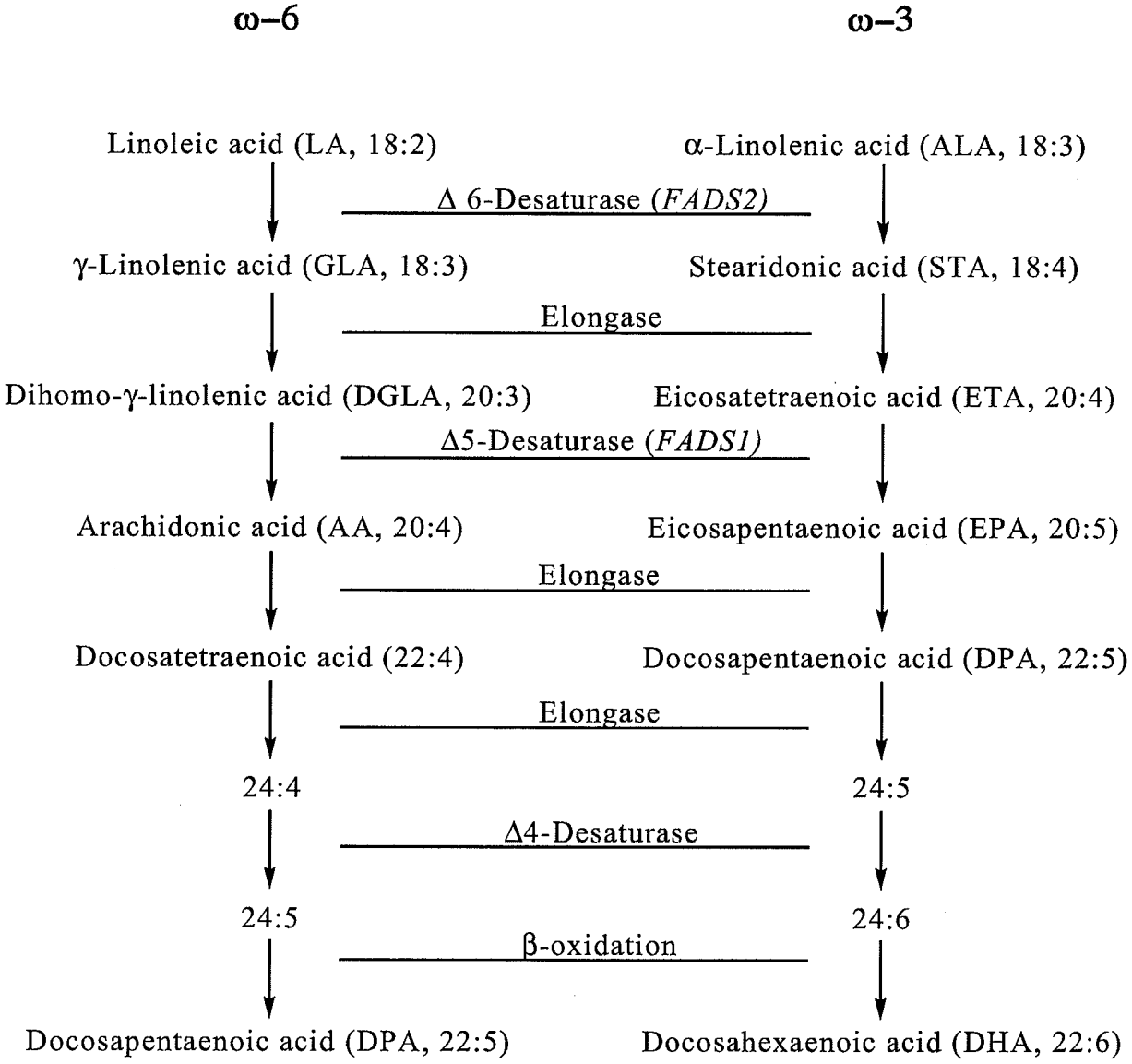

ω–6
ω–3
Linoleic acid (LA, 18:2)
α-Linolenic acid (ALA, 18:3)
Δ 6-Desaturase (FADS2)
γ-Linolenic acid (GLA, 18:3)
Stearidonic acid (STA, 18:4)
Elongase
Dihomo-γ-linolenic acid (DGLA, 20:3)
Eicosatetraenoic acid (ETA, 20:4)
Δ5-Desaturase (FADS1)
Arachidonic acid (AA, 20:4)
Eicosapentaenoic acid (EPA, 20:5)
Elongase
Docosatetraenoic acid (22:4)
Docosapentaenoic acid (DPA, 22:5)
Elongase
24:4
24:5
Δ4-Desaturase
24:5
24:6
β-oxidation
Docosapentaenoic acid (DPA, 22:5)
Docosahexaenoic acid (DHA, 22:6)

FIG. 1

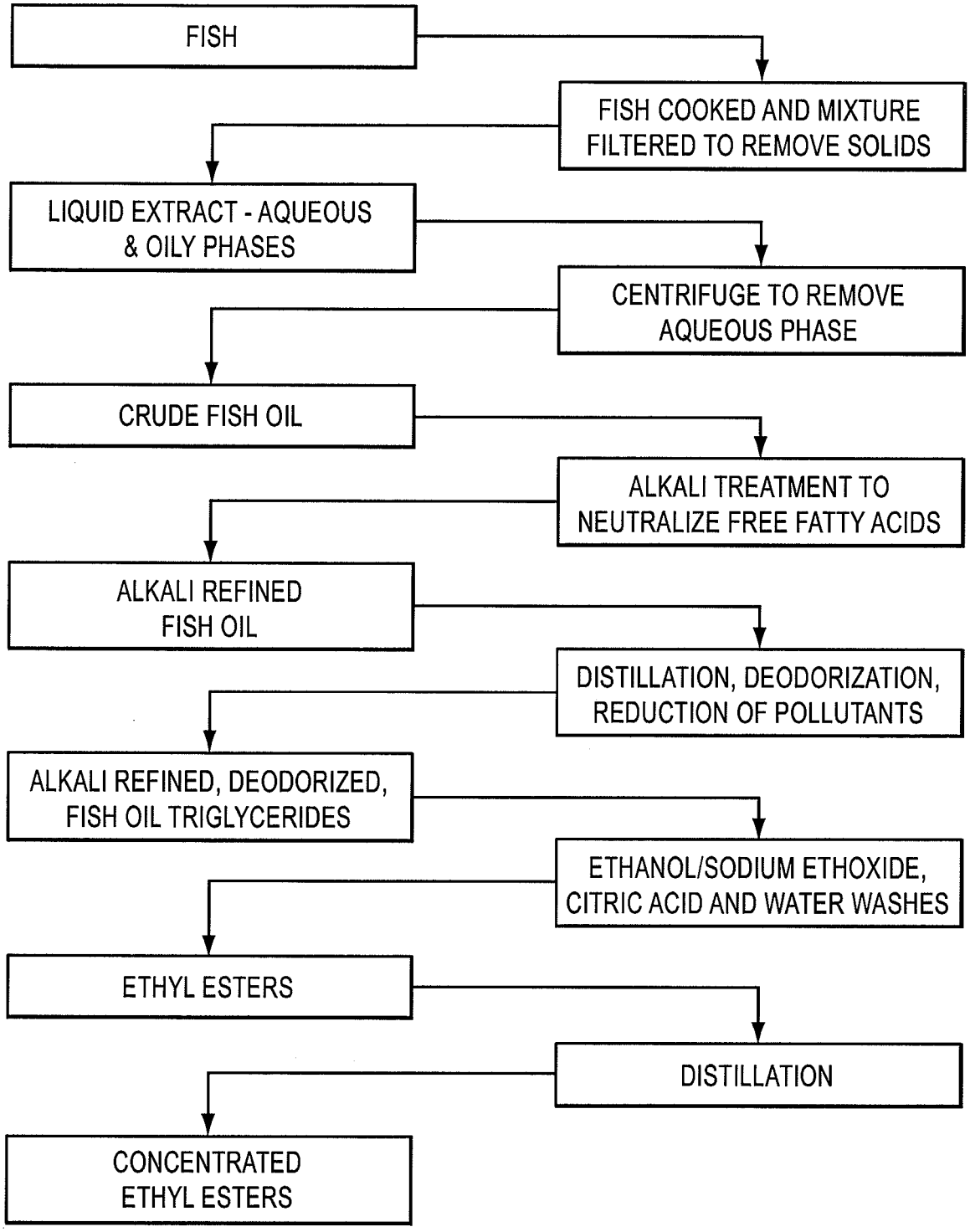

FISH
FISH COOKED AND MIXTURE FILTERED TO REMOVE SOLIDS
LIQUID EXTRACT - AQUEOUS & OILY PHASES
CENTRIFUGE TO REMOVE AQUEOUS PHASE
CRUDE FISH OIL
ALKALI TREATMENT TO NEUTRALIZE FREE FATTY ACIDS
ALKALI REFINED FISH OIL
DISTILLATION, DEODORIZATION, REDUCTION OF POLLUTANTS
ALKALI REFINED, DEODORIZED, FISH OIL TRIGLYCERIDES
ETHANOL/SODIUM ETHOXIDE, CITRIC ACID AND WATER WASHES
ETHYL ESTERS
DISTILLATION
CONCENTRATED ETHYL ESTERS

FIG. 2

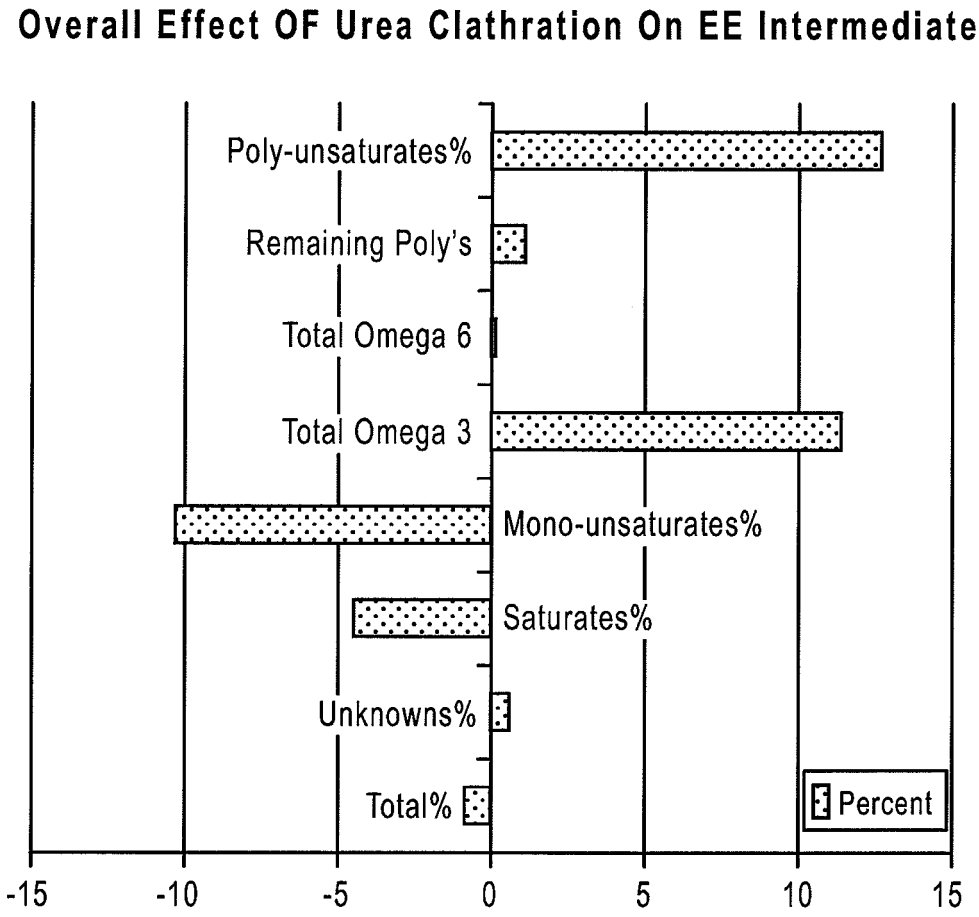

Overall Effect OF Urea Clathration On EE Intermediate
Poly-unsaturates%
Remaining Poly's
Total Omega 6
Total Omega 3
Mono-unsaturates%
Saturates%
Unknowns%
Total%
Percent
-15
-10
-5
0
5
10
15

FIG. 3A

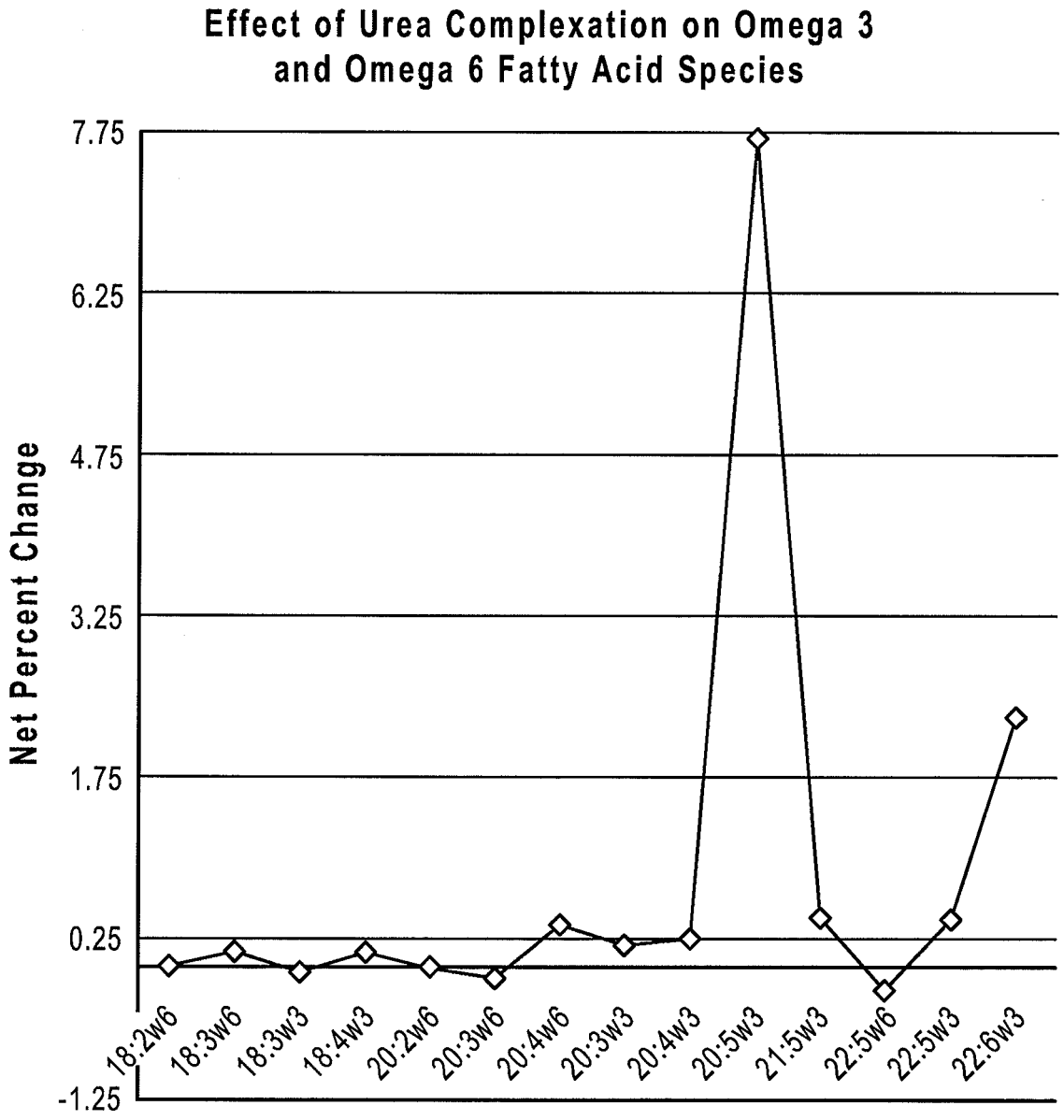

Effect of Urea Complexation on Omega 3 and Omega 6 Fatty Acid Species
Net Percent Change
7.75
6.25
4.75
3.25
1.75
0.25
-1.25
18:2w6
18:3w6
18:3w3
18:4w3
20:2w6
20:3w6
20:4w6
20:3w3
20:4w3
20:5w3
21:5w3
22:5w6
22:5w3
22:6w3

FIG. 3B

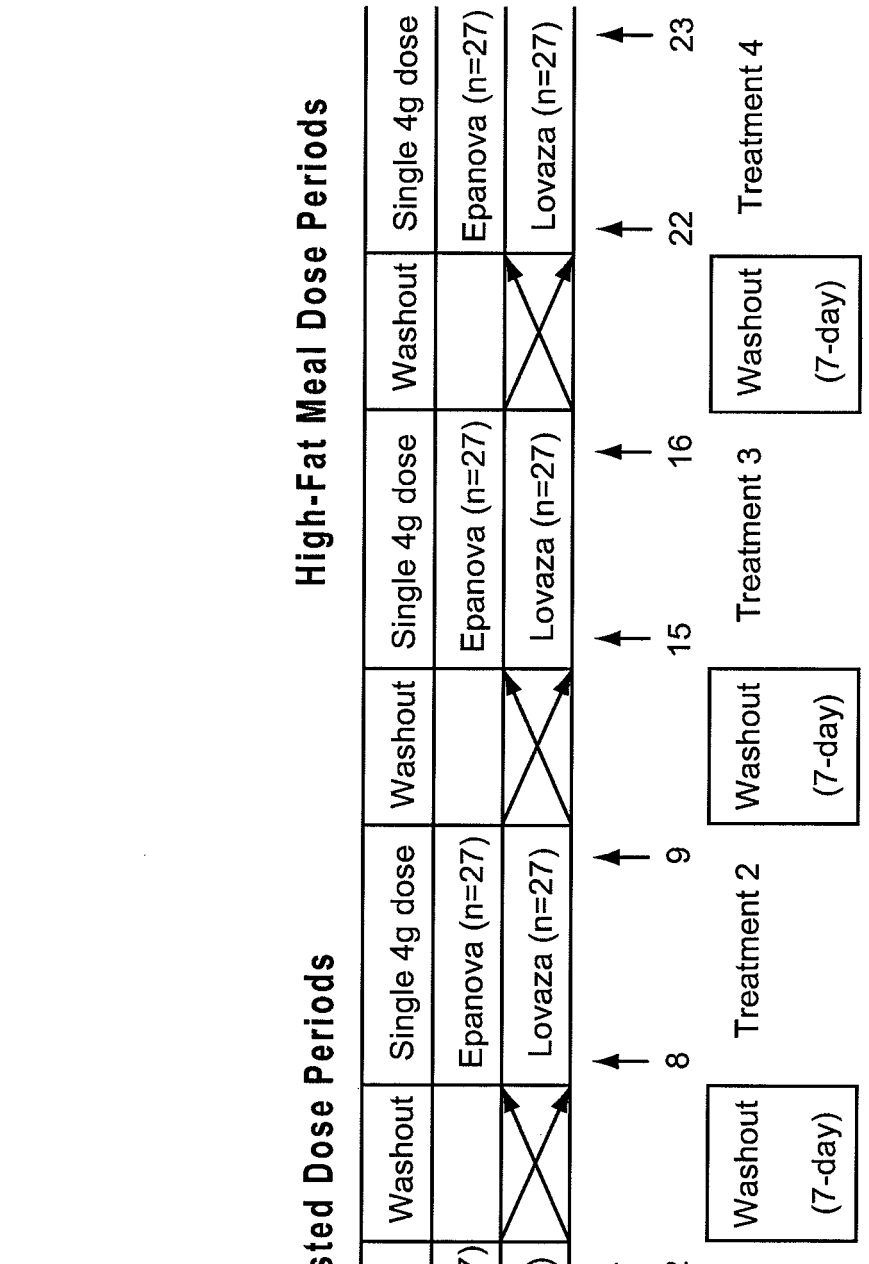

Fasted Dose Periods
High-Fat Meal Dose Periods
Single 4g dose
Washout
Single 4g dose
Washout
Single 4g dose
Epanova (n=27)
Epanova (n=27)
Epanova (n=27)
Epanova (n=27)
Lovaza (n=27)
Lovaza (n=27)
Lovaza (n=27)
Lovaza (n=27)
1
2
8
9
15
16
22
23
Treatment 1
Washout (7-day)
Treatment 2
Washout (7-day)
Treatment 3
Washout (7-day)
Treatment 4
(INDICATES CLINIC VISIT AND DAY OF STUDY)

FIG. 4

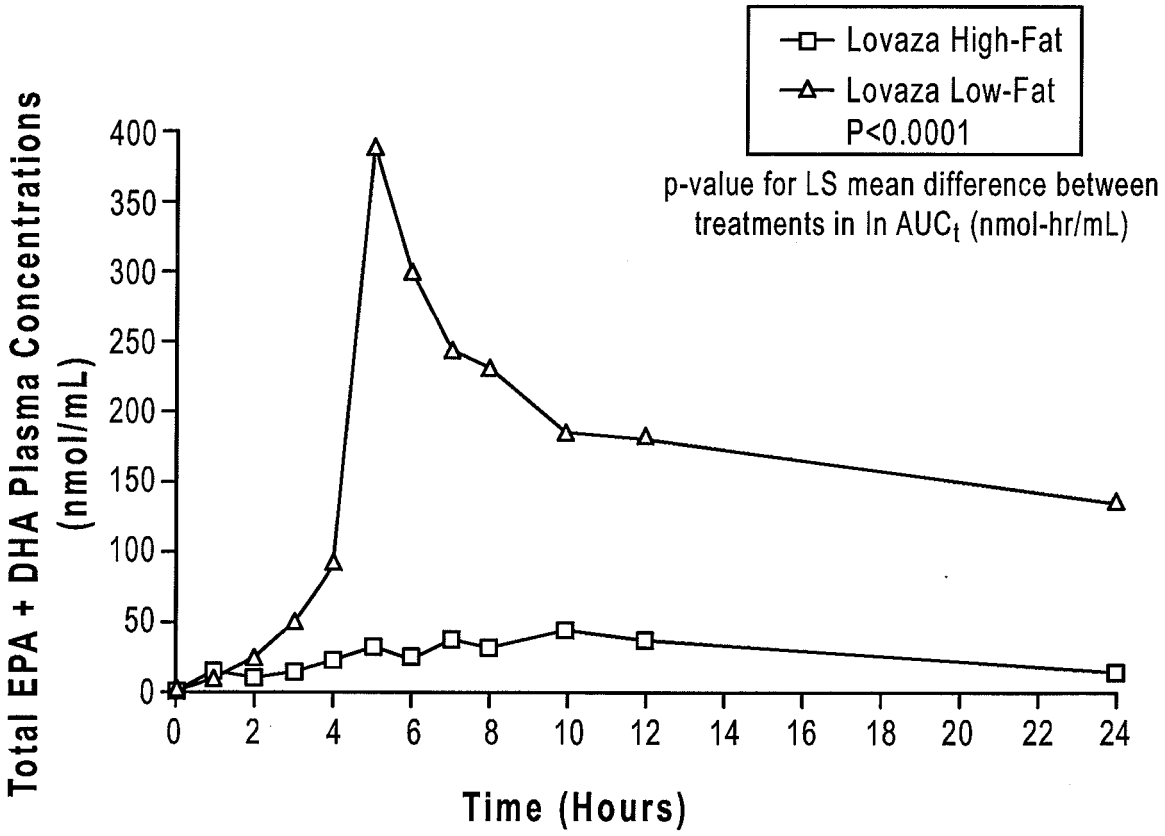

Lovaza High-Fat
Lovaza Low-Fat
P<0.0001
p-value for LS mean difference between treatments in ln AUC$_t$ (nmol-hr/mL)
Total EPA + DHA Plasma Concentrations (nmol/mL)
400
350
300
250
200
150
100
50
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hours)

FIG. 5

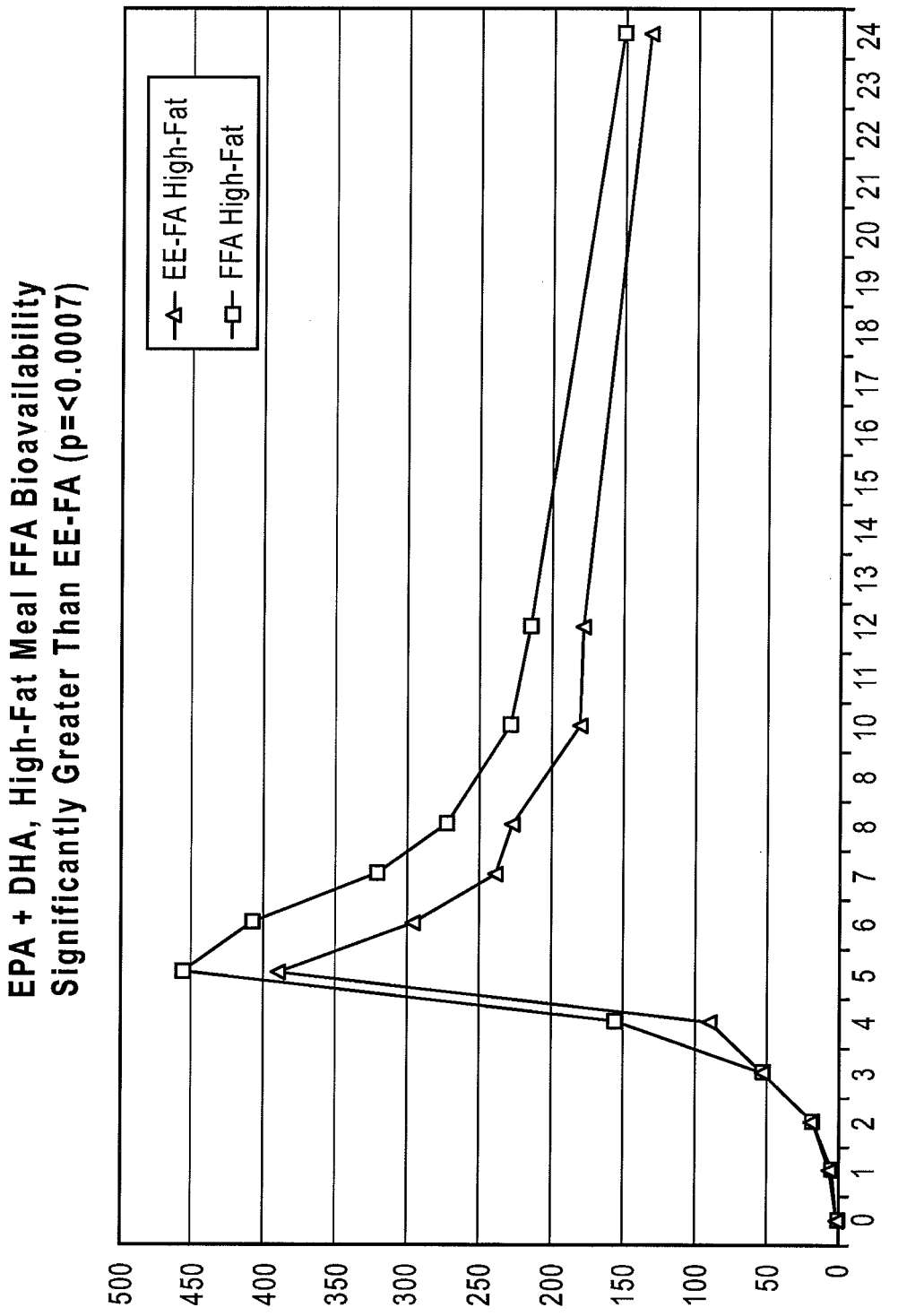

EPA + DHA, High-Fat Meal FFA Bioavailability
Significantly Greater Than EE-FA (p=<0.0007)
EE-FA High-Fat
FFA High-Fat
500
450
400
350
300
250
200
150
100
50
0
0 1 2 3 4 5 6 7 8 8 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

FIG. 6

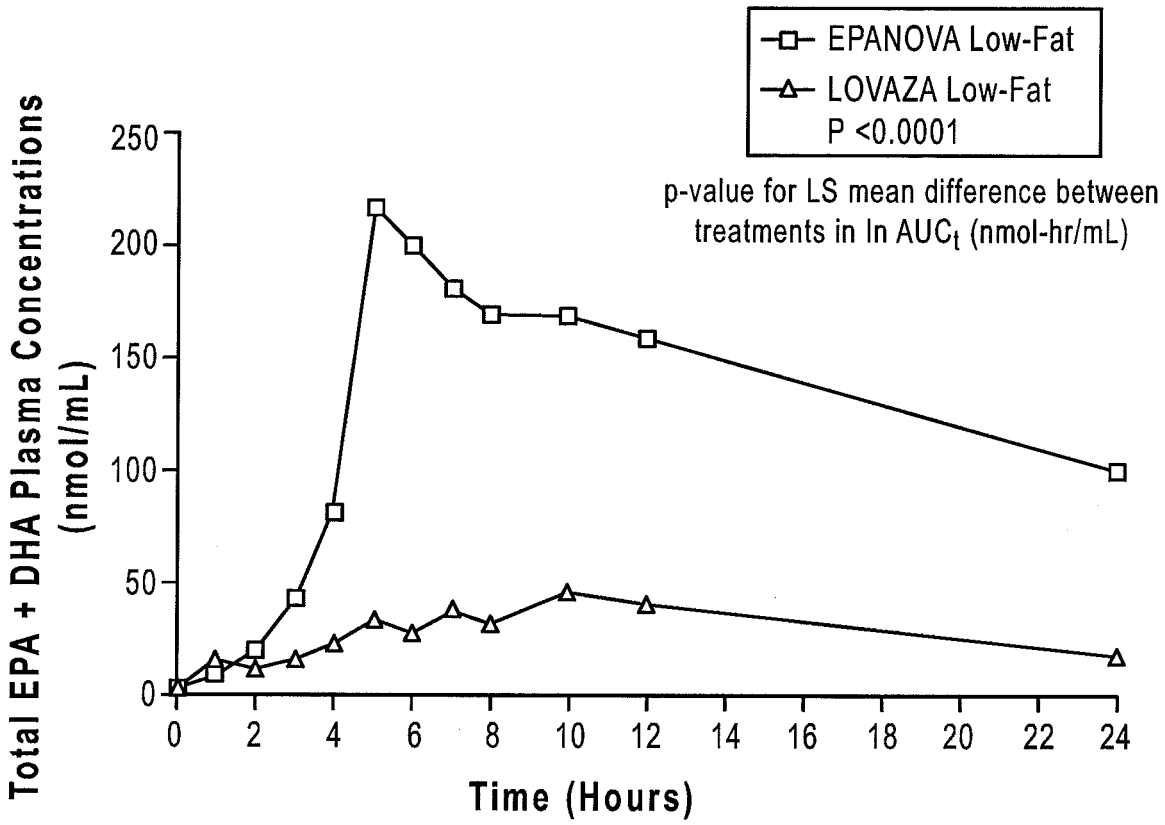

EPANOVA Low-Fat
LOVAZA Low-Fat
P <0.0001
p-value for LS mean difference between treatments in ln AUCt (nmol-hr/mL)
Total EPA + DHA Plasma Concentrations (nmol/mL)
250
200
150
100
50
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hours)

FIG. 7

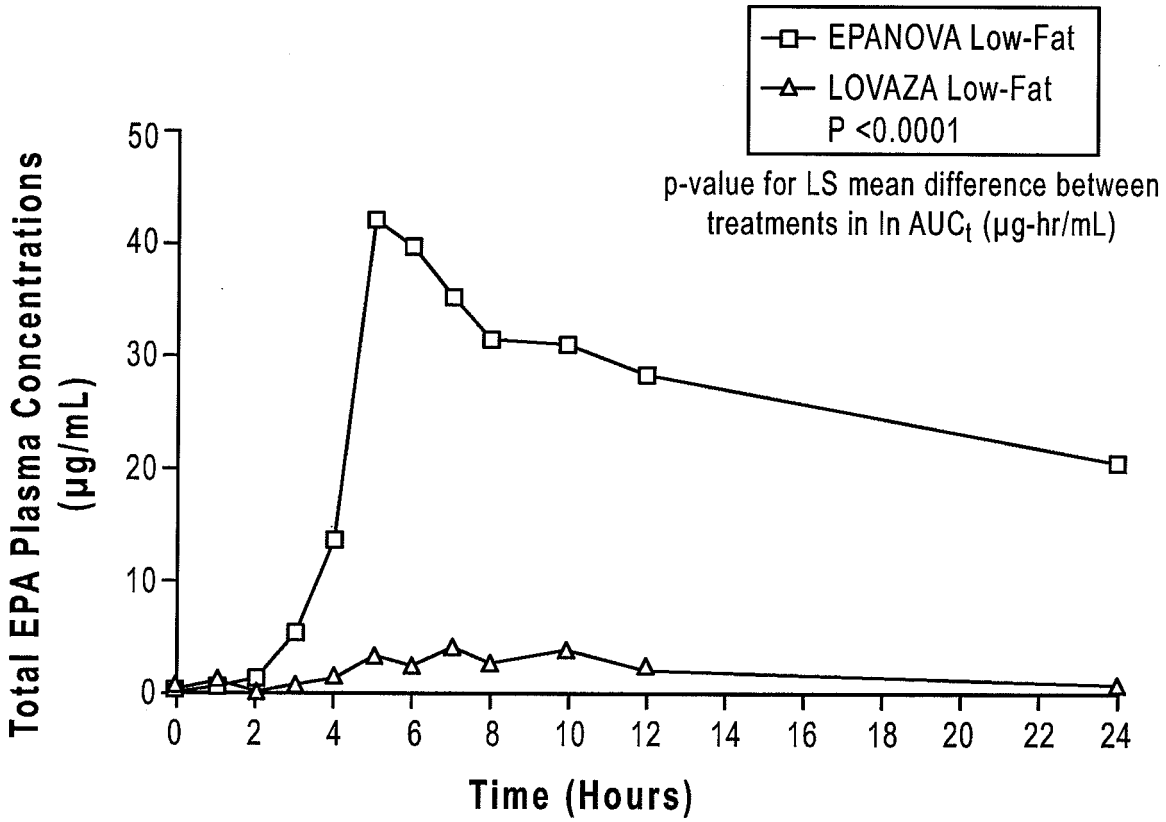

EPANOVA Low-Fat
LOVAZA Low-Fat
P <0.0001
p-value for LS mean difference between treatments in ln AUCt (µg-hr/mL)
Total EPA Plasma Concentrations (µg/mL)
0
10
20
30
40
50
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hours)

