# Icosabutate for the Treatment of Very High Triglycerides

A Placebo-controlled, Randomized, Double-blind, 12-week Clinical Trial

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On behalf of Investigators

*Sponsored by Pronova BioPharma, BASF*

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| Disclosure potential conflicts of interest | |
|---|---|
| Research contracts: | Amarin, Amgen, Ardea, Arisaph, Catabasis, Cymabay, Eisai, Elcelyx, Eli Lilly, Esperion, Hanmi, Hisun, Hoffman LaRoche, Home Access, Janssen, Johnson and Johnson, Merck, Necktar, Novartis, Novo Nordisk, Omthera, Orexigen, Pfizer, Pronova, Regeneron, Sanofi, Takeda, TIMI, VIVUS, and Wpu Pharmaceuticals |
| Consulting: | Alnylam, Amarin, Amgen, Astra Zeneca, Eisai, Eli Lilly, Merck, Novartis, NovoNordisk, Regeneron, Sanofi and Takeda. |
| Employment in industry: | - |
| Stockholder of a healthcare company: | - |
| Owner of a healthcare company: | - |
| Other: | - |

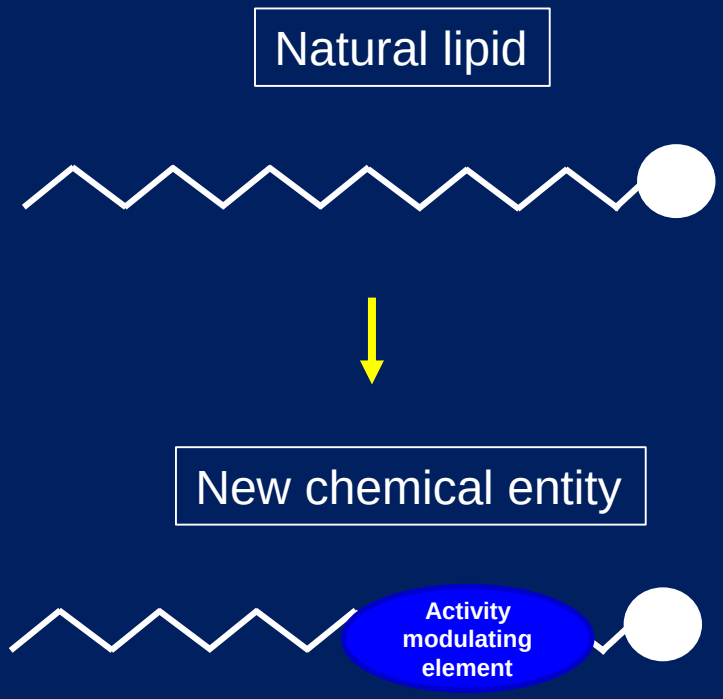
# Background

- Current non-statin therapeutic options for TG > 500 mg/dL (5.6 mmol/L) include fibrates, niacin, and prescription (Rx) omega-3
- Rx omega-3 are often taken in doses of 4 grams/day to achieve clinical efficacy
- Many patients are still unable to achieve TG levels < 500 mg/dL
- Icosabutate is a novel, *S*tructurally *E*nhanced *F*atty *A*cid (SEFA) that compared with conventional Rx omega-3 therapies is designed to
  - Increase potency → Lower dose
  - Improve efficacy → Larger TG-reductions
  - Preserve safety

} Efficacious and convenient, oral, once daily approach

# Icosabutate

- Synthetic EPA derivative (NCE)
  - Not incorporated into complex lipids
  - Direct hepatic delivery via portal vein following absorption
- Once daily, oral treatment
- Rapid, predictable absorption regardless of food intake
- Demonstrated large TG *and* Apo C3 reductions in hypercholesterolemic subjects in an exploratory phase Ib trial



# Study objective

- Proof-of-concept study to assess the efficacy and safety of icosabutate for lowering triglycerides in patients with severe hypertriglyceridemia

