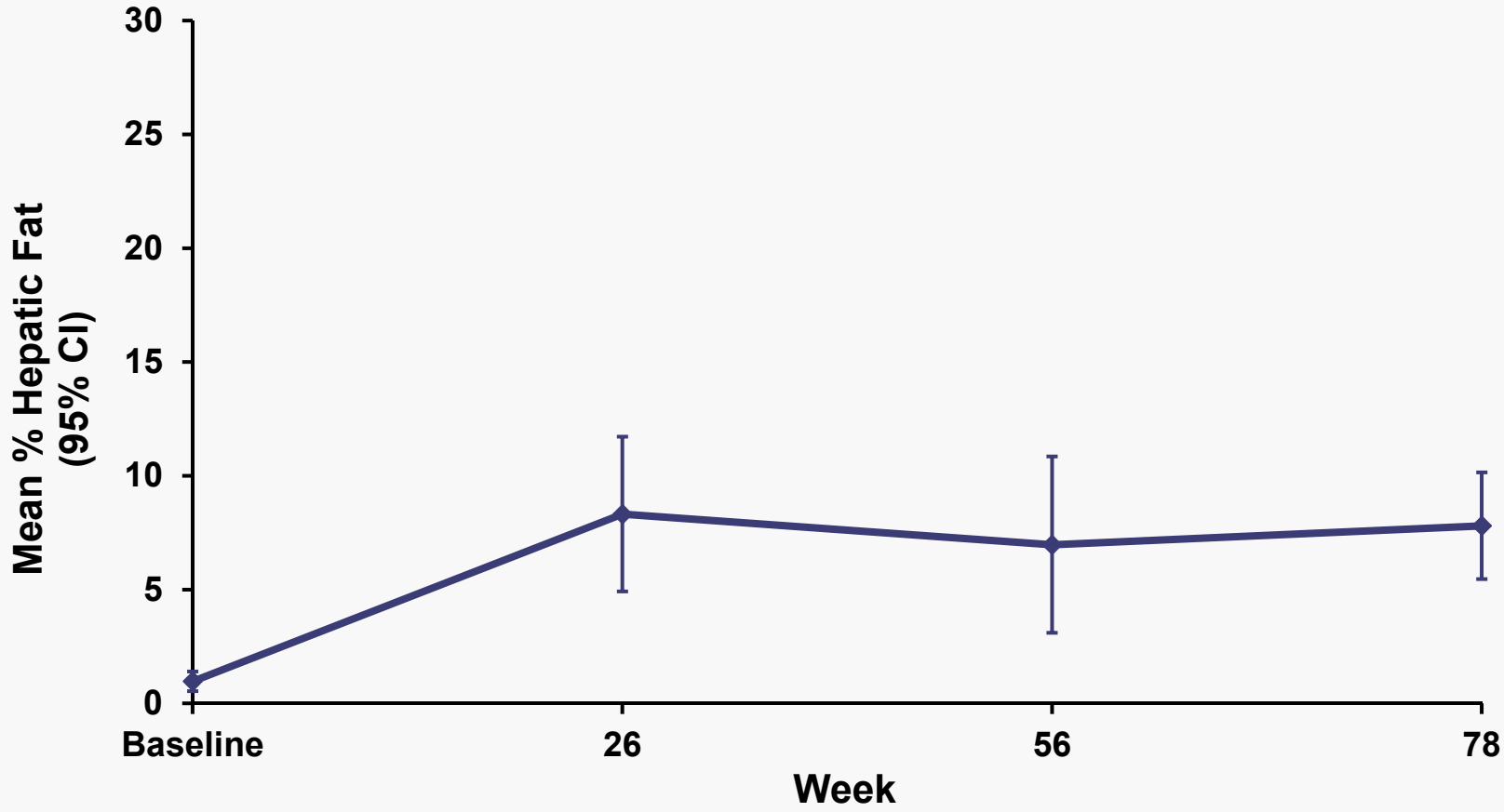
CS-081

ALT Elevations (>3 - ≤5x ULN) May Resolve Without Dose Reduction



CS-082

Hepatic Fat Content as Measured by MRS in Phase 3
(Safety Population)



N:	22	21	20	20
Mean (%):	0.97	8.32	6.97	7.80
Range (%):	0 to 3.8	0.8 to 33.6	0.4 to 37.7	0.6 to 19.0

CS-083

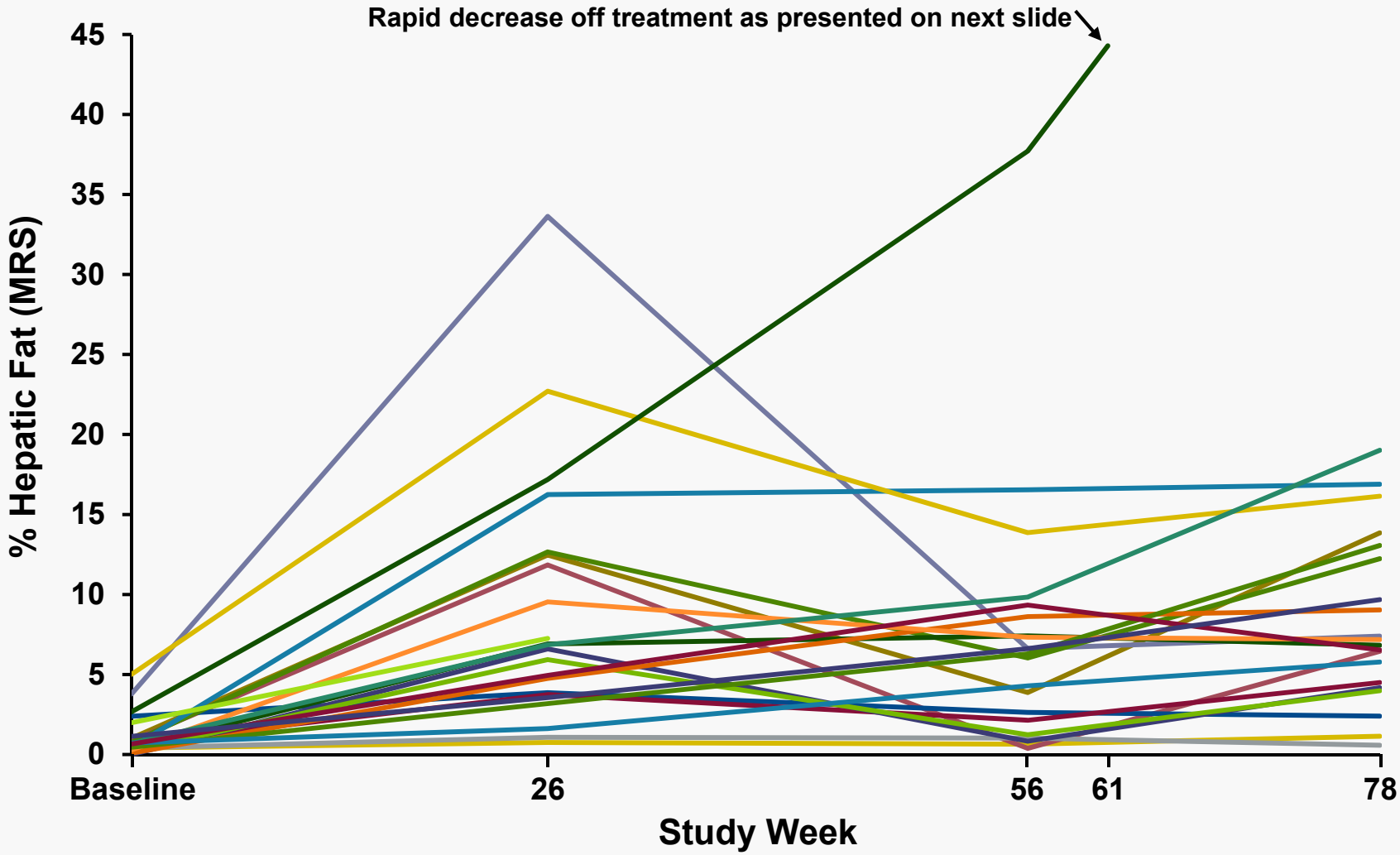
Maximum Categorical Changes in % Hepatic Fat in Phase 3
(Safety Population)

Maximum Absolute Increase in % Hepatic Fat	Efficacy Phase Weeks 0-26 n (%)	Safety Phase Weeks 26-78 n (%)	Entire Trial Weeks 0-78 n (%)
# of evaluable patients	22	22	23
≤5%	9 (41)	6 (27)	5 (22)
>5% to ≤10%	6 (27)	8 (36)	8 (35)
>10% to ≤15%	4 (18)	3 (14)	4 (17)
>15% to ≤20%	1 (5)	4 (18)	3 (13)
>20% to ≤25%	1 (5)	0	1 (4)
>25%	1 (5)	1 (5)	2 (9)

Adapted from Table 53 of FDA briefing document.

