

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pegozafermin

A long-acting glycoPEGylated analog of fibroblast growth factor 21 engineered to recapitulate the endocrine metabolic activity of native FGF21, developed by 89bio for the treatment of metabolic dysfunction-associated steatohepatitis and severe hypertriglyceridemia.

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ABSTRACT

Pegozafermin (BIO89-100) is a glycoPEGylated recombinant analog of human fibroblast growth factor 21 (FGF21), a hepatokine central to the regulation of lipid metabolism, glucose homeostasis, and energy expenditure. The compound was engineered using site-specific glycosylation and PEGylation to extend the circulating half-life from approximately 0.5 to 2 hours (native FGF21) to 55 to 100 hours, enabling once-weekly or once-every-two-week subcutaneous administration while preserving the receptor binding profile of the native hormone. Pegozafermin signals through the FGF receptor 1c (FGFR1c) and FGF receptor 3c in complex with the obligate coreceptor beta-klotho (KLB), activating the extracellular signal-regulated kinase 1/2 (ERK1/2) cascade and downstream transcription factors that govern hepatic de novo lipogenesis, adipose tissue adiponectin secretion, fatty acid oxidation, and insulin sensitivity. The compound was originally developed by Teva Pharmaceutical Industries and subsequently licensed to 89bio, Inc. in 2019 for global development (excluding Israel).

In the Phase 2b ENLIVEN trial (Loomba et al., 2023, New England Journal of Medicine), 222 patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) and stage F2 or F3 fibrosis were randomized to pegozafermin 15 mg weekly, 30 mg weekly, 44 mg every two weeks, or placebo for 24 weeks. The co-primary histological endpoints were met at both the 30 mg weekly and 44 mg every-two-week doses: fibrosis improvement of at least one stage without worsening of steatohepatitis was achieved in 26 percent and 27 percent of treated patients, respectively, compared

with 7 percent on placebo. NASH resolution without fibrosis worsening was achieved in 23 percent and 26 percent, respectively, compared with 2 percent on placebo. Hepatic fat fraction measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF) decreased by 48.2 percent (30 mg weekly) and 41.9 percent (44 mg every two weeks) versus 5.0 percent on placebo. Alanine aminotransferase levels normalized in 59 to 65 percent of treated patients versus 24 percent on placebo, and the fibrosis biomarker PRO-C3 decreased by 17 to 18 percent versus a 6.4 percent increase on placebo.

In the Phase 2 ENTRIGUE trial in severe hypertriglyceridemia (Bhatt et al., 2023, Nature Medicine), pegozafermin at doses of 9 to 27 mg weekly or 36 mg every two weeks produced a pooled median triglyceride reduction of 57.3 percent versus 11.9 percent on placebo, with 79.7 percent of treated patients achieving triglycerides below 500 mg/dL compared with 29.4 percent on placebo. Secondary lipid endpoints included reductions in non-HDL cholesterol (18.3 percent), apolipoprotein B (10.5 percent), apolipoprotein C3 (41.9 percent), and increases in HDL cholesterol of up to 44.5 percent at the 27 mg weekly dose.

Safety across both trials was characterized by mild-to-moderate gastrointestinal adverse events (nausea, diarrhea) and injection site reactions. No hepatotoxicity, drug-induced liver injury, or clinically significant bone density changes were observed. One treatment-related serious adverse event (acute pancreatitis in a patient with gallbladder sludge) was reported in the ENLIVEN trial.

Pegozafermin received Breakthrough Therapy designation from the United States Food and Drug Administration and Priority Medicines (PRIME) designation from the European Medicines

Agency for the treatment of MASH with fibrosis in September 2023. The compound is currently in Phase 3 development in the ENLIGHTEN program (MASH with fibrosis and compensated cirrhosis) and the ENTRUST program (severe hypertriglyceridemia). This monograph reviews the compound identification, discovery and development history, molecular pharmacology of the FGF21 signaling axis, pharmacokinetics, preclinical pharmacology, clinical evidence base, sourcing and quality verification, reconstitution and handling, stack interactions and combinations, adverse events and safety signal, and a comparative assessment of five alternative metabolic liver disease candidates against pegozafermin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Pegzofermin (recommended INN; WHO).

Development codes: BIO89-100 (89bio). The compound was originally developed at Teva Pharmaceutical Industries under internal designations prior to the 2019 license to 89bio. The BIO89-100 code is the canonical identifier in the Phase 1b/2a, ENLIVEN, and ENTRIGUE clinical trial publications [1, 2, 3].

Chemical Abstracts Service registry number: 2410938-04-0 (pegzofermin). The CAS registry number refers to the glycoPEGylated protein conjugate.

UNII (Unique Ingredient Identifier): Assigned by the FDA Substance Registration System for regulatory tracking.

DrugBank identifier: DB19062.

1.2 Structural class and chemistry

Pegzofermin is a recombinant protein analog of human fibroblast growth factor 21 (FGF21), a 181-amino-acid endocrine hormone of the FGF19 subfamily (FGF15/19, FGF21, FGF23). Native FGF21 is encoded by the FGF21 gene on chromosome 19 and is secreted primarily by hepatocytes in response to metabolic stress, fasting, peroxisome proliferator-activated receptor alpha (PPARalpha) activation, and endoplasmic reticulum stress.

The pegzofermin molecule consists of a modified human FGF21 polypeptide backbone bearing site-specific mutations engineered to facilitate conjugation, coupled to a polyethylene glycol (PEG) moiety through a glycosylation-mediated linkage (glycoPEGylation). The glycoPEGylation technology employs enzymatic glycosyltransferases to attach PEG chains at defined glycosylation sites on the protein backbone, producing a homogeneous, site-specific conjugate rather than the heterogeneous mixture that results from conventional amine-reactive PEGylation chemistry. This approach preserves the tertiary structure of the FGF21 protein and its receptor binding interface while substantially increasing the hydrodynamic radius and reducing renal clearance.

Molecular weight: The total molecular weight of the pegozafermin conjugate (protein plus PEG) has not been publicly disclosed at precise analytical resolution. The FGF21 protein component is approximately 19.5 kDa; the PEG moiety contributes additional mass depending on the PEG chain length employed in the glycoPEGylation process. The conjugate molecular weight is estimated in the range of 40 to 60 kDa based on pharmacokinetic behavior and size-exclusion chromatographic properties reported in the population pharmacokinetic analysis [4].

Physical properties: Pegozafermin is supplied as a sterile, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. The formulation is maintained in a buffered aqueous solution at controlled pH for protein stability.

Structural distinction from other FGF21 analogs: Pegozafermin is distinguished from pegbelfermin (BMS-986036, a conventional PEGylated FGF21 analog developed by Bristol-Myers Squibb) by the site-specific glycoPEGylation technology. Pegbelfermin employs a non-specific PEGylation chemistry that produces a more heterogeneous conjugate population, which may contribute to reduced receptor binding efficiency and the mixed clinical results observed in the FALCON Phase 2b trials. Pegozafermin is also structurally distinct from efruxifermin (AKR-001, Akero Therapeutics), which is a bivalent Fc-FGF21 fusion protein composed of two FGF21 chains covalently linked to a human immunoglobulin G1 Fc domain, producing a dimeric construct with enhanced receptor binding avidity.

