Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolemia

Code: LOM/EU/014
Date of preparation: November 2024

Online activity details

This resource has been downloaded from a touchDATA POINT, hosted on touchCARDIO. The full activity, which includes video resources, can be accessed at:

www.touchcardio.com/atherosclerosis/learning-zone/long-term-hepatic-safety-hofh/

This content is for healthcare professionals based in Europe, Israel and Saudi Arabia only.

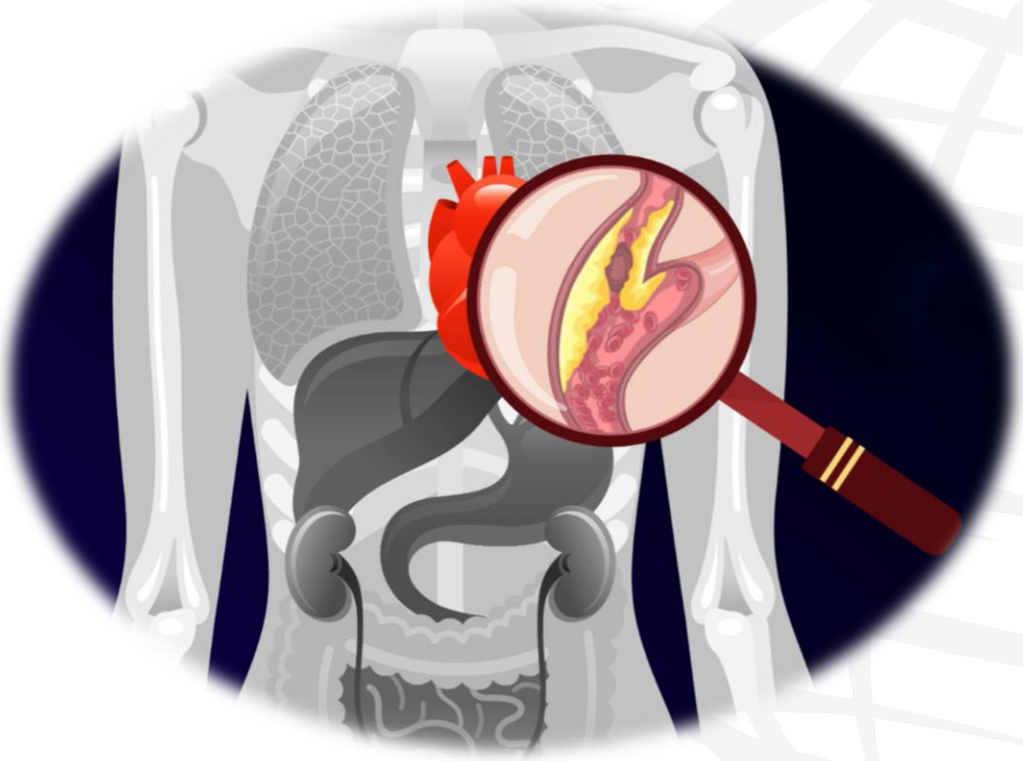
Learning objectives

After watching the touchDATA POINT activity, participants should be better able to:

- ✓ Understand the novel mechanism of action of lomitapide
- ✓ Describe key hepatic safety outcomes of the lomitapide Phase 3 and extension clinical trial and the LOWER registry
- ✓ Recall that the hepatic safety of lomitapide remained favourable for up to 9 years

What is HoFH?

- HoFH is a very rare autosomal semi-dominant genetic condition, which is characterized by extremely elevated LDL-cholesterol from birth[1]
- This leads to accelerated atherosclerosis and cardiovascular disease, often resulting in an early death[1]
  - Mortality risk increases with higher LDL-cholesterol levels
- As people with HoFH often lack residual LDL-receptor activity, therapies independent of this pathway are required to reduce LDL-cholesterol in the blood[1]
  - These can include non-pharmacological therapies, such as lipoprotein apheresis, and pharmacological therapies, such as lomitapide



Homozygous familial hypercholesterolemia; LDL, low density lipoprotein.

1. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. Eur Heart J. 2023;44(25):2277–91.