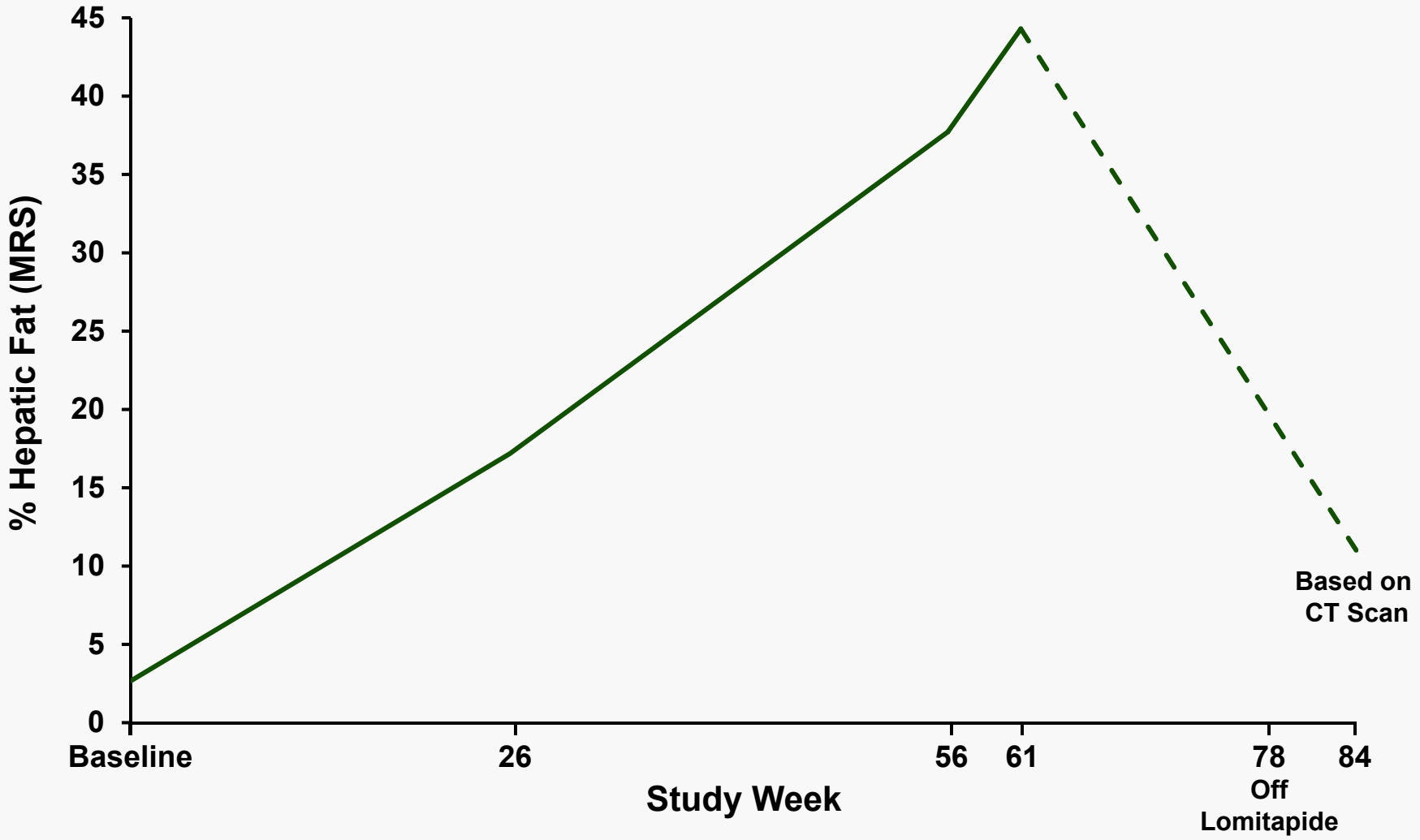
CS-084

Percent Hepatic Fat by Individual Patient in Phase 3
(Safety Population)



CS-085

Percent Hepatic Fat for Patient 32-001



CS-086

ALT Was a Reasonable Surrogate for Degree of Hepatic Fat

- 3 of 4 patients with ALT >5x ULN had >20% hepatic fat
- 1 patient with ALT >5x ULN with a contraindication to MRI (pacemaker/defribrillator) had a CT scan showing ‘moderate’ steatosis
- ALT was correlated with magnitude of hepatic fat accumulation ($r=0.73$, $P<0.0001$)
- ALT had good predictive value for hepatic fat based on ROC analysis
- ALT appears to be a reasonable surrogate for the degree of hepatic fat

Summary of Hepatic Safety in the Phase 3 Study

- 4 of 29 patients experienced transient and reversible ALT elevations ≥5x ULN with dose reduction or temporary interruption
- ALT/AST elevations were manageable and reversible
- No significant elevations in bilirubin or alkaline phosphatase; no Hy's law cases
- Hepatic fat increased modestly during dose escalation and then stabilized
- No subjects discontinued lomitapide treatment based on liver function test elevations or hepatic related adverse events

Patient with Severe Hypertriglyceridemia Receiving Lomitapide via Compassionate Use for >13 Years

- 56 year old female
- 41-year history of recurrent acute pancreatitis associated with severe hypertriglyceridemia
- Past medical history: pancytopenia associated with fatty infiltration of bone marrow, severe hepatosplenomegaly and hepatic steatosis
- Lomitapide initiated 14 June 1999
- ALT/AST during treatment ranged from <2x to 4x ULN

Patient with Severe Hypertriglyceridemia Receiving Lomitapide via Compassionate Use for >13 Years

- 5 liver biopsies performed after 1, 3, 5, 9, and 13 years on lomitapide
- 2008 (9 years): marked, predominantly macrovesicular, steatosis and mild steatohepatitis; no significant fibrosis; no stainable iron
- Repeat biopsy June 2012 for fluctuating ALT/AST (≤4 x ULN)
  - Severe steatosis >66% of hepatocytes
  - Frequent ballooning degeneration, Mallory bodies present
  - Mild to moderate mixed inflammatory infiltrate
  - Stage 3 fibrosis with incomplete nodule formation
- Investigator continues lomitapide based on favorable benefit/risk assessment (prevention of acute pancreatitis)
- ALT and AST normalized

Hepatic Steatosis: A Hepatologist's Perspective

Naga Chalasani, MD, FACG
Professor of Medicine and Cellular & Integrative Physiology
Director, Division of Gastroenterology And Hepatology
Indiana University School Of Medicine

Causes of Hepatic Lipid Accumulation

- Obesity/T2DM/Insulin resistance (NAFLD)
- Excessive alcohol consumption
- Abeta & hypobetalipoproteinemia
- Total parenteral nutrition
- Starvation
- Lipodystrophy
- Drugs

Hepatology 2012; 55: 2005-2023
NAFLD Practice Guideline 2012 by the AASLD/ACG/AGA

Nonalcoholic fatty liver disease

- NAFLD is present in 30% US adults and 10-15% children
- General criteria for diagnosis include imaging evidence of steatosis with no competing etiologies, or significant alcohol consumption
- Fatty liver and nonalcoholic steatohepatitis (NASH) are part of the NAFLD spectrum

Hepatology 2012; 55: 2005-2023
NAFLD Practice Guideline 2012 by the AASLD/ACG/AGA

Distinction between fatty liver and NASH

- Fatty liver is histologically characterized by macrovesicular steatosis with no additional pathology. Fatty liver is generally considered benign from a hepatic standpoint.

