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OBETICHOLIC ACID: DISCOVERY, CLINICAL TRANSLATION, AND REGULATORY WITHDRAWAL

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ABSTRACT – The twenty-fifth anniversary of the discovery of obeticholic acid (OCA) in 2027 offers an opportunity to reconsider its scientific contribution and clinical trajectory. First described in 2002 as 6α-ethyl-chenodeoxycholic acid, OCA helped establish the farnesoid X receptor (FXR) as a therapeutic target linking bile acid homeostasis to inflammation and fibrosis. This review follows the molecule from its discovery and early biological characterization through pharmaceutical development to the withdrawal of its primary biliary cholangitis (PBC) authorizations in the European Union and the United States. Clinical trials demonstrated biochemical efficacy in PBC and biopsy-defined fibrosis improvement in non-cirrhotic metabolic dysfunction-associated steatohepatitis but did not establish corresponding long-term clinical benefit. Pruritus, adverse lipoprotein changes, and hepatic safety concerns complicated treatment, while the COBALT confirmatory trial failed to verify benefit in its randomized analysis despite favorable external-control comparisons. This history highlights the distinction between pharmacological activity, surrogate responses, and patient benefit. It also raises questions about whether earlier prioritization of lower exposure and complementary therapies could have improved tolerability, without assuming that these strategies would have prevented withdrawal. OCA's legacy extends to subsequent FXR ligands and approaches emphasizing molecular selectivity, tissue distribution, and temporal control of receptor activation. Its experience supports continued FXR investigation while underscoring that therapeutic value requires sustained clinical benefit and acceptable safety.

KEYWORDS: Farnesoid X receptor, Bile acid signaling, Primary biliary cholangitis, Metabolic dysfunction-associated steatohepatitis, Liver fibrosis, Drug development.

INTRODUCTION

2027 marks the twenty-fifth anniversary of the discovery of obeticholic acid (OCA), first described in 2002 as 6α-ethyl-chenodeoxycholic acid, a potent and selective agonist of the farnesoid X receptor (FXR)[1]. This anniversary offers an opportunity to revisit a scientific trajectory whose significance extends beyond the fate of a single molecule. OCA helped establish FXR as a pharmacologically tractable target, linking the recognition of bile acids as signaling molecules to experimental investigation and clinical development[2,3]. The collaboration between medicinal chemistry and experimental hepatology that produced the compound also shaped the questions that have guided my work on bile acid signaling over the decades that followed. OCA's history illustrates both the opportunities and the difficulties of translating an emerging biological pathway into treatment. Its discovery provided a tool for investigating FXR function and helped establish the rationale for targeting bile acid signaling in cholestasis and fibrosis. Its clinical development subsequently revealed the challenges of translating receptor activation and improvements in surrogate endpoints

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into sustained patient benefit. This review follows that progression from discovery through clinical development to withdrawal. It considers the experimental findings that supported the original therapeutic hypotheses, the evidence generated in primary biliary cholangitis and steatohepatitis, and the efficacy and safety questions that ultimately determined OCA's clinical fate. This paper aims to assess what this experience contributed to the development of FXR as a therapeutic target and how its lessons might inform future approaches to bile acid receptor pharmacology.

BILE ACIDS AS FXR LIGANDS AND THE DISCOVERY OF OCA

The scientific foundations for the development of OCA were laid shortly before its discovery. Bile acids had traditionally been understood as products of hepatic cholesterol metabolism and as detergents required for intestinal lipid absorption[4]. Their therapeutic use, particularly that of ursodeoxycholic acid (UDCA), preceded the identification of bile acid receptors, and explanations of their activity initially emphasized their physicochemical properties and effects on the bile acid pool[5]. In 1999, three groups[6-8] showed that bile acids act as endogenous ligands for FXR, NR1H4, a nuclear receptor identified in 1995 by Forman et al[9]. This discovery provided a molecular framework for understanding how bile acids regulate their own synthesis and transport (Figure 1). It also suggested that these processes could be modified pharmacologically, an approach of particular interest in cholestatic disorders, where impaired hepatic handling and elimination of bile acids contribute to liver injury.

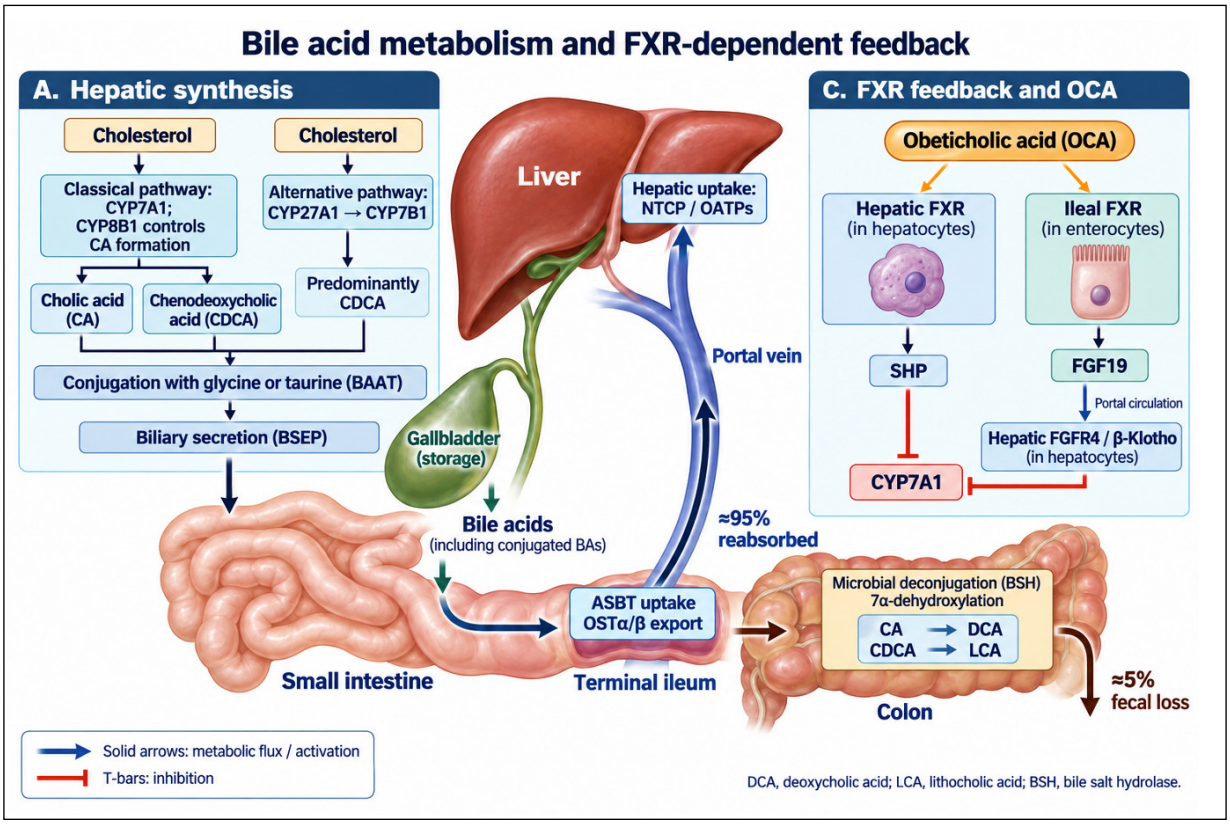

Figure 1. Bile acid metabolism and FXR-dependent feedback regulation.
Primary bile acids are synthesized from cholesterol through the classical and alternative pathways, conjugated with glycine or taurine, and secreted into bile. Following intestinal delivery, approximately 95% are reabsorbed and returned to the liver through the portal circulation. Microbial deconjugation and 7α-dehydroxylation generate secondary bile acids, including deoxycholic acid from cholic acid and lithocholic acid from chenodeoxycholic acid. OCA activates hepatic and intestinal FXR. Hepatic induction of SHP and intestinal induction of FGF19, acting through hepatic FGFR4/β-Klotho, provide complementary signals that suppress CYP7A1-dependent bile acid synthesis.
Arrows indicate transport, metabolic flux, or activation; terminal bars indicate inhibition.
BAAT, bile acid–CoA:amino acid N-acyltransferase; BSEP, bile salt export pump; ASBT, apical sodium-dependent bile acid transporter; OSTα/β, organic solute transporter α/β; NTCP, sodium taurocholate cotransporting polypeptide; OATPs, organic anion-transporting polypeptides; SHP, small heterodimer partner; FGF19, fibroblast growth factor 19.

At the University of Perugia, these emerging concepts brought medicinal chemistry and experimental hepatology into close collaboration. Building on the discovery that chenodeoxycholic acid (CDCA) was the most potent endogenous ligand of FXR, we were able to generate a potent semisynthetic derivative of this bile acid. Medicinal chemistry led by Roberto Pellicciari was integrated with biological studies at the University of Perugia, with contributions from Patrick R. Maloney, Derek J. Parks, and Timothy M. Willson, who were then working at GlaxoSmithKline in the United States. Medicinal chemistry studies[10,11] also explored other FXR ligands and modifications of the bile acid scaffold. This collaboration led to the development and characterization of 6α-ethyl-chenodeoxycholic acid (6E-CDCA), subsequently designated INT-747 and, later, obeticholic acid (Figure 2). OCA provided a pharmacological tool for investigating whether selective FXR activation could modify disease processes, helping move the receptor from a regulator of bile acid physiology toward a candidate therapeutic target[3]. Its increased potency over CDCA made receptor function more accessible to experimental investigation, but the therapeutic consequences remained uncertain. The immediate task was to determine how FXR activation influenced bile acid handling and liver injury, and whether these effects justified further development.

FROM A CHEMICAL MODIFICATION TO A THERAPEUTIC HYPOTHESIS

The increased potency of 6E-CDCA made it possible to investigate FXR activation more systematically. The central question, however, extended beyond receptor pharmacology: could activation of FXR coordinate a response that protected the liver in disease-relevant models? The initial therapeutic rationale centered on bile acid homeostasis (Figure 1). Hepatic FXR activation induces the small heterodimer partner (SHP), a nuclear receptor that participates in the suppression of bile acid synthesis[12,13]. Intestinal FXR activation provides a complementary endocrine signal through fibroblast growth factor 19 (FGF19)[14] in humans and its rodent orthologue, FGF15[14]. FXR also regulates transport systems controlling hepatic bile acid uptake and export (Figure 1)[13], and intestinal immunity[15]. Together, these actions suggested that receptor activation could limit potentially harmful intracellular bile acid accumulation.

Experimental findings supported this hypothesis in selected settings. In models of non-obstructive cholestasis, 6α-ethyl-chenodeoxycholic acid showed anticholestatic activity[16], connecting receptor activation with functional improvement in the injured liver. These observations provided a rationale for further development, while leaving an important question unresolved: under which conditions would modifying bile acid synthesis and transport remain protective? The therapeutic hypothesis therefore required assessment across different forms and stages of injury, rather than extrapolation from a single favorable experimental setting.

IDENTIFYING FXR AS A TARGET FOR ANTIFIBROTIC THERAPY

A second therapeutic hypothesis emerged from investigations of liver fibrosis. During the early development of OCA, attention expanded from bile acid homeostasis to the cellular programs responsible for scar formation. Hepatic stellate cells, the

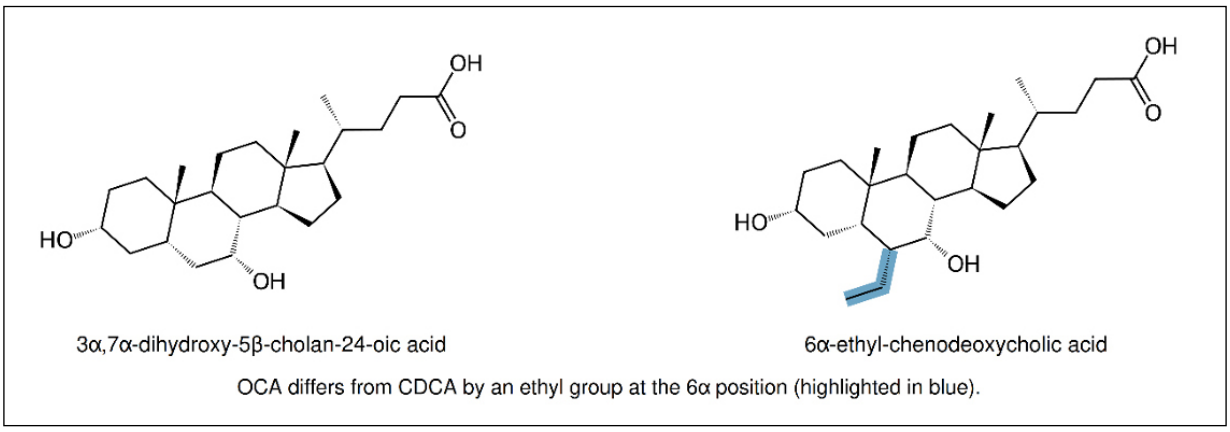

Figure 2. Chemical structures of chenodeoxycholic acid and obeticholic acid.
Comparison of chenodeoxycholic acid (CDCA), an endogenous FXR agonist, and obeticholic acid (OCA; 6α-ethyl-chenodeoxycholic acid). OCA retains the bile acid scaffold and the 3α- and 7α-hydroxyl groups of CDCA, with the addition of an ethyl group at the 6α position. This modification substantially increases FXR agonist potency. Stereochemical bonds indicate the orientation of substituents.

principal cellular effectors of extracellular matrix deposition during liver injury, became central to this investigation[17].