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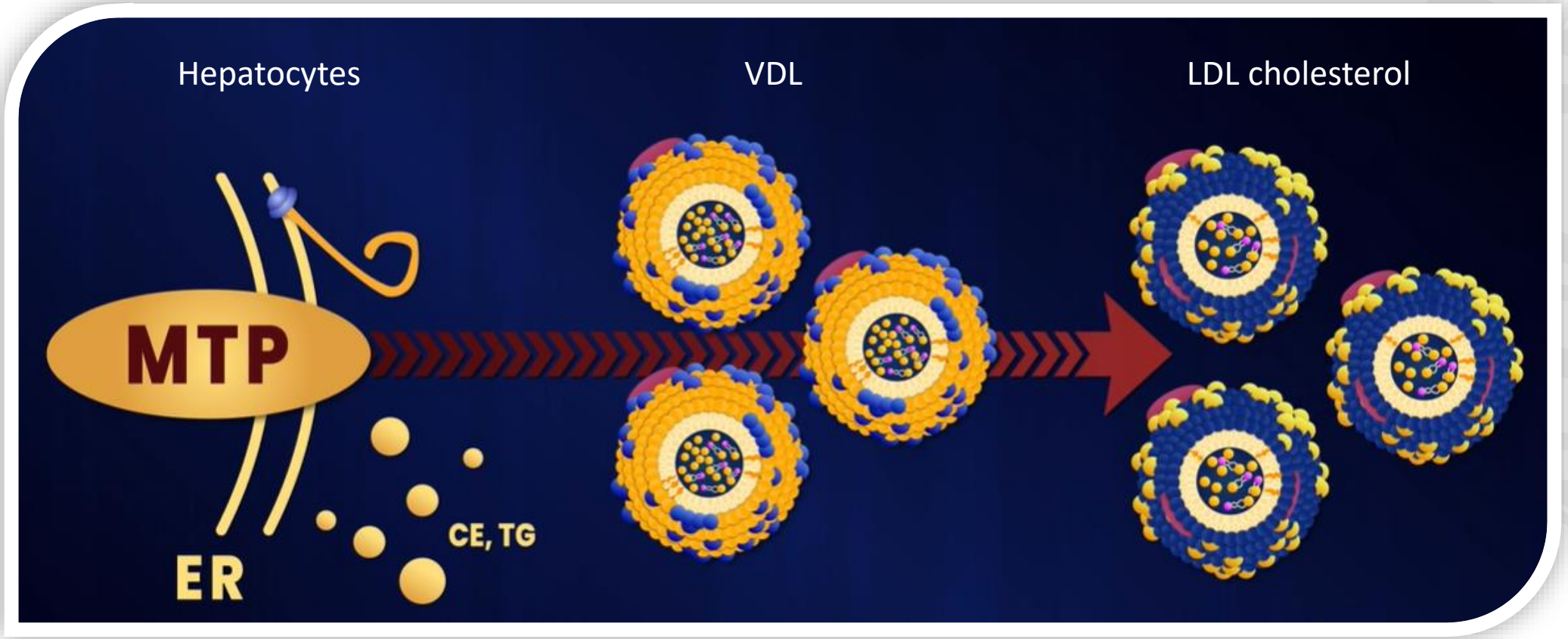
Lomitapide

- Lomitapide is an oral MTP inhibitor – MTP is involved in the production and release of VLDL (a precursor to LDL-cholesterol) from hepatocytes into the plasma[1]

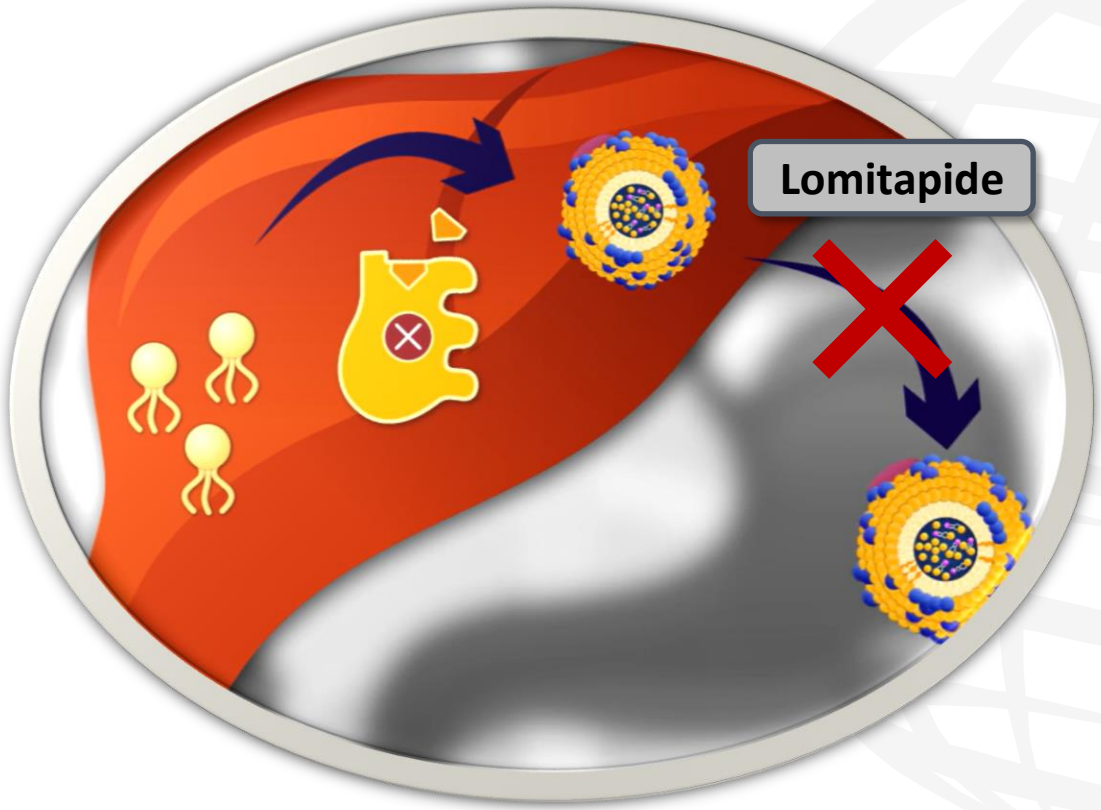


CE, cholesteryl ester; ER, endoplasmic reticulum; MTP, microsomal triglyceride transfer protein; TG, triglycerides; VLDL, very low-density lipoprotein.