- NASH is histologically advanced fatty liver. It is characterized by steatosis, inflammation, hepatocyte ballooning, and fibrosis. It can lead to cirrhosis in a smaller proportion of patients.

Hepatology 2012; 55: 2005-2023
NAFLD Practice Guideline 2012 by the AASLD/ACG/AGA.

Drug induced Hepatic Steatosis

Increased Synthesis	**Tamoxifen** **Alcohol (also decreased β oxidation)**
Mitochondrial Dysfunction (decreased β oxidation)	**Valproate** **Anti-Retroviral agents** **Methotrexate**
Decreased Export	**Tetracycline (also decreased β-oxidation)** **Amiodarone (increased lipogenesis and decreased β-oxidation)** **MTP inhibitors**
Unclear	**Chemotherapeutic agents (Oxaloplatin, Irinotecan, Floxuridine)**
Inducing weight gain and metabolic risk factors	**Antipsychotic compounds** **Corticosteroids**

Few Additional Thoughts

- Hepatic steatosis is fairly dynamic
- No clinically significant relationship between severity of steatosis and steatohepatitis or fibrosis
- Other lipid species (hepatic free cholesterol, ceramide, free fatty acids) are likely far more important lipotoxic mediators
- NAFLD and drug induced hepatic steatosis are distinct entities. No known association between drug induced steatosis and cardiovascular disease

Choi SS, Diehl AM. Curr Opin Lipidol 2008;19:295-300
Yamaguchi K, et al. Hepatology 2007;45:1366-1374
Ibrahim SH, Kohli R, Gores GJ. J Pediatr Gastroenterol Nutr 2011; 53:131-140

Hepatic Steatosis from Lomitapide Not Likely to Have Long-term Serious Consequences

- Accumulation appears to plateau
- Appears reversible
- End stage liver disease appears rare in patients with Abeta & Hypobetalipoproteinemia
- CK18 fragments and fibrosis markers have not shown a progressive increase
- Hepatic TG may not be the lipotoxic mediator to cause hepatocyte damage and fibrosis

Safety Considerations for Clinical Use

Mark Sumeray, MD
Chief Medical Officer
Aegerion Pharmaceuticals, Inc

Dosage Adjustment and Monitoring in Patients With Liver Aminotransferase Elevations >3x ULN

ALT/AST Levels	Treatment and Monitoring Recommendations
>3 and ≤5 x ULN	Continue same dose of lomitapide, or reduce the dose if levels continue to rise.
>5 and ≤10 x ULN	Reduce the dose to the previous level. Continue to monitor at least every 2 weeks until levels <5 x ULN.
>10 x ULN	Stop treatment with lomitapide. Monitor at least every 2 weeks. Reintroduce lomitapide once levels <5 x ULN. If levels remain >10 x ULN, consult a hepatologist.

If aminotransferase elevations are accompanied by clinical symptoms of liver injury or increases in bilirubin ≥2 x ULN, stop treatment and consult a hepatologist.

Important Considerations for Clinical Use

- Contraindicated in the following situations:
  - Concomitant use of ≥80 mg simvastatin
  - Concomitant use with moderate or strong inhibitors of CYP 3A4
  - Pregnant women; acceptable contraception required

Important Considerations for Clinical Use

- Dosing
  - Dose escalation same as Phase 3 study based on acceptable safety and tolerability
- GI tolerability
  - Dietary guidance to adhere to the low fat diet
  - Dose adjustment as appropriate
- Alcohol
  - Use alcohol with caution because of the potential of alcohol to induce or exacerbate liver injury

Important Considerations for Clinical Use

- Drug-drug interactions
  - Statins:
    Monitor for adverse events that are associated with the use of high doses of statins when co-administering with lomitapide
  - Coumarin anticoagulants:
    Monitor INR before and during treatment with lomitapide

Summary of Safety

- Gastrointestinal events were common across the program, but manageable with dose adjustment and adherence to a low fat diet
- Aminotransferase elevations are responsive to dose reduction, reversible and asymptomatic
- Hepatic fat content remains <10% in most patients and is reversible within 4-6 weeks
- Recommendations for clinical use will ensure safe and appropriate prescribing to optimize benefit-risk

Managing the Risks of Lomitapide in Clinical Practice

Martha J. Carter

Chief Regulatory Officer & Senior Vice President
Aegerion Pharmaceuticals, Inc.

CR-104

Lomitapide Risk Management Goals

- Risk mitigation
  - To educate prescribers about
    - The approved indication for use of lomitapide
    - The risk of hepatic effects
    - The need to monitor patients during treatment as per product labeling
  - To limit access to patients in whom therapy with lomitapide is medically appropriate
- Risk assessment
  - To evaluate long-term safety and effectiveness of risk mitigation measures through an observational cohort study

Risk Evaluation and Mitigation Strategy (REMS) Elements

- Specially certify and enroll prescribers
- Control and limit distribution via a single specialty pharmacy
- Ensure dispensing only to patients with a prescription from an enrolled prescriber and documentation of safe-use conditions

Physician's Attestation to Enroll in REMS and Prescribe Lomitapide

Physicians will confirm that they:

- Have been trained on the educational materials
- Understand the indication for lomitapide
- Understand the risks associated with lomitapide, including hepatic effects and teratogenicity
- Acknowledge the need to monitor hepatic transaminases during treatment
- Agree to counsel the patient on the risks of lomitapide and instruct the patient to read the Medication Guide carefully

Requirements to Complete Prescription Authorization Form

- The certified prescriber must attest to:
  - Understanding indication for use
  - Certifying appropriateness of therapy for the patient i.e., medically necessary
  - Obtaining aminotransferase levels in accordance with prescribing information

REMS Evaluation

- Enhanced pharmacovigilance
- Audits of the specialty pharmacy
- Surveys of prescribers to evaluate understanding of risk mitigation strategies
- Observational cohort study to document patient characteristics and frequency of monitoring

Observational Cohort Study (Global Registry)

- ≥300 patients initiating treatment with lomitapide followed for 5 years
- Outcomes of interest:
  - Long-term safety profile
    - Serious hepatic events
    - Tumors
    - Pregnancy outcomes
    - Cardiac events
  - Patterns of use
    - Compliance with screening and monitoring
  - Long term effectiveness in controlling serum lipid levels

