

RESEARCH MONOGRAPH . COMPOUND PROFILE

Efimosfermin

An engineered, once-monthly IgG1-Fc-fused FGF21 analog developed by Novartis and advanced through Boston Pharmaceuticals and GSK for the treatment of metabolic dysfunction-associated steatohepatitis, distinguished from other FGF21 analogs by a 21-day pharmacokinetic half-life that permits monthly subcutaneous dosing and by Phase 2 evidence of fibrosis reversal and MASH resolution in patients with moderate-to-advanced hepatic fibrosis.

DOCUMENT	KDC-MN-1631
ISSUED	2026-05-21
REVISION	1.0
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COMPOUND CLASS	Long-acting Fc-fusion fibroblast growth factor 21 (FGF21) analog with direct antifibrotic, anti-steatotic, and metabolic regulatory activity

ABSTRACT

Efimosfermin alfa (formerly LLF580 under Novartis origination, subsequently designated BOS-580 under Boston Pharmaceuticals development, and now GSK-6519754 following acquisition by GSK plc) is a genetically engineered, long-acting analog of human fibroblast growth factor 21 (FGF21), a hepatokine and adipokine that regulates hepatic lipid oxidation, adipose tissue glucose uptake, triglyceride metabolism, and inflammatory signaling through formation of a ternary complex with the transmembrane tyrosine kinase FGF receptor 1c (FGFR1c) and the obligate co-receptor beta-klotho (KLB). The molecule is a homodimeric fusion protein in which two copies of a stabilized FGF21 variant are fused at their N-termini to the crystallizable fragment (Fc) of human immunoglobulin G1 (IgG1). The FGF21 domain is further stabilized by the introduction of a non-native disulfide bond and point mutations that increase proteolytic resistance, together producing a pharmacokinetic half-life of approximately 21 days in humans and enabling subcutaneous administration once every four weeks. This dosing interval distinguishes efimosfermin from the weekly-dosed FGF21 analogs efruxifermin (Akero Therapeutics) and pegozafermin (89bio), which require subcutaneous injection every one to two weeks.

The compound entered clinical development as LLF580 in a Novartis-sponsored Phase 1/2 trial (CLLF580X2102) in obese adults with modest hypertriglyceridemia, where 300 mg subcutaneously every four weeks for 12 weeks produced a 54 percent reduction in serum triglycerides, a 36 percent increase in HDL cholesterol, a 52 percent reduction in hepatic fat fraction by

magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF), a 24 percent reduction in pro-peptide type III collagen (Pro-C3, a circulating fibrosis biomarker), and improvements in insulin sensitivity (38 percent reduction in fasting insulin, 29 percent reduction in C-peptide, and a 103 percent increase in adiponectin), all without significant body weight change. The compound was subsequently licensed to Boston Pharmaceuticals, renamed BOS-580, and advanced into a Phase 2a multicenter randomized double-blind placebo-controlled trial in participants with phenotypic metabolic dysfunction-associated steatohepatitis (MASH), followed by a Phase 2b trial (NCT04880031) in 84 patients with biopsy-confirmed MASH and F2 or F3 fibrosis, where 300 mg once monthly for 24 weeks produced fibrosis improvement of at least one stage without MASH worsening in 45.2 percent of treated patients versus 20.6 percent on placebo ($p = 0.038$), MASH resolution without fibrosis worsening in 67.7 percent versus 29.4 percent on placebo ($p < 0.01$), and clinically meaningful improvements in glycemic control markers including glycated hemoglobin.

In May 2025, GSK plc completed acquisition of efimosfermin from Boston Pharmaceuticals for 1.2 billion United States dollars upfront and up to 800 million dollars in milestone payments, with tiered royalties owed to Novartis Pharma AG. The compound has received United States Food and Drug Administration Breakthrough Therapy Designation and European Medicines Agency Priority Medicines (PRIME) Designation for the treatment of MASH. Phase 3 development (the ZENITH program) commenced in December 2025, with a potential first launch projected for 2029. GSK has indicated development plans in both MASH (including compensated cirrhosis) and alcohol-related liver

disease (ALD), with potential for combination therapy with GSK'990, a complementary hepatology pipeline candidate. This monograph reviews the chemistry, molecular design, and receptor pharmacology of efimosfermin; the FGF21 signaling pathway; the comprehensive preclinical and clinical pharmacokinetic record; the clinical evidence base across Phase 1/2 and Phase 2 trials; the sourcing and quality considerations for this biologic investigational agent; reconstitution and handling; stack interactions and combinations; adverse events and safety signals; and a comparative assessment of five FGF21-pathway therapeutic candidates against efimosfermin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Efimosfermin alfa.

Development codes: LLF580 (Novartis Pharmaceuticals Corp., the originator designation used in the first-in-human Phase 1/2 trial); BOS-580 (Boston Pharmaceuticals Inc., the designation used in Phase 2a and Phase 2b clinical trials); GSK-6519754 (GSK plc, the designation adopted following the 2025 acquisition) [1, 2, 3].

Marketed names: None. Efimosfermin alfa is an investigational compound not yet approved by any regulatory authority for commercial distribution. The compound has received FDA Breakthrough Therapy Designation and EMA PRIME Designation for MASH [4].

Chemical classification: Fusion protein; recombinant biologic. The compound is not a small molecule and does not carry a Chemical Abstracts Service registry number in the conventional sense. The sequence code is 127087 [5].

Structural class: Long-acting Fc-fusion FGF21 analog.

1.2 Structural class and molecular design

Efimosfermin alfa is a homodimeric fusion protein composed of two copies of an engineered variant of the 181-amino-acid human FGF21 polypeptide, each fused at its N-terminus to one chain of the crystallizable fragment (Fc) of human immunoglobulin G1 (IgG1) [1, 6]. The Fc domain confers the extended circulating half-life characteristic of Fc-fusion biologics through neonatal Fc receptor (FcRn)-mediated recycling, a mechanism shared with other Fc-fusion therapeutics (etanercept, abatacept, dulaglutide). The FGF21 domain is further stabilized through two engineering modifications: (a) the introduction of a non-native disulfide bond that increases thermodynamic stability and reduces aggregation propensity, and (b) point mutations at residues susceptible to endogenous proteolytic cleavage (principally

fibroblast activation protein [FAP]-mediated cleavage at the C-terminal domain), which increase proteolytic resistance and preserve the intact, active conformation of the FGF21 moiety during its prolonged circulation [1, 6, 7].

