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Research Article

Keywords:

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11457775/v1

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Global Landscape of MASH Therapeutics: Mechanistic Diversification and Clinical Evolution

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Abstract

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease. While resmetirom and semaglutide recently gained approval, effective therapies for MASH-related compensated cirrhosis (F4) remain lacking. This study systematically characterizes the global MASH trial portfolio to outline developmental trends and guide future trial design.

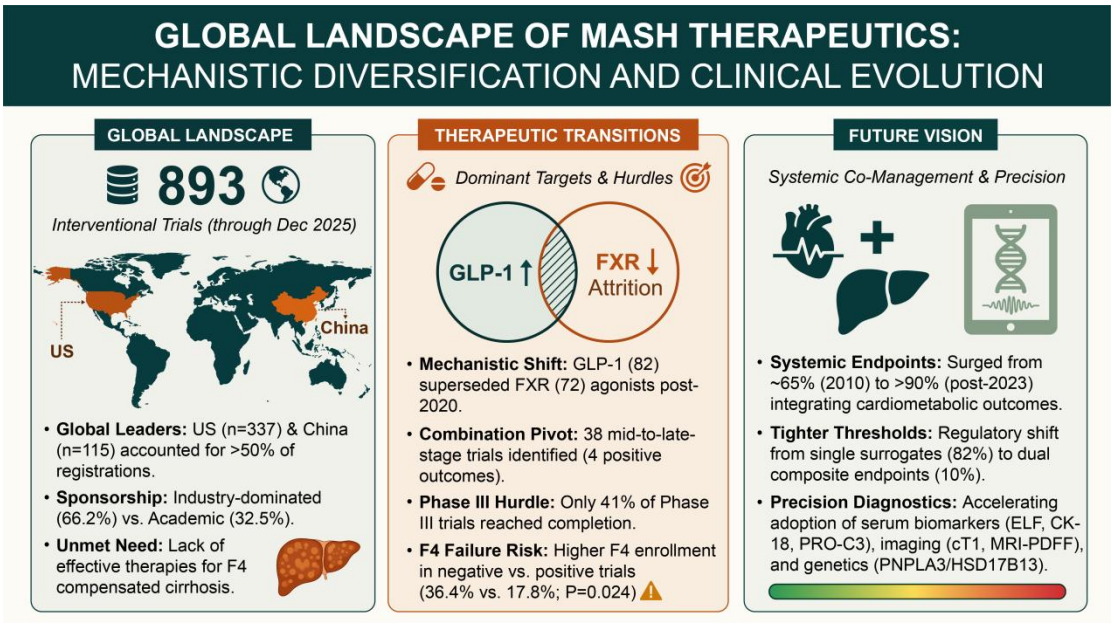
Method: We analyzed the Informa repository for interventional MASH trials registered through December 2025. Excluding observational studies, 893 trials were included. Trial metadata, mechanisms of action (MOAs), patient inclusion criteria, endpoints, and diagnostic modalities were extracted and independently verified.

Findings: The US (n=337) and China (n=115) led global registrations. GLP-1 receptor agonists (82) and FXR agonists (72) dominated mechanistic exploration, though only 41% of Phase III trials completed. Notably, negative-outcome trials enrolled

significantly more F4 patients than successful trials (36.4% vs. 17.8%; P=0.024). Post-2020, GLP-1 agonists superseded FXR agonists in pipeline dominance. We identified 38 mid-to-late-stage combination trials, four completing with positive outcomes. Cardiometabolic endpoint integration surged from ~65% (2010) to >90% (post-2023), alongside increased adoption of non-invasive biomarkers.

Conclusion: The MASH therapeutic pipeline is pivoting toward systemic, multi-mechanistic combination strategies integrating cardiometabolic co-management and non-invasive precision diagnostics. These insights inform the rational design of next-generation therapeutics for advanced disease.

Graphical Abstract



Keywords: MASH; clinical trials; drug development; combination therapy; cardiometabolic endpoints; compensated cirrhosis; GLP-1 receptor agonists; FXR agonists; non-invasive biomarkers; precision diagnostics.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major global health burden, affecting approximately 38% of the population[1]. In 20-30% of cases, simple steatosis progresses to metabolic dysfunction-associated steatohepatitis (MASH) characterized by inflammation, hepatocyte ballooning, and potential fibrosis, which is associated with significantly higher morbidity and mortality, notably from poor cardiovascular, oncological, and hepatic outcomes[2].