Benefit:Risk Assessment

Robert A. Hegele, MD, FRCPC

Canada Research Chair in Human Genetics

Distinguished University Professor of Medicine

Robarts Research Institute

The University of Western Ontario, London ON

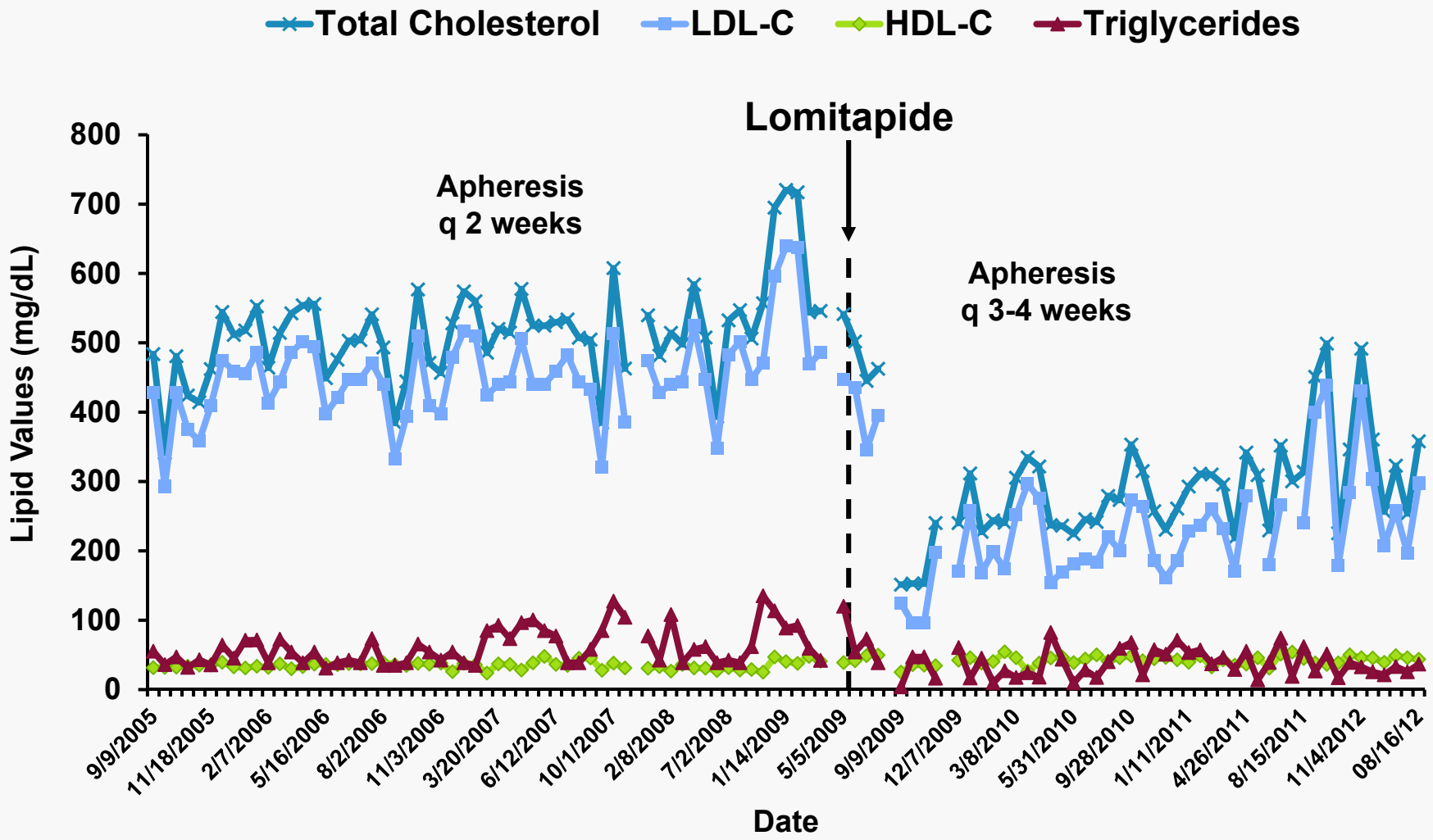
Case Study: Phase 3 Patient

- 24 yr male university student
- Age 5: diagnosed with HoFH
  - Baseline LDL-C: 720 mg/dL
  - Achilles tendon and knuckle xanthomas
  - Fibroblast – receptor negative
  - DNA – compound heterozygote *LDLR* Q718X and del exon 1-6
  - Began apheresis every 2 weeks
- Age 17: bilateral corneal arcus, tendon xanthomas
  - Asymptomatic CHD: coronary angiography: 50% RCA
- Age 21: moderate AR and TR
- Age 22: asymptomatic sinus bradycardia

Case Study: Phase 3 Patient

- On Rx: average LDL-C 380 mg/dL pre-apheresis plus
  - Rosuvastatin 40 mg daily
  - Ezetimibe 10 mg daily
  - Coated Aspirin 81 mg daily
  - Ramipril 10 mg daily
- Age 22: entered lomitapide phase 3 study: titrated to 60 mg daily
  - Back-titrated to stable 40 mg daily dose
  - Historically best LDL-C 104 mg/dL (78.2% decrease)
  - Mild GI symptoms
  - Liver fat: 2.6% at baseline, 8.7% at week 26 and 6.5% at week 78

Case Study: Effect of Lomitapide Rx



CB-114

Case Study: Effect of Lomitapide Rx

Currently on lomitapide 40 mg daily

- Average LDL-C ~200 mg/dL (-58% from treated baseline)
- Week 36: increased interval between LDL-apheresis (q 3-4 weeks)
- Achilles tendon xanthomas – shrank, less painful
- Excellent exercise tolerance: basketball, rowing
- Has taken lomitapide for > 3 years (commenced Rx May 19, 2009)
- Mild GI symptoms: non-serious diarrhea
- Long term LFTs clinically acceptable

HoFH is a Devastating Disease Caused by Uncontrolled LDL-C

- Premature and aggressive CVD
- Isolated genetic defect in LDLR function
- Severely elevated LDL-C without adequate treatment options
- Lowering LDL-C is the standard of care for HoFH patients
- Substantial evidence linking LDL-C with CV outcomes

Lomitapide Has a Favorable Benefit-Risk Profile in HoFH

- Evidence presented today of dramatic reductions in LDL-C in these patients with lomitapide
- Expectation of benefit – prolonged and healthier life
- Risks of lomitapide treatment are uncertain and unlikely to emerge until many years of exposure
- Balanced against certain and immediate risk of fatal or morbid CV event
- Company's commitment to further study lomitapide and implement comprehensive risk mitigation activities
- Clear demonstration of favorable benefit-risk in HoFH

Conclusion

Mark Sumeray, MD

Experts Consultants

- **John Balser, PhD**
  - Consulting Statistician, Veristat, Inc.
- **Joseph Costa, PhD, DABT**
  - Consulting Toxicologist
- **Barry Dvorchik, PhD, FCP**
  - Consulting Clinical Pharmacologist, Barry Dvorchik & Associates
- **Antonio M. Gotto, Jr., MD, DPh**
  - Weill Medical College of Cornell University
- **James H. Lewis, MD**
  - Professor of Medicine, and Director of Hepatology, Division of Gastroenterology, Georgetown University
- **Annette Stemhagen, DrPH, FISPE**
  - Senior Vice President Safety, Epidemiology, Registries and Risk Management, UBC