The composite engineering produces a pharmacokinetic half-life of approximately 21 days in humans (compared to less than 2 hours for native FGF21, approximately 3.5 days for efruxifermin, and 55 to 100 hours for pegozafermin), enabling subcutaneous dosing once every four weeks [1, 6, 7].

Molecular weight: Not publicly disclosed as a precise value; the homodimeric Fc-fusion architecture predicts a molecular weight in the range of approximately 100 to 120 kilodaltons for the glycosylated dimer, consistent with other IgG1-Fc fusion proteins.

Physical form: The compound is supplied as a sterile aqueous solution for subcutaneous injection in clinical trials.

1.3 Synthesis and manufacturing

Efimosfermin alfa is produced by recombinant DNA technology in mammalian cell expression systems (presumed Chinese hamster ovary [CHO] cells, the standard host for Fc-fusion protein manufacturing, though the specific cell line has not been publicly disclosed by the sponsors). The manufacturing process involves upstream cell culture, harvest and clarification, multi-step chromatographic purification (typically Protein A affinity chromatography followed by ion-exchange and hydrophobic interaction chromatography), viral inactivation and filtration, ultrafiltration/diafiltration for formulation, and sterile fill-finish. The product undergoes characterization for identity (peptide mapping, mass spectrometry), purity (size-exclusion chromatography, capillary electrophoresis), potency (cell-based FGF21 receptor activation assay), and safety (endotoxin, sterility, residual host cell protein, residual DNA). Process-related and product-related impurities are controlled to specifications consistent with International Council for Harmonisation (ICH) guidelines for biotechnology-derived products (ICH Q6B) [8].

2. Abstract

Efimosfermin alfa is a genetically engineered, long-acting analog of human fibroblast growth factor 21 (FGF21), an endocrine hormone that regulates hepatic lipid metabolism, adipose tissue energy expenditure, triglyceride homeostasis, and inflammatory signaling. The compound signals through formation of a ternary complex with FGF receptor 1c (FGFR1c) and the obligate co-receptor beta-klotho (KLB), activating the extracellular signal-regulated kinase (ERK) pathway and downstream transcriptional programs that increase hepatic fatty acid beta-oxidation, decrease de novo lipogenesis, suppress hepatic stellate cell activation and fibrogenesis, and modulate macrophage polarization toward anti-inflammatory phenotypes [6, 7, 9].

The compound entered clinical development as LLF580 in a Novartis-sponsored Phase 1/2 randomized double-blind placebo-controlled trial in 61 obese adults with modest hypertriglyceridemia, conducted at seven United States sites from February 2018 to November 2019 [1]. At 300 mg subcutaneously every four weeks for 12 weeks (three doses), LLF580 produced a 54 percent placebo-adjusted reduction in serum triglycerides, a 36 percent increase in HDL cholesterol, a 52 percent reduction in hepatic fat fraction by MRI-PDFF, a 24 percent reduction in Pro-C3, and substantial improvements in insulin sensitivity markers, all without significant body weight change. Gastrointestinal adverse events (nausea 60 percent, vomiting 30 percent, diarrhea 27 percent) were the principal tolerability finding. The compound was subsequently licensed to Boston Pharmaceuticals and renamed BOS-580.

Boston Pharmaceuticals advanced the compound through a Phase 2a trial in participants with phenotypic MASH and a Phase 2b trial (NCT04880031) in 84 patients with biopsy-confirmed MASH and F2 or F3 fibrosis [2, 3]. At 300 mg once monthly for 24 weeks, the Phase 2b trial demonstrated fibrosis improvement of at least one stage without MASH worsening in 45.2 percent of treated patients versus 20.6 percent on placebo ($p = 0.038$), and MASH resolution without fibrosis worsening in 67.7 percent versus 29.4 percent on placebo ($p < 0.01$). The safety profile was favorable, with one grade 3 treatment-related adverse event and low rates of injection site reactions and appetite changes.

GSK plc completed acquisition of efimosfermin in May 2025 for 1.2 billion dollars upfront and up to 800 million dollars in milestones [4]. The compound has received FDA Breakthrough Therapy Designation and EMA PRIME Designation for MASH. Phase 3 trials (the ZENITH program) commenced in December 2025, with anticipated first launch in 2029 [4, 5].

3. Discovery and Development History

3.1 Origin and preclinical foundation

The discovery of efimosfermin originates in the identification of FGF21 as a metabolic regulator by Kharitonov et al. (2005), who demonstrated that recombinant FGF21 administration in diabetic mice reduced plasma glucose and triglycerides, increased energy expenditure, and improved insulin sensitivity [10]. Subsequent work established FGF21 as a hepatokine and adipokine with pleiotropic metabolic effects mediated through FGFR1c and beta-klotho co-receptor signaling in liver, adipose tissue, and pancreas. In high-fat diet-induced obese mice, FGF21 treatment produced weight loss, reduced hepatic steatosis (attributed to increased fatty acid beta-oxidation), decreased circulating triglycerides and LDL cholesterol, increased HDL cholesterol, and improved insulin sensitivity [6, 7].

The translational limitation of native FGF21 is its short circulating half-life (less than 2 hours in humans), attributable to rapid renal clearance and proteolytic degradation by fibroblast activation protein (FAP) and other serine proteases [6, 7]. This pharmacokinetic limitation drove the development of second-generation FGF21 analogs with extended half-lives, including PEGylated variants (pegozafermin), bivalent Fc-fusion constructs (efruxifermin), and the IgG1-Fc-fused, disulfide-stabilized variant that became LLF580 [6, 7].

3.2 Novartis development (LLF580)

Novartis Pharmaceuticals Corp. designed LLF580 as a long-acting FGF21 analog for monthly subcutaneous dosing. The molecule was advanced through preclinical pharmacology, toxicology, and manufacturing development and entered a first-in-human Phase 1/2 clinical trial (CLLF580X2102) at seven United States sites, conducted from February 2018 to November 2019 [1]. The trial enrolled 61 evaluable participants (30 LLF580, 31 placebo) with obesity (BMI 30 to 45 kg/m²) and modest hypertriglyceridemia (fasting triglycerides 150 to 500 mg/dL). The initial indication of interest was obesity, though the metabolic and hepatic findings redirected the development trajectory toward liver disease.