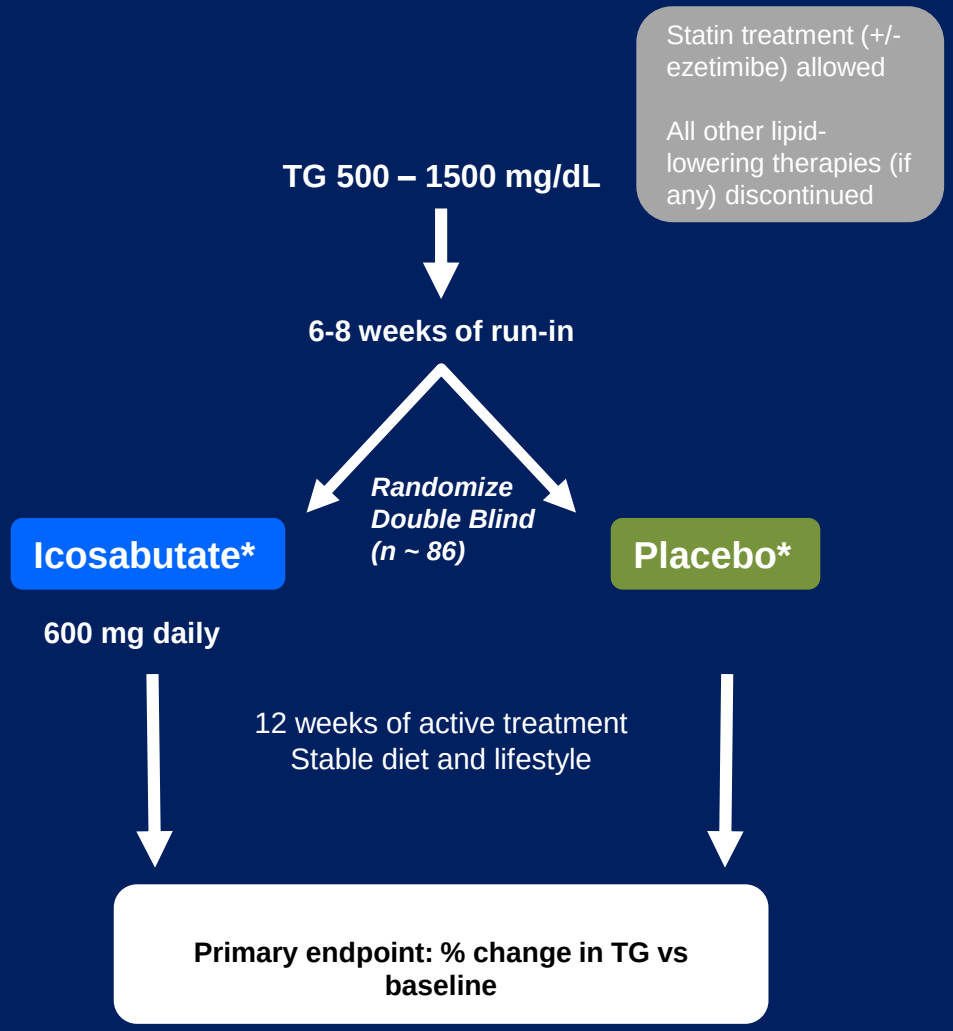
# Study design

## Key inclusion

- Men and women
- 18 – 79 years
- TG level ≥500 mg/dL and ≤1500 mg/dL
- +/- stable dose of statin

## Key exclusion

- Other non-statin lipid-lowering therapy (except ezetimibe)
- Fredrickson type I or III
- Apo C2 deficiency
- Recent (< 6 months) CV event