1.3 Synthesis and manufacture

Pegozafermin is produced by recombinant expression of the modified human FGF21 polypeptide in a microbial or mammalian expression system, followed by purification, enzymatic glycoPEGylation using glycosyltransferase-mediated conjugation, and final purification to produce the drug substance. The manufacturing process is proprietary to 89bio. The drug product is formulated as a sterile solution in prefilled syringes or vials for subcutaneous injection.

The glycoPEGylation step is the critical manufacturing innovation. Glycosyltransferase enzymes (typically sialyltransferases or galactosyltransferases) catalyze the attachment of PEG-modified sugar nucleotide donors to specific acceptor sites on the protein backbone, producing a defined conjugate with predictable stoichiometry and site specificity. This enzymatic approach avoids the heterogene-

ity of chemical PEGylation and is the basis of the extended half-life and preserved biological activity of pegozafermin relative to native FGF21 and to conventionally PEGylated analogs.

2. Abstract

Pegozafermin (BIO89-100) is a glycoPEGylated recombinant analog of human fibroblast growth factor 21 (FGF21) engineered for extended circulating half-life and preserved receptor binding, under development by 89bio, Inc. for the treatment of metabolic dysfunction-associated steatohepatitis (MASH, formerly nonalcoholic steatohepatitis or NASH) and severe hypertriglyceridemia (SHTG) [1, 2, 3]. The compound signals through the canonical FGF21 receptor complex consisting of FGF receptor 1c (FGFR1c) and the obligate transmembrane coreceptor beta-klotho (KLB), activating ERK1/2 signaling cascades that regulate hepatic lipid metabolism, adipose tissue adiponectin secretion, insulin sensitivity, and energy expenditure.

The principal clinical evidence base comprises two completed Phase 2 programs. In the ENLIVEN Phase 2b trial (Loomba et al., 2023), pegozafermin at 30 mg weekly and 44 mg every two weeks met both co-primary histological endpoints in patients with biopsy-confirmed NASH and F2 or F3 fibrosis over 24 weeks of treatment [2]. Fibrosis improvement of at least one stage without worsening of steatohepatitis was achieved in 26 to 27 percent of treated patients versus 7 percent on placebo; NASH resolution without fibrosis worsening was achieved in 23 to 26 percent versus 2 percent on placebo. In the ENTRIGUE Phase 2 trial (Bhatt et al., 2023), pegozafermin produced a 57.3 percent median reduction in triglycerides versus 11.9 percent on placebo in patients with severe hypertriglyceridemia [3].

The compound is currently in Phase 3 development: the ENLIGHTEN program comprises two global trials (ENLIGHTEN-Fibrosis and ENLIGHTEN-Cirrhosis) in MASH patients with F2-F3 fibrosis and compensated cirrhosis, respectively, with co-primary endpoints of fibrosis improvement and MASH resolution at 52 weeks [5, 6]. The ENTRUST Phase 3 trial evaluates pegozafermin in approximately 360 patients with severe hypertriglyceridemia [7]. Pegozafermin received Breakthrough Therapy designation from the FDA and PRIME designation from the EMA in 2023.

The safety profile across completed trials is characterized by mild-to-moderate gastrointestinal adverse events (nausea in up to 32 percent, diarrhea in up to 24 percent) and injection site reactions (up to 15 percent), with no hepatotoxicity, drug-induced liver injury, or clinically significant metabolic safety signals. The compound

is not yet approved by any regulatory authority. This monograph reviews the complete pharmacology, pharmacokinetics, clinical evidence, and comparative positioning of pegozafermin within the emerging MASH therapeutic landscape.

3. Discovery and Development History

3.1 Origin of FGF21 as a therapeutic target

Fibroblast growth factor 21 was identified as a metabolic regulator by Kharitonov et al. (2005), who demonstrated that administration of recombinant FGF21 to ob/ob and db/db mice reduced plasma glucose, triglycerides, and insulin levels without inducing hypoglycemia or mitogenic effects [8]. These findings established FGF21 as an endocrine member of the FGF superfamily with distinctive metabolic activity, distinct from the paracrine and autocrine FGFs involved in growth and development. Subsequent studies demonstrated that FGF21 promotes fatty acid oxidation, increases adiponectin secretion, improves insulin sensitivity, and reduces hepatic steatosis in multiple rodent models of metabolic disease [9, 10].

The therapeutic potential of FGF21 was limited by the short circulating half-life of the native hormone (approximately 0.5 to 2 hours in humans), which necessitated continuous infusion or very frequent dosing for pharmacological effect. Multiple pharmaceutical programs addressed this limitation through protein engineering, PEGylation, Fc fusion, and other half-life extension technologies.

3.2 Development at Teva and licensing to 89bio

Pegozafermin was originally developed at Teva Pharmaceutical Industries using a proprietary glycoPEGylation technology to extend FGF21 half-life while preserving receptor binding activity. The glycoPEGylation approach, which employs enzymatic glycosyltransferase-mediated conjugation of PEG to specific glycosylation sites on the modified FGF21 polypeptide, was selected to avoid the heterogeneity and potential loss of biological activity associated with conventional chemical PEGylation.

89bio, Inc. was incorporated in January 2018 as a clinical-stage biopharmaceutical company focused on metabolic and liver diseases. In 2019, 89bio entered into a license agreement with Teva acquiring exclusive worldwide rights (excluding Israel) to develop, manufacture, and commercialize the compound, designated

BIO89-100 [11]. 89bio subsequently conducted a Phase 1 healthy volunteer study and initiated the clinical development program that produced the Phase 1b/2a, ENLIVEN, and ENTRIGUE trials.

3.3 Phase 1 and Phase 1b/2a development

The Phase 1 single-ascending-dose study in 58 healthy volunteers demonstrated dose-proportional pharmacokinetics, a half-life of 55 to 100 hours supporting weekly or biweekly dosing, and pharmacodynamic activity including triglyceride reductions of up to 51 percent, LDL cholesterol reductions of up to 37 percent, and HDL cholesterol increases of up to 36 percent after a single dose [1, 12].

The Phase 1b/2a multiple-ascending-dose study (Loomba et al., 2022, Lancet Gastroenterology and Hepatology) enrolled 101 participants with biopsy-confirmed NASH or NAFLD at high risk of NASH and randomized them to pegozafermin at weekly or every-two-week subcutaneous doses or placebo for 12 weeks [1]. Significant absolute reductions in hepatic fat fraction by MRI-PDFF were observed at week 13 in the pegozafermin groups compared with an increase in the placebo group. ALT improvements of approximately 35 U/L from baseline and decreased PRO-C3 fibrosis biomarker levels were reported.

3.4 Phase 2b and Phase 2 pivotal trials

The ENLIVEN Phase 2b trial (Loomba et al., 2023, published in the New England Journal of Medicine) enrolled 222 patients with biopsy-confirmed NASH and F2 or F3 fibrosis at 61 United States sites [2]. The trial met both co-primary histological endpoints at the 30 mg weekly and 44 mg every-two-week doses and provided the basis for advancement to Phase 3 development.

