

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pemvidutide

A 29-amino-acid unimolecular peptide engineered for equipotent GLP-1 and glucagon receptor co-agonism, conjugated to a proprietary glycolipid moiety for weekly subcutaneous dosing, under clinical development for metabolic dysfunction-associated steatohepatitis, obesity, and alcohol use disorder.

DOCUMENT	KDC-MN-1410
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodi ac bio l abs Research
COMPOUND CLASS	Balanced dual glucagon-like peptide-1 (GLP-1) and glucagon receptor agonist peptide with glycolipid half-life extension

ABSTRACT

Pemvidutide (ALT-801; CAS 2538014-94-5; UNII A35F525WBG; molecular formula C₁₈₂H₂₇₅N₃₉O₅₄; molecular weight 3873.42 g/mol) is a synthetic 29-amino-acid peptide that functions as a balanced (1:1) dual agonist of the glucagon-like peptide-1 receptor (GLP-1R) and the glucagon receptor (GCGR), developed by Altimune, Inc. (Gaithersburg, Maryland) for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), obesity, alcohol use disorder (AUD), and alcohol-associated liver disease (ALD). The compound incorporates sequence elements derived from both GLP-1 and glucagon and is conjugated to an 18-carbon diacid alkyl chain through a proprietary glycosidic linkage (designated EuPort), which provides near-quantitative but transient binding to serum albumin and extends the plasma half-life to a duration consistent with once-weekly subcutaneous administration without dose titration [1, 2]. The dual receptor mechanism differentiates pemvidutide from selective GLP-1 receptor agonists such as semaglutide and liraglutide: GLP-1R activation suppresses appetite through hypothalamic and brainstem satiety circuits, delays gastric emptying, and improves glycemic control, while GCGR activation directly stimulates hepatic fatty acid beta-oxidation, suppresses de novo lipogenesis, and increases energy expenditure through thermogenic pathways, producing a composite antisteatotic and weight-reducing pharmacology that is mechanistically suited to liver-predominant metabolic disease [3, 4, 5]. In the translational AMLN diet-induced obese mouse model of NASH, pemvidutide at 10 nmol/kg subcutaneous produced approximately 25 percent body weight reduction, significant reductions in liver triglycerides, galectin-3,

collagen type 1 alpha 1, and NAFLD Activity Score, with efficacy exceeding that of semaglutide and elafibranor at equimolar doses on composite histological endpoints [6]. Clinical development has advanced through Phase 1 studies (NCT04561245, 100 subjects), Phase 1b/2a studies in MASLD (NCT05006885, 95 subjects; NCT05292911, 64 subjects), the Phase 2 MOMENTUM obesity trial (391 subjects, 48 weeks), and the Phase 2b IMPACT trial in biopsy-confirmed MASH (NCT05989711, 212 subjects) [1, 7, 8, 9, 10]. In the Phase 1b/2a MASLD study (Harrison et al. 2025), 12 weeks of pemvidutide at 1.8 mg weekly produced a 68.5 percent relative reduction in liver fat content by MRI-proton density fat fraction versus 4.4 percent for placebo ($p < 0.001$), with 55.6 percent of treated subjects achieving liver fat normalization to 5 percent or below [8]. Extension to 24 weeks produced 75.2 percent liver fat reduction at 1.8 mg and 6.2 percent body weight reduction versus placebo [7]. In the MOMENTUM trial, pemvidutide at 2.4 mg weekly for 48 weeks produced mean weight loss of 15.6 percent versus 2.2 percent on placebo, with body composition analysis demonstrating 78.1 percent of weight loss attributable to fat mass and 21.9 percent to lean mass [9, 10]. In the Phase 2b IMPACT trial (Nouredin et al. 2025) in 212 patients with biopsy-confirmed MASH and fibrosis stages F2 or F3, pemvidutide met the primary endpoint of MASH resolution without fibrosis worsening: 59.1 percent at 1.2 mg and 52.1 percent at 1.8 mg versus 19.1 percent for placebo ($p < 0.0001$ for both comparisons) [11]. Topline 48-week data demonstrated continued antifibrotic activity with statistically significant improvements in Enhanced Liver Fibrosis score and liver stiffness measurement versus placebo [12]. The United States Food and Drug Administration has granted Breakthrough Therapy Designation for pemvidutide in MASH (January 2026) and Fast Track designations for both MASH and AUD [13, 14]. Phase 3

registrational programs for MASH and the VELOCITY Phase 3 program for obesity are in planning as of May 2026. Safety across completed trials has been favorable; adverse events are predominantly gastrointestinal (nausea, diarrhea, decreased appetite), mild to moderate in severity, and concentrated in the first 16 weeks of treatment. No imbalances in cardiac events, arrhythmias, or clinically meaningful heart rate increases have been observed. This monograph reviews the compound identification, structural pharmacology, mechanism of action, pharmacokinetics, preclinical and clinical evidence base, sourcing and quality verification, reconstitution and handling, stack interactions, adverse events, and a comparative assessment of five alternative agents (survodutide, semaglutide, tirzepatide, cotadutide, resmetirom) against pemvidutide on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Pemvidutide. The name was recommended by the World Health Organization in the -dutide stem series, indicating a peptide acting at the glucagon receptor family.

Development code: ALT-801 (Altimune, Inc.). The development code is the canonical identifier in the preclinical pharmacology and Phase 1 clinical literature and appears on all ClinicalTrials.gov registrations for the compound [1, 6].

Chemical Abstracts Service registry number: 2538014-94-5.

Unique Ingredient Identifier (UNII): A35F525WBG (United States Food and Drug Administration Substance Registration System).

Marketed names: None as of May 2026. The compound is in clinical development and has not received marketing authorization in any jurisdiction.

1.2 Structural class and chemistry

Pemvidutide is a synthetic linear peptide of the proglucagon-derived dual agonist class. The compound is designed on the oxyntomodulin scaffold, a 37-amino-acid peptide produced by post-translational processing of proglucagon in enteroendocrine L-cells of the distal ileum and colon [3, 15]. Endogenous oxyntomodulin contains the full 29-amino-acid glucagon sequence at its N-terminus followed by an 8-amino-acid C-terminal extension and activates both GLP-1R and GCGR with relatively low potency compared to the dedicated ligands GLP-1(7-36)amide and glucagon. Pemvidutide is engineered through amino acid substitutions to enhance receptor affinity, confer resistance to dipeptidyl peptidase-4 (DPP-4) proteolysis, and achieve a balanced (approximately 1:1) ratio of GLP-1R to GCGR activation [4, 5, 6].

Molecular formula: C₁₈₂H₂₇₅N₃₉O₅₄.

Molecular weight: 3873.42 g/mol.

Physical properties: White to off-white lyophilized powder or clear to slightly opalescent solution for injection. Soluble in aqueous buffers at physiological pH. The compound is supplied as an aqueous formulation for subcutaneous injection in clinical studies.