In a series of studies[18,19] carried out at the University of Perugia, FXR activation was identified as a potential antifibrotic strategy. These investigations linked the activity of 6E-CDCA to SHP-mediated suppression of profibrotic programs in hepatic stellate cells and reduced fibrosis in experimental models of liver injury (Figure 3). The close interaction between experimental hepatology and medicinal chemistry allowed the compound to serve both as a tool for investigating receptor function and as a candidate for therapeutic development.

These findings suggested that bile acid signaling could influence tissue remodeling as well as metabolic homeostasis, broadening the potential relevance of FXR beyond cholestasis[16] to chronic liver diseases in which fibrosis determines prognosis[17] (Figure 3).

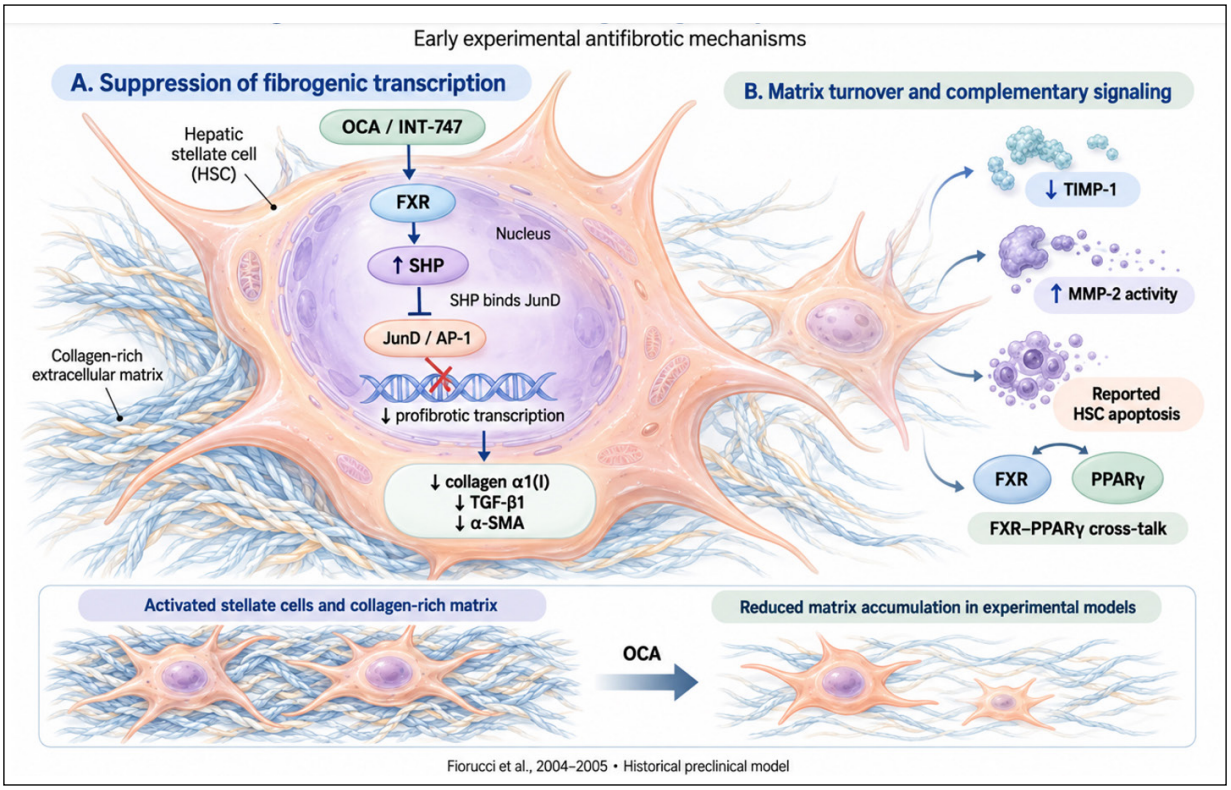

Figure 3. OCA–FXR–SHP signaling in hepatic stellate cells: early experimental antifibrotic mechanisms.
Schematic representation of mechanisms reported in early experimental studies. **A**, OCA/INT-747 activates FXR and induces SHP, which interacts with JunD and suppresses AP-1-dependent profibrotic transcription. Reported responses include reduced collagen α1(I), transforming growth factor β1 (TGF-β1), and α-smooth muscle actin (α-SMA). **B**, Complementary findings include reduced tissue inhibitor of metalloproteinases 1 (TIMP-1), increased matrix metalloproteinase 2 (MMP-2) activity, enhanced susceptibility to stellate-cell apoptosis, and interactions between FXR and peroxisome proliferator-activated receptor γ (PPARγ) signaling. The lower panel illustrates reduced matrix accumulation in experimental models. These findings arose from different experimental settings and should not be interpreted as a single universally established pathway or as proof of fibrosis reversal in patients. Arrows indicate activation or reported responses; terminal bars indicate inhibition. Figure created based on findings reported in Fiorucci et al[18,19].

This mechanistic foundation subsequently contributed to the rationale for investigating FXR agonism in steatohepatitis[20]. The interpretation nevertheless depended on the experimental setting. Reduced stellate cell activation or matrix accumulation during ongoing injury did not necessarily demonstrate reversal of established fibrosis[21]. Nor could favorable results in one model establish efficacy across diseases with different causes, stages, and fibrogenic environments[22]. The early studies, however, supported further investigation while leaving the magnitude, durability, and clinical significance of an antifibrotic response unresolved[23].

The distinction between non-obstructive cholestasis and complete biliary obstruction[24] observed in bile duct-ligated animals is of translational relevance[18]. Suppression of bile acid synthesis, stimulation of canalicular export, and changes in basolateral transport can have different con-

sequences depending on whether bile can leave the liver. Under complete obstruction, adaptive mechanisms that redirect bile acids toward the systemic circulation and subsequent renal elimination may become essential[25]. Experimental evidence that FXR activation could interfere with these responses challenged the assumption that receptor activation would invariably protect the injured liver[26].

These observations did not predict OCA's subsequent clinical trajectory[27], and complete experimental obstruction should not be equated with primary biliary cholangitis. However, they reinforced a principle relevant to its antifibrotic development: the consequences of FXR activation depend on the nature and stage of injury, the cells engaged by treatment, and the physiological functions that remain intact.

FROM ACADEMIC DISCOVERY TO INTERCEPT PHARMACEUTICALS AND CLINICAL DEVELOPMENT

Developing 6E-CDCA required an organizational framework that could connect academic discovery with pharmaceutical development. Intercept Pharmaceuticals, established in September 2002, provided that framework. Its founding brought together Mark Pruzanski, a physician and biotechnology entrepreneur, Roberto Pellicciari and Stefano Fiorucci at the University of Perugia, and Steven Kliewer at the University of Texas Southwestern. A contemporary account[28] by Jennifer Boggs identifies these founding participants and describes Fiorucci and Pellicciari as directing the company's drug discovery activities in Perugia. The September 2002 inception date is independently documented in Intercept's 2012 Form S-1 registration statement[29]. During these formative years, my laboratory's contribution centered on characterizing the effects of the compound, subsequently designated INT-747, on bile acid physiology, cholestasis, and experimental liver fibrosis[16,30]. This work linked receptor pharmacology to disease-relevant biological responses and helped define therapeutic hypotheses that supported further development.

A particularly informative contemporary record is Intercept's press release (Intercept Pharmaceuticals Announces Publication of Study Demonstrating Its Lead Compound Can Reverse Liver Fibrosis), preserved in the BioSpace archive[31]. The announcement explicitly identifies Stefano Fiorucci as the company's scientific co-founder and describes the fibrosis studies as investigations led by his team. It also records the significance the company's leadership attributed to these findings: the experimental results strengthened the therapeutic rationale for INT-747 and supported its advancement toward human clinical trials. The release therefore documents both the Perugia laboratory's scientific contribution and its place in the company's early development strategy.

The announcement captures the expectations surrounding the molecule. INT-747 was presented as a candidate for fibrotic and cholestatic liver diseases, with antifibrotic activity forming part of the development rationale from an early stage. The description of fibrosis reversal concerned experimental findings and the company's interpretation; it did not establish reversal of fibrosis in patients.

The collaboration remained visible in subsequent company communications. In Intercept Pharmaceuticals Researchers Present Data At DDW Highlighting Role Of FXR In Inflammatory Bowel Disease, an announcement concerning Digestive Disease Week in 2006[32], Fiorucci was again identified as an Intercept co-founder. The release described investigations of FXR-dependent regulation of intestinal inflammation and fibrosis and identified Kliewer as a co-founder in discussing complementary studies of intestinal defense. These communications illustrate the breadth of the early scientific program, which investigated bile acid signaling in metabolic regulation, tissue injury, and intestinal homeostasis.

The transition to clinical development changed the questions that this experimental foundation had to answer. Receptor activation and favorable responses in animal models supported further investigation, but therapeutic use required evidence of efficacy at tolerable doses in defined patient populations.

Primary biliary cholangitis (PBC) offered a compelling initial rationale[33,34]. UDCA had substantially improved disease management[35], but patients with an inadequate response or intolerance continued to need additional treatment. FXR agonism[36] offered a distinct mechanism, with biochemical effects that could be measured within a practical trial period[34,37-41]. Alkaline phosphatase and bilirubin were particularly relevant because of their association with prognosis in PBC[42,43]. Their use supported a development strategy based on surrogate endpoints[44], while introducing a distinction that would become central to OCA's history: an association between a biomarker and prognosis does not, by itself, establish that a treatment-induced change in that biomarker improves clinical outcomes[34,38-41].

The parallel interest in nonalcoholic steatohepatitis (NASH), now termed metabolic dysfunction-associated steatohepatitis (MASH)[45], arose from the metabolic, anti-inflammatory, and antifibrotic effects reported experimentally[20,46-50]. FXR activation appeared capable of in-

fluencing several interacting components of the disease, providing a rationale for investigation beyond cholestasis. The two clinical programs nevertheless addressed different biological and clinical settings. PBC involved chronic cholestatic injury, whereas MASH combined metabolic dysfunction, hepatocellular injury, inflammation, and fibrosis, often in patients with substantial cardiovascular risk. Dose selection also differed, with the MASH program investigating higher doses. OCA therefore required a separate assessment of benefit and risk in each indication. Biochemical efficacy in PBC did not establish efficacy in MASH, and a histological antifibrotic response in MASH did not clarify whether treatment improved clinical outcomes in PBC. These distinctions provide the framework for interpreting the trials that followed.

CLINICAL PROMISE AND THE EMERGENCE OF A DIFFICULT THERAPEUTIC WINDOW: PBC

The clinical development of OCA demonstrated that the original pharmacological hypothesis could translate into measurable effects in patients. Phase 2 studies[34,38] and the phase 3 POISE trial[51] showed improvements in biochemical markers of cholestasis, principally in patients with an inadequate response to ursodeoxycholic acid (UDCA). In the POISE study[51], the composite biochemical endpoint was achieved by 46% of patients receiving OCA 5 mg with possible titration to 10 mg and 47% receiving 10 mg, compared with 10% receiving placebo. These findings established biochemical efficacy, while leaving the question of long-term clinical benefit unresolved[52].

The results supported accelerated approval of OCA in the United States in May 2016 and conditional marketing authorization in the European Union in December of the same year. OCA became a second-line treatment for adults with PBC who had an inadequate response to or were intolerant of UDCA. For those involved in the early experimental work, this was a significant milestone: modification of an endogenous bile acid had produced a medicine that acted through a receptor whose role in bile acid signaling had been identified only a few years before the project began. Approval, however, left an essential question unanswered. OCA had improved biochemical markers associated with prognosis but had not demonstrated prevention of hepatic decompensation, reduction in transplantation, or prolonged survival. The accelerated and conditional pathways permitted earlier access while requiring subsequent verification of clinical benefit[53]. The distinction between a prognostic marker and a surrogate that reliably captures treatment benefit would become central to OCA's later history.

Long-term extensions documented sustained biochemical responses among patients continuing treatment, and comparisons with external cohorts suggested favorable clinical outcomes. Such evidence deserved consideration in a slowly progressive disease in which clinical events may take years to accumulate. It also supported the view that the initial biochemical response was not simply a transient pharmacological effect[34,38-41,52].

However, their interpretation required attention to the populations observed. Open-label follow-up preferentially describes patients who remain on treatment and available for assessment. Comparisons with external cohorts introduce potential differences in disease severity, treatment history, clinical management, and outcome ascertainment. Patients who tolerate and continue OCA may differ systematically from those who discontinue it. Statistical adjustment can address measured differences but cannot ensure that unmeasured confounding has been removed. These limitations constrained the strength of the clinical conclusions without diminishing the evidence of sustained biochemical activity.

Pruritus emerged as the clearest tolerability limitation[34,38]. In the POISE study[51], it was reported in 56% of patients in the titration group and 68% in the fixed 10-mg group, compared with 38% receiving placebo. The greater frequency at the higher starting dose reinforced the importance of dose selection and gradual titration. In a disease already associated with potentially disabling itching, treatment-related worsening could require additional medication, interruption, or permanent discontinuation.