Conclusion

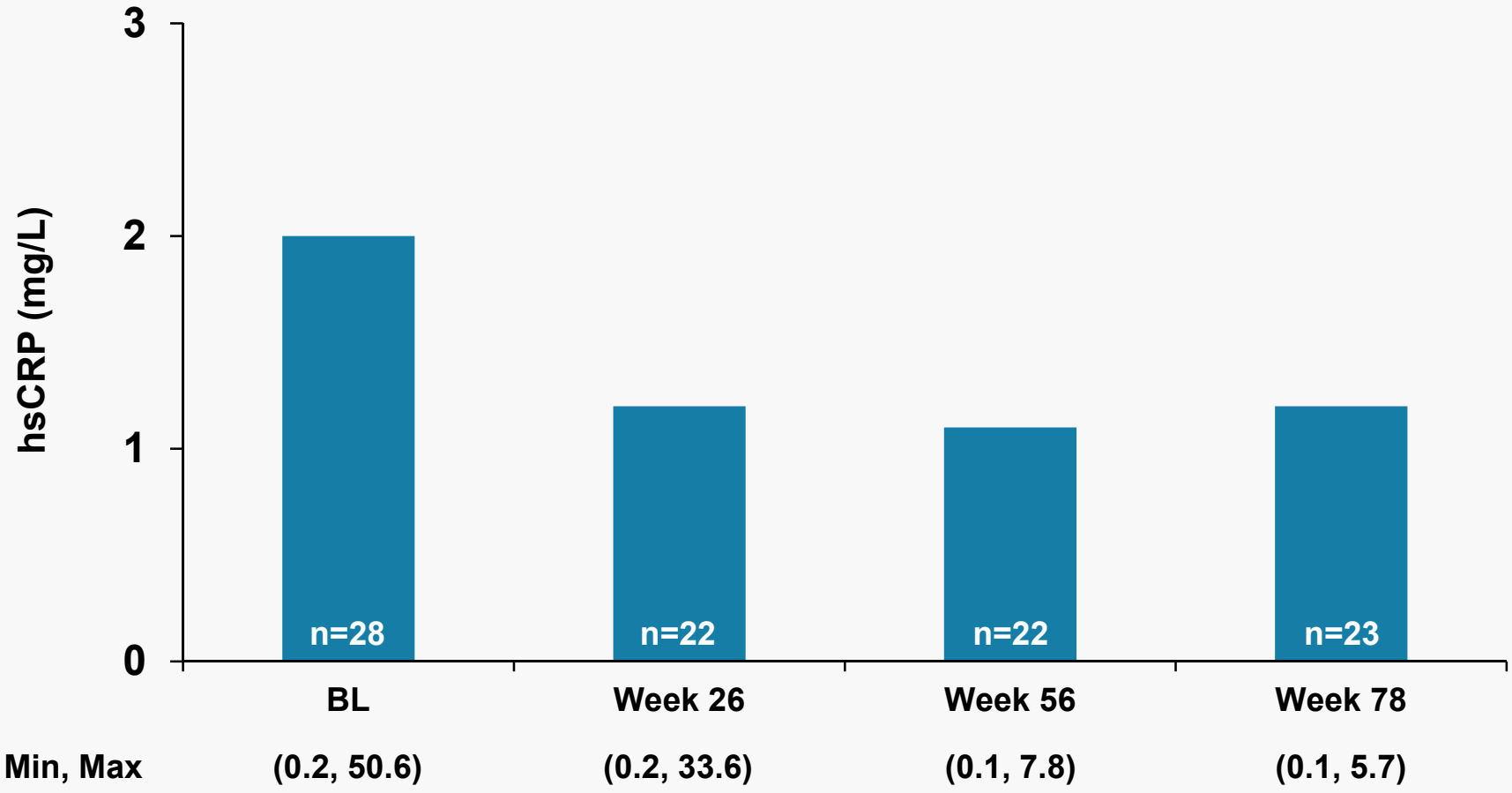
Mark Sumeray, MD

Experts Consultants

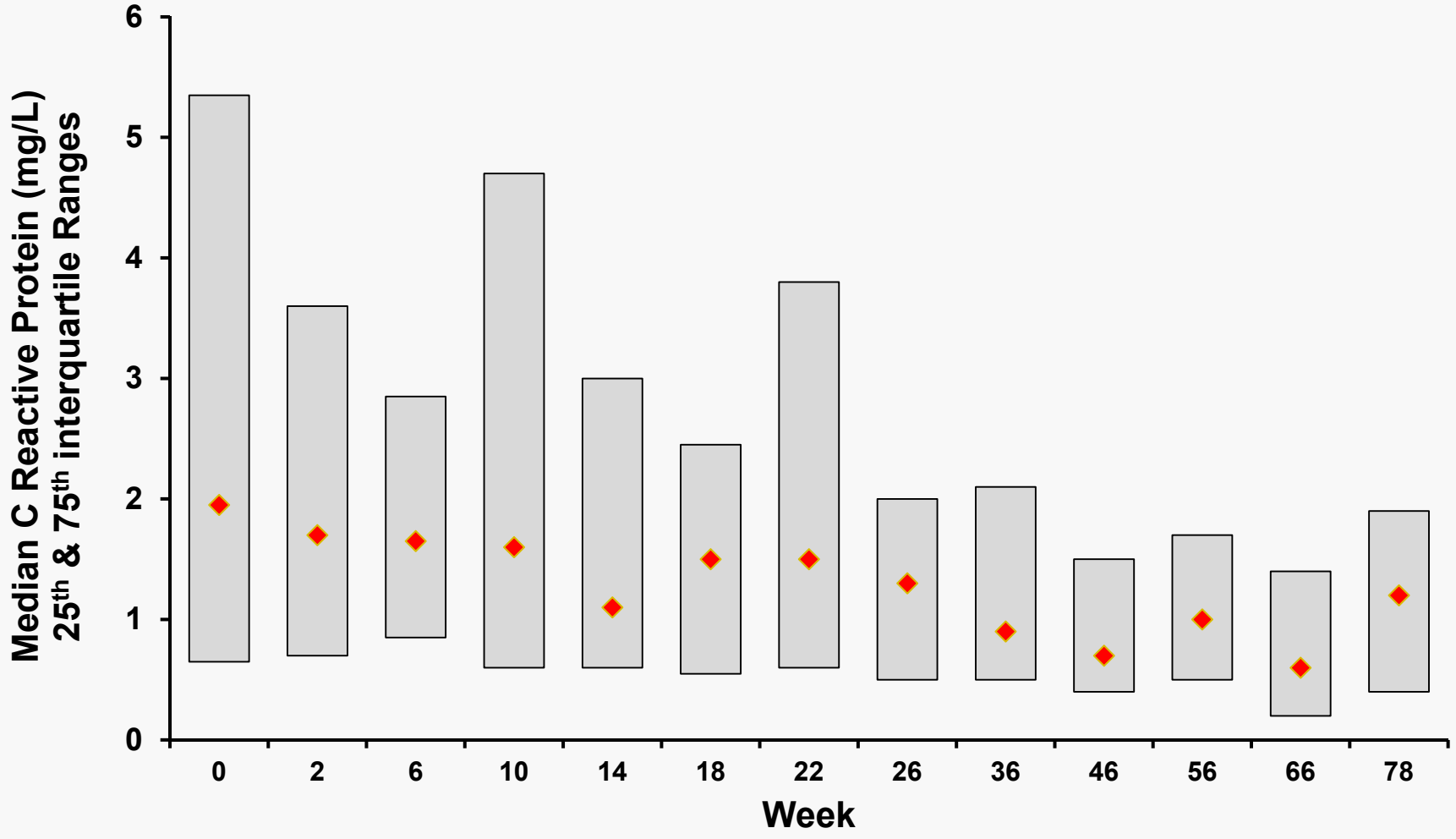
- **John Balser, PhD**
  - Consulting Statistician, Veristat, Inc.
- **Joseph Costa, PhD, DABT**
  - Consulting Toxicologist
- **Barry Dvorchik, PhD, FCP**
  - Consulting Clinical Pharmacologist, Barry Dvorchik & Associates
- **Antonio M. Gotto, Jr., MD, DPh**
  - Weill Medical College of Cornell University
- **James H. Lewis, MD**
  - Professor of Medicine, and Director of Hepatology, Division of Gastroenterology, Georgetown University
- **Annette Stemhagen, DrPH, FISPE**
  - Senior Vice President Safety, Epidemiology, Registries and Risk Management, UBC

Backup Slides

Median Levels of hsCRP in Phase 3
(Safety Population)



Highly-Sensitive C-Reactive Protein in Phase 3
(Safety Population)



SA-105

Proposed Design of the Observational Cohort Study (Global Registry)

- Study design
  - Long-term, multicenter, prospective, observational cohort study of patients treated with lomitapide
- Site selection
  - A heterogeneous sample of sites in all regions where lomitapide is approved
- Study population
  - At least 300 patients who are being treated with lomitapide
- Duration of follow-up
  - Five years from the date of last patient enrolled
  - Enrolled patients followed, even if lomitapide therapy discontinued