The ENTRIGUE Phase 2 trial (Bhatt et al., 2023, published in Nature Medicine) enrolled 85 patients with severe hypertriglyceridemia (baseline triglycerides 500 to 2000 mg/dL) at 50 sites across the United States and Europe [3]. The trial met its primary endpoint of triglyceride reduction, with the pooled pegozafermin group achieving a 57.3 percent reduction versus 11.9 percent on placebo.

3.5 Regulatory designations and Phase 3 advancement

In September 2023, the FDA granted Breakthrough Therapy designation and the EMA granted PRIME designation for pegozafermin for the treatment of MASH with liver fibrosis, based on the ENLIVEN Phase 2b results [13]. 89bio reached alignment with both the FDA and EMA on the Phase 3 program design.

The Phase 3 ENLIGHTEN-Fibrosis trial was initiated in the first half of 2024, with a target enrollment of approximately 1,000 patients with non-cirrhotic MASH (F2-F3 fibrosis) randomized 1:1:1 to 30 mg weekly, 44 mg every two weeks, or placebo, with co-primary endpoints at week 52 [5]. The ENLIGHTEN-Cirrhosis trial enrolls MASH patients with compensated cirrhosis (F4) [6]. The ENTRUST Phase 3 trial in severe hypertriglyceridemia randomizes approximately 360 patients to pegozafermin 20 mg weekly, 30 mg weekly, or placebo [7]. Primary enrollment in the ENLIGHTEN-MASH cohort was completed by mid-2025. Topline results from the Phase 3 programs are anticipated in 2026 and 2027.

3.6 Partnership with Genentech

89bio entered into a licensing and collaboration agreement with Genentech (a member of the Roche Group), expanding the development and commercialization resources available for the pegozafermin program. The partnership reflects the strategic importance of the MASH indication and the competitive positioning of pegozafermin within the FGF21 analog class.

4. Molecular Pharmacology

4.1 FGF21 signaling pathway

FGF21 is an endocrine member of the FGF19 subfamily of fibroblast growth factors. Unlike the paracrine FGFs (FGF1 through FGF10), the endocrine FGFs (FGF15/19, FGF21, FGF23) have reduced heparan sulfate binding affinity and circulate as hormones, with tissue specificity determined by the expression pattern of the Klotho family of coreceptors [8, 9].

FGF21 signals through a binary receptor complex consisting of an FGF receptor tyrosine kinase (FGFR1c in adipose tissue, FGFR1c and FGFR3c in liver) and the obligate transmembrane coreceptor beta-klotho (KLB) [14]. Beta-klotho is a single-pass transmembrane protein expressed predominantly in liver, adipose tissue (white and brown), and pancreas; its restricted expression pattern is the principal determinant of FGF21 tissue selectivity. In the absence of beta-klotho, FGF21 does not bind FGFR1c at physiologically relevant concentrations, and no signaling occurs.

The binding sequence proceeds in two steps: FGF21 first engages the D3 domain of FGFR1c through its N-terminal region, then the C-terminal tail of FGF21 interacts with the extracellular domain of beta-klotho, stabilizing a ternary complex that promotes FGFR dimerization and trans-autophosphorylation [14, 15]. The activated FGFR phosphorylates FGF receptor substrate 2 (FRS2), which recruits the GRB2-SOS complex and activates the RAS-RAF-MEK-ERK1/2 mitogen-activated protein kinase cascade. ERK1/2 phosphorylation is the canonical readout of FGF21 signaling in vitro and in vivo.

4.2 Downstream metabolic effects

The metabolic consequences of FGF21-FGFR1c-beta-klotho signaling are tissue-specific and collectively produce the metabolic phenotype observed in preclinical models and in the clinical trials of pegozafermin.

Liver: FGF21 signaling reduces hepatic de novo lipogenesis through suppression of the sterol regulatory element-binding protein 1c (SREBP-1c) pathway. It enhances fatty acid beta-oxidation through upregulation of PPARalpha target genes. It reduces very-low-density lipoprotein (VLDL) secretion and hepatic triglyceride accumulation. The net hepatic effect is reduced steatosis, which is the proximal driver of the MRI-PDFF reductions observed in clinical trials (up to 48 percent reduction at 30 mg weekly in ENLIVEN) [2, 16].

Adipose tissue: FGF21 is a potent inducer of adiponectin secretion from white adipose tissue. Adiponectin is an insulin-sensitizing, anti-inflammatory, and anti-fibrotic adipokine that amplifies the hepatic effects of FGF21 through activation of PPARalpha and AMP-activated protein kinase (AMPK) in the liver. In the ENLIVEN trial, adiponectin levels increased by approximately 30 percent in the 30 mg weekly group [2]. FGF21 also promotes browning of white adipose tissue and thermogenesis in brown adipose tissue through upregulation of uncoupling protein 1 (UCP1) [9, 17].

Pancreas: FGF21 exerts anti-apoptotic and anti-inflammatory effects on pancreatic beta cells, reducing endoplasmic reticulum stress and preserving beta-cell function. These effects contribute to the insulin-sensitizing phenotype observed in clinical trials [16].

Skeletal muscle: FGF21 promotes fatty acid oxidation and glucose uptake in skeletal muscle, contributing to improved whole-body insulin sensitivity.

4.3 Anti-fibrotic mechanism

The improvement in hepatic fibrosis observed with pegozafermin treatment is likely mediated through both direct and indirect mechanisms. The reduction in hepatic steatosis and steatohepatitis removes the proximal inflammatory stimulus for hepatic stellate cell activation and collagenous matrix deposition. Adiponectin, induced by FGF21 signaling, has direct anti-fibrotic activity through suppression of transforming growth factor beta (TGF-beta) signaling in hepatic stellate cells and through promotion of matrix metalloproteinase-mediated collagen degradation [18]. The decrease in the fibrosis biomarker PRO-C3 (a neoepitope of type III collagen formation) by 17 to 18 percent in the ENLIVEN trial supports active fibrosis regression rather than mere stabilization [2].

4.4 Effects on lipid metabolism

The triglyceride-lowering activity of pegozafermin in severe hypertriglyceridemia operates through multiple lipid-metabolic pathways. FGF21 reduces hepatic VLDL-triglyceride secretion, enhances lipoprotein lipase-mediated peripheral triglyceride clearance, and reduces apolipoprotein C3 levels (a potent inhibitor of lipoprotein lipase). In the ENTRIGUE trial, apolipoprotein C3 was reduced by 41.9 percent in the pooled pegozafermin group, and apolipoprotein B48 (a marker of chylomicron particles) was reduced by 73 percent at the 27 mg weekly dose, indicating enhanced chylomicron clearance [3]. The HDL cholesterol increase (up to 44.5 percent at 27 mg weekly) reflects improved reverse cholesterol transport and is consistent with the adiponectin-mediated metabolic profile.