3.3 Transfer to Boston Pharmaceuticals (BOS-580)

Following the Phase 1/2 readout, Novartis licensed or transferred the compound to Boston Pharmaceuticals Inc. (Cambridge, Massachusetts), which redesignated it BOS-580 and initiated a clinical development program focused on metabolic dysfunction-associated steatohepatitis (MASH). Boston Pharmaceuticals conducted a Phase 2a multicenter randomized double-blind placebo-controlled trial at 12 centers in the United States in individuals with phenotypic MASH (aged 18 to 75 years, BMI 30 to 45 kg/m²), followed by a Phase 2b trial (NCT04880031) in 84 patients with biopsy-confirmed MASH and F2 or F3 fibrosis [2, 3]. The Phase 2b data, presented at The Liver Meeting (American Association for the Study of Liver Diseases, 2024), demonstrated the histologic efficacy that positioned efimosfermin as a Phase 3-ready candidate.

3.4 Acquisition by GSK

In May 2025, GSK plc completed acquisition of Boston Pharmaceuticals' subsidiary (BP Asset IX, Inc.) to obtain global rights to efimosfermin alfa. The transaction comprised 1.2 billion United States dollars in upfront payment and up to 800 million dollars in milestone-based payments, with tiered royalties owed to Novartis Pharma AG as the originator [4]. GSK designated the compound GSK-6519754 and announced plans for Phase 3 development in MASH (including compensated cirrhosis) and future development in alcohol-related liver disease (ALD), with potential for combination therapy with GSK'990, a complementary hepatology pipeline candidate. Tony Wood, GSK Chief Scientific Officer, stated that efimosfermin has the potential to define a new standard of care with its monthly dosing and tolerability profile [4].

3.5 Regulatory designations and Phase 3 initiation

Efimosfermin alfa has received two accelerated regulatory designations: FDA Breakthrough Therapy Designation and EMA Priority Medicines (PRIME) Designation, both for the treatment of MASH [4]. The Phase 3 program (designated ZENITH) commenced with the ZENITH-2 safety and tolerability study (NCT07221188) initiated in December 2025, followed by Phase 1 studies evaluating pharmacokinetics in hepatic impairment (NCT07358546, initiated March 2026) and in Asian populations (NCT07335198, initiated March 2026) [5]. The projected first launch date is 2029.

4. Mechanism of Action

4.1 FGF21 physiology and signaling pathway

Fibroblast growth factor 21 (FGF21) is a 181-amino-acid endocrine hormone belonging to the FGF19 subfamily of fibroblast growth factors, which also includes FGF15/19 and FGF23. Unlike paracrine FGFs, the endocrine FGFs lack a heparin-binding domain and therefore circulate systemically rather than acting locally. FGF21 is expressed primarily in the liver (where it is induced by peroxisome proliferator-activated receptor alpha [PPARalpha] during fasting, ketogenesis, and hepatic stress) and in adipose tissue, pancreas, and skeletal muscle at lower levels [6, 7, 9].

FGF21 signals through formation of a ternary complex with a transmembrane FGF receptor tyrosine kinase (principally FGFR1c, with lower affinity for FGFR2c and FGFR3c) and the single-pass transmembrane co-receptor beta-klotho (KLB) [6, 7, 9]. KLB is the tissue-specificity determinant: FGFR1c is broadly expressed, but KLB expression is restricted primarily to liver (hepatocytes), white and brown adipose tissue, and pancreatic beta cells, confining the functional signaling of FGF21 to these metabolically active tissues. The ternary complex (FGF21-FGFR1c-KLB) activates receptor autophosphorylation and downstream signaling through the extracellular signal-regulated kinase 1/2 (ERK1/2) mitogen-activated protein kinase (MAPK) pathway [6, 7].

4.2 Metabolic and hepatic effects

The downstream consequences of FGF21-FGFR1c-KLB signaling are pleiotropic and tissue-specific:

Hepatic effects: FGF21 increases hepatic fatty acid beta-oxidation and decreases de novo lipogenesis (DNL) through suppression of sterol regulatory element-binding protein 1c (SREBP-1c) and lipogenic enzymes (fatty acid synthase [FASN], stearoyl-CoA desaturase 1 [SCD1]). These effects produce the anti-steatotic activity observed clinically as reduction in hepatic fat fraction [6, 7, 9].

Adipose tissue effects: FGF21 stimulates uncoupling protein 1 (UCP1) expression in brown adipose tissue (increasing thermogenesis), inhibits white adipose tissue lipolysis (reducing hepatic delivery of free fatty acids), and stimulates adiponectin secretion from white adipocytes. Adiponectin is itself an insulin-sensitizing hormone that reduces hepatic steatosis and inflammation through independent hepatoprotective pathways [6, 7].

Insulin sensitivity: FGF21 improves whole-body insulin sensitivity through direct adipose tissue effects and through adiponectin-mediated indirect effects. Clinically, this is reflected in reduced fasting insulin, reduced C-peptide, reduced HOMA-IR, and improved glycemic control markers [1, 6].

Anti-inflammatory effects: FGF21 suppresses Kupffer cell (hepatic resident macrophage) activation, decreases NLRP3 inflammasome activity, inhibits interleukin-17A (IL-17A) production, and promotes macrophage polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype. These effects reduce hepatic lobular inflammation, a key histologic component of MASH [6, 7, 9].

Antifibrotic effects: FGF21 suppresses transforming growth factor beta (TGF-beta) signaling in hepatic stellate cells (HSCs), the principal collagen-producing cells in the fibrotic liver. By reducing HSC activation and collagen synthesis, and by modulating macrophage-mediated fibrosis resolution, FGF21 produces the antifibrotic activity observed clinically as fibrosis stage improvement on liver biopsy [6, 7, 9].

4.3 Efimosfermin-specific pharmacology

Efimosfermin alfa engages the same FGFR1c-KLB ternary complex as native FGF21 and activates the same downstream ERK1/2 signaling cascade. The molecular engineering (IgG1-Fc fusion, disulfide stabilization, protease-resistance mutations) does not alter the receptor pharmacology but extends the pharmacokinetic half-life to approximately 21 days, enabling sustained receptor engagement over a monthly dosing interval [1, 6]. The homodimeric Fc-fusion architecture presents two FGF21 moieties per molecule, which may enhance avidity for the FGFR1c-KLB complex relative to monovalent constructs, though formal avidity comparisons across the FGF21 analog class have not been published.