* Both taken as 6x100 mg

# Statistical methodologies

## Sample size

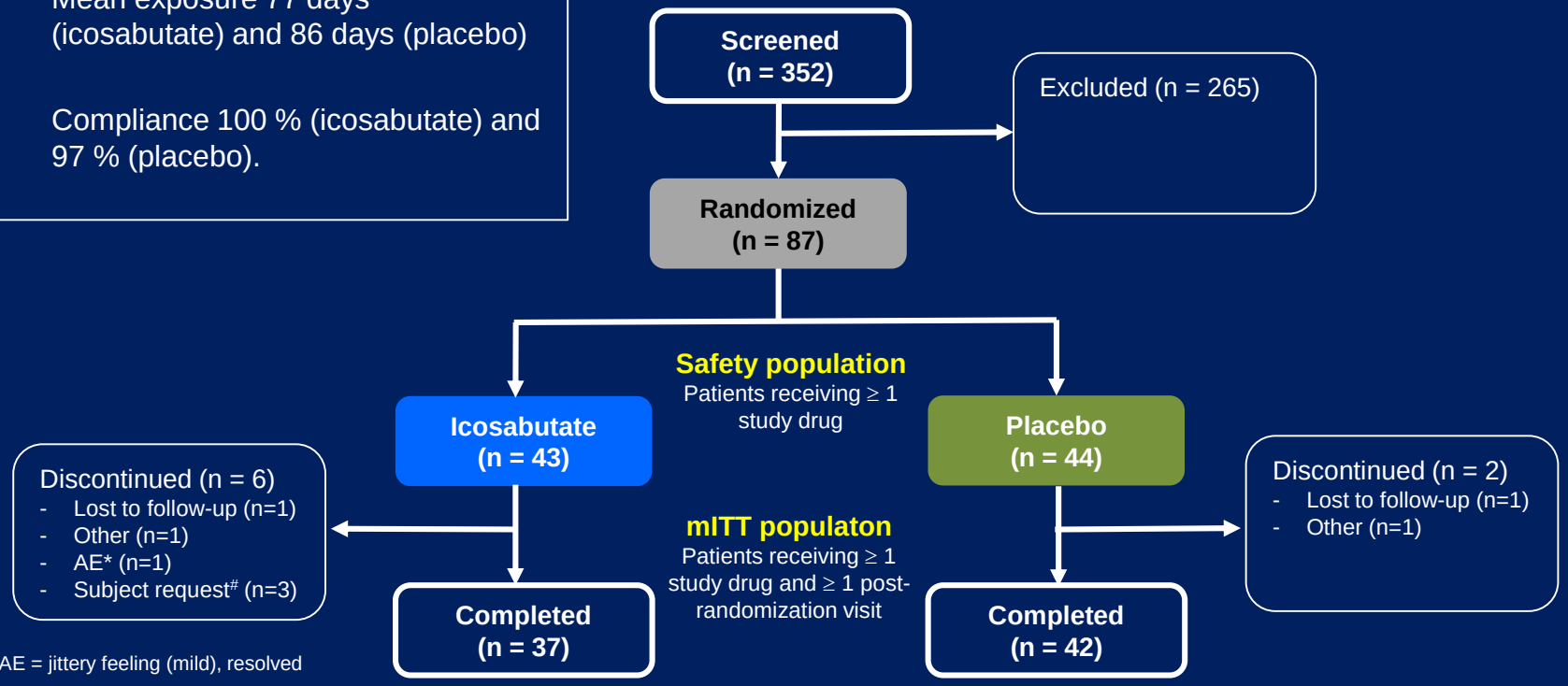
- Hypothesis: 30 % difference in fasting TG from baseline for icosabutate vs placebo
- Standard deviation in TG measurements of 45 %
- Type 1 error 0.05
- ~ 86 subjects; > 80 % power

## Primary efficacy evaluation

- Primary analysis on mITT population (≥ 1 dose of study treatment; ≥ 1 post-randomization visit)
- ANCOVA model with treatment, gender, statin therapy as factors
- If significant departures from normality, non-parametric approach
- Non-parametric test of significance:
  - Hodges-Lehman asymptotic 95 % confidence intervals (primary test)
  - Wilcoxon rank-sum p-values (supplementary)

# Study metrics and conduct

- Patients enrolled from July 2013 to March 2014
- Mean exposure 77 days (icosabutate) and 86 days (placebo)
- Compliance 100 % (icosabutate) and 97 % (placebo).