4.5 Pegozafermin versus native FGF21

Pegozafermin recapitulates the receptor binding profile and downstream signaling of native FGF21 while substantially extending the pharmacokinetic half-life through the glycoPEG moiety. The glycoPEGylation does not occlude the FGFR1c or beta-klotho binding interfaces, as the PEG attachment site is remote from the receptor-interacting regions of the FGF21 polypeptide. The extended half-life (55 to 100 hours versus 0.5 to 2 hours for native FGF21) enables sustained receptor engagement and continuous metabolic signaling between weekly or biweekly doses, producing pharmacodynamic effects that exceed what transient exposure to native FGF21 can achieve.

5. Pharmacokinetics

5.1 Absorption

Pegozafermin is administered by subcutaneous injection. Absorption from the subcutaneous depot is slow and sustained, consistent with the large hydrodynamic radius of the glycoPEGylated protein conjugate. Time to peak plasma concentration (Tmax) after subcutaneous injection is approximately 24 to 72 hours, depending on dose and injection site [4, 12].

Bioavailability after subcutaneous injection has not been publicly reported at precise analytical resolution but is estimated to be in the range typical of PEGylated protein therapeutics (approximately 50 to 80 percent).

5.2 Distribution

As a PEGylated protein with an estimated molecular weight of 40 to 60 kDa, pegozafermin distributes primarily in the plasma and extracellular fluid compartments. The volume of distribution is limited relative to small-molecule drugs, consistent with restricted tissue penetration of large-molecular-weight biologics. Distribution to the liver, adipose tissue, and other target organs expressing beta-klotho is mediated by receptor-dependent uptake.

5.3 Metabolism and elimination

Pegozafermin is metabolized by proteolytic degradation to peptide fragments and amino acids, the standard elimination pathway for protein therapeutics. The PEG moiety is excreted renally following proteolytic release from the protein backbone. The glycoPEGylation substantially reduces renal clearance of the intact conjugate by increasing the effective hydrodynamic radius above the glomerular filtration threshold, which is the principal mechanism of half-life extension.

Half-life: The terminal elimination half-life of pegozafermin is 55 to 100 hours (approximately 2.3 to 4.2 days), demonstrating dose-proportional pharmacokinetics across the clinical dose range [4, 12]. This half-life supports once-weekly or once-every-two-week dosing regimens.

Body weight effect: Population pharmacokinetic modeling indicates approximately 10 percent increase in drug clearance for every 10 kg increase in body weight, consistent with the volume of distribution scaling observed with other PEGylated protein therapeutics [4].

5.4 Dose proportionality

Pharmacokinetic exposure (area under the concentration-time curve and maximum plasma concentration) increases in a dose-proportional manner across the studied dose range (9 to 44 mg subcutaneous), supporting linear pharmacokinetics within the therapeutic range [4, 12].

5.5 Routes of administration

Pegozafermin is administered exclusively by subcutaneous injection. The clinical trial regimens employ prefilled syringes with injection into the abdomen, thigh, or upper arm. Weekly and every-two-week dosing schedules have been evaluated, with both regimens producing clinically meaningful pharmacodynamic effects in the ENLIVEN and ENTRIGUE trials [2, 3].

5.6 Special populations

Hepatic impairment: Population pharmacokinetic data from the ENLIVEN trial included patients with varying degrees of hepatic dysfunction (F2 and F3 fibrosis). No dose-limiting pharmacokinetic alterations attributable to hepatic impairment have been reported. The Phase 3 ENLIGHTEN-Cirrhosis trial will provide pharmacokinetic data in patients with compensated cirrhosis (F4).

Renal impairment: No formal renal impairment pharmacokinetic study has been reported. As a PEGylated protein therapeutic, pegozafermin clearance may be affected by severe renal impairment; however, the primary elimination pathway is proteolytic degradation rather than intact renal excretion.

Body mass index: Given the 10 percent clearance increase per 10 kg body weight, obese patients (who constitute a substantial proportion of the MASH population) may have modestly reduced drug exposure at a fixed dose. The clinical dosing regi-

mens in Phase 3 employ fixed doses (not weight-based), and the ENLIVEN trial enrolled a population with mean BMI of approximately 36 kg/m² without dose adjustment [2].

6. Preclinical Pharmacology

6.1 Rodent models of metabolic liver disease

Native FGF21 and FGF21 analogs, including pegozafermin, have been extensively characterized in rodent models of nonalcoholic fatty liver disease and steatohepatitis. Administration of FGF21 analogs to diet-induced obese mice, ob/ob mice, db/db mice, and methionine-choline-deficient diet-fed mice reduces hepatic steatosis, improves insulin sensitivity, decreases plasma triglycerides, and reduces hepatic inflammation and fibrosis [8, 9, 17].

The preclinical pharmacology of pegozafermin specifically has been reported in nonclinical regulatory filings supporting the IND application. Published data demonstrate that pegozafermin produces dose-dependent reductions in hepatic triglyceride content, plasma triglycerides, and plasma glucose in diet-induced obese mouse models, with pharmacodynamic effects persisting for 5 to 7 days after a single subcutaneous dose, consistent with the extended half-life [12].

6.2 Nonhuman primate pharmacology

FGF21 analogs have been studied in nonhuman primates (cynomolgus and rhesus macaques), demonstrating triglyceride reduction, improved insulin sensitivity, and increased adiponectin levels consistent with the rodent pharmacology. Pegozafermin-specific nonhuman primate pharmacology data have not been published in the peer-reviewed literature but are included in the regulatory submissions.

6.3 In vitro receptor pharmacology

Pegozafermin activates ERK1/2 phosphorylation in cell lines expressing FGFR1c and beta-klotho (the standard in vitro assay for FGF21 receptor activity) with potency comparable to native FGF21 [12]. The glycoPEGylation does not reduce receptor binding affinity or signaling efficacy in these assays, confirming that the PEG attachment site is remote from the receptor-interacting surfaces of the FGF21 polypeptide.

6.4 Safety pharmacology

Nonclinical safety pharmacology studies (cardiovascular, respiratory, central nervous system) have not revealed safety signals that would preclude clinical development. FGF21 is not mitogenic; unlike paracrine FGFs (FGF1, FGF2), it does not stimulate cell proliferation through FGFR-mediated signaling, and no neoplastic findings have been attributed to FGF21 administration in chronic rodent toxicology studies [8, 17]. This lack of mitogenicity is a distinguishing feature of the endocrine FGF subfamily and a favorable safety attribute for chronic metabolic disease therapy.

7. Clinical Evidence Base

7.1 Phase 1b/2a: NASH and NAFLD

The Phase 1b/2a multiple-ascending-dose trial (Loomba et al., 2022) was a randomized, double-blind, placebo-controlled study enrolling 101 participants with biopsy-confirmed NASH or NAFLD at high risk of NASH [1]. Participants received pegzofermin at multiple dose levels administered once weekly or once every two weeks by subcutaneous injection for 12 weeks. The primary endpoint was change in hepatic fat fraction measured by MRI-PDFF at week 13.

Significant absolute reductions in hepatic fat fraction were observed with pegzofermin compared with placebo. ALT reductions of approximately 35 U/L from baseline were reported, along with decreases in the fibrosis biomarker PRO-C3. Pegzofermin was generally well tolerated, with the most common treatment-related adverse event being mild increase in appetite, which was not associated with body weight gain.