Despite the escalating prevalence and clinical severity of the disease, the therapeutic armamentarium for MASH has historically been severely limited. A recent watershed moment occurred with the consecutive US Food and Drug Administration (FDA) accelerated approvals of resmetirom (2024) and semaglutide (2025) for noncirrhotic MASH with moderate-to-advanced fibrosis (F2–F3)[3]. Furthermore, other emerging pharmacologic agents (e.g., the GLP-1/glucagon dual agonist pemvidutide) have demonstrated encouraging histological efficacy in late-stage clinical trials. However, despite these clinical breakthroughs, critical unmet needs remain, most notably the profound lack of effective therapies for MASH-related compensated cirrhosis (F4) and the ongoing necessity to validate long-term clinical outcome benefits for these newly approved agents[4]. Previous reviews have mapped subsets of the MASH/NASH drug pipeline, but a comprehensive, temporally resolved analysis spanning mechanistic diversification, endpoint evolution, and diagnostic advancement has been lacking. Driven by these challenges and the recent nomenclature update, the current developmental pipeline is traversing a highly dynamic yet fragmented transitional phase, rapidly shifting toward multi-target combinations, non-invasive diagnostics, and systemic cardiometabolic endpoints. To address this complex field and provide a comprehensive overview to inform future trial designs, we performed a systematic analysis of the global clinical trial portfolio for MASH to delineate overarching developmental trajectories and advance novel therapeutic strategies.

Methods

We systematically searched the Informa database (synthesizing ClinicalTrials.gov and >58,000 global registries) for pharmacological MASH/NASH trials registered through December 2025. Two independent investigators screened de-duplicated records, strictly excluding observational studies.

Extracted data encompassed fundamental metadata (e.g., phases, execution status, sponsors, geographic distribution) and granular variables across three core domains: (1)

Therapeutic strategies, including specific mechanisms of action (MOAs) and multi-drug combinations; (2) Trial design and outcomes, focusing on patient inclusion criteria (particularly F4 cirrhosis), endpoint architectures, and definitive efficacy readouts; and (3) Diagnostics, assessing the utilization of invasive biopsies versus non-invasive tests (NITs) and advanced imaging. The two investigators standardized unstructured data and resolved discrepancies via consensus, ensuring that inherent registry limitations did not compromise the macroscopic trends analyzed[5].

Statistical analyses were performed using R software (version 4.5.2). Categorical variables were summarized as frequencies and percentages. F4 inclusion rates between trial outcome groups were compared using Pearson's χ^2 and Fisher's exact tests (reporting odds ratios, 95% CIs, and unadjusted two-sided P values). Temporal trends were quantitatively aggregated and visualized using the dplyr and ggplot2 packages. Full search terms are provided in the Supplementary Table.

Results

Global Landscape and Characteristics of MASH Clinical Trials

To identify high-quality clinical trials on pharmacological interventions for MASH, a systematic search of the Informa database was conducted. As of December 2025, a total of 893 interventional trials were identified following the rigorous exclusion of observational studies, and these were included for final overall analysis (**Fig. 1**). Our analysis of the geographic distribution revealed that global clinical research in MASH is highly concentrated. The United States (337 trials) and China (115 trials) represent the two leading contributors, collectively accounting for more than half of all registered trials worldwide **(Fig. 1A)**. An evaluation of the temporal evolution of clinical trials reveals a marked and continuous expansion in research activity, with a marked increase since 2010 **(Fig. 1B).** Notably, this growth was primarily driven by a surge in early-stage trials (Phases I and II), indicating a heightened focus on early exploratory and innovative drug development in this therapeutic field.

Regarding the specific types of interventions, natural products emerged as the dominant intervention class in historical clinical trials (42 trials), followed by vitamin E and probiotic therapy **(Fig. 1C)**. Concurrently, a group of modern pharmacological agents, including semaglutide, saroglitazar and metformin, were also prominently represented. When categorizing trials by the primary drug's mechanism of action (MOA) (excluding trials with "Unidentified pharmacological activity"), Glucagon-like peptide-1 receptor agonists (GLP-1 RA) constituted the most intensively investigated class (82 trials), followed closely by Farnesoid X receptor (FXR) agonists (72 trials) **(Fig. 1D)**. Beyond these top two categories, the field featured significant activity targeting PPAR receptors (gamma and alpha agonists totaling 81 trials), sodium/glucose cotransporter 2 (SGLT-2) (41 trials), and thyroid hormone receptor beta (THR-β) (39 trials). A spectrum of other innovative mechanisms, including fibroblast growth factor 21 agonism (FGF21) and acetyl-CoA carboxylase inhibition, were also actively explored.

In terms of trial execution status, the majority of the analyzed trials are classified as completed (64.1%), with 9.7% of the total currently being open for enrollment **(Fig. 1E)**. The distribution of sponsor types, detailed in **Figure 1F**, was dominated by industry, with "Industry, all other pharma" (n = 410), "Industry, Top 20 Pharma" (n = 154), and "Industry, generic" (n = 27) together accounting for 591 trials (66.2%). Academic institutions were the second-largest single sponsor category (n = 290; 32.5%). Government agencies (n = 27), cooperative groups (n = 7), and not-for-profit funders (n = 1) each contributed fewer than 30 trials.

Operational Hurdles and the Impact of Advanced Fibrosis Enrollment

To evaluate the operational efficiency and translational hurdles within the MASH clinical landscape, we first stratified trial execution status across different clinical phases. While early-stage exploratory trials (Phase I) demonstrated a highly robust completion rate of 73%, late-stage trials exhibited lower completion frequencies. Notably, only 41% of Phase III trials were classified as completed, with the remainder being open or prematurely terminated **(Fig. 2A)**.