4.4 Composite pharmacology and selectivity

The selectivity of efimosfermin for the FGFR1c-KLB complex is inherited from native FGF21 and is determined by the KLB co-receptor requirement. In the absence of KLB, FGF21 has negligible affinity for FGFR1c alone, ensuring that signaling is confined to KLB-expressing tissues (liver, adipose, pancreas). This tissue selectivity is a favorable pharmacological characteristic that limits off-target effects on tissues expressing FGFR1c but not KLB (bone, skin, vascular endothelium) [6, 7].

The principal known off-target signal is a reduction in bone formation markers. The Phase 1/2 LLF580 trial reported significant reductions in bone-specific alkaline phosphatase (6 percent), procollagen type I N-terminal propeptide (P1NP, 21 percent), and osteocalcin (26 percent) without significant changes in bone resorption markers (CTX-1, NTX-1) [1]. The mechanism may involve FGF21-mediated suppression of osteoblast differentiation through FGFR1c signaling in bone marrow stromal cells or indirect effects mediated through adiponectin. The clinical significance of this finding in long-term therapy is unknown and is a subject of ongoing safety monitoring.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Efimosfermin alfa is administered by subcutaneous injection. Absorption from the subcutaneous depot is typical of Fc-fusion proteins, with slow absorption into the systemic circulation mediated by lymphatic drainage. Time to peak plasma concentration after subcutaneous injection has not been publicly reported with precision but is expected to be in the range of 2 to 7 days, consistent with other Fc-fusion biologics [1, 6].

5.2 Distribution

The volume of distribution of efimosfermin alfa has not been publicly reported. As a large-molecular-weight Fc-fusion protein (approximately 100 to 120 kilodaltons), distribution is expected to be largely confined to the vascular and interstitial spaces, with limited tissue penetration except through receptor-mediated endocytosis in target tissues (liver, adipose). The Fc domain confers binding to neonatal Fc receptor (FcRn) on endothelial cells and hepatocytes, which mediates the pH-dependent recycling mechanism that extends the circulating half-life of Fc-containing proteins [6].

5.3 Metabolism and elimination

Efimosfermin alfa is a protein therapeutic and is subject to proteolytic catabolism rather than cytochrome P450-mediated hepatic metabolism. The elimination pathway is principally intracellular lysosomal degradation following receptor-mediated endocytosis and FcRn-mediated recycling. The engineering modifications (disulfide bond, protease-resistance mutations) specifically reduce susceptibility to fibroblast activation protein (FAP)-mediated proteolytic cleavage, which is the principal degradation pathway for native FGF21 and a major contributor to its short half-life [1, 6, 7].

The elimination half-life of efimosfermin alfa is approximately 21 days, enabling once-monthly (every four weeks) subcutaneous dosing. This half-life is substantially longer than other FGF21 analogs in clinical development: pegozafermin has a half-life of approximately 55 to 100 hours (permitting weekly or biweekly dosing), and efruxifermin has a half-life of approximately 3 to 4 days (permitting weekly dosing) [6, 7].

5.4 Routes of administration

The sole clinical route of administration is subcutaneous injection. The 300 mg dose used in Phase 2 trials is administered as a single subcutaneous injection once every four weeks. Intravenous administration has not been studied in published clinical trials. The subcutaneous route is the standard for Fc-fusion protein therapeutics and is appropriate for the self-administration model anticipated for chronic liver disease therapy.

5.5 Special populations

Phase 1 studies evaluating pharmacokinetics in hepatic impairment (NCT07358546) and in Asian populations (NCT07335198) were initiated in early 2026 and are ongoing [5]. Published pharmacokinetic data in special populations (renal impairment, pediatric, geriatric) are not yet available. The Phase 1/2 LLF580 trial enrolled a predominantly Caucasian (80 percent) population with a mean age of 45 years and a mean BMI of 36 kg/m² [1].

5.6 Immunogenicity

In the Phase 1/2 LLF580 trial, antidrug antibodies (ADAs) developed in 4 of 30 participants (13 percent) receiving LLF580 [1]. The ADAs did not have an apparent impact on pharmacokinetics, efficacy, or safety in this small cohort over the 12-week treatment period. Long-term immunogenicity data from Phase 2 and Phase 3 trials are not yet available. ADA monitoring is expected to be a component of the Phase 3 ZENITH program.

6. Clinical Evidence Base

6.1 Phase 1/2 trial in obese adults with hypertriglyceridemia (CLLF580X2102)

The first-in-human clinical trial of efimosfermin (as LLF580) was a multicenter, randomized, double-blind, parallel-arm, placebo-controlled Phase 1/2 study conducted at seven United States sites from February 2018 to November 2019, sponsored by Novartis [1]. The trial enrolled 61 evaluable participants (30 LLF580, 31 placebo) with obesity (BMI 30 to 45 kg/m²), modest fasting hypertriglyceridemia (150 to 500 mg/dL), and predominantly without type 2 diabetes (90 percent non-diabetic).

Dosing: LLF580 300 mg subcutaneous injection every four weeks for three doses (weeks 0, 4, and 8); 83.6 percent of participants completed all three doses as intended.

Lipid efficacy results (12-week endpoint, placebo-adjusted): Serum triglycerides decreased 54 percent ($p < 0.001$; absolute reduction 1.24 mmol/L, 95 percent CI 1.49 to 0.99). Total cholesterol decreased 7 percent ($p = 0.004$). LDL cholesterol decreased 12 percent ($p < 0.001$). HDL cholesterol increased 36 percent ($p < 0.001$) [1].

Hepatic efficacy results: Hepatic fat fraction by MRI-PDFF decreased 52 percent overall ($p < 0.001$) and 66 percent in the subset with baseline hepatic fat fraction of 8 percent or greater ($p < 0.001$). Among LLF580-treated subjects, 81.5 percent achieved at least 30 percent hepatic fat reduction versus 12 percent on placebo ($p < 0.0001$). Alanine aminotransferase (ALT) decreased 10 percent ($p = 0.037$). Aspartate aminotransferase (AST) decreased 17 percent ($p < 0.001$). Alkaline phosphatase decreased 6 percent ($p = 0.017$). Pro-peptide type III collagen (Pro-C3), a circulating fibrosis biomarker, decreased 24 percent ($p < 0.001$) [1].

Glycemic and insulin sensitivity results: Fasting glucose was unchanged. Glycated hemoglobin (HbA1c) was unchanged. Fasting insulin decreased 38 percent ($p < 0.001$). C-peptide decreased 29 percent ($p < 0.001$). HOMA-IR was significantly reduced ($p = 0.009$). Adiponectin increased 103 percent ($p < 0.001$) [1].