1. Goulooze SC, Cohen AF, Rissmann R. Lomitapide. Br J Clin Pharmacol. 2015;80(2):179–81.

Potential adverse effects with lomitapide

- By inhibiting MTP, lomitapide reduces VLDL (and thereby LDL-cholesterol levels) in plasma[1]
- However, this can also lead to an accumulation of TG in the liver[1]
- As such, lomitapide can potentially lead to an increase in hepatic steatosis and idiosyncratic hepatotoxicity (an unpredictable form of drug induced liver injury)[2,3*]



*Which occurs in the therapeutic dosing range of the drug

1. Goulooze SC, Cohen AF, Rissmann R. Lomitapide. Br J Clin Pharmacol. 2015;80(2):179–81;
2. Larrey D, D'Erasmo L, O'Brien S, Arca M; Italian Working Group on Lomitapide. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. Liver Int 2023;43(2):413–23;
3. Meunier L, Larrey D. Drug-induced liver injury: biomarkers, requirements, candidates, and validation. Front Pharmacol. 2019;10:1482.

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Evaluating hepatic safety with lomitapide

- To evaluate hepatic safety with lomitapide in HoFH, data were aggregated from both clinical and real-world sources:[1-3]

Lomitapide pivotal Phase 3 clinical trial and extension phase[2]	Real-world Italian cohort of patients treated with lomitapide	Lomitapide Observational Worldwide Evaluation Registry (LOWER)[3]
N=26	N=34	N=226
Median 5.1 years follow-up	Up to 9.5 years follow-up	Up to 9 years follow-up
Median dose 40 mg/day	Mean dose 15.6 mg/day	Mean dose (EU) 17.4 mg/day

1. Larrey D, D'Erasmo L, O'Brien S, Arca M; Italian Working Group on Lomitapide. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. Liver Int 2023;43(2):413–23; 2. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 2013;381(9860):40–6; 3. Blom D, Underberg J, Cannon CP, et al. The Lomitapide Observational Worldwide Evaluation Registry (LOWER) – nine-year effectiveness and safety data in HoFH. Poster presented at NLA Scientific Sessions, May 30 to June 2, 2024, Las Vegas, NV.

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Hepatic safety outcomes

- Data from these studies enabled the long-term evaluation of:[1]
  - Liver transaminase deviations
  - Instances of Hy's law*
  - Hepatic steatosis
  - Hepatic stiffness or fibrosis
  - Biomarkers of hepatic inflammation and fibrosis

*Hy's law predicts the risk of mortality from drug-induced liver injury based on hepatic transaminase elevation >3 x ULN and bilirubin elevation >2 x ULN.
ULN, upper limit of normal.

1. Larrey D, D'Erasmo L, O'Brien S, Arca M; Italian Working Group on Lomitapide. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. Liver Int 2023;43(2):413–23.

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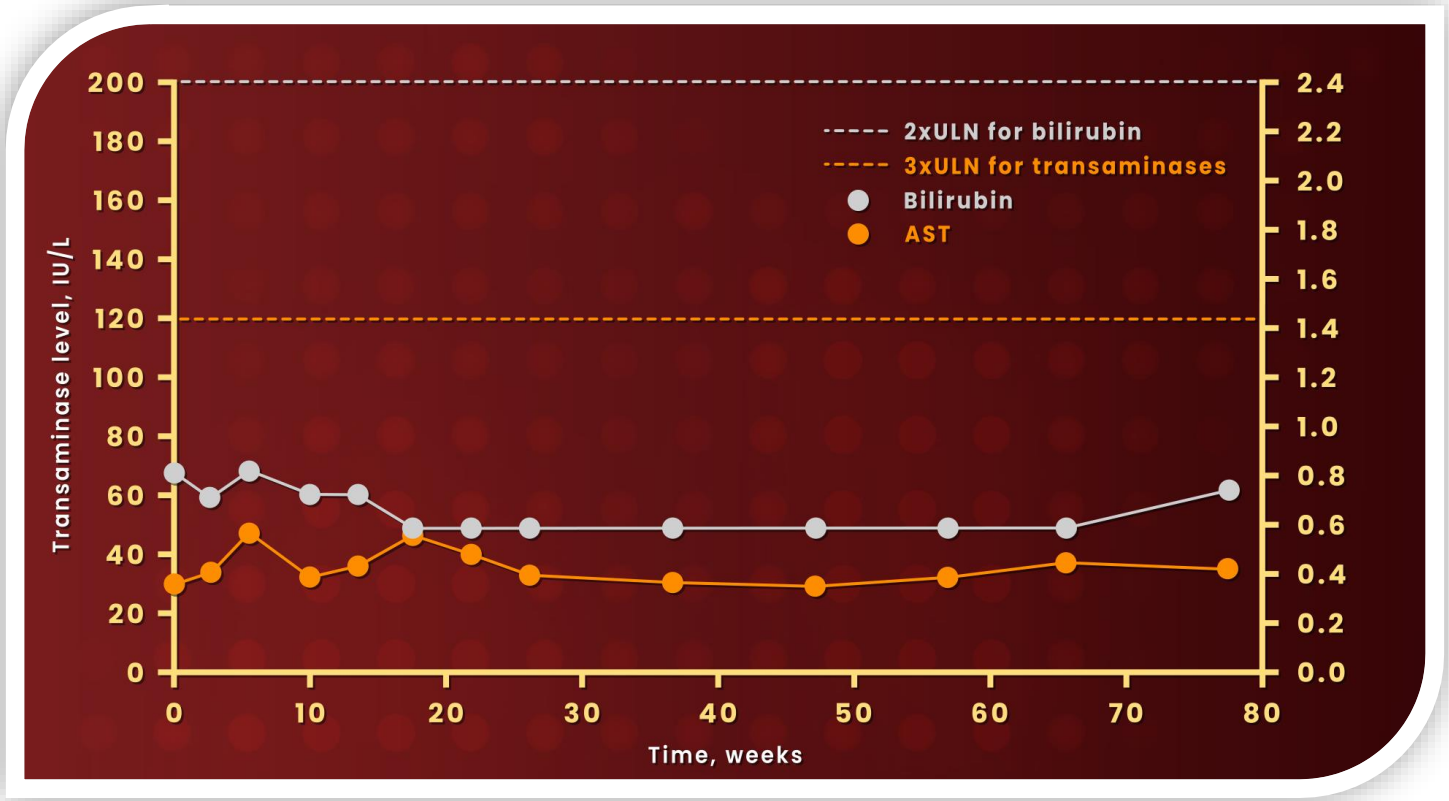
Hy’s law – hepatic transaminase levels