Patient enrollment criteria, particularly the inclusion of subjects with advanced fibrosis or cirrhosis (F4), significantly impact trial outcomes. To evaluate the temporal trends of F4 inclusion in efficacy-driven studies, the analysis was restricted to Phase II and Phase III trials initiated between 2015 and 2025. Phase I and Phase IV trials were excluded to avoid confounding from early-stage safety evaluations and post-marketing surveillance studies, respectively, which possess distinct operational objectives and enrollment thresholds. This targeted temporal analysis revealed a fluctuating trend in the incorporation of F4 patients into trial protocols. The inclusion rate of cirrhotic patients peaked notably at 26.2% in 2021, followed by a period of fluctuating inclusion rates, eventually settling at 22.6% in 2024 before declining again **(Fig. 2B)**.

Importantly, a retrospective cross-analysis of the 153 Phase II/III efficacy trials with definitive outcomes identified a statistically significant association between the inclusion of cirrhotic patients and trial outcome. Trials with "Negative" outcomes (defined as failure to meet primary efficacy endpoints or safety-related termination; n = 33) had an F4 criteria inclusion rate of 36.4% (12/33) , more than twice that of trials achieving their primary endpoints (17.8%, 19/107; $\chi^2 = 5.07$, df = 1, P = 0.024; Fisher exact P = 0.032; OR 0.38, 95% CI 0.16–0.90; risk difference 18.6 percentage points, 95% CI 0.7–36.6) **(Fig. 2C)**. This observation aligns with the elevated biological complexity of compensated cirrhotic livers, where advanced fibrosis and disrupted hepatic microenvironment reduce the likelihood of treatment response. This association does not establish causality. Confounding factors such as stricter endpoint requirements in cirrhosis populations and more advanced disease pathophysiology may also contribute to the higher failure rate.

Evolutionary Trends of Core MOAs and the Transition Toward Combination Therapies

To delineate the mechanistic trajectory of MASH therapeutics, monotherapy trials were initially stratified across seven highly investigated core mechanisms of action (MOAs): farnesoid X receptor (FXR) agonists, glucagon-like peptide-1 (GLP-1) receptor agonists, peroxisome proliferator-activated receptor-alpha (PPAR-α) and gamma (PPAR-γ)

agonists, sodium/glucose cotransporter 2 (SGLT-2) inhibitors, thyroid hormone receptor beta (THR-β) agonists, and fibroblast growth factor 21 (FGF21) analogs. Phase stratification revealed stark contrasts in pipeline maturity **(Fig. 2D)**. While FXR and GLP-1 MOAs dominated early-stage (Phase I/II) volume, FXR agonists exhibited severe pipeline attrition, characterized by a massive early footprint but minimal progression to late-stage (Phase III/IV) evaluation. This translational bottleneck stems primarily from safety and tolerability hurdles, namely pruritus and low-density lipoprotein (LDL) elevation, endemic to early-generation FXR agonists. Conversely, PPAR-γ agonists and SGLT-2 inhibitors demonstrated robust late-stage representation, driven largely by the strategic repurposing of safety-validated anti-diabetic portfolios for MASH indications **(Fig. 2D)**.

Longitudinal analysis of relative MOA share (2015–2025) highlighted a structural shift (Fig. 2E). Prior to 2019, FXR mechanisms held predominant pipeline share. Post-2020, GLP-1 agonists expanded aggressively, superseding historical FXR dominance. This crossover signifies a fundamental pivot in MASH drug development: shifting from localized intrahepatic interventions toward systemic metabolic regulation. Concurrently, THR-β agonists, specifically targeting hepatic lipotoxicity, maintained a resilient and steady upward developmental trajectory.

Driven by the multifaceted pathophysiology of MASH, interlinking lipotoxicity, systemic inflammation, and fibrogenesis, clinical strategies are increasingly pivoting to multi-MOA combinations. Analysis identified 38 mid-to-late stage (Phase II-IV) combination trials. Matrix mapping revealed that GLP-1 and FXR agonists serve as the foundational backbones for dual-MOA synergies **(Fig. 2F)**. Prominent intra-core pairings include GLP-1 + FXR (n=5), GLP-1 + SGLT-2 (n=3), and FXR or GLP-1 paired with THR-β (n=2 each) to simultaneously address distinct disease pathways. Alongside these core pairings, a prevalent strategy integrates a primary MASH MOA with adjunctive agents classified as "Other" (e.g., PPAR-γ + Other, n=7; FXR + Other, n=6). Delineation of this dataset reveals that these adjunctive agents are strategically selected for specific metabolic optimization or complementary

anti-fibrotic/inflammatory actions, primarily encompassing HMG-CoA reductase inhibitors (e.g., atorvastatin), acetyl-CoA carboxylase (ACC) inhibitors (e.g., firsocostat), omega-3 fatty acids, dipeptidyl peptidase-4 (DPP-4) inhibitors, and CCR2/CCR5 dual antagonists.