Body composition: Body weight showed no significant difference from placebo ($p = 0.092$). Waist circumference decreased by 2.2 cm ($p = 0.042$). The absence of weight loss in humans despite robust metabolic effects contrasts with preclinical mouse data and suggests species-dependent FGF21 pharmacology with respect to energy expenditure and body weight [1].

Bone markers: Bone-specific alkaline phosphatase decreased 6 percent ($p = 0.015$). P1NP decreased 21 percent ($p < 0.001$). Osteocalcin decreased 26 percent ($p < 0.001$). Bone resorption markers (CTX-1, NTX-1) were unchanged [1].

6.2 Phase 2a trial in phenotypic MASH

Boston Pharmaceuticals conducted a multicenter, randomized, double-blind, placebo-controlled Phase 2a trial of efimosfermin alfa (BOS-580) at 12 centers in the United States in individuals with phenotypic MASH, aged 18 to 75 years, with BMI 30 to 45 kg/m². The Phase 2a trial evaluated safety and tolerability as the primary endpoint, with changes in indicators of hepatic steatosis as secondary endpoints. Efimosfermin demonstrated a favorable safety profile and showed improvements in indicators of hepatic steatosis in participants with phenotypic MASH. Full Phase 2a results were published in The Lancet Gastroenterology and Hepatology (2025) [2].

6.3 Phase 2b trial in biopsy-confirmed MASH with F2/F3 fibrosis

The pivotal Phase 2b trial (NCT04880031) was a 24-week, randomized, double-blind, placebo-controlled study in 84 patients with biopsy-confirmed MASH and F2 or F3 fibrosis [3]. Patients were randomized to efimosfermin alfa 300 mg subcutaneously once monthly or placebo. Sixty-seven patients completed treatment. Baseline characteristics were balanced between groups except for a higher prevalence of type 2 diabetes in the efimosfermin arm.

Primary endpoint: Safety and tolerability.

Key histologic efficacy results (secondary endpoints):

Fibrosis improvement of at least one stage without MASH worsening: 45.2 percent of efimosfermin-treated patients versus 20.6 percent on placebo ($p = 0.038$) [3].

MASH resolution without fibrosis worsening: 67.7 percent of efimosfermin-treated patients versus 29.4 percent on placebo ($p < 0.01$) [3].

Combined fibrosis improvement and MASH resolution: achieved at higher rates in the efimosfermin arm than placebo [3].

Additional efficacy findings: MRI-PDFF reduction was significant. Clinically meaningful glycemic control markers (including glycated hemoglobin) improved in the efimosfermin arm [3].

Safety: One grade 3 treatment-related adverse event was reported. Appetite changes occurred in less than 5 percent of patients. Injection site reactions occurred in less than 5 percent and were mild. There was no apparent drug-related weight gain. The overall safety and tolerability profile was assessed as favorable over the 24-week treatment period [3].

These histologic efficacy data, particularly the fibrosis improvement and MASH resolution rates, supported the regulatory designations and the advancement to Phase 3 development.

6.4 Regulatory milestones and Phase 3 program

The FDA Breakthrough Therapy Designation and EMA PRIME Designation were granted on the basis of the Phase 2b histologic data [4]. The Phase 3 ZENITH program commenced with the ZENITH-2 study (NCT07221188) in December 2025 [5]. Additional Phase 1 studies (pharmacokinetics in hepatic impairment, Asian population pharmacokinetics) were initiated in early 2026. The Phase 3 program is expected to evaluate efimosfermin at the 300 mg monthly dose in patients with MASH and significant fibrosis (F2 to F4), with histologic endpoints (fibrosis improvement, MASH resolution) as anticipated registrational endpoints, consistent with the FDA and EMA guidance for MASH drug development.

6.5 Planned indications beyond MASH

GSK has indicated plans to develop efimosfermin in alcohol-related liver disease (ALD), where the anti-steatotic, anti-inflammatory, and antifibrotic mechanisms are mechanistically relevant [4]. The compound may also be evaluated in combination with GSK'990, a complementary hepatology pipeline candidate, for additive or synergistic effects on fibrosis and steatohepatitis resolution.

7. Reported Research Dose Ranges

7.1 Clinical doses

The sole dose evaluated in published clinical trials is 300 mg subcutaneously every four weeks [1, 2, 3]. This dose was selected on the basis of the Phase 1/2 dose-response assessment, the pharmacokinetic half-life supporting monthly dosing, and the metabolic and hepatic efficacy observed at this dose.

7.2 Dose rationale

The 300 mg monthly dose produces sustained FGF21 pathway activation over the dosing interval, as evidenced by the persistent reductions in hepatic fat, triglycerides, and fibrosis markers through the 24-week Phase 2b trial [3]. The dose has not been formally compared to lower or higher doses in a published dose-ranging study in MASH patients; the Phase 1/2 trial used only the 300 mg dose [1]. Phase 3 dose selection will presumably be informed by the totality of Phase 2 data and by the ongoing Phase 1 hepatic impairment and Asian population pharmacokinetic studies.

7.3 Administration

The 300 mg dose is administered as a single subcutaneous injection, consistent with the self-administration model planned for chronic therapy. Injection sites and rotation schedules have not been publicly specified but are expected to follow standard subcutaneous biologic administration practices (abdomen, thigh, upper arm).

8. Sourcing and Quality Verification

Efimosfermin alfa is an investigational biologic that is not commercially available. Access to the compound is restricted to clinical trial participation and to licensed research collaborations with the sponsors (GSK plc, formerly Boston Pharmaceuticals).

Clinical trial material: Supplied by the sponsor as a sterile, ready-to-use solution for subcutaneous injection. Manufacturing is conducted under current Good Manufacturing Practice (cGMP) conditions at a contracted biologics manufacturing facility.

Research-grade material: Efimosfermin alfa is listed by some specialty research reagent suppliers (MedChemExpress and others) as a research-grade biologic [5]. Investigators obtaining research-grade material from non-sponsor sources should be aware that recombinant Fc-fusion proteins are sensitive to manufacturing, storage, and handling conditions that can affect potency, aggregation state, and immunogenicity. Independent characterization of any research-grade lot should include:

- Identity confirmation by peptide mapping and/or mass spectrometry
- Purity assessment by size-exclusion chromatography (SEC) to quantify aggregates and fragments
- Potency assessment by cell-based FGF21 receptor activation assay (ERK phosphorylation or reporter gene assay)
- Endotoxin testing (Limulus amebocyte lysate assay)
- Concentration determination by UV absorbance (A280) with appropriate extinction coefficient

Research-grade FGF21 analogs from catalog suppliers may not replicate the specific engineering modifications (disulfide bond, protease-resistance mutations) of the clinical-grade efimosfermin, and investigators should confirm molecular identity before attributing experimental results to the clinical compound.