FIG. 8

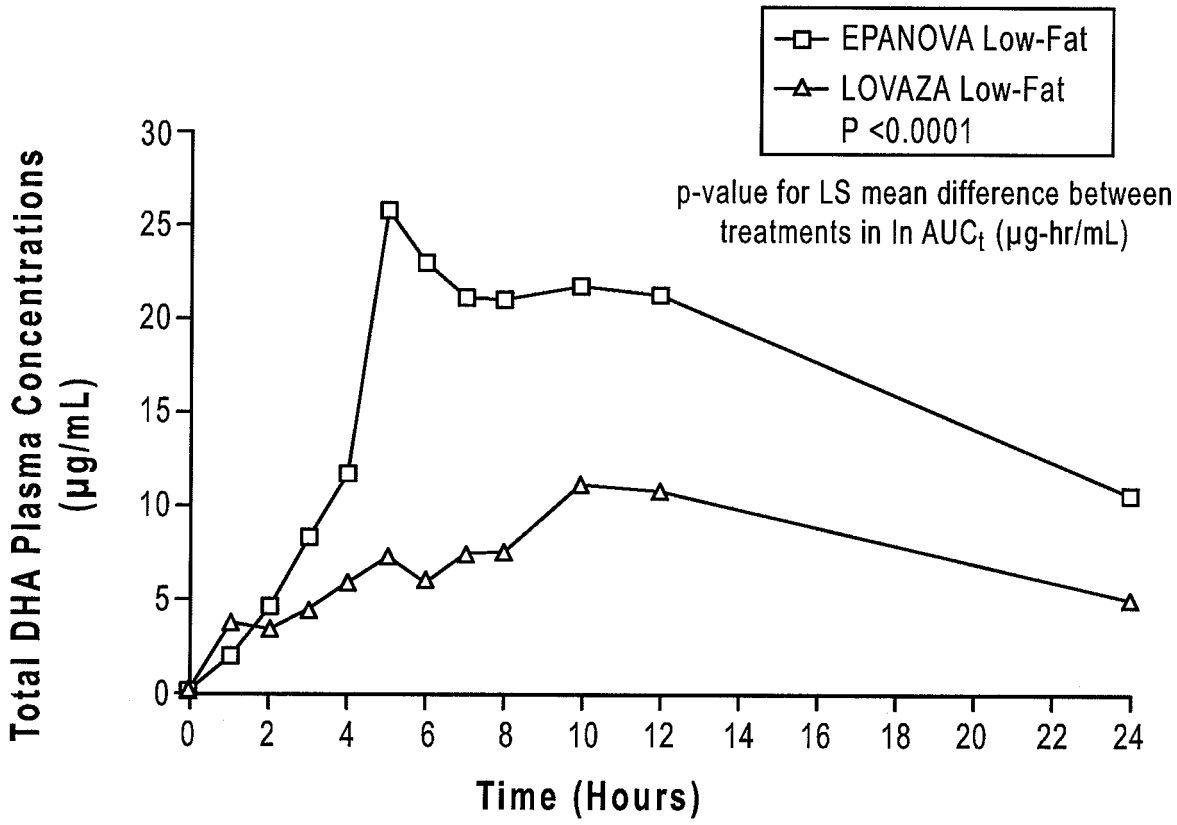

EPANOVA Low-Fat
LOVAZA Low-Fat
P <0.0001
p-value for LS mean difference between treatments in ln AUCt (µg-hr/mL)
Total DHA Plasma Concentrations (µg/mL)
0
5
10
15
20
25
30
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hours)

FIG. 9

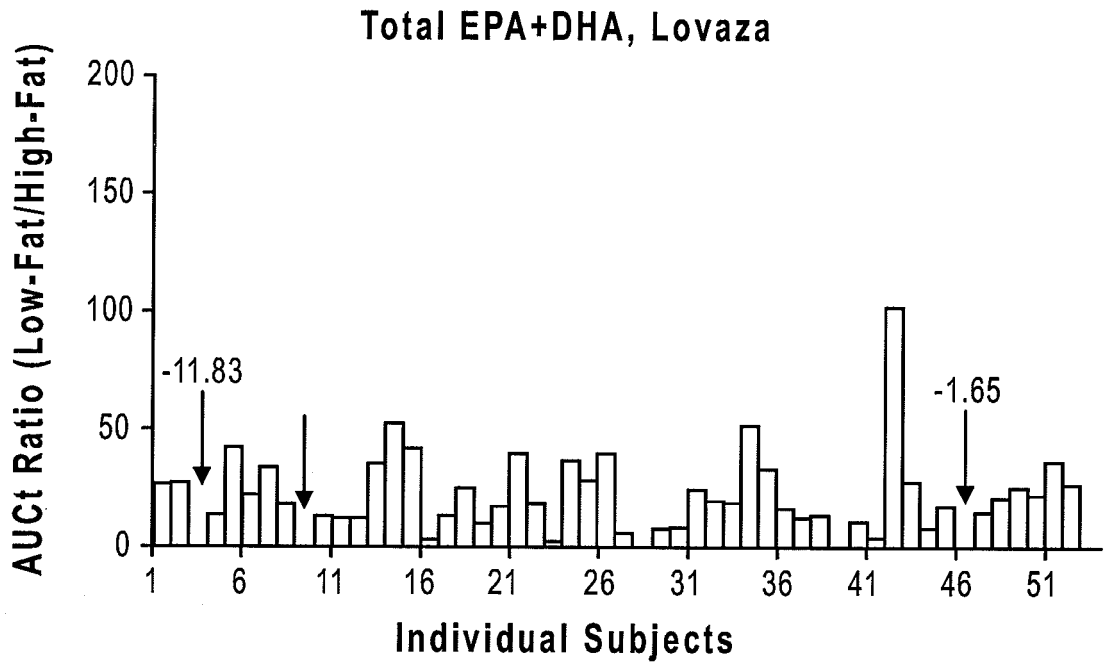


FIG. 10A

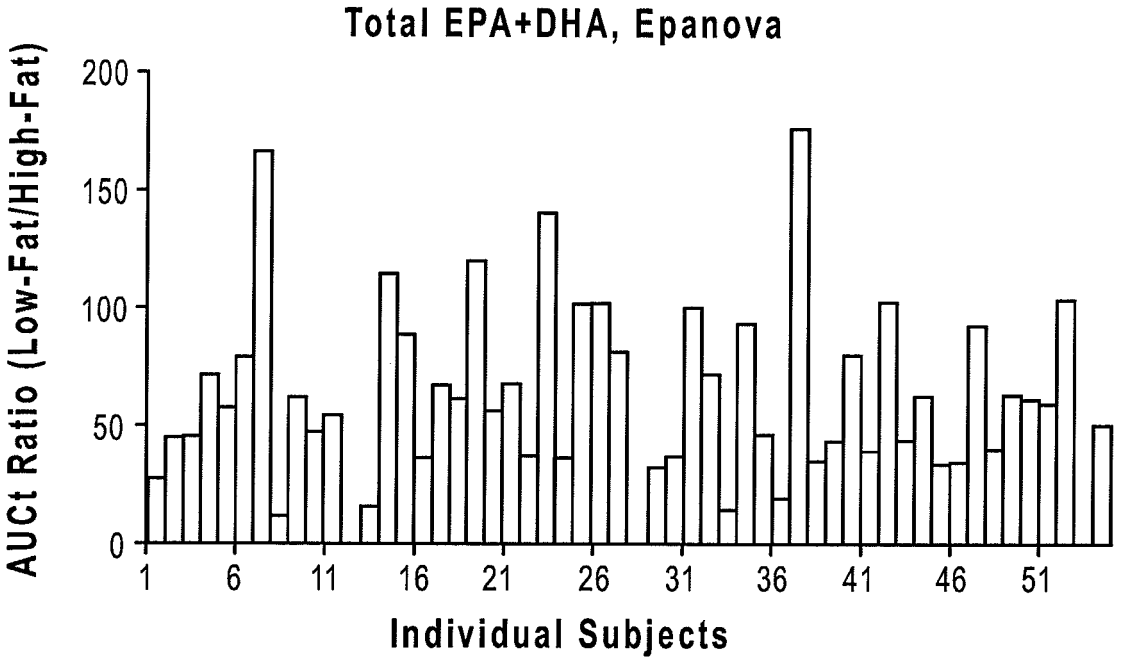


FIG. 10B

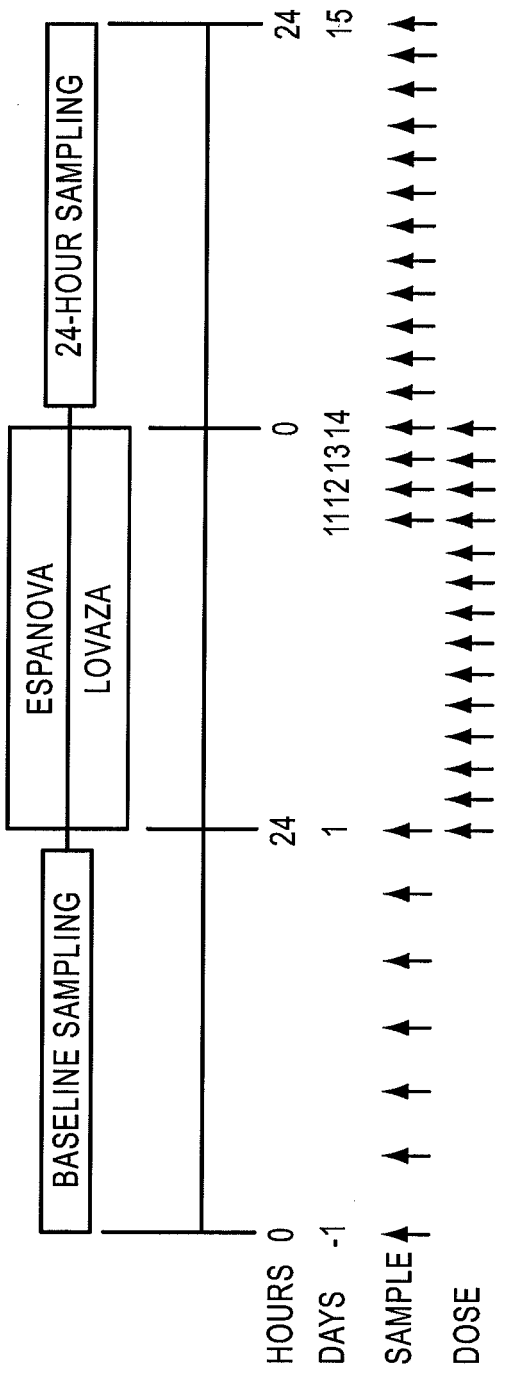

BASELINE SAMPLING
ESPANOVA
LOVAZA
24-HOUR SAMPLING
HOURS 0 24 0 24
DAYS -1 1 11 12 13 14 15
SAMPLE
DOSE

FIG. 11

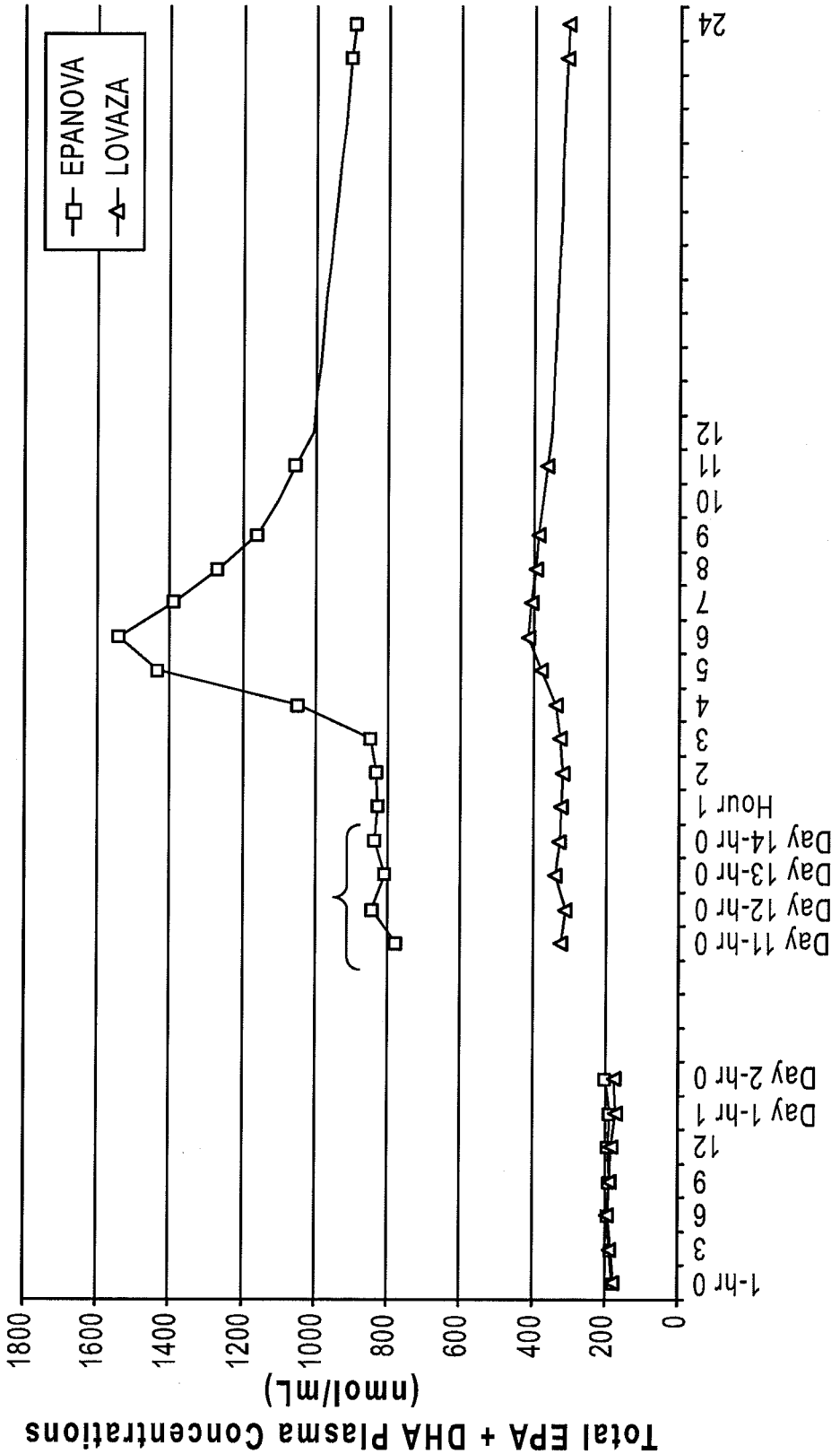

Total EPA + DHA Plasma Concentrations
(nmol/mL)
1800
1600
1400
1200
1000
800
600
400
200
0
EPANOVA
LOVAZA
1-hr 0
3
6
9
12
Day 1-hr 1
Day 2-hr 0
Day 11-hr 0
Day 12-hr 0
Day 13-hr 0
Day 14-hr 0
Hour 1
2
3
4
5
6
7
8
9
10
11
12
24
Time (Days or Hours)

FIG. 12A

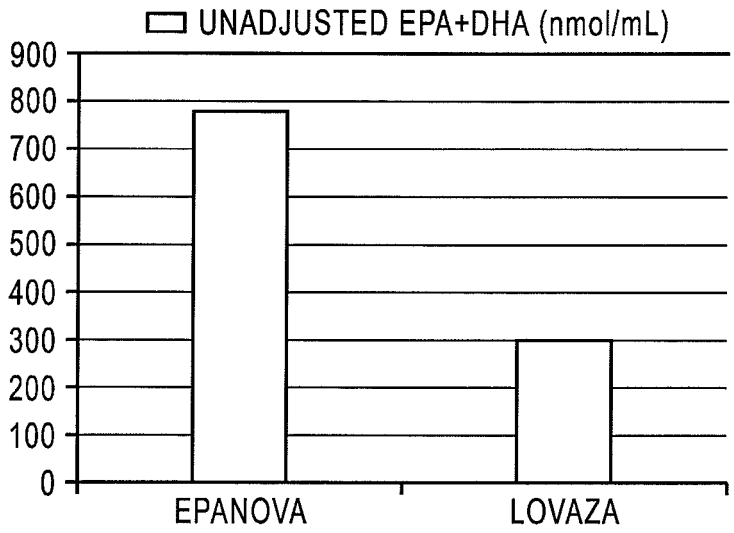


FIG. 12B

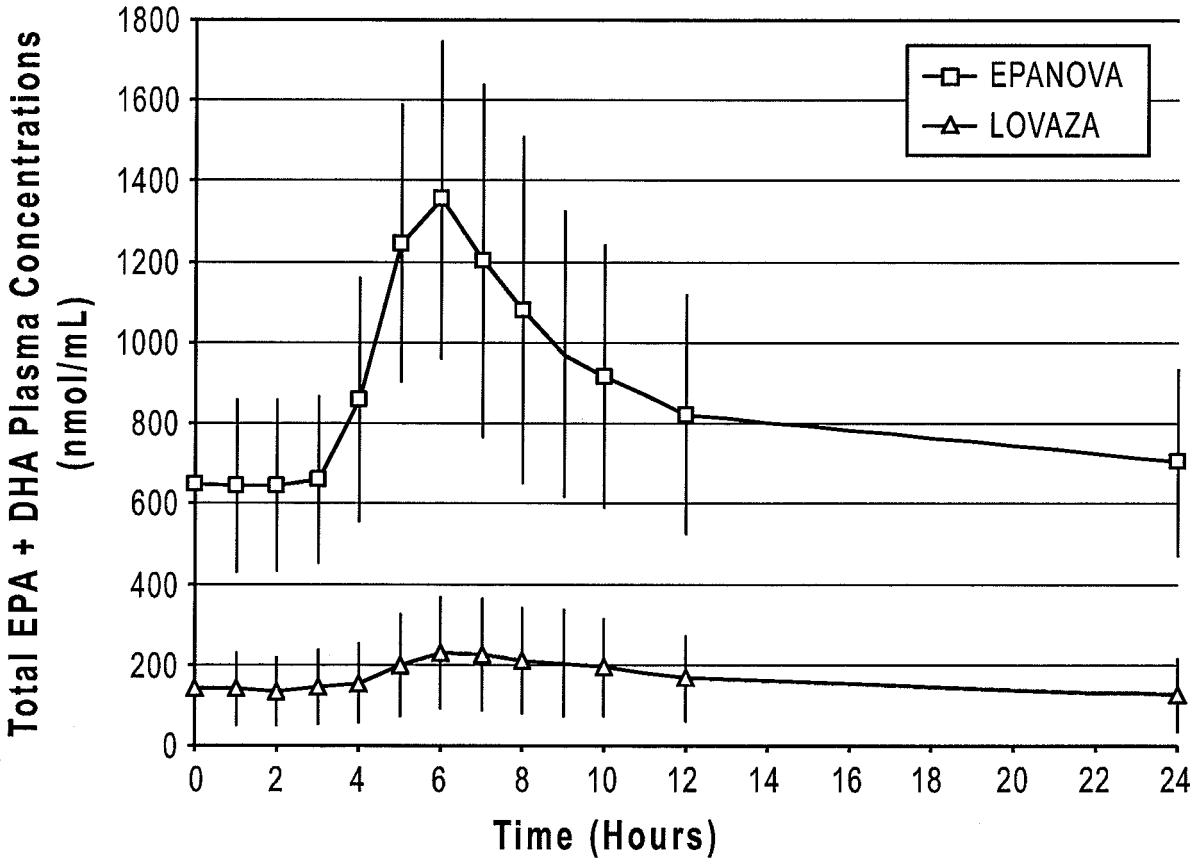


FIG. 13

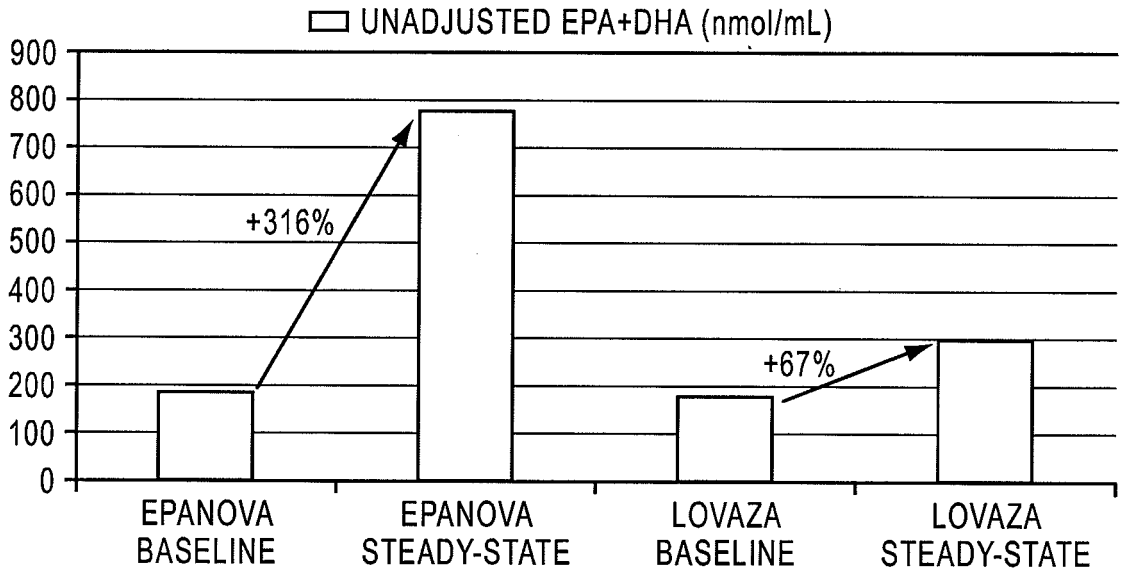


FIG. 14A

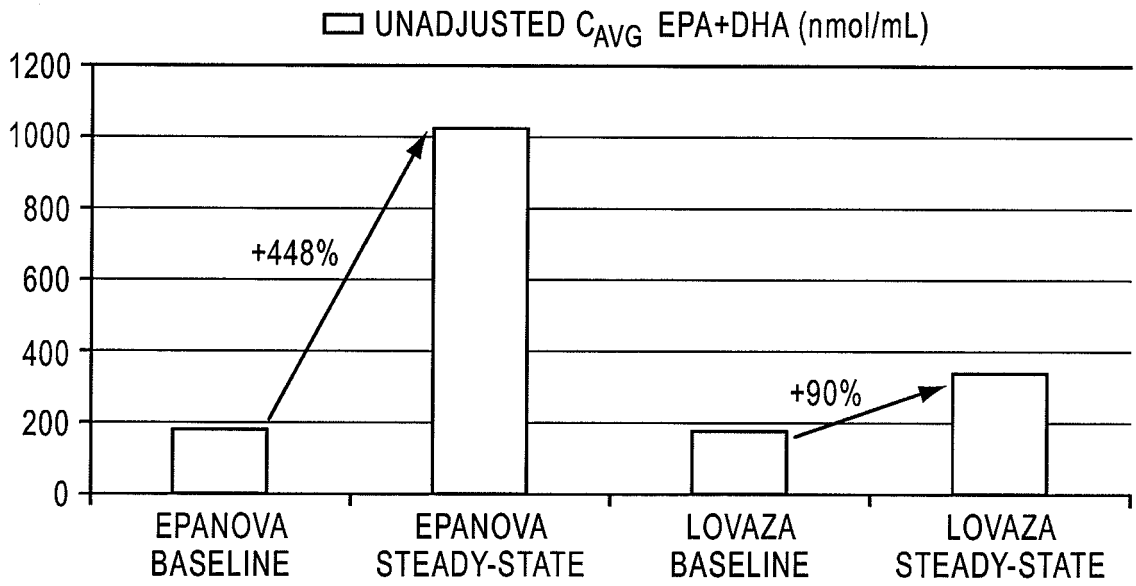


FIG. 14B

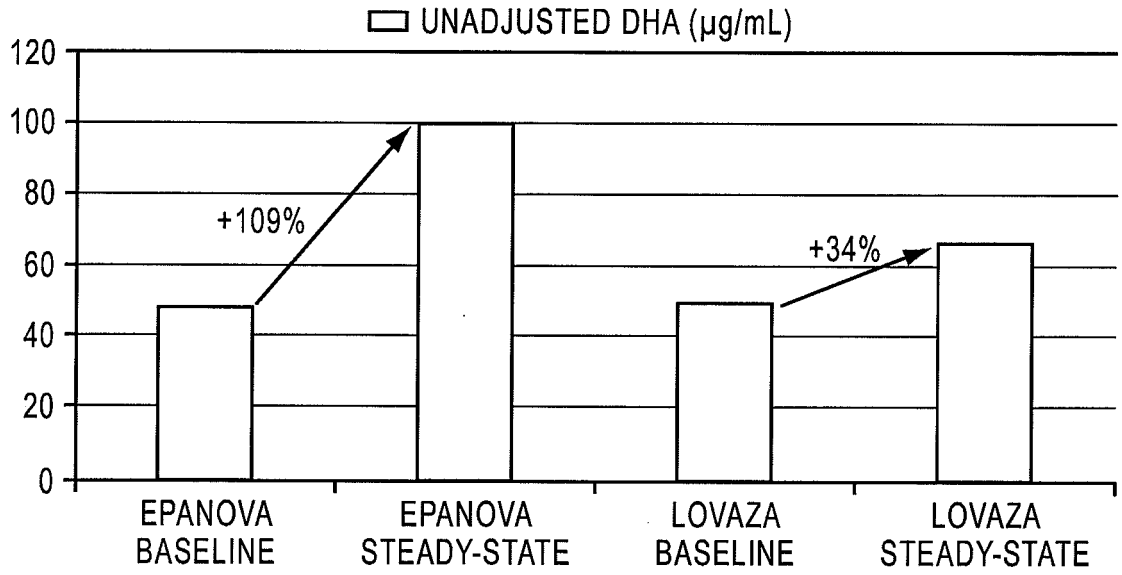


FIG. 15A

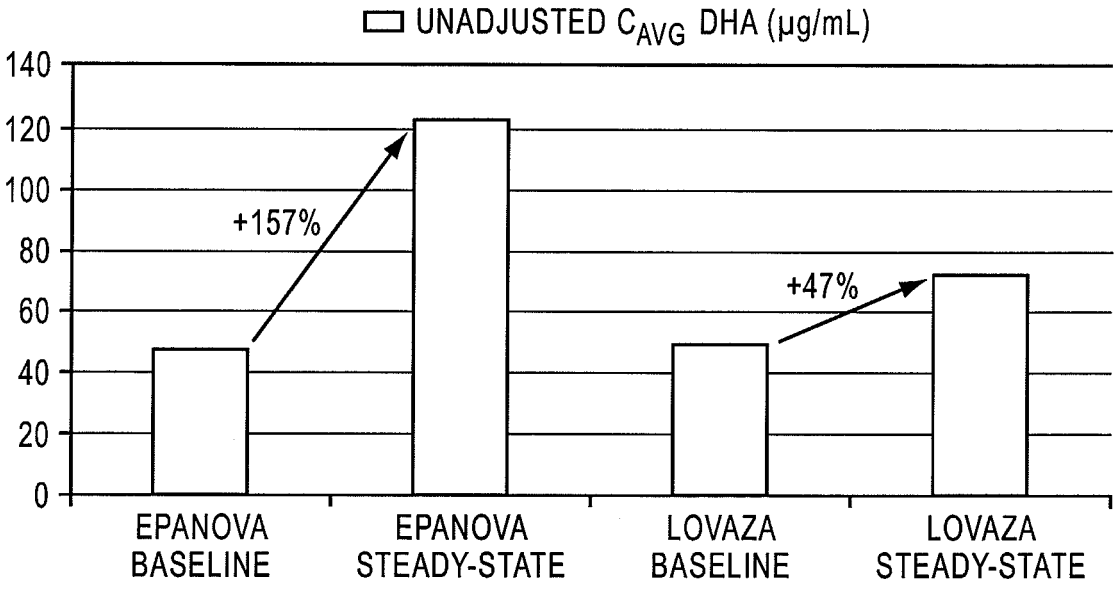


FIG. 15B

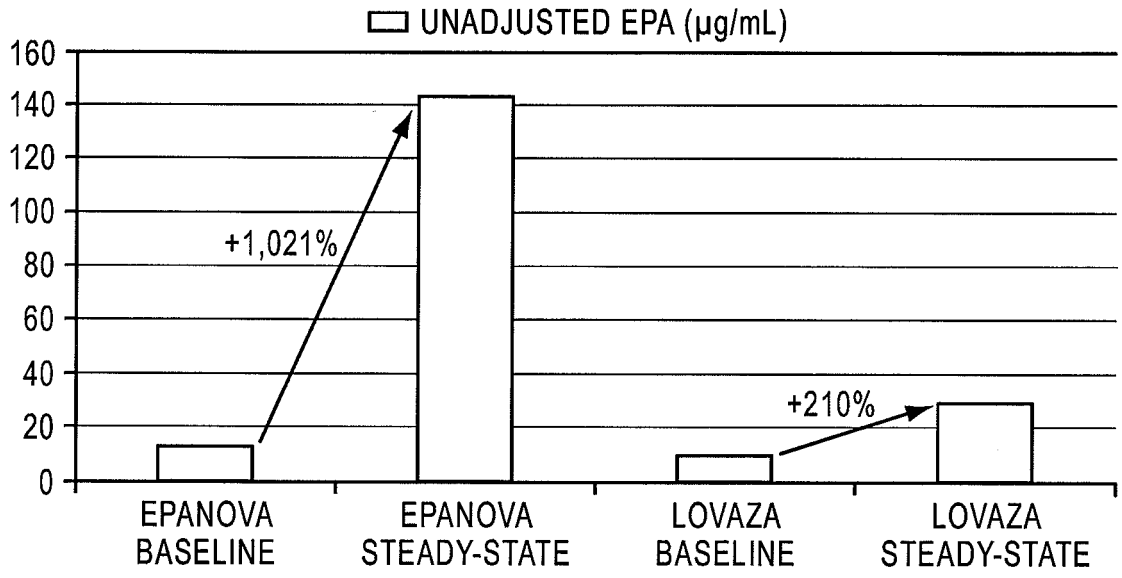


FIG. 16A

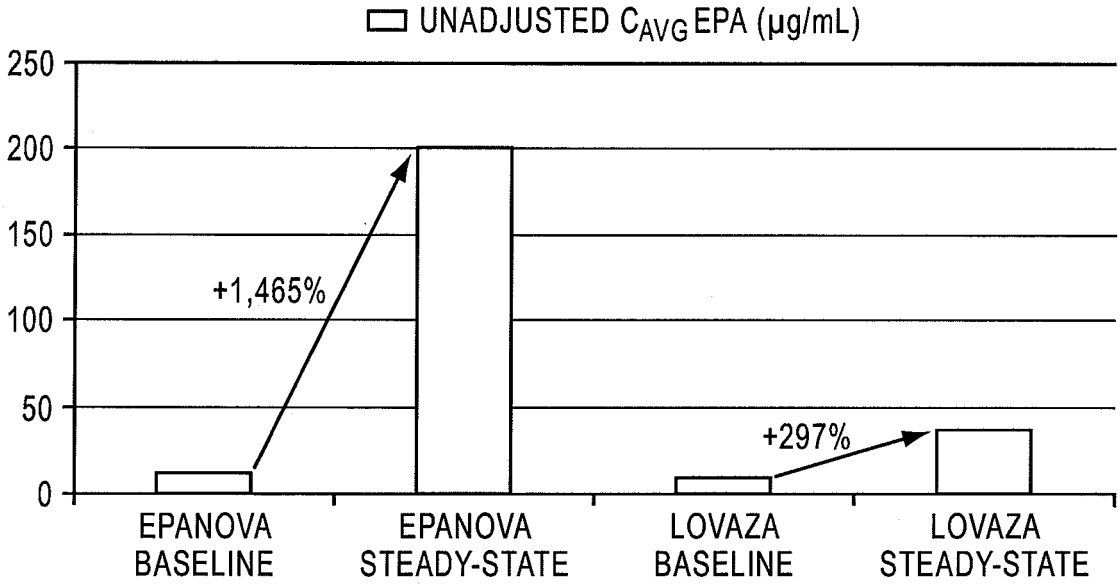


FIG. 16B

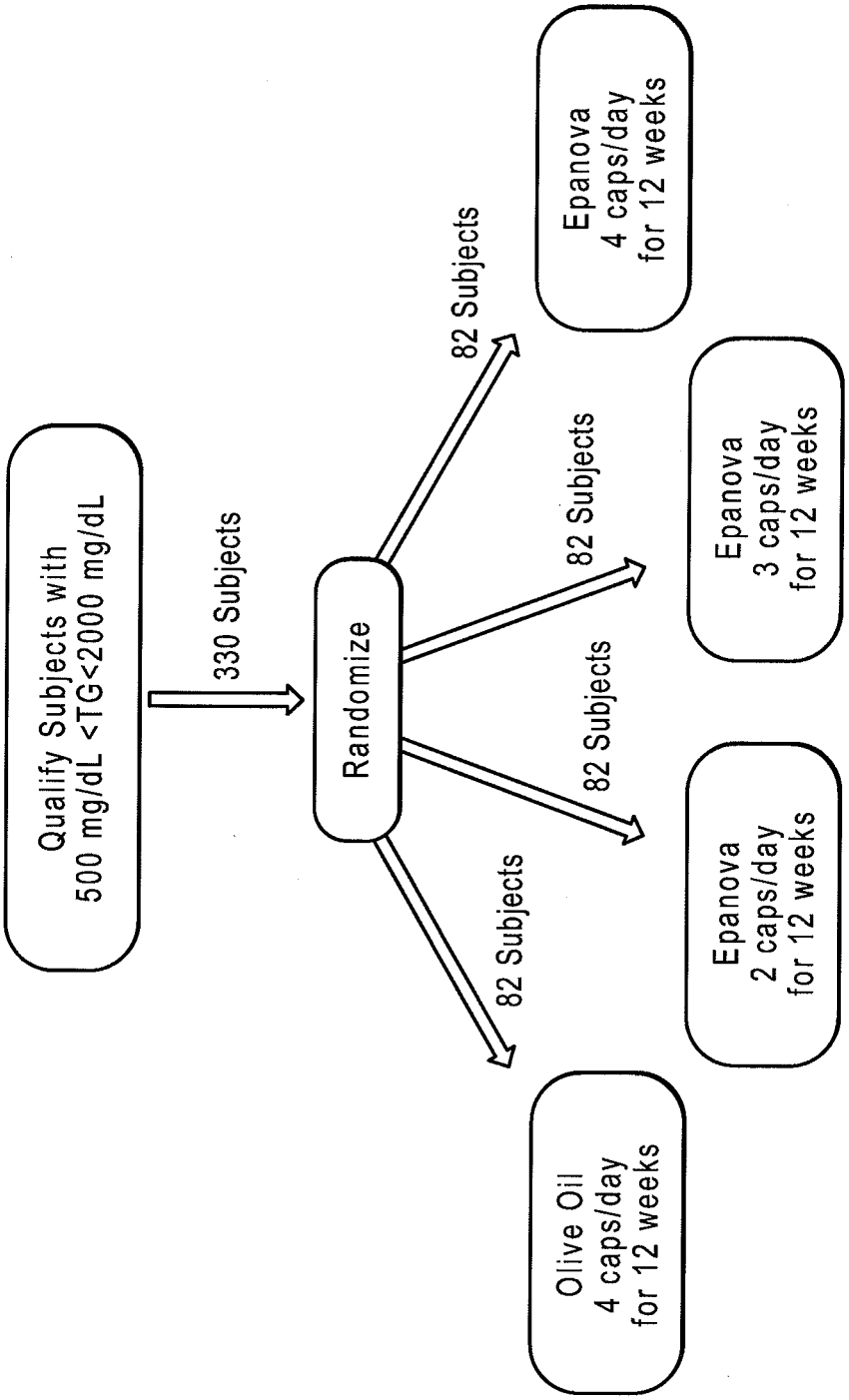

Qualify Subjects with
500 mg/dL <TG<2000 mg/dL
330 Subjects
Randomize
82 Subjects
Epanova
4 caps/day
for 12 weeks
82 Subjects
Epanova
3 caps/day
for 12 weeks
82 Subjects
Epanova
2 caps/day
for 12 weeks
82 Subjects
Olive Oil
4 caps/day
for 12 weeks