Combination regimens are meant to do two things beyond the liver target: offset adverse events that belong to a single mechanism, and manage cardiovascular risk. Four mid-to-late-stage combination trials are complete and have reported outcomes **(Table 1).** Their registered primary endpoints were hepatic fat imaging in a monotherapy-versus-placebo comparison (NCT05415722), safety and tolerability (NCT03987074), and lipid metabolism (NCT02633956). None assessed histological efficacy. Obeticholic acid plus atorvastatin follows this pattern: the combination reversed OCA-induced LDL elevation without compromising hepatic safety, but the trial's primary endpoint was lipid metabolism and histology was not assessed. The more complex regimens now under study, such as the triple combination of semaglutide, cilofexor, and firsocostat, aim to act on systemic metabolism, steatosis, and fibrogenesis at the same time. No completed trial has shown that adding a second agent improves histological outcomes over monotherapy, so clinical superiority has yet to be tested in adequately powered head-to-head trials.

Paradigm Shifts in Trial Endpoints and the Pivot to Systemic Co-management

Parallel to the mechanistic shift from liver-directed targets toward systemic metabolic regulation, the selection of trial endpoints has undergone a congruent evolution to capture the multi-systemic effects of investigational agents. The definitive success of these interventions largely depends on how clinical efficacy is measured and validated. Mapping primary and secondary endpoints in MASH trials delineated a six-domain assessment paradigm: histological outcomes, non-invasive tests (NITs), metabolic/systemic parameters, liver biochemistry, clinical/safety metrics, and patient-reported outcomes (PROs) **(Fig. 3A)**. However, stratifying primary endpoints by clinical phase revealed a distinctly stage-dependent strategy. Phase I trials are primarily anchored in clinical and safety metrics. Phase II diversifies, leveraging NITs and liver

biochemistry to gauge preliminary efficacy. Crucially, pivotal Phase III trials are overwhelmingly dominated by histological outcomes, reflecting the strict regulatory mandate for biopsy-confirmed MASH resolution or fibrosis improvement. Post-approval Phase IV trials subsequently pivot away from invasive histology, refocusing on non-invasive cardiometabolic and long-term safety evaluations **(Fig. 3B)**.

Endpoint selection is also intrinsically dictated by the MOA. Cross-sectional mapping of Phase II-IV trials across the seven core targets revealed distinct developmental priorities. Liver-directed agents, such as FGF21 agonists, heavily concentrate on histological endpoints (71.4%). Conversely, broad-spectrum metabolic modulators like GLP-1 receptor agonists exhibit a pleiotropic footprint, balancing histological (47.2%), metabolic (43.4%), and biochemical (43.4%) readouts. SGLT-2 inhibitors and PPAR agonists preferentially utilize NITs (e.g., MRI-PDFF) for efficacy. Notably, despite regulatory pushes for patient-centricity, Patient-Reported Outcomes (PROs) remain chronically underutilized, rarely exceeding 10% coverage across any core target **(Fig. 3C)**.

Longitudinally, trial designs reflect a shift toward systemic cardiometabolic co-management. Integration of cardiometabolic endpoints (spanning glycemic control, weight management, and cardiovascular outcomes) surged from approximately 65% in 2010 to consistently exceeding 90% post-2023 **(Fig. 4A)**. This evolutionary trajectory is consistent with the 2023 international nomenclature update from NASH to MASH. Both developments reflect the long-standing, cumulative shift in the scientific understanding of the disease as a hepatic manifestation of systemic metabolic dysfunction, rather than an isolated liver disorder.

Despite this growing emphasis on systemic outcomes, hepatic efficacy remains the core readout for evaluating therapeutic response in MASH trials. We further stratified efficacy endpoints into three tiers of escalating regulatory stringency: Tier 1 (single surrogate endpoints, such as standalone histology or non-invasive tests), Tier 2 (dual composite endpoints, requiring both MASH resolution and no fibrosis worsening), and Tier 3 (hard clinical outcomes, including death, liver transplantation, or hepatic

decompensation). Temporal analysis across four trial initiation eras revealed a gradual shift toward more stringent endpoint designs **(Fig. 4B)**. The proportion of Tier 1 endpoints decreased from 93% in 2012–2015 to 82% in 2022–Present. Conversely, Tier 2 endpoints increased from 1% to 10% over the same period. Tier 3 outcomes remained consistently low across all eras, ranging from 4% to 8%. Collectively, these data show that while histological surrogates remain the dominant efficacy readout, regulatory thresholds have progressively tightened over time.

