THR-ß Agonism and Other Novel Mechanisms for the Treatment of MASLD/MASH

FDA-Approved Therapy

THR-ß agonist

In the liver, THR-ß agonists affect de novo lipogenesis and cholesterol metabolism by:

In MAESTRO-NASH, patients with resmetirom experienced the following:

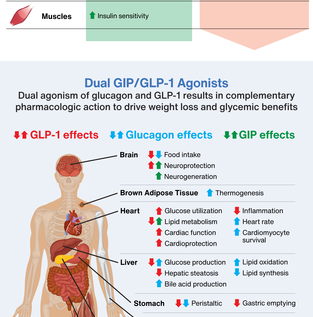
Insulin Sensitivity	MASH Resolution + NAS ≥2 Improvement (without worsening of fibrosis)	Fibrosis Improvement	Lipid Benefits
—	✓	✓	✓

FDA approval: Resmetirom is approved in the US for the treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in conjunction with diet and exercise.

Therapies in Development

Pan-PPAR Agonist

PPARs are nuclear receptors with key regulatory functions in metabolism, inflammation, and fibrogenesis



GLP-RA

GLP-RAs act directly on GLP-1 receptors to regulate several metabolic actions, including hormone secretion by pancreatic islet cells, gut motility, and satiety

	INCREASES	DECREASES
Liver	↑ Hepatic insulin sensitivity	↓ Hepatic glucose production ↓ De novo lipogenesis ↓ Steatosis
Pancreas	↑ β-cell function ↑ Insulin biosynthesis	↓ Glucagon secretion
Heart and vessels	↑ Cardioprotection ↑ Vascular protection	
Brain	↑ Satiety	↓ Body weight ↓ Food intake
GI tract		↓ Gastric emptying
Kidneys	↑ Natriuresis ↑ Nephroprotection	
Muscles	↑ Insulin sensitivity	

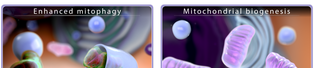
Dual GIP/GLP-1 Agonists

Dual agonism of glucagon and GLP-1 results in complementary pharmacologic action to drive weight loss and glycemic benefits

↑↑ GLP-1 effects ↓↓ Glucagon effects ↑↑ GIP effects

FGF21

- Metabolic hormone that regulates energy expenditure and glucose and lipid metabolism
- Reduces liver fat by central hepatic and peripheral actions
- Reduces liver fibrosis via metabolic pathway regulation and increased adiponectin production



Therapy	Mechanism	Insulin Sensitivity	MASH Resolution (without worsening of fibrosis)	Fibrosis Improvement	Lipid Benefits
Phase 3 Candidates					
Lanifibranor	Pan-PPAR agonist	✓	✓	✓	✓
Semaglutide	GLP-1RA	✓	✓	✓	—
Efruxifermin	FGF21	✓	✓	✓	✓
Pegozafermin	FGF21	✓	✓	✓	✓
Select Phase 2b Candidates					
Denifanstat	FASN-i	—	✓	✓	—
Tirzepatide	Twincretin: GLP-1/GIP	✓	✓	✓	—
Survodutide	Trincretin: Glucagon/ GLP-1 receptor dual agonist	✓	—	✓	✓

Abbreviations

BAT: brown adipose tissue
CRF: corticotropin-releasing factor
ER: endoplasmic reticulum
FA: fatty acid
FASN-i: fatty acid synthase inhibitor
FDA: US Food and Drug Administration
FGF21: fibroblast growth factor 21
GI: gastrointestinal
GIP: gastric inhibitory polypeptide
GLP-1: glucagon-like peptide-1
GLP-1RA: glucagon-like peptide-1 receptor agonist
HPA: hypothalamic-pituitary-adrenal
HPT: hypothalamic-pituitary-thyroid
IL: interleukin
iNOS: inducible NO synthase
MASH: metabolic dysfunction-associated steatohepatitis
MASLD: metabolic dysfunction-associated steatotic liver disease
NAS: Nonalcoholic Fatty Liver Disease Activity Score
NASH: nonalcoholic steatohepatitis
PPAR: peroxisome proliferator-activated receptor
ROS: reactive oxygen species
SAF: steatosis, activity, fibrosis
SCN/PVN: suprachiasmatic nucleus/paraventricular nucleus
SNA: sympathetic nerve activation
TGF: transforming growth factor
THR: thyroid hormone receptor
TNF: tumor necrosis factor
VLDL: very-low-density lipoprotein
WAT: white adipose tissue

References

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