Long-Term Efficacy and Safety of the Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide in Patients With Homozygous Familial Hypercholesterolemia

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Homozygous familial hypercholesterolemia is a genetic disorder characterized by low-density lipoprotein (LDL)-receptor dysfunction, markedly elevated levels of LDL-cholesterol (LDL-C) and premature atherosclerosis. Patients are often poorly responsive to conventional lipid-lowering therapies that upregulate LDL-receptor expression.[1]

Lomitapide inhibits microsomal triglyceride transfer protein, which lipidates nascent apolipoprotein (apo)B-containing lipoproteins. In a pivotal 78-week open-label trial, lomitapide, titrated to the maximal tolerable dose, decreased LDL-C by 50% at the end of the efficacy phase (week 26) in patients with homozygous familial hypercholesterolemia.[2] The principal adverse events included gastrointestinal disturbances, hepatic enzyme elevations, and increased liver fat.

Here we provide additional long-term efficacy and safety data, including an exploratory analysis of the potential metabolic consequences of hepatic fat accumulation from an extension trial (NCT00943306). Patients continued on lomitapide at the maximally tolerated dose until transition to commercial or compassionate lomitapide. Lipid-lowering therapies, including apheresis, could be modified at the investigator's discretion if LDL-C was <100 mg/dL. Both studies received institutional review board and regulatory approval, and all participants provided informed consent. Significance of the percent changes from baseline was assessed using a mixed linear model; correlations were assessed with Pearson correlation.

Nineteen (mean age, 30.4 years; 10 male/9 female) of the 23 patients who completed the pivotal trial enrolled in the extension trial, and 17 completed week 126 (78 weeks pivotal + 48 weeks extension) assessments (primary efficacy end point). Three patients discontinued prematurely (relocation, elevated transaminases and excess alcohol, sudden cardiac death). The median lomitapide dose remained mostly consistent at 40 mg (range, 20–60 mg) from week 36 in the pivotal study to week 282 in the extension trial. Overall, the median treatment duration with lomitapide across both trials was 5.1 years (range, 2.1–5.7 years).

Among the 17 patients who completed week 126, LDL-C decreased from 356±127 mg/dL at baseline to 189±120 mg/dL at week 126, a mean percent change of –45.5% (95% confidence interval [CI], –61.6 to –29.4; $P<0.001$). LDL-C reduction was maintained for the duration of the extension trial ($P<0.001$; Figure, A). From baseline through week 246, a total of 14 (74%) patients achieved LDL-C <100 mg/dL, and 11 (58%) patients achieved LDL-C <70 mg/dL on at least 1 occasion. LDL-C reduction was independent of residual LDL-receptor functionality.

The most common adverse events reported were gastrointestinal, including diarrhea, nausea, dyspepsia, and vomiting. For most drug-related adverse events, the incidence was lower in the extension trial compared with the pivotal trial (42.1% versus 84.2%). Major adverse cardiovascular events occurred in 2 patients (sudden cardiac death and coronary artery bypass graft).