Technological Penetration of Emerging Biomarkers and Non-Invasive Diagnostics

Alongside the broadening of endpoint scope and escalating efficacy thresholds, core hepatic evaluation remains bottlenecked by the invasive nature of traditional liver biopsies. To bypass this, the non-invasive biomarker field is rapidly advancing. Extracellular matrix and apoptosis markers, specifically the Enhanced Liver Fibrosis (ELF) score (n=75) and CK-18 (n=64), serve as the established serological baseline **(Fig. 4C)**. Since 2014, PRO-C3 has rapidly gained traction (n=45) as a dynamic marker for active fibrogenesis. More recently, the field has pivoted toward precision medicine and advanced imaging, integrating corrected T1 (cT1) mapping (n=16) and genetic stratification (PNPLA3 risk / HSD17B13 protective alleles) **(Fig. 4D)**. This cumulative technological evolution signals increasing industry interest in constructing non-invasive, composite diagnostic algorithms capable of reducing reliance on histological endpoints in future pivotal trials.

Discussion

Our analysis of 893 MASH trials reveals a critical shift toward systemic management, though an efficacy bottleneck persists in advanced cirrhosis. Notably, F4 inclusion was significantly associated with trial failure (36.4% vs. 17.8%; P=0.024). This reflects a structural mismatch: while early MASH responds to metabolic improvements, compensated cirrhosis is driven by dense extracellular matrix cross-linking and severe hemodynamic alterations, rendering upstream metabolic interventions less effective[6].

To overcome this efficacy ceiling, the pipeline is transitioning toward combination regimens. Post-2020, GLP-1 and THR-β agonists (e.g., resmetirom[7]) largely superseded early FXR agonists4. However, recognizing the limits of monotherapy in advanced fibrosis[8,9], developers increasingly use these agents as backbones for multi-drug therapies[10]. We identified 38 such trials; four achieved positive outcomes (Table 1) by pairing a metabolic or inflammatory backbone with orthogonal agents to mitigate adverse events or target downstream fibrogenesis. This dual approach addresses interconnected fibrogenic pathways[11,12]. Furthermore, to optimize outcomes in cirrhosis, next-generation strategies must concurrently target metabolic-fibrotic injury and altered hemodynamics (e.g., pairing FGF21 analogues with nonselective β-blockers)[13].

Parallel to mechanistic diversification, the integration of cardiometabolic endpoints surged from ~65% (2010) to >90% (post-2023). This reflects the decades-long consensus—formalized by the 2023 NASH-to-MASH nomenclature shift—that MASH is a systemic metabolic disease rather than an isolated hepatic disorder[14,15,22].

Concurrently, regulatory efficacy thresholds have tightened, shifting from single surrogates toward dual composite endpoints (histological improvement without worsening)[16]. Due to the slow progression of early MASH, the FDA and EMA permit histological surrogates for non-cirrhotic stages[17,18]. Conversely, they strictly mandate hard clinical outcomes for F4 trials, where histological improvement lacks prognostic validation and clinical events are more frequent[19]. This stringent framework, alongside insufficient drug target engagement and the biological barriers of advanced fibrosis, largely drives the high Phase III attrition observed in our analysis.

To navigate biopsy limitations[20], non-invasive diagnostics are rapidly advancing. While ELF[21] and CK-18[22] established early baselines, trials increasingly adopt dynamic biomarkers (PRO-C3)[23], advanced imaging (cT1, MRI-PDFF)[24], and genetic risk stratification (PNPLA3, HSD17B13) to precisely enrich cohorts and reduce heterogeneity[25]. AI-based pathology tools further enhance early efficacy detection[26].

Limitations include registry reporting biases, difficulty attributing efficacy in multi-drug trials, and potential selective publication bias driven by high industry sponsorship (66.2%). Future studies require advanced statistical modeling to precisely isolate the pharmacodynamic contributions within these complex regimens[27].

Conclusion

In conclusion, the MASH drug development field is rapidly advancing, though it remains characterized by geographic disparities, dominant industry sponsorship, and a critical need for mechanistic diversification. The expanding clinical portfolio, synergized with the shift toward systemic cardiometabolic endpoints and non-invasive precision diagnostics, establishes a robust foundation for future disease management. Ultimately, these macroscopic insights aim to guide the rational design of next-generation therapeutics and optimize translational efficiency, improving clinical outcomes for patients afflicted with this multifaceted metabolic syndrome.

Acknowledgements The authors confirm that this research was conducted without any commercial or financial affiliations that could beviewed as a potential conflict of interest.

Author Contributions Qingshang Li, Zirui Zhangand Jiayi Wei wrote the manuscript; Xiaona Hu, Yuanwen Chen and Zhijun Bao provided methodological and revised the manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Funding This research was funded by the Key Specialized Disease Project (2022, ZDZB2221) and Key department of Huadong Hospital (2022, ZDXK2213). Shanghai Science and Technology Committee (STCSM) (Grant No. 24YF2704400).

Data availability The underlying trial records were retrieved from the Informa Trialtrove database (Pharma Intelligence, https://www.pharmaintelligence.informa.com/), a subscription-based resource accessed through an institutional licence.

Conflict of interest The authors have not disclosed any competing interests.

Ethical approval Not applicable.

Figure legends

Figure 1. Clinical trials landscape for MASH.

(A) Geographic distribution of global trials. **(B)** Annual trial distribution by clinical phase. **(C)** Top 20 primary tested drugs. **(D)** Top 20 primary mechanisms of action (MOAs). **(E)** Proportional distribution of trial execution statuses. **(F)** Trial sponsorship categories.