Glycolipid conjugation (EuPort): Pemvidutide incorporates an 18-carbon diacid alkyl chain covalently attached to the peptide backbone through a novel glycosidic linkage, a proprietary modification designated EuPort by Altimmune [1, 2]. This glycolipid surfactant provides near-quantitative (estimated greater than 99 percent) but transient binding to circulating serum albumin, which protects the peptide from enzymatic degradation and renal filtration and extends the terminal elimination half-life from minutes (native oxyntomodulin) to days, sufficient for once-weekly subcutaneous administration [1, 2]. The glycosidic attachment chemistry is distinct from the direct lysine acylation used in semaglutide (C18 fatty diacid), liraglutide (C16 fatty acid palmitate), and tirzepatide (C20 fatty diacid).

Receptor activation ratio: Pemvidutide is described as a balanced GLP-1/glucagon dual receptor agonist, indicating approximately equipotent activation of GLP-1R and GCGR in functional cell-based assays [6, 8]. This balanced profile distinguishes pemvidutide from cotadutide (which favors GLP-1R approximately 5-fold over GCGR) and from survodutide (which also favors GLP-1R over GCGR). The balanced agonism is hypothesized to maximize the hepatic antisteatotic contribution from GCGR activation while maintaining the appetite-suppressive and glycemic benefits from GLP-1R activation [4, 5, 6].

1.3 Synthesis

The synthesis of pemvidutide has not been described in full detail in the public domain. Based on the general methodology for peptides of this class, the 29-amino-acid peptide backbone is produced by solid-phase peptide synthesis using standard Fmoc (9-fluorenylmethoxycarbonyl) chemistry on an automated peptide synthesizer, followed by on-resin or solution-phase conjugation of the EuPort glycolipid moiety to a designated residue on the peptide chain [1]. The glycosidic linkage between the alkyl chain and the peptide is a proprietary element of the Altimmune platform; the precise attachment chemistry (O-glycosidic, N-glycosidic, or a mixed linker) has not been disclosed. Purification is by preparative reversed-phase high-performance liquid chromatography (RP-HPLC), with characterization by mass spectrometry, amino acid analysis, and bioassay for receptor potency.

Manufacturing is conducted under current Good Manufacturing Practice (cGMP) conditions for clinical supply. The specific details of resin loading, coupling reagents, side-chain protection strategy, conjugation chemistry, and purification conditions are proprietary.

2. Abstract

Pemvidutide (ALT-801) is a glycolipid-conjugated synthetic peptide that activates both the glucagon-like peptide-1 receptor (GLP-1R) and the glucagon receptor (GCGR) with balanced potency, engineered to replicate and surpass the dual incretin activity of the endogenous proglucagon-derived hormone oxyntomodulin while conferring pharmacokinetic stability sufficient for once-weekly subcutaneous dosing without dose titration [1, 2, 3]. The compound is in clinical development by Altimmune, Inc. for metabolic dysfunction-associated steatohepatitis (MASH), obesity, alcohol use disorder with overweight (AUD), and alcohol-associated liver disease (ALD).

The dual receptor mechanism produces a composite pharmacology in which GLP-1R activation drives appetite suppression, delayed gastric emptying, and glycemic improvement, while GCGR activation drives hepatic fatty acid oxidation, increased energy expenditure, reduced hepatic de novo lipogenesis, and direct mobilization of hepatic lipid stores [3, 4, 5]. This composite mechanism provides a liver-directed therapeutic action that is independent of weight loss and is the principal mechanistic basis for liver fat reductions exceeding those predicted from weight loss alone [6, 8].

Clinical development has progressed through Phase 1, Phase 1b/2a, Phase 2, and Phase 2b studies. The MOMENTUM Phase 2 trial demonstrated mean weight loss of 15.6 percent at the 2.4 mg dose over 48 weeks, with 78.1 percent of weight loss attributable to fat mass and only 21.9 percent to lean mass, a ratio more favorable than that reported with semaglutide [9, 10]. In the MASLD Phase 1b/2a study, pemvidutide at 1.8 mg weekly produced 68.5 percent relative liver fat reduction at 12 weeks, with 55.6 percent achieving liver fat normalization [8]. The Phase 2b IMPACT trial in 212 patients with biopsy-confirmed MASH demonstrated MASH resolution without worsening fibrosis in 59.1 percent at 1.2 mg versus 19.1 percent on placebo, with continued antifibrotic improvement through 48 weeks [11, 12]. The compound has received FDA Breakthrough Therapy Designation for MASH and Fast Track designations for MASH and AUD [13, 14]. Phase 3 registrational programs are in planning. Safety is dominated by mild-to-moderate gastrointestinal events concentrated in the first 16 weeks, with no cardiac safety signals identified across the clinical program.

3. Discovery and Development History

3.1 Origin and rationale

The pharmacological concept underlying pemvidutide derives from the endogenous proglucagon-derived peptide oxyntomodulin, a 37-amino-acid hormone released from intestinal L-cells after nutrient ingestion that activates both GLP-1R and GCGR [3, 15]. Clinical studies of oxyntomodulin infusion in humans demonstrated that dual receptor activation produces weight loss, appetite suppression, and energy expenditure increases, but the native hormone has a plasma half-life of approximately 12 minutes due to rapid DPP-4 cleavage and renal clearance, precluding therapeutic use [15, 16]. Multiple pharmaceutical programs have therefore pursued synthetic analogs with enhanced receptor potency, DPP-4 resistance, and pharmacokinetic extension through fatty acid acylation, PEGylation, or Fc fusion to enable weekly dosing [4, 5].

Altimmune, Inc., a clinical-stage biopharmaceutical company based in Gaithersburg, Maryland, developed pemvidutide as a structurally optimized dual GLP-1/glucagon agonist peptide with balanced receptor activation and conjugation to the proprietary EuPort glycolipid moiety for albumin-mediated half-life extension [1, 2]. The compound was designated ALT-801 during preclinical development.

3.2 Preclinical development

The preclinical pharmacology of ALT-801 was characterized by Nestor et al. (2022) in Scientific Reports using the Amylin Liver NASH (AMLN) diet-induced obese C57BL/6J mouse model with biopsy-confirmed steatohepatitis and fibrosis [6]. In a 12-week treatment study, ALT-801 at 5 and 10 nmol/kg subcutaneous was compared to semaglutide at 10 nmol/kg subcutaneous and elafibranor at 78 micromol/kg oral. ALT-801 at 10 nmol/kg reduced body weight to the normal lean range (approximately 25 percent reduction), significantly reduced liver triglycerides, total cholesterol, galectin-3 (hepatic inflammation marker), and collagen type 1 alpha 1 (fibrosis marker), with composite NAFLD Activity Score improvements exceeding those

of semaglutide and elafibranor [6]. In a preclinical hamster model of free-choice alcohol intake, pemvidutide demonstrated greater than 80 percent reduction in alcohol preference, providing the rationale for the AUD clinical program [14].

3.3 Clinical development timeline

The FDA cleared the Investigational New Drug (IND) application for pemvidutide in obesity in July 2021 [17]. The clinical program has proceeded through the following milestones:

Phase 1 (NCT04561245): First-in-human single and multiple ascending dose study in 100 subjects with overweight or obesity. Completed October 2021. Established safety, tolerability, and pharmacokinetics supporting once-weekly dosing [1].

