

# Efficacy and Safety of Ezetimibe Monotherapy in Children with Heterozygous Familial or Nonfamilial Hypercholesterolemia

## BACKGROUND

- Familial hypercholesterolemia is an inherited disorder of lipoprotein metabolism.
- As of now, after failure of lifestyle modification/diet intervention, the first line therapy is a statin depending on cardiovascular risk. Other lipid-lowering drugs may also be used when statins are contraindicated, not tolerated or not controlling dyslipidemia alone.

## OBJECTIVE

- To evaluate the lipid-altering efficacy and safety of ezetimibe monotherapy in young children with heterozygous familial hypercholesterolemia (HeFH) or nonfamilial hypercholesterolemia (nonFH).

## METHODS

- **Design:** Multiple site, randomized, double-blind, parallel-group, place-controlled trial; Duration: 12 weeks
- **Inclusion criteria:** Fasting triglyceride levels  $\leq 300$  mg/dL, clinical laboratory values within normal limits or clinically acceptable to the investigator, ALT and/or AST  $\leq 1.5$  the upper limit of normal, serum creatinine  $< 2.0$  mg/dL and were free of any clinically important disease other than hypercholesterolemia that would interfere with study evaluation.
- **Exclusion criteria:** Hypersensitivity or any contraindication to ezetimibe; any cardiac disorder or disorders of the hematologic, digestive, or central nervous systems (including cerebrovascular disease, anorexia nervosa) and degenerative disease that would limit study evaluation/participation; diabetes mellitus type 1 or 2; uncontrolled endocrine metabolic disease, unstable thyroid hormone replacement therapy with thyroid stimulating hormone levels outside the normal range; clinically significant impairment of renal function, dysproteinemia, nephrotic syndrome, or other renal disease; active or chronic hepatic or biliary disease; history of partial ileal bypass or disease that affects significant function of the ileum; HIV infection; known coagulopathy; medical history consistent with HoFH; and use of LDL apheresis or plasma apheresis. Known lipid-altering therapies, foods, or supplements were prohibited within a predefined time period prior to randomization.
- **Primary outcome measure:** To compare the efficacy of ezetimibe with placebo in the percentage change from baseline in LDL-C at week 12.
- **Secondary outcome measures:**
  - Percentage change from baseline in Total Cholesterol at Week 12
  - Percentage change from baseline in Apolipoprotein B at Week 12
  - Percentage change from baseline High-density Lipoprotein Cholesterol at Week 12
  - Percentage change From Baseline in Non-HDL-C at Week 12
  - Percent change from baseline in LDL-C, TC, HDL-C, Non-HDL-C and TG at Week 2, 4 and 8
  - Percentage change from baseline in Apolipoprotein A-I at Week 12
  - Percentage change from baseline in TC:HDL-C Ratio at Week 2, 4, 8 and 12
  - Percentage change from baseline in LDL-C:HDL-C Ratio at Week 2, 4, 8 and 12

Percentage change from baseline in Apo B:Apo A-I Ratio at Week 12

Percentage change from baseline in High-sensitivity C-reactive Protein at Week 4 and 12

Percent change from baseline in Sitosterol, Campesterol, Cholestanol and Lathosterol at Week 2, 4, 8 and 12

- 138 patients received either
  - Ezetimibe 10 mg tablet (93 patients) + diet stabilization
  - OR
  - Placebo + diet stabilization
- Power was not stated
- Data handling methods were intention-to-treat and per protocol; each analysis used for different variables (side effects vs efficacy)

## RESULTS

- 4 patients in the ezetimibe group discontinued the study. 3 were due to adverse events. 1 due to elevated ALT levels, 1 due to prurigo starting on day 48 and 1 due to congenital epileptic events. The other patient withdrew consent. There were no patients that discontinued the study in the placebo group.
- **Primary outcome measure:** After 12 weeks of treatment, reduction of LDL-C was significantly greater with ezetimibe 10 mg than placebo with a p value <0.001.
- **Secondary outcome measures:** Ezetimibe produced significantly greater percent reductions from baseline than placebo in total cholesterol, non-HDL-C, Apo B, and all measured lipid and lipoprotein ratios (all with p values <0.001); change in triglycerides was nominally significant ( $P = .021$ ) but not statistically significant after prespecified multiplicity adjustment. The effect of ezetimibe on HDL-C, Apo AI, and hs-CRP was not significantly different than placebo.
- **Author's conclusion:** Ezetimibe monotherapy produced clinically relevant reductions in LDL-C and other key lipid variables in young children with primary HeFH or clinically important nonFH, with a favorable safety/tolerability profile.

## STRENGTHS

- Placebo-controlled experimental design was used
- Double-blinded study
- Random assignment for each group was used
- Washout period (up to 13 weeks) was given for patients
- Compliance was addressed (mean of 95%)

## LIMITATIONS

- Power was not stated
- Inclusion and exclusion criteria limited the study population
- Diet and exercise was not measured throughout the study
- Standardization of each site was not addressed
  - Could lead to different lifestyles, diets and handling of the patients
- Funded by the manufacturer of ezetimibe (Zetia), Merck
- Most of the authors are/were employees of Merck and may hold stock in the company

## CONCLUSION

- The study showed that ezetimibe monotherapy produced reductions in LDL-C and other lipid variables in young otherwise healthy children
  - Currently, a statin is considered first line based on cardiovascular risk after failure with lifestyle/diet intervention
  - Ezetimibe could be considered in children with statin intolerance, when contraindicated or in combination
- Further research:
  - Bigger studies in patients that represent the population would help to understand the full comparison of ezetimibe to statins.
  - Ezetimibe hasn't been shown to decrease cardiovascular events in patients like statins have. Therefore, more studies are needed to assess this outcome.
  - Study the effects of ezetimibe on childhood development.

**Reference:** Kuster MD, Caceres MS, Coll MD, Cuffie MD, Gagne MD, Jacobson MD, et al. Efficacy and Safety of Ezetimibe Monotherapy in Children with Heterozygous Familial or Nonfamilial Hypercholesterolemia. *J Pediatrics*. 2015; 166(6): 1377-1384. Available at: [www.sciencedirect.com](http://www.sciencedirect.com). Accessed May 22, 2015.

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