FIG. 17

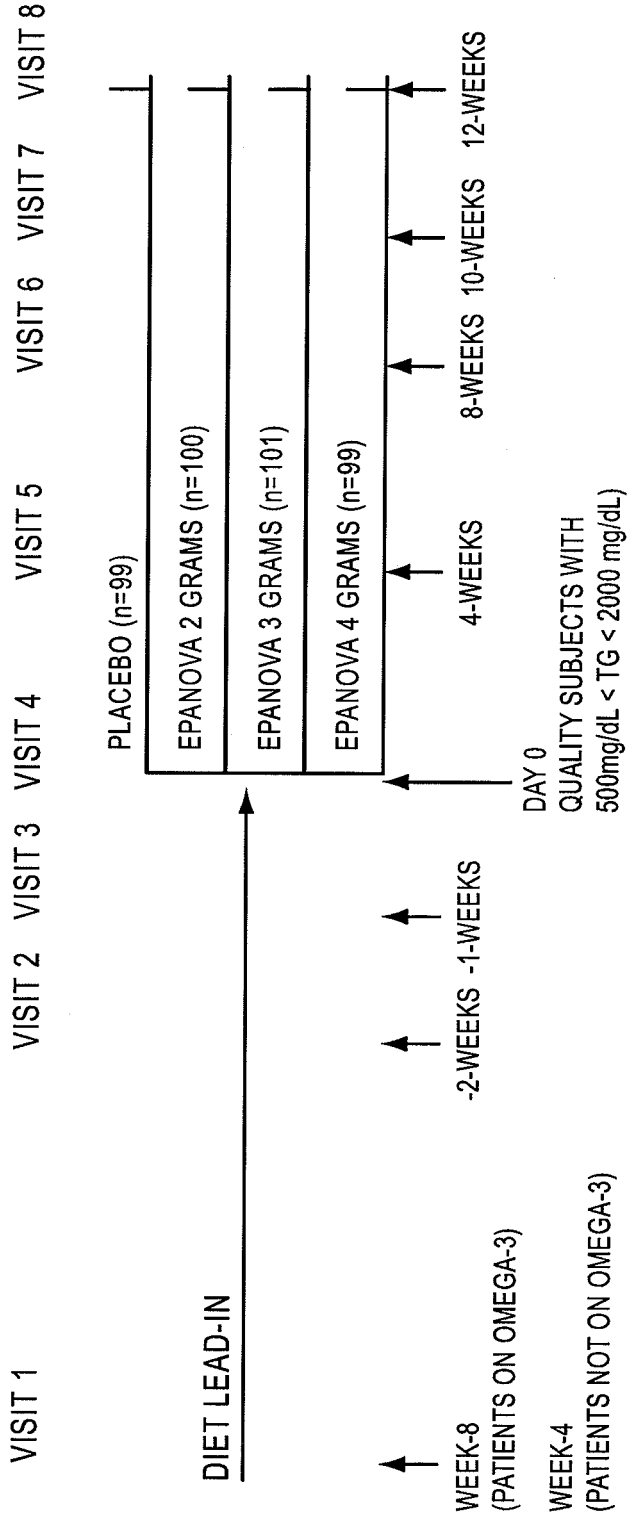

VISIT 1
VISIT 2
VISIT 3
VISIT 4
VISIT 5
VISIT 6
VISIT 7
VISIT 8
DIET LEAD-IN
WEEK-8
(PATIENTS ON OMEGA-3)
WEEK-4
(PATIENTS NOT ON OMEGA-3)
-2-WEEKS
-1-WEEKS
DAY 0
QUALITY SUBJECTS WITH
500mg/dL < TG < 2000 mg/dL)
4-WEEKS
8-WEEKS
10-WEEKS
12-WEEKS
PLACEBO (n=99)
EPANOVA 2 GRAMS (n=100)
EPANOVA 3 GRAMS (n=101)
EPANOVA 4 GRAMS (n=99)

FIG. 18

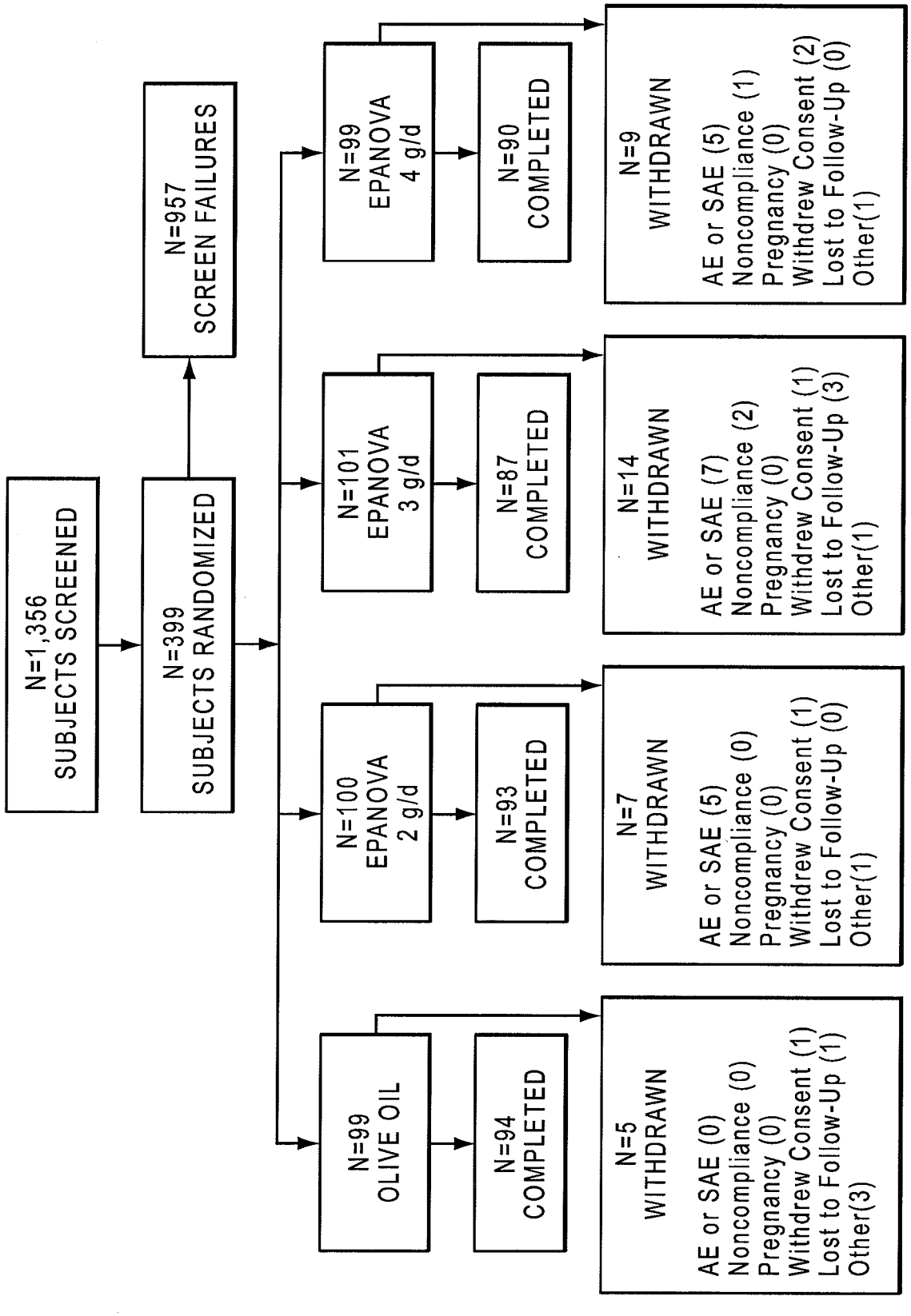

N=1,356
SUBJECTS SCREENED
N=399
SUBJECTS RANDOMIZED
N=957
SCREEN FAILURES
N=99
OLIVE OIL
N=94
COMPLETED
N=5
WITHDRAWN
AE or SAE (0)
Noncompliance (0)
Pregnancy (0)
Withdrew Consent (1)
Lost to Follow-Up (1)
Other(3)
N=100
EPANOVA
2 g/d
N=93
COMPLETED
N=7
WITHDRAWN
AE or SAE (5)
Noncompliance (0)
Pregnancy (0)
Withdrew Consent (1)
Lost to Follow-Up (0)
Other(1)
N=101
EPANOVA
3 g/d
N=87
COMPLETED
N=14
WITHDRAWN
AE or SAE (7)
Noncompliance (2)
Pregnancy (0)
Withdrew Consent (1)
Lost to Follow-Up (3)
Other(1)
N=99
EPANOVA
4 g/d
N=90
COMPLETED
N=9
WITHDRAWN
AE or SAE (5)
Noncompliance (1)
Pregnancy (0)
Withdrew Consent (2)
Lost to Follow-Up (0)
Other(1)

FIG. 19

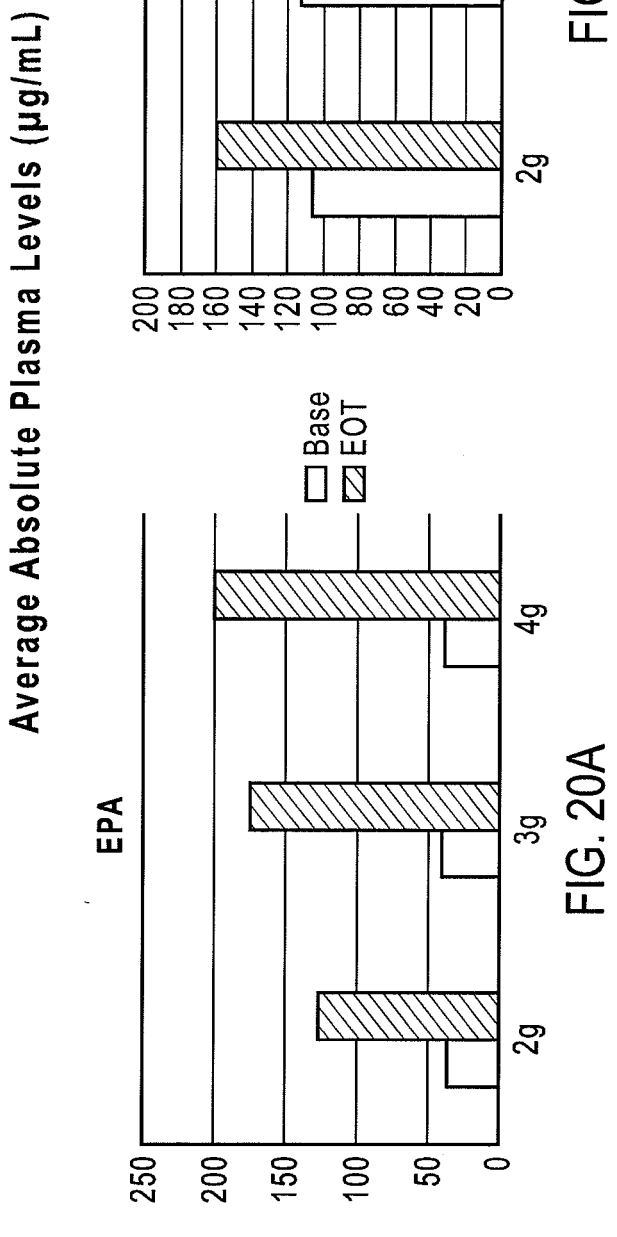


FIG. 20A

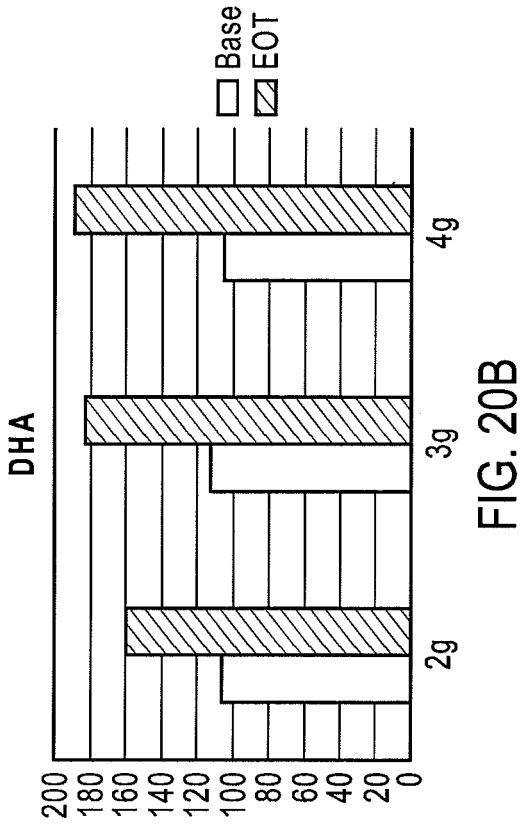


FIG. 20B

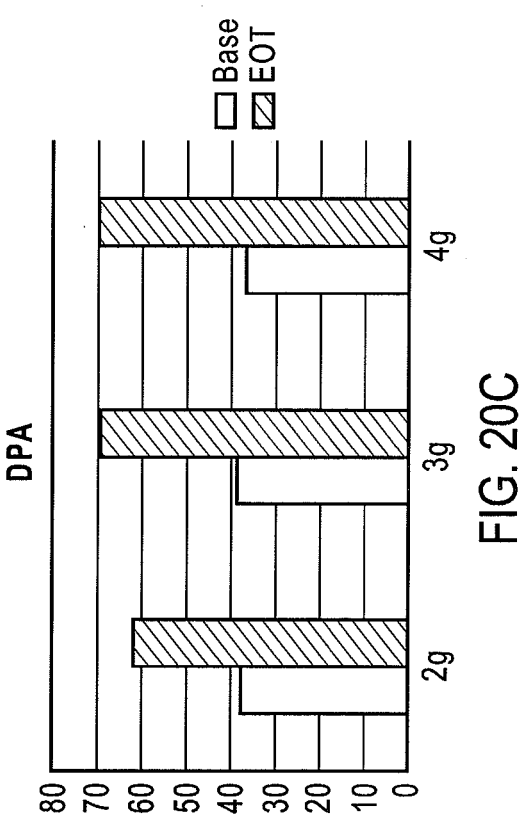


FIG. 20C

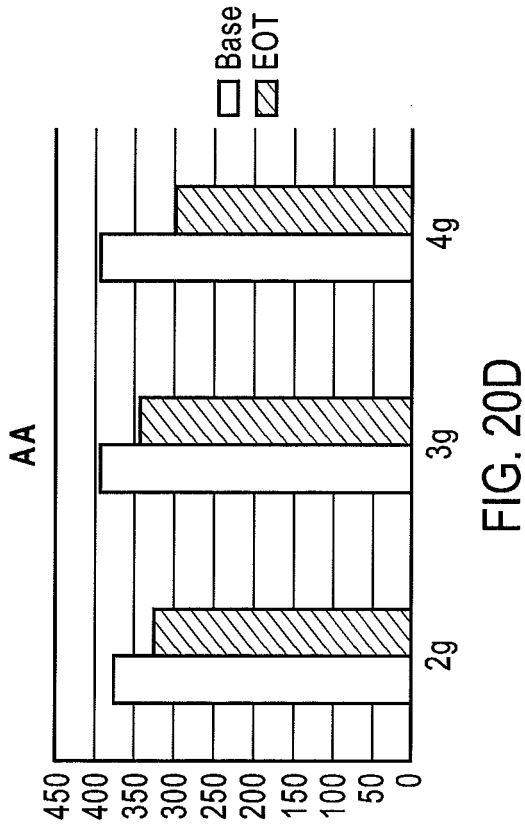


FIG. 20D

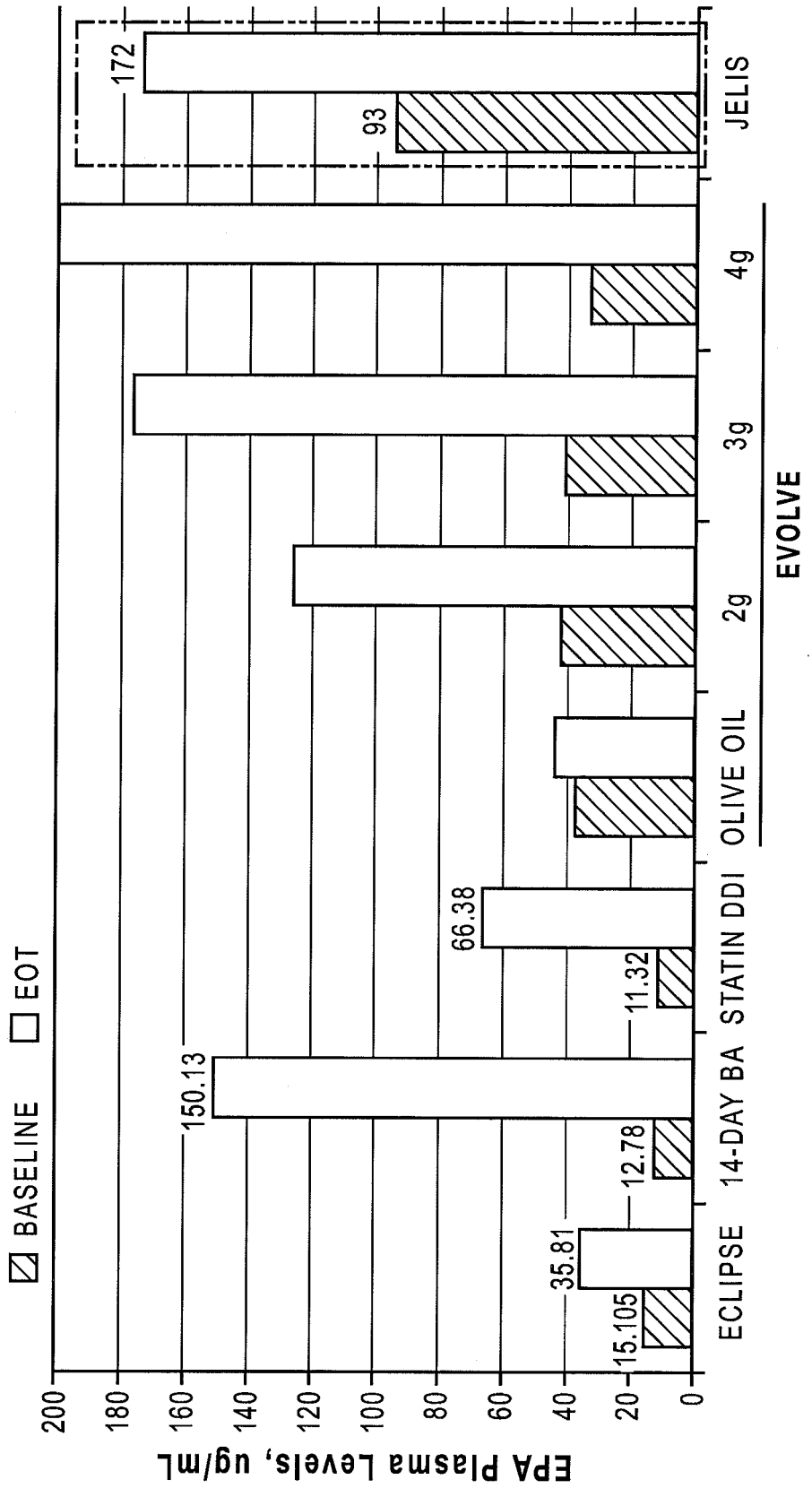

EPA Plasma Levels, ug/mL
200
180
160
140
120
100
80
60
40
20
0
BASELINE
EOT
15.105
35.81
12.78
150.13
11.32
66.38
172
93
ECLIPSE
14-DAY BA
STATIN DDI
OLIVE OIL
2g
3g
4g
EVOLVE
JELIS

FIG. 20E

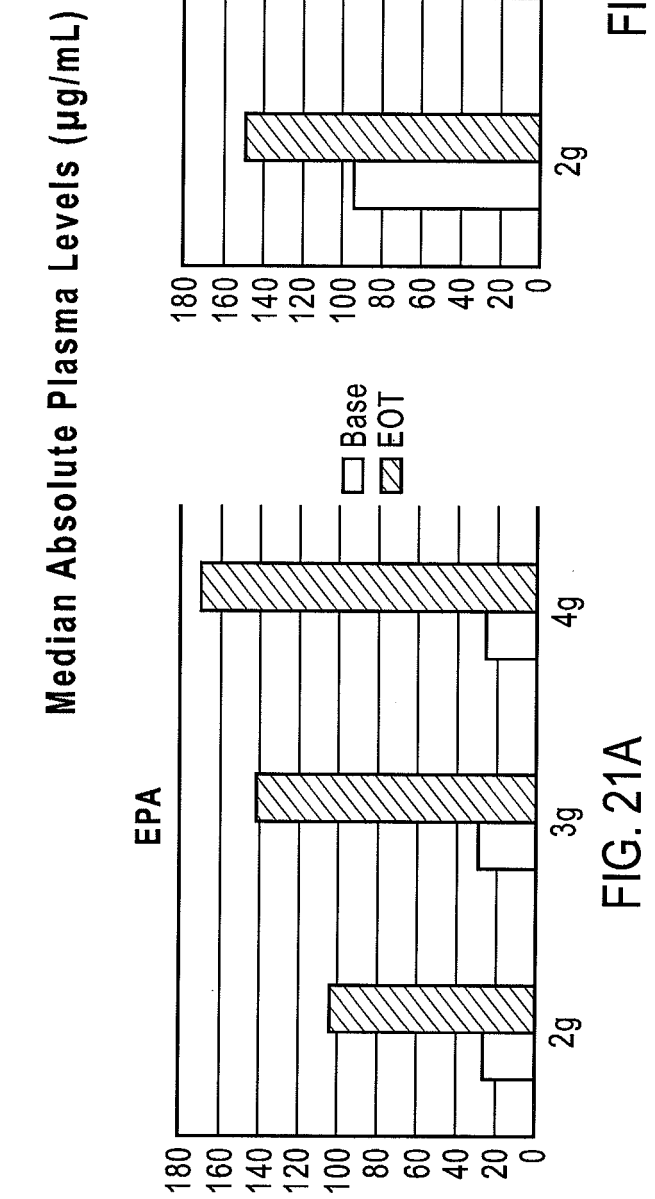


FIG. 21A

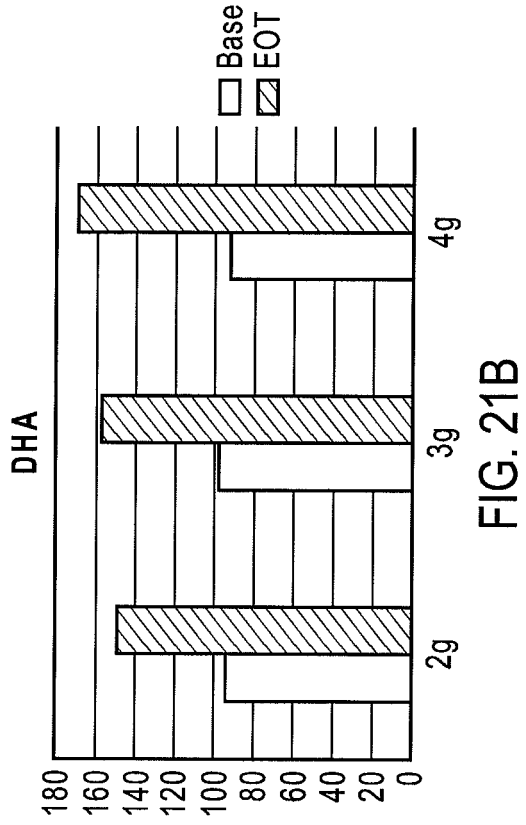


FIG. 21B

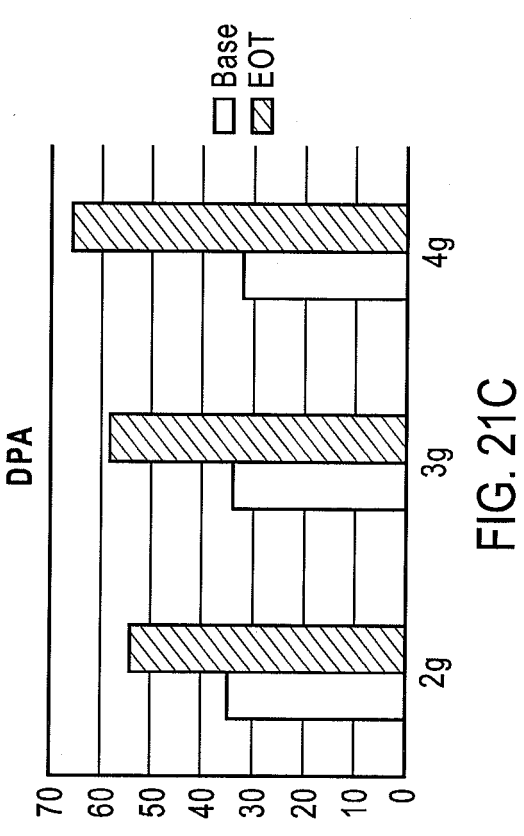


FIG. 21C

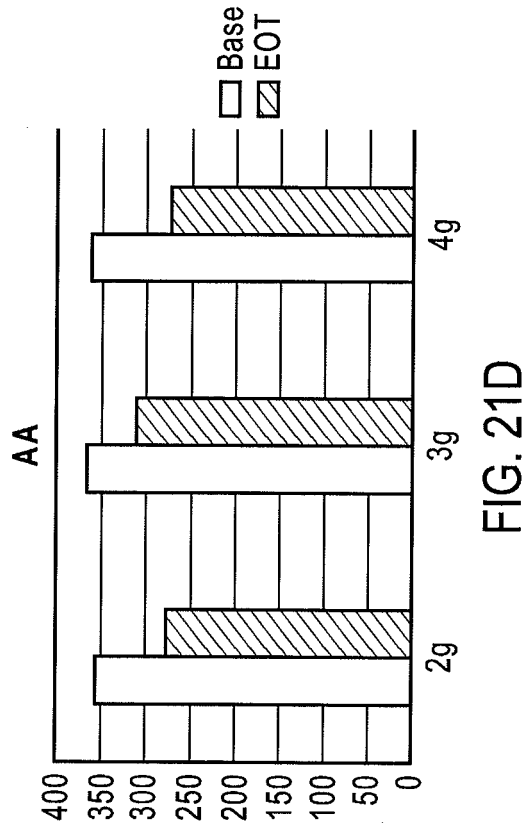


FIG. 21D

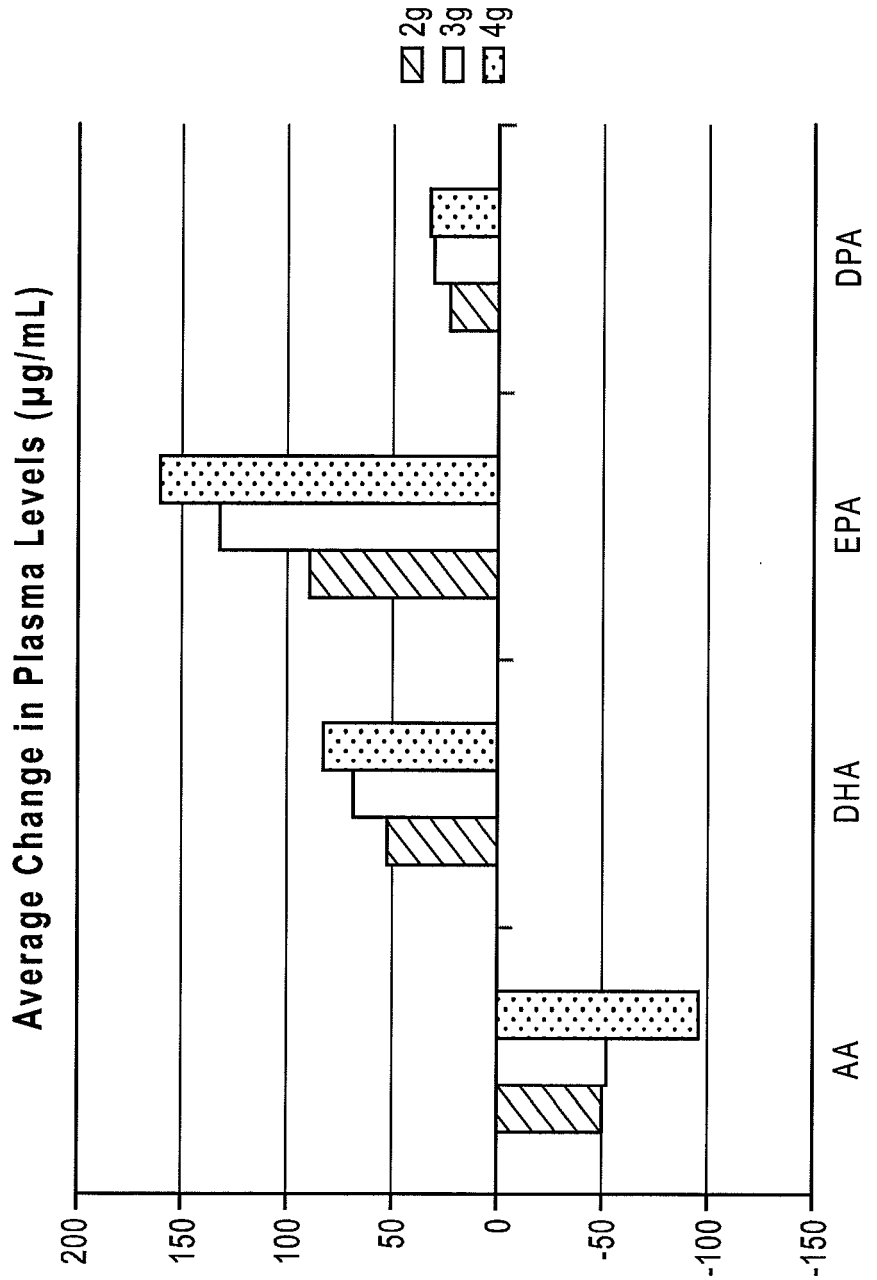

2g
3g
4g
Average Change in Plasma Levels (µg/mL)
200
150
100
50
0
-50
-100
-150
AA
DHA
EPA
DPA