OCA also altered lipoprotein metabolism (Figure 4), including reductions in HDL cholesterol[51]. These changes raised a separate question about the metabolic consequences of sustained FXR activation. They should be distinguished from symptomatic intolerance: a laboratory change in lipid concentrations does not itself demonstrate

cardiovascular harm, but it requires assessment within the overall benefit–risk balance.

The early PBC experience therefore established both the clinical activity of FXR-directed treatment and the demands of its prolonged use. Biochemical efficacy had to coexist with acceptable tolerability and ultimately translate into improved clinical outcomes. The original therapeutic question had become more precise: could modification of bile acid signaling be maintained safely and change the course of disease?

THE MASH PROGRAM: AN ANTIFIBROTIC SIGNAL AND ITS CLINICAL LIMITS

The development of OCA in steatohepatitis, then termed NASH and now MASH[45], tested a broader therapeutic hypothesis than the PBC program (Tables I-III). Here, the question was whether FXR activation could influence metabolic injury, inflammation, and fibrosis sufficiently to modify liver histology. For those involved in the early experimental investigations, this program provided an opportunity to examine whether the antifibrotic activity observed in the laboratory had relevance to human disease[20,46-50].

The phase 2 FLINT trial[48] provided an initial clinical signal. After 72 weeks, its primary endpoint—a reduction of at least two points in the NAFLD activity score without worsening fibrosis—was achieved in 45% of evaluable patients receiving OCA, compared with 21% receiving placebo. This represented improvement in histological disease activity, although it should not be equated with resolution of steatohepatitis.

The REGENERATE trial[54] subsequently provided stronger evidence of an effect on fibrosis in patients with non-cirrhotic disease. In the updated consensus assessment of the month-18 biopsies, improvement of at least one fibrosis stage without worsening steatohepatitis occurred in 22.4% of patients receiving OCA 25 mg, compared with 9.6% receiving placebo[49]. These findings supported the clinical relevance of the original antifibrotic hypothesis. They did not, however, establish that the histological response would prevent cirrhosis, hepatic decompensation, or death, nor did they identify the cellular mechanism responsible for the improvement[54].

The response was also selective. OCA did not demonstrate a statistically significant benefit on steatohepatitis resolution without worsening fibrosis[50]. That result narrowed the scope of its demonstrated activity, but it should not be cited as the sole reason for non-approval. The FDA framework allowed either fibrosis improvement without worsening steatohepatitis or steatohepatitis resolution without worsening fibrosis to support consideration for accelerated approval. Achieving one endpoint nevertheless required an acceptable overall benefit–risk balance[55].

Tolerability and safety complicated that assessment (Tables II and III). Pruritus affected treatment acceptability, while increases in LDL cholesterol were particularly relevant in a population already carrying substantial cardiovascular risk (Table III). Although the lipid changes did not themselves establish an increase in cardiovascular events, their management added to the burden of prolonged treatment. The regulatory assessment[55] also considered serious cholestatic drug-induced liver injury and whether monitoring could detect such injury early enough to limit its consequences. These concerns extended beyond symptomatic intolerance and formed part of the broader hepatic safety history of OCA.

The MASH program therefore demonstrated histological activity without securing approval for the indication. Its contribution to FXR-directed pharmacology remains important: it showed that treatment could influence fibrosis stage in human disease. At the same time, it exposed the demands of translating that response into an acceptable long-term therapy. The magnitude and reliability of the biopsy improvement had to be weighed against the treatment burden, potential harm, and uncertainty regarding subsequent clinical benefit.

UNDERSTANDING ADVERSE EFFECTS: EXPOSURE, DISEASE STAGE, AND BIOLOGICAL CONTEXT

The safety history of OCA encompasses several distinct problems. Pruritus, changes in lipoprotein metabolism, and serious hepatic events raised different questions about receptor biology, molecular selectivity, and drug exposure. Distinguishing these mechanisms is essential to understanding how a compound with convincing experimental activity developed an increasingly complex clinical benefit–risk profile (Tables II and III).

Table I. Main clinical trials of obeticholic acid.

Trial/principal report	Phase	Population	Main contribution
Primary biliary cholangitis (PBC)			
PBC add-on dose-ranging study Hirschfield et al[38], 2015	II	165 patients with inadequate response to UDCA.	Established ALP reduction and identified dose-related pruritus.
PBC monotherapy study Kowdley et al[34], 2018	II	59 patients not receiving UDCA.	Biochemical efficacy over 12 weeks; extension up to 6 years. Pruritus limited treatment persistence.
POISE Nevens et al[51], 2016	III	217 randomized patients with inadequate response to or intolerance of UDCA.	Pivotal biochemical efficacy trial supporting approval in 2016.
POISE open-label extension Trauner et al[52], 2019	Extension	193 participants from POISE.	Sustained biochemical responses; no concurrent randomized control group.
COBALT/Study 747-302 Kowdley et al[41], 2025	III	334 patients with PBC.	Randomized analysis did not verify clinical benefit. Central to regulatory reassessment; crossover and early termination complicated interpretation.
MASH and the early metabolic development program			
Early metabolic study Mudaliar et al[47], 2013	II	64 patients with type 2 diabetes and presumed NAFLD.	Improved clamp-measured insulin sensitivity over 6 weeks; changes in liver markers and lipids.
FLINT Neuschwander-Tetri et al[48], 2015	IIb	283 patients with non-cirrhotic NASH.	Histological improvement and an antifibrotic signal; pruritus and adverse lipid changes.
CONTROL Pockros et al[49], 2019	II	84 patients with NASH.	Atorvastatin counteracted the OCA-associated increase in LDL cholesterol.
REGENERATE Younossi et al[50], 2019; Sanyal et al[54], 2023	III	Non-cirrhotic NASH with fibrosis; 931 F2-F3 patients in the original primary efficacy analysis.	Fibrosis improvement without worsening NASH, particularly with OCA 25 mg/day; did not secure approval.
REVERSE Intercept Pharmaceuticals, 2022[56]	III	919 patients with compensated NASH cirrhosis.	No significant improvement in the primary fibrosis endpoint at 18 months.
Primary sclerosing cholangitis (PSC)			
AESOP Kowdley et al[37], 2020	II	76 patients with PSC.	ALP reduction over 24 weeks; long-term clinical benefit not established.

Years indicate the principal publication, except for REVERSE (sponsor announcement, 2022). COBALT appeared online in 2024 and in the 2025 journal issue. The early metabolic study enrolled presumed NAFLD, not biopsy-confirmed MASH. Original NASH/NAFLD terminology is retained. ALP, alkaline phosphatase; MASH, metabolic dysfunction-associated steatohepatitis; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Table II. Pruritus incidence according to obeticholic acid dose.

Trial and principal report	Duration	Placebo	OCA 5-10 mg/day	OCA 10 mg/day	OCA 25 mg/day	OCA 50 mg/day
Primary biliary cholangitis						
PBC add-on dose-ranging study Hirschfield et al[38], 2015	12 weeks	50%	—	47%	85%*	80%
PBC monotherapy study Kowdley et al[34], 2018	12 weeks	35%	—	70%	—	94%
POISE Nevens et al[51], 2016	12 months	38%	56%†	68%	—	—
MASH historically reported as NASH						
FLINT Neuschwander-Tetri et al[48], 2015	Up to 72 weeks	6%	—	—	23%	—
REGENERATE interim analysis Younossi et al[50], 2019	18 months	19%	—	28%	51%	—

Patients reporting pruritus during the randomized treatment period, expressed as a percentage of each treatment group. Dose comparisons should be interpreted within each trial.
— Dose not studied in that trial.
*The Hirschfield full-text adverse-event section reports 85% for 25 mg/day, whereas its abstract reports 87%. The full-text value is used here.
† POISE began with 5 mg/day, with possible escalation to 10 mg/day after 6 months according to response and tolerability. This is a titration strategy, not a fixed 5 mg arm.
Severity matters as well as incidence. In POISE, severe pruritus occurred in 7% with placebo, 19% with OCA titration, and 23% with fixed OCA 10 mg/day. In REGENERATE, severe pruritus occurred in <1%, <1%, and 5% with placebo, OCA 10 mg/day, and OCA 25 mg/day, respectively; approximately 9% receiving 25 mg/day discontinued because of pruritus.

Table III. Lipoprotein outcomes in clinical studies of obeticholic acid.

Trial or analysis First author and year	Population and exposure	LDL and total cholesterol	HDL, triglycerides and particle findings	Time course or lipid management
Healthy volunteers				
Two phase I studies Pencek et al[57], 2016	68 healthy adults; OCA 5, 10 or 25 mg/day; 14 or 20 days.	LDL-C increased during repeated dosing.	HDL-C and HDL particle concentrations decreased; medium and small HDL particles accounted for the particle reduction.	Changes occurred over short exposure; these studies did not assess cardiovascular outcomes.
Primary biliary cholangitis				
POISE Nevens et al[51], 2016	217 randomized patients; OCA 5-10 or 10 mg/day *vs.* placebo; 12 months.	The principal lipid safety signal was HDL-C reduction.	Month 12 mean HDL-C reduction from baseline: 12% with 5-10 mg, 19% with 10 mg and 2% with placebo.	HDL-C reductions appeared within 2 weeks and persisted. Percentages are within-arm changes, not placebo-adjusted effects.
MASH and the early metabolic development program				
Exploratory metabolic trial Mudaliar et al[47], 2013	64 patients with type 2 diabetes and presumed NAFLD; OCA 25 or 50 mg/day *vs.* placebo; 6 weeks.	LDL-C increased with OCA.	HDL-C and triglyceride reductions were reported, particularly with 50 mg/day.	Early evidence that human lipid responses differed from favorable preclinical metabolic predictions.
FLINT Neuschwander-Tetri et al[48], 2015	283 randomized patients with noncirrhotic NASH; OCA 25 mg/day *vs.* placebo; up to 72 weeks.	Total cholesterol and LDL-C increased.	HDL-C decreased; triglycerides were not significantly different between groups at week 72.	Changes developed early and attenuated during treatment; lipid differences resolved after withdrawal.
FLINT particle substudy Siddiqui et al[58], 2020	196 participants (99 OCA, 97 placebo); NMR at baseline and weeks 12, 72 and 96.	Week 12 LDL particles: 1667 *vs.* 1,329 nmol/L; large LDL: 475 *vs.* 308; small LDL: 1015 *vs.* 872 (OCA *vs.* placebo).	Total HDL particles decreased, especially large and medium HDL. Total VLDL particles were unchanged; large VLDL decreased and small VLDL increased.	LDL particle differences resolved 24 weeks after stopping OCA. This is a substudy of FLINT, not an independent trial.
CONTROL Pockros et al[49], 2019	84 patients with NASH; OCA 5, 10 or 25 mg/day *vs.* placebo; 16 weeks after statin washout.	At week 4, LDL-C and LDL particle concentrations increased in all OCA arms, predominantly through large LDL particles.	Particle analysis characterized the LDL rise; larger particle size does not establish cardiovascular safety.	Atorvastatin 10 mg/day started at week 4 reduced LDL-C and LDL particles below baseline by week 8.
REGENERATE Younossi et al[50], 2019	Noncirrhotic NASH with fibrosis; OCA 10 or 25 mg/day *vs.* placebo; 18-month interim analysis.	OCA 25 mg: LDL-C change +22.6 mg/dL at week 4 and +4.0 mg/dL at month 18 (within-arm least-squares means).	Early LDL-C elevation was the prominent reported lipid-management issue.	The rise attenuated during follow-up with lipid management, including statins; this does not demonstrate cardiovascular benefit.
Exploratory HDL analysis Kim et al[59], 2024	20 OCA-treated patients with MASH; 10 with and 10 without diabetes; 18 months; no lipid-lowering drugs.	No significant change in total cholesterol or LDL-C in this small, selected sample.	No significant HDL-C or cholesterol-efflux change. Without diabetes, HDL pro-inflammatory index increased, and ceruloplasmin activity decreased; with diabetes, pre-β HDL increased.	Exploratory analysis of clinical-trial samples; small groups and no concurrent placebo comparison limit interpretation.

Historical NAFLD/NASH terminology is retained. Particle concentrations are distinct from cholesterol concentrations. FLINT particle values are baseline-adjusted group means. Selected outcomes are not directly comparable across populations or durations. No study here establishes an effect on cardiovascular events.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MASH, metabolic dysfunction-associated steatohepatitis; NMR, nuclear magnetic resonance; OCA, obeticholic acid; VLDL, very-low-density lipoprotein.

PRURITUS: RECEPTOR SELECTIVITY AND SENSORY SIGNALING

Pruritus was the most conspicuous limitation of OCA treatment, but its mechanism should not be attributed automatically to FXR activation. Bile acids interact with several receptors, including sensory receptors capable of initiating itch[60,61]. A chemically modified bile acid can therefore retain biological activities beyond the nuclear receptor for which it was developed.

An important advance was the identification of Mas-related G-protein-coupled receptor X4 (MRGPRX4) as a human bile acid-responsive receptor implicated in cholestatic itch[61,62]. Subsequent structural and functional studies[62,63] demonstrated that OCA can directly activate MRGPRX4. These findings provide a molecular explanation for how the compound might stimulate pruritogenic signaling independently of its intended action on FXR. They also suggest that modifications preserving FXR activity while reducing MRGPRX4 activation could improve the tolerability of bile acid-derived drugs. However, the experimental evidence does not establish how much of the itching experienced by individual OCA-treated patients is attributable to this pathway[64].