- No Hy’s law cases were identified with lopitamide, and mean aminotransferase and bilirubin levels from the pivotal phase 3 trial remained below thresholds – any isolated transaminase elevations were not accompanied by significant increases in bilirubin[1]



AST, aspartate aminotransferase.

1. Larrey D, D'Erasmo L, O'Brien S, Arca M; Italian Working Group on Lomitapide. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. Liver Int 2023;43(2):413–23.

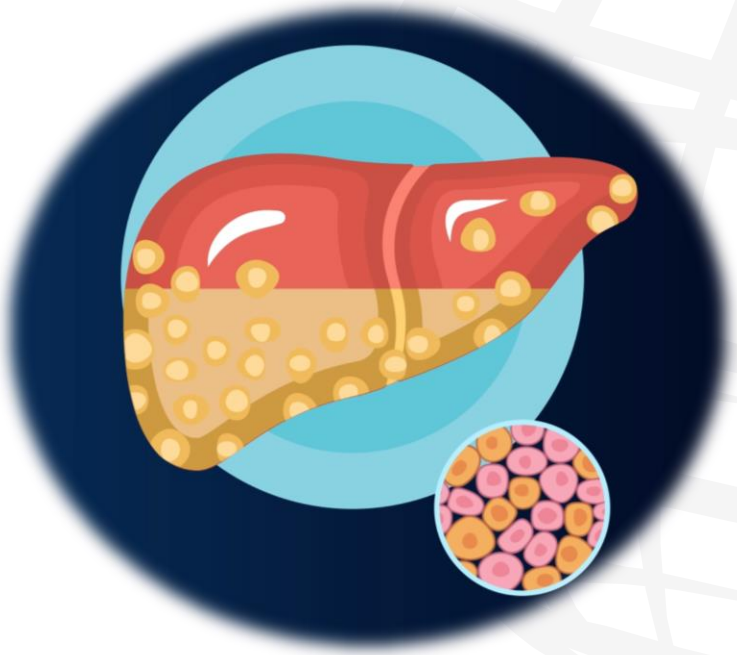
Hepatic adverse events

- In the LOWER registry, most first hepatic events occurred within the first 12 months of treatment (during lomitapide titration)[1]
- Over 9 years of follow-up:[1]