FIG. 22A

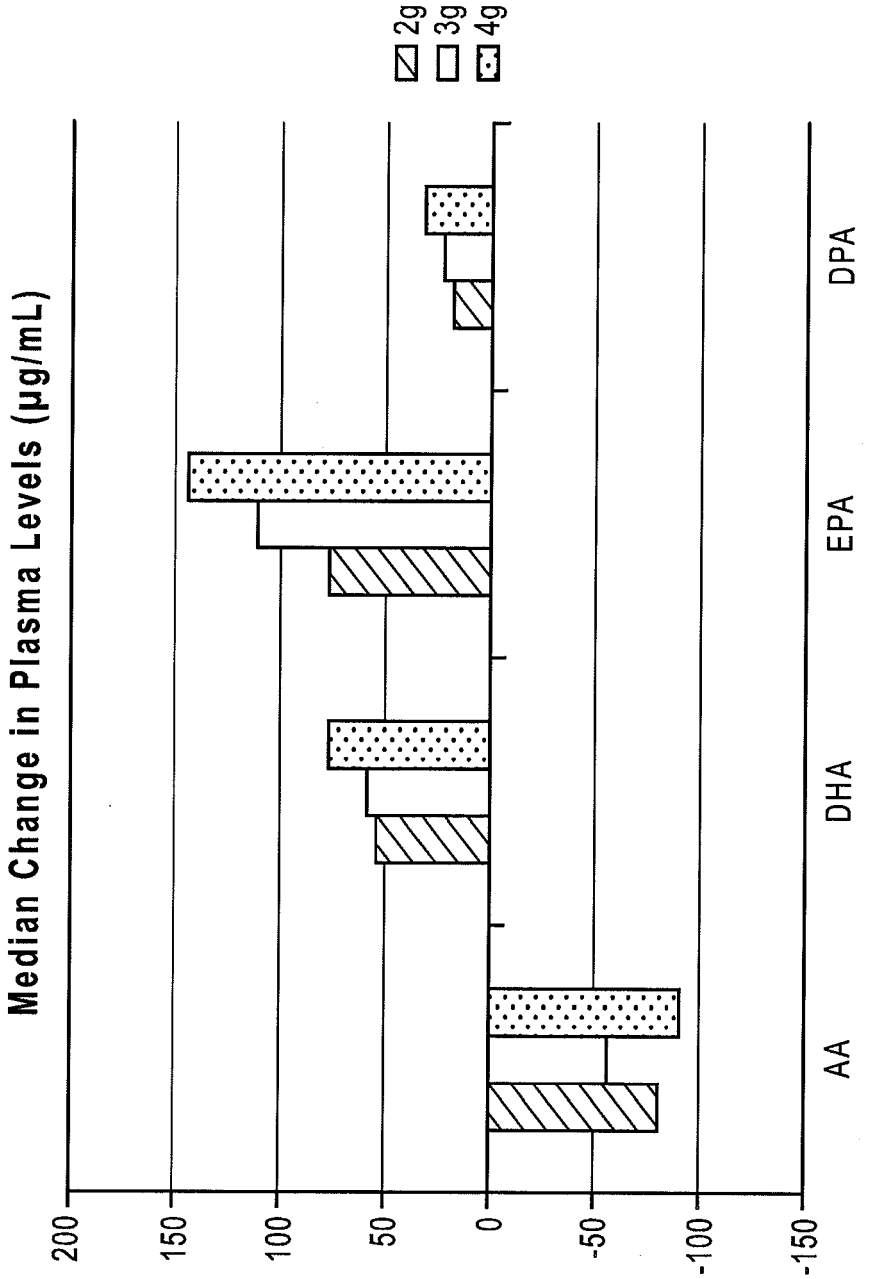

2g
3g
4g
Median Change in Plasma Levels (µg/mL)
200
150
100
50
0
-50
-100
-150
AA
DHA
EPA
DPA

FIG. 22B

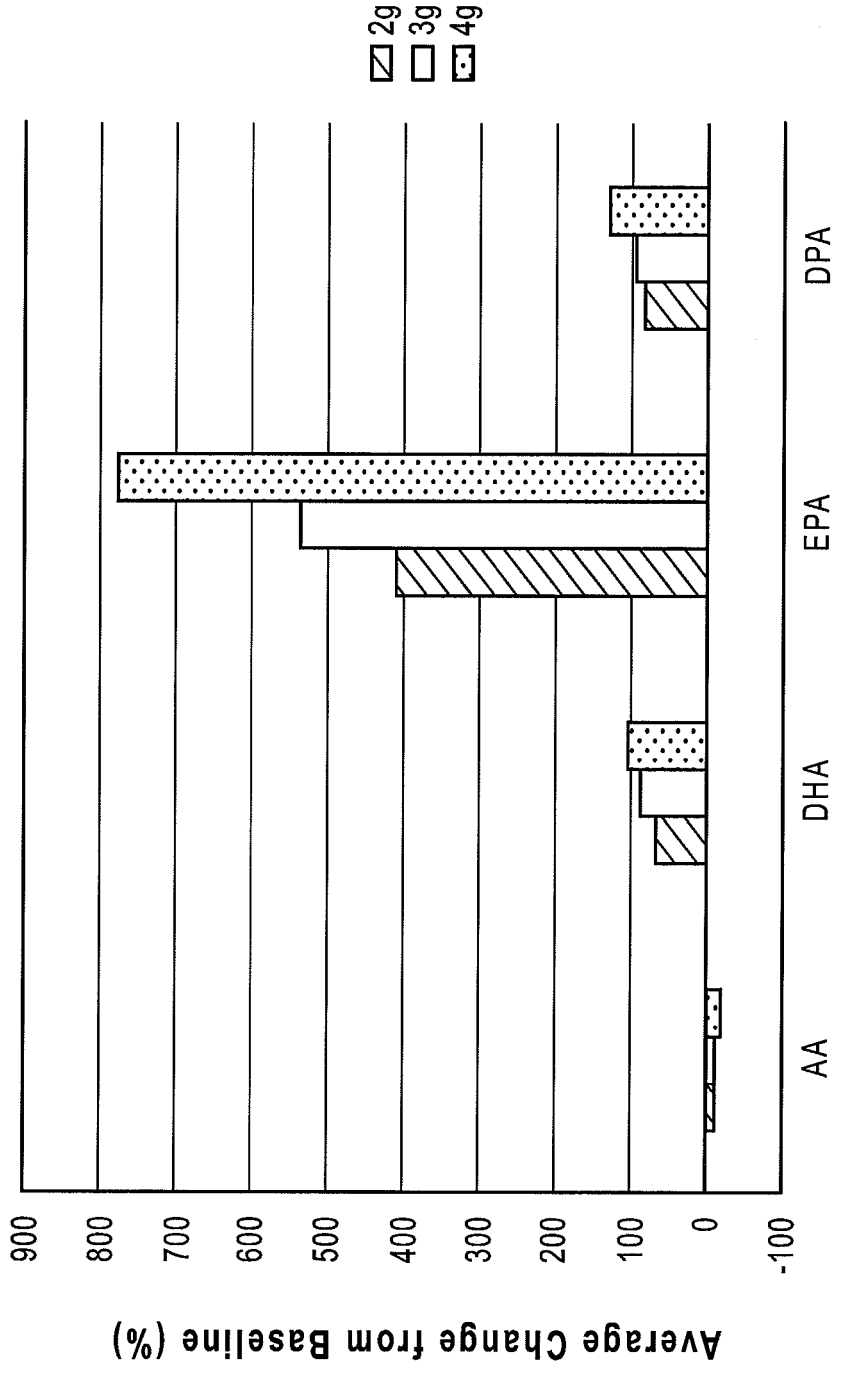

2g
3g
4g
900
800
700
600
500
400
300
200
100
0
-100
AA
DHA
EPA
DPA
Average Change from Baseline (%)

FIG. 23A

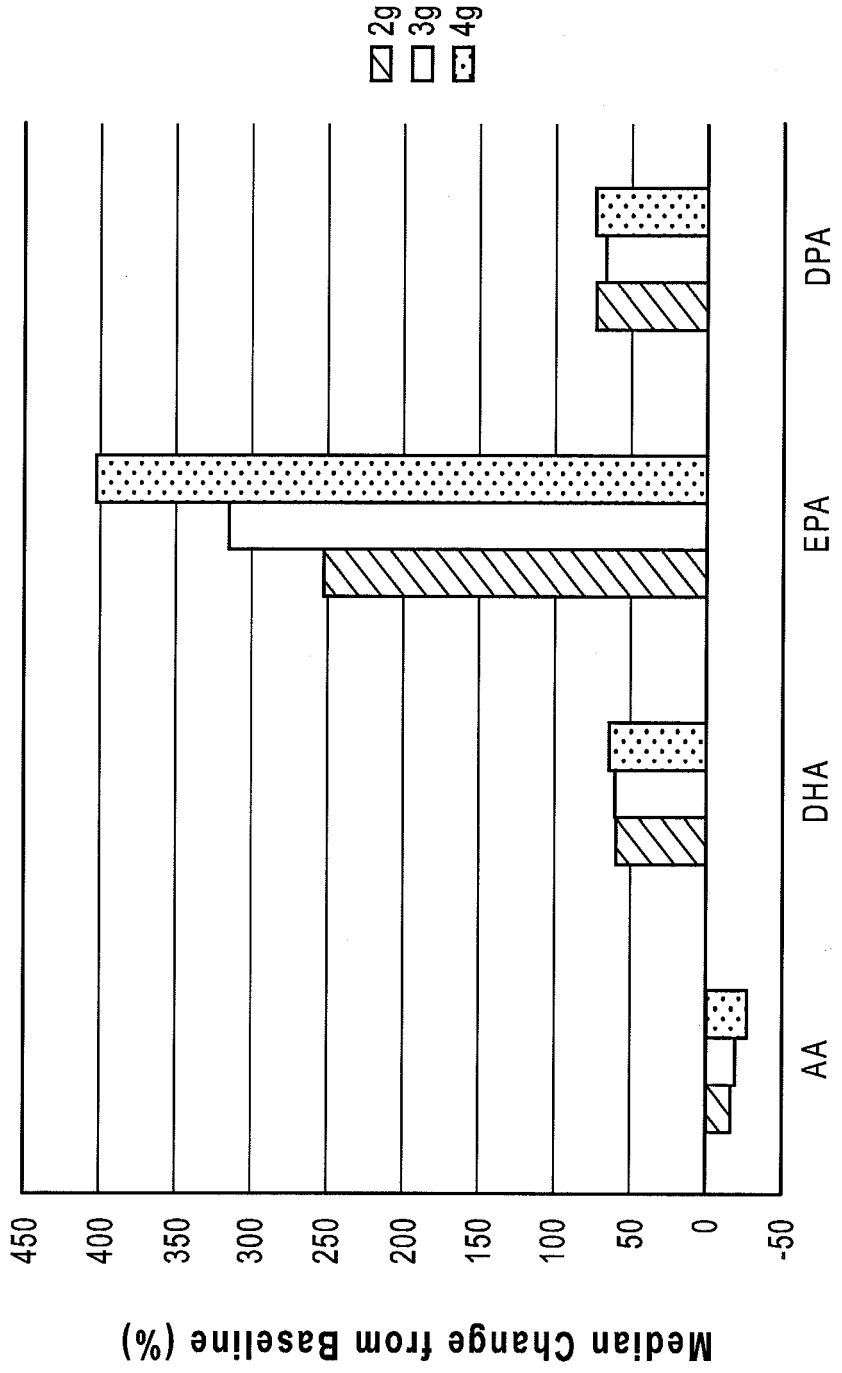

2g
3g
4g
DPA
EPA
DHA
AA
450
400
350
300
250
200
150
100
50
0
-50
Median Change from Baseline (%)

FIG. 23B

FIG. 24A

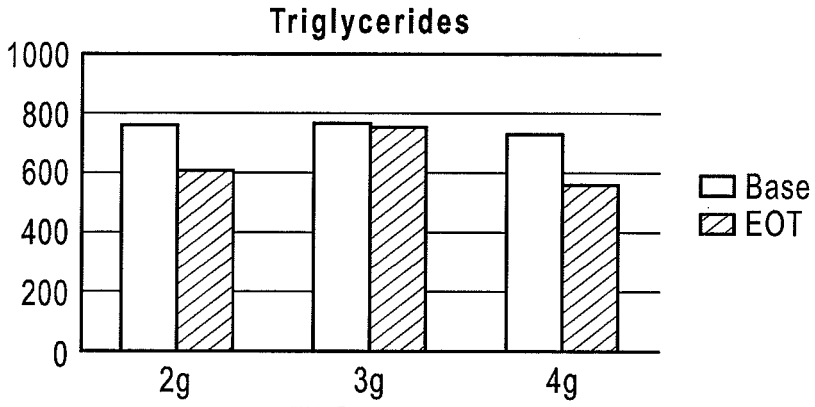


FIG. 24A

FIG. 24B

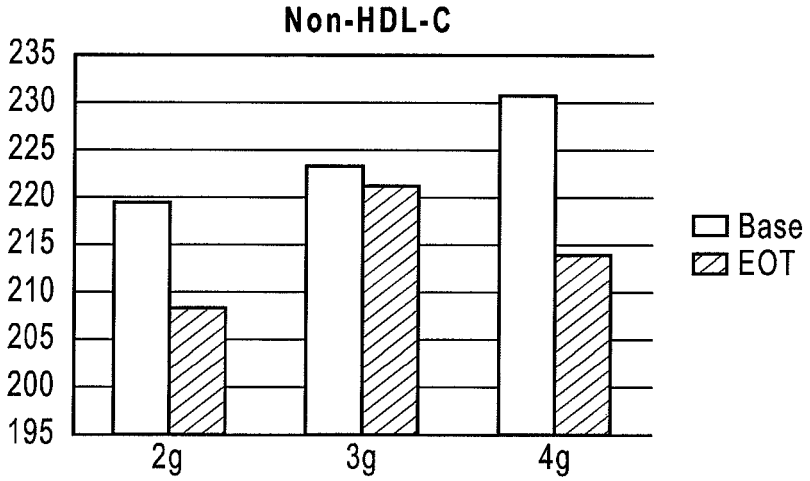


FIG. 24B

FIG. 24C

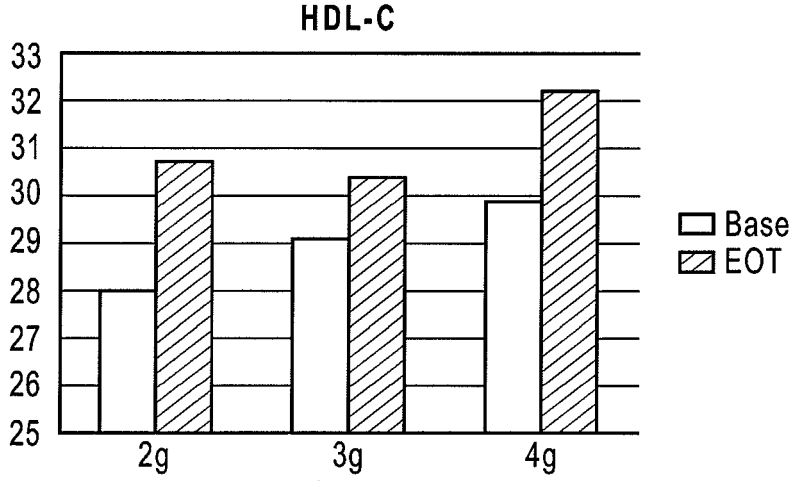


FIG. 24C

Average Absolute Plasma Levels (mg/dL)

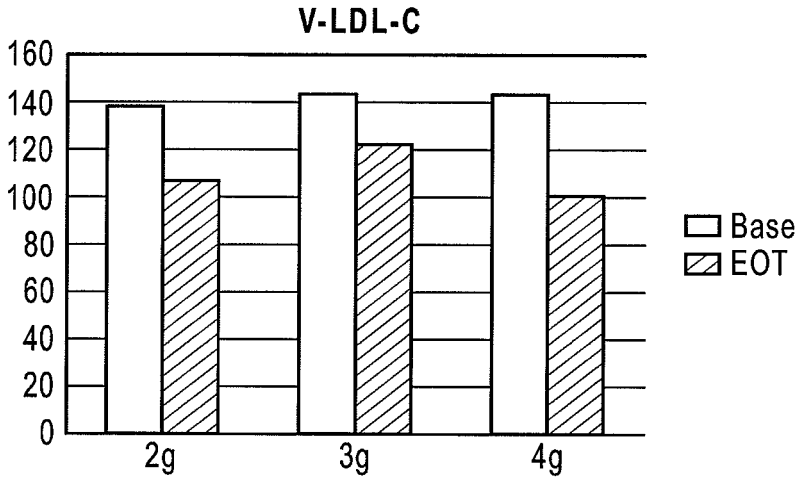


FIG. 24D

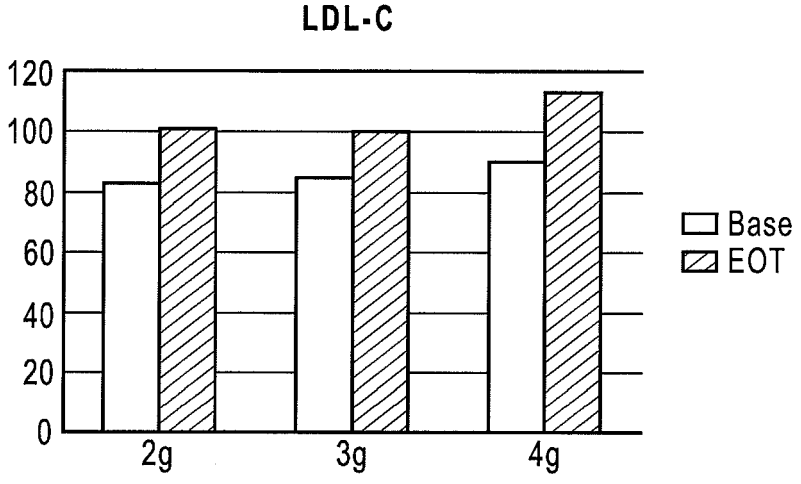


FIG. 24E

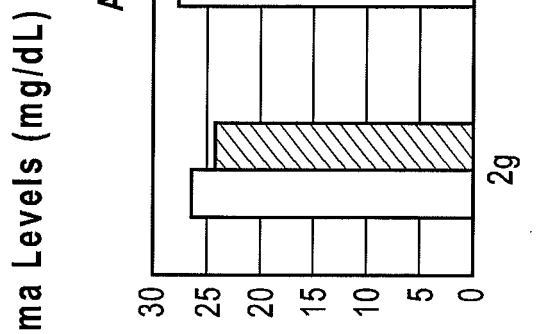


FIG. 24G

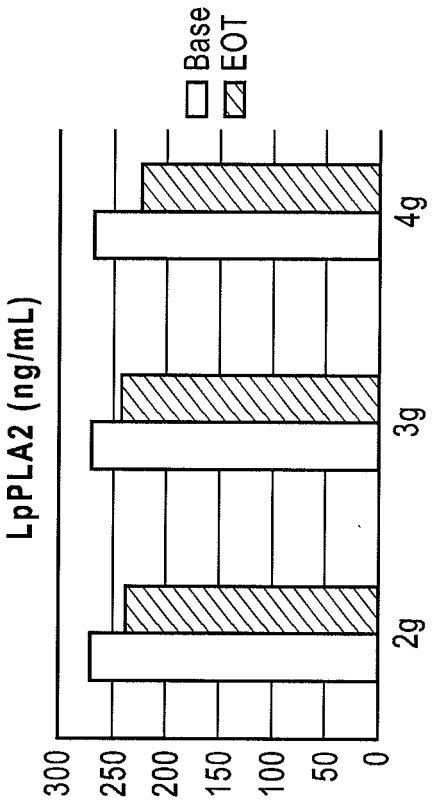


FIG. 24I

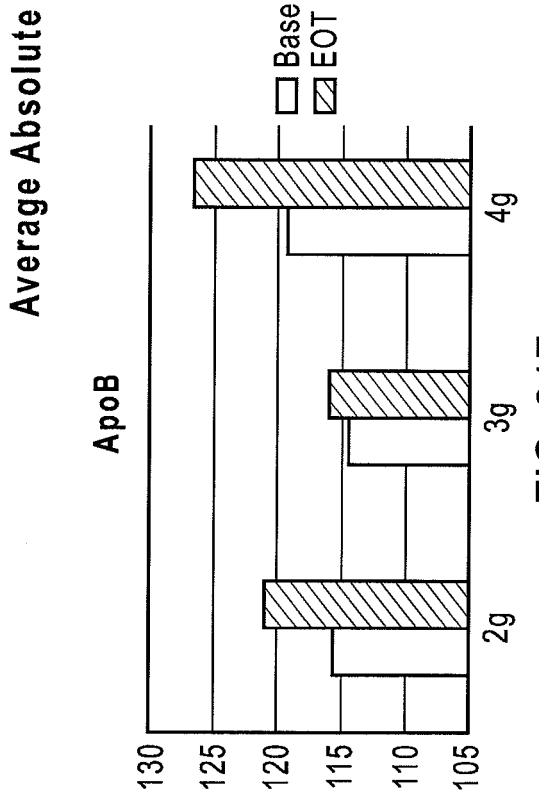


FIG. 24F

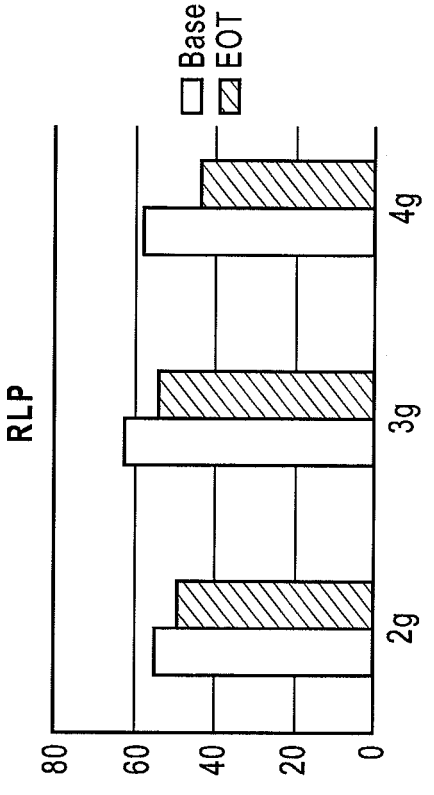


FIG. 24H

Average Absolute Plasma Levels (mg/dL)

Median Absolute Plasma Levels (mg/dL)

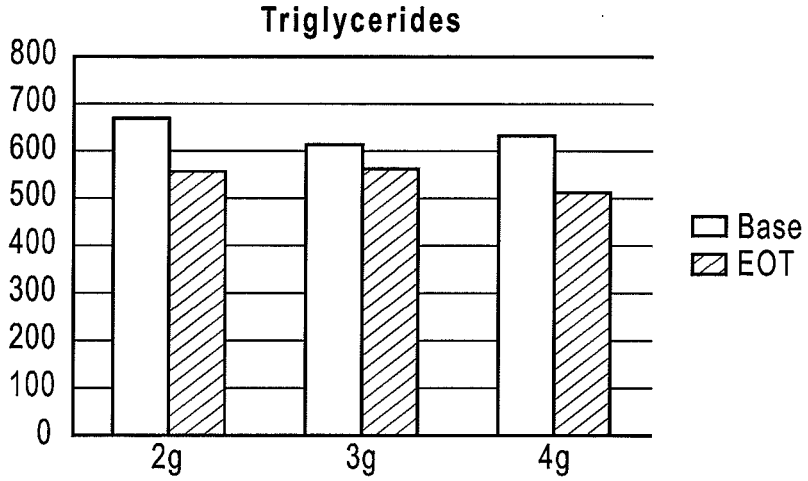


FIG. 25A

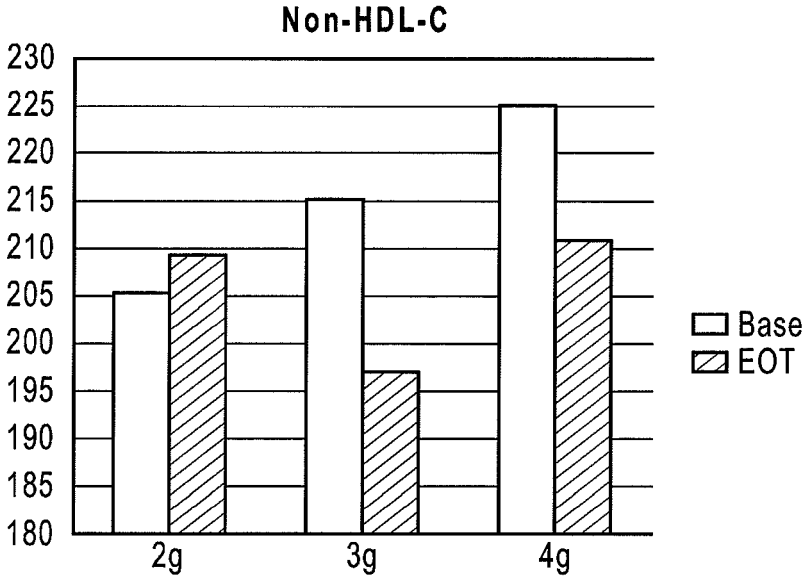


FIG. 25B

FIG. 25C

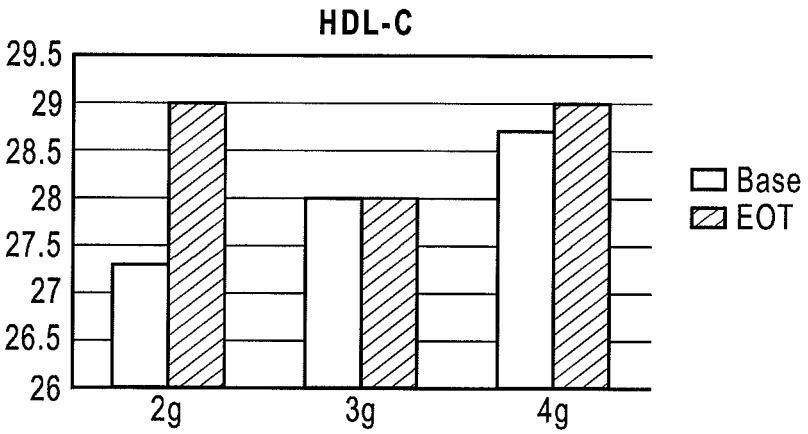


FIG. 25D

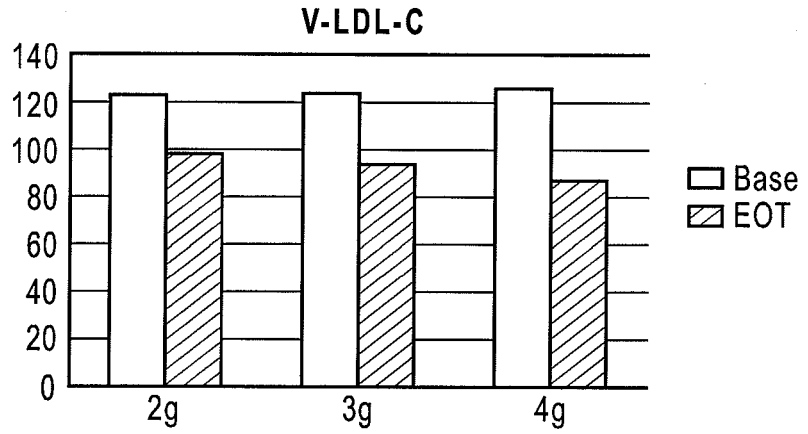
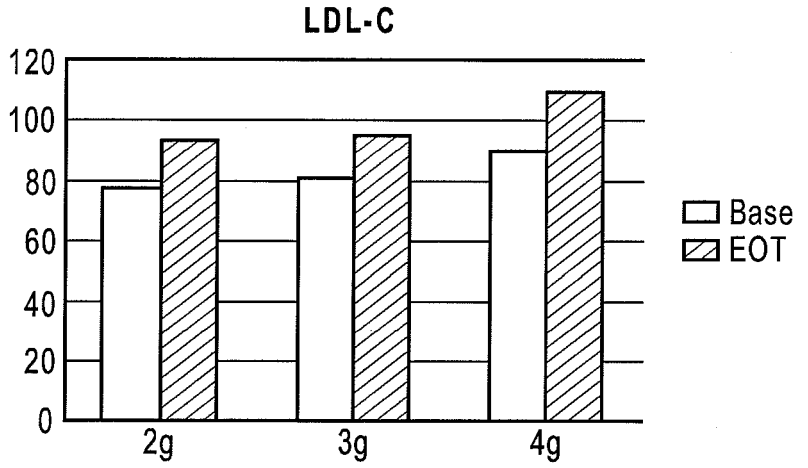