7.2 Phase 2b ENLIVEN trial: NASH with fibrosis

The ENLIVEN trial (Loomba et al., 2023, New England Journal of Medicine) was a Phase 2b, randomized, double-blind, placebo-controlled trial conducted at 61 United States sites [2]. A total of 222 patients with biopsy-confirmed NASH and stage F2 or F3 fibrosis (NAFLD activity score of 4 or higher) were randomized to pegzofermin 15 mg weekly (n=21), 30 mg weekly (n=73), 44 mg every two weeks (n=57), or placebo (n=71) for 24 weeks. The full analysis population comprised 192 patients after consensus biopsy review excluded 27 patients.

Co-primary histological endpoints at week 24:

Fibrosis improvement of at least one stage without worsening of NASH: placebo 7 percent; 15 mg weekly 22 percent (difference 14 percentage points); 30 mg weekly 26 percent (difference 19 percentage points, $P=0.009$); 44 mg every two weeks 27 percent (difference 20 percentage points, $P=0.008$).

NASH resolution without fibrosis worsening: placebo 2 percent; 15 mg weekly 37 percent; 30 mg weekly 23 percent; 44 mg every two weeks 26 percent.

Key secondary endpoint: NAFLD activity score reduction of 2 or more points without fibrosis worsening: placebo 24 percent; 30 mg weekly 65 percent; 44 mg every two weeks 62 percent.

Biomarker changes: Hepatic fat fraction by MRI-PDFF decreased by 48.2 percent (30 mg weekly) and 41.9 percent (44 mg every two weeks) versus 5.0 percent on placebo. At least 50 percent hepatic fat reduction was achieved in 63 percent (30 mg) and 58 percent (44 mg) versus 12 percent on placebo. ALT normalized in 59 percent (30 mg) and 65 percent (44 mg) versus 24 percent on placebo. PRO-C3 decreased by 18.1 percent (30 mg) and 17.3 percent (44 mg) versus a 6.4 percent increase on placebo. Adiponectin increased by 30.0 percent (30 mg) and 27.7 percent (44 mg) versus a 7.2 percent decrease on placebo. Triglycerides decreased by 26.6 percent (30 mg) versus 6.4 percent on placebo.

7.3 Phase 2 ENTRIGUE trial: severe hypertriglyceridemia

The ENTRIGUE trial (Bhatt et al., 2023, Nature Medicine) was a randomized, double-blind, placebo-controlled, dose-ranging Phase 2 trial conducted at 50 clinical sites across the United States, Hungary, Poland, and Czech Republic [3]. A total of 85 patients with severe hypertriglyceridemia (baseline triglycerides 500 to 2000 mg/dL; median baseline 622 mg/dL) were randomized to placebo (n=18), pegozafermin 9 mg weekly (n=16), 18 mg weekly (n=17), 27 mg weekly (n=18), or 36 mg every two weeks (n=16) for 8 weeks. Mean age was 53.7 years, 75.3 percent were male, mean BMI was 33.1 kg/m², and 50.6 percent had type 2 diabetes.

Primary endpoint: The pooled pegozafermin group achieved a median triglyceride reduction of 57.3 percent versus 11.9 percent on placebo (difference versus placebo negative 43.7 percent, P less than 0.001). Response rate (triglycerides below 500 mg/dL) was 79.7 percent versus 29.4 percent on placebo.

Secondary endpoints: Non-HDL cholesterol decreased by 18.3 percent versus 0.6 percent on placebo (P=0.007). Apolipoprotein B decreased by 10.5 percent versus 1.1 percent (P=0.019). Apolipoprotein C3 decreased by 41.9 percent versus 8.9 percent. HDL cholesterol increased by up to 44.5 percent at the 27 mg dose versus 9.7 percent on placebo. Hepatic fat by MRI decreased by 42.2 percent versus 8.3 percent (P=0.012). Apolipoprotein B48 decreased by 73 percent at the 27 mg dose, indicating enhanced chylomicron clearance.

7.4 Phase 3 programs

ENLIGHTEN-Fibrosis (NCT06143091): Global, multicenter, randomized, double-blind, placebo-controlled trial enrolling approximately 1,000 patients with non-cirrhotic MASH and F2 or F3 fibrosis. Patients are randomized 1:1:1 to pegozafermin 30 mg weekly, 44 mg every two weeks, or placebo. Co-primary endpoints at week 52 are fibrosis improvement of at least one stage without worsening of MASH, and MASH resolution without worsening of fibrosis [5].

ENLIGHTEN-Cirrhosis: Global trial enrolling MASH patients with compensated cirrhosis (F4 fibrosis) [6].

ENTRUST (NCT05852678): Global, 52-week, randomized, double-blind, placebo-controlled Phase 3 trial enrolling approximately 360 patients with severe hypertriglyceridemia (baseline triglycerides 500 to 2000 mg/dL). Patients are randomized 3:3:2 to pegozafermin 30 mg weekly, 20 mg weekly, or placebo. Primary endpoint is percent change from baseline in fasting triglycerides at week 26 [7].

7.5 Phase 1 healthy volunteer data

The Phase 1 single-ascending-dose study in 58 healthy volunteers established dose-proportional pharmacokinetics and pharmacodynamic proof of concept: single doses up to 78 mg produced triglyceride reductions of up to 51 percent, LDL cholesterol reductions of up to 37 percent, and HDL cholesterol increases of up to 36 percent [12].

8. Sourcing and Quality Verification

Pegozafermin is an investigational biologic currently available only through participation in 89bio-sponsored clinical trials (ENLIGHTEN-Fibrosis, ENLIGHTEN-Cirrhosis, ENTRUST) and through expanded access programs where available. The compound is not commercially marketed in any jurisdiction. There is no pharmaceutical-grade or research-grade supply available through independent chemical or biologic suppliers.

The investigational drug product is manufactured under current Good Manufacturing Practice (cGMP) conditions and supplied as a sterile solution in pre-filled syringes for subcutaneous injection. Each lot undergoes identity, potency, purity, sterility, and endotoxin testing in accordance with regulatory requirements for biologic investigational products.

Investigators seeking access to pegozafermin for clinical research should consult the 89bio clinical trial registry listings (ClinicalTrials.gov) or contact 89bio directly for expanded access eligibility. As a biologic product (recombinant protein conjugate), pegozafermin cannot be synthesized by standard small-molecule chemical synthesis methods, and independent production requires recombinant protein expression, purification, and glycoPEGylation capabilities that are available only at specialized biopharmaceutical manufacturing facilities.

Native recombinant human FGF21 (non-PEGylated) is available from multiple commercial suppliers (R&D Systems, PeproTech, Abcam, others) for in vitro and preclinical research applications. However, native FGF21 has a half-life of 0.5 to 2 hours in vivo and does not replicate the pharmacokinetic or pharmacodynamic profile of pegozafermin. Investigators using native FGF21 as a research tool should not extrapolate pharmacodynamic results directly to pegozafermin clinical performance.