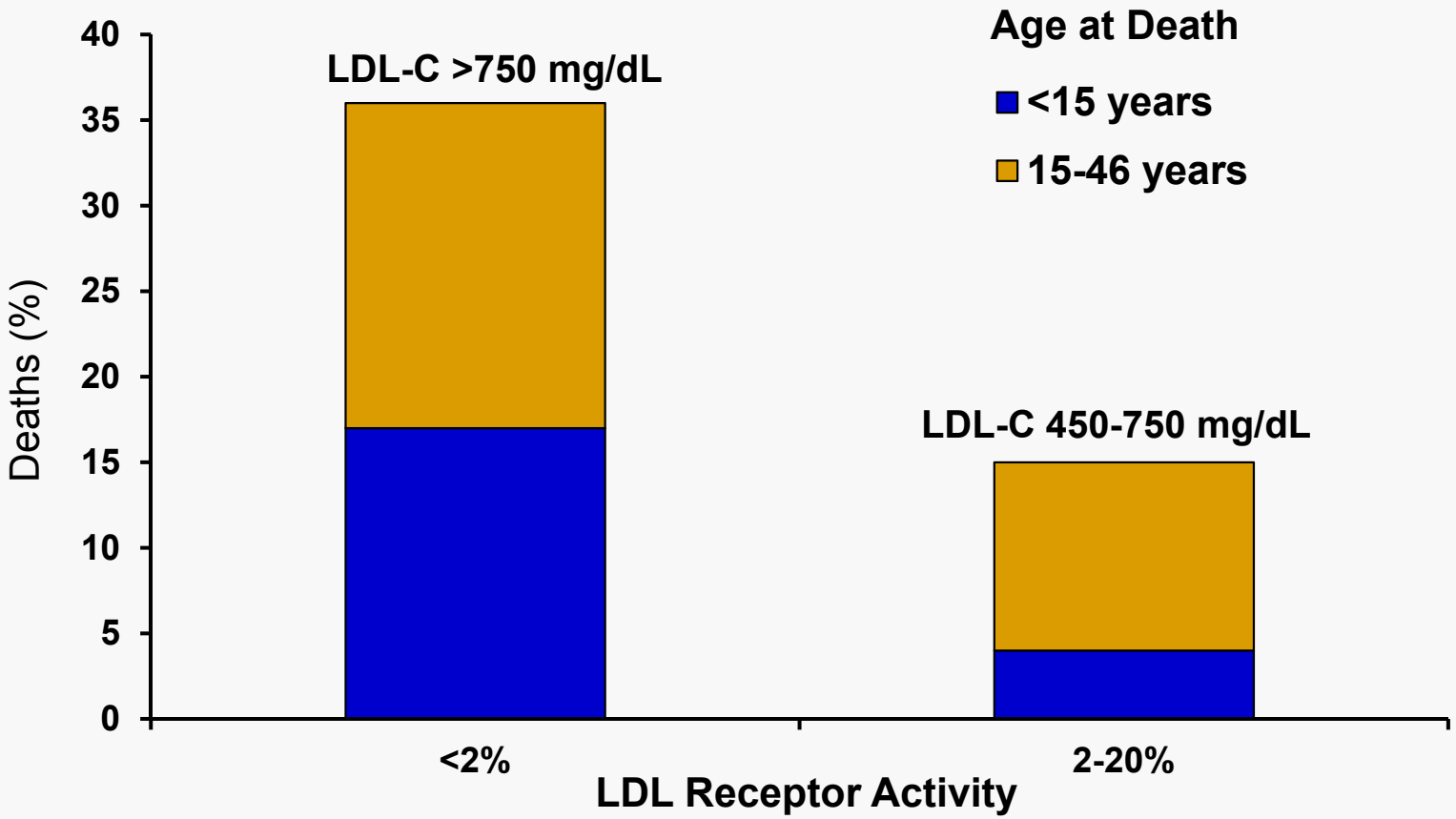
Observational Cohort Study Data Collection

- **Enrollment Visit:**
  - Date of informed consent
  - Patient contact information
  - Screening and confirmation of Patient Diagnosis
  - Patient demographics
  - Clinical presentation
  - Family history
  - Medical History and concurrent conditions
  - Concomitant medications
  - Results of baseline laboratory testing
  - The patient will complete self-administered questionnaire for patient reported outcomes

Observational Cohort Study
Proposed Data Collection

- **Follow up visits:**
- Longitudinal data collection estimated to occur every 3 months, as per usual care
  - Updated contact information
  - Current treatment regimen for hypercholesterolemia
  - Other medications, including dosage change
  - Interim alcohol use history
  - Results of most recent serum lipid profile
  - Results of relevant history, diagnostic tests or procedures if performed during the period since last data submission
  - Interim MAJOR adverse cardiovascular events
  - Information on AESI and any new SAE that occurred the last data submission

HoFH Patients Without LDL Receptor Activity Have Higher LDL-C Levels and Earlier Mortality



Adapted from Goldstein JL, Hobbs HH, Brown MS. Familial Hypercholesterolemia, Metabolic Basis of Inherited Disease (1993).