A complementary hypothesis involves interleukin-31 (IL-31), a cytokine with established pruritogenic activity. Studies with the nonsteroidal FXR agonist cilofexor found that treatment increased circulating IL-31 in patients with NASH and that these increases were associated with greater pruritus severity[65]. This observation suggests that receptor-mediated changes in cytokine signaling may contribute to itching during FXR agonist treatment, even when the molecule lacks a bile acid scaffold. Nevertheless, evidence obtained with cilofexor should not be presented as direct proof that IL-31 mediates OCA-associated pruritus.

Earlier experimental work also implicated GPBAR1, or TGR5, in bile acid-induced itching in mice[60]. This mechanism cannot be transferred directly to humans: species differences in sensory receptor biology limit the explanatory value of the murine findings. More broadly, cholestatic pruritus is unlikely to reflect one mediator alone[66]. Direct sensory receptor activation, cytokine signaling, and the underlying cholestatic environment may contribute in different proportions. The observed dose relationship is consistent with greater stimulation of these pathways at higher exposure, but it does not identify the responsible mechanism.

DYSLIPIDEMIA: MODIFYING CHOLESTEROL DISPOSAL AND LIPOPROTEIN HANDLING

The effects of OCA on lipoproteins were closely connected to the physiological functions of FXR (Figure 4 and Table III). Conversion of cholesterol into bile acids constitutes an important route of cholesterol disposal.

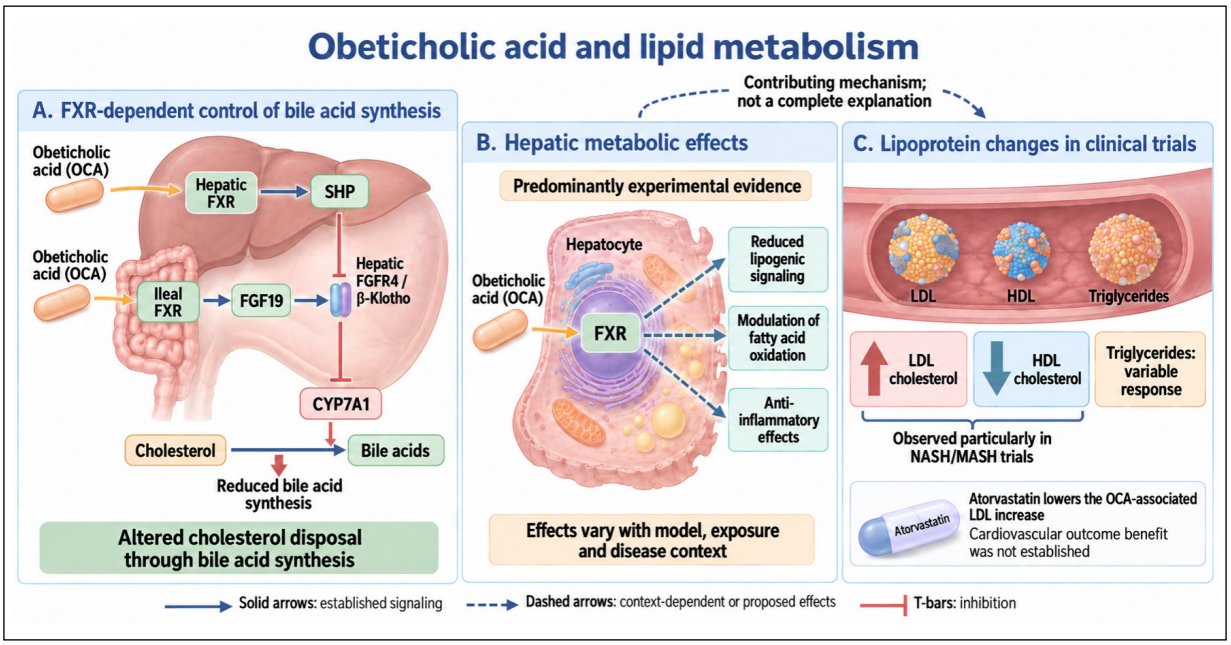

Figure 4. Effects of OCA on cholesterol disposal and lipoprotein metabolism.
A, Hepatic FXR–SHP signaling and intestinal FXR–FGF19 signaling suppress CYP7A1-dependent conversion of cholesterol into bile acids, potentially reducing cholesterol disposal through this pathway. **B**, Hepatic metabolic responses depend on exposure, disease context, and species; favorable findings in experimental models do not necessarily predict the human lipoprotein response. **C**, Clinical studies have reported increased LDL cholesterol and LDL particle concentrations, particularly in MASH, together with reductions in HDL cholesterol in several settings. Atorvastatin counteracted the LDL response in CONTROL[49], but this did not establish long-term cardiovascular safety. The figure summarizes interacting mechanisms and clinical observations rather than a complete causal explanation of OCA-associated lipid changes[67,68].
LDL, low-density lipoprotein; HDL, high-density lipoprotein; MASH, metabolic dysfunction-associated steatohepatitis.

FXR activation suppresses this pathway through hepatic SHP-dependent regulation and intestinal production of FGF19, which signals to hepatocytes to inhibit CYP7A1, the rate-limiting enzyme in the classical bile acid synthesis pathway[69]. The feedback system that limits bile acid production can therefore also reduce cholesterol catabolism. This provides a plausible contribution to the increase in LDL cholesterol observed during OCA treatment, particularly in MASH. The complete response nevertheless involves several processes, including cholesterol synthesis, lipoprotein production, receptor-mediated clearance, and HDL metabolism. OCA-associated reductions in HDL cholesterol further indicate that sustained FXR activation influences multiple components of cholesterol handling. These clinical observations caution against assuming that favorable metabolic responses in selected animal models will translate directly to humans.

The clinical studies summarized in Tables I and III documented changes in lipoprotein particle concentrations as well as conventional cholesterol measurements. Importantly, these effects were pharmacologically manageable. In the CONTROL trial[49], LDL cholesterol and LDL particle concentrations increased during the initial period of OCA treatment, while the subsequent introduction of atorvastatin reduced both measures below baseline by week 8. This demonstrated that statin treatment could counter the LDL response; it did not establish that all cardiovascular consequences of prolonged OCA exposure had been neutralized[49].

The distinction is particularly relevant in MASH, where cardiovascular disease contributes substantially to morbidity and mortality[46,70]. A treatment targeting liver fibrosis must be evaluated within that broader clinical setting[71]. An improvement in hepatic histology and an unfavorable change in circulating lipoproteins can coexist, making the overall therapeutic assessment more demanding than either observation considered alone.

HEPATIC SAFETY: EXPOSURE AND ADAPTIVE RESPONSES

Hepatic safety introduced a further level of complexity. OCA undergoes glycine and taurine conjugation, and the parent compound and active conjugates participate in enterohepatic recirculation. Its disposition therefore depends on hepatic handling, biliary secretion, and intestinal reabsorption. Impaired liver function can substantially increase exposure, creating an interaction between disease stage, dose, and the risk of toxicity.

Early safety concerns included excessive dosing frequency in patients with moderate or severe hepatic impairment. Subsequent restrictions went beyond dose adjustment. In 2021, contraindications encompassed decompensated cirrhosis, a previous episode of hepatic decompensation, and compensated cirrhosis with evidence of portal hypertension. The clinically relevant distinction was therefore not simply between compensated and decompensated disease: portal hypertension could identify vulnerability despite apparently preserved compensation[72].

Later reports of serious hepatic injury in patients without cirrhosis challenged an explanation based entirely on excessive exposure in advanced disease or inappropriate prescribing[72]. These observations expanded the safety concern beyond the population initially considered most susceptible. However, they did not establish a single mechanism responsible for the injury.

Experimental studies offer additional possibilities. In some investigations[73], FXR was shown to suppress constitutive androstane receptor-mediated activation of the basolateral transporter MRP4. This transporter can contribute to an adaptive response during cholestasis by redirecting bile acids from hepatocytes toward the systemic circulation and subsequent renal elimination. These findings illustrate how activating a receptor that suppresses bile acid synthesis can also constrain a compensatory disposal route. The relevance of this mechanism depends on the physiological context, particularly the availability of canalicular and biliary outflow. It should not be presented as a demonstrated explanation for OCA-associated clinical liver injury. Rather, it identifies a potential tension within FXR biology: responses that support homeostasis under one condition may become disadvantageous when another route of elimination is compromised.

A further line of investigation concerned the balance between MAFG and nuclear factor erythroid 2-related factor 2 (NRF2), a regulator of antioxidant and cytoprotective responses. Studies[74] from our group linked OCA-associated injury in rodent models of cholestasis to increased MAFG activity and suppression of NRF2-dependent protective signaling. These findings extended the mechanistic concern beyond bile acid synthesis and transport to the capacity of hepatocytes to withstand injury. Their emergence many years after OCA's discovery also illustrated how important consequences of receptor activation could remain incompletely characterized during development.

Neither the transporter findings nor the MAFG–NRF2 observations establish the mechanism responsible for clinical hepatic events. They do, however, identify a common biological question: can sustained FXR activation limit adaptive responses that become essential in an injured liver? This remains one of the most instructive aspects of the OCA experience. Understanding a receptor's principal physiological function does not ensure that the consequences of its sustained pharmacological activation are fully understood. Molecular interactions, exposure, disease stage, and the liver's adaptive capacity all influence whether a response that supports homeostasis remains therapeutically beneficial.

THE COBALT TRIAL AND WITHDRAWAL: THE CHALLENGE OF INTERPRETING DISCORDANT EVIDENCE

COBALT[41], a phase 3b/4 clinical trial in patients with PBC, was intended to verify the clinical benefit of OCA in PBC (Table I). This was particularly important because the initial approval was based on improvements in biochemical markers, and it remained necessary to demonstrate whether these improvements translated into meaningful clinical benefits. The trial therefore addressed the question that biochemical efficacy alone could not resolve—whether treatment changed the subsequent course of disease.

The randomized intention-to-treat analysis did not demonstrate superiority over placebo. The primary composite endpoint occurred in 28.6% of patients assigned to OCA and 28.9% assigned to placebo, with a hazard ratio of 1.01 (95% confidence interval, 0.68-1.51)[41]. This was the principal comparison through which the confirmatory trial was intended to establish benefit. The confidence interval allowed uncertainty in both directions, but the analysis did not provide the required positive evidence.

COBALT also illustrated the difficulties of conducting a prolonged outcomes trial after a treatment had become commercially available. Treatment discontinuation, crossover to commercial therapy, functional unblinding, and early termination complicated interpretation. Access to OCA outside the trial reduced the separation between the randomized treatment strategies, particularly when patients assigned to placebo subsequently received active treatment[41].

These limitations warrant consideration without displacing the primary result. Intention-to-treat analysis preserves the comparison created by randomization and estimates the effect of treatment assignment under the conditions encountered in the trial. When exposure converges between groups, that comparison may become less informative about the effect of sustained treatment. Conversely, analyses that censor crossover or focus on continued exposure require additional assumptions and can introduce selection bias. The difficulties explain why the trial was challenging to interpret; they do not establish that uninterrupted OCA treatment would have improved outcomes.

Comparisons with external control populations, included in the published COBALT analysis, suggested a more favorable effect. In the published COBALT analysis, the weighted comparison with an external cohort produced a hazard ratio of 0.39 for the clinical composite endpoint. This finding supported further discussion of possible benefit but represented a different comparison from the randomized analysis. External controls can provide valuable information, particularly in rare diseases, but cannot recreate randomization. Differences in disease severity, treatment selection, follow-up, outcome ascertainment, and unmeasured prognostic factors may influence the apparent effect. The disagreement could not be resolved simply by choosing the more favorable estimate. The randomized analysis failed to confirm benefit, while the external-control comparison suggested benefit under assumptions that could not be fully verified.

Failure to confirm clinical benefit in COBALT, together with the subsequent benefit–risk assessments, led to withdrawal in the European Union and United States. In the European Union, the reassessment concluded that clinical benefit had not been confirmed and that supportive studies and real-world evidence did not adequately counterbalance the confirmatory trial findings. The European Commission revoked the conditional marketing authorization on 30 August 2024. A court order temporarily suspended that decision on 4 September 2024; the suspension was canceled on 26 November 2024, bringing the revocation back into effect[75]. On 23 September 2026, the General Court dismissed the action brought by Advanz Pharma against the Commission's revocation decision in Case T-455/24 (Advanz Pharma Ltd v European Commission; ECLI:EU:T:2026:585), leaving that decision in place[76].

The United States followed a separate regulatory course. In December 2024, the FDA communicated concerns about serious liver injury in patients without cirrhosis, extending the safety discussion beyond the population previously considered most vulnerable. On 27 August 2025, the agency recommended that Intercept request withdrawal, stating that the post-marketing trial had not verified clinical benefit and that OCA-treated patients with early-stage disease at baseline had experienced an excess of liver transplants and deaths[77]. Intercept submitted its withdrawal request on 10 September 2025, while recording disagreement with the agency's assessment. Approval was formally withdrawn on 24 November 2025[77].

Withdrawal was jurisdiction-specific rather than worldwide. The European and US decisions ended the respective authorizations; failure to obtain a MASH indication was a separate regulatory event.