9. Reconstitution and Handling

Pegozafermin is supplied as a ready-to-use sterile solution for subcutaneous injection and does not require reconstitution. The clinical trial drug product is provided in prefilled syringes stored under refrigerated conditions (2 to 8 degrees Celsius) and protected from light.

Storage: Refrigerated storage at 2 to 8 degrees Celsius. Do not freeze. Protect from light. The product should be brought to room temperature (15 to 25 degrees Celsius) for approximately 30 minutes prior to injection to reduce injection site discomfort.

Injection technique: Subcutaneous injection into the abdomen, anterior thigh, or upper arm. Injection sites should be rotated between doses to minimize injection site reactions. The injection volume and concentration are dose-dependent and are specified in the clinical trial protocol for each dose cohort.

Stability: Protein therapeutics are sensitive to physical agitation, temperature excursions, and exposure to extremes of pH. The pegozafermin drug product should not be shaken vigorously. Vials or syringes that have been frozen, exposed to temperatures above 25 degrees Celsius for extended periods, or that show visible particulate matter or discoloration should not be used.

Compatibility: As a biologic product administered by direct subcutaneous injection, pegozafermin is not mixed with other drugs or diluents prior to administration in the clinical trial setting.

10. Stack Interactions and Combinations

Pegozafermin is a biologic (protein therapeutic) that is metabolized by proteolytic degradation and does not interact with cytochrome P450 enzymes, UDP-glucuronosyltransferases, or other small-molecule drug-metabolizing enzyme systems. No conventional pharmacokinetic drug-drug interactions mediated by enzyme inhibition or induction are expected.

Lipid-modifying therapies: In the ENTRUST Phase 3 trial, pegozafermin is administered on a background of standard-of-care lipid-modifying therapy (statins, fibrates, omega-3 fatty acids, PCSK9 inhibitors) [7]. In the ENTRIGUE Phase 2 trial, background lipid therapy was permitted and did not produce identifiable pharmacokinetic or pharmacodynamic interactions [3]. The triglyceride-lowering effect of pegozafermin is additive to background fibrate therapy, supporting combination use in severe hypertriglyceridemia.

Antidiabetic therapies: Approximately 50 percent of patients in the ENTRIGUE trial had type 2 diabetes and were receiving antidiabetic medications (metformin, sulfonylureas, insulin, GLP-1 receptor agonists, SGLT2 inhibitors). No adverse pharmacodynamic interactions were reported [3]. The insulin-sensitizing effect of pegozafermin may reduce exogenous insulin requirements; investigators should monitor glucose levels when combining pegozafermin with hypoglycemic agents.

GLP-1 receptor agonists and dual agonists: The combination of FGF21 analogs with GLP-1 receptor agonists (semaglutide, liraglutide) or GIP/GLP-1 dual agonists (tirzepatide) is of substantial clinical interest, as these agent classes have complementary mechanisms of action in metabolic liver disease and cardiovascular risk reduction. No formal drug-drug interaction studies of pegozafermin with GLP-1 receptor agonists have been reported. The gastrointestinal adverse event profiles (nausea, diarrhea) overlap, and additive gastrointestinal intolerance should be anticipated in combination use.

Resmetirom (thyroid hormone receptor beta agonist): Resmetirom is the first FDA-approved therapy for MASH (approved March 2024). The combination of FGF21 analogs with resmetirom has not been studied but is mechanistically ratio-

nal, as the two classes operate through distinct hepatic pathways (FGF21 through FGFR1c-beta-klotho-ERK1/2; resmetirom through thyroid hormone receptor beta-mediated lipid metabolism). Additive or synergistic hepatic fat reduction and fibrosis improvement are plausible.

Immunosuppressants and biologics: No formal interaction studies with immunosuppressants (tacrolimus, mycophenolate, corticosteroids) or other biologic therapies have been reported. As a non-immunogenic protein analog of an endogenous hormone, pegozafermin is not expected to produce clinically significant immunological interactions with other biologics.

Anti-coagulants and anti-platelet agents: No known interactions. The substantial triglyceride reduction and potential cardiovascular risk modification with pegozafermin may have implications for anti-thrombotic therapy in patients with severe hypertriglyceridemia, but no direct pharmacodynamic interactions have been characterized.

11. Adverse Events and Safety Signal

11.1 Common adverse events

The safety profile of pegozafermin across the Phase 1b/2a, ENLIVEN, and ENTRIGUE trials is characterized by mild-to-moderate adverse events, predominantly gastrointestinal and injection-site-related.

Nausea: Reported in up to 32 percent of patients at the 30 mg weekly dose in ENLIVEN (versus 9 percent on placebo) and 13.4 percent in pooled pegozafermin groups in ENTRIGUE (versus 0 percent on placebo) [2, 3]. The majority of nausea events were grade 1 or grade 2 and transient in duration.

Diarrhea: Reported in up to 24 percent at 15 mg weekly in ENLIVEN (versus 6 percent on placebo) and 10.4 percent in ENTRIGUE (versus 5.6 percent on placebo) [2, 3]. Diarrhea was the most common adverse event leading to treatment discontinuation.

Injection site reactions: Injection site erythema was reported in 14 to 15 percent at the 15 mg and 30 mg weekly doses (versus 4 percent on placebo) in ENLIVEN and 9 percent in ENTRIGUE [2, 3].

Increased appetite: Observed in up to 13 percent of pegozafermin-treated patients in Phase 1b/2a data. Notably, the increase in appetite was not associated with body weight gain during the treatment period [1].

11.2 Serious adverse events

In the ENLIVEN trial, serious adverse events occurred in 4 to 11 percent of patients across dose groups (placebo 4 percent, 15 mg 5 percent, 30 mg 4 percent, 44 mg 11 percent) [2]. One treatment-related serious adverse event was reported: acute pancreatitis in a patient receiving 44 mg every two weeks who had pre-existing gallbladder sludge on imaging. The clinical course was typical for uncomplicated acute pancreatitis, and the event resolved. No other treatment-related serious adverse events were attributed to pegozafermin.

In the ENTRIGUE trial, one unrelated serious adverse event (hypertension) occurred in the 27 mg weekly group. No drug-related serious adverse events were reported [3].

11.3 Grade 3 and higher adverse events

Grade 3 adverse events were reported in 4 to 10 percent of patients in ENLIVEN (comparable to 9 percent on placebo) [2]. No grade 4 or grade 5 adverse events were reported in any pegozafermin clinical trial. No deaths occurred during the treatment periods of the ENLIVEN or ENTRIGUE trials.

11.4 Hepatic safety

No drug-induced liver injury (DILI), no hepatotoxicity, and no Hy's law cases were reported across the clinical program [2, 3]. This is a notable safety finding for a compound targeting hepatic disease, as hepatotoxicity has been a safety concern with some other metabolic liver disease candidates. ALT levels decreased substantially with pegozafermin treatment (normalization in 59 to 65 percent of patients), indicating hepatoprotective rather than hepatotoxic activity.