FIG. 25E



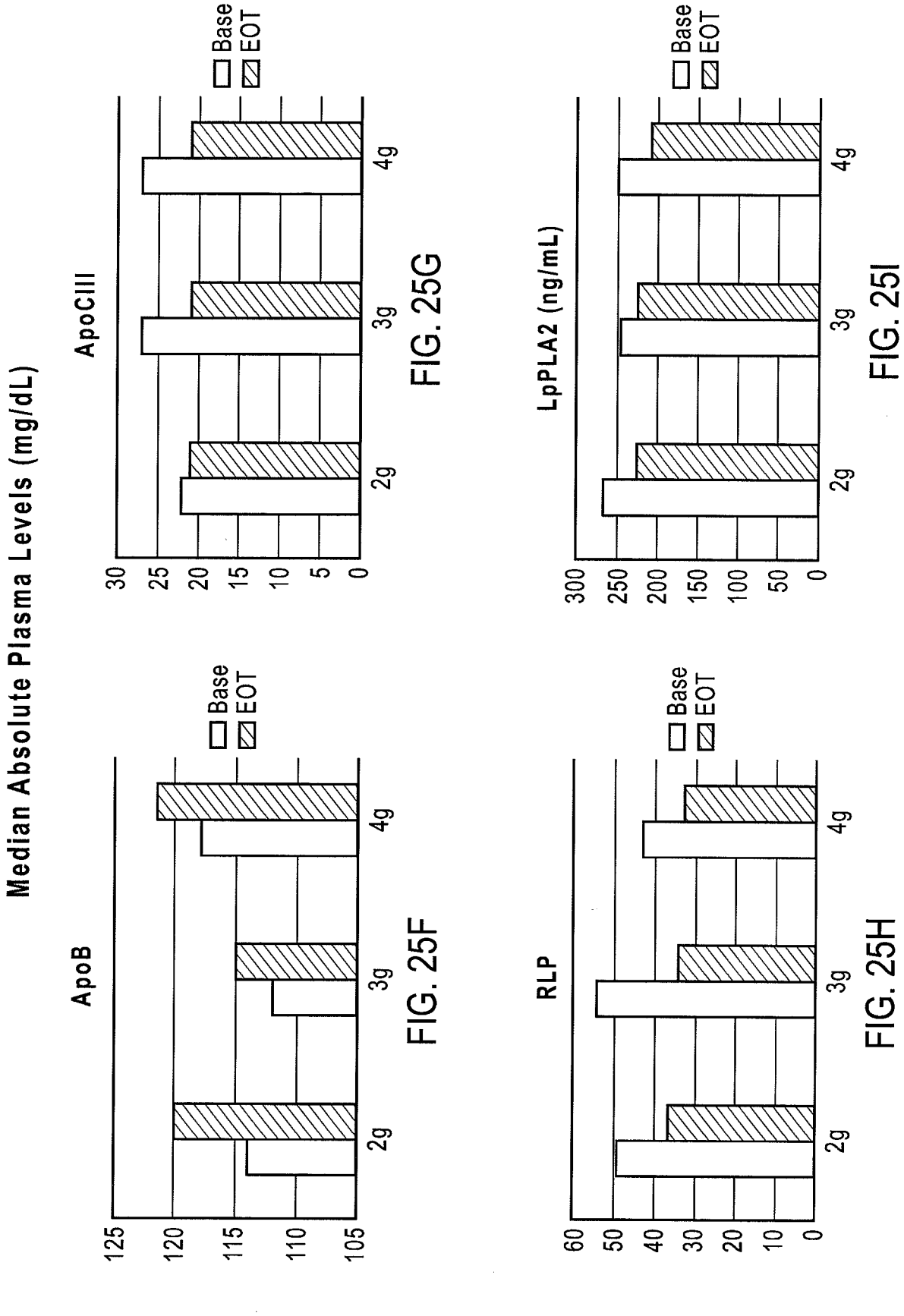


FIG. 25G

FIG. 25I

FIG. 25F

FIG. 25H

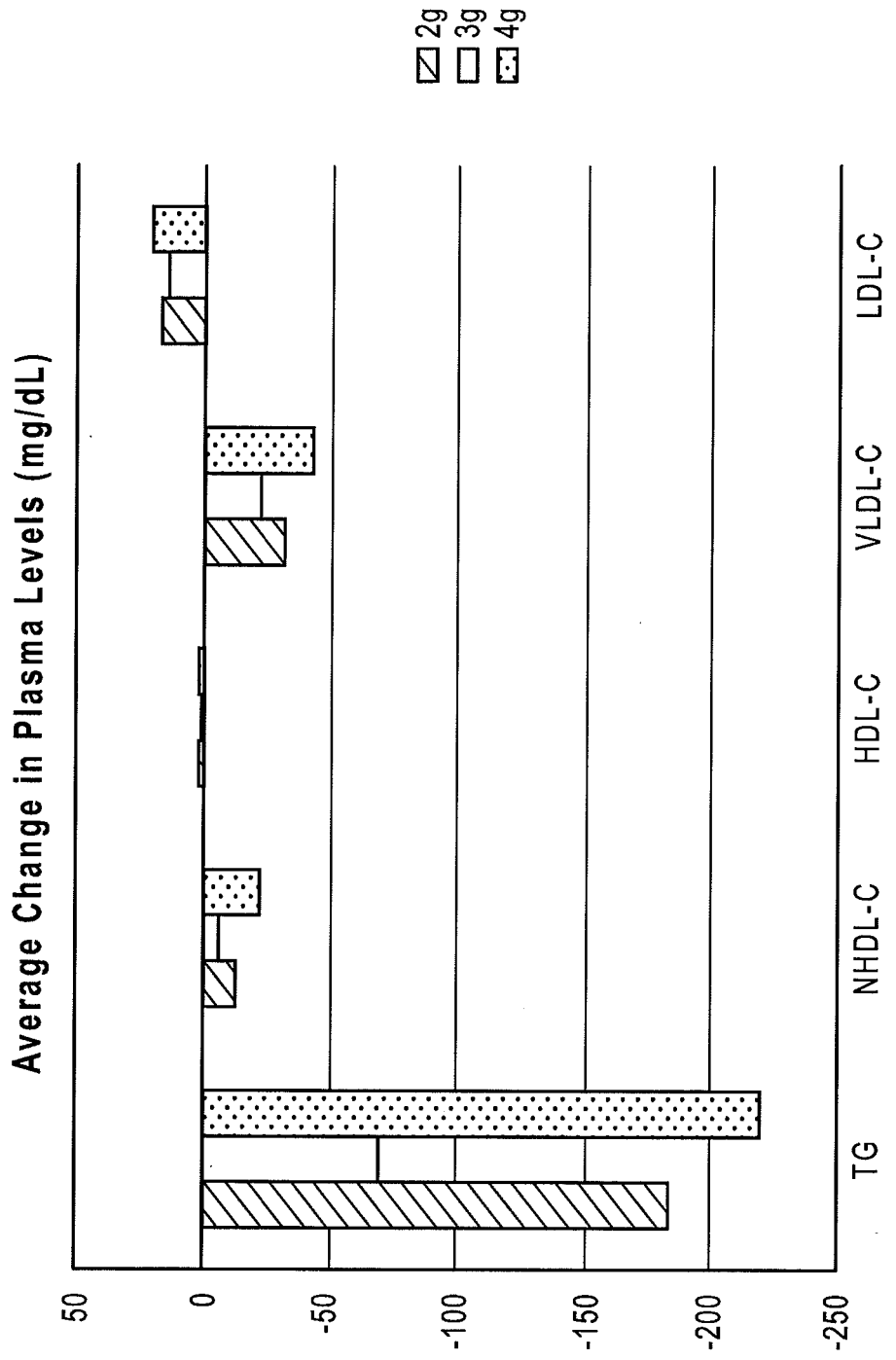

2g
3g
4g
Average Change in Plasma Levels (mg/dL)
50
0
-50
-100
-150
-200
-250
TG
NHDL-C
HDL-C
VLDL-C
LDL-C

FIG. 26A

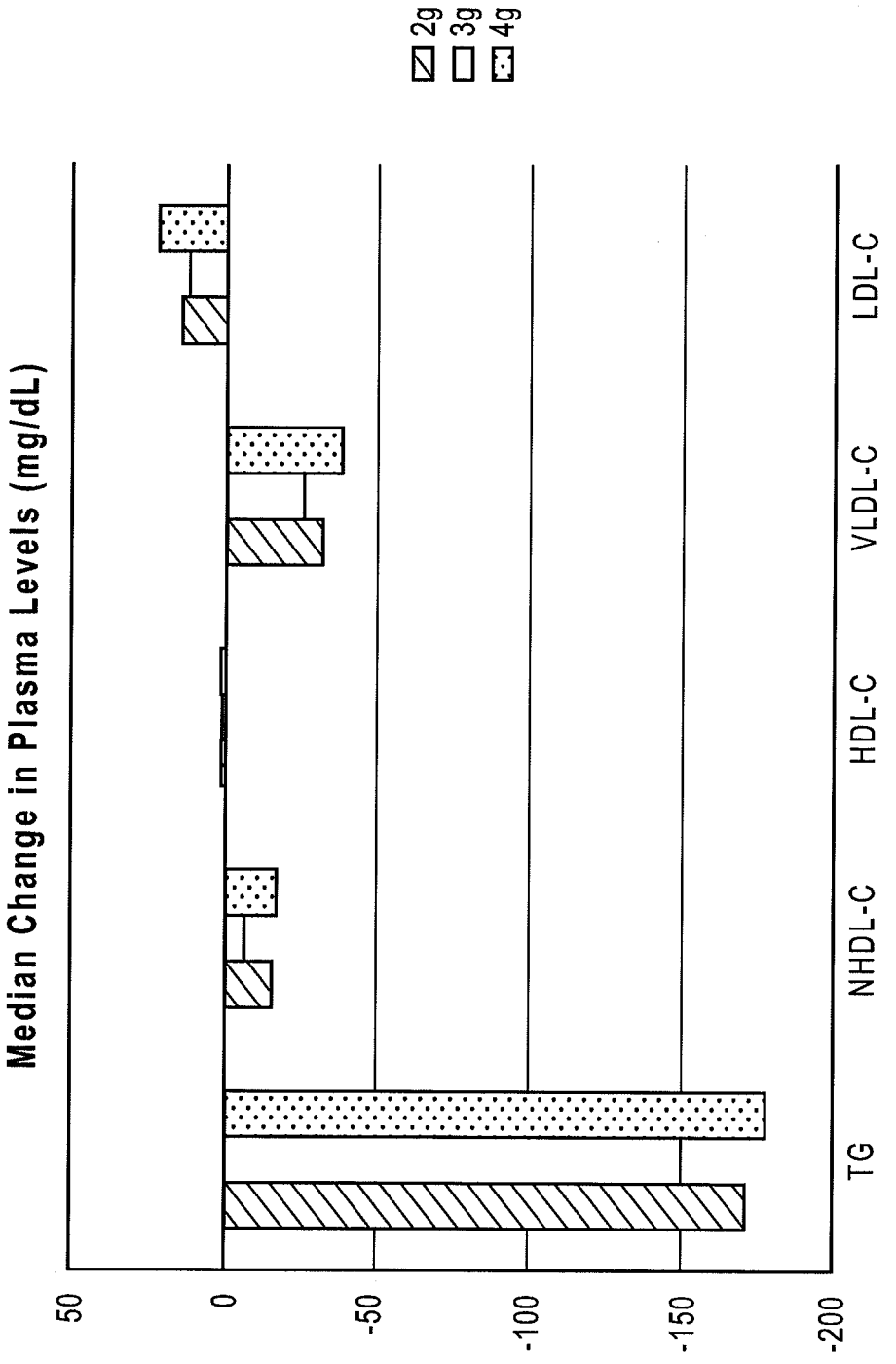

2g
3g
4g
Median Change in Plasma Levels (mg/dL)
50
0
-50
-100
-150
-200
TG
NHDL-C
HDL-C
VLDL-C
LDL-C

FIG. 26B

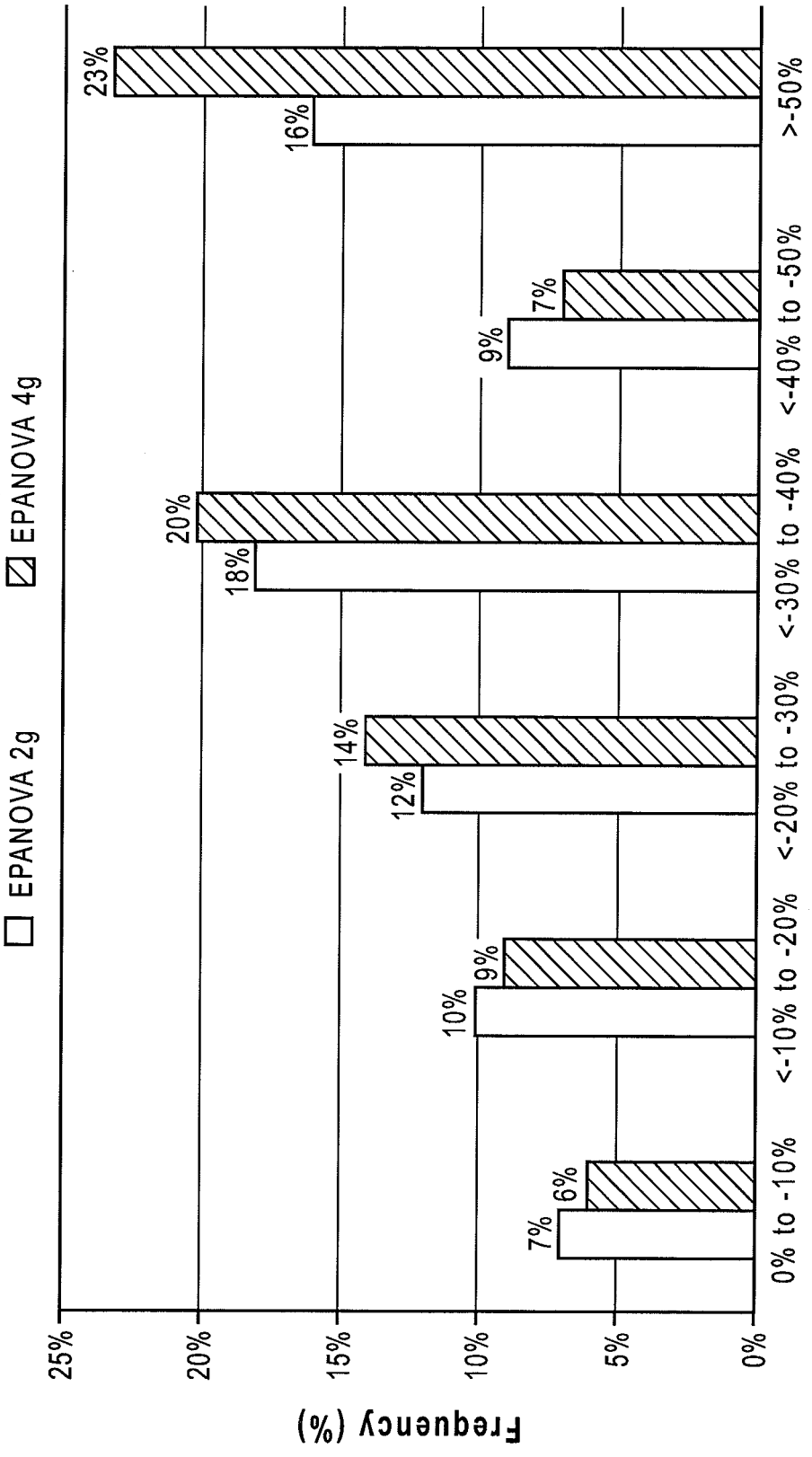

EPANOVA 2g
EPANOVA 4g
Frequency (%)
25%
20%
15%
10%
5%
0%
23%
16%
7%
9%
20%
18%
14%
12%
9%
10%
6%
7%
>-50%
<-40% to -50%
<-30% to -40%
<-20% to -30%
<-10% to -20%
0% to -10%

FIG. 27

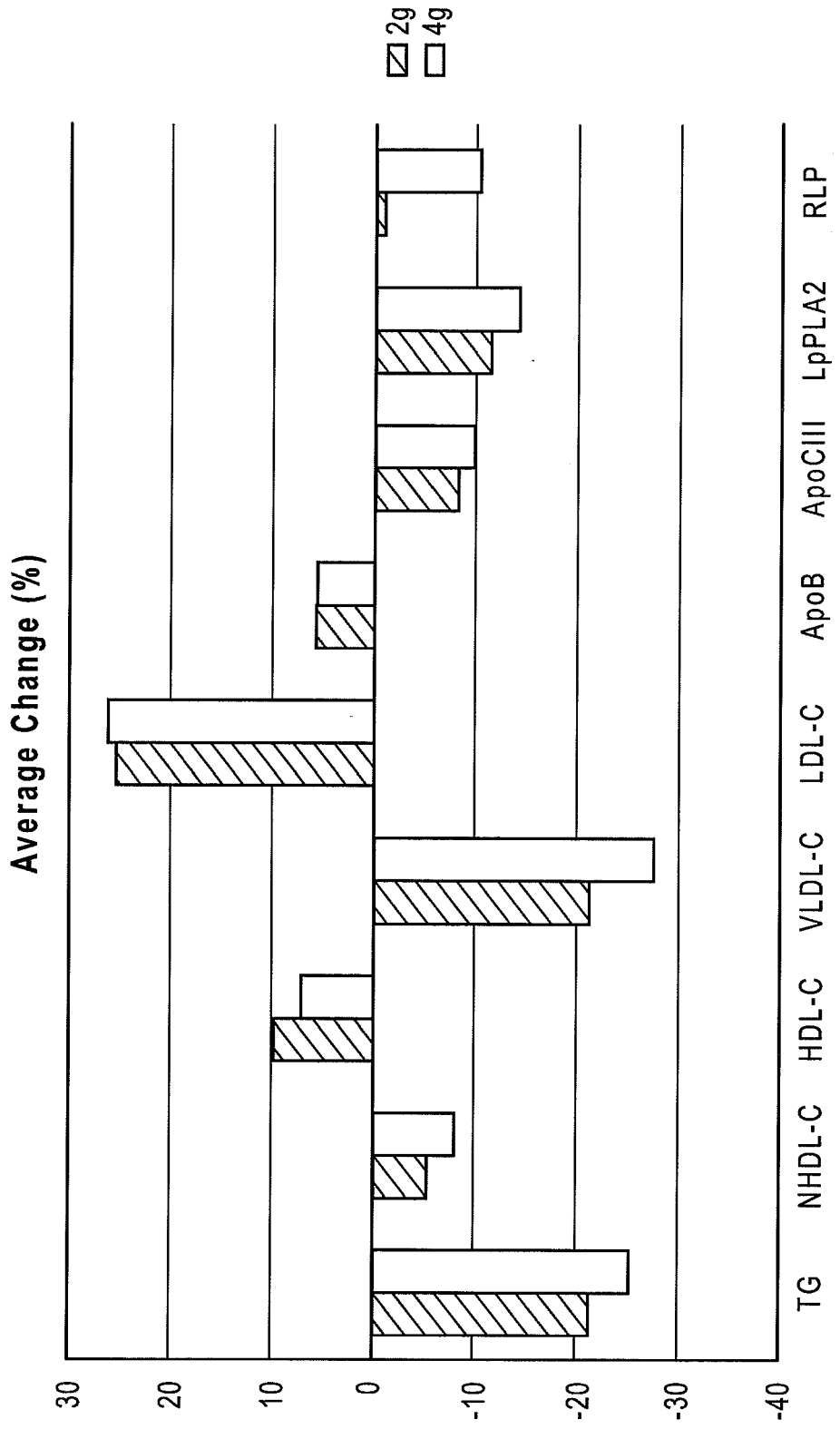

2g
4g
Average Change (%)
30
20
10
0
-10
-20
-30
-40
TG
NHDL-C
HDL-C
VLDL-C
LDL-C
ApoB
ApoCIII
LpPLA2
RLP

FIG. 28A

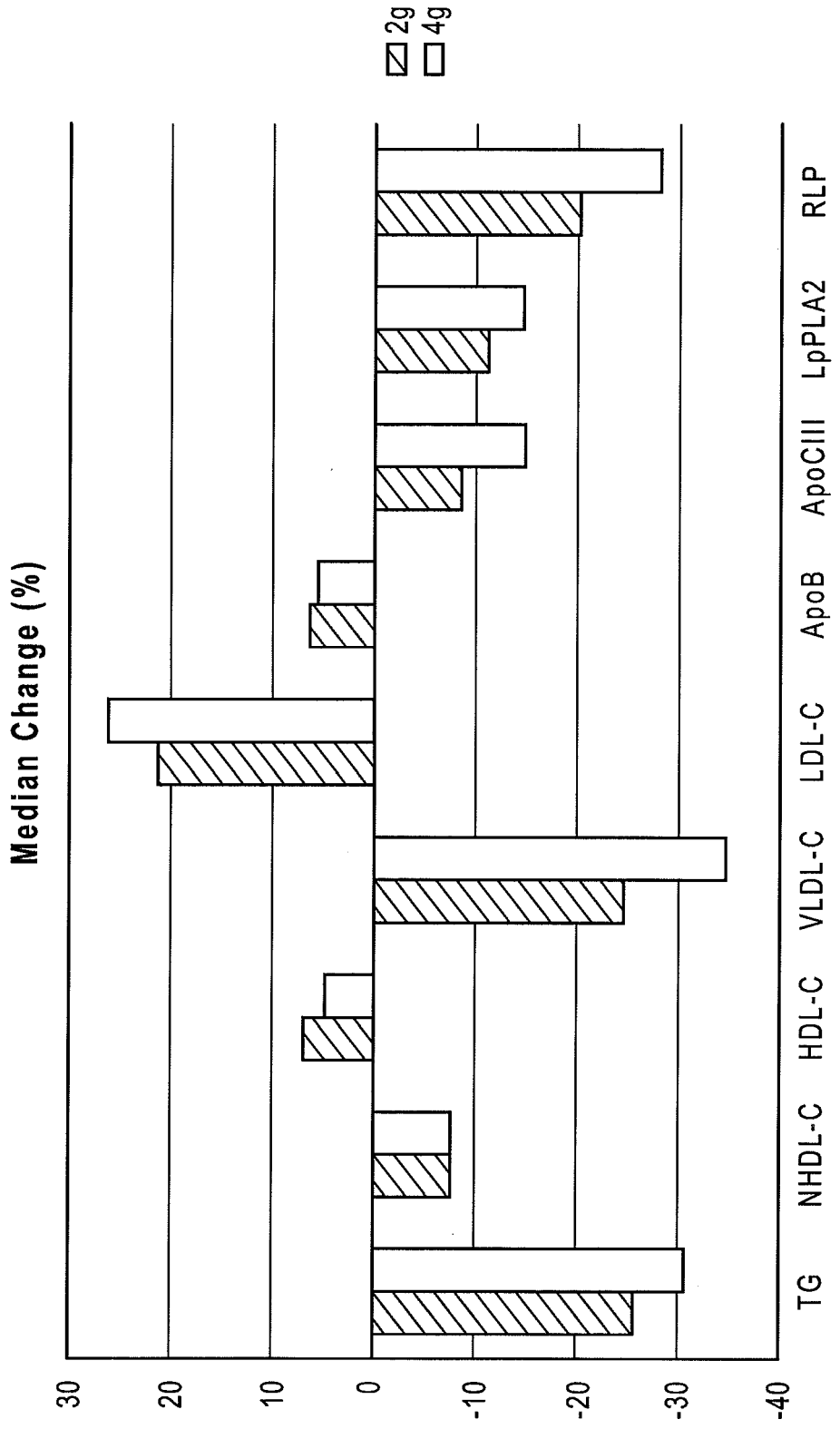

2g
4g
Median Change (%)
30
20
10
0
-10
-20
-30
-40
TG
NHDL-C
HDL-C
VLDL-C
LDL-C
ApoB
ApoCIII
LpPLA2
RLP

FIG. 28B

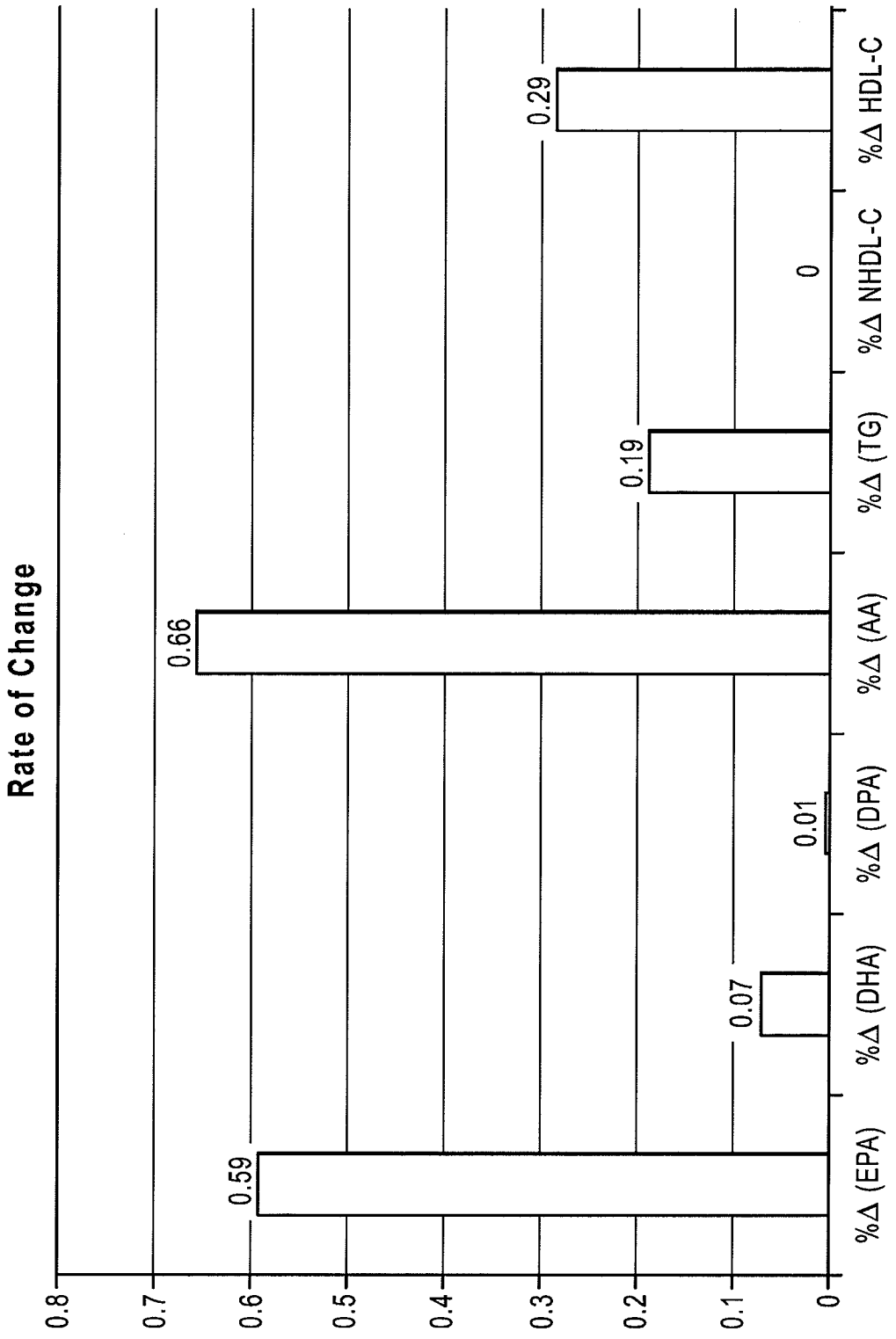

Rate of Change
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.59
0.07
0.01
0.66
0.19
0
0.29
%Δ (EPA)
%Δ (DHA)
%Δ (DPA)
%Δ (AA)
%Δ (TG)
%Δ NHDL-C
%Δ HDL-C

FIG. 29

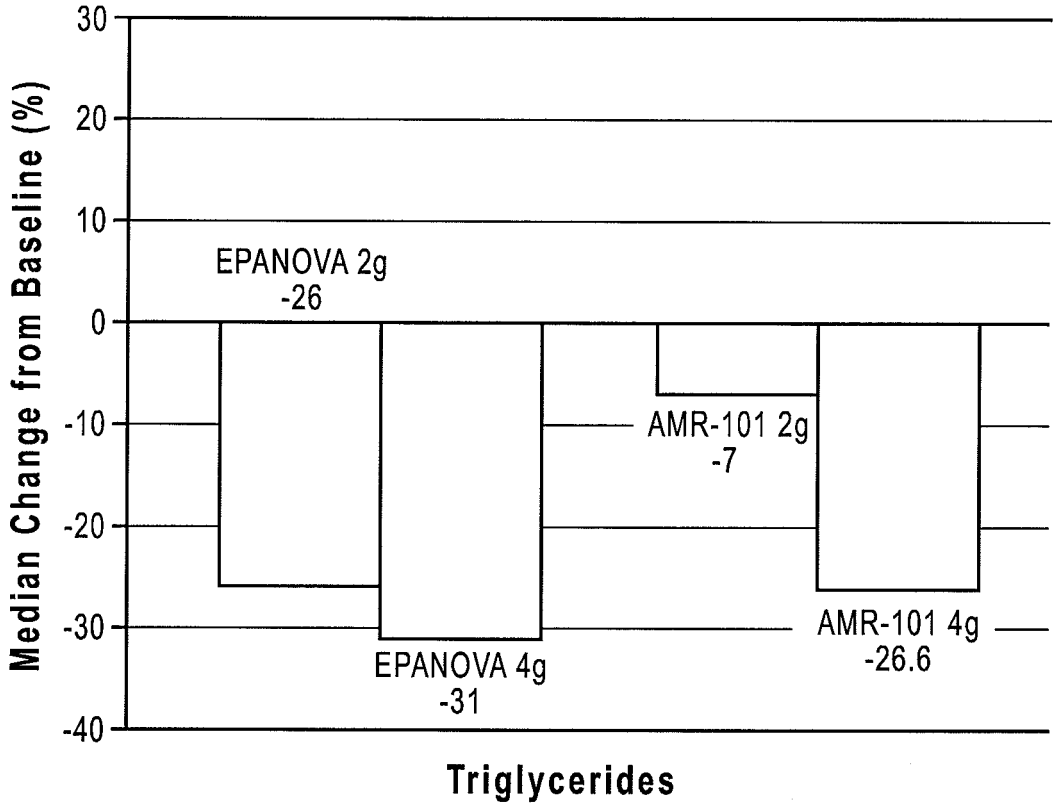

30
20
10
0
-10
-20
-30
-40
Median Change from Baseline (%)
EPANOVA 2g
-26
EPANOVA 4g
-31
AMR-101 2g
-7
AMR-101 4g
-26.6
Triglycerides

FIG. 30

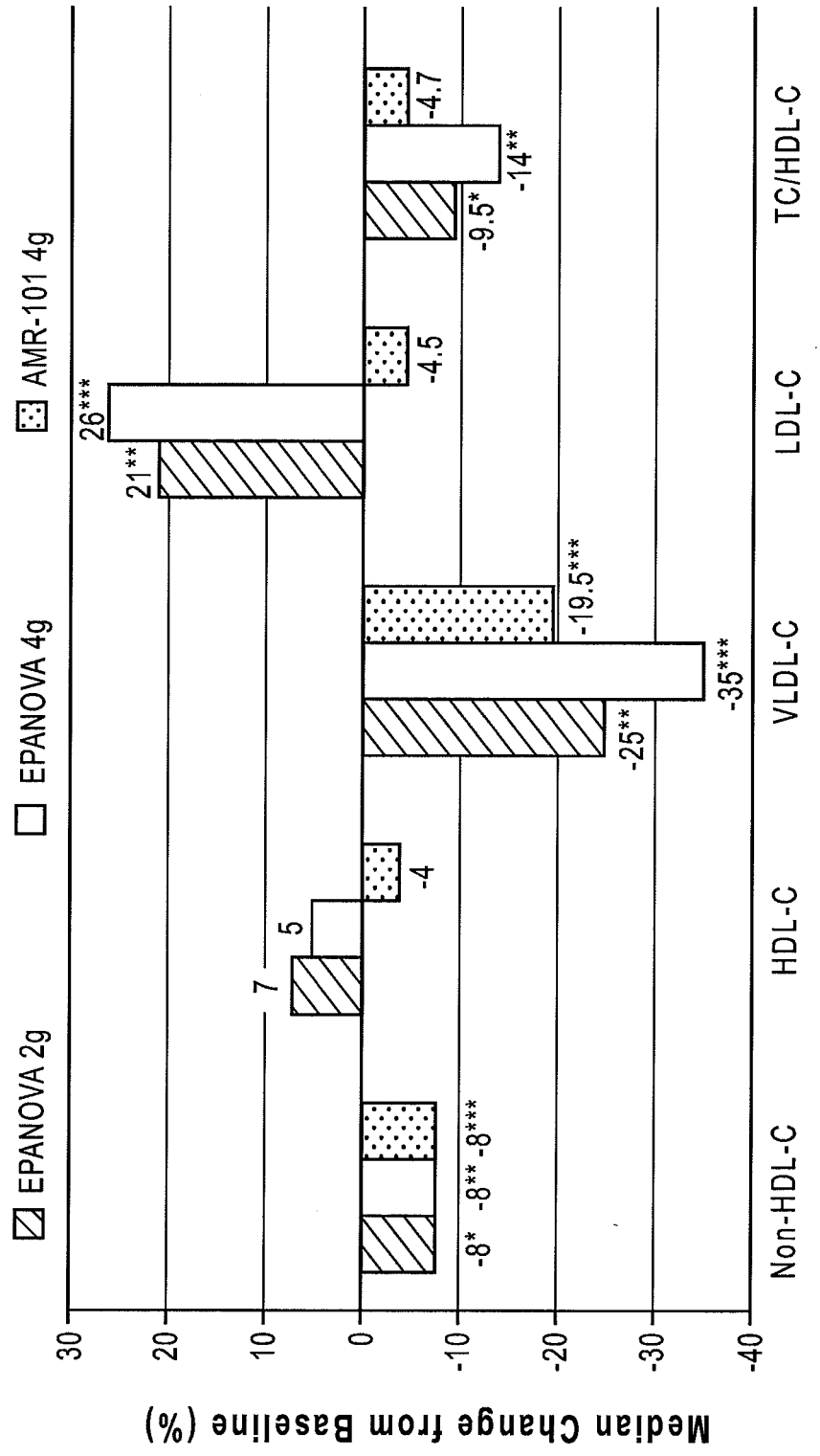

EPANOVA 2g
EPANOVA 4g
AMR-101 4g
Median Change from Baseline (%)
30
20
10
0
-10
-20
-30
-40
Non-HDL-C
HDL-C
VLDL-C
LDL-C
TC/HDL-C
-8*
-8**
-8***
7
5
-4
26***
21**
-4.5
-9.5*
-14**
-4.7
-19.5***
-35***
-25**