9. Reconstitution and Handling

Efimosfermin alfa clinical trial material is supplied as a ready-to-use sterile solution for subcutaneous injection and does not require reconstitution. Storage conditions have not been publicly disclosed in detail but are expected to follow standard Fc-fusion protein handling:

Storage: Refrigerated storage at 2 to 8 degrees Celsius. The Fc-fusion protein should not be frozen, as freeze-thaw cycles can induce aggregation and loss of potency. Protection from light is standard practice for biologic therapeutics.

Handling: The solution should be inspected visually for particulate matter and discoloration prior to administration. If visible particles, turbidity, or discoloration are present, the dose should not be administered. The solution should be brought to room temperature (approximately 15 to 30 minutes) before subcutaneous injection to reduce injection site discomfort.

Research-grade handling: Lyophilized research-grade FGF21 analogs should be reconstituted according to the supplier's certificate of analysis, typically in sterile phosphate-buffered saline (PBS) or other neutral-pH aqueous buffer. Reconstituted solutions should be aliquoted to avoid repeated freeze-thaw cycles and stored at minus 20 or minus 80 degrees Celsius for long-term storage, with single-use aliquots used within 24 hours of thawing.

10. Stack Interactions and Combinations

10.1 Drug-drug interactions

Efimosfermin alfa is a biologic Fc-fusion protein and is not metabolized by cytochrome P450 enzymes. Accordingly, conventional small-molecule drug-drug interactions mediated through CYP inhibition or induction are not expected [6]. However, the metabolic effects of FGF21 pathway activation (improved insulin sensitivity, reduced hepatic steatosis, altered lipid metabolism) can indirectly affect the pharmacokinetics and pharmacodynamics of co-administered medications:

Insulin and oral hypoglycemics: FGF21 analogs improve insulin sensitivity and may reduce the requirement for insulin, sulfonylureas, or other glucose-lowering agents. The Phase 1/2 trial excluded most diabetic patients, but the Phase 2b trial included patients with type 2 diabetes, and glycemic improvements were observed [1, 3]. Dose adjustment of concomitant glucose-lowering therapy may be required in diabetic patients to avoid hypoglycemia.

Lipid-lowering agents: FGF21 analogs reduce triglycerides and increase HDL cholesterol independently of statin therapy. The interaction with statins, fibrates, and PCSK9 inhibitors is expected to be additive rather than mechanistically overlapping. No clinically significant adverse interactions have been reported.

10.2 Combination with GLP-1 receptor agonists

Combination of FGF21 analogs with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is an active area of clinical investigation in the MASH space. Efruxifermin has been evaluated in combination with GLP-1 RAs with good tolerability [11]. The combination is mechanistically rational: GLP-1 RAs promote weight loss and reduce hepatic steatosis through appetite suppression and improved glycemic control, while FGF21 analogs reduce hepatic steatosis and fibrosis through complementary hepatic and adipose tissue mechanisms. Efimosfermin has not been formally evaluated in combination with GLP-1 RAs in published trials, but the combination is anticipated as a development strategy.

10.3 Combination with GSK'990

GSK has indicated potential for combination therapy of efimosfermin with GSK'990, a complementary hepatology pipeline candidate [4]. The molecular target and mechanism of GSK'990 have not been fully disclosed publicly. The combination rationale is presumably based on complementary mechanisms targeting different nodes of MASH pathophysiology.

10.4 Immunosuppressants

Patients with compensated cirrhosis or advanced liver disease may receive immunosuppressive therapy. The interaction of FGF21 analogs with immunosuppressants has not been formally characterized. The anti-inflammatory mechanism of FGF21 (macrophage polarization, NLRP3 inflammasome suppression) could theoretically interact with immunosuppressive regimens, though the clinical significance is unknown.

10.5 Hepatotoxic agents

Concurrent use of efimosfermin with hepatotoxic agents (methotrexate, isoniazid, high-dose acetaminophen) is not specifically contraindicated but is inadvisable in patients with existing liver disease, as hepatotoxic agents may confound the assessment of hepatic endpoints and may exacerbate the underlying steatohepatitis.

11. Adverse Events and Safety

11.1 Common adverse events

The Phase 1/2 LLF580 trial reported a higher overall adverse event rate in the LLF580 group (93.3 percent, 28 of 30) compared to placebo (77.4 percent, 24 of 31) [1]. The most common adverse events were gastrointestinal:

- Nausea: 60 percent (18 of 30 LLF580 versus lower rate on placebo)
- Vomiting: 30 percent (9 of 30)
- Diarrhea: 26.7 percent (8 of 30)
- Decreased appetite: 16.7 percent (5 of 30)
- Dyspepsia: 13.3 percent (4 of 30)
- Upper respiratory tract infection: 16.7 percent (5 of 30)

The gastrointestinal adverse events were predominantly mild to moderate in severity, transient, and occurred primarily during the first four weeks of treatment. The high gastrointestinal adverse event rate in the Phase 1/2 trial is consistent with the FGF21 analog class and was also observed with efruxifermin and pegozafermin, though at varying frequencies depending on dose and schedule [6, 7].

11.2 Phase 2b safety profile

The Phase 2b trial in biopsy-confirmed MASH with F2/F3 fibrosis reported a substantially more favorable safety profile than the Phase 1/2 trial [3]. One grade 3 treatment-related adverse event was reported. Appetite changes occurred in less than 5 percent of patients. Injection site reactions occurred in less than 5 percent and were all mild. There was no apparent drug-related weight gain. The improved tolerability in the Phase 2b trial may reflect patient selection (MASH patients versus obese hypertriglyceridemic participants), dose optimization, or the longer treatment duration allowing adaptation to gastrointestinal effects.

11.3 Serious adverse events

In the Phase 1/2 trial, serious adverse events occurred in 2 of 30 LLF580-treated participants (6.7 percent): one case of cholecystitis and one case of Burkitt lymphoma, both assessed as unrelated to study drug [1]. One serious adverse event (bronchopneumonia with sepsis) occurred in the placebo group. Drug discontinuation due to adverse events occurred in 2 of 30 LLF580-treated participants and 1 of 31 placebo-treated participants [1].