19% (n=42)
experienced a hepatic AE

21% (n=46)
had elevated liver enzymes

6% (n=13)
discontinued lomitapide due to hepatic enzyme levels

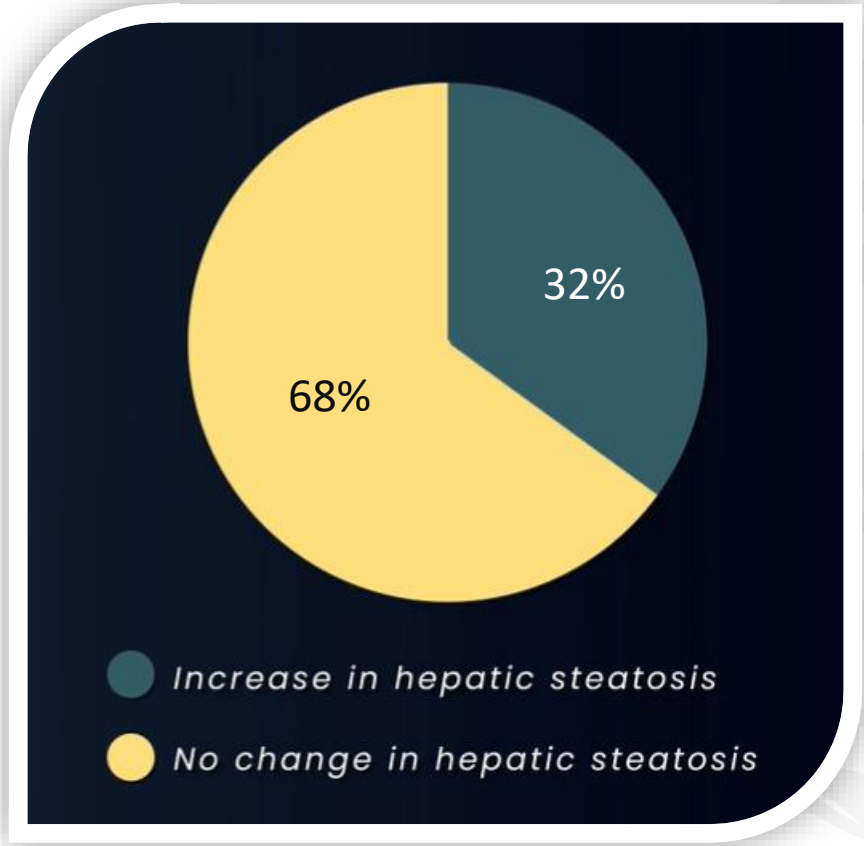


AE, adverse event.

1. Blom D, Underberg J, Cannon CP, et al. The Lomitapide Observational Worldwide Evaluation Registry (LOWER) – nine-year effectiveness and safety data in HoFH. Poster presented at NLA Scientific Sessions, May 30 to June 2, 2024, Las Vegas, NV

Hepatic steatosis

- Ultrasound data from the Italian cohort study (n=22)* revealed evidence of a mild-to-moderate increase in hepatic fat[1]
- However, over two thirds of patients (n=15; 68.2%) showed no increase in hepatic steatosis[1]
- Of the remaining patients with increased hepatic steatosis, there was no evident association with lomitapide exposure (duration) or dose[1]