FIG. 31

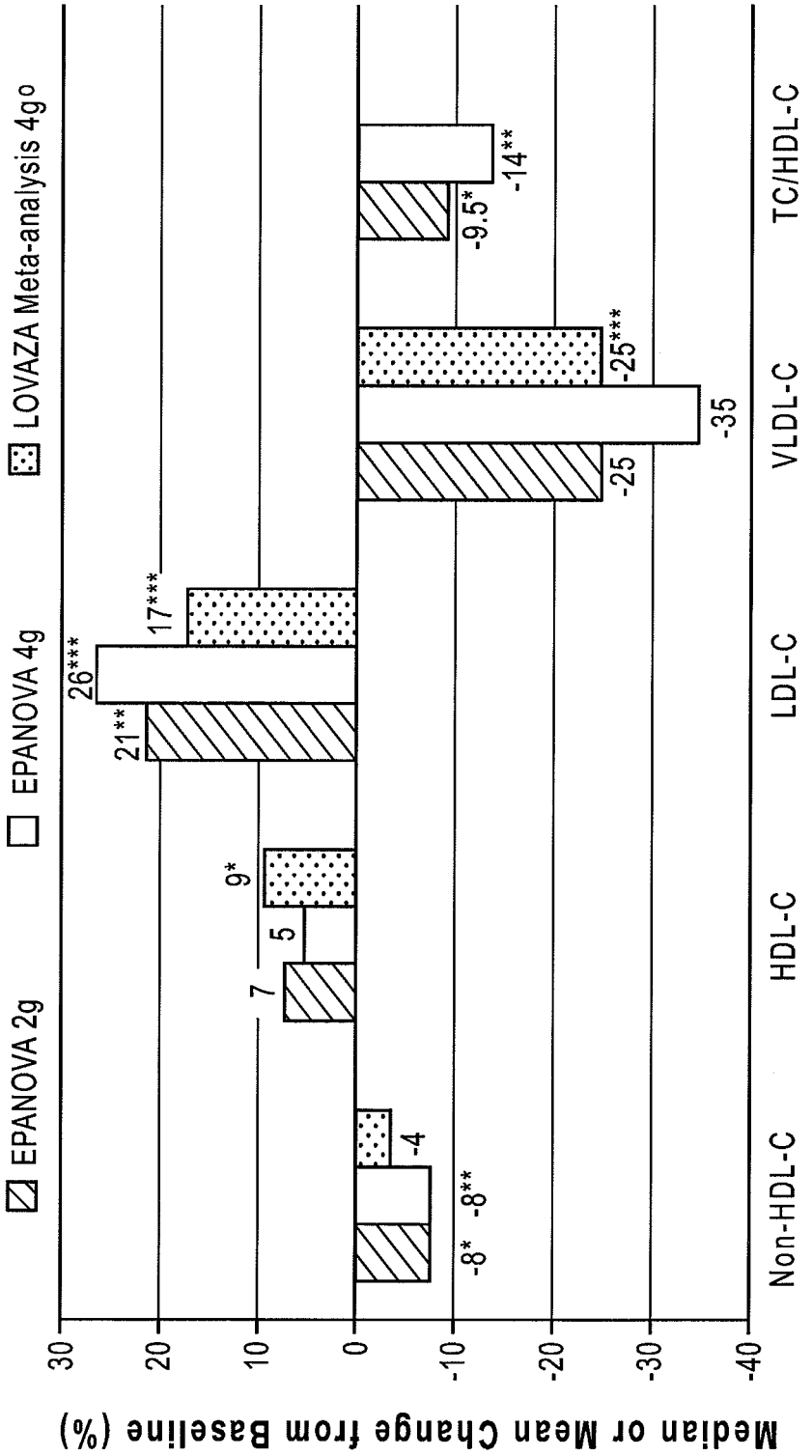

EPANOVA 2g
EPANOVA 4g
LOVAZA Meta-analysis 4g°
Median or Mean Change from Baseline (%)
30
20
10
0
-10
-20
-30
-40
Non-HDL-C
HDL-C
LDL-C
VLDL-C
TC/HDL-C
-8*
-8**
-4
7
5
9*
21**
26***
17***
-9.5*
-14**
-25
-25***
-35

FIG. 32

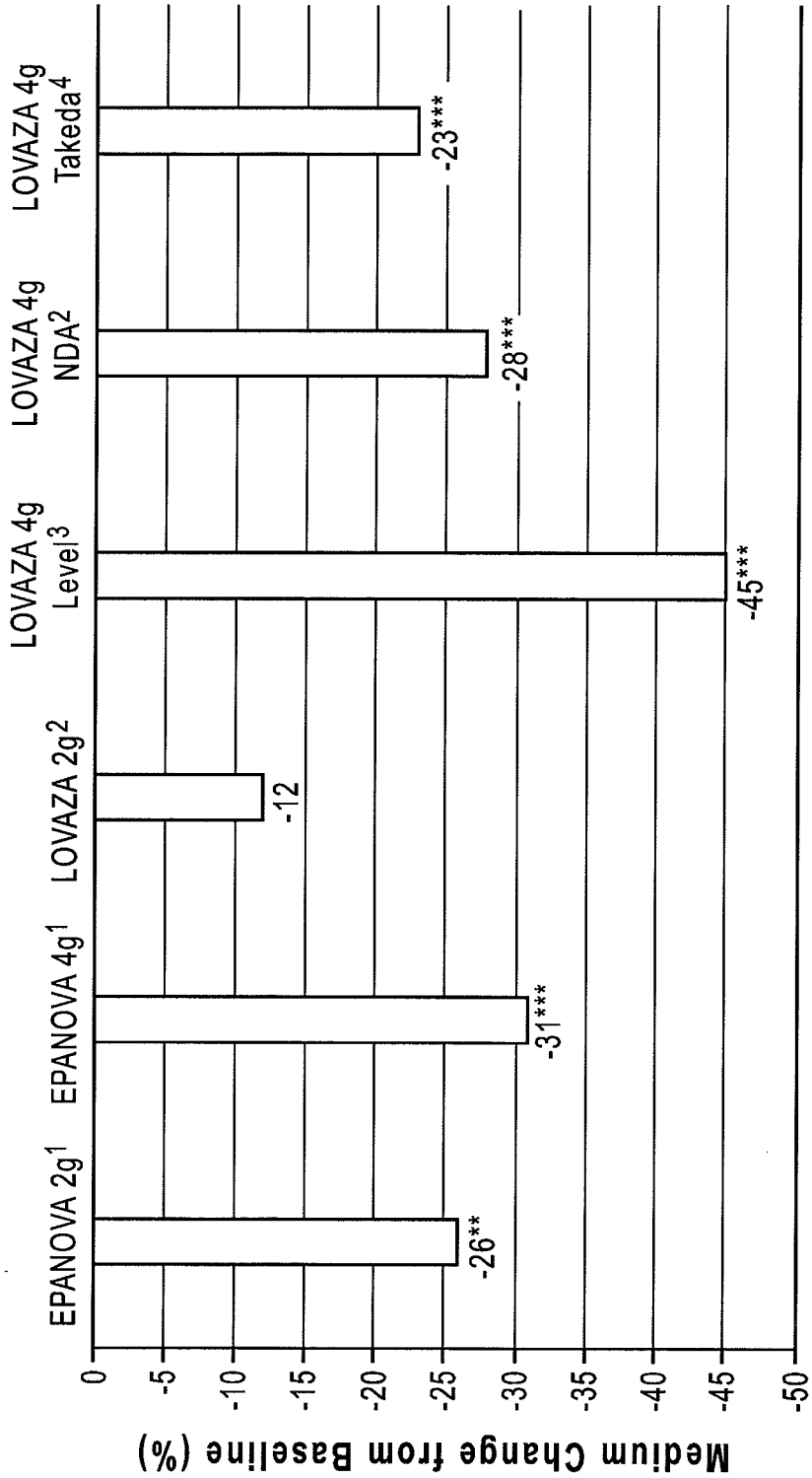

Medium Change from Baseline (%)
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
EPANOVA 2g[1]
-26**
EPANOVA 4g[1]
-31***
LOVAZA 2g[2]
-12
LOVAZA 4g Level[3]
-45***
LOVAZA 4g NDA[2]
-28***
LOVAZA 4g Takeda[4]
-23***

FIG. 33

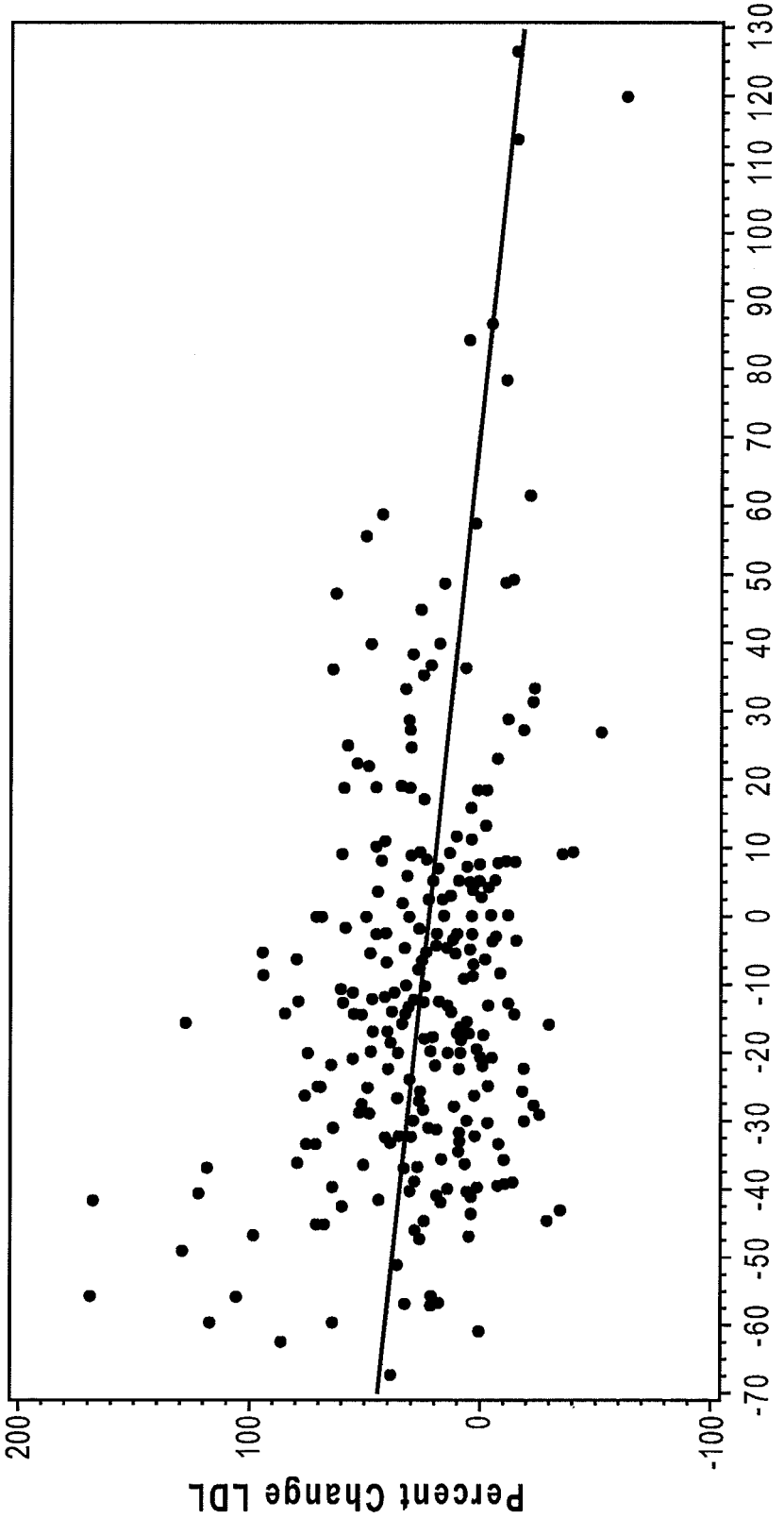

Percent Change LDL
200
100
0
-100
-70 -60 -50 -40 -30 -20 -10 0 10 20 30 40 50 60 70 80 90 100 110 120 130
Percent Change APOC3

FIG. 34

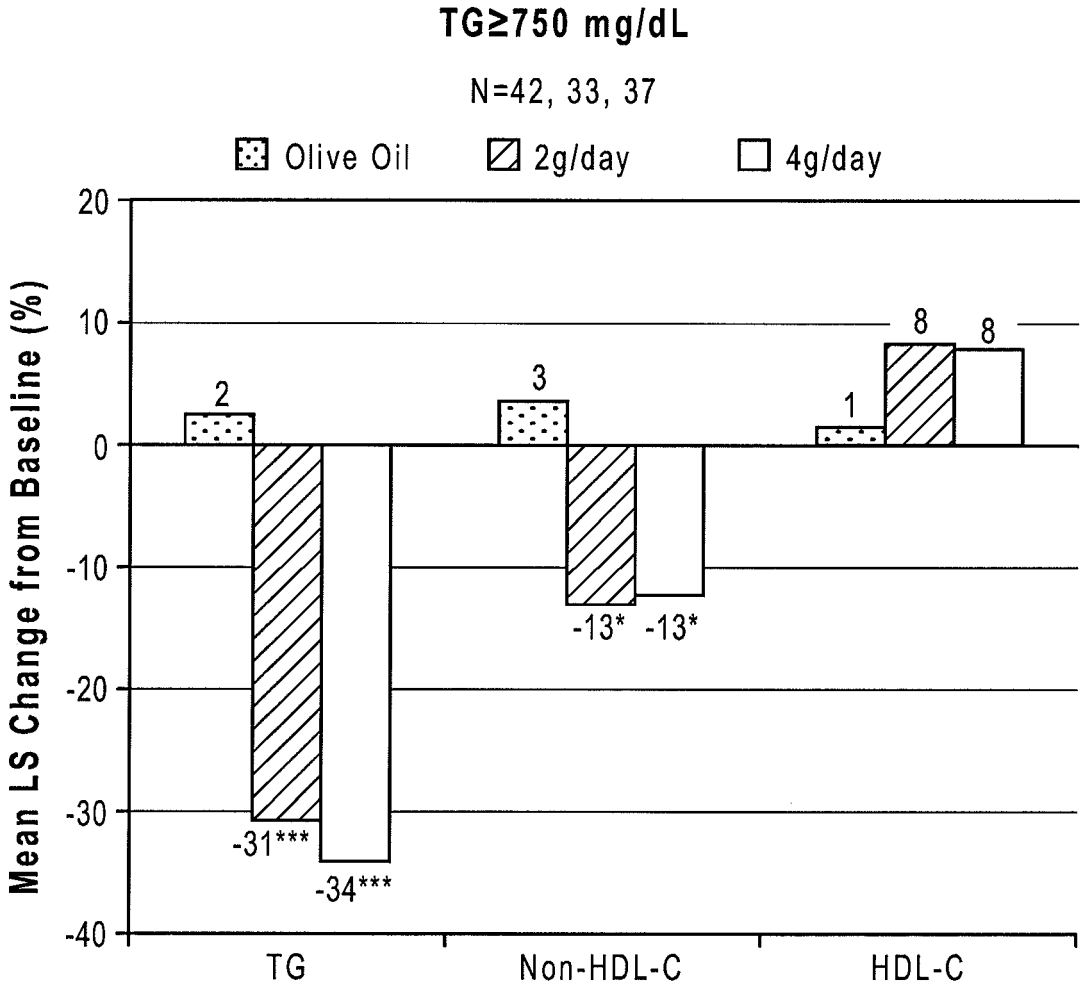

TG≥750 mg/dL
N=42, 33, 37
Olive Oil
2g/day
4g/day
Mean LS Change from Baseline (%)
20
10
0
-10
-20
-30
-40
2
-31***
-34***
3
-13*
-13*
1
8
8
TG
Non-HDL-C
HDL-C

FIG. 35

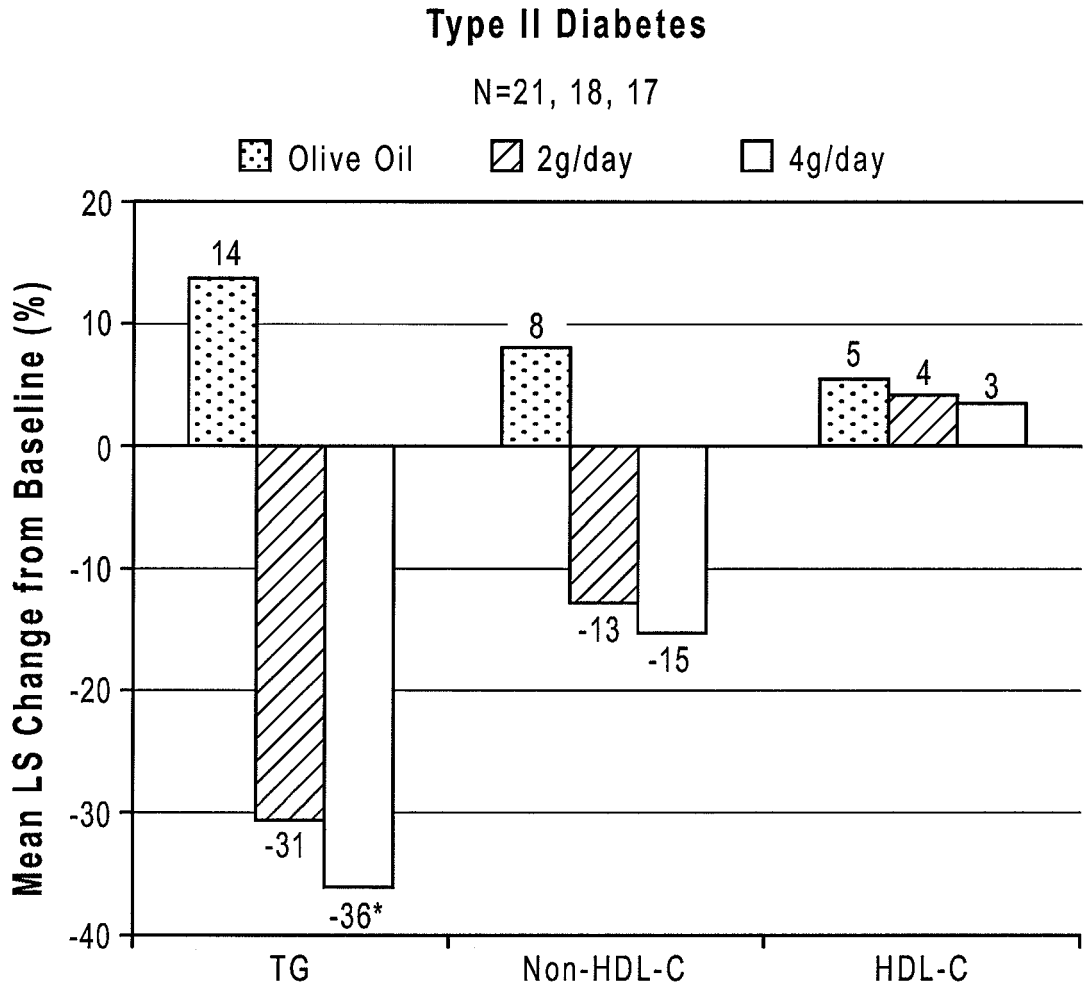

Type II Diabetes
N=21, 18, 17
Olive Oil
2g/day
4g/day
Mean LS Change from Baseline (%)
20
10
0
-10
-20
-30
-40
14
-31
-36*
8
-13
-15
5
4
3
TG
Non-HDL-C
HDL-C

FIG. 36

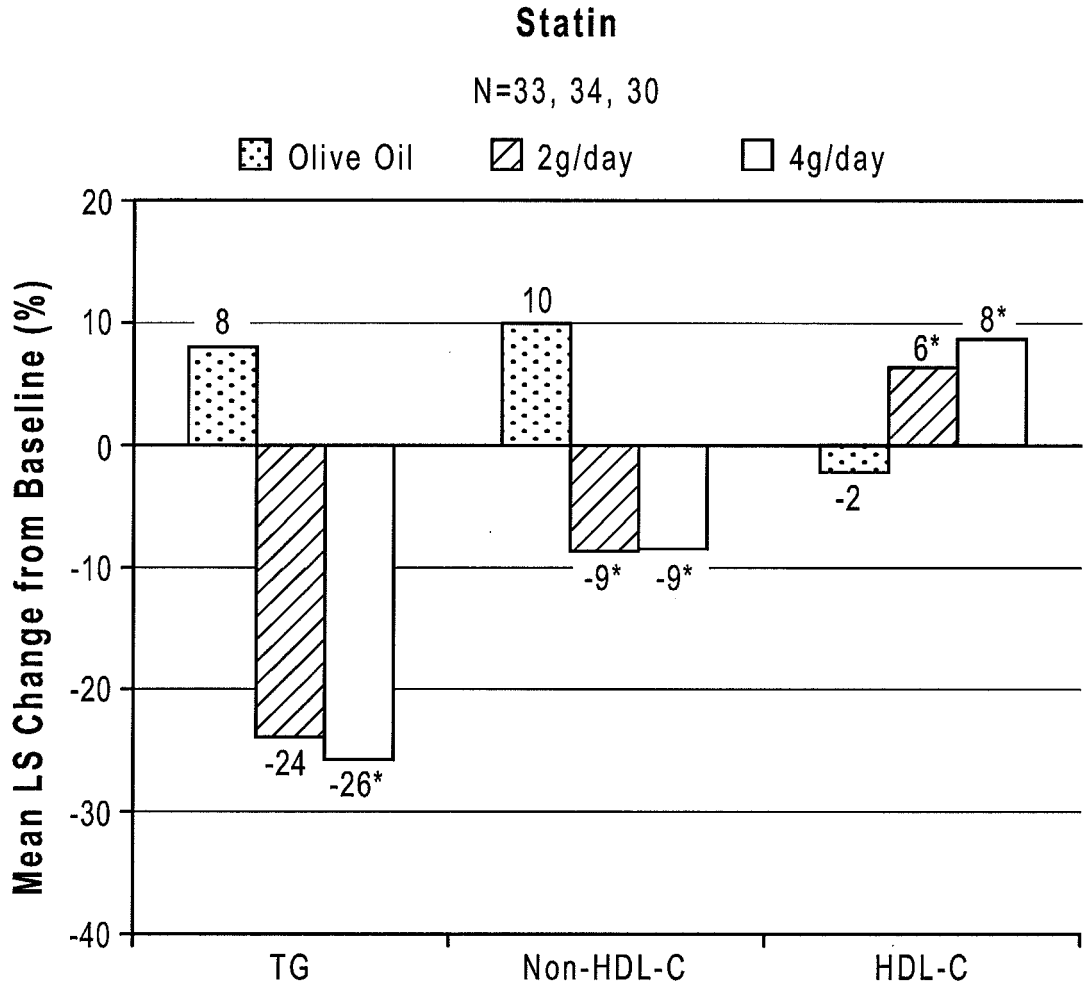

Statin
N=33, 34, 30
Olive Oil
2g/day
4g/day
Mean LS Change from Baseline (%)
20
10
0
-10
-20
-30
-40
8
-24
-26*
10
-9*
-9*
-2
6*
8*
TG
Non-HDL-C
HDL-C

FIG. 37

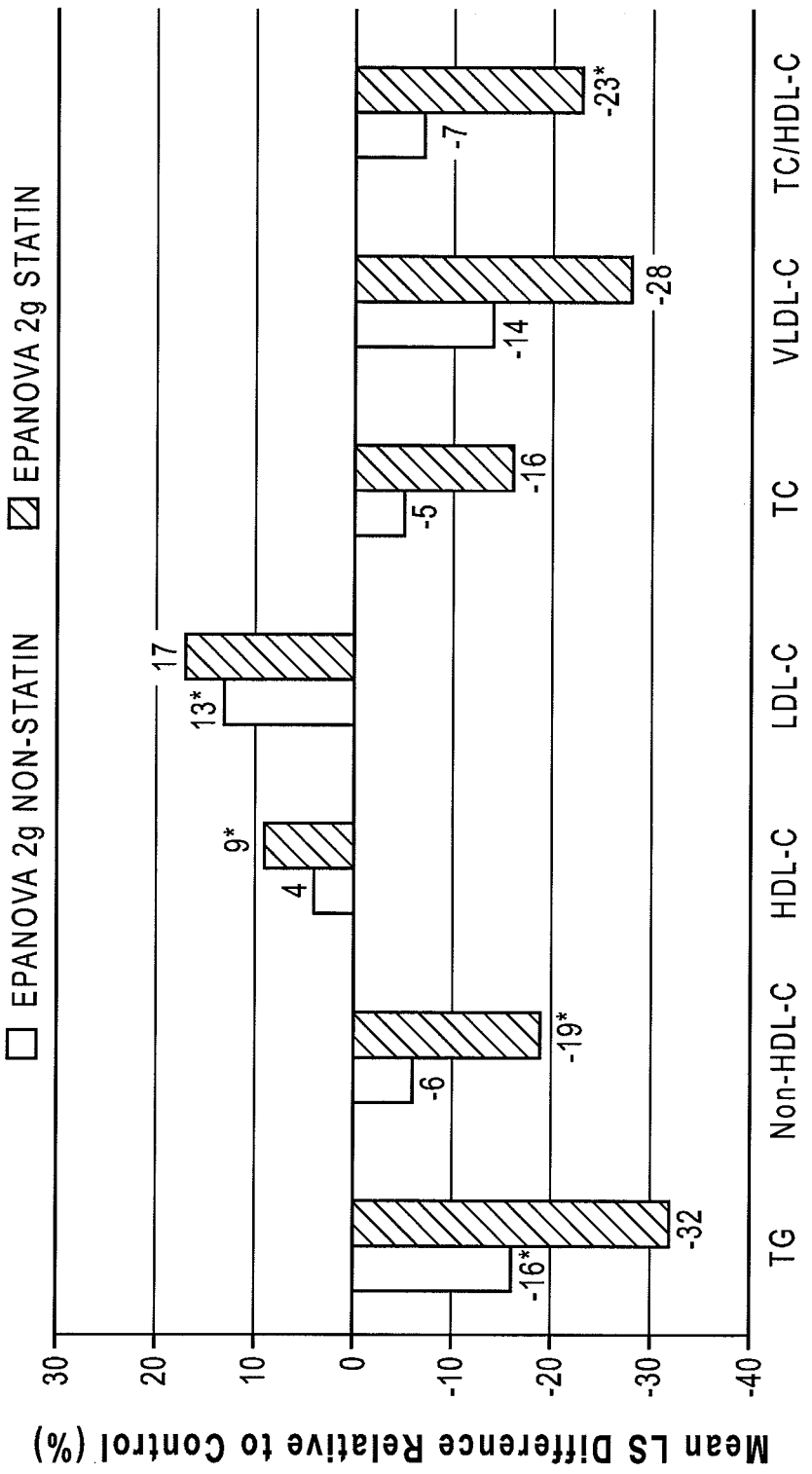

EPANOVA 2g NON-STATIN
EPANOVA 2g STATIN
Mean LS Difference Relative to Control (%)
30
20
10
0
-10
-20
-30
-40
TG
Non-HDL-C
HDL-C
LDL-C
TC
VLDL-C
TC/HDL-C
-16*
-32
-6
-19*
4
9*
13*
17
-5
-16
-14
-28
-7
-23*

FIG. 38

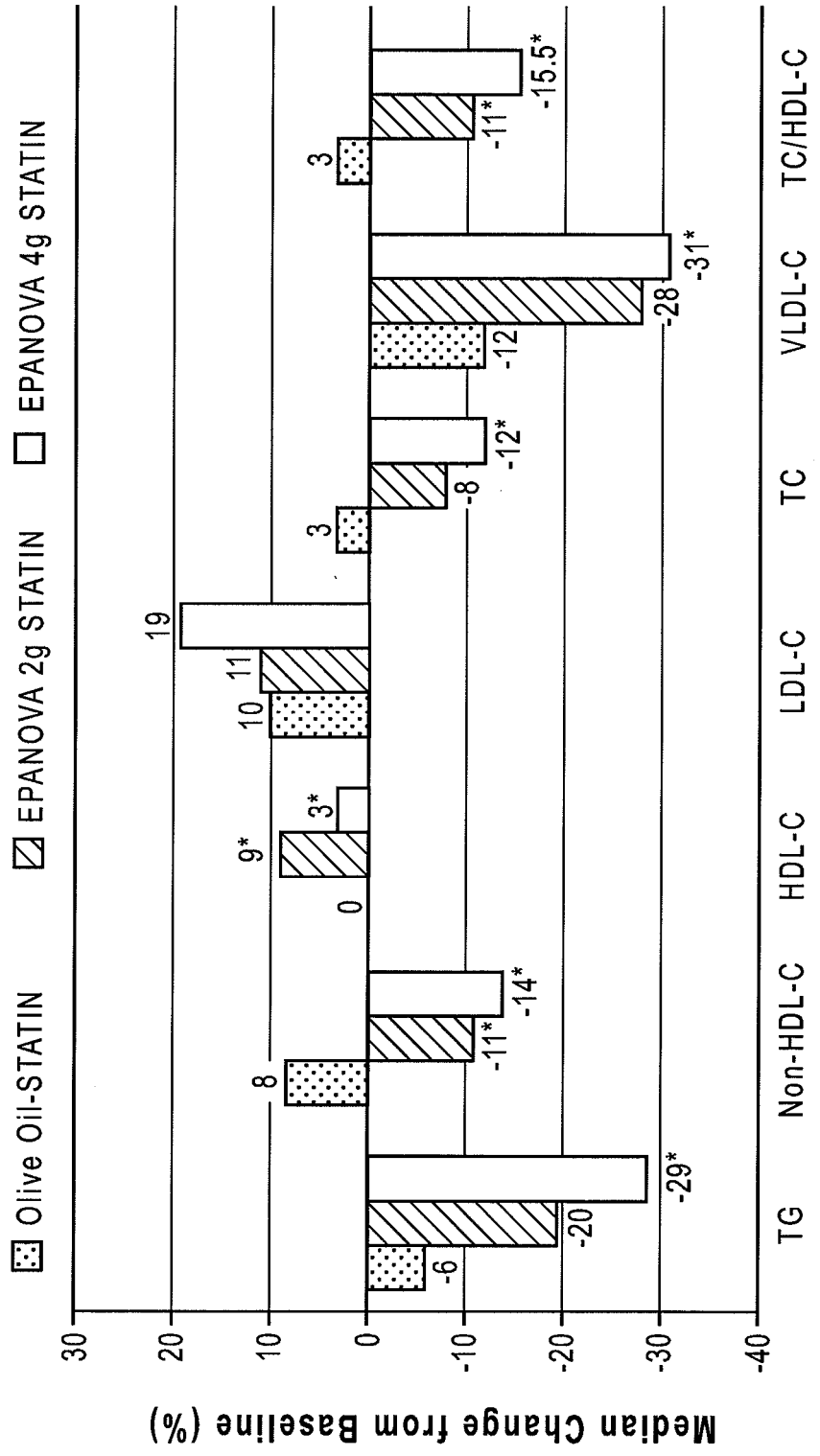

Olive Oil-STATIN
EPANOVA 2g STATIN
EPANOVA 4g STATIN
Median Change from Baseline (%)
30
20
10
0
-10
-20
-30
-40
TG
Non-HDL-C
HDL-C
LDL-C
TC
VLDL-C
TC/HDL-C
-6
8
0
10
3
19
3
-20
-11*
-11*
9*
11
-8
-28
-14*
3*
-12*
-12
-29*
-15.5*
-31*

FIG. 39

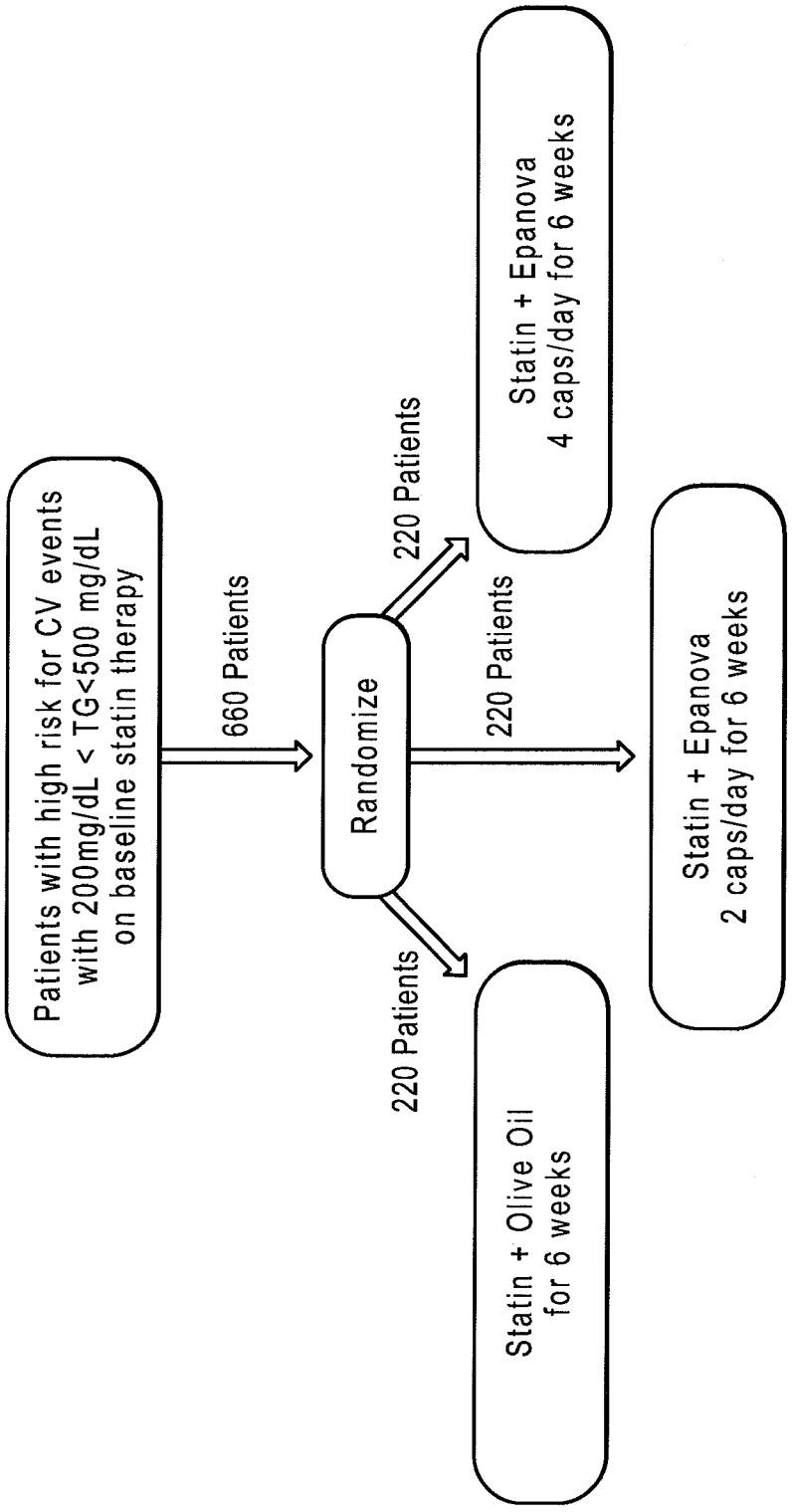

Patients with high risk for CV events
with 200mg/dL < TG<500 mg/dL
on baseline statin therapy
660 Patients
Randomize
220 Patients
Statin + Epanova
4 caps/day for 6 weeks
220 Patients
Statin + Epanova
2 caps/day for 6 weeks
220 Patients
Statin + Olive Oil
for 6 weeks