Drug-drug interaction study (NCT04972396): Evaluated pemvidutide 1.8 mg at steady state with metformin, warfarin, digoxin, atorvastatin, and oral contraceptives in 40 subjects. Completed May 2022. No clinically significant pharmacokinetic interactions reported [1].

Phase 1b/2a MASLD, 12 weeks (NCT05006885): Randomized, double-blind, placebo-controlled study in 95 subjects with MASLD. Published by Harrison et al. (2025) in the Journal of Hepatology [8].

Phase 1b/2a MASLD, 24-week extension (NCT05292911): Extension study in 64 subjects. Published by Browne et al. (2025) in JHEP Reports [7].

Phase 2 MOMENTUM obesity trial: 48-week randomized, double-blind, placebo-controlled study in 391 subjects with overweight or obesity without diabetes. Topline results reported November 2023; data presented at the American Diabetes Association 84th Scientific Sessions, June 2024 [9, 10].

Phase 2b IMPACT MASH trial (NCT05989711): Multicenter, randomized, double-blind, placebo-controlled study in 212 patients with biopsy-confirmed MASH, F2/F3 fibrosis. Twenty-four-week results published in The Lancet (Nouredin et al. 2025); 48-week topline results reported December 2025 [11, 12].

FDA Breakthrough Therapy Designation for MASH granted January 2026 [13]. FDA Fast Track designations for MASH and AUD [14]. RECLAIM Phase 2 trial for AUD initiated May 2025 [18]. Phase 3 registrational programs for MASH and VELOCITY Phase 3 for obesity in planning as of May 2026.

4. Mechanism of Action

Pemvidutide is a unimolecular dual agonist that activates two G-protein-coupled receptors of the class B1 (secretin) family: the glucagon-like peptide-1 receptor (GLP-1R) and the glucagon receptor (GCGR). The two receptor activities produce complementary and in some cases synergistic metabolic effects that constitute the mechanistic basis for the compound's activity across obesity, hepatic steatosis, steatohepatitis, and fibrosis.

4.1 GLP-1 receptor agonism

The GLP-1 receptor is expressed on pancreatic beta cells, hypothalamic arcuate and paraventricular nuclei, the area postrema and nucleus tractus solitarius of the brainstem, vagal afferent neurons, gastric smooth muscle, and cardiomyocytes [19]. GLP-1R activation by pemvidutide produces the following principal pharmacological effects:

Appetite suppression and satiety: Activation of GLP-1R in the hypothalamus and brainstem stimulates proopiomelanocortin (POMC) neurons and inhibits neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons, reducing food intake and increasing meal-induced satiety [19].

Delayed gastric emptying: GLP-1R activation on vagal afferents and gastric smooth muscle slows gastric emptying, contributing to postprandial satiety and reducing postprandial glucose excursions. This effect tachyphylaxes partially with chronic dosing.

Glucose-dependent insulin secretion: GLP-1R activation on pancreatic beta cells potentiates glucose-stimulated insulin secretion through cyclic adenosine monophosphate (cAMP)-dependent mechanisms. The glucose dependence provides an intrinsic safeguard against hypoglycemia [19].

Glucagon suppression: GLP-1R activation produces paracrine suppression of glucagon secretion from pancreatic alpha cells, reducing hepatic glucose output. This effect is partially counterbalanced by the direct GCGR agonism of pemvidutide, a pharmacological tension important for the glycemic safety profile in non-diabetic populations.

4.2 Glucagon receptor agonism

The glucagon receptor is expressed at highest density on hepatocytes and at lower density on renal tubular cells, pancreatic beta cells, adipocytes, and cardiomyocytes [4, 20]. GCGR activation produces:

Hepatic fatty acid beta-oxidation: GCGR activation on hepatocytes stimulates mitochondrial beta-oxidation of fatty acids through cAMP-dependent activation of carnitine palmitoyltransferase 1 (CPT1) and downstream oxidative enzymes [4, 5, 20]. This is the principal liver-directed mechanism and the primary basis for the potent liver fat reduction observed with pemvidutide that exceeds weight-loss-dependent effects alone.

Suppression of de novo lipogenesis: GCGR activation reduces hepatic de novo lipogenesis through downregulation of sterol regulatory element-binding protein 1c (SREBP-1c) and fatty acid synthase expression [4, 5]. Combined with increased oxidation, this produces a net reduction in hepatic triglyceride content.

Increased energy expenditure: GCGR activation increases resting energy expenditure through hepatic substrate cycling, activation of brown and beige adipose tissue thermogenesis, increased hepatic oxygen consumption, and stimulation of fibroblast growth factor 21 (FGF21) release [4, 16]. The energy expenditure component may contribute to the favorable body composition (high proportion of fat loss, low proportion of lean mass loss) observed with pemvidutide.

Hepatic glucose output: GCGR activation stimulates glycogenolysis and gluconeogenesis, increasing hepatic glucose output. In the context of pemvidutide, concurrent GLP-1R-mediated insulin secretion and glucagon suppression counterbalance this effect, producing a net glycemic effect that is approximately neutral or mildly glucose-lowering in non-diabetic populations [8, 11].

4.3 Synergistic and complementary effects

The balanced activation of GLP-1R and GCGR by pemvidutide produces effects that exceed the sum of the individual receptor contributions in several domains [4, 5, 16]:

Liver fat reduction combines GCGR-driven hepatic fatty acid oxidation and lipogenesis suppression (direct, weight-independent) with GLP-1R-driven caloric reduction and reduced adipose lipolytic substrate delivery to the liver (indirect,

weight-dependent). Clinical data demonstrate liver fat reductions of 68.5 percent at 12 weeks, substantially exceeding the 4.3 percent body weight loss at the same timepoint [8].

Weight loss combines GLP-1R-driven appetite suppression with GCGR-driven energy expenditure increases, producing a dual mechanism of negative energy balance [9, 10].

Body composition: The GCGR-mediated increase in energy expenditure appears to favor fat mass mobilization over lean mass catabolism. In the MOMENTUM trial, 78.1 percent of weight loss was fat mass and only 21.9 percent lean mass, a ratio more favorable than the approximately 60 to 65 percent fat mass loss reported with semaglutide in the STEP trials [10].

4.4 The glycemic balance

A central pharmacological consideration for GLP-1/glucagon dual agonists is the management of opposing glycemic effects [4, 5]. Pemvidutide's balanced 1:1 potency ratio produces a net glycemic effect that is approximately neutral in non-diabetic populations. In the IMPACT trial, which included both diabetic and non-diabetic participants, no clinically significant hyperglycemia was observed [11]. The glycemic profile in larger type 2 diabetes populations remains to be fully characterized in Phase 3 studies.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Pemvidutide is administered by subcutaneous injection. Absorption from the subcutaneous depot is gradual, mediated by the EuPort glycolipid conjugation, which promotes formation of a peptide-albumin complex at the injection site that enters the systemic circulation through lymphatic and capillary absorption [1, 2]. Compared to semaglutide, pemvidutide demonstrates a longer time to maximum concentration (T_{max}), a substantially lower maximum concentration (C_{max}), and a similar area under the concentration-time curve (AUC) [1, 2]. This flattened pharmacokinetic envelope is the proposed mechanistic basis for the observation that pemvidutide does not require the gradual dose titration (typically over 4 to 8 weeks) standard with semaglutide, tirzepatide, and other GLP-1R agonists, as gastrointestinal adverse events with GLP-1-based agents correlate with peak plasma concentration [1, 2].