As of October 2026, OCA remained listed as marketed in Canada and available in Australia[78,79], with continued licensing and availability reported in the United Kingdom[80]. Switzerland separately announced withdrawal of authorization in August 2025[81]. Commercial marketing should be distinguished from compassionate-use or named-patient supply, which may remain possible for existing patients after withdrawal of authorization[75].

The clinical implications of OCA withdrawal should also be considered alongside the availability of newer PBC therapies. Elafibranor, a dual PPARα/δ agonist, and seladelpar, a selective PPARδ agonist, provide alternatives for adults with an inadequate response to UDCA or intolerance of it. The pivotal ELATIVE[82] and RESPONSE[83] trials demonstrated biochemical efficacy; seladelpar also improved pruritus in patients with moderate-to-severe baseline itching. Both have received conditional authorization in the European

Union[67,84]. These developments broaden treatment options, but biochemical response should not be mistaken for confirmation of long-term clinical benefit.

For those involved in the original discovery, this outcome requires distinguishing scientific contribution from therapeutic justification. Withdrawal does not erase the biochemical activity demonstrated in PBC or the histological findings generated in MASH. It does establish that, when considered alongside the clinical outcomes and safety evidence, those observations were insufficient to sustain authorization. A historical perspective must preserve both conclusions: OCA helped establish FXR as a pharmacologically tractable target, while its clinical trajectory exposed the limits of translating receptor activity and surrogate responses into an acceptable long-term treatment.

IS OCA AN EFFECTIVE ANTI-FIBROTIC AGENT? RESULTS FROM CLINICAL TRIALS

Reduced extracellular matrix accumulation in an experimental model, improvement of fibrosis stage on a liver biopsy, and prevention of fibrosis-related clinical complications represent different levels of evidence[85]. OCA generated findings at the first two levels, while its ability to improve long-term clinical outcomes remained unconfirmed. The early experimental studies[18,19,68] connected FXR activation with modulation of profibrotic signaling and inflammatory responses in hepatic stellate cells (Figure 3). They provided a rationale for clinical development, but their interpretation depended on the experimental design. Reduced fibrosis during ongoing injury could reflect direct modulation of fibrogenic cells, attenuation of the injury that activates them, or both. Demonstrating less scar accumulation did not necessarily establish removal of an existing scar. On the other hand, reversing fibrosis in clinical settings has proved difficult[86], although resmetirom[87], semaglutide[88], and pegozafermin[89] have demonstrated biopsy-defined fibrosis improvement (Figure 5).

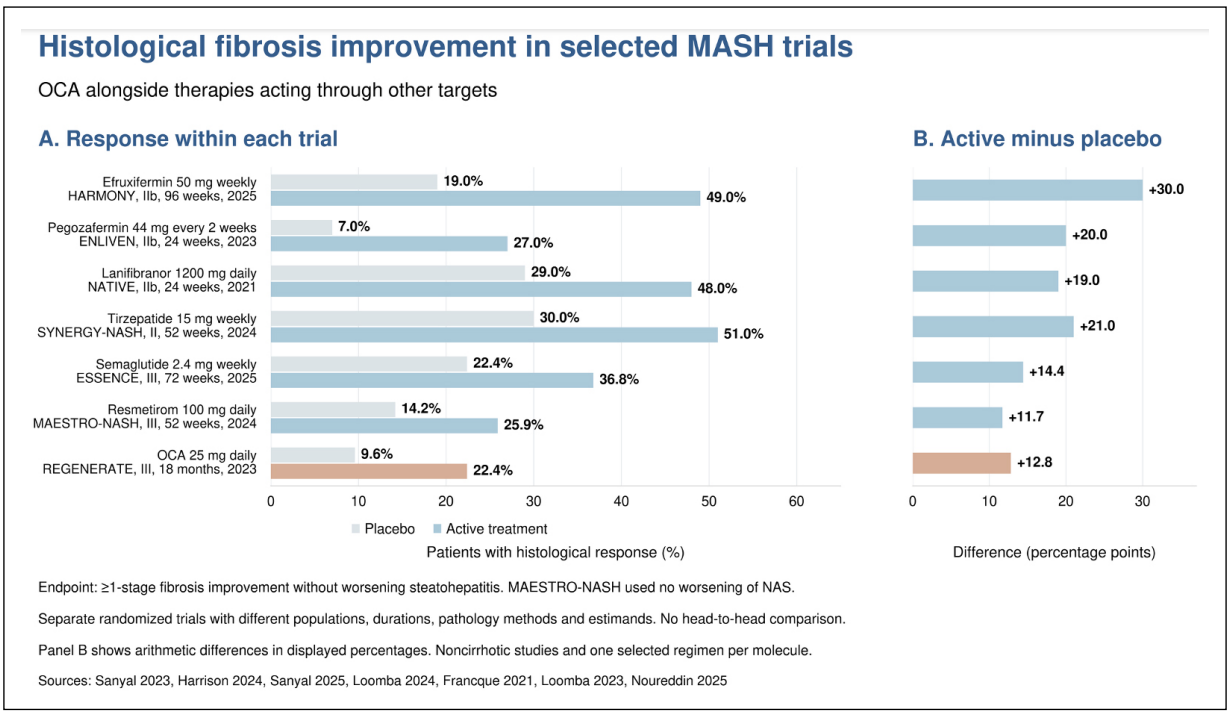

Figure 5. Histological fibrosis improvement in selected randomized MASH trials.
A, Proportions of patients achieving at least one-stage fibrosis improvement without worsening steatohepatitis in selected treatment and placebo groups. MAESTRO-NASH trial[87] defined the accompanying requirement as no worsening of the NAFLD activity score. Trials shown are HARMONY (efruxifermin)[90], ENLIVEN (pegozafermin)[89], NATIVE (lanifibranor)[91], SYNERGY-NASH (tirzepatide)[92], ESSENCE (semaglutide)[88], MAESTRO-NASH (resmetirom)[87] and REGENERATE (OCA)[54]. The OCA values derive from the updated 2023 consensus biopsy analysis. **B**, Arithmetic differences between the displayed active-treatment and placebo response rates, expressed in percentage points. One selected regimen is shown per compound. Differences in populations, treatment duration, biopsy assessment, endpoint definitions, and statistical methods preclude direct efficacy ranking. These are separate placebo-controlled trials, not head-to-head comparisons, and histological responses do not themselves establish prevention of liver-related clinical events.
NAFLD, nonalcoholic fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; OCA, obeticholic acid.

The REGENERATE trial[50,54] provided evidence that the OCA hypothesis had relevance to human disease. In the updated consensus assessment, fibrosis improvement without worsening steatohepatitis occurred in 22.4% of patients receiving OCA 25 mg, compared with 9.6% receiving placebo – a placebo-adjusted difference of 12.8 percentage points[50,54,93]. This supports a histological antifibrotic effect in non-cirrhotic MASH. Its interpretation nevertheless requires qualification. Fibrosis stage is an ordinal assessment of tissue architecture rather than a direct measurement of total hepatic collagen[94,95]. Sampling variability and differences between pathologists can affect the classification of paired biopsies[85,96]. A one-stage improvement does not establish restoration of liver architecture, resolution of portal hypertension, or durable regression after treatment withdrawal[94]. Nor does the clinical response identify a specifically stellate-cell-mediated mechanism, because OCA also influences hepatocellular injury, inflammation, and intestinal–hepatic signaling.

The positive REGENERATE[50] findings concerned non-cirrhotic fibrosis. In contrast, the REVERSE trial[56] in patients with compensated MASH-related cirrhosis did not meet its primary fibrosis endpoint. The non-cirrhotic results therefore cannot be extended to established cirrhosis.

The most defensible conclusion is that OCA demonstrated experimental antifibrotic activity and biopsy-defined fibrosis improvement in non-cirrhotic MASH. It did not establish reversal of advanced disease or prevention of its clinical consequences. Failure to obtain a MASH indication does not invalidate the histological findings, but those findings alone did not establish an acceptable long-term antifibrotic treatment.

HOW OCA'S HISTORY SHAPED THE DEVELOPMENT OF FXR LIGANDS

OCA development helped move FXR from receptor biology into human pharmacology. Its clinical development demonstrated measurable biochemical and histological responses, while revealing liabilities that subsequent ligands would need to address. Its withdrawal therefore tempered therapeutic expectations for FXR without resolving the potential of every compound acting on this receptor.

An important consequence was the expansion of medicinal chemistry beyond the bile acid scaffold. Nonsteroidal agonists, including cilofexor[97] and tropifexor[98], enabled investigators to explore FXR activation using molecules with different structures and pharmacokinetic properties[3]. Their development broadened the question from whether a modified bile acid could become a medicine to whether alternative ligands could deliver a more favorable balance between receptor activity, tissue exposure, and tolerability. Both compounds subsequently underwent randomized clinical investigation in steatohepatitis.

OCA also made clear that potency alone was an insufficient objective for ligand optimization. Strong receptor activation could coexist with pruritus, unfavorable lipoprotein changes, or hepatic safety concerns. The relevant goal became an exposure that produced useful biological effects without imposing unacceptable consequences during prolonged treatment. This required attention to molecular selectivity and disposition, alongside conventional measurements of receptor potency.

The distinction between effects related to OCA's structure and those potentially shared by FXR agonists became particularly important. Direct activation of the human itch receptor MRGPRX4 provides a plausible contribution to OCA-associated pruritus and a specific opportunity for chemical modification[62]. Structure-guided studies have explored bile acid derivatives designed to retain therapeutic receptor activity while reducing this additional interaction. This work shows how knowledge of an adverse effect can redirect drug discovery.

However, changing the scaffold does not automatically eliminate itching. Pruritus was also observed with the nonsteroidal agonist tropifexor, and studies with cilofexor[65] linked FXR activation to increases in the pruritogenic cytokine IL-31 (Table IV). These observations suggest that multiple pathways may contribute to intolerance. They also caution against treating every adverse effect as either entirely specific to OCA or an unavoidable consequence of activating FXR. Assessing the relative contributions of receptor-mediated signaling, additional molecular interactions, exposure, and underlying disease is required for each compound.

Table IV. Selected clinical trials of FXR agonists other than obeticholic acid.

FXR agonist	Trial or program	Population	Phase	ClinicalTrials.gov ID	Registry status
Tropifexor (LJN452)	FLIGHT-FXR: dose-ranging monotherapy	Non-cirrhotic MASH	2	NCT02855164	Terminated
Tropifexor	ELIVATE: alone or with licogliflozin	MASH with liver fibrosis	2	NCT04065841	Terminated
Cilofexor (GS-9674)	Phase 2 program: cilofexor, firsocostat and selonsertib	MASH	2	NCT02781584	Completed
Cilofexor	ATLAS: individual agents and combinations	MASH with bridging fibrosis or compensated cirrhosis	2	NCT03449446	Completed
Cilofexor	Placebo-controlled PBC study	PBC without cirrhosis	2	NCT02943447	Terminated
Cilofexor	PRIMIS	Non-cirrhotic PSC	3	NCT03890120	Terminated
EDP-305	ARGON: dose-ranging monotherapy	MASH	2	NCT03421431	Completed
EDP-305	ARGON-2	Biopsy-confirmed MASH	2b*	NCT04378010	Terminated
EDP-305	INTREPID	PBC	2	NCT03394924	Completed
Nidufexor (LMB763)	Dose-ranging safety and efficacy study	MASH	2	NCT02913105	Terminated
Vonafexor (EYP001/ EYP001a)	LIVIFY	Suspected or biopsy-confirmed fibrotic MASH	2a*	NCT03812029	Completed
TERN-101 (LY2562175)	LIFT	Presumed non-cirrhotic MASH	2a*	NCT04328077	Completed
TERN-101	DUET: TERN-501 alone or with TERN-101	Presumed non-cirrhotic MASH	2	NCT05415722	Completed
MET409	Alone or with empagliflozin	MASH with type 2 diabetes	2	NCT04702490	Unknown
MET642	Placebo-controlled safety and efficacy study	MASH	2	NCT04773964	Completed
PX-104	Open-label pilot study	NAFLD/MASLD	2	NCT01999101	Completed
Linafexor (CS0159)†	Pulsatile FXR agonist: first-in-human PK/PD	Healthy volunteers	1	NCT05082779	Completed
Linafexor (CS0159)†	Safety, tolerability, PK and efficacy	MASH	2	NCT05591079	Completed
Linafexor (CS0159)†	Placebo-controlled PBC study	PBC	2	NCT05896124	Active, not recruiting
Linafexor (CS0159)†	Placebo-controlled PSC study	PSC	2	NCT05896137	Active, not recruiting
Linafexor (CS0159)†	Phase 3 PBC study	PBC with inadequate response or intolerance to UDCA	3	NCT07282353	Recruiting

Representative trials in liver disease, including completed and terminated studies. ClinicalTrials.gov registry status checked 11 October 2026.
†Temporal pharmacology: linafexor is a rapidly cleared, non-bile-acid agonist designed for pulsatile FXR activation. Phase 1 data show transient FGF19 induction and C4 suppression. This does not yet establish long-term clinical efficacy or safety. Other agents are not classified as pulsatile solely based on half-life[99].
Historical NASH/NAFLD terminology is rendered as MASH/MASLD where appropriate. *Phase 2a/2b follows study descriptions; the structured registry field records Phase 2. Termination does not itself establish a safety problem or discontinuation of the entire drug program. Unknown indicates that the registry status has not been sufficiently updated.
Combination partners: TERN-501, thyroid hormone receptor-beta agonist; empagliflozin, SGLT2 inhibitor; licogliflozin, SGLT1/2 inhibitor; firsocostat, acetyl-CoA carboxylase inhibitor; selonsertib, ASK1 inhibitor. These agents are not FXR agonists.
FXR, farnesoid X receptor; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
Source: linked ClinicalTrials.gov study records[100].