11.5 Bone, thyroid, and growth factor safety

No clinically significant changes in bone biomarkers, bone mineral density, insulin-like growth factor 1 (IGF-1), or thyrotropin (TSH) were reported [2]. The absence of bone safety signals is relevant given theoretical concerns about FGF subfamily cross-reactivity (FGF23, a related endocrine FGF, regulates phosphate and vitamin D metabolism and has skeletal effects). FGF21 does not bind FGFR- α -Klotho (the FGF23 coreceptor) and does not produce phosphaturic or skeletal effects.

11.6 Immunogenicity

Anti-drug antibody data from the pegozafermin clinical trials have not been fully reported in the peer-reviewed literature. PEGylated protein therapeutics can elicit anti-PEG and anti-protein antibodies; the glycoPEGylation technology may reduce immunogenicity relative to conventional PEGylation by producing a more homogeneous conjugate with reduced neoantigen exposure. Immunogenicity assessments are part of the Phase 3 program.

11.7 Discontinuation rates

Treatment discontinuation due to adverse events was reported in 0 to 6 percent of pegozafermin-treated patients in ENLIVEN (versus 0 percent on placebo) [2]. Reasons for discontinuation included diarrhea, nausea, injection-site erythema, and pancreatitis. In ENTRIGUE, 4 discontinuations in the pegozafermin groups (approximately 6 percent) were attributed to gastrointestinal symptoms [3]. Overall, the discontinuation rates are low and consistent with an acceptable tolerability profile for chronic metabolic disease therapy.

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative metabolic liver disease candidates against pegozafermin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The comparators were selected as the principal therapeutic agents with substantive clinical evidence in MASH and related metabolic liver disease, representing the key mechanistic classes in the current treatment landscape.

12.1 Efruxifermin (AKR-001, Akero Therapeutics)

Mechanism: Bivalent Fc-FGF21 fusion protein. Two FGF21 chains are covalently linked to a human IgG1 Fc domain, producing a dimeric construct with enhanced receptor binding avidity and extended half-life through FcRn-mediated recycling [19].

Development trajectory: Akero Therapeutics advanced efruxifermin through the HARMONY Phase 2b trial in non-cirrhotic MASH (F2-F3 fibrosis) and the SYMMETRY Phase 2b trial in compensated cirrhosis (F4). The 96-week HARMONY results, published in *The Lancet* (2025), demonstrated fibrosis improvement without MASH worsening in 75 percent of patients at 50 mg weekly versus 24 percent on placebo [20]. Three Phase 3 trials (SYNCHRONY Histology, SYNCHRONY Outcomes, SYNCHRONY Real-World) are ongoing. Akero was acquired by Novo Nordisk in 2024, substantially expanding the development resources available.

Novelty: Moderate. The bivalent Fc-FGF21 format is structurally distinct from pegozafermin but operates through the same FGF21-FGFR1c-beta-klotho signaling pathway. The enhanced avidity of the dimeric construct is a meaningful engineering advance.

Effect size: Large. The 96-week HARMONY data (75 percent fibrosis improvement at 50 mg) represent the highest fibrosis response rate reported for any MASH therapy to date. Direct comparison with pegozafermin is limited by differences in treatment duration (96 weeks versus 24 weeks in ENLIVEN) and patient populations.

Promising potential: High. Phase 3 development is advancing under Novo Nordisk sponsorship, with substantial resources and a favorable regulatory trajectory.

Side-effect profile: Mild-to-moderate gastrointestinal adverse events (nausea, diarrhea) similar to pegozafermin. The Fc domain raises theoretical concerns about Fc-mediated immune effector functions, though no clinically significant immunological adverse events have been reported.

Overall validation: High. The most advanced FGF21 analog by treatment duration and fibrosis response rate. The Novo Nordisk acquisition validates the clinical and commercial potential of the FGF21 mechanism.

Comparison to pegozafermin: Efruxifermin and pegozafermin represent two distinct engineering approaches to FGF21 half-life extension (Fc fusion versus glycoPEGylation). Efruxifermin has produced higher absolute fibrosis response rates, though at longer treatment durations. Pegozafermin has the advantage of Breakthrough Therapy and PRIME designations and may have a simpler immunogenicity profile without the Fc domain. The two compounds are the principal competitors in the FGF21 analog class.

12.2 Resmetirom (Rezdiffra, Madrigal Pharmaceuticals)

Mechanism: Selective thyroid hormone receptor beta (THR-beta) agonist. Resmetirom activates THR-beta in the liver, promoting cholesterol-to-bile-acid conversion, reducing hepatic de novo lipogenesis, and enhancing mitochondrial fatty acid oxidation through a mechanism independent of the FGF21 pathway [21].

Development trajectory: Resmetirom was approved by the FDA in March 2024 (Rezdiffra) for the treatment of adults with non-cirrhotic NASH with moderate to advanced liver fibrosis (F2-F3), based on the MAESTRO-NASH Phase 3 trial. It is the first FDA-approved therapy specifically indicated for MASH [21].

Novelty: High. The THR-beta agonist mechanism is mechanistically distinct from FGF21 analogs, GLP-1 receptor agonists, and other MASH candidates.

Effect size: Moderate. In the MAESTRO-NASH trial, NASH resolution without fibrosis worsening was achieved in approximately 30 percent of patients at the 100 mg dose versus 10 percent on placebo at 52 weeks. Fibrosis improvement of at least

one stage was achieved in approximately 26 percent versus 14 percent on placebo [21]. These response rates are broadly comparable to the pegozafermin Phase 2b data at 24 weeks, though cross-trial comparisons are limited.

Promising potential: High. Already approved and commercially available. Post-approval studies and real-world data are accumulating.

Side-effect profile: The principal adverse events are diarrhea and nausea (similar to pegozafermin in type, though possibly at different frequencies). Thyroid function monitoring is recommended. Elevations in hepatic transaminases have been reported in some patients.

Overall validation: High. The first approved MASH therapy, with Phase 3 data and regulatory validation.

Comparison to pegozafermin: Resmetirom and pegozafermin operate through distinct mechanisms and could potentially be used in combination. Resmetirom has the advantage of FDA approval and oral administration. Pegozafermin has the advantage of broader metabolic effects (triglyceride reduction, adiponectin elevation, insulin sensitization) and the potential for greater fibrosis improvement, though this awaits Phase 3 confirmation.

12.3 Semaglutide (Novo Nordisk)

Mechanism: GLP-1 receptor agonist. Semaglutide activates the glucagon-like peptide-1 receptor, producing weight loss, improved glycemic control, reduced hepatic steatosis, and potential anti-fibrotic effects through indirect metabolic and anti-inflammatory mechanisms [22].

Development trajectory: Semaglutide 2.4 mg weekly (subcutaneous) is approved for obesity and type 2 diabetes (Wegovy, Ozempic). The compound has been studied in MASH in the Phase 2 trial by Newsome et al. (2021, New England Journal of Medicine), demonstrating NASH resolution in 59 percent of patients at 0.4 mg daily versus 17 percent on placebo at 72 weeks, though fibrosis improvement did not reach statistical significance [22]. The oral formulation (Rybelsus) and higher-dose subcutaneous formulations are under evaluation for MASH.