5.2 Distribution

Pemvidutide circulates primarily bound to serum albumin through the EuPort glycolipid moiety, with estimated albumin binding of greater than 99 percent [1, 2]. The high albumin binding restricts glomerular filtration and proteolytic access, extending the circulating half-life. Volume of distribution is expected to be small (approximately 0.05 to 0.1 L/kg), consistent with the high degree of albumin binding that restricts distribution to plasma and interstitial fluid compartments. Tissue distribution to the liver (principal GCGR target), pancreas, hypothalamus, brainstem, and gastrointestinal tract is expected based on the receptor pharmacology.

5.3 Metabolism

Pemvidutide is metabolized through general peptide proteolysis following dissociation from albumin. The compound is resistant to DPP-4 cleavage at the N-terminus through amino acid substitutions in the peptide backbone. The albumin conjugation

tion provides additional protection from proteolytic enzymes through steric shielding. No cytochrome P450-dependent metabolism is expected. The absence of CYP-mediated metabolism predicts a low potential for CYP-mediated drug-drug interactions, consistent with the results of the Phase 1 drug-drug interaction study [1].

5.4 Elimination

The elimination half-life supports once-weekly dosing. The exact terminal half-life has not been published in a peer-reviewed pharmacokinetic study but is estimated at approximately 5 to 7 days based on the weekly dosing interval and the pharmacokinetic class characteristics of albumin-bound peptide therapeutics [1, 2]. Clearance is driven by proteolytic metabolism rather than renal filtration (the albumin-bound complex is too large for glomerular filtration) or hepatic CYP metabolism.

5.5 Routes of administration

Subcutaneous injection is the only route evaluated in clinical trials. The compound is formulated as a sterile aqueous solution for subcutaneous injection. Doses evaluated include 1.2 mg, 1.8 mg, and 2.4 mg administered once weekly [8, 9, 11]. Injection sites used in clinical trials include the abdomen, thigh, and upper arm.

5.6 Special populations

Pemvidutide has been evaluated primarily in adult populations. The MOMENTUM trial enrolled subjects aged 18 to 65 years with BMI of 30 kg/m² or greater, or 27 kg/m² or greater with at least one weight-related comorbidity, excluding subjects with type 2 diabetes [9]. The IMPACT trial enrolled adult patients with biopsy-confirmed MASH and F2 or F3 fibrosis, with and without type 2 diabetes [11]. Pediatric, geriatric, renal impairment, and hepatic impairment pharmacokinetic data have not been published. The compound is investigational and not recommended for use during pregnancy or lactation.

6. Preclinical Pharmacology

6.1 AMLN diet-induced obese mouse model of NASH

The principal preclinical pharmacology study was published by Nestor et al. (2022) in Scientific Reports [6]. Male C57BL/6J mice were fed the AMLN diet (40 percent kcal fat from trans-fat, 20 percent fructose, 2 percent cholesterol) for 32 weeks to establish obesity, hepatic steatosis, inflammation, and fibrosis, modeling the histological features of human NASH. After disease establishment, mice were randomized to 12 weeks of treatment with vehicle, ALT-801 at 5 nmol/kg or 10 nmol/kg subcutaneous, semaglutide at 10 nmol/kg subcutaneous, or elafibranor at 78 micromol/kg oral.

Body weight: ALT-801 at 10 nmol/kg reduced body weight to the normal lean range (approximately 30 grams from a baseline of approximately 40 grams), a reduction of approximately 25 percent. Semaglutide at the same molar dose produced approximately 15 to 18 percent reduction. Elafibranor produced minimal weight loss [6].

Liver triglycerides and cholesterol: ALT-801 at both doses significantly reduced hepatic triglycerides and total cholesterol versus vehicle ($p < 0.05$). Reductions at the high dose exceeded those of semaglutide and elafibranor [6].

Hepatic inflammation: Galectin-3, a validated marker of hepatic inflammation in NASH, was significantly reduced by ALT-801 at both doses versus vehicle ($p < 0.05$), with reductions significantly greater than elafibranor and numerically greater than semaglutide [6].

Hepatic fibrosis: Collagen type 1 alpha 1, a marker of stellate cell activation and collagen deposition, was significantly reduced by ALT-801 at both doses versus vehicle ($p < 0.05$). This antifibrotic effect is notable because GLP-1R monoagonists have generally not demonstrated significant direct antifibrotic activity in preclinical NASH models [6].

NAFLD Activity Score: The composite NAS was improved in all ALT-801-treated animals, with the high-dose group showing significantly greater improvement than the active comparators on multiple histological components [6].

6.2 Alcohol preference model

In a preclinical hamster model of free-choice alcohol intake, pemvidutide treatment produced greater than 80 percent reduction in alcohol preference compared to baseline [14, 18]. The mechanism is attributed to GLP-1R-mediated modulation of mesolimbic reward circuitry, a pathway characterized with selective GLP-1R agonists and preserved with dual agonist pharmacology. The GCGR component may provide additional hepatoprotective benefit through reduction of alcohol-associated steatosis and inflammation.

6.3 Mechanism validation

The preclinical data support the hypothesis that GCGR activation adds hepatic fatty acid oxidation and energy expenditure effects to the appetite-suppressive effects of GLP-1R activation. The observation that ALT-801 exceeded semaglutide on hepatic steatosis and inflammation endpoints at equimolar dosing, despite comparable weight loss magnitude, provides indirect evidence that the hepatic benefits are driven at least in part by direct GCGR-mediated mechanisms rather than weight loss alone [6].

7. Clinical Evidence Base

7.1 Phase 1: Single and multiple ascending dose (NCT04561245)

The first-in-human study enrolled 100 subjects with overweight or obesity in single and multiple ascending dose cohorts [1]. The study established the safety profile (predominantly gastrointestinal adverse events: nausea, decreased appetite, diarrhea), confirmed pharmacokinetics supporting once-weekly dosing with a flattened concentration-time profile relative to semaglutide, and demonstrated dose-dependent body weight reduction in the multiple dose cohorts. The pharmacokinetic data confirmed the delayed Tmax, reduced Cmax, and similar AUC that characterize the EuPort-modified absorption profile [1, 2].

7.2 Phase 1b/2a: 12-week MASLD study (NCT05006885)

Harrison et al. (2025) published results in the Journal of Hepatology of a randomized, double-blind, placebo-controlled study in 95 adults with MASLD (BMI 28 kg/m² or greater, liver fat content 10 percent or greater by MRI-PDFF) [8]. Participants were randomized to pemvidutide 1.2 mg, 1.8 mg, or 2.4 mg weekly or placebo for 12 weeks.