FIG. 40

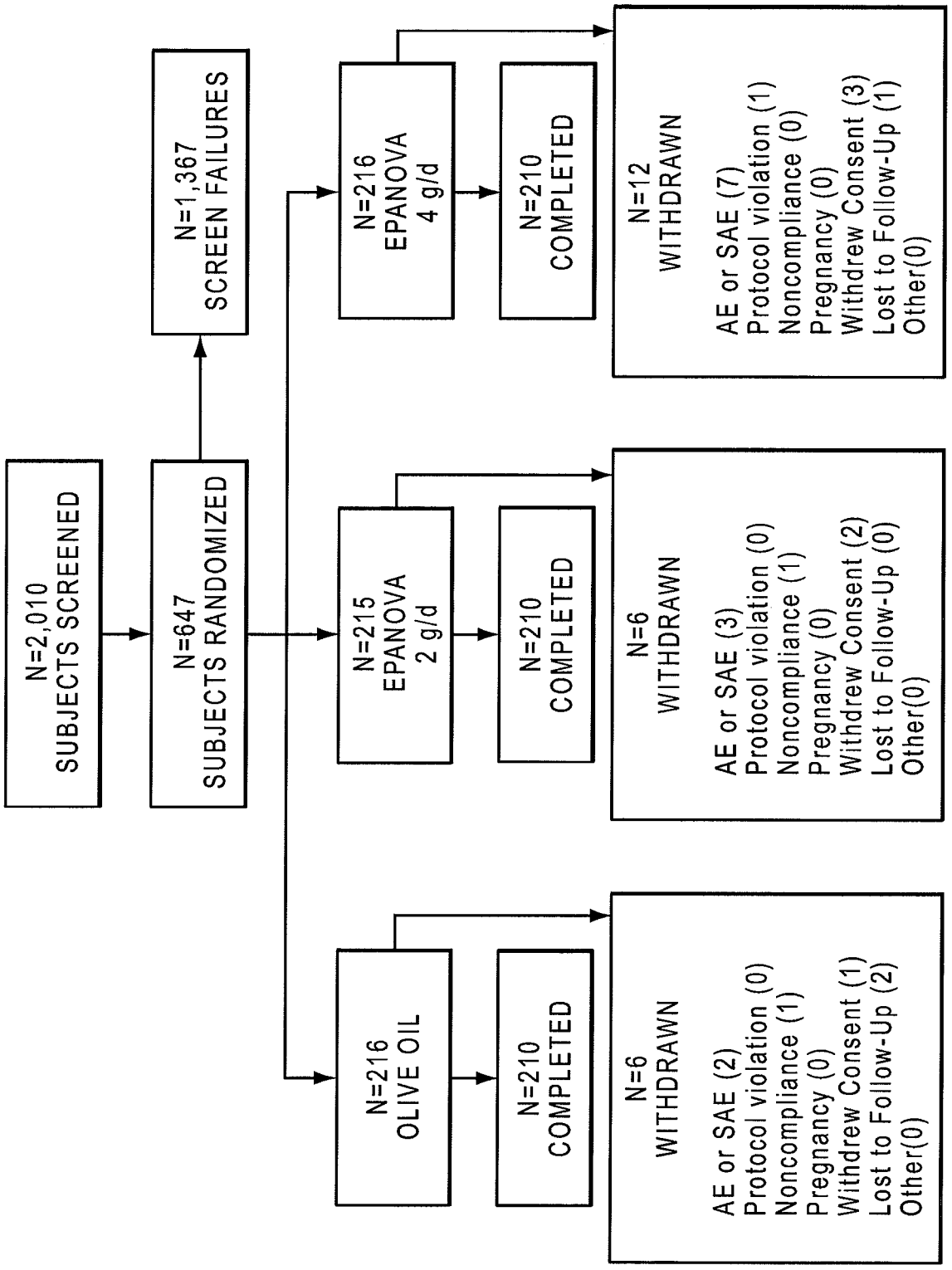

N=2,010
SUBJECTS SCREENED
N=647
SUBJECTS RANDOMIZED
N=1,367
SCREEN FAILURES
N=216
EPANOVA
4 g/d
N=210
COMPLETED
N=12
WITHDRAWN
AE or SAE (7)
Protocol violation (1)
Noncompliance (0)
Pregnancy (0)
Withdrew Consent (3)
Lost to Follow-Up (1)
Other(0)
N=215
EPANOVA
2 g/d
N=210
COMPLETED
N=6
WITHDRAWN
AE or SAE (3)
Protocol violation (0)
Noncompliance (1)
Pregnancy (0)
Withdrew Consent (2)
Lost to Follow-Up (0)
Other(0)
N=216
OLIVE OIL
N=210
COMPLETED
N=6
WITHDRAWN
AE or SAE (2)
Protocol violation (0)
Noncompliance (1)
Pregnancy (0)
Withdrew Consent (1)
Lost to Follow-Up (2)
Other(0)

FIG. 41

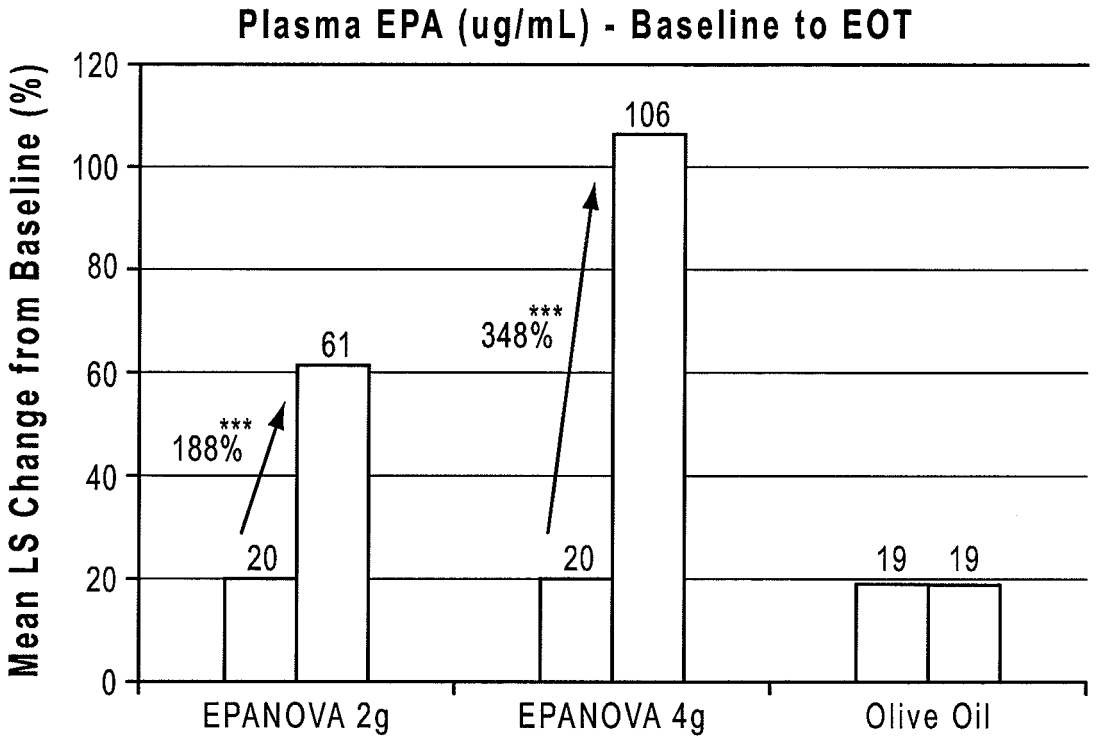


FIG. 42A

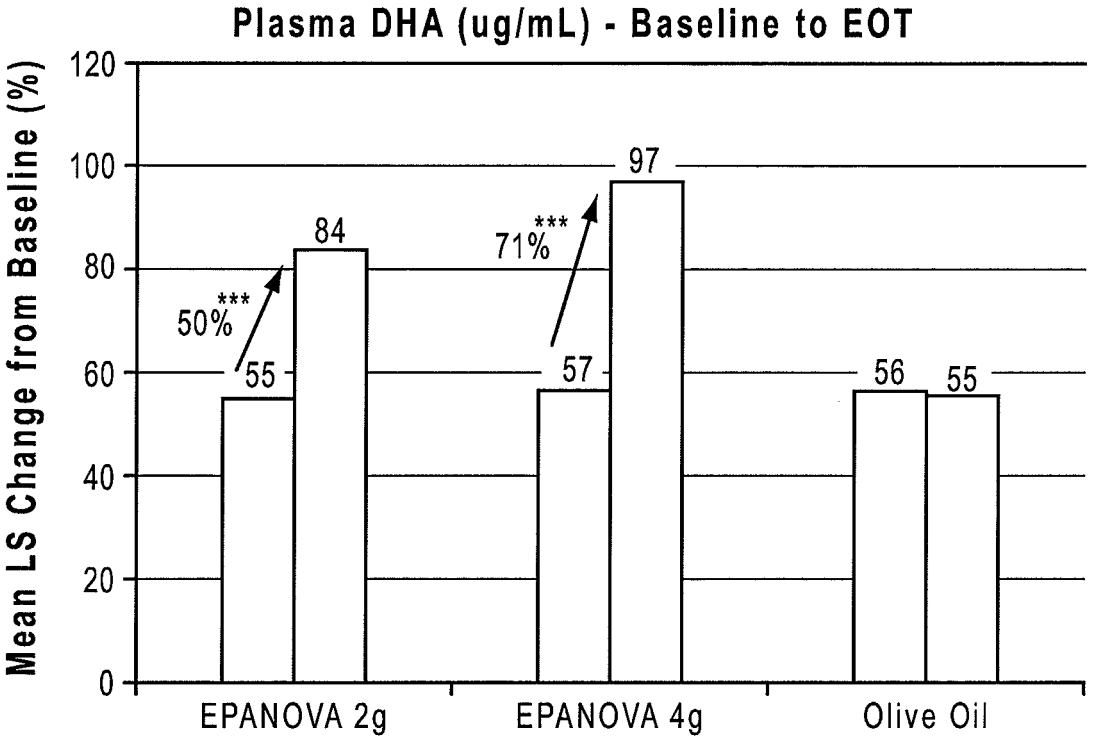


FIG. 42B

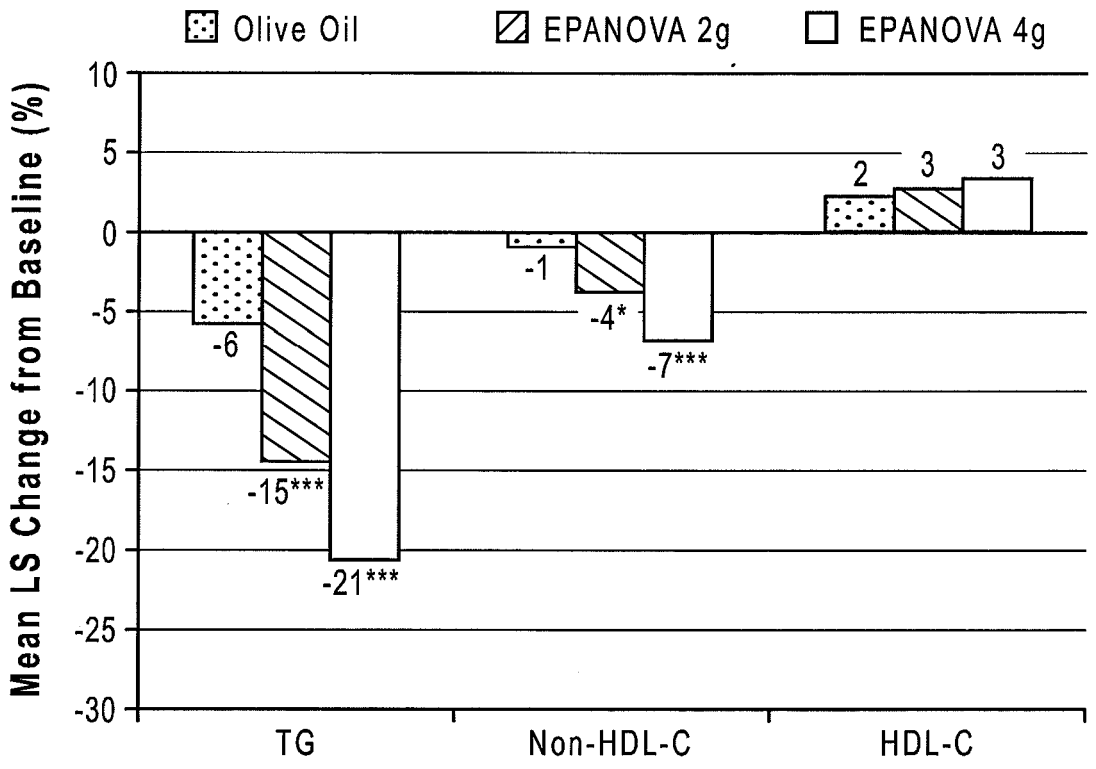

Olive Oil
EPANOVA 2g
EPANOVA 4g
Mean LS Change from Baseline (%)
10
5
0
-5
-10
-15
-20
-25
-30
-6
-15***
-21***
-1
-4*
-7***
2
3
3
TG
Non-HDL-C
HDL-C

FIG. 43

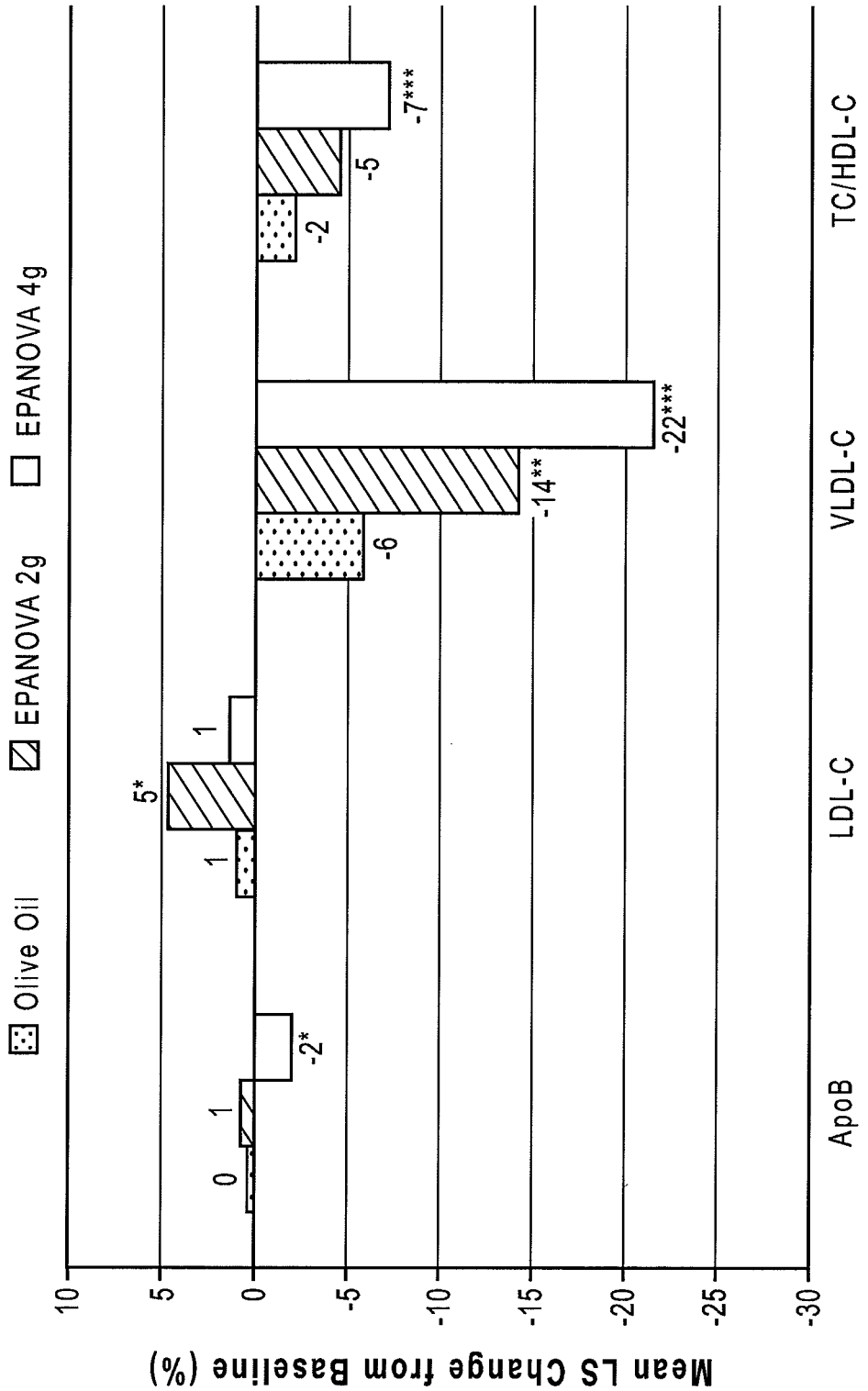

Olive Oil
EPANOVA 2g
EPANOVA 4g
Mean LS Change from Baseline (%)
10
5
0
-5
-10
-15
-20
-25
-30
ApoB
LDL-C
VLDL-C
TC/HDL-C
0
1
-2*
1
5*
1
-6
-14**
-22***
-2
-5
-7***

FIG. 44

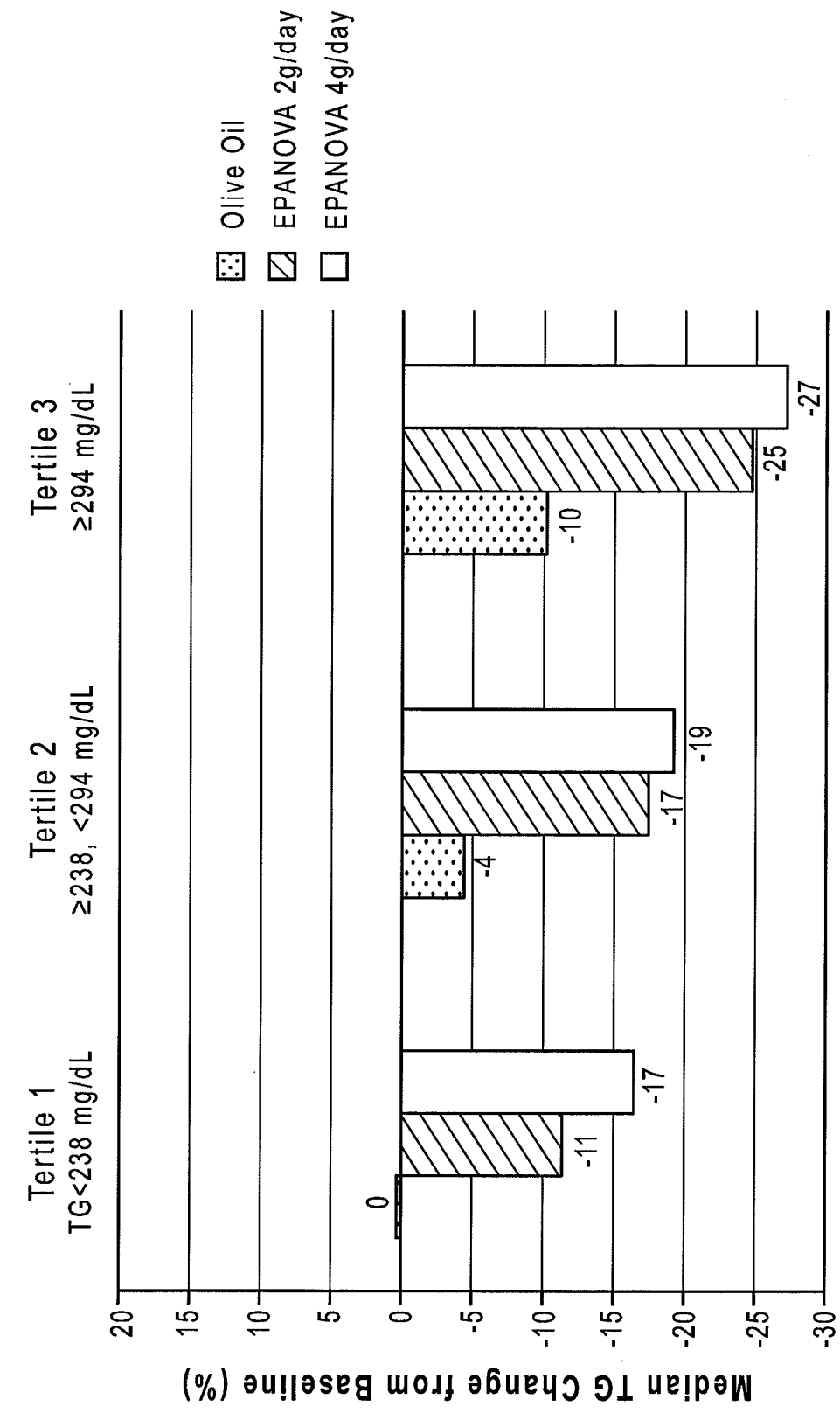

Olive Oil
EPANOVA 2g/day
EPANOVA 4g/day
Tertile 1
TG<238 mg/dL
Tertile 2
≥238, <294 mg/dL
Tertile 3
≥294 mg/dL
0
-11
-17
-4
-17
-19
-10
-25
-27
20
15
10
5
0
-5
-10
-15
-20
-25
-30
Median TG Change from Baseline (%)

FIG. 45

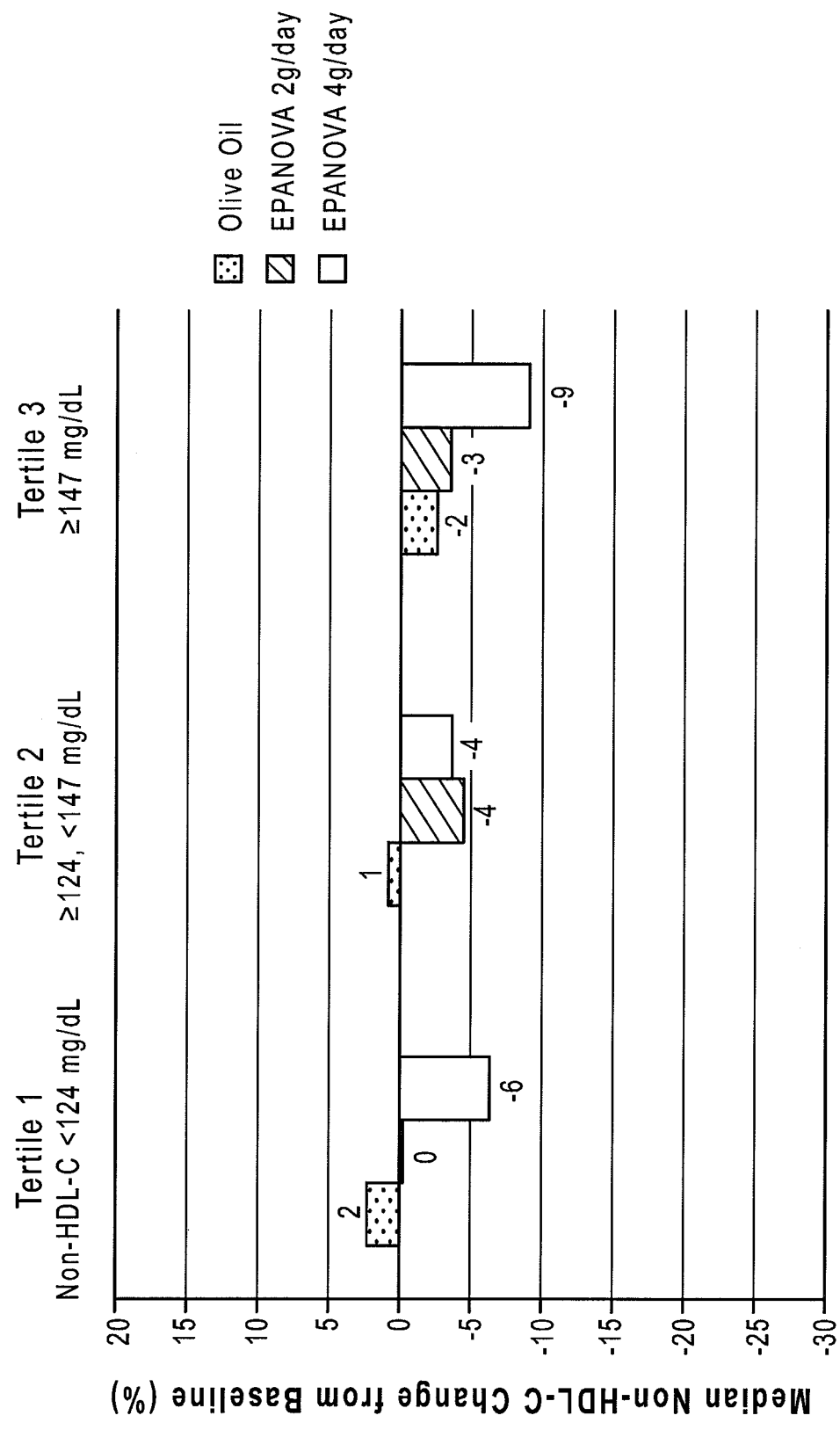

Olive Oil
EPANOVA 2g/day
EPANOVA 4g/day
Tertile 1
Non-HDL-C <124 mg/dL
Tertile 2
≥124, <147 mg/dL
Tertile 3
≥147 mg/dL
Median Non-HDL-C Change from Baseline (%)
20
15
10
5
0
-5
-10
-15
-20
-25
-30
2
0
-6
1
-4
-4
-2
-3
-9

FIG. 46

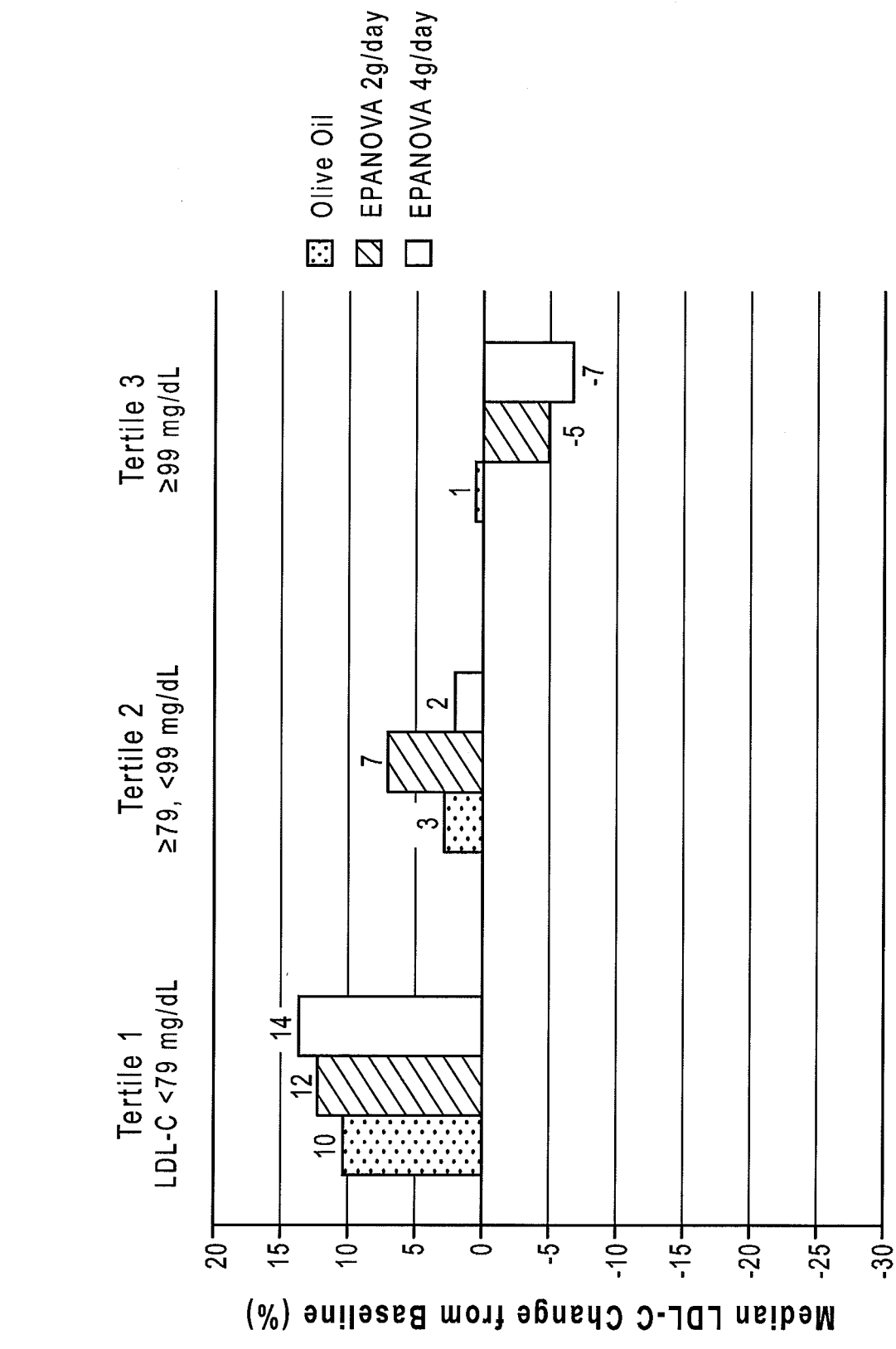

Olive Oil
EPANOVA 2g/day
EPANOVA 4g/day
Tertile 1
LDL-C <79 mg/dL
Tertile 2
≥79, <99 mg/dL
Tertile 3
≥99 mg/dL
Median LDL-C Change from Baseline (%)
20
15
10
5
0
-5
-10
-15
-20
-25
-30
14
12
10
7
3
2
1
-5
-7

FIG. 47

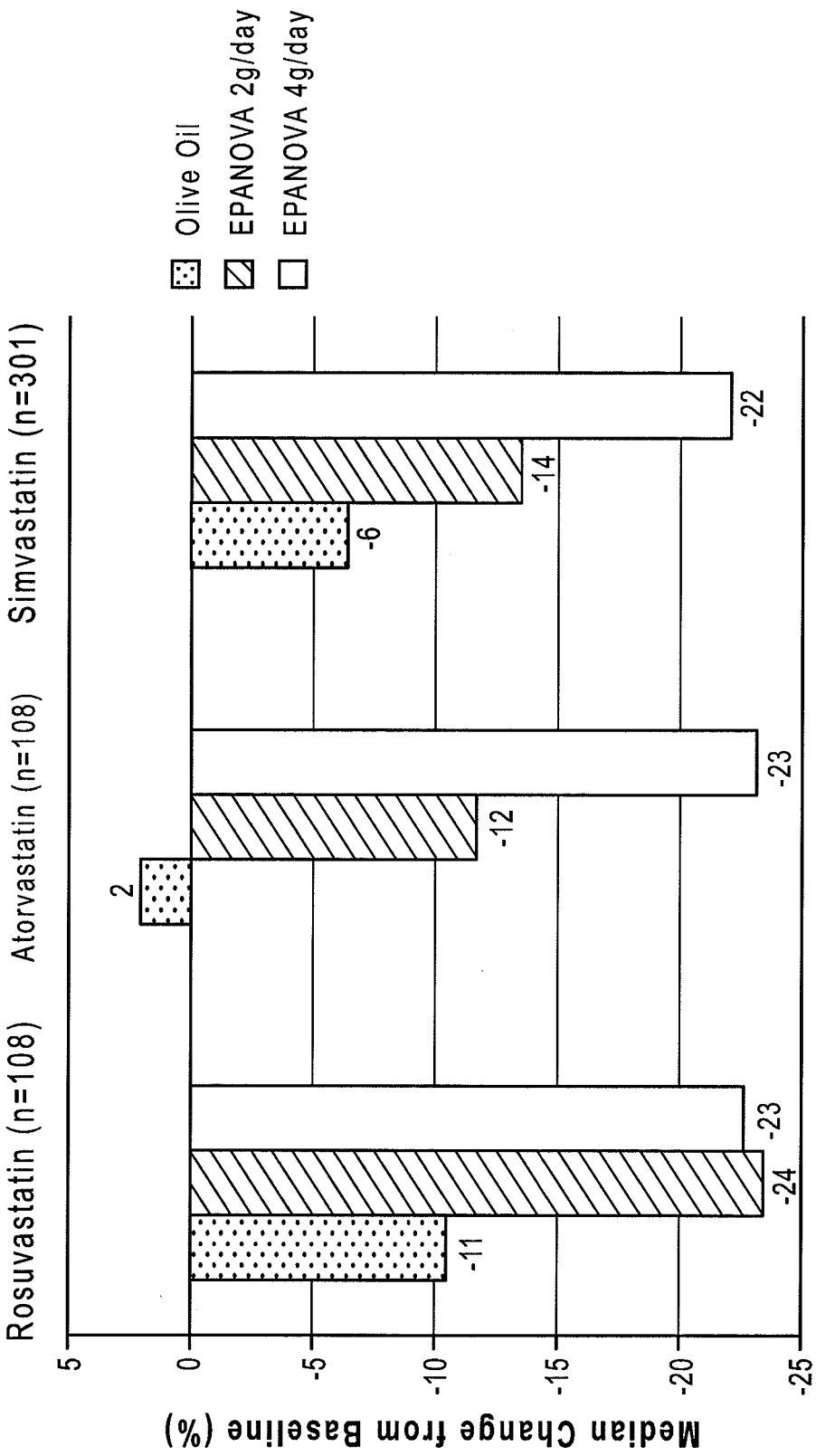

Olive Oil
EPANOVA 2g/day
EPANOVA 4g/day
Median Change from Baseline (%)
5
0
-5
-10
-15
-20
-25
Rosuvastatin (n=108)
Atorvastatin (n=108)
Simvastatin (n=301)
-11
-24
-23
2
-12
-23
-6
-14
-22