*AE = jittery feeling (mild), resolved

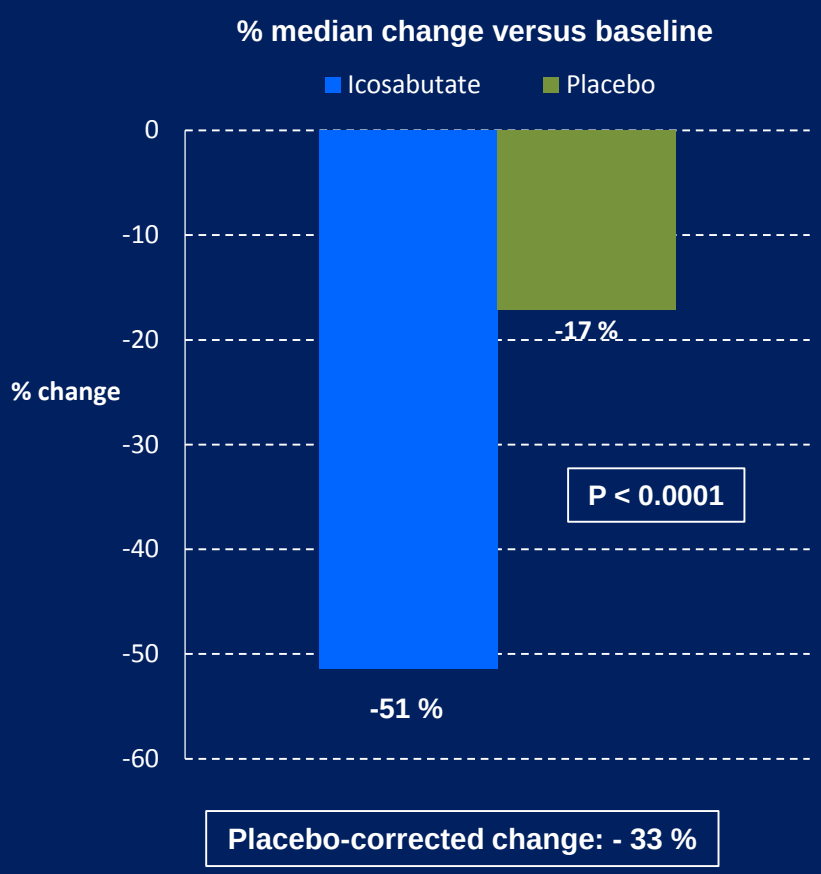
# Reasons for discontinuation:
Moved to different state (n=2)
Enrolled in other study (n=1)