Liver fat reduction: Relative reductions from baseline were 46.6 percent (1.2 mg), 68.5 percent (1.8 mg), and 57.1 percent (2.4 mg) versus 4.4 percent (placebo); $p < 0.001$ versus placebo for all treatment groups [8].

Response rates at 1.8 mg: 94.4 percent achieved 30 percent or greater liver fat reduction; 72.2 percent achieved 50 percent or greater reduction; 55.6 percent achieved normalization to 5 percent or below [8].

Body weight: Mean reduction of 4.3 percent at 1.8 mg versus placebo ($p < 0.001$) [8].

Biomarkers: ALT reduction of 13.8 IU/L versus placebo ($p = 0.029$); corrected T1 reduction of 75.9 milliseconds versus placebo ($p = 0.002$) at the 1.8 mg dose [8].

Safety: No severe or serious drug-related adverse events. Most common events were nausea, decreased appetite, and diarrhea, predominantly mild and transient [8].

7.3 Phase 1b/2a: 24-week extension (NCT05292911)

Browne et al. (2025) published 24-week results in JHEP Reports from 64 participants who continued at their assigned doses [7].

Liver fat reduction at 24 weeks: 56.3 percent (1.2 mg), 75.2 percent (1.8 mg), and 76.4 percent (2.4 mg) relative reduction versus 14.0 percent (placebo) [7].

Response rates at 1.8 mg: 84.6 percent achieved 50 percent or greater liver fat reduction; 53.8 percent achieved normalization [7].

Body weight: 6.2 percent reduction at 1.8 mg versus placebo ($p < 0.001$) [7].

The continued improvement from 12 to 24 weeks demonstrates that the anti-steatotic effect had not plateaued at 12 weeks [7].

7.4 Phase 2 MOMENTUM: Obesity (48 weeks)

The MOMENTUM trial was a 48-week, multicenter, randomized, double-blind, placebo-controlled Phase 2 study in 391 subjects with overweight or obesity (BMI 30 kg/m² or greater, or BMI 27 kg/m² or greater with comorbidity) without type 2 diabetes [9, 10]. Subjects were randomized 1:1:1:1 to pemvidutide 1.2 mg, 1.8 mg, 2.4 mg, or placebo weekly with diet and exercise.

Weight loss at week 48: 10.3 percent (1.2 mg), 11.2 percent (1.8 mg), 15.6 percent (2.4 mg), and 2.2 percent (placebo) [9].

At the 2.4 mg dose, more than 30 percent of subjects achieved 20 percent or greater weight loss, and 48 percent of subjects with baseline obesity no longer met the BMI threshold for obesity [9].

Weight loss was continuing at week 48 with no evidence of plateau [9].

Body composition: MRI-based analysis in 50 subjects demonstrated 78.1 percent of weight loss attributable to fat mass and 21.9 percent to lean mass. This lean mass preservation ratio is more favorable than historical data with semaglutide (approx-

mately 60 to 65 percent fat, 35 to 40 percent lean) and is attributed to the GCGR-mediated increase in energy expenditure and preferential fat mobilization [10].

Metabolic improvements: Robust reductions in BMI, total cholesterol, LDL cholesterol, and triglycerides and improvements in blood pressure, with no imbalances in cardiac events, arrhythmias, or clinically meaningful heart rate increases [9].

Safety: Only one (1.0 percent) drug-related serious adverse event (vomiting at 2.4 mg). Discontinuation rates due to adverse events were 6.2 percent (placebo), 5.1 percent (1.2 mg), 19.2 percent (1.8 mg), and 19.6 percent (2.4 mg), with most discontinuations occurring in the first 16 weeks [9].

7.5 Phase 2b IMPACT: MASH with fibrosis (NCT05989711)

The IMPACT trial was an international, multicenter, randomized, double-blind, placebo-controlled Phase 2b study at 83 sites in the United States and Australia, enrolling 212 patients with biopsy-confirmed MASH and F2 or F3 fibrosis, with and without diabetes [11, 12]. Patients were randomized to pemvidutide 1.2 mg weekly, 1.8 mg weekly, or placebo for 24 weeks without dose titration.

MASH resolution (co-primary endpoint, met): MASH resolution without worsening fibrosis in 59.1 percent (1.2 mg) and 52.1 percent (1.8 mg) versus 19.1 percent (placebo); $p < 0.0001$ for both comparisons [11].

Fibrosis improvement (co-primary endpoint, not met): Fibrosis improvement by at least one stage without worsening MASH was 34.5 percent (1.2 mg) and 36 percent (1.8 mg) versus approximately 28 percent (placebo); the differences were not statistically significant [11]. The failure to meet the fibrosis endpoint at 24 weeks is consistent with the understanding that fibrosis regression requires longer treatment (48 to 72 weeks).

Weight loss: Up to 6.2 percent at 24 weeks with no evidence of plateauing [11].

Forty-eight-week topline results: Continued treatment produced statistically significant improvements versus placebo in Enhanced Liver Fibrosis (ELF) score and liver stiffness measurement (LSM) by transient elastography, with additional reductions from week 24 across both doses, supporting ongoing antifibrotic activity [12].

7.6 Alcohol use disorder and alcohol-associated liver disease

The RECLAIM Phase 2 trial (NCT06987513) evaluating pemvidutide 2.4 mg weekly in 100 patients with AUD and overweight was initiated in May 2025 [18]. The RESTORE Phase 2 trial (NCT07009860) evaluating pemvidutide 2.4 mg weekly in 100 patients with alcohol-associated liver disease was initiated in 2025. The FDA granted Fast Track designation for pemvidutide in AUD [14]. Clinical results are not yet available.

8. Sourcing and Quality Verification

Pemvidutide is an investigational compound not approved for clinical use in any jurisdiction as of May 2026. All clinical trial material is manufactured by or on behalf of Altimune, Inc. under cGMP. The drug product is supplied as a sterile aqueous solution for subcutaneous injection.

Research-grade pemvidutide (ALT-801) has been listed by specialty chemical suppliers (MedChemExpress, others) as a research reagent [21]. Investigators acquiring research-grade material should confirm:

- Peptide identity by mass spectrometry (confirmation of molecular weight at 3873.42 plus or minus 1 for the intact molecule by electrospray ionization)
- Purity by reversed-phase HPLC (area-percent purity, ideally greater than 95 percent)
- Peptide content determination by amino acid analysis or UV absorbance
- Endotoxin testing (limulus amebocyte lysate) for any preparation intended for in vivo research
- Bioactivity confirmation by GLP-1R and GCGR functional cell-based assay

Third-party research-grade material may not incorporate the proprietary EuPort glycolipid conjugation and may therefore have substantially different pharmacokinetic properties (shorter half-life, higher peak concentration, requirement for more frequent dosing) compared to the clinical formulation. Investigators should treat material without confirmed glycolipid conjugation as pharmacokinetically distinct from the clinical compound. Lot-to-lot variability should be anticipated, and independent analytical confirmation is essential for any investigation requiring dose-response precision.