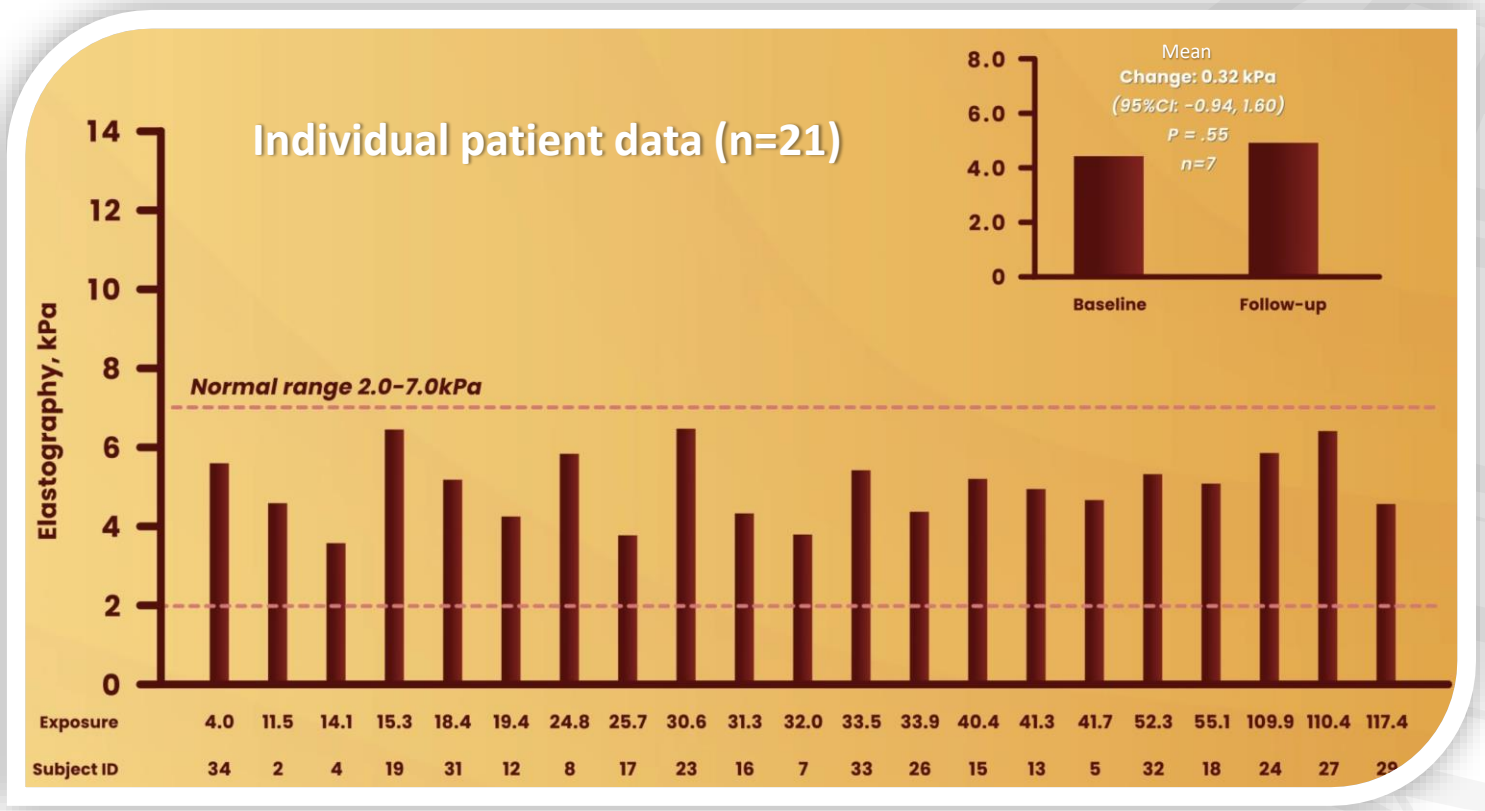


*Patients who had an ultrasound at baseline and follow-up.

1. Larrey D, D'Erasmo L, O'Brien S, Arca M; Italian Working Group on Lomitapide. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. Liver Int 2023;43(2):413–23.

Hepatic stiffness and FIB-4

- For the 21 patients assessed with transient elastography in the Italian cohort study, hepatic stiffness remained within the normal range (2.0–7.0 kPa) for up to 9.5 years[1]
  - Mean change from baseline: 0.32 kPa; P=0.55
- This was also consistent with mean FIB-4 scores below a threshold predictive of fibrosis[1]



1. Larrey D, D'Erasmo L, O'Brien S, Arca M; Italian Working Group on Lomitapide. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. Liver Int 2023;43(2):413–23.

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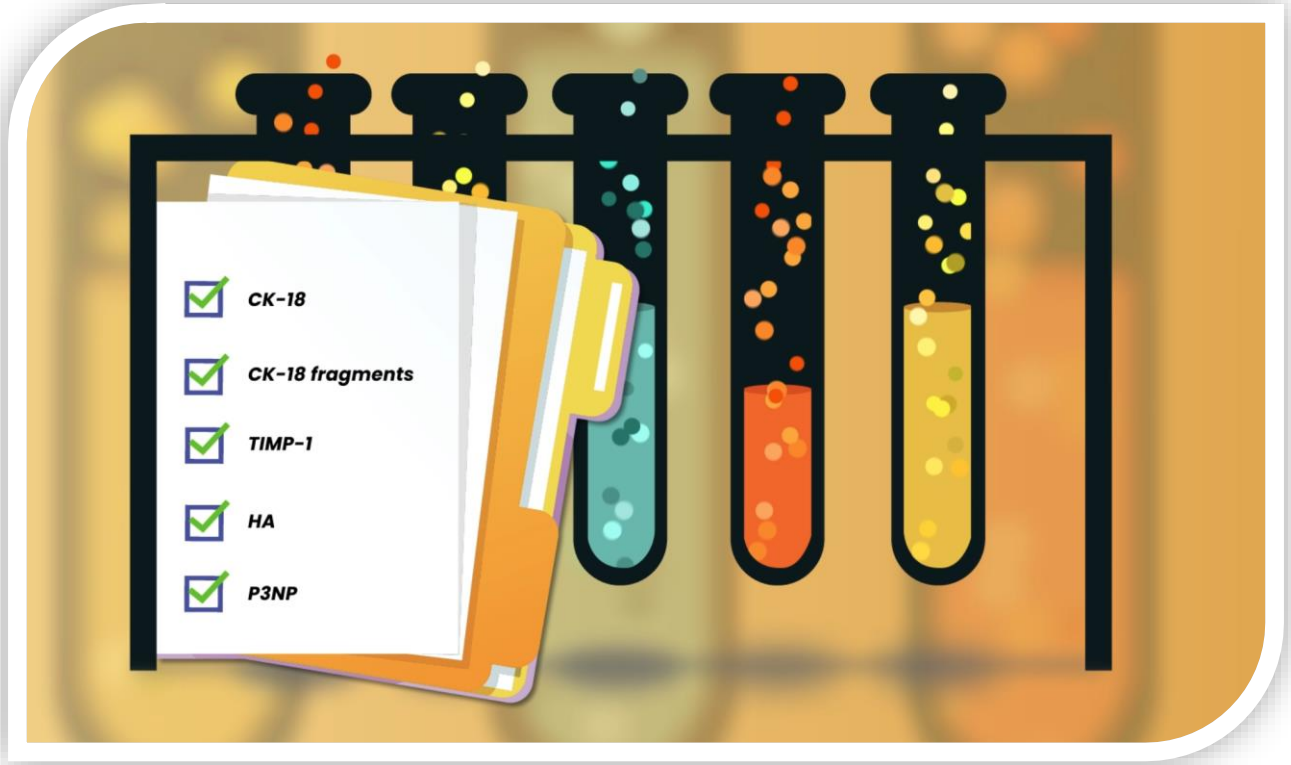
Other hepatic factors