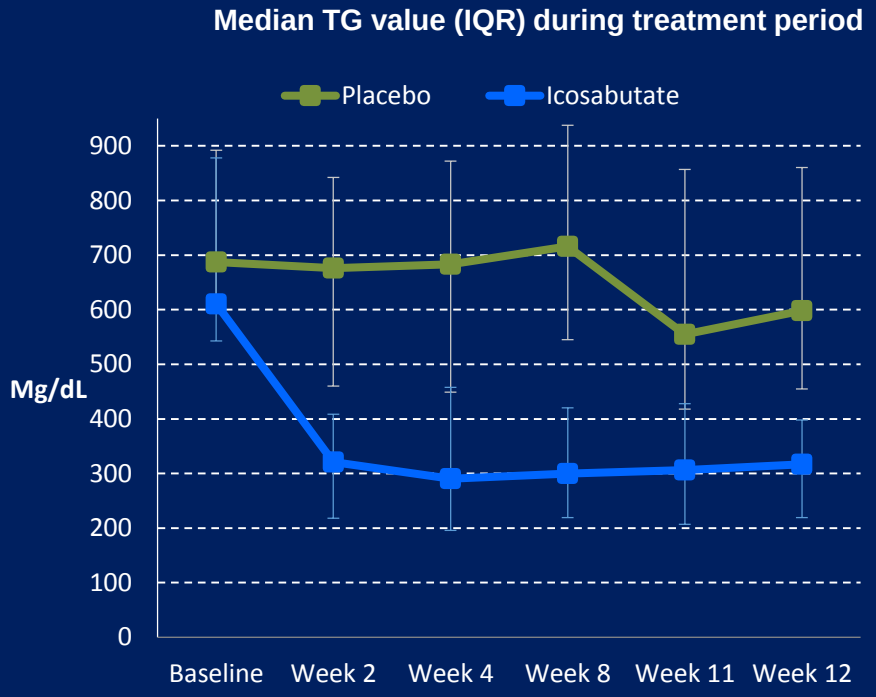
# Baseline characteristics and lipids

| Characteristic | Icosabutate, 600 mg (n = 43) | Placebo ( n = 44) |
|---|---|---|
| **Age (years, mean ± SD)** | 54 ± 9 | 52 ± 11 |
| **Male, n (%)** | 29 (67) | 31 (71) |
| **Body mass index, (kg/m$^2$, mean ±SD)** | 31.7 ± 4.4 | 32.3 ±4.6 |
| **Race, n (%)** | | |
| White/Caucasian | 39 (89) | 40 (93) |
| Black | 2 (5) | 2 (5) |
| **Diabetes, n (%)** | 18 (42) | 17 (39) |
| **Hypertension , n (%)** | 21 (49) | 25 (57) |
| **On statin at randomization – n (%)** | 9 (21) | 9 (21) |
| **Lipids (mg/dL, median, IQR)** | | |
| **Triglycerides** | 611 (543, 878) | 688 (596, 892) |
| **LDL-C** | 95 (75, 134) | 79 (55, 97) |
| **HDL-C** | 32 (29, 37) | 31 (26, 33) |
| **Non-HDL-C** | 226 (190, 265) | 207 (180, 246) |
| **Apolipoprotein B** | 127 (105, 156) | 109 (99, 119) |
| **Apolipoprotein C3** | 30 (24, 34) | 28 (23, 33) |

# Primary endpoint

## % change in triglycerides versus baseline




- 88 % of icosabutate treated patients achieved a TG < 500 mg/dL vs
- 37 % in placebo group (p < 0.001)

# Secondary endpoints

## Lipids and lipoproteins

| | Icosabutate, 600 mg (n = 41) | Placebo ( n = 43) |
|---|---|---|
| **Non-HDL-C** | | |
| Baseline | 226 | 206 |
| 12 week | 195 | 189 |
| % change vs baseline | -8.1 % | -1.6 % |
| **% change vs placebo (p-value)** | **-7.1 % (p = 0.06)** | |
| **HDL-C** | | |
| Baseline | 32 | 31 |
| 12 week | 38 | 29 |
| % change vs baseline | 23.4 % | 4.0 % |
| **% change vs placebo (p-value)** | **18.3 % (p<0.001)** | |
| **LDL-C** | | |
| Baseline | 95 | 79 |
| 12 week | 141 | 82 |
| % change vs baseline | 42.6 % | 14.0 % |
| **% change vs placebo (p-value)** | **28.4 % (p<0.001)** | |
| **VLDL-C** | | |
| Baseline | 106 | 119 |
| 12 week | 51 | 100 |
| % change vs baseline | - 50.9 % | -19.7 % |
| **% change vs placebo (p-value)** | **- 35.7 % (p<0.001)** | |
| **RLP-C** | | |
| Baseline | 38 | 49 |
| 12 week | 19 | 39 |
| % change vs baseline | - 49.9 % | - 18.8 % |
| **% change vs placebo (p-value)** | **- 35.5 % (p<0.001)** | |
| **Apolipoprotein B** | | |
| Baseline | 127 | 109 |
| 12 week | 129 | 107 |
| % change vs baseline | -1.1 % | -1.8 % |
| **% change vs placebo (p-value)** | **2.4 % (p=0.5)** | |
| **Apolipoprotein C3** | | |
| Baseline | 30 | 28 |
| 12 week | 16 | 27 |
| % change vs baseline | - 41.3 % | - 5.0 % |
| **% change vs placebo (p-value)** | **- 34.8 % (p<0.001)** | |