9. Reconstitution and Handling

The clinical formulation of pemvidutide is a ready-to-use sterile aqueous solution that does not require reconstitution. Formulation details (buffer, pH, excipients) have not been published but are expected to follow standard peptide injectable formulation principles (phosphate or histidine buffer, pH 6.0 to 7.4, with a surfactant such as polysorbate 20 or 80).

Storage: The drug product should be stored refrigerated (2 to 8 degrees Celsius) and protected from light. The solution should not be frozen.

For research-grade preparations supplied as lyophilized powder, reconstitution in sterile water for injection or phosphate-buffered saline (pH 7.4) at concentrations of 1 to 10 mg/mL is appropriate. For cell-based assays, stock solutions of 1 to 10 mM in dimethyl sulfoxide (DMSO) may be used, with final DMSO concentration maintained below 0.1 percent (v/v). Stock solutions should be aliquoted into single-use volumes and stored at minus 20 degrees Celsius (short-term) or minus 80 degrees Celsius (long-term). Repeated freeze-thaw cycles should be limited to no more than 3 to 5. Working dilutions should be prepared in the assay or dosing buffer immediately before use. Low-binding polypropylene or glass containers are recommended to minimize adsorptive peptide losses.

10. Stack Interactions and Combinations

Pemvidutide interacts with several drug classes through its dual-receptor pharmacology and gastrointestinal effects. Investigators should consider:

Insulin and insulin secretagogues: GLP-1R-mediated potentiation of insulin secretion may produce additive hypoglycemic effects with exogenous insulin, sulfonylureas, or meglitinides. The concurrent GCGR agonism partially counterbalances hypoglycemic risk through increased hepatic glucose output. In non-diabetic populations the risk is low; in diabetic populations, glucose-lowering agent dose adjustment may be required.

Other GLP-1R agonists: Concurrent use with semaglutide, liraglutide, exenatide, or dulaglutide is pharmacologically redundant for the GLP-1R component and produces additive gastrointestinal adverse events. The combination is not recommended.

Tirzepatide and other dual/multi-agonists: Concurrent use with tirzepatide (GLP-1/GIP), retatrutide (GLP-1/GIP/GCGR), or survodutide (GLP-1/GCGR) produces overlapping receptor activation with unpredictable dose-response and additive adverse effects. Not recommended outside controlled research settings.

Oral medications affected by gastric emptying: GLP-1R-mediated delayed gastric emptying may alter absorption kinetics of orally administered medications. The Phase 1 drug-drug interaction study evaluated warfarin, digoxin, atorvastatin, metformin, and oral contraceptives without clinically significant interactions [1]. Investigators should consider monitoring drug levels for narrow-therapeutic-index compounds during pemvidutide initiation.

Metformin: No clinically significant pharmacokinetic interaction. The combination has complementary mechanisms (metformin acts through hepatic AMPK activation) and is pharmacologically rational.

Lipid-lowering agents: Concurrent statins, ezetimibe, or PCSK9 inhibitors may produce additive lipid-lowering effects. The combination is not expected to be adverse and may be therapeutically beneficial.

Hepatotoxic agents: Given the liver-directed mechanism, concurrent use with hepatotoxic agents (methotrexate, high-dose acetaminophen, isoniazid) should be monitored with hepatic function testing.

Alcohol: Alcohol co-exposure is anticipated in the AUD/ALD clinical population. Alcohol has direct hepatotoxic effects and promotes steatosis, inflammation, and fibrosis. The pharmacological rationale for pemvidutide in AUD combines GLP-1R-mediated reduction in reward-seeking behavior with GCGR-mediated hepatoprotection.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events across clinical trials are gastrointestinal, consistent with GLP-1R agonist class effects [7, 8, 9, 11]:

- Nausea: the most common adverse event, reported in approximately 15 to 33 percent of treated participants depending on dose and study. Predominantly mild to moderate, concentrated in the first 2 to 4 weeks of treatment, declining with continued dosing
- Decreased appetite: approximately 10 to 15 percent
- Diarrhea: approximately 5 to 10 percent; mild to moderate, generally self-limiting
- Vomiting: approximately 3 to 8 percent; more common at higher doses
- Constipation: low frequency, mild
- Injection site reactions: infrequent, mild

11.2 Treatment discontinuation

In the MOMENTUM trial, discontinuation rates due to adverse events were 6.2 percent (placebo), 5.1 percent (1.2 mg), 19.2 percent (1.8 mg), and 19.6 percent (2.4 mg), with the majority occurring in the first 16 weeks [9]. Only one drug-related serious adverse event (vomiting at 2.4 mg) was reported across the trial.

11.3 Cardiac safety

No imbalances in cardiac events, arrhythmias, or clinically meaningful heart rate increases have been observed across the clinical program [9, 11]. Improvements in blood pressure and serum lipids were observed. The cardiac profile is notable because semaglutide and other GLP-1R agonists produce modest dose-dependent heart rate increases (2 to 4 beats per minute).

11.4 Hepatic safety

Pemvidutide produced reductions in ALT and other hepatic biomarkers consistent with the disease-modifying mechanism [8, 11]. No drug-induced liver injury or hepatic enzyme elevations beyond those attributable to the underlying liver disease have been reported.

11.5 Glycemic safety

No clinically significant hyperglycemia has been reported despite the theoretical risk from GCGR-mediated hepatic glucose output. In the MASLD studies (approximately 27 to 29 percent with type 2 diabetes), modest glycemic improvement was observed [7, 8]. The balanced dual agonism design produces GLP-1R-mediated insulin potentiation that offsets GCGR-mediated gluconeogenesis.

11.6 Theoretical safety considerations

The following class-related theoretical considerations apply:

- Pancreatitis: reported rarely with GLP-1R agonists (approximately 0.1 to 0.3 percent); not reported with pemvidutide but the dataset is limited
- Thyroid C-cell tumors: GLP-1R agonists produce C-cell hyperplasia and medullary thyroid carcinoma in rodents at supraphysiological doses; clinical relevance in humans is uncertain
- Cholelithiasis: rapid weight loss from any cause increases gallstone risk
- Lean mass loss: a concern with all incretin-based weight loss therapies, though pemvidutide's body composition data (21.9 percent lean mass loss) appear favorable relative to the class

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative agents against pemvidutide, evaluated on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators were selected to represent the principal competitive landscape for pemvidutide across MASH and obesity indications.

12.1 Survodutide (BI 456906)

Mechanism: Dual GLP-1R/GCGR agonist with a potency ratio favoring GLP-1R activation over GCGR activation (approximately 5:1). Developed by Boehringer Ingelheim and Zealand Pharma [22].

Development trajectory: Completed Phase 2 trials in obesity and MASH. In the Phase 2 MASH trial (Sanyal et al. 2024, NEJM), survodutide at 6 mg produced MASH resolution in 83 percent and fibrosis improvement in 52 percent at 48 weeks [22]. Phase 3 programs (SYNCHRONIZE) for obesity and MASH underway.

Novelty: Low. The GLP-1R/GCGR dual agonist mechanism is shared with pemvidutide.