A further direction has been to control where receptor activation occurs. Experimental studies with the gut-restricted agonist fexaramine[101] demonstrated that intestinal FXR activation could generate endocrine and metabolic responses without comparable direct activation of hepatic FXR target genes.

This introduced tissue distribution as a variable in therapeutic design. Nevertheless, these findings were obtained in mice and did not establish clinical efficacy or safety in human liver disease. Moreover, restricting direct exposure to one compartment does not confine all biological consequences to that compartment, because intestinal FXR communicates with the liver through endocrine signaling (Figure 1).

Changes in FGF19, bile acid synthesis markers, liver enzymes, or liver fat can demonstrate pharmacological activity, but cannot independently establish an antifibrotic treatment benefit. Likewise, a favorable biopsy response must be weighed against tolerability, hepatic safety, cardiovascular implications, and evidence that the benefit persists. Comparisons between agonists therefore require attention to dose, population, treatment duration, and endpoint rather than an assumption that activity at the same receptor makes the compounds clinically interchangeable.

OCA's history leaves the broader FXR hypothesis open, but more precisely defined. Its outcome cannot be generalized to every agonist, and alternative chemistry or tissue targeting cannot be assumed to ensure success. The continuing question is whether FXR signaling can be modulated at an exposure and in a biological context that deliver sustained benefit with acceptable safety.

CONCLUSIONS

The history of OCA illustrates both the opportunities and the demands of translational pharmacology. Modification of an endogenous bile acid produced a potent FXR agonist, helped establish bile acid signaling as a therapeutic field, and generated measurable biochemical and histological responses in patients. Withdrawal of its authorizations in the European Union and United States demonstrated that these achievements were insufficient to sustain approval when clinical benefit remained unconfirmed and safety concerns accumulated.

Receptor potency does not, by itself, define therapeutic value. Its significance depends on molecular selectivity, tissue exposure, duration of action, and the physiological condition of the treated organ. Experimental efficacy likewise requires interpretation within the model that generated it. Prevention of matrix accumulation differs from reversal of established fibrosis, non-obstructive cholestasis differs from complete biliary obstruction, and murine bile acid physiology differs from that of humans. The early findings justified clinical investigation while leaving questions that only studies in patients could resolve.

With hindsight, greater emphasis on the lowest effective exposure and complementary therapies might have improved tolerability. In POISE[51], starting at 5 mg with subsequent titration produced a biochemical response rate similar to that achieved with a fixed 10-mg dose, while pruritus was less frequent. Although the trial established neither equivalence between regimens nor the efficacy of sustained lower dosing, it supported evaluating escalation according to incremental benefit.

Combination treatment offered a related opportunity. Most patients in the pivotal PBC program already received OCA alongside UDCA; the question was whether additional mechanisms could reduce reliance on higher OCA exposure. An uncontrolled retrospective study[44] reported additional biochemical improvement with UDCA, OCA, and fibrates. Fibrates offer a complementary PPAR-mediated approach[102,103], but these findings did not establish long-term clinical benefit or demonstrate that lower OCA doses would suffice.

In MASH, combining an antifibrotic intervention with treatment of the metabolic drivers of injury was also biologically plausible. However, the stronger fibrosis evidence emerged at 25 mg, creating a potential trade-off between tolerability and efficacy. A randomized, open-label phase 2 trial[104] combining semaglutide with cilofexor and/or firsocostat demonstrated the feasibility of investigating complementary mechanisms but cannot establish what an OCA combination would have achieved. Similarly, CONTROL[49] showed that atorvastatin could counter OCA-associated LDL increases, without establishing long-term cardiovascular safety or addressing pruritus and hepatic injury.

The clinical program reinforced the distinction between prognostic association and treatment benefit. Biochemical markers and biopsy endpoints remain valuable, particularly in slowly progressive diseases, but their improvement does not automatically establish prevention of decompensation, transplantation, or death. Approval based on surrogate responses must therefore be accompanied by a feasible confirmatory program that anticipates recruitment difficulties, discontinuation, crossover, and commercial access.

OCA's outcome leaves the broader FXR hypothesis open. Some liabilities may reflect receptor-mediated biology, whereas others may depend on additional molecular interactions, enterohepatic disposition, or disease stage. Alternative scaffolds,

tissue distribution, and temporal patterns of activation offer opportunities for improvement, but require their own clinical validation.

Participation in the early work makes the distinction between discovery and therapeutic validation particularly important. Recognizing OCA's scientific contribution also requires acknowledging the limitations revealed by its clinical development. As the twenty-fifth anniversary of its discovery approaches, its enduring legacy lies in the knowledge it generated about bile acid signaling and the requirements for translating that biology into treatment. The task now is to use those lessons to develop therapies that deliver sustained patient benefit with acceptable safety.

Conflict of Interest

Stefano Fiorucci was a scientific co-founder of Intercept Pharmaceuticals and served as scientific vice-president during its early development for three years. The author declares no current financial interest related to obeticholic acid or Intercept Pharmaceuticals.

AI Disclosure

AI-assisted tools (ChatGPT, OpenAI) were used to support language editing and preparation of schematic illustrations. The author is responsible for the accuracy, integrity, and final content of the manuscript.

Ethics Approval and Informed Consent

Not applicable due to the nature of the study.

REFERENCES

1. Pellicciari R, Fiorucci S, Camaioni E, Clerici C, Costantino G, Maloney PR, Morelli A, Parks DJ, Willson TM. 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem 2002; 45: 3569-3572.
2. Fiorucci S, Di Giorgio C, Distrutti E. Obeticholic Acid: An Update of Its Pharmacological Activities in Liver Disorders. Handb Exp Pharmacol 2019; 256: 283-295.
3. Fiorucci S, Urbani G, Distrutti E, Biagioli M. Obeticholic Acid and Other Farnesoid-X-Receptor (FXR) Agonists in the Treatment of Liver Disorders. Pharmaceuticals (Basel) 2025; 18: 1424.
4. Hofmann AF. Biliary secretion and excretion in health and disease: current concepts. Ann Hepatol 2007; 6: 15-27.
5. Achufusi TGO, Safadi AO, Mahabadi N. Ursodeoxycholic Acid. 2023 Feb 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
6. Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel JB, Willson TM, Zavacki AM, Moore DD, Lehmann JM. Bile acids: natural ligands for an orphan nuclear receptor. Science 1999; 284: 1365-1368.
7. Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf DJ, Shan B. Identification of a nuclear receptor for bile acids. Science 1999; 284: 1362-1365.
8. Wang H, Chen J, Hollister K, Sowers LC, Forman BM. Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. Mol Cell 1999; 3: 543-553.
9. Forman BM, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, Noonan DJ, Burka LT, McMorris T, Lamph WW, Evans RM, Weinberger C. Identification of a nuclear receptor that is activated by farnesol metabolites. Cell 1995; 81: 687-693.
10. Sepe V, Marchianò S, Finamore C, Baronissi G, Di Leva FS, Carino A, Biagioli M, Fiorucci C, Cassiano C, Monti MC, Del Gaudio F, Novellino E, Limongelli V, Fiorucci S, Zampella A. Novel Isoxazole Derivatives with Potent FXR Agonistic Activity Prevent Acetaminophen-Induced Liver Injury. ACS Med Chem Lett 2019; 10: 407-412.
11. Sepe V, Renga B, Festa C, D'Amore C, Masullo D, Cipriani S, Di Leva FS, Monti MC, Novellino E, Limongelli V, Zampella A, Fiorucci S. Modification on ursodeoxycholic acid (UDCA) scaffold. discovery of bile acid derivatives as selective agonists of cell-surface G-protein coupled bile acid receptor 1 (GP-BAR1). J Med Chem 2014; 57: 7687-7701.
12. Seol W, Choi HS, Moore DD. An orphan nuclear hormone receptor that lacks a DNA binding domain and heterodimerizes with other receptors. Science 1996; 272: 1336-1339.
13. Goodwin B, Jones SA, Price RR, Watson MA, McKee DD, Moore LB, Galardi C, Wilson JG, Lewis MC, Roth ME, Maloney PR, Willson TM, Kliewer SA. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell 2000; 6: 517-526.
14. Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, Luo G, Jones SA, Goodwin B, Richardson JA, Gerard RD, Repa JJ, Mangelsdorf DJ, Kliewer SA. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell Metab 2005; 2: 217-225.
15. Vavassori P, Mencarelli A, Renga B, Distrutti E, Fiorucci S. The bile acid receptor FXR is a modulator of intestinal innate immunity. J Immunol 2009; 183: 6251-6261.
16. Fiorucci S, Clerici C, Antonelli E, Orlandi S, Goodwin B, Sadeghpour BM, Sabatino G, Russo G, Castellani D, Willson TM, Pruzanski M, Pellicciari R, Morelli A. Protective effects of 6-ethyl chenodeoxycholic acid, a farnesoid X receptor ligand, in estrogen-induced cholestasis. J Pharmacol Exp Ther 2005; 313: 604-612.
17. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. Nat Rev Gastroenterol Hepatol 2017; 14: 397-411.
18. Fiorucci S, Antonelli E, Rizzo G, Renga B, Mencarelli A, Riccardi L, Orlandi S, Pellicciari R, Morelli A. The nuclear receptor SHP mediates inhibition of hepatic stellate cells by FXR and protects against liver fibrosis. Gastroenterology 2004; 127: 1497-1512.
19. Fiorucci S, Rizzo G, Antonelli E, Renga B, Mencarelli A, Riccardi L, Orlandi S, Pruzanski M, Morelli A, Pellicciari R. A farnesoid x receptor-small heterodimer partner regulatory cascade modulates tissue metalloproteinase inhibitor-1 and matrix metalloprotease expression in hepatic stellate cells and promotes resolution of liver fibrosis. J Pharmacol Exp Ther 2005; 314: 584-595.
20. Ratziu V, Sanyal AJ, Loomba R, Rinella M, Harrison S, Anstee QM, Goodman Z, Bedossa P, MacConell L, Shringarpure R, Shah A, Younossi Z. REGENERATE: Design of a pivotal, randomised, phase 3 study evaluating the safety and efficacy of obeticholic acid in patients with fibrosis due to nonalcoholic steatohepatitis. Contemp Clin Trials 2019; 84: 105803.