# Secondary endpoints

## Inflammation and glucose metabolism

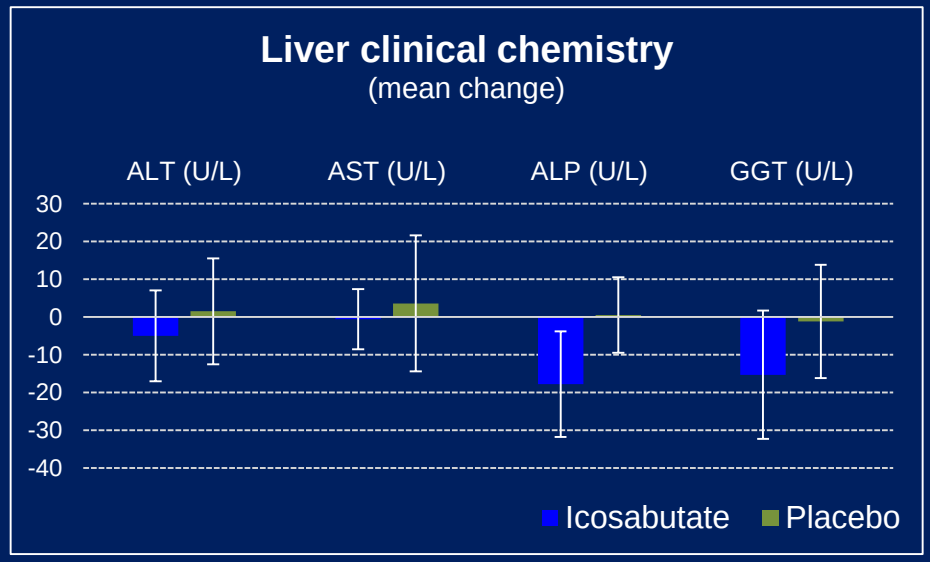
| | Icosabutate, 600 mg (n = 41) | Placebo ( n = 43) |
|---|---|---|
| **Lp-PLA2 (mg/dL)** | | |
| Baseline | 239 | 252 |
| 12 week | 206 | 244 |
| % change vs baseline | -12.8 % | -4.3 % |
| **% change vs placebo (p-value)** | **-13.6 % (p=0.003)** | |
| **CRP (mg/dL)** | | |
| Baseline | 3.0 | 2.4 |
| 12 week | 1.9 | 2.6 |
| change vs baseline | -0.7 | -0.3 |
| **change vs placebo (p-value)** | **-0.7 (p=0.16)** | |
| **HbA1C (%)** | | |
| Baseline | 5.9 | 6.1 |
| 12 week | 6.0 | 6.2 |
| change vs baseline | 0.1 | 0.1 |
| **change vs placebo (p-value)** | **0.0 (p=0.64)** | |
| **Fasting plasma glucose (mg/dL)** | | |
| Baseline | 117 | 112 |
| 12 week | 106 | 119 |
| change vs baseline | - 6 | - 1 |
| **change vs placebo (p-value)** | **- 5 (p=0.26)** | |
| **Fasting plasma insulin (mIU/L)** | | |
| Baseline | 20.2 | 21.1 |
| 12 week | 15.7 | 19.9 |
| change vs baseline | -4.8 | - 0.3 |
| **change vs placebo (p-value)** | **- 5.8 (p=0.001)** | |
| **HOMA-IR** | | |
| Baseline | 6.7 | 7.2 |
| 12 week | 4.3 | 6.8 |
| change vs baseline | - 1.8 | -0.2 |
| **change vs placebo (p-value)** | **- 2.1 (p=0.006)** | |