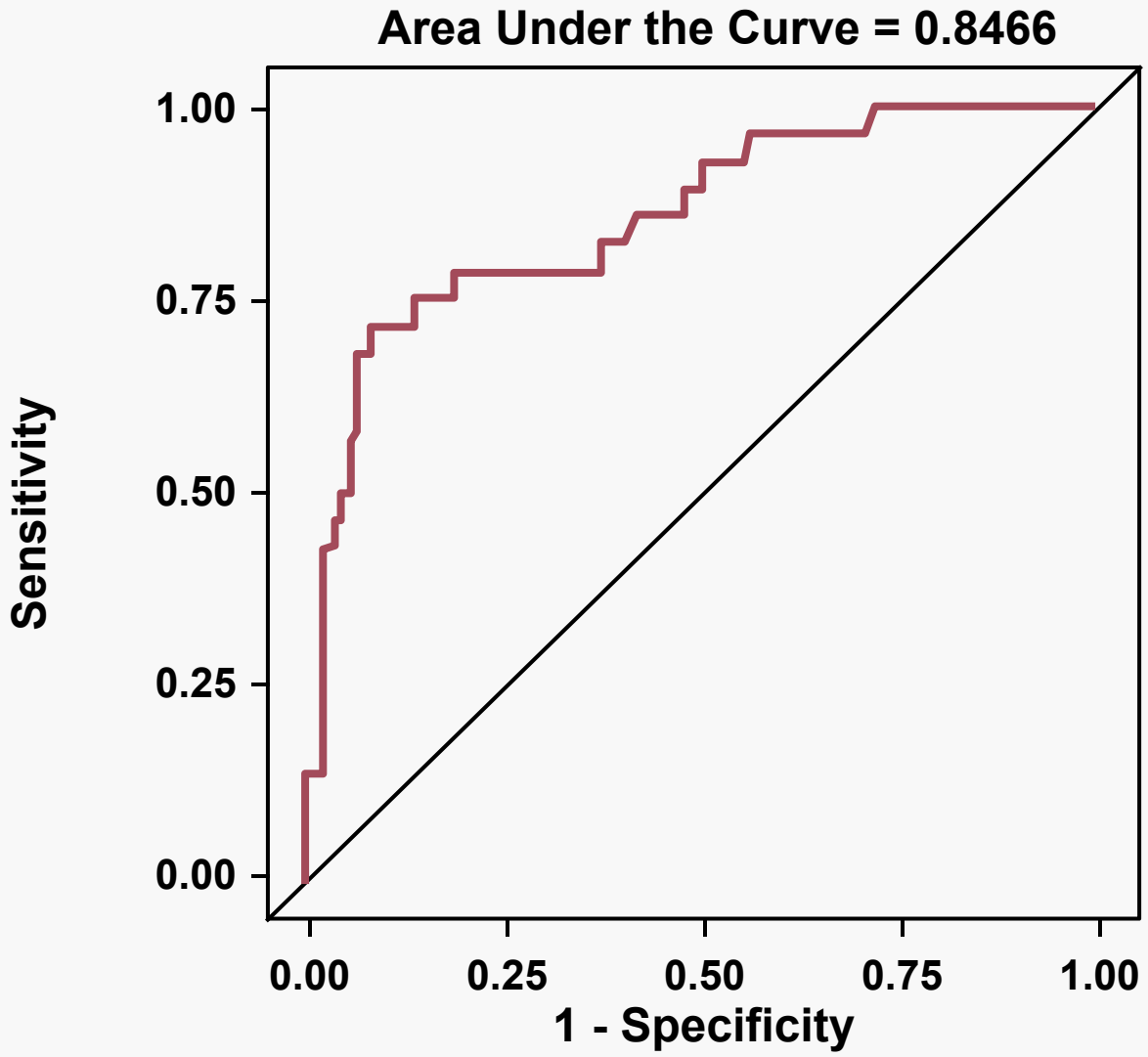
ML-021

Correlations of Change in Percent Hepatic Fat from Baseline in the Phase 3 Study (Safety Population)

	Statistic	ALT	AST	Triglycerides	LDL-C
Week 26	n	22	22	22	22
	r Coefficient	0.5424	0.5460	-0.4101	-0.5020
	95% CI	0.1439, 0.7796	0.1489, 0.7815	-0.7402, 0.0237	-0.7572, -0.0901
	p-value	0.0081	0.0076	0.0576	0.0161
Week 56	n	21	21	21	21
	r Coefficient	0.5145	0.4117	-0.4366	-0.5528
	95% CI	0.0937, 0.7690	-0.0346, 0.7110	-0.7255, 0.0048	-0.7897, -0.1455
	p-value	0.0158	0.0634	0.0470	0.0083
Week 78	n	21	21	21	21
	r Coefficient	0.4250	0.3485	-0.1936	-0.2117
	95% CI	-0.0189, 0.7188	-0.1065, 0.6734	-0.5738, 0.2643	-0.5860, 0.2471
	p-value	0.0542	0.1228	0.4054	0.3618

SA-001

ROC Curve: Maximum ALT Prior to Reaching 30% Hepatic Fat
(Studies 733-004, CV145-002, CV145-009, UP-1001, 733-005)