Figure 2. Operational Status, Patient Inclusion Criteria, and Mechanistic Trends in MASH Clinical Trials.

(A) Stacked bar chart illustrates the distribution of trial execution statuses across different clinical phases. All identified clinical trials with explicitly reported phase and execution status information were included for this analysis. **(B)** Combined line and bar chart illustrates the temporal evolution of advanced fibrosis or compensated cirrhosis (F4) patient inclusion. Only efficacy-driven Phase II and Phase III trials initiated between 2015 and 2025 were included for this analysis, excluding Phase I and IV studies to avoid confounding from safety or post-marketing objectives. **(C)** A bar chart illustrates the inclusion rates of F4 patients stratified by definitive trial clinical outcomes. Phase II and III efficacy trials with reported outcomes were included for this analysis. F4 inclusion rates by trial outcome (n = 153: Positive 107, Indeterminate 13, Negative 33); P values from Pearson's χ^2 and Fisher's exact tests; **(D)** Grouped horizontal bar chart illustrates the trial distribution across seven core MOA, stratified by early versus late clinical stages. **(E)** A 100% stacked area chart illustrates the longitudinal shifts in the relative pipeline share among the core targets. Monotherapy trials evaluating the seven primary MOA initiated between 2015 and 2025 were included for the analysis in **(D)** and **(E)**. **(F)** A matrix heatmap illustrates the target pairings utilized in multi-drug regimens, with the number of star symbols

indicating the exact count of completed trials that achieved positive clinical outcomes for each specific combination. Phase II-IV combination therapy trials were included for this analysis.

Figure 3. Evolution of Trial Endpoints in MASH Clinical Trials.

(A) A treemap illustrates the overarching composition and relative distribution of primary and secondary endpoint domains. **(B)** A stacked bar chart illustrates the proportional distribution of primary endpoint domains stratified across clinical developmental phases. All clinical trials with explicitly reported endpoints and clinical phase information were included for the analysis in **(A)** and **(B)**. **(C)** A matrix heatmap illustrates the coverage of specific endpoint domains across the seven core target mechanisms. Phase II-IV monotherapy trials evaluating these primary MOA were included for this analysis.

Figure 4. Evolution of Efficacy Thresholds, and Non-Invasive Biomarkers in MASH Clinical Trials.

(A) A multi-line chart illustrates the longitudinal trends in the incorporation of individual and overall systemic cardiometabolic endpoints, with the vertical dashed line denoting the 2023 international nomenclature update from NASH to MASH. **(B)** An alluvial diagram illustrates the temporal shifts in the stringency tiers of hepatic efficacy endpoints across four distinct trial initiation eras. Phase II-IV initiated between 2012 and 2025 with explicitly reported primary endpoint descriptions evaluating hepatic efficacy were included for this analysis. Tier 1: single surrogate endpoints or non-invasive tests; Tier 2: dual composite endpoints requiring both MASH resolution and no fibrosis worsening; Tier 3: hard clinical outcomes including death, liver transplantation, or hepatic decompensation. **(C)** A polar area chart illustrates the cumulative utilization and relative distribution of emerging non-invasive biomarkers and genetic risk stratifications. **(D)** A longitudinal bubble chart illustrates the annual adoption timeline of specific emerging biomarkers, with the numbers inside each bubble indicating the exact count of newly initiated trials

388 utilizing that respective biomarker in a given year.

Table 1. Overview of Key Completed Combination Therapy Trials in MASH. Registration numbers: TERN-101 + TERN-501 (NCT05415722); semaglutide + cilofexor + firsocostat (NCT03987074); obeticholic acid + atorvastatin (NCT02633956); omega-3-acid ethyl esters (NCT00760513).

Trial ID (Phase)	NCT Number	Specific Regimen	Combination Strategy	Mechanism of Action	Patient Population	Endpoints Evaluated	Key Clinical Findings
351832 (Phase IIa)	NCT05415722	TERN-101 + TERN-501	FXR agonist + THR-β/GLP-1 agonist	Synergistic targeting to simultaneously improve lipid metabolism and reverse hepatic fibrogenesis.	Overweight/obese adults with presumed MASH diagnosed by imaging and elastography.	Primary: Change in MRI-PDFF at Week 12. Secondary: Change in cT1 relaxation time; overall safety.	Demonstrated dose-dependent liver fat reduction and synergistic improvements in MRI-PDFF and cT1 markers at Week 12. Well-tolerated.
351494 (Phase II)	NCT03987074	Semaglutide + Cilofexor + Firsocostat	GLP-1 RA + FXR agonist + ACC inhibitor	Combines systemic metabolic optimization with direct hepatic targeting of lipogenesis, inflammation, and fibrosis.	Biopsy-confirmed NASH with stage 2-3 fibrosis, OR clinical equivalent by non-invasive tests.	Primary: Treatment-Emergent Adverse Events (TEAEs) up to Week 24. Secondary: Changes in MRI-PDFF, ELF score, and TE/MRE.	Confirmed multi-parameter hepatic improvements across steatosis and stiffness. Regimens were well-tolerated with predominantly mild gastrointestinal events.