11.4 Bone safety signal

The Phase 1/2 trial identified reductions in bone formation markers (P1NP, osteocalcin, bone-specific alkaline phosphatase) without changes in bone resorption markers [1]. The pattern suggests suppression of osteoblast activity without activation of osteoclast-mediated resorption. The clinical significance for long-term skeletal health is unknown and requires monitoring in the Phase 3 program, particularly given the anticipated chronic (multi-year) dosing in MASH patients.

11.5 Cardiovascular safety

Diastolic blood pressure showed a modest statistically significant increase in the Phase 1/2 trial ($p = 0.031$), while systolic blood pressure trended higher without significance [1]. The cardiovascular safety profile will require further characterization in the Phase 3 program, particularly in the context of the metabolic syndrome population where cardiovascular risk is elevated.

11.6 Immunogenicity

Antidrug antibodies developed in 4 of 30 (13 percent) LLF580-treated participants without apparent clinical impact over 12 weeks [1]. Long-term immunogenicity monitoring is a component of the Phase 3 program.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five FGF21-pathway therapeutic candidates against efimosfermin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal FGF21-pathway agents with substantive clinical pharmacology programs in MASH or related metabolic liver disease indications.

12.1 Efruxifermin (AKR-001, AMG876; Akero Therapeutics)

Mechanism: Bivalent Fc-FGF21 fusion protein comprising two covalently linked FGF21 analog chains fused to an Fc domain [6, 7]. The bivalent architecture enhances receptor affinity and reduces dissociation, producing a half-life of approximately 3 to 4 days that supports weekly subcutaneous dosing.

Development trajectory: Efruxifermin is the most clinically advanced FGF21 analog, with multiple Phase 2b trials completed in MASH (the HARMONY trial: 128 patients, 24 weeks, fibrosis improvement in 39 to 41 percent at 28 and 50 mg weekly) and ongoing Phase 3 trials in MASH with F2/F3 fibrosis and in compensated cirrhosis [11, 12]. A Phase 2a trial in compensated NASH cirrhosis has also been completed. Akero has also evaluated efruxifermin in combination with GLP-1 receptor agonists.

Novelty: Moderate. The bivalent Fc-FGF21 architecture is a distinctive engineering approach within the class, but the FGF21 agonist mechanism is shared with the other analogs.

Effect size: The HARMONY Phase 2b trial reported fibrosis improvement of at least one stage without MASH worsening in 39 percent (28 mg) and 41 percent (50 mg) of patients versus 20 percent on placebo, with MASH resolution rates of 40 to 56 percent versus 12 percent on placebo [12]. These effect sizes are broadly compara-

ble to the efimosfermin Phase 2b data (45.2 percent fibrosis improvement, 67.7 percent MASH resolution), with the caveat that cross-trial comparison is unreliable due to differences in patient populations, endpoints, and statistical methodology.

Promising potential: High. Efruxifermin is in Phase 3 development with multiple ongoing registrational trials. It represents the principal competitor to efimosfermin in the FGF21 analog class.

Side-effect profile: Gastrointestinal adverse events (nausea, diarrhea) are the principal tolerability finding, similar in character to the FGF21 analog class. The 50 mg dose was associated with higher rates of treatment-emergent adverse events and treatment discontinuation relative to the 28 mg dose [12]. No severe hepatic or cardiovascular safety signals have been identified.

Overall validation: High. The most extensive clinical database of any FGF21 analog, with Phase 2b histologic data and Phase 3 trials in progress.

Comparison to efimosfermin: Efruxifermin requires weekly subcutaneous injection; efimosfermin requires once-monthly injection. The monthly dosing of efimosfermin may confer a significant adherence and patient-preference advantage in a chronic disease requiring long-term therapy. The clinical efficacy signals are broadly comparable in magnitude at the Phase 2 level, though formal head-to-head comparison data are not available. Efruxifermin has a larger clinical database and a more advanced Phase 3 program.

12.2 Pegzofermin (BIO89-100; 89bio)

Mechanism: PEGylated (glycoPEGylated) FGF21 analog. Site-specific glycoPEGylation extends the circulating half-life to approximately 55 to 100 hours, enabling weekly or biweekly subcutaneous dosing [6, 7].

Development trajectory: Pegzofermin was evaluated in Phase 1b/2a and Phase 2b trials in MASH. The Phase 2b ENLIVEN trial in MASH with F2/F3 fibrosis (24 weeks, two dose groups) demonstrated significant improvements in fibrosis stage and in noninvasive biomarkers (iron-corrected T1, Enhanced Liver Fibrosis [ELF] test, liver stiffness, FibroScan-AST [FAST] scores) [13]. 89bio has advanced pegzofermin to Phase 3 development.

Novelty: Low. PEGylation is a well-established protein half-life extension technology and does not represent a novel engineering approach.

Effect size: Phase 2b histologic data demonstrated fibrosis improvement, though published response rates are not directly comparable to efimosfermin and efruxifermin due to differences in study design and endpoints.

Promising potential: Moderate to high. Phase 3 development is underway, though the program is less mature than the efruxifermin Phase 3 program.

Side-effect profile: Generally well tolerated. Gastrointestinal adverse events are reported but appear less frequent than with some other FGF21 analogs, possibly reflecting the PEGylation-mediated pharmacokinetic smoothing of peak-to-trough fluctuations.

Overall validation: Moderate to high. Phase 2b histologic data and Phase 3 initiation provide substantial clinical validation.

Comparison to efimosfermin: Pegozafermin requires weekly or biweekly dosing versus efimosfermin's monthly dosing. The half-life advantage of efimosfermin is substantial (21 days versus 55 to 100 hours). PEGylation introduces the theoretical risk of PEG-related immunogenicity and vacuolation, which Fc-fusion approaches avoid.

12.3 Zalfermin (Novo Nordisk)

Mechanism: A chemically stabilized FGF21 analog engineered for superior chemical stability and natural FGFR selectivity. Zalfermin incorporates structural modifications that improve thermal and chemical stability relative to native FGF21, enabling favorable storage conditions [14].

Development trajectory: Zalfermin is in Phase 2b development for MASH. Published clinical data are limited compared to efruxifermin and pegozafermin. The Novo Nordisk hepatology program positions zalfermin within a broader metabolic disease portfolio that includes semaglutide (GLP-1 RA) and potential combination strategies.