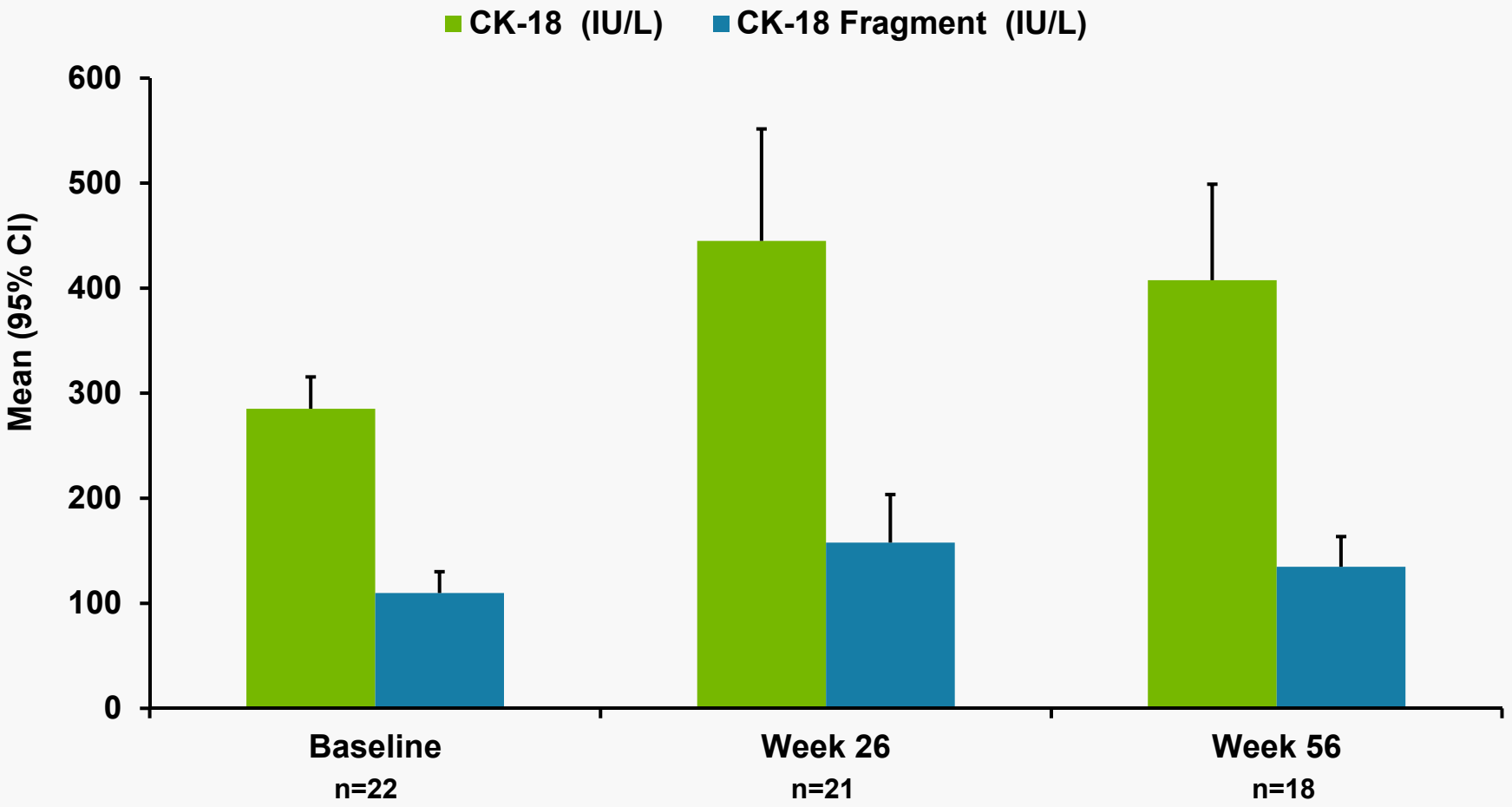
SA-221

Diagnostic Criteria for HoFH From the Literature

Publication	Diagnostic criteria for HoFH
Seftel et al.	• Serum cholesterol concentration >14.3 mmol/L (550 mg/dL) • Appearance of xanthomas during first decade of life • Hypercholesterolemia or clinical signs of hypercholesterolemia in both parents
Moorjani et al.	• Plasma cholesterol levels >550 mg/dL • Appearance of xanthomas at an early age • Detection of hypercholesterolemia in both parents
Haitas et al.	• Hypercholesterolemia in both parents (when available) • Total serum cholesterol >13 mmol/L (500 mg/dL) þ presence of xanthomas in first decade of life
Raal et al.	• Untreated serum LDL consistently >12 mmol/L • Appearance of xanthomas in first decade of life • Hypercholesterolemia, or its clinical features, documented in both parents • Confirmation by DNA analysis for LDLR mutations
Goldstein	• Unique yellow-orange cutaneous xanthomas (frequently present at birth) • Tendon xanthomas, corneal arcus, generalized atherosclerosis during childhood • Plasma cholesterol >650 mg/dL in non-jaundiced child
Gagne et al.	Two mutant alleles at LDLR confirmed by genetic testing or • LDL-C 220 mg/dL (5.69 mmol/L) while receiving lipid-lowering therapy at the highest tolerated dose (<15% response) • LDL-C >90th percentile in 2 first-degree relatives • Presence of tendonous xanthomas and/or manifestations of premature coronary heart disease or corneal arcus
Marais et al.	• Childhood cutaneous or tendonous xanthomata • Total cholesterol >15 mmol/L (600 mg/dL) • Both parents should have severe hypercholesterolemia (>7.5 mmol/L or 300 mg/dL) or tendonous xanthomas • Family history of premature ischemic heart disease
Kolansky et al.	• Total cholesterol >500 mg/dL • Xanthomas at an early age • Presence of hypercholesterolemia in proband's parents or other first-degree relative
Marais et al.	Clinical criteria: • Fasting LDL >500 mg/dL (12.9 mmol/L), triglycerides < 600 mg/dL (6.8 mmol/L) • Either xanthomata before age 10 years or FH in both parents • Genetic criteria: identification of 2 LDLR gene mutations • Functional criteria: <30% uptake compared to normal of LDL and up-regulated fibroblasts
Santos et al.	Untreated LDL >500 mg/dL Plus at least one: • Genetic testing confirmation of 2 mutated LDL-R alleles • Tendonous and/or tuberous xanthoma prior to age 10 years • Documented elevated LDL and both parents consistent with HeFH (LDL >200 mg/dL). If parent unavailable, history of CAD in first-degree relative (male <55 years or female <60 years of age)
Raal et al.	• Untreated LDL cholesterol >13 mmol/L • And either appearance of xanthomas before age 10 years or familial hypercholesterolemia in both parents
Mabuchi et al.	• Juvenile xanthomatosis with plasma cholesterol about 2 times that of parents or other family members with HeFH • Genetic diagnostic criteria: true homozygosity, compound heterozygosity, or double heterozygosity for FH genes

F.J. Raal, R.D. Santos. *Atherosclerosis* 223 (2012) 262e268.

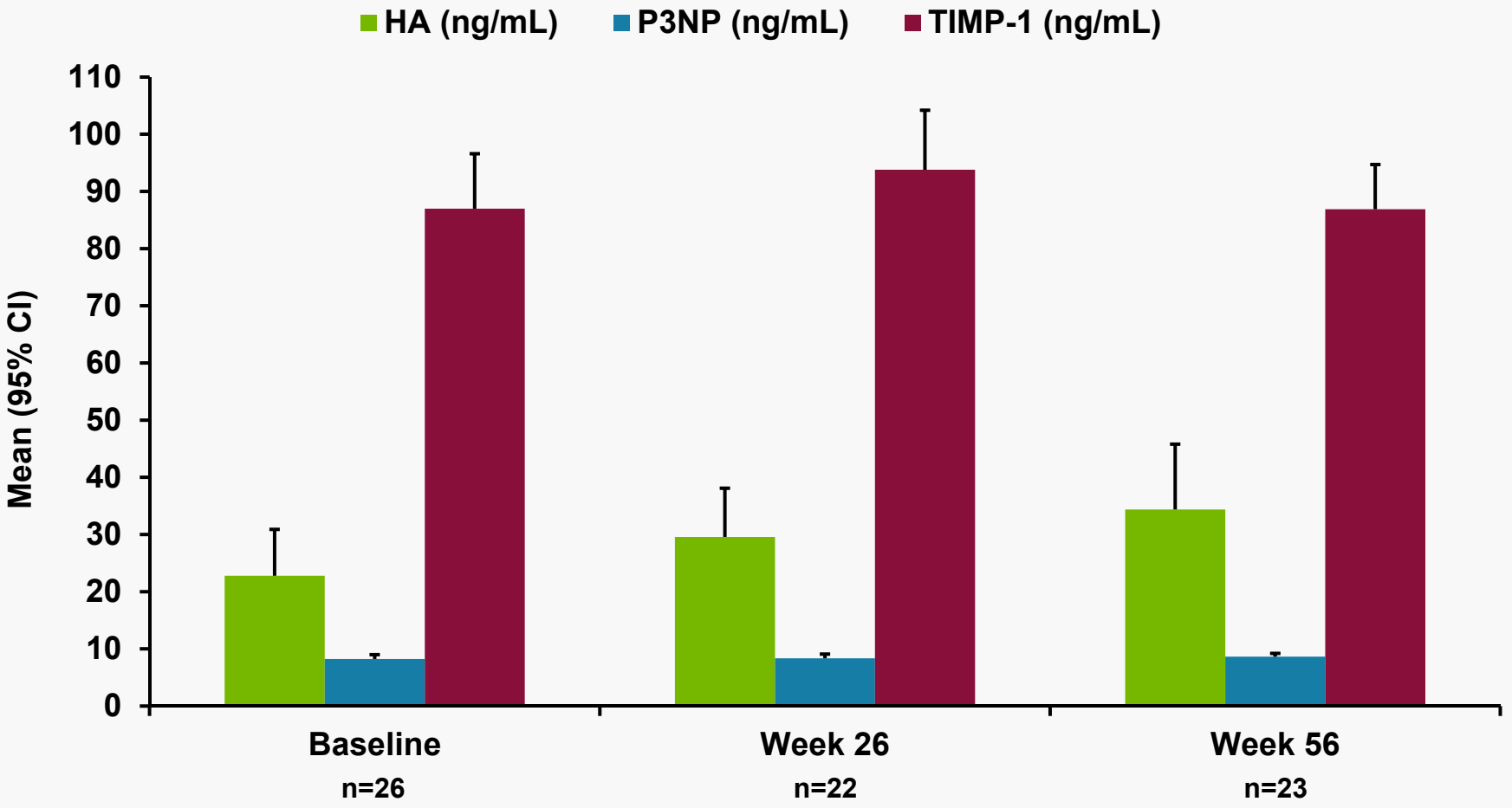
Mean (95% CI) CK-18 & CK-18 Fragment in Phase 3
(Safety Population)



SA-144

Mean (95% CI) Enhanced Liver Fibrosis (ELF) Results in Phase 3

Safety Population



SA-145

Hepatic Biomarker Values and Change from Baseline to Week 56
(Safety Population)

		Hepatic Biomarker (N=29)					
Timepoint	Statistic	CK-18 (IU/L)	CK-18 Fragment (IU/L)	HA (ng/Ml)	P3NP (ng/Ml)	TIMP-1 (ng/Ml)	DS
Baseline	N	22	22	26	26	26	26
	Mean (SD)	285.3 (68.03)	109.9 (45.52)	22.8 (19.87)	8.24 (1.919)	87.0 (23.82)	-1.687 (0.5820)
	Median	271.0	109.5	19.5	8.05	83.0	-1.647
	Min,Max	156,448	38,232	4,100	5.5,12.6	51,153	-2.65,-0.46
	95% CI	255.1,315.5	89.7,130.1	14.8,30.9	7.5,9.0	77.3,96.6	-1.9,-1.5
Week 56	N	18	18	23	23	23	23
	Mean (SD)	407.6 (183.88)	134.8 (57.78)	34.4 (26.22)	8.66 (1.288)	86.9 (18.13)	-1.331 (0.5808)
	Median	369.5	121.0	29.0	8.30	87.0	-1.336
	Min,Max	178,890	75,259	8,112	6.3,10.6	59,139	-2.21,-0.34
	95% CI	316.1,499.0	106.0,163.5	23.1,45.8	8.1,9.2	79.0,94.7	-1.6,-1.1
Change from Baseline to Week 56	N	18	18	22	22	22	22
	Mean (SD)	115.2 (193.95)	21.5 (64.00)	12.4 (24.48)	0.31 (1.822)	3.5 (21.06)	0.410 (0.5149)
	Median	48.0	0.5	8.5	0.60	7.0	0.417
	Min,Max	-55,650	-88,165	-34,92	-2.9,3.7	-58,42	-0.83,1.23
	95% CI	18.8,211.7	-10.3,53.3	1.6,23.3	-0.5,1.1	-5.8,12.8	0.2,0.6