Effect size: Substantial. Weight loss up to 18.7 percent at 48 weeks; MASH resolution 83 percent and fibrosis improvement 52 percent at 48 weeks. These rates exceed pemvidutide's 24-week IMPACT data, though the longer treatment duration is a confounding factor.

Promising potential: High. Active Phase 3 programs; strong industry sponsor.

Side-effect profile: Gastrointestinal adverse events at rates of 40 to 60 percent at higher doses, exceeding pemvidutide's rates. Dose titration required over multiple weeks.

Overall validation: High. The most clinically advanced GLP-1/GCGR dual agonist alongside pemvidutide.

Comparison to pemvidutide: Survodutide's GLP-1R-favoring ratio contrasts with pemvidutide's balanced 1:1 ratio. Pemvidutide's advantages include no-titration dosing, lower gastrointestinal adverse event rates, and potentially greater direct hepatic GCGR engagement from the balanced ratio. Survodutide's advantages include numerically greater weight loss and longer-duration MASH efficacy data with both histological endpoints met. Head-to-head comparison has not been performed.

12.2 Semaglutide (Ozempic/Wegovy)

Mechanism: Selective GLP-1 receptor agonist. No glucagon receptor activity. C18 fatty diacid-acylated for weekly dosing [23].

Development trajectory: Approved for type 2 diabetes (Ozempic), obesity (Wegovy), and cardiovascular risk reduction. In MASH, the Phase 2 NASH trial (Newsome et al. 2021, NEJM) demonstrated NASH resolution in 59 percent at 0.4 mg daily at 72 weeks, but fibrosis improvement was not statistically significant [24]. Phase 3 MASH trials are underway.

Novelty: Low in the dual agonist context. Semaglutide is a selective GLP-1R agonist without GCGR activity.

Effect size: Weight loss of 14.9 percent at 68 weeks in STEP 1 [23]. NASH resolution comparable to pemvidutide at 59 percent but at 72 weeks versus pemvidutide's 59.1 percent at 24 weeks; no significant fibrosis improvement.

Promising potential: Very high. Established standard of care for obesity with extensive real-world evidence.

Side-effect profile: Gastrointestinal adverse events are the principal signal. Dose titration over 4 to 8 weeks required. Body composition data suggest 35 to 40 percent lean mass loss, less favorable than pemvidutide.

Overall validation: Very high. FDA-approved in multiple indications.

Comparison to pemvidutide: Pemvidutide's principal advantages are the direct GCGR-mediated hepatic mechanism (supporting greater liver fat reduction independent of weight), favorable body composition (78 percent fat loss), and no-titration dosing. Semaglutide's advantages are extensive clinical evidence, multiple approved indications, established safety record, and commercial availability. The ob-

servation that pemvidutide achieves comparable MASH resolution rates (59.1 percent) in 24 weeks versus semaglutide's 59 percent in 72 weeks is notable, though direct comparison across different trial designs requires caution.

12.3 Tirzepatide (Mounjaro/Zepbound)

Mechanism: Dual GLP-1R/GIP receptor (GIPR) agonist. No glucagon receptor activity. C20 fatty diacid-acylated for weekly dosing [25].

Development trajectory: Approved for type 2 diabetes (Mounjaro) and obesity (Zepbound). The SYNERGY-NASH Phase 2 trial produced MASH resolution in up to 73.6 percent and fibrosis improvement in 47 percent at 52 weeks [26]. The most advanced dual incretin agonist with the largest safety database.

Novelty: Moderate. GLP-1R/GIPR dual agonism is mechanistically distinct from GLP-1R/GCGR; no direct hepatic GCGR mechanism.

Effect size: Very large. Weight loss of 20.9 percent at 72 weeks in SURMOUNT-1 [25]. MASH resolution 73.6 percent at 52 weeks. These effect sizes exceed currently reported pemvidutide data.

Promising potential: Very high. FDA-approved; additional filings anticipated for MASH.

Side-effect profile: Gastrointestinal adverse events at 30 to 50 percent; dose titration over 4 to 20 weeks required. Large Phase 3 safety database without unexpected serious signals.

Overall validation: Very high. The most clinically validated dual incretin agonist.

Comparison to pemvidutide: Tirzepatide and pemvidutide engage different second receptors (GIPR versus GCGR). Tirzepatide lacks the direct hepatic fatty acid oxidation and energy expenditure effects of GCGR activation. Tirzepatide produces greater absolute weight loss and has established regulatory approval. Pemvidutide's potential advantages are the GCGR-mediated hepatic mechanism, the body composition profile with 78 percent fat mass loss, no-titration dosing, and expansion into alcohol-related indications. Whether GCGR agonism (pemvidutide) or GIPR agonism (tirzepatide) is superior for liver-predominant metabolic disease is a central unanswered question.

12.4 Cotadutide (MEDI0382)

Mechanism: Dual GLP-1R/GCGR agonist with approximately 5:1 ratio favoring GLP-1R. Developed by AstraZeneca [27].

Development trajectory: Completed Phase 2 trials in type 2 diabetes and obesity. A 54-week Phase 2b trial demonstrated dose-dependent HbA1c reduction and weight loss of approximately 5 to 7 percent. AstraZeneca has deprioritized the program following mixed results and competitive landscape considerations [27].

Novelty: Low. Mechanism shared with pemvidutide and survodutide.

Effect size: Moderate. Weight loss of approximately 5 to 7 percent at 54 weeks and improvements in hepatic fat, but effect sizes generally smaller than semaglutide at matched timepoints.

Promising potential: Low. Development deprioritized; uncertain path to Phase 3.

Side-effect profile: Gastrointestinal adverse events similar to other GLP-1R agonists. No unique safety signals.

Overall validation: Low to moderate. Multiple Phase 2 trials completed but program deprioritized.

Comparison to pemvidutide: Pemvidutide has produced substantially greater effect sizes in both weight loss (15.6 percent versus 5 to 7 percent) and liver fat reduction (68.5 percent relative versus smaller reductions). The GLP-1R-favoring ratio of cotadutide may have limited the GCGR-mediated hepatic contribution relative to pemvidutide's balanced ratio. Pemvidutide has a more advanced and active clinical program.

12.5 Resmetirom (Rezdiffra)

Mechanism: Selective thyroid hormone receptor beta (THR-beta) agonist. Entirely distinct from the incretin/glucagon axis. THR-beta activation in hepatocytes stimulates fatty acid oxidation, reduces lipid accumulation, and lowers serum lipids. Does not affect appetite, body weight, or gastric emptying [28].

Development trajectory: First therapy approved by the FDA specifically for MASH (March 2024), based on the Phase 3 MAESTRO-NASH trial. Approved for adults with non-cirrhotic MASH and F2/F3 fibrosis [28].

Novelty: High. The THR-beta agonist mechanism is orthogonal to incretin/glucagon dual agonism.

Effect size: In MAESTRO-NASH, resmetirom 80 mg produced MASH resolution in 29.9 percent and fibrosis improvement in 25.9 percent at 52 weeks, rates numerically lower than pemvidutide's IMPACT 24-week results (59.1 percent MASH resolution) [28]. Direct comparison is limited by trial design differences.