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Key Words: lomitapide

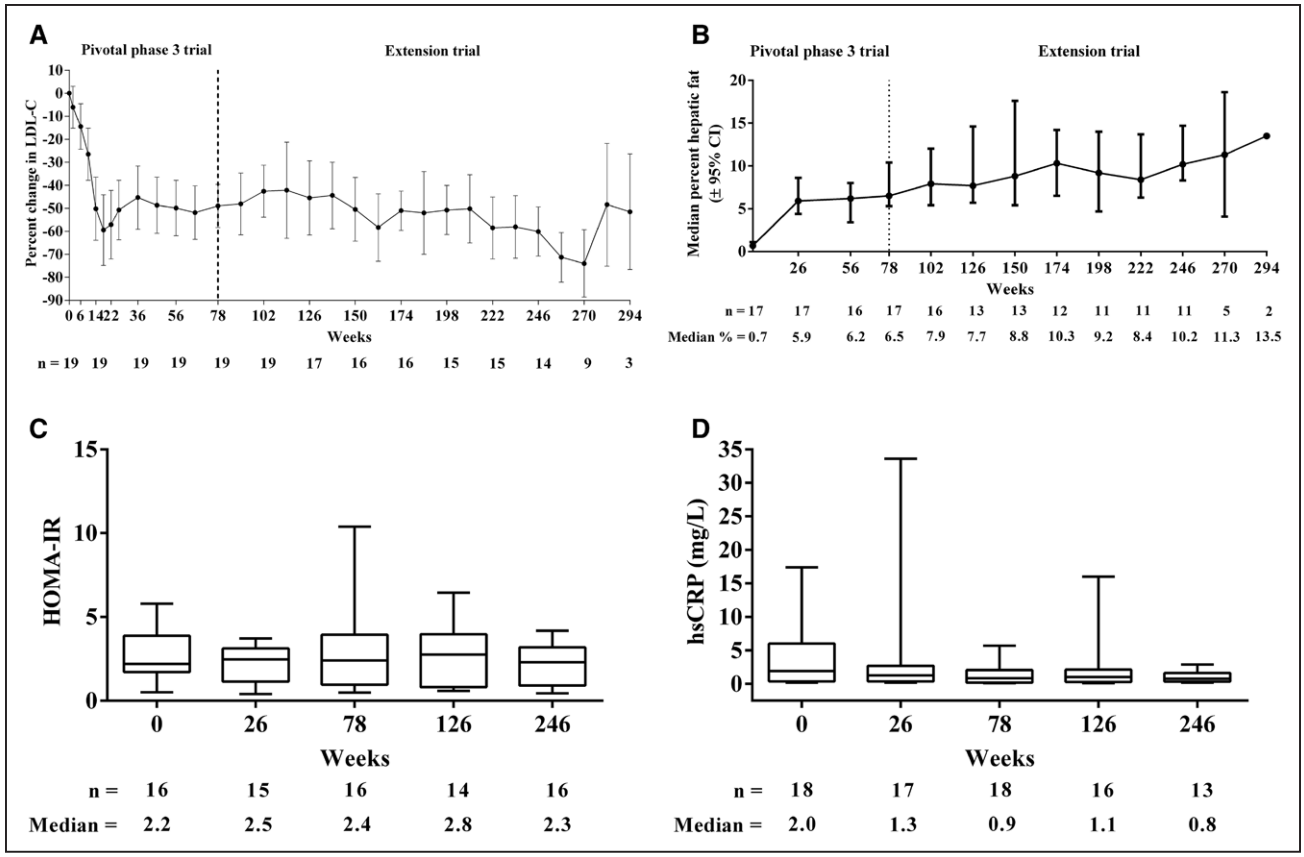

Figure. Changes in LDL-C, percent hepatic fat, HOMA-IR, and hsCRP during the pivotal phase 3 and extension trials. **A,** Percent change from baseline in low-density lipoprotein cholesterol (LDL-C) levels during the pivotal phase 3 and extension trials. Data are shown as mean±95% confidence interval. Decrease in n over time was largely because of transitioning patients to commercial/compassionate use lomitapide. At week 270, <50% of patients had data. Low patient numbers at the end of the study make assessment of efficacy unreliable. n indicates number of patients evaluated at each time point. **B,** Percent hepatic fat during the pivotal phase 3 and extension trials. Values assessed by nuclear magnetic resonance spectroscopy. Only 17 patients had an assessment after baseline performed. Data are shown as median±95% confidence interval. Decrease in n over time was largely because of transitioning patients to commercial/compassionate use lomitapide. At week 270, <50% of patients had data. Low patient numbers at the end of the study make assessment of hepatic fat content unreliable. n indicates number of patients evaluated at each time point. **C,** HOMA-IR over time. The central line represents the median HOMA-IR, the box encloses the 25th to 75th percentiles of the distribution, and the outer bars are drawn to the minimum and maximum values. HOMA-IR indicates homeostatic model assessment of estimated insulin resistance. **D,** hsCRP over time. The central line represents the median hsCRP, the box encloses the 25th to 75th percentiles of the distribution, and the outer bars are drawn to the minimum and maximum values. hsCRP indicates high-sensitivity C-reactive protein.

During the extension trial, 4 out of 19 (21.1%) patients experienced a ≥5× upper limit of normal increase in alanine aminotransferase or aspartate aminotransferase. Increases ≥5× upper limit of normal were typically associated with concomitant use of cytochrome P450 3A4 inhibitors or excess alcohol use. These events were successfully managed by discontinuing offending medication, lomitapide dose reductions or suspension, and reintroduction of lomitapide after normalization of transaminases.

Eighteen patients had ≥1 assessment after baseline of hepatic fat by nuclear magnetic resonance spectroscopy. Median hepatic fat increased from 0.7% (95% CI, 0.5–1.1) at baseline to 6.5% (95% CI, 5.3–10.4) at week 78 and was 7.7% (95% CI, 5.7–14.6), 10.3% (95% CI, 6.5–14.2), and 10.2% (95% CI, 8.3–14.7) at weeks 126, 174, and 246, respectively (Figure, B). The percent change in hepatic fat was significantly inversely correlated to only the change in LDL-C at week 26 (r=–0.59; P=0.010) and the change in high-density lipoprotein cholesterol at end of study (r=–0.53; P=0.033). No correlation was detected between hepatic fat and aspartate aminotransferase/alanine aminotransferase ratio, and no overt liver disease was observed.

Median glucose, insulin, and homeostatic model assessment of estimated insulin resistance (Figure, C) were stable throughout the study, and the median percent changes from baseline were not significantly different. The percent change in hepatic fat was significantly negatively correlated to the change in glucose at week

26 only (r=–0.52; P=0.036) and was not significantly correlated to changes in insulin or homeostatic model assessment of estimated insulin resistance at any time point. Median high-sensitivity C-reactive protein levels decreased progressively, resulting in statistically significant changes throughout the trial, with a decrease of ≈60% from baseline to week 246 (Figure, D).