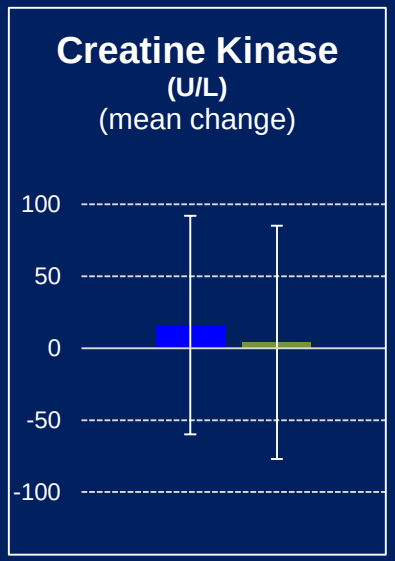
HOMA-IR = (FPG (mg/dL) x fasting insulin (uIU/ml)) / 405

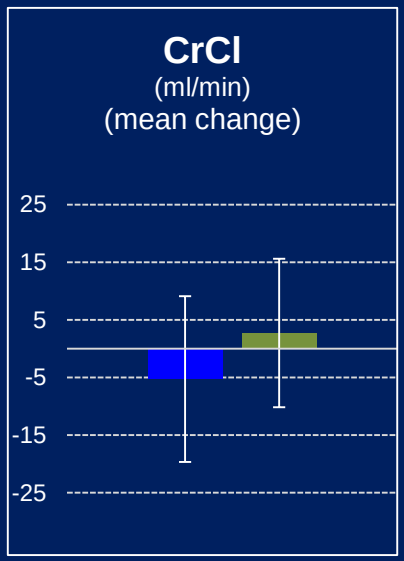
# Safety

| Adverse events | Icosabutate, 600 mg (n = 43) | Placebo ( n = 43) |
|---|---|---|
| **Subjects with any treatment-emergent AE, n (%)** | **25 (58)** | **29 (67)** |
| Mild | 11 (26) | 23 (54) |
| Moderate | 13 (30) | 5 (12) |
| Severe | 1 (2) [1] | 1 (2)[3] |
| **Serious Adverse Event** | 0 (0) | 1 (2)[4] |
| **TEAE leading to discontinuation or withdrawal** | 1 (2)[2] | 0 (0) |

1. Preferred term «dyspepsia». Experienced after administration of first dose of study drug. Subject recovered and completed study with no further dyspepsia.
2. Preferred term «Jittery feeling». Considered mild. Subject recovered.
3. Preferred term «high blood pressure». Subject recoved and completed study.
4. Preferred term «Acute retrocecal appendicities». Experienced in screening period. Not study-related.



# Summary and conclusion

- Efficacy
  - Icosabutate reduced fasting plasma triglycerides by 51 % vs baseline and 33 % vs placebo
  - Icosabutate numerically decreased non-HDL-C levels, with:
    - ~ 50% reduction in VLDL-C and RLP-C
    - ~ 40% reduction in Apo C3
    - ~ 12% reduction in Lp-PLA2
    - Significant increases in LDL-C and HDL-C
    - No significant change in Apo B or CRP
    - Significant reduction in fasting plasma insulin and HOMA-IR
- Safety
  - Reported adverse events were similar between icosabutate and placebo
  - No clinically relevant changes in clinical chemistry, vital signs, electrocardiography
  - No change in fasting plasma glucose, reduced fasting plasma insulin
- Conclusion
  - At 15 % of a 4 gram dose typical of other Rx omega-3, icosabutate produces significant reductions in triglycerides levels with 88 % of patients reaching the target of < 500 mg/dL
  - Icosabutate is a potent TG-lowering drug designed for convenient once daily, oral administration

# THANKS to all investigators and patients

**Investigators**

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