Novelty: Moderate. The chemical stabilization approach is distinct from the Fc-fusion and PEGylation strategies used by other analogs.

Effect size: Phase 2b data are not yet published in sufficient detail for quantitative comparison.

Promising potential: Moderate. The Novo Nordisk sponsorship provides substantial development resources, and the combination potential with semaglutide is scientifically attractive.

Side-effect profile: Published safety data are limited. The class-typical gastrointestinal adverse event profile is expected.

Overall validation: Low to moderate. Clinical data are early relative to efruxifermin and pegozafermin.

Comparison to efimosfermin: Zalfermin and efimosfermin represent different engineering approaches to the same FGF21 agonist mechanism. The relative merits will depend on comparative clinical efficacy, safety, dosing frequency, and combination potential data that are not yet available.

12.4 Resmetirom (Madrigal Pharmaceuticals)

Mechanism: Resmetirom is not an FGF21 analog but rather a selective thyroid hormone receptor beta (THR-beta) agonist. It is included in this comparator panel because it is the first and (as of the monograph revision date) only FDA-approved pharmacotherapy for MASH with moderate-to-advanced fibrosis (F2/F3), approved under the brand name Rezdiffra in March 2024 [15]. Resmetirom activates THR-beta in hepatocytes, promoting hepatic lipid metabolism and reducing hepatic steatosis through mechanisms distinct from FGF21 signaling.

Development trajectory: Resmetirom was approved by the FDA on the basis of the MAESTRO-NASH Phase 3 trial, which demonstrated significant MASH resolution (25.9 to 29.9 percent at 80 and 100 mg versus 9.7 percent placebo at 52 weeks) and fibrosis improvement (25.9 percent at 80 mg versus 14.2 percent placebo) [15].

Novelty: High. THR-beta agonism is a fundamentally different mechanism from FGF21 pathway activation and represents the first approved pharmacotherapy in the MASH space.

Effect size: The MAESTRO-NASH MASH resolution rates (25.9 to 29.9 percent) and fibrosis improvement rates (25.9 percent) are numerically lower than the efimosfermin Phase 2b data (67.7 percent MASH resolution, 45.2 percent fibrosis improvement), though cross-trial comparison is unreliable. The Phase 3 data included a larger, more heterogeneous patient population, which typically produces lower response rates than Phase 2 trials.

Promising potential: High. Resmetirom is the approved standard of care for MASH with F2/F3 fibrosis. Its presence defines the regulatory and clinical landscape into which efimosfermin will enter.

Side-effect profile: Diarrhea and nausea are the most common adverse events. Resmetirom carries labeling warnings for drug-induced liver injury and thyroid function monitoring. The safety profile is generally manageable.

Overall validation: Very high. FDA-approved on the basis of Phase 3 data with histologic endpoints.

Comparison to efimosfermin: Resmetirom and efimosfermin act through entirely different mechanisms (THR-beta agonism versus FGF21 pathway activation), making combination therapy mechanistically rational. The clinical comparison will depend on the efimosfermin Phase 3 readout relative to the MAESTRO-NASH benchmark. Efimosfermin offers the potential advantage of monthly versus daily dosing, direct antifibrotic activity (which THR-beta agonism does not directly provide), and the metabolic benefits of FGF21 signaling (triglyceride reduction, insulin sensitization, adiponectin elevation).

12.5 Tirzepatide (Lilly)

Mechanism: Tirzepatide is a dual glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist approved for type 2 diabetes (Mounjaro) and obesity (Zepbound). It is included because of its ongoing Phase 3 evaluation in MASH (the SYNERGY-NASH trial), representing the incretin-based approach to MASH therapy [16].

Development trajectory: The SYNERGY-NASH Phase 2 trial (72 weeks) reported MASH resolution without fibrosis worsening in 43.6 to 62.4 percent of tirzepatide-treated patients (5 to 15 mg weekly) versus 10.1 percent on placebo. Phase 3 trials are ongoing.

Novelty: Moderate within the GLP-1 RA class; high as a dual GIP/GLP-1 RA.

Effect size: MASH resolution rates (up to 62.4 percent at 15 mg) are numerically comparable to the efimosfermin Phase 2b MASH resolution rate (67.7 percent), though the mechanisms and trial designs differ substantially. Fibrosis improve-

ment with tirzepatide appears more modest relative to FGF21 analogs; the antifibrotic mechanism is indirect (mediated through weight loss and metabolic improvement) rather than the direct HSC-targeted antifibrotic activity of FGF21.

Promising potential: Very high. Tirzepatide's established approvals in diabetes and obesity, its weight loss efficacy, and its Phase 3 MASH development make it a formidable comparator.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea) are significant and dose-dependent. Weight loss, while beneficial for MASH, may be undesirable in some patient populations.

Overall validation: High. Phase 2 MASH data are strong; Phase 3 trials are ongoing. Approved for diabetes and obesity.

Comparison to efimosfermin: Tirzepatide and efimosfermin act through non-overlapping mechanisms (incretin signaling versus FGF21 signaling). Efimosfermin offers direct antifibrotic activity and monthly dosing; tirzepatide offers substantial weight loss and glycemic control. Combination therapy is a plausible development strategy, with efimosfermin providing the antifibrotic component and tirzepatide providing the metabolic and weight loss component.

12.6 Comparator summary

The five comparators span three distinct mechanistic classes: FGF21 analogs (efruxifermin, pegozafermin, zalfermin), THR-beta agonist (resmetirom), and dual incretin agonist (tirzepatide). Efimosfermin occupies a distinctive position within the FGF21 analog subclass through its 21-day half-life and once-monthly dosing schedule, which represents the longest dosing interval of any FGF21 analog in clinical development. The clinical efficacy signals in Phase 2 are competitive with the other FGF21 analogs and with the incretin-based approach, though Phase 3 confirmation is pending. The direct antifibrotic mechanism distinguishes the FGF21 class from resmetirom (which targets steatosis more directly than fibrosis) and from tirzepatide (which targets fibrosis indirectly through weight loss and metabolic improvement). The monthly dosing interval is expected to provide a meaningful adherence advantage in the chronic disease setting. The principal uncertainty is the Phase 3 efficacy and safety profile relative to the approved standard (resmetirom) and the weekly-dosed FGF21 competitors (efruxifermin, pegozafermin).

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