269972 (Phase II)	NCT02633956	Obeticholic acid (OCA) + Atorvastatin	FXR agonist + HMG-CoA reductase inhibitor	Adjunctive statin is integrated strictly to mitigate OCA-induced hyperlipidemia and maintain cardiovascular safety.	Biopsy-confirmed NASH with stage 1-4 fibrosis, absent of hepatic decompensation.	Primary: Effect on LDL concentration (change from baseline at Week 16). Secondary: Broad lipid profile and liver safety.	Atorvastatin rapidly reversed OCA-induced LDL increases to below baseline levels. Successfully optimized lipoproteins while preserving hepatic safety.
162642 (Phase IV)	NCT00760513	Omega-3-acid ethyl esters eicosapentaenoic acid + docosahexenoic acid	PPAR-α agonist & DGAT2 inhibitor	Multi-pathway lipid regulation to systematically reduce hepatic steatosis via PPAR-α agonism and DGAT2 inhibition.	Biopsy or imaging-diagnosed steatosis associated with elevated metabolic syndrome features.	Primary: Percentage of liver fat by MRS at 18 months. Secondary: Insulin sensitivity, CIMT, and cardiovascular risk markers.	High tissue DHA enrichment effectively decreased liver fat. Highlighted broad systemic and cardiovascular cross-benefits in early NAFLD/T2DM patients.