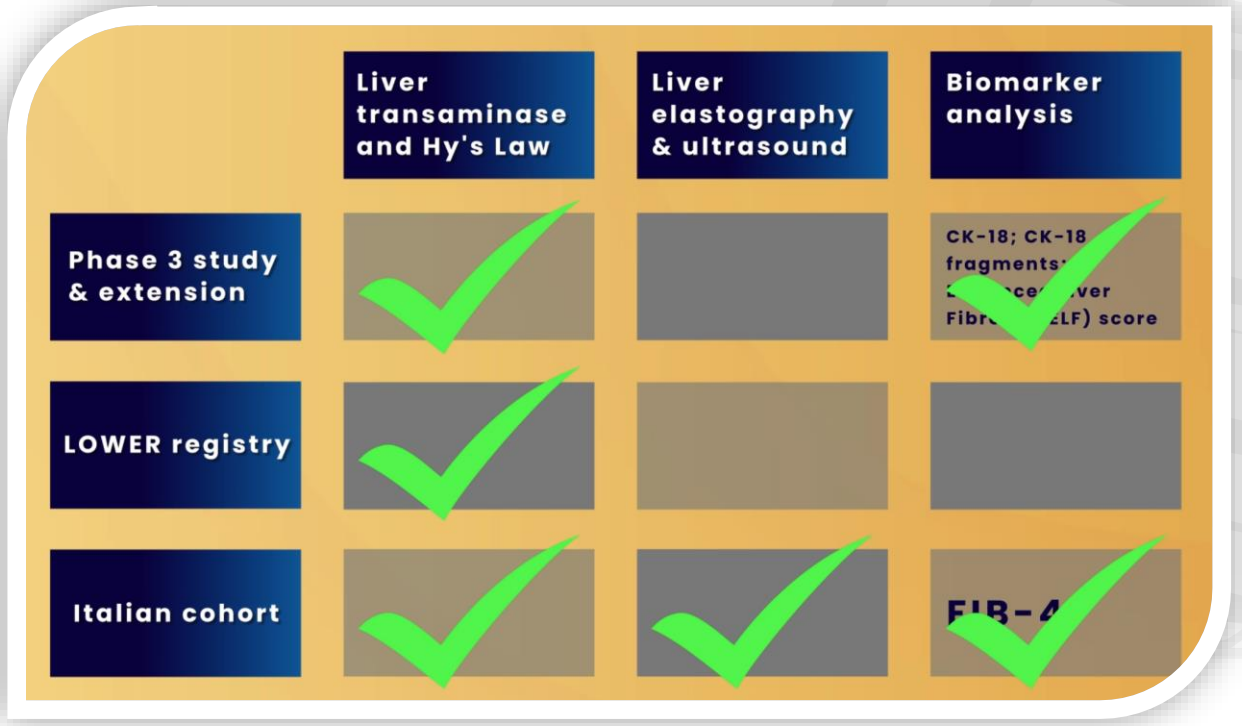
- Lomitapide treatment was not associated with a clinically relevant change in any of the other hepatic biomarkers investigated[1]



1. Larrey D, D'Erasmo L, O'Brien S, Arca M; Italian Working Group on Lomitapide. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. Liver Int 2023;43(2):413–23.

Summary

- While lomitapide was associated with mild-to-moderate accumulation of hepatic fat (as expected based on its mechanism of action),[1] this did not translate into clinically meaningful increases in biomarkers of hepatocellular damage.[1]
- In addition, hepatic imaging for fibrosis remained normal through 9 years of follow-up.[1]
- Despite alterations in some liver parameters with lomitapide, no HoFH patient progressed to develop NASH or cirrhosis[1]
- Longer term follow-up of these patients is underway, and will continue to provide valuable effectiveness and safety information for lomitapide



NASH, non-alcoholic steatohepatitis.

1. Larrey D, D'Erasmo L, O'Brien S, Arca M; Italian Working Group on Lomitapide. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. Liver Int 2023;43(2):413–23.

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PRESCRIBING INFORMATION - Lojuxta®▼ (lomitapide) hard capsules

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See below for how to report adverse reactions.

Before prescribing Lojuxta, please refer to the full Summary of Product Characteristics (SmPC)[i].

Active Ingredient: Each hard capsule contains 5 mg, 10 mg or 20 mg lomitapide (as lomitapide mesylate).

Indication: Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH). Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