21. Rosenthal SB, Liu X, Ganguly S, Dhar D, Pasillas MP, Ricciardelli E, Li RZ, Troutman TD, Kisseleva T, Glass CK, Brenner DA. Heterogeneity of HSCs in a Mouse Model of NASH. Hepatology 2021; 74: 667-685.
22. Geervliet E, Karkdijk E, Bansal R. Inhibition of intrahepatic monocyte recruitment by Cenicriviroc and extracellular matrix degradation by MMP1 synergistically attenuate liver inflammation and fibrogenesis in vivo. Sci Rep 2024; 14: 16897.
23. Azizsoltani A, Niknam B, Taghizadeh-Teymorloei M, Ghoodjani E, Dianat-Moghadam H, Alizadeh E. Therapeutic implications of obeticholic acid, a farnesoid X receptor agonist, in the treatment of liver fibrosis. Biomed Pharmacother 2025; 189: 118249.
24. Fiorucci S, Urbani G, Di Giorgio C, Biagioli M, Distrutti E. Bile Acids-Based Therapies for Primary Sclerosing Cholangitis: Current Landscape and Future Developments. Cells 2024; 13: 1650.
25. Trauner M, Boyer JL. Bile salt transporters: molecular characterization, function, and regulation. Physiol Rev 2003; 83: 633-671.
26. Fiorucci S, Marchianò S, Di Giorgio C, Urbani G, Monti MC, Zampella A, Distrutti E, Biagioli M. Bile acids as mediators of microbiota signaling in entero-hepatic disorders. Biochem Pharmacol 2026; 253: 118341.
27. Sohal A, Alamgir M, Kowdley KV. New therapies for primary biliary cholangitis. Hepatol Int 2026; 20: 587-595.
28. Boggs J. Intercept brings in $41M to target FXR in liver disease. 2006. Available at: https://www.bioworld.com/articles/459582. Accessed October 16, 2026.
29. Intercept Pharmaceuticals. Intercept Pharmaceuticals Form S-1 registration statement. 2012. Available at: https://www.sec.gov/Archives/edgar/data/1270073/000114420412049445/v321826_s1.htm. Accessed October 16, 2026.
30. Pellicciari R, Costantino G, Fiorucci S. Farnesoid X receptor: from structure to potential clinical applications. J Med Chem 2005; 48: 5383-5403.
31. Intercept Pharmaceuticals. Intercept Pharmaceuticals announces publication of study demonstrating its lead compound can reverse liver fibrosis. 2005. Available at: https://www.biospace.com/b-intercept-pharmaceuticals-b-announces-publication-of-study-demonstrating-its-lead-compound-can-reverse-liver-fibrosis. Accessed October 16, 2026.
32. Intercept Pharmaceuticals. Intercept Pharmaceuticals researchers present data at DDW highlighting role of FXR in inflammatory bowel disease. 2006. Available at: https://www.biospace.com/intercept-pharmaceuticals-researchers-present-data-at-ddw-highlighting-role-of-fxr-in-inflammatory-bowel-disease. Accessed October 16, 2026.
33. Goet JC, Hirschfield GM. Guideline review: British Society of Gastroenterology/UK-PBC Primary Biliary Cholangitis treatment and management guidelines. Frontline Gastroenterol 2019; 10: 316-319.
34. Kowdley KV, Luketic V, Chapman R, Hirschfield GM, Poupon R, Schramm C, Vincent C, Rust C, Parés A, Mason A, Marschall HU, Shapiro D, Adorini L, Sciacca C, Beecher-Jones T, Böhm O, Pencek R, Jones D, Obeticholic Acid PBC Monotherapy Study Group. A randomized trial of obeticholic acid monotherapy in patients with primary biliary cholangitis. Hepatology 2018; 67: 1890-1902.
35. Harms MH, van Buuren HR, Corpechot C, Thorburn D, Janssen HLA, Lindor KD, Hirschfield GM, Parés A, Floreani A, Mayo MJ, Invernizzi P, Battezzati PM, Nevens F, Ponsioen CY, Mason AL, Kowdley KV, Lammers WJ, Hansen BE, van der Meer AJ. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. J Hepatol 2019; 71: 357-365.
36. Fiorucci S, Distrutti E. The Pharmacology of Bile Acids and Their Receptors. Handb Exp Pharmacol 2019; 256: 3-18.
37. Kowdley KV, Vuppalanchi R, Levy C, Floreani A, Andreone P, LaRusso NF, Shrestha R, Trotter J, Goldberg D, Rushbrook S, Hirschfield GM, Schiano T, Jin Y, Pencek R, MacConell L, Shapiro D, Bowlus CL, AESOP Study Investigators. A randomized, placebo-controlled, phase II study of obeticholic acid for primary sclerosing cholangitis. J Hepatol 2020; 73: 94-101.
38. Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, Kowdley KV, Vincent C, Bodenheimer HC, Parés A, Trauner M, Marschall HU, Adorini L, Sciacca C, Beecher-Jones T, Castelloe E, Böhm O, Shapiro D. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology 2015; 148: 751-761.e8.
39. Harms MH, Hirschfield GM, Floreani A, Mayo MJ, Parés A, Liberman A, Malecha ES, Pencek R, MacConell L, Hansen BE. Obeticholic acid is associated with improvements in AST-to-platelet ratio index and GLOBE score in patients with primary biliary cholangitis. JHEP Rep 2021; 3: 100191.
40. D'Amato D, De Vincentis A, Malinverno F, Viganò M, Alvaro D, Pompili M, Picciotto A, Palitti VP, Russello M, Storato S, Pigozzi MG, Calvaruso V, De Gasperi E, Lleo A, Castellaneta A, Pellicelli A, Cazzagon N, Floreani A, Muratori L, Fagiuoli S, Niro GA, Feletti V, Cozzolongo R, Terreni N, Marzioni M, Pellicano R, Pozzoni P, Baiocchi L, Chessa L, Rosina F, Bertino G, Vinci M, Morgando A, Vanni E, Scifo G, Sacco R, D'Antò M, Bellia V, Boldizzoni R, Casella S, Omazzi B, Poggi G, Cristoferi L, Gerussi A, Ronca V, Venere R, Ponziani F, Cannavò M, Mussetto A, Fontana R, Losito F, Frazzetto E, Distefano M, Colapietro F, Labanca S, Marconi G, Grassi G, Galati G, O'Donnell SE, Mancuso C, Mulinacci G, Palermo A, Claar E, Izzi A, Picardi A, Invernizzi P, Carbone M, Vespasiani-Gentilucci U, Italian PBC Registry and the Club Epatologi Ospedalieri (CLEO)/Associazione Italiana Gastroenterologi ed Endoscopisti Digestivi Ospedalieri (AIGO) PBC Study Group. Real-world experience with obeticholic acid in patients with primary biliary cholangitis. JHEP Rep 2021; 3: 100248.
41. Kowdley KV, Hirschfield GM, Coombs C, Malecha ES, Bessonova L, Li J, Rathnayaka N, Mells G, Jones DE, Trivedi PJ, Hansen BE, Smith R, Wason J, Hiu S, Kareithi DN, Mason AL, Bowlus CL, Muller K, Carbone M, Berenguer M, Milkiewicz P, Adekunle F, Villamil A. COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis With Placebo and External Controls. Am J Gastroenterol 2025; 120: 390-400.
42. Angulo P, Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Kamath PS, Dickson ER. Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. Liver 1999; 19: 115-121.
43. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017; 67: 145-172.
44. Soret PA, Lam L, Carrat F, Smets L, Berg T, Carbone M, Invernizzi P, Leroy V, Trivedi P, Cazzagon N, Weiler-Normann C, Alric L, Rosa-Hezode I, Heurgué A, Cervoni JP, Dumortier J, Potier P, Roux O, Silvain C, Bureau C, Anty R, Larrey D, Levy C, Pares A, Schramm C, Nevens F, Chazouillères O, Corpechot C. Combination of fibrates with obeticholic acid is able to normalise biochemical liver tests in patients with difficult-to-treat primary biliary cholangitis. Aliment Pharmacol Ther 2021; 53: 1138-1146.

45. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP, Arrese M, Bataller R, Beuers U, Boursier J, Bugianesi E, Byrne CD, Castro Narro GE, Chowdhury A, Cortez-Pinto H, Cryer DR, Cusi K, El-Kassas M, Klein S, Eskridge W, Fan J, Gawrieh S, Guy CD, Harrison SA, Kim SU, Koot BG, Korenjak M, Kowdley KV, Lacaille F, Loomba R, Mitchell-Thain R, Morgan TR, Powell EE, Roden M, Romero-Gómez M, Silva M, Singh SP, Sookoian SC, Spearman CW, Tiniakos D, Valenti L, Vos MB, Wong VW, Xanthakos S, Yilmaz Y, Younossi Z, Hobbs A, Villota-Rivas M, Newsome PN, NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023; 78: 1966-1986.
46. Fiorucci S, Distrutti E. Linking liver metabolic and vascular disease via bile acid signaling. Trends Mol Med 2022; 28: 51-66.
47. Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, Adorini L, Sciacca CI, Clopton P, Castelloe E, Dillon P, Pruzanski M, Shapiro D. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013; 145: 574-582.e1.
48. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, Chalasani N, Dasarathy S, Diehl AM, Hameed B, Kowdley KV, McCullough A, Terrault N, Clark JM, Tonascia J, Brunt EM, Kleiner DE, Doo E, NASH Clinical Research Network. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015; 385: 956-965.
49. Pockros PJ, Fuchs M, Freilich B, Schiff E, Kohli A, Lawitz EJ, Hellstern PA, Owens-Grillo J, Van Biene C, Shringarpure R, MacConell L, Shapiro D, Cohen DE. CONTROL: A randomized phase 2 study of obeticholic acid and atorvastatin on lipoproteins in nonalcoholic steatohepatitis patients. Liver Int 2019; 39: 2082-2093.
50. Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, Bedossa P, Geier A, Beckebaum S, Newsome PN, Sheridan D, Sheikh MY, Trotter J, Knapple W, Lawitz E, Abdelmalek MF, Kowdley KV, Montano-Loza AJ, Boursier J, Mathurin P, Bugianesi E, Mazzella G, Olveira A, Cortez-Pinto H, Graupera I, Orr D, Gluud LL, Dufour JF, Shapiro D, Campagna J, Zaru L, MacConell L, Shringarpure R, Harrison S, Sanyal AJ, REGENERATE Study Investigators. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019; 394: 2184-2196.
51. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, Drenth JP, Pockros PJ, Regula J, Beuers U, Trauner M, Jones DE, Floreani A, Hohenester S, Luketic V, Shiffman M, van Erpecum KJ, Vargas V, Vincent C, Hirschfield GM, Shah H, Hansen B, Lindor KD, Marschall HU, Kowdley KV, Hooshmand-Rad R, Marmon T, Sheeron S, Pencek R, MacConell L, Pruzanski M, Shapiro D, POISE Study Group. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med 2016; 375: 631-643.
52. Trauner M, Nevens F, Shiffman ML, Drenth JPH, Bowlus CL, Vargas V, Andreone P, Hirschfield GM, Pencek R, Malecha ES, MacConell L, Shapiro D. Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study. Lancet Gastroenterol Hepatol 2019; 4: 445-453.
53. Food and Drug Administration. Ocaliva prescribing information. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000Lbl.pdf. Accessed October 16, 2026.
54. Sanyal AJ, Ratziu V, Loomba R, Anstee QM, Kowdley KV, Rinella ME, Sheikh MY, Trotter JF, Knapple W, Lawitz EJ, Abdelmalek MF, Newsome PN, Boursier J, Mathurin P, Dufour JF, Berrey MM, Shiff SJ, Sawhney S, Capozza T, Leyva R, Harrison SA, Younossi ZM. Results from a new efficacy and safety analysis of the REGENERATE trial of obeticholic acid for treatment of pre-cirrhotic fibrosis due to non-alcoholic steatohepatitis. J Hepatol 2023; 79: 1110-1120.
55. Food and Drug Administration. Obeticholic acid briefing materials Gastrointestinal Drugs Advisory Committee May 19, 2023. Available at: https://www.fda.gov/media/168327/download. Accessed October 16, 2026.
56. Intercept Pharmaceuticals. REVERSE phase 3 study of obeticholic acid in compensated cirrhosis due to NASH did not meet its primary endpoint. 2022. Available at: https://www.biospace.com/ceuticals-announces-reverse-phase-3-study-of-obeticholic-acid-oca-in-compensated-cirrhosis-due-to-nash-did-not-meet-its-primary-endpoint. Accessed October 16, 2026.
57. Pencek R, Marmon T, Roth JD, Liberman A, Hooshmand-Rad R, Young MA. Effects of obeticholic acid on lipoprotein metabolism in healthy volunteers. Diabetes Obes Metab 2016; 18: 936-940.
58. Siddiqui MS, Van Natta ML, Connelly MA, Vuppalanchi R, Neuschwander-Tetri BA, Tonascia J, Guy C, Loomba R, Dasarathy S, Wattacheril J, Chalasani N, Sanyal AJ, NASH CRN. Impact of obeticholic acid on the lipoprotein profile in patients with non-alcoholic steatohepatitis. J Hepatol 2020; 72: 25-33.
59. Kim C, Tsai TH, Lopez R, McCullough A, Kasumov T. Obeticholic acid's effect on HDL function in MASH varies by diabetic status. Lipids 2024; 59: 221-231.
60. Alemi F, Kwon E, Poole DP, Lieu T, Lyo V, Cattaruzza F, Cevikbas F, Steinhoff M, Nassini R, Materazzi S, Guerrero-Alba R, Valdez-Morales E, Cottrell GS, Schoonjans K, Geppetti P, Vanner SJ, Bunnett NW, Corvera CU. The TGR5 receptor mediates bile acid-induced itch and analgesia. J Clin Invest 2013; 123: 1513-1530.
61. Yu H, Zhao T, Liu S, Wu Q, Johnson O, Wu Z, Zhuang Z, Shi Y, Peng L, He R, Yang Y, Sun J, Wang X, Xu H, Zeng Z, Zou P, Lei X, Luo W, Li Y. MRGPRX4 is a bile acid receptor for human cholestatic itch. Elife 2019; 8: e48431.
62. Yang J, Zhao T, Fan J, Zou H, Lan G, Guo F, Shi Y, Ke H, Yu H, Yue Z, Wang X, Bai Y, Li S, Liu Y, Wang X, Chen Y, Li Y, Lei X. Structure-guided discovery of bile acid derivatives for treating liver diseases without causing itch. Cell 2024; 187: 7164-7182.e18.
63. Yang J, Shen R, Wang C, Zhu W, Ke H, Fan J, Zhang M, Liu Y, Li S, Li G, Wang X, Li Y, Cao C, Lei X. Development of a clinically viable MRGPRX4 inverse agonist for cholestatic itch treatment. Nat Chem Biol 2026; 22: 1599-1609.
64. Levy C, Manns M, Hirschfield G. New Treatment Paradigms in Primary Biliary Cholangitis. Clin Gastroenterol Hepatol 2023; 21: 2076-2087.
65. Xu J, Wang Y, Khoshdeli M, Peach M, Chuang JC, Lin J, Tsai WW, Mahadevan S, Minto W, Diehl L, Gupta R, Trauner M, Patel K, Noureddin M, Kowdley KV, Gulamhusein A, Bowlus CL, Huss RS, Myers RP, Chung C, Billin AN. IL-31 levels correlate with pruritus in patients with cholestatic and metabolic liver diseases and is farnesoid X receptor responsive in NASH. Hepatology 2023; 77: 20-32.
66. Hirschfield GM, Bowlus CL, Jones DEJ, Kremer AE, Mayo MJ, Tanaka A, Andreone P, Jia J, Jin Q, Macías-Rodríguez RU, Cobitz AR, Currie BM, Gorey C, Lazic I, Podmore D, Ribeiro A, Shannon JB, Swift B, McLaughlin MM, Levy C, GLISTEN Study Group. Linerixibat in patients with primary biliary cholangitis and cholestatic pruritus (GLISTEN): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2026; 11: 22-33.