Figure 1

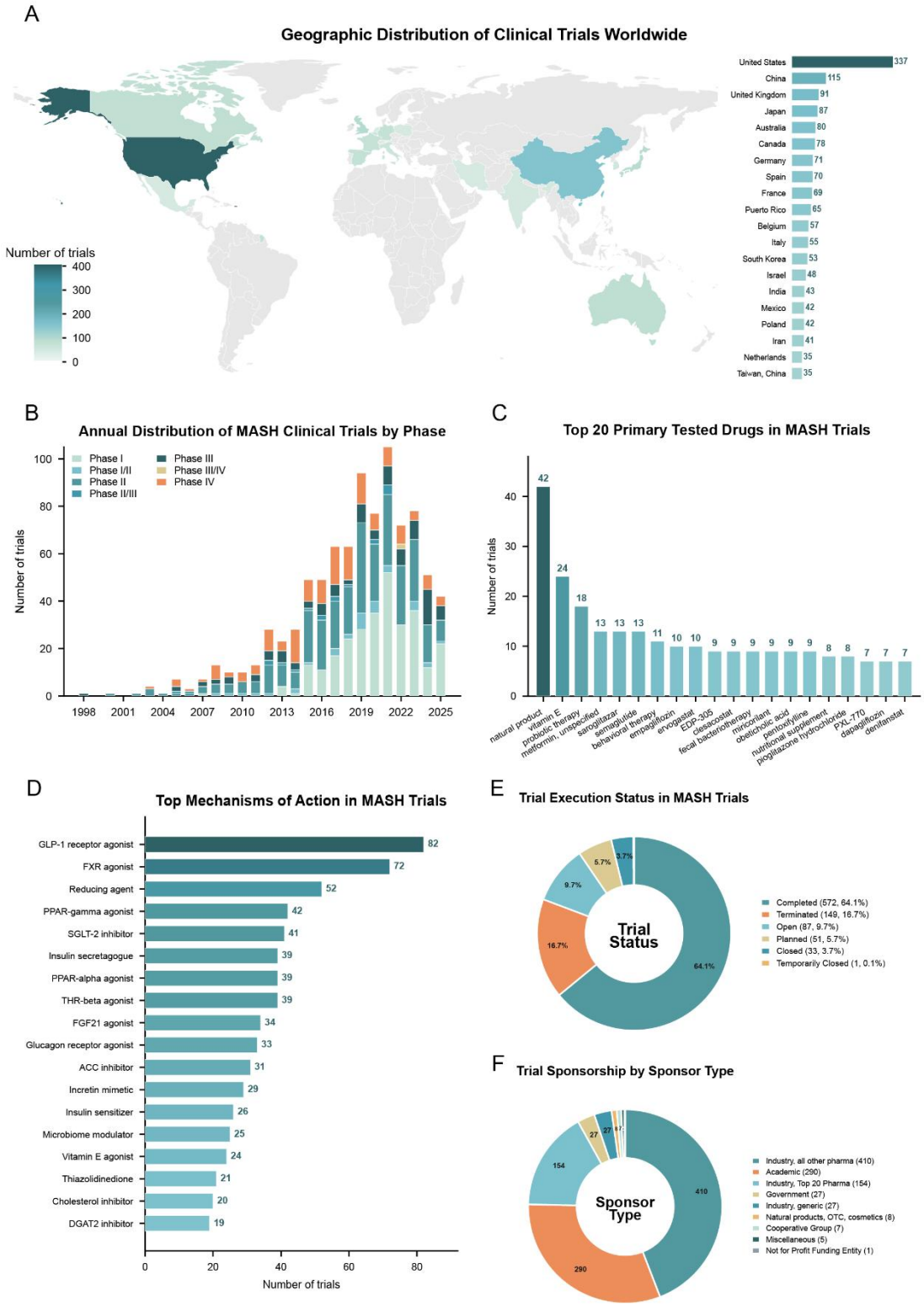

A
Geographic Distribution of Clinical Trials Worldwide
Number of trials
400
300
200
100
0
United States 337
China 115
United Kingdom 91
Japan 87
Australia 80
Canada 78
Germany 71
Spain 70
France 69
Puerto Rico 65
Belgium 57
Italy 55
South Korea 53
Israel 48
India 43
Mexico 42
Poland 42
Iran 41
Netherlands 35
Taiwan, China 35
B
Annual Distribution of MASH Clinical Trials by Phase
Phase I
Phase I/II
Phase II
Phase II/III
Phase III
Phase III/IV
Phase IV
Number of trials
1998 2001 2004 2007 2010 2013 2016 2019 2022 2025
C
Top 20 Primary Tested Drugs in MASH Trials
Number of trials
natural product 42
vitamin E 24
probiotic therapy 18
metformin, unspecified 13
saroglitazar 13
semaglutide 13
behavioral therapy 11
empagliflozin 10
elafibranor 10
EDP-305 9
obeticholic acid 9
fecal bacteriotherapy 9
miricorilant 9
pentoxifylline 9
nutritional supplement 8
pioglitazone hydrochloride 8
PXL-770 7
dapagliflozin 7
denifanstat 7
D
Top Mechanisms of Action in MASH Trials
GLP-1 receptor agonist 82
FXR agonist 72
Reducing agent 52
PPAR-gamma agonist 42
SGLT-2 inhibitor 41
Insulin secretagogue 39
PPAR-alpha agonist 39
THR-beta agonist 39
FGF21 agonist 34
Glucagon receptor agonist 33
ACC inhibitor 31
Incretin mimetic 29
Insulin sensitizer 26
Microbiome modulator 25
Vitamin E agonist 24
Thiazolidinedione 21
Cholesterol inhibitor 20
DGAT2 inhibitor 19
Number of trials
E
Trial Execution Status in MASH Trials
Trial Status
64.1%
16.7%
9.7%
5.7%
3.7%
Completed (572, 64.1%)
Terminated (149, 16.7%)
Open (87, 9.7%)
Planned (51, 5.7%)
Closed (33, 3.7%)
Temporarily Closed (1, 0.1%)
F
Trial Sponsorship by Sponsor Type
Sponsor Type
410
290
154
27
27
Industry, all other pharma (410)
Academic (290)
Industry, Top 20 Pharma (154)
Government (27)
Industry, generic (27)
Natural products, OTC, cosmetics (8)
Cooperative Group (7)
Miscellaneous (5)
Not for Profit Funding Entity (1)

Figure 2


A
Trial Phase Distribution Across Execution Status
Active/Planned
Completed
Other
Terminated
I
I/II
II
II/III
III
III/IV
IV
n = 286
n = 35
n = 308
n = 18
n = 96
n = 2
n = 148
Proportion of trials (%)
B
Evolution of F4/Cirrhosis Inclusion in Phase II-III Trials (2015-2025)
Total Phase II/III trials
F4/Cirrhosis trials
F4 inclusion rate
Total Phase II/III trials
F4 inclusion rate (%)
15.4%
21.4%
22.2%
21.7%
15.2%
10.0%
26.2%
18.8%
8.8%
22.6%
13.3%
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
C
F4 Inclusion Rate by Definitive Trial Outcome
P = 0.024
F4 inclusion rate (%)
17.8%
7.7%
36.4%
Positive
(n=107, F4=19)
Indeterminate
(n=13, F4=1)
Negative
(n=33, F4=12)
D
Monotherapy Trial Distribution by Target & Clinical Stage
FGF21
FXR
GLP-1
PPAR-α
PPAR-γ
SGLT-2
THR-β
72.7%
27.3%
86.4%
13.6%
76.4%
23.6%
71.9%
28.1%
59.5%
40.5%
22.6%
77.4%
83.8%
16.2%
Early Stage (Phase I-II)
Late Stage (Phase III-IV)
Number of single-agent trials
E
Internal Competition of 7 Core Targets in Monotherapy (2015-2025)
Relative Share (%)
FGF21 Agonist
FXR Agonist
GLP-1 Agonist
PPAR-α Agonist
PPAR-γ Agonist
SGLT-2 Inhibitor
THR-β Agonist
Trial start year
F
MASH Combination Therapy Matrix (Phase II-IV)
★ Represents one 'Completed, Positive outcome' trial
FXR
GLP-1
PPAR-α
PPAR-γ
SGLT-2
THR-β
Other
Number of Combination Trials
FGF21
FXR
GLP-1
PPAR-α
PPAR-γ
SGLT-2
THR-β

Figure 3