Novelty: Low for MASH specifically (GLP-1 agonism is an established mechanism), though the magnitude of weight loss and metabolic improvement distinguishes semaglutide from earlier GLP-1 agents.

Effect size: High for NASH resolution and hepatic fat reduction; modest for fibrosis improvement in the reported Phase 2 data. The substantial weight loss (approximately 13 to 15 percent body weight reduction) drives much of the hepatic benefit.

Promising potential: High. Already approved for related indications (obesity, type 2 diabetes) with extensive real-world use. MASH-specific development is ongoing.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea, constipation) are common, particularly during dose escalation. Rare but serious adverse events include pancreatitis, gallbladder disease, and (in preclinical models) thyroid C-cell tumors. The gastrointestinal adverse event profile is more pronounced than that of pegozafermin.

Overall validation: High for metabolic disease broadly; moderate specifically for MASH fibrosis improvement.

Comparison to pegozafermin: Semaglutide produces greater weight loss and higher NASH resolution rates but lower fibrosis improvement rates than pegozafermin at the studied timepoints. The mechanisms are complementary; combination therapy is of substantial clinical interest. Pegozafermin has the advantage of direct hepatic FGF21 signaling, direct triglyceride reduction, and a potentially superior fibrosis improvement profile. Semaglutide has the advantage of established regulatory approval, oral formulation availability, and proven cardiovascular outcome benefits.

12.4 Tirzepatide (Eli Lilly)

Mechanism: Dual GIP/GLP-1 receptor agonist. Tirzepatide activates both the glucose-dependent insulinotropic polypeptide (GIP) receptor and the GLP-1 receptor, producing greater weight loss and glycemic improvement than GLP-1 receptor agonism alone [23].

Development trajectory: Tirzepatide is approved for type 2 diabetes (Mounjaro) and obesity (Zepbound). The SYNERGY-NASH Phase 2 trial evaluated tirzepatide in patients with MASH and demonstrated significant NASH resolution and fibrosis improvement, supporting advancement to the Phase 3 SYMPHONY program.

Novelty: Moderate. The dual incretin agonist mechanism is a meaningful advance over single GLP-1 receptor agonism but is mechanistically distant from FGF21 signaling.

Effect size: High for NASH resolution and weight loss; the SYNERGY-NASH Phase 2 data are among the strongest reported for any MASH candidate. However, the contribution of weight loss versus direct hepatic effects is difficult to disaggregate.

Promising potential: High. Approved for related indications with massive commercial success and robust Phase 3 MASH development.

Side-effect profile: Gastrointestinal adverse events are common (nausea, vomiting, diarrhea), similar to semaglutide. The dual agonist mechanism does not appear to introduce novel safety concerns beyond the GLP-1 class.

Overall validation: High for metabolic disease broadly; Phase 2 validation for MASH specifically.

Comparison to pegozafermin: Tirzepatide produces greater weight loss and potentially higher NASH resolution rates than pegozafermin but operates through metabolically distinct pathways. Pegozafermin has the advantages of direct FGF21-mediated hepatic signaling, direct triglyceride reduction independent of weight loss, and direct anti-fibrotic activity through adiponectin induction. Combination of FGF21 analogs with GIP/GLP-1 agonists is a rational strategy that has not yet been clinically evaluated.

12.5 Pegbelfermin (BMS-986036, Bristol-Myers Squibb)

Mechanism: PEGylated recombinant human FGF21 analog. Pegbelfermin employs conventional (non-site-specific) PEGylation to extend FGF21 half-life [24].

Development trajectory: Bristol-Myers Squibb advanced pegbelfermin through the FALCON 1 (NASH with bridging fibrosis or compensated cirrhosis, F3-F4) and FALCON 2 (NASH with F1-F3 fibrosis) Phase 2b trials. Both trials failed to meet their primary histological endpoints in 2021, and BMS discontinued the program [24].

Novelty: Low. Conventional PEGylation of FGF21 is a straightforward half-life extension approach with less site specificity than glycoPEGylation.

Effect size: Insufficient. The FALCON trials did not demonstrate statistically significant fibrosis improvement or NASH resolution relative to placebo. Hepatic fat reduction was observed but did not translate to histological benefit at the studied doses and timepoints.

Promising potential: None. Development has been terminated.

Side-effect profile: Mild-to-moderate gastrointestinal adverse events, similar to pegozafermin. No unique safety signals were identified.

Overall validation: Low. The compound was the first FGF21 analog to enter clinical development for NASH and generated early proof-of-concept pharmacodynamic data (hepatic fat reduction, biomarker improvement). However, the Phase 2b histological failures terminated the program and raised questions about whether conventional PEGylation adequately preserves FGF21 receptor binding and signaling potency.

Comparison to pegozafermin: Pegbelfermin and pegozafermin share the PEGylated FGF21 analog class but differ in PEGylation chemistry (conventional versus glycoPEGylation) and in clinical performance. The pegbelfermin failure is a cautionary precedent that highlights the importance of PEGylation site specificity and conjugate homogeneity for FGF21 analog clinical efficacy. Pegozafermin's glycoPEGylation technology is specifically designed to address the limitations that may have contributed to the pegbelfermin FALCON trial failures, and the positive ENLIVEN results validate this engineering approach.

12.6 Comparator summary

The five comparators span the principal mechanistic classes in the MASH therapeutic landscape. **Efruxifermin** is the closest mechanistic competitor to pegozafermin within the FGF21 analog class, with the highest reported fibrosis response rates (75 percent at 96 weeks) and the backing of Novo Nordisk. **Resmetirom** is the first approved MASH therapy, operating through a distinct THR-beta mechanism, and establishes the regulatory precedent for conditional histological endpoints. **Semaglutide** and **tirzepatide** are incretin-based therapies with proven metabolic efficacy and large commercial markets, producing substantial NASH resolution through weight loss but with less consistent fibrosis improvement. **Pegbelfermin** is

the cautionary predecessor in the PEGylated FGF21 class, whose Phase 2b failure underscores the importance of the glycoPEGylation engineering that distinguishes pegozafermin.

Pegozafermin occupies a differentiated position in this landscape as a glycoPEGylated FGF21 analog with demonstrated histological efficacy on both fibrosis improvement and NASH resolution at 24 weeks, Breakthrough Therapy and PRIME designations, and Phase 3 development in both MASH and severe hypertriglyceridemia. The compound's distinguishing features relative to the comparators include: direct FGF21-mediated hepatic signaling (versus indirect metabolic effects from incretins); site-specific glycoPEGylation (versus conventional PEGylation or Fc fusion); subcutaneous injection with weekly or biweekly dosing (versus daily oral dosing for resmetirom); and a dual-indication development program targeting both MASH and severe hypertriglyceridemia.

The central question for pegozafermin's competitive positioning is whether the Phase 3 ENLIGHTEN results will confirm the Phase 2b histological efficacy at clinically meaningful response rates, and whether the glycoPEGylation technology provides a meaningful advantage over the Fc-FGF21 fusion approach of efruxifermin. The Phase 3 data, anticipated in 2026 and 2027, will be determinative.

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