Dosage and Administration: *Adults:* The recommended starting dose is 5 mg once daily to be taken orally. After 2 weeks the dose may be increased to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and to the maximum recommended dose of 60 mg. Dose escalation should be gradual to minimise gastrointestinal adverse reactions and aminotransferase elevations. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided. Patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment. *Dose modifications:* Prescribers should consult the SmPC for full details of dose adjustments for elderly patients, patients with hepatic impairment, renal impairment or receiving weak CYP3A4 inhibitors. When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half. The dose of Lojuxta should be taken 12 hours apart from any other weak CYP3A4 inhibitor. *Children and adolescents below the age of 18 years:* Safety and efficacy of Lojuxta have not been established. **Contraindications:** Hypersensitivity to lomitapide or to any of the excipients. Patients with the following conditions: moderate to severe hepatic impairment; unexplained persistent abnormal liver function tests; and significant or chronic bowel disease. Concomitant administration of >40 mg simvastatin or strong or moderate CYP3A4 inhibitors. Pregnancy. **Warnings and precautions:** *Liver enzyme abnormalities:* Lomitapide can cause elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and hepatic steatosis. There is a concern that lomitapide could induce steatohepatitis. Liver function tests should be monitored closely before initiating treatment with Lojuxta. If baseline liver tests are abnormal, consider initiating treatment of Lojuxta after appropriate investigation by a hepatologist. In the first year, liver-related tests should be measured before each increase in dose or monthly, whichever occurs first. After the first year, tests should be performed at least every three months and before any increase in dose. Refer to the SmPC for full details of dose modifications in the event of elevated hepatic aminotransferases. *Hepatic Steatosis and risk of progressive liver disease:* Regular screening for steatohepatitis/fibrosis should be performed at baseline and annually. If results indicate the presence of steatohepatitis/fibrosis, a liver biopsy should be considered and if the condition is proven, the benefit-risk should be reassessed and treatment stopped if necessary. *Dehydration* – Severe diarrhoea may put patients at risk of dehydration. Caution in vulnerable patients (e.g. elderly, on diuretics). *Use of alcohol:* Alcohol is not recommended during Lojuxta treatment. *Lactose:* Lojuxta contains lactose, so should not be given to patients with rare hereditary problems of galactose intolerance, total-lactase deficiency or glucose-galactose malabsorption. *Effects on ability to drive and use machines* – Adverse reactions such as dizziness and fatigue have been associated with Lojuxta. **Interactions:** Prescribers should consult the SmPC for full details of interactions. Weak CYP3A4 inhibitors may substantially increase the exposure of lomitapide (See Dosage and administration). Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta and the use of St. John's Wort should be avoided with Lojuxta. Lomitapide increases plasma concentrations of HMG-CoA reductase inhibitors ('statins'). Patients using statins in addition to Lojuxta should be advised of the potential increased risk of myopathy and report any unexplained muscle pain, tenderness or weakness. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. Lomitapide increases the plasma concentrations of warfarin. Patients taking warfarin should undergo regular monitoring of the INR, and the dose of warfarin should be adjusted as clinically indicated. Caution should be exercised when Lojuxta is used with other medicinal products known to have potential for hepatotoxicity, such as isotretinoin, amiodarone, paracetamol (>4g/day for ≥3days/week), methotrexate, tetracyclines and tamoxifen. Bile acid sequestrants can interfere with the absorption of oral medicines and should be taken at least 4 hours before or after Lojuxta. Co-administration of Lojuxta with P-gp substrates may increase the absorption of P-gp substrates. Patients should avoid grapefruit juice.

Pregnancy and Breastfeeding: Lojuxta is contraindicated during pregnancy. Absence of pregnancy should be confirmed before initiating treatment and effective contraception should be initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used for 7 days after resolution of symptoms. Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see Interactions above). There are no reliable data on the use of Lojuxta in pregnant women. *Breast-feeding:* It is not known whether lomitapide is excreted into human milk. Whether to discontinue breast-feeding or discontinue Lojuxta should be decided, taking into account the importance of treatment with Lojuxta to the mother.

Undesirable effects: Prescribers should consult the SmPC for full details of adverse drug reactions (ADRs). The most serious ADRs during treatment were liver aminotransferase abnormalities. The most common ADRs were gastrointestinal effects including diarrhoea, nausea, dyspepsia and vomiting. Gastrointestinal ADRs occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide. *Adverse reactions reported in the HoFH clinical trials: Very common ADRs (≥1/10)* – increased ALT or AST, weight decrease, decreased appetite, diarrhoea, nausea, vomiting, abdominal discomfort, abdominal pain, abdominal distension, dyspepsia, flatulence and constipation. *Common ADRs (≥1/100 to <1/10)* – gastroenteritis, dizziness, headache, migraine, gastritis, rectal tenesmus, aerophagia, defaecation urgency, eructation, frequent bowel movements, gastric dilatation, gastric disorder, gastroesophageal reflux disease, haemorrhoidal haemorrhage, regurgitation, hepatic steatosis, hepatotoxicity, hepatomegaly, ecchymosis, papule, rash erythematous, xanthoma, fatigue, INR increase or abnormal, blood alkaline phosphatase increase, blood potassium decrease, carotene decrease, liver function test abnormal, transaminase increase, prothrombin time prolonged, Vitamin E decrease and Vitamin K decrease.

Legal category: POM.

Marketing Authorisation Numbers:
5 mg dose: 1412211475,
10 mg dose: 1412211474,
20 mg dose: 1412211476

Marketing Authorisation Holder: Amryt Pharmaceuticals DAC, 45 Mespil Road, Dublin 4, Ireland.
Tel: +800 44474 447 (freephone) or+ 44 1604 549952.

Date of last approved SmPC: February 2022.

To report Adverse Events:

The National Pharmacovigilance Centre (NPC)-Saudi Food and Drug Authority (SFDA)
SFDA call center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa/

Amryt Local Pharmacovigilance:
E-mail: qppv-saudi@pharmaknowl.com
Phone: +966112777729 / +966112404409

i Lojuxta® (lomitapide) hard capsules Summary of Product Characteristics.