67. European Medicines Agency. Lyvdelzi European public assessment report. 2025. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/lyvdelzi. Accessed October 16, 2026.
68. Fiorucci S, Marchianò S, Urbani G, Di Giorgio C, Distrutti E, Zampella A, Biagioli M. Immunology of bile acids regulated receptors. Prog Lipid Res 2024; 95: 101291.
69. Gadaleta RM, Moschetta A. Metabolic Messengers: fibroblast growth factor 15/19. Nat Metab 2019; 1: 588-594.
70. Marchianò S, Biagioli M, Bordoni M, Morretta E, Di Giorgio C, Vellecco V, Roselli R, Bellini R, Massa C, Cari L, Urbani G, Ricci P, Monti MC, Giordano A, Brancaleone V, Bucci M, Zampella A, Distrutti E, Cieri E, Cirino G, Fiorucci S. Defective Bile Acid Signaling Promotes Vascular Dysfunction, Supporting a Role for G-Protein Bile Acid Receptor 1/Farnesoid X Receptor Agonism and Statins in the Treatment of Nonalcoholic Fatty Liver Disease. J Am Heart Assoc 2023; 12: e031241.
71. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024; 81: 492-542.
72. Food and Drug Administration. Serious liver injury being observed in patients without cirrhosis taking Ocaliva to treat primary biliary cholangitis. 2024. Available at: https://www.fda.gov/drugs/drug-safety-communications/serious-liver-injury-being-observed-patients-without-cirrhosis-taking-ocaliva-obeticholic-acid-treat. Accessed October 16, 2026.
73. Renga B, Migliorati M, Mencarelli A, Cipriani S, D'Amore C, Distrutti E, Fiorucci S. Farnesoid X receptor suppresses constitutive androstane receptor activity at the multidrug resistance protein-4 promoter. Biochim Biophys Acta 2011; 1809: 157-165.
74. Carino A, Biagioli M, Marchianò S, Fiorucci C, Bordoni M, Roselli R, Di Giorgio C, Baldoni M, Ricci P, Monti MC, Morretta E, Zampella A, Distrutti E, Fiorucci S. Opposite effects of the FXR agonist obeticholic acid on Mafg and Nrf2 mediate the development of acute liver injury in rodent models of cholestasis. Biochim Biophys Acta Mol Cell Biol Lipids 2020; 1865: 158733.
75. European Medicines Agency. Ocaliva referral. 2024. Available at: https://www.ema.europa.eu/en/medicines/human/referrals/ocaliva. Accessed October 16, 2026.
76. General Court of the European Union. Judgment of the General Court of 23 September 2026, Advanz Pharma Ltd v European Commission, Case T-455/24, ECLI:EU:T:2026:585. 2026. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:62024TJ0455_EXT. Accessed October 16, 2026.
77. Food and Drug Administration. Intercept Pharmaceuticals Inc et al Withdrawal of approval of new drug application for Ocaliva. 2025. Available at: https://www.federalregister.gov/documents/2025/11/24/2025-20767/intercept-pharmaceuticals-inc-et-al-withdrawal-of-approval-of-new-drug-application-for-ocaliva. Accessed October 16, 2026.
78. Health Canada. Ocaliva Drug Product Database current product information. 2026. Available at: https://health-products.canada.ca/dpd-bdpp/info.do?code=95104&lang=en. Accessed October 16, 2026.
79. Healthdirect Australia. Ocaliva medicines information. 2026. Available at: https://www.healthdirect.gov.au/medicines/brand/amt,1243381000168108/ocaliva. Accessed October 16, 2026.
80. PBC Foundation. Obeticholic acid information and regulatory updates. 2026. Available at: https://www.pbc-foundation.international/obeticholic-acid/. Accessed October 16, 2026.
81. Swissmedic. Ocaliva clinical benefit not confirmed revocation of authorization. 2025. Available at: https://www.swissmedic.ch/swissmedic/it/home/medicamenti-per-uso-umano/sorveglianza-del-mercato/health-professional-communication--hpc-/hpc-ocaliva-obeticholsaeure.html. Accessed October 16, 2026.
82. Kowdley KV, Bowlus CL, Levy C, Akarca US, Alvares-da-Silva MR, Andreone P, Arrese M, Corpechot C, Francque SM, Heneghan MA, Invernizzi P, Jones D, Kruger FC, Lawitz E, Mayo MJ, Shiffman ML, Swain MG, Valera JM, Vargas V, Vierling JM, Villamil A, Addy C, Dietrich J, Germain JM, Mazain S, Rafailovic D, Taddé B, Miller B, Shu J, Zein CO, Schattenberg JM, ELATIVE Study Investigators' Group. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. N Engl J Med 2024; 390: 795-805.
83. Hirschfield GM, Bowlus CL, Mayo MJ, Kremer AE, Vierling JM, Kowdley KV, Levy C, Villamil A, Ladrón de Guevara Cetina AL, Janczewska E, Zigmond E, Jeong SH, Yilmaz Y, Kallis Y, Corpechot C, Buggisch P, Invernizzi P, Londoño Hurtado MC, Bergheanu S, Yang K, Choi YJ, Crittenden DB, McWherter CA, RESPONSE Study Group. A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis. N Engl J Med 2024; 390: 783-794.
84. European Medicines Agency. Iqirvo European public assessment report. 2024. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/iqirvo. Accessed October 16, 2026.
85. Pai RK, Jairath V, Hogan M, Zou G, Adeyi OA, Anstee QM, Aqel BA, Behling C, Carey EJ, Clouston AD, Corey K, Feagan BG, Kleiner DE, Ma C, McFarlane SC, Noureddin M, Ratziu V, Valasek MA, Younossi ZM, Harrison SA, Loomba R. Reliability of histologic assessment for NAFLD and development of an expanded NAFLD activity score. Hepatology 2022; 76: 1150-1163.
86. Anstee QM, Neuschwander-Tetri BA, Wai-Sun Wong V, Abdelmalek MF, Rodriguez-Araujo G, Landgren H, Park GS, Bedossa P, Alkhouri N, Tacke F, Sanyal AJ. Cenicriviroc Lacked Efficacy to Treat Liver Fibrosis in Nonalcoholic Steatohepatitis: AURORA Phase III Randomized Study. Clin Gastroenterol Hepatol 2024; 22: 124-134. e1.
87. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, Labriola D, Moussa SE, Neff GW, Rinella ME, Anstee QM, Abdelmalek MF, Younossi Z, Baum SJ, Francque S, Charlton MR, Newsome PN, Lanthier N, Schiefke I, Mangia A, Pericàs JM, Patil R, Sanyal AJ, Noureddin M, Bansal MB, Alkhouri N, Castera L, Rudraraju M, Ratziu V, MAESTRO-NASH Investigators. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med 2024; 390: 497-509.
88. Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, Cali AMG, Bugianesi E, Rinella ME, Roden M, Ratziu V, ESSENCE Study Group. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med 2025; 392: 2089-2099.
89. Loomba R, Sanyal AJ, Kowdley KV, Bhatt DL, Alkhouri N, Frias JP, Bedossa P, Harrison SA, Lazas D, Barish R, Gottwald MD, Feng S, Agollah GD, Hartsfield CL, Mansbach H, Margalit M, Abdelmalek MF. Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH. N Engl J Med 2023; 389: 998-1008.

90. Noureddin M, Frias JP, Neff GW, Lucas KJ, Behling C, Bedossa P, Dubourg J, Chan D, Burch M, Fong E, de Temple B, Minerva M, Barrett K, Shringarpure R, Tillman EJ, Rolph T, Cheng A, Yale K. Safety and efficacy of once-weekly efruxifermin versus placebo in metabolic dysfunction-associated steatohepatitis (HARMONY): 96-week results from a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. Lancet 2025; 406: 719-730.
91. Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, Loomba R, Harrison SA, Balabanska R, Mateva L, Lanthier N, Alkhouri N, Moreno C, Schattenberg JM, Stefanova-Petrova D, Vonghia L, Rouzier R, Guillaume M, Hodge A, Romero-Gómez M, Huot-Marchand P, Baudin M, Richard MP, Abitbol JL, Broqua P, Junien JL, Abdelmalek MF, NATIVE Study Group. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. N Engl J Med 2021; 385: 1547-1558.
92. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, Yoneda M, Behling C, Cummings OW, Tang Y, Brouwers B, Robins DA, Nikooie A, Bunck MC, Haupt A, Sanyal AJ, SYNERGY-NASH Investigators. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. N Engl J Med 2024; 391: 299-310.
93. Younossi ZM, Stepanova M, Nader F, Loomba R, Anstee QM, Ratziu V, Harrison S, Sanyal AJ, Schattenberg JM, Barritt AS, Noureddin M, Bonacci M, Cawkwell G, Wong B, Rinella M, RandomizEd Global Phase 3 Study to Evaluate the Impact on NASH with FibRosis of Obeticholic Acid TreatmEnt (REGENERATE) Study Investigators. Obeticholic Acid Impact on Quality of Life in Patients With Nonalcoholic Steatohepatitis: REGENERATE 18-Month Interim Analysis. Clin Gastroenterol Hepatol 2022; 20: 2050-2058.e12.
94. Anstee QM, Castera L, Loomba R. Impact of non-invasive biomarkers on hepatology practice: Past, present and future. J Hepatol 2022; 76: 1362-1378.
95. Castera L, Rinella ME, Tsochatzis EA. Noninvasive Assessment of Liver Fibrosis. N Engl J Med 2025; 393: 1715-1729.
96. Lazarus JV, Castera L, Mark HE, Allen AM, Adams LA, Anstee QM, Arrese M, Alqahtani SA, Bugianesi E, Colombo M, Cusi K, Hagström H, Loomba R, Romero-Gómez M, Schattenberg JM, Thiele M, Valenti L, Wong VW, Yilmaz Y, Younossi ZM, Francque SM, Tsochatzis EA. Real-world evidence on non-invasive tests and associated cut-offs used to assess fibrosis in routine clinical practice. JHEP Rep 2023; 5: 100596.
97. Trauner M, Gulamhusein A, Hameed B, Caldwell S, Shiffman ML, Landis C, Eksteen B, Agarwal K, Muir A, Rushbrook S, Lu X, Xu J, Chuang JC, Billin AN, Li G, Chung C, Subramanian GM, Myers RP, Bowlus CL, Kowdley KV. The Nonsteroidal Farnesoid X Receptor Agonist Cilofexor (GS-9674) Improves Markers of Cholestasis and Liver Injury in Patients With Primary Sclerosing Cholangitis. Hepatology 2019; 70: 788-801.
98. Hernandez ED, Zheng L, Kim Y, Fang B, Liu B, Valdez RA, Dietrich WF, Rucker PV, Chianelli D, Schmeits J, Bao D, Zoll J, Dubois C, Federe GC, Chen L, Joseph SB, Klickstein LB, Walker J, Molteni V, McNamara P, Meeusen S, Tully DC, Badman MK, Xu J, Laffitte B. Tropifexor-Mediated Abrogation of Steatohepatitis and Fibrosis Is Associated With the Antioxidative Gene Expression Profile in Rodents. Hepatol Commun 2019; 3: 1085-1097.
99. Zang Y, Shi J, Zhao G, Tang B, Liu M, Yao B, Wang G, Pan H, Yang S, Deng R, Zhao Y, Zhang Z, Guo HR, Sun DD, Wang H, Gao L, Yu J, Diao X, Li Y, Li J, Xu HE. A first-in-class pulsatile FXR agonist for bile-acid-related liver diseases. Nature 2026; 655: 758-768.
100. National Library of Medicine. ClinicalTrials.gov study records for selected FXR agonists. 2026. Available at: https://clinicaltrials.gov/. Accessed October 16, 2026.
101. Fang S, Suh JM, Reilly SM, Yu E, Osborn O, Lackey D, Yoshihara E, Perino A, Jacinto S, Lukasheva Y, Atkins AR, Khvat A, Schnabl B, Yu RT, Brenner DA, Coulter S, Liddle C, Schoonjans K, Olefsky JM, Saltiel AR, Downes M, Evans RM. Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. Nat Med 2015; 21: 159-165.
102. Bhushan S, Sohal A, Kowdley KV. Primary Biliary Cholangitis and Primary Sclerosing Cholangitis Therapy Landscape. Am J Gastroenterol 2025; 120: 151-158.
103. Reig A, Álvarez-Navascués C, Vergara M, Gómez-Domínguez E, Gallego-Moya A, Pérez-Medrano IM, Fábrega E, Hernández-Guerra M, Berenguer M, Estevez P, Arencibia A, Morillas RM, Horta D, Albillos A, Casado M, De la Cruz G, Fernandez-Bonilla E, Molina E, Hijona L, Diago M, Fernández-Rodriguez CM, González-Santiago JM, Sala M, Gómez-Camarero J, Romero-Gomez M, Suárez F, Vargas V, Ferre-Aracil C, Andrade RJ, Chahri N, Parés A. Obeticholic Acid and Fibrates in Primary Biliary Cholangitis: Comparative Effects in a Multicentric Observational Study. Am J Gastroenterol 2021; 116: 2250-2257.
104. Alkhouri N, Herring R, Kabler H, Kayali Z, Hassanein T, Kohli A, Huss RS, Zhu Y, Billin AN, Damgaard LH, Buchholtz K, Kjær MS, Balendran C, Myers RP, Loomba R, Noureddin M. Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: A randomised, open-label phase II trial. J Hepatol 2022; 77: 607-618.