Promising potential: Moderate to high. The only approved MASH therapy. However, effect sizes are modest relative to the dual agonist class, and the compound does not produce weight loss.

Side-effect profile: Diarrhea, nausea (at lower rates than GLP-1R agonists), and transient hepatic transaminase elevations. Generally well tolerated.

Overall validation: High. FDA-approved and commercially available. Current standard of care for MASH.

Comparison to pemvidutide: Pemvidutide and resmetirom represent orthogonal mechanisms. Pemvidutide produces greater MASH resolution rates and additionally produces significant weight loss, lipid improvement, and metabolic benefit, none of which resmetirom provides. Resmetirom's advantage is approved regulatory status and commercial availability. The two compounds could potentially be combined for additive hepatic benefit through complementary mechanisms (GCGR-mediated and THR-beta-mediated fatty acid oxidation), though this combination has not been studied.

12.6 Comparator summary

The five comparators span the competitive landscape for MASH and obesity pharmacotherapy. **Survodutide** is the most direct competitor, sharing the GLP-1/GCGR mechanism but with a GLP-1R-favoring ratio and greater weight loss at longer treatment durations. **Semaglutide** is the established obesity standard of care but lacks the GCGR hepatic mechanism and achieves comparable MASH resolution rates only at substantially longer treatment durations. **Tirzepatide** produces the greatest absolute weight loss but engages GIPR rather than GCGR and lacks direct hepatic lipid oxidation effects. **Cotadutide** shares the dual agonist mechanism but has been deprioritized after modest results. **Resmetirom** is the only approved MASH therapy, operating through an entirely distinct mechanism with more modest efficacy but established regulatory status.

Pemvidutide occupies a differentiated position through three principal characteristics: the balanced 1:1 GLP-1R:GCGR potency ratio that maximizes direct hepatic effects; the favorable body composition profile with 78.1 percent fat mass loss; and the flattened pharmacokinetic profile that eliminates dose titration. The FDA Breakthrough Therapy Designation positions the compound for an expedited registration pathway. Principal uncertainties include competitive dynamics with survodutide, Phase 3 performance at registration scale, the glycemic profile in type 2 diabetes populations, and long-term safety characterization from larger studies.

13. References

1. Altimune, Inc. Pemvidutide (ALT-801) Phase 1 12-week results. Investor presentation, September 2021. ClinicalTrials.gov identifier NCT04561245.
2. Altimune, Inc. Pemvidutide product profile. Company technical documentation, 2022.
3. Day JW, Ottaway N, Patterson JT, et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat Chem Biol.* 2009;5(10):749-757.
4. Habegger KM, Heppner KM, Geary N, Bartness TJ, DiMarchi R, Tschop MH. The metabolic actions of glucagon revisited. *Nat Rev Endocrinol.* 2010;6(12):689-697.
5. Pocai A, Carber PE, Bianchi E, et al. Glucagon-like peptide 1/glucagon receptor co-agonism promotes beta-oxidation and reverses obesity and hepatic steatosis in mice. *Diabetes.* 2009;58(10):2258-2266.
6. Nestor JJ, Parkes D, Feigh M, Suschak JJ, Harris MS. Effects of ALT-801, a GLP-1 and glucagon receptor dual agonist, in a translational mouse model of non-alcoholic steatohepatitis. *Sci Rep.* 2022;12(1):6439.
7. Browne SK, Suschak JJ, Tomah S, Gutierrez JA, Yang J, Georges B, Roberts MS, Harris MS. Safety and efficacy of 24 weeks of pemvidutide in metabolic dysfunction-associated steatotic liver disease: a randomized, controlled clinical trial. *JHEP Rep.* 2025;7(11):101483.
8. Harrison SA, Browne SK, Suschak JJ, Tomah S, Gutierrez JA, Yang J, Roberts MS, Harris MS. Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: a randomized, double-blind, placebo-controlled study. *J Hepatol.* 2024;81(5):801-811.
9. Altimune, Inc. Altimune announces positive topline results from MOMENTUM 48-week Phase 2 obesity trial of pemvidutide. Press release, November 30, 2023.
10. Frias JP, Mather KJ, Engel SS, et al. Pemvidutide, a GLP-1/glucagon dual receptor agonist, in subjects with overweight or obesity: a 48-week, placebo-controlled, Phase 2 (MOMENTUM) trial. *Diabetes.* 2024;73(Supplement 1):262-OR.

11. Noureddin M, Harrison SA, Loomba R, et al. Safety and efficacy of weekly pemvidutide versus placebo for metabolic dysfunction-associated steatohepatitis (IMPACT): 24-week results from a multicentre, randomised, double-blind, phase 2b study. *Lancet*. 2025;406(10472):2167-2178.
12. Altimmune, Inc. Altimmune announces that pemvidutide achieved key measures of success at 48 weeks in IMPACT Phase 2b MASH trial. Press release, December 2025.
13. Altimmune, Inc. Altimmune receives FDA Breakthrough Therapy Designation for pemvidutide in MASH. Press release, January 2026.
14. Altimmune, Inc. Altimmune announces FDA Fast Track designation for pemvidutide in alcohol use disorder (AUD). Press release, 2025.
15. Wynne K, Park AJ, Small CJ, et al. Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. *Diabetes*. 2005;54(8):2390-2395.
16. Cegla J, Troke RC, Jones B, et al. Coinfusion of low-dose GLP-1 and glucagon in man results in a reduction in food intake. *Diabetes*. 2014;63(11):3711-3720.
17. Altimmune, Inc. Altimmune announces FDA clearance of pemvidutide (ALT-801) IND for obesity. Press release, July 2021.
18. Altimmune, Inc. Altimmune announces initiation of RECLAIM Phase 2 trial evaluating the efficacy and safety of pemvidutide in alcohol use disorder (AUD). Press release, May 2025.
19. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab*. 2018;27(4):740-756.
20. Anderson SL. Emerging concepts in obesity management: focus on glucagon receptor agonist combinations. *Drugs Context*. 2025;14:2024-12-2.
21. MedChemExpress. Pemvidutide (ALT-801): GLP-1R/GCGR agonist. Product catalog entry, 2024.
22. Sanyal AJ, Bedossa P, Engel SS, et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med*. 2024;391(4):311-319.
23. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.

24. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med*. 2021;384(12):1113-1124.
25. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(4):327-338.
26. Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med*. 2024;391(4):299-310.
27. Nahra R, Wang T, Gadde KM, et al. Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: a 54-week randomized phase 2b study. *Diabetes Care*. 2021;44(6):1433-1442.
28. Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med*. 2024;390(6):497-509.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Pemvidutide is an investigational compound that has not been approved by any regulatory authority for any indication as of May 2026. The United States Food and Drug Administration has granted Breakthrough Therapy Designation for MASH and Fast Track designations for MASH and alcohol use disorder. Investigators should consult ClinicalTrials.gov and the Altimmune clinical development program for the most current regulatory and clinical status. Research-grade material from third-party suppliers may differ in pharmacokinetic properties from the clinical formulation. Analytical confirmation of identity, purity, and receptor potency is recommended for all research-grade lots.