FIG. 48

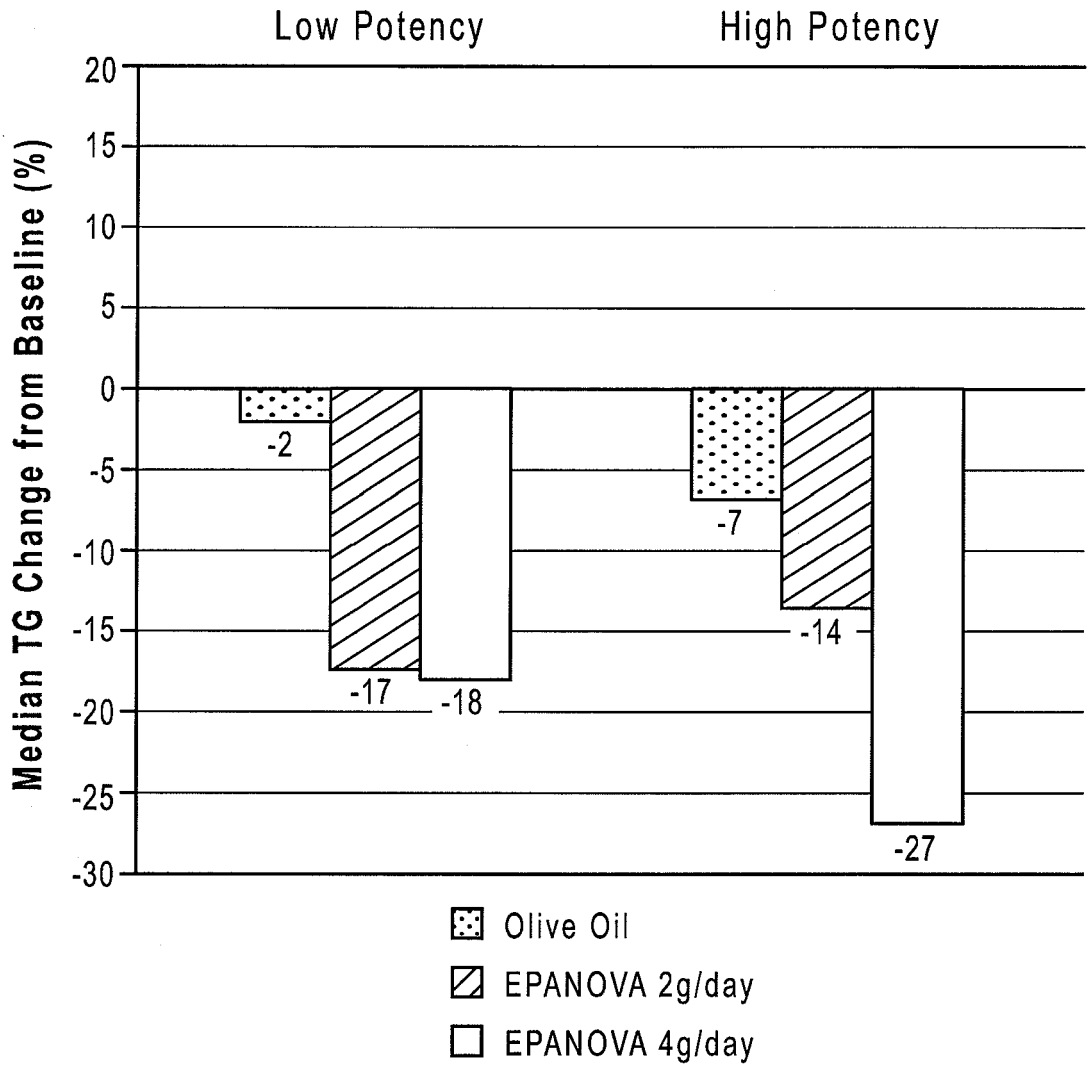

Low Potency
High Potency
Median TG Change from Baseline (%)
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-2
-17
-18
-7
-14
-27
Olive Oil
EPANOVA 2g/day
EPANOVA 4g/day

FIG. 49

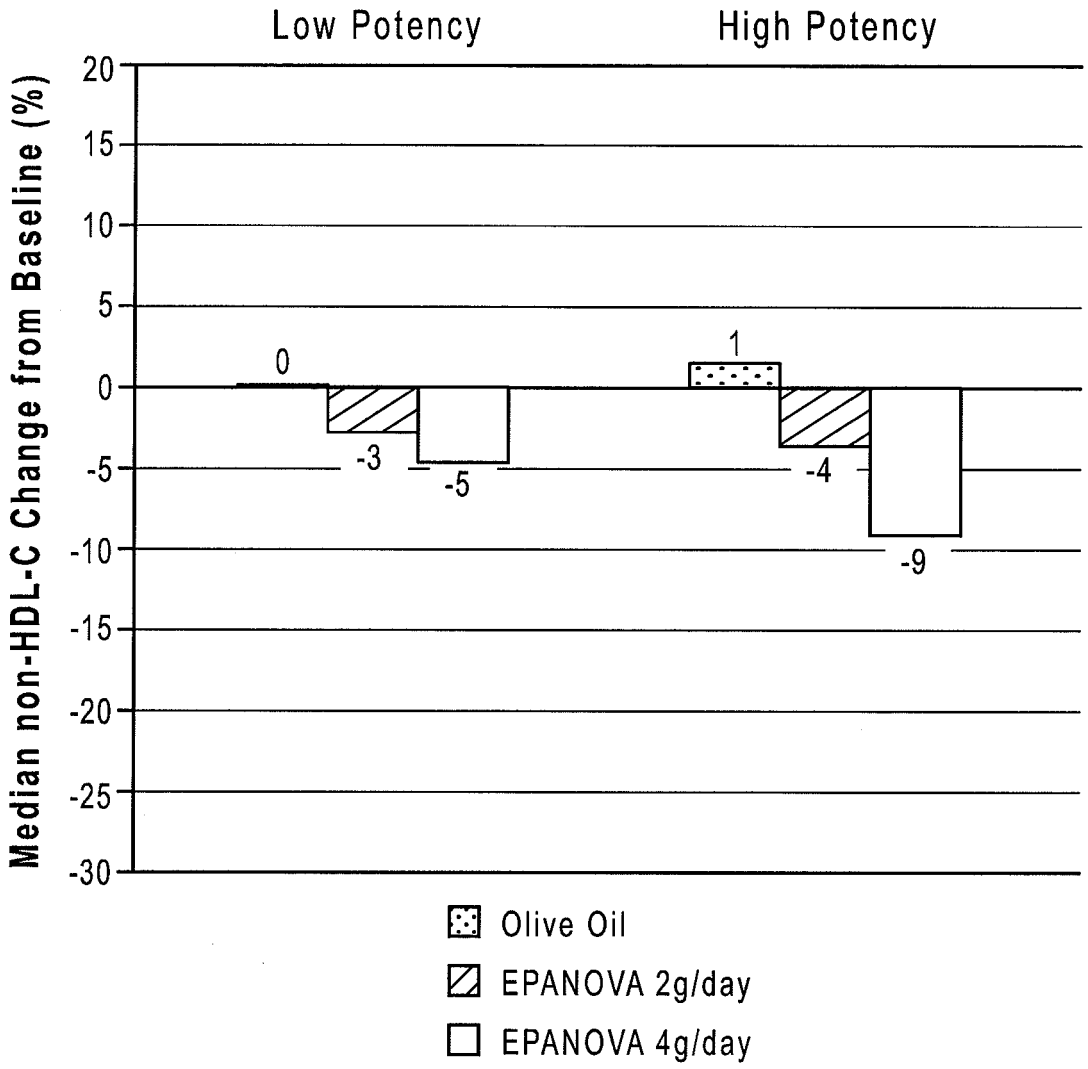

Low Potency
High Potency
Median non-HDL-C Change from Baseline (%)
20
15
10
5
0
-5
-10
-15
-20
-25
-30
0
-3
-5
1
-4
-9
Olive Oil
EPANOVA 2g/day
EPANOVA 4g/day

FIG. 50

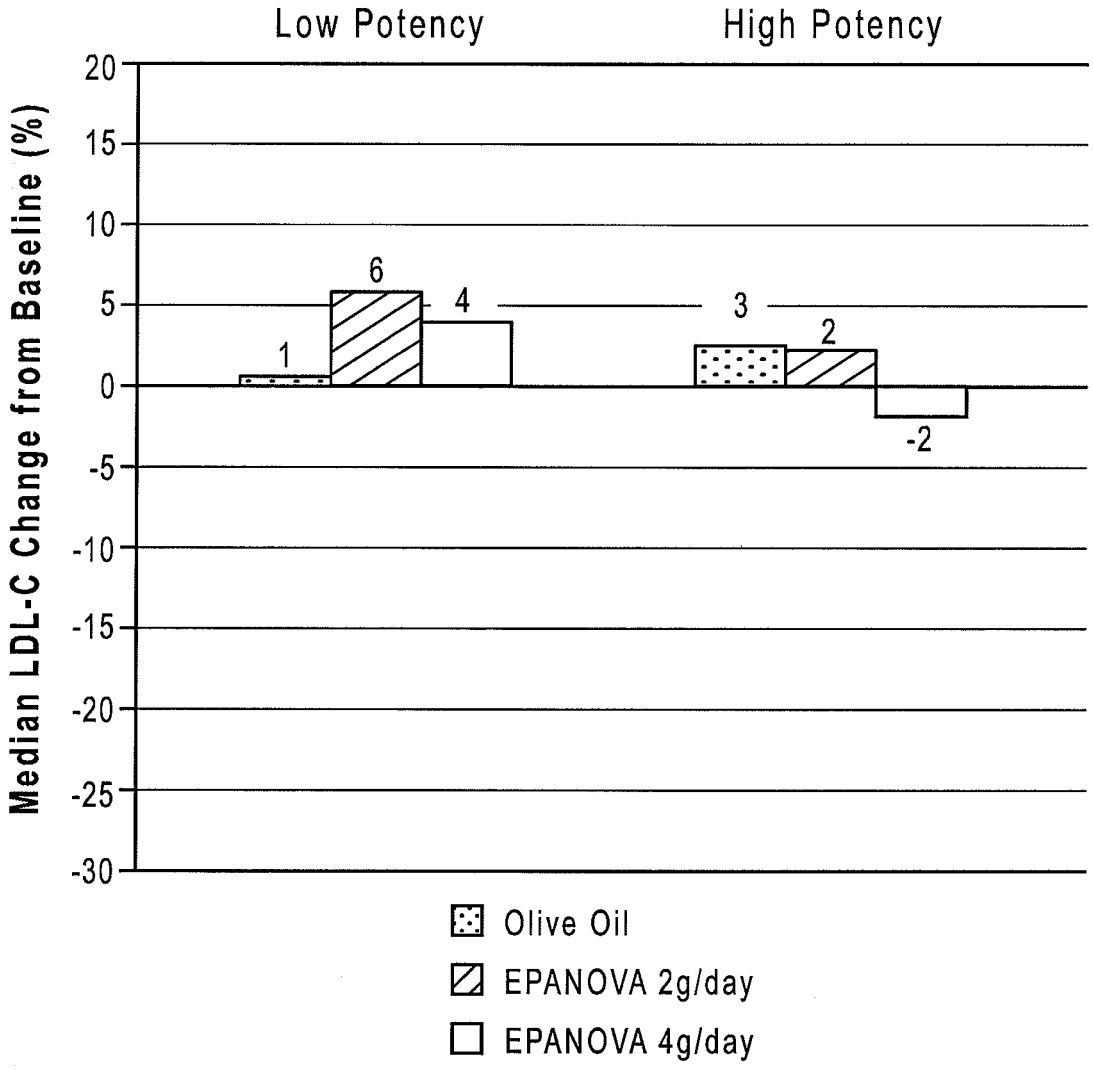

Low Potency
High Potency
Median LDL-C Change from Baseline (%)
20
15
10
5
0
-5
-10
-15
-20
-25
-30
1
6
4
3
2
-2
Olive Oil
EPANOVA 2g/day
EPANOVA 4g/day

FIG. 51

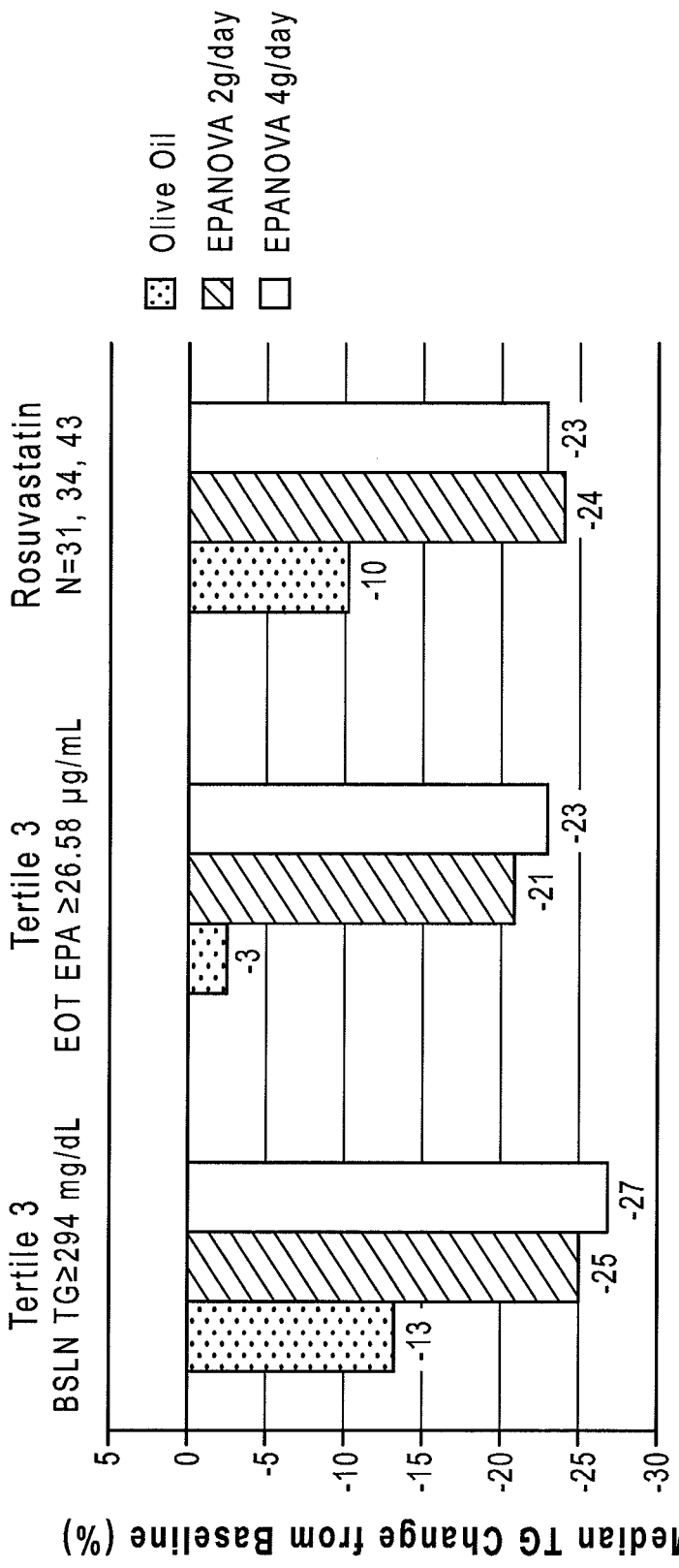

Olive Oil
EPANOVA 2g/day
EPANOVA 4g/day
Tertile 3
BSLN TG≥294 mg/dL
Tertile 3
EOT EPA ≥26.58 µg/mL
Rosuvastatin
N=31, 34, 43
-13
-25
-27
-3
-21
-23
-10
-24
-23
5
0
-5
-10
-15
-20
-25
-30
Median TG Change from Baseline (%)

FIG. 52

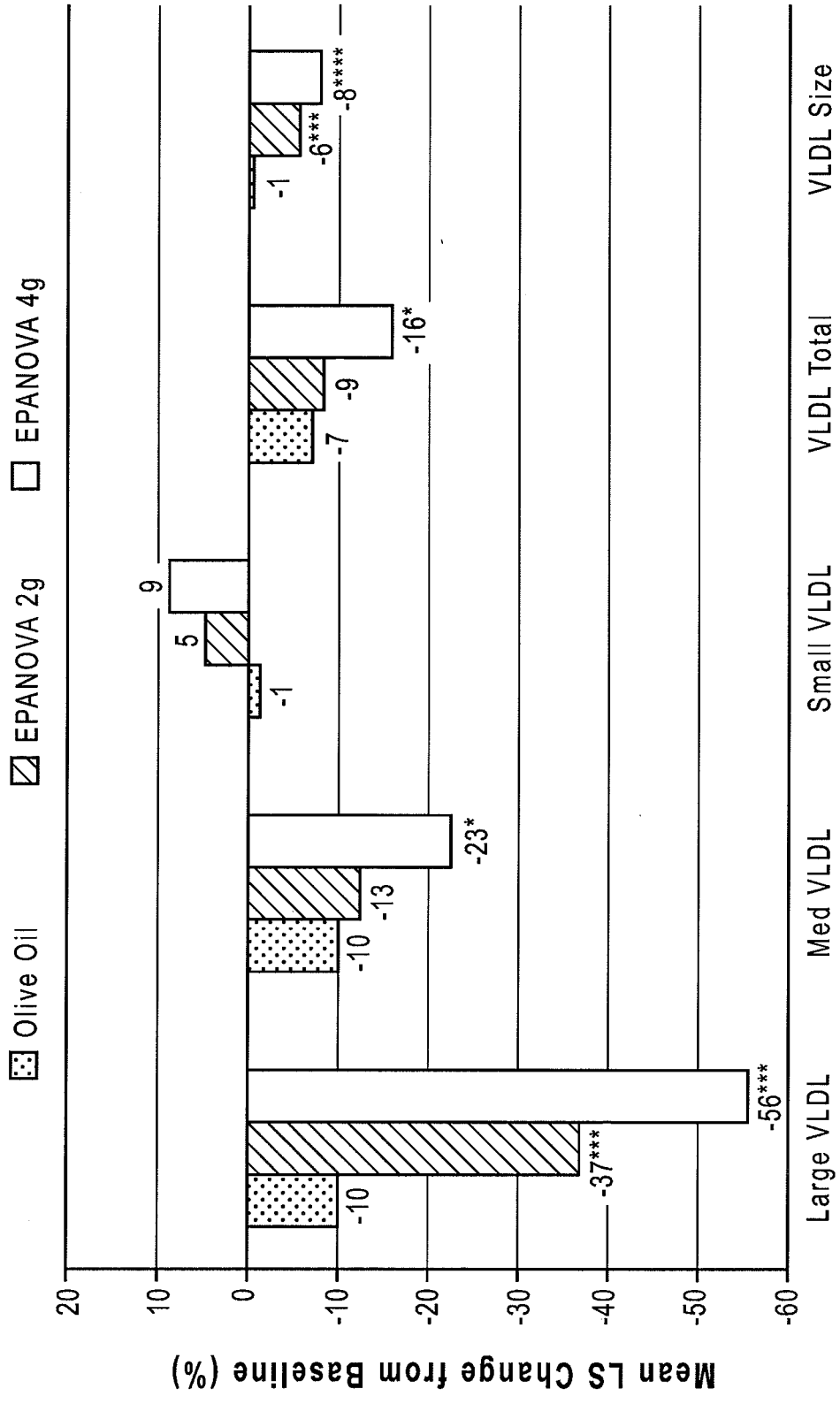

Olive Oil
EPANOVA 2g
EPANOVA 4g
Mean LS Change from Baseline (%)
20
10
0
-10
-20
-30
-40
-50
-60
Large VLDL
Med VLDL
Small VLDL
VLDL Total
VLDL Size
-10
-37***
-56***
-10
-13
-23*
-1
5
9
-7
-9
-16*
-1
-6***
-8****

FIG. 53

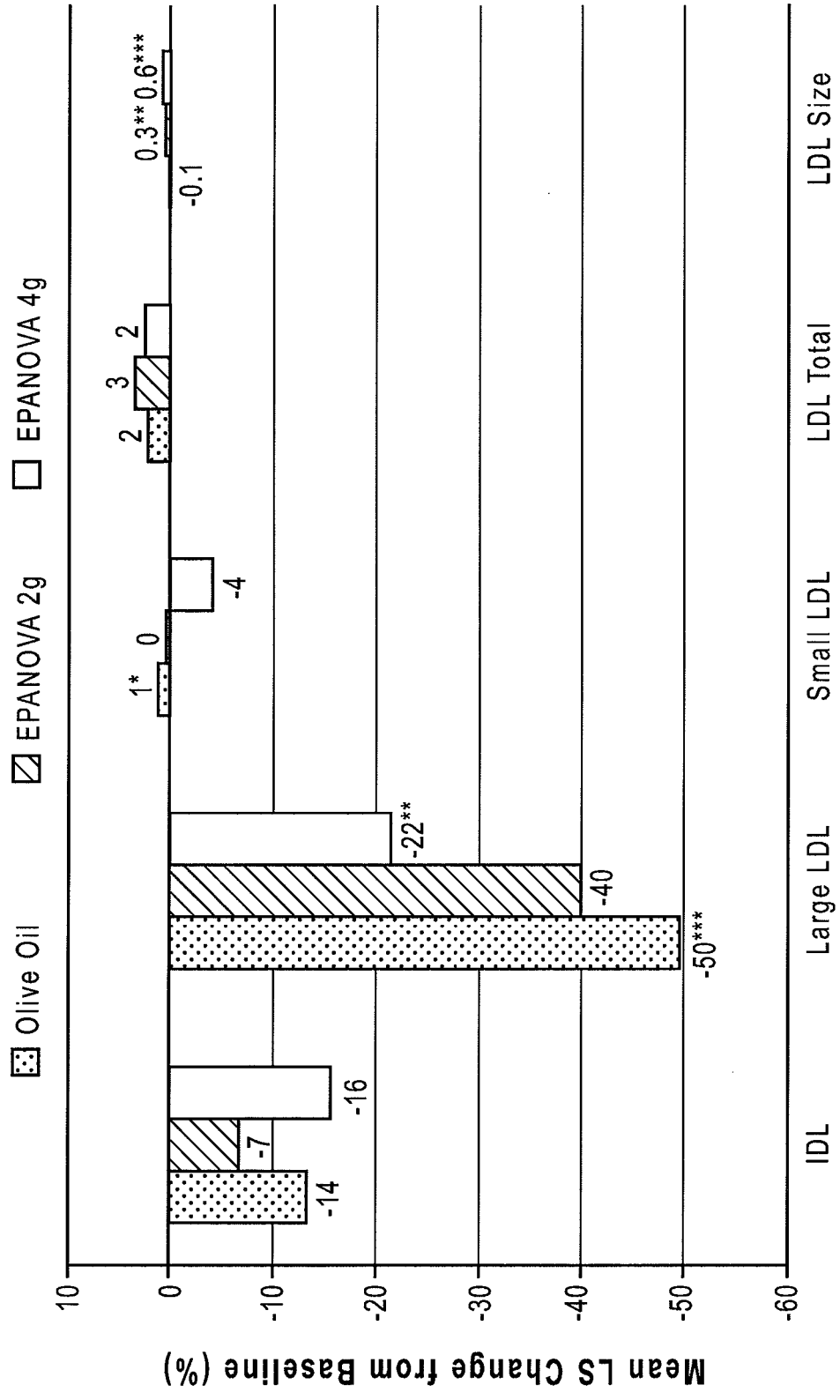

Olive Oil
EPANOVA 2g
EPANOVA 4g
Mean LS Change from Baseline (%)
10
0
-10
-20
-30
-40
-50
-60
IDL
Large LDL
Small LDL
LDL Total
LDL Size
-14
-7
-16
2
3
2
1*
0
-4
-22**
-40
-50***
0.3**
0.6***
-0.1

FIG. 54

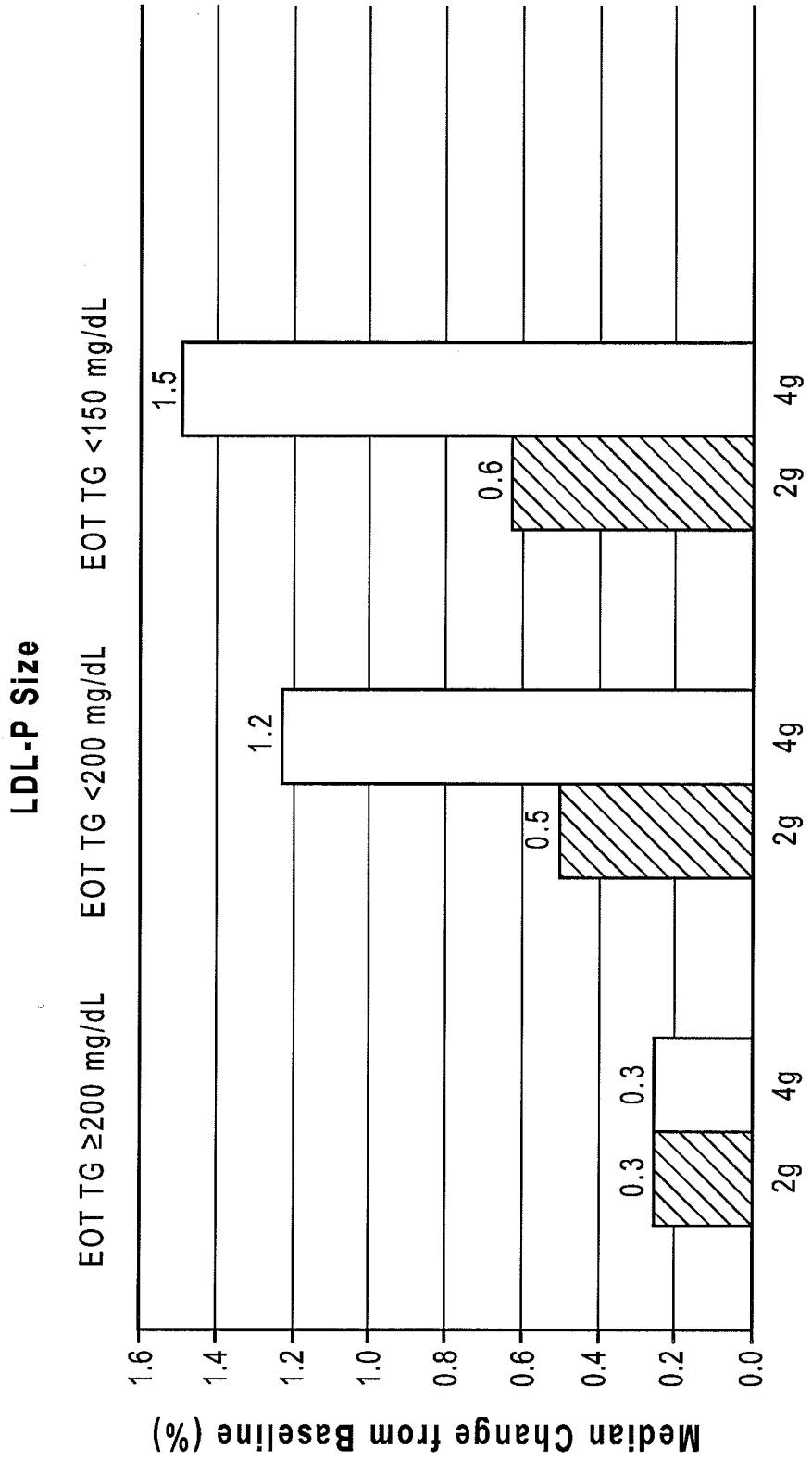
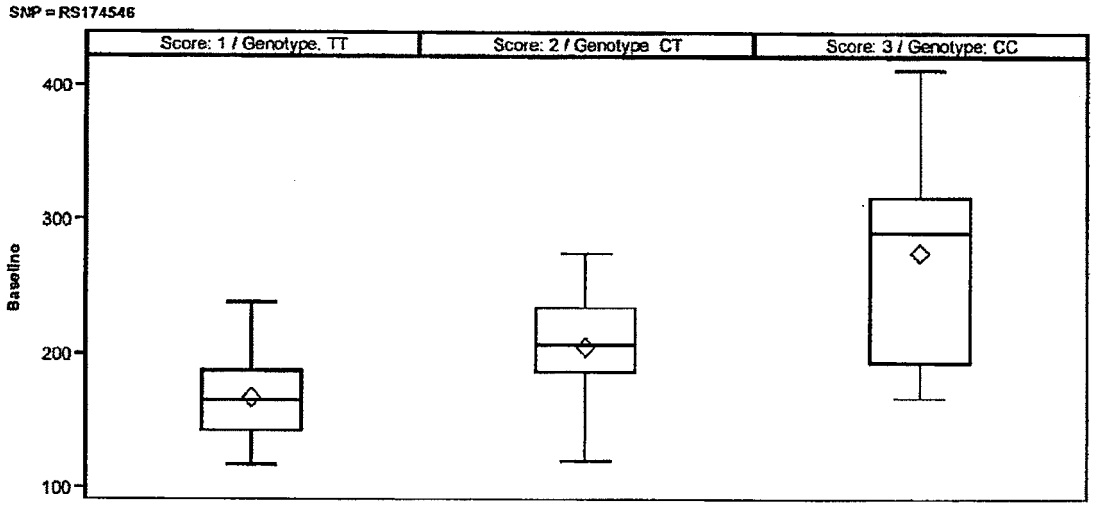

LDL-P Size
EOT TG ≥200 mg/dL
EOT TG <200 mg/dL
EOT TG <150 mg/dL
Median Change from Baseline (%)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.3
0.3
0.5
1.2
0.6
1.5
2g
4g
2g
4g
2g
4g

FIG. 55

A


SNP = RS174546
Score: 1 / Genotype: TT
Score: 2 / Genotype: CT
Score: 3 / Genotype: CC
Baseline
400
300
200
100

B

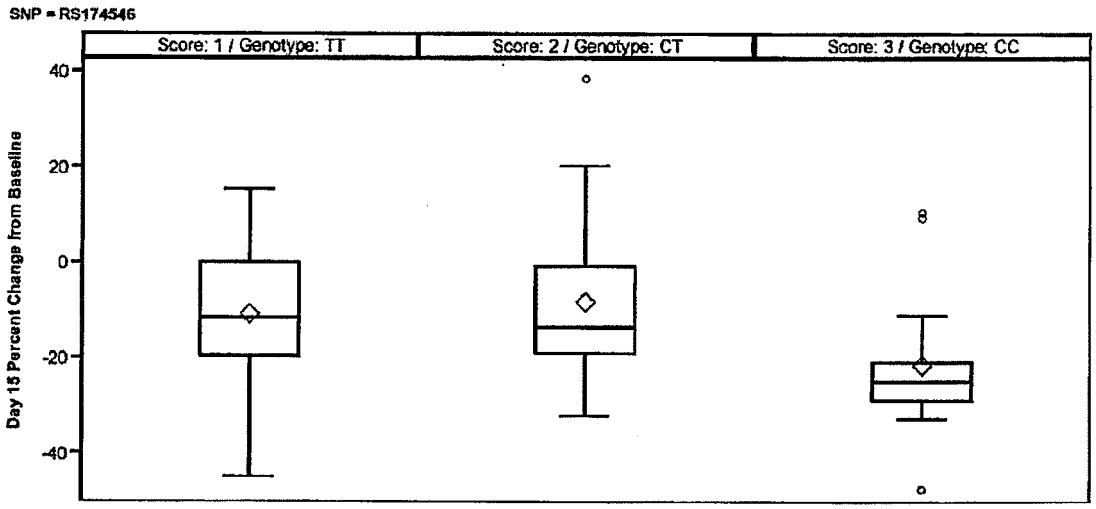

SNP = RS174546
Score: 1 / Genotype: TT
Score: 2 / Genotype: CT
Score: 3 / Genotype: CC
Day 15 Percent Change from Baseline
40
20
0
-20
-40
8

FIG. 56