The results of this extension trial are consistent with those of the pivotal trial and indicate that lomitapide treatment added to other lipid-lowering therapies is highly effective in lowering LDL-C levels with acceptable tolerability and no new safety signals.[2,3] Furthermore, in our exploratory post hoc analysis, we found no significant changes in glucose, insulin, homeostatic model assessment of estimated insulin resistance, or increase in high-sensitivity C-reactive protein and there was no correlation of these parameters with the increase in hepatic fat. An observational exposure registry, LOWER (Lomitapide Observational Worldwide Evaluation Registry) (ClinicalTrials.gov. Unique identifier: NCT02135705), will document long-term outcomes in clinical practice, including cardiovascular outcomes and evaluation of atherosclerotic burden.[4]

ACKNOWLEDGMENTS

Dr Foulds was the medical officer for this study, and Drs Foulds and Bloedon designed the study in collaboration with the authors. Drs Blom, Averna, du Toit Theron, Sirtori, Hegele, Shah, Gaudet, Stefanutti, Vigna, and Cuchel were principal investigators who recruited patients. Dr Foulds reviewed the data, and all authors contributed to the data interpretation. Drs Blom and Cuchel wrote the initial draft, and all authors critically reviewed and provided feedback at various stages through submission. All authors reviewed and approved the final version of the manuscript. Robert Schupp and Simone Boniface of inScience Communications, Springer Healthcare, provided medical writing support funded by Aegerion Pharmaceuticals. Dr Alighiero Bondioli was a principal investigator who recruited patients. Mark McBride of Instat Consulting, Inc., provided statistical assistance. Jian Wang and Adam McIntyre of Robarts Research provided assistance for the post hoc LDL-receptor mutation taxonomy. The authors and Aegerion Pharmaceuticals thank the patients who participated in the extension study.

SOURCES OF FUNDING

The study and manuscript development were sponsored and funded by Aegerion Pharmaceuticals. The authors, and not Aegerion Pharmaceuticals, are responsible for the content of this manuscript.

DISCLOSURES

Dr Blom has received research support from Amgen and Aegerion (both significant); received honoraria from MSD, AstraZeneca, Pfizer, Sanofi-Aventis, Amgen, and Servier (all modest); and served as a consultant/advisory board member for AstraZeneca, MSD, Aegerion, Gemphire, and Amgen (all modest). Dr Averna has received speaker fees from Abbott-Mylan, Aegerion, Amgen, Alexion, Chisei, MSD, Sanofi, and Sigma Tau (all modest); participated in an advisory board for Abbot-Mylan, Aegerion, Amgen, Alexion, Chisei, Kowa, MSD, Sanofi, and Sigma Tau (all modest); and received research support from Actelion and MSD (all modest). Dr Hegele has participated in an advisory board and received speaker fees from Aegerion, Amgen, Gemphire, Lilly, Merck, Pfizer, Regeneron, Sanofi, and Valeant (all modest). Dr Gaudet has received research support from FH Canada, Aegerion, Chisei, DalCor Pharma (all modest), Amgen, Akcea, AstraZeneca, Cymbay, Esperion, GlaxoSmithKline, Gemphire, Ionis, Pfizer, Regeneron, and Sanofi (all significant); and served as a consultant for Aegerion, Chiesi, Cymabay, uniQure (all modest), Amgen, Akcea, Ionis, Regeneron, and Sanofi (all significant). Dr Stefanutti has received research support (significant) and served as an expert witness (modest) for Aegerion. Drs Foulds and Bloedon were employees of Aegerion at the time of writing the manuscript (significant), and Dr Foulds holds stock in Novelion (modest), the parent company of Aegerion. Dr Cuchel has received research support from National Institutes of Health/National Heart, Lung, and Blood Institute (significant), support for the conduct of clinical trials from Sanofi, Regeneron, and Regenex (all significant), and speaker fees from Aegerion (significant). The other authors report no conflicts of interest.

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From University of Cape Town, South Africa (D.J.B.); Università di Palermo, Italy (M.R.A.); University of Pennsylvania, Philadelphia (E.A.M., D.J.R. M.C.); Netcare Private Hospital, Bloemfontein, South Africa (H.d.T.T.); Ospedale Niguarda, Milano, Italy (R.A.H.); University of Western Ontario, London, Canada (R.A.H.); Cedars-Sinai Heart Institute, Los Angeles, CA (P.K.S.); Université de Montreal, Chicoutimi, Quebec, Canada (D.G.); Università di Roma Sapienza, Italy (C.S.); Università di Ferrara, Italy (G.B.V.); CHRU Montpellier, France (D.L.); and Aegerion Pharmaceuticals, Cambridge, MA (L.T.B., P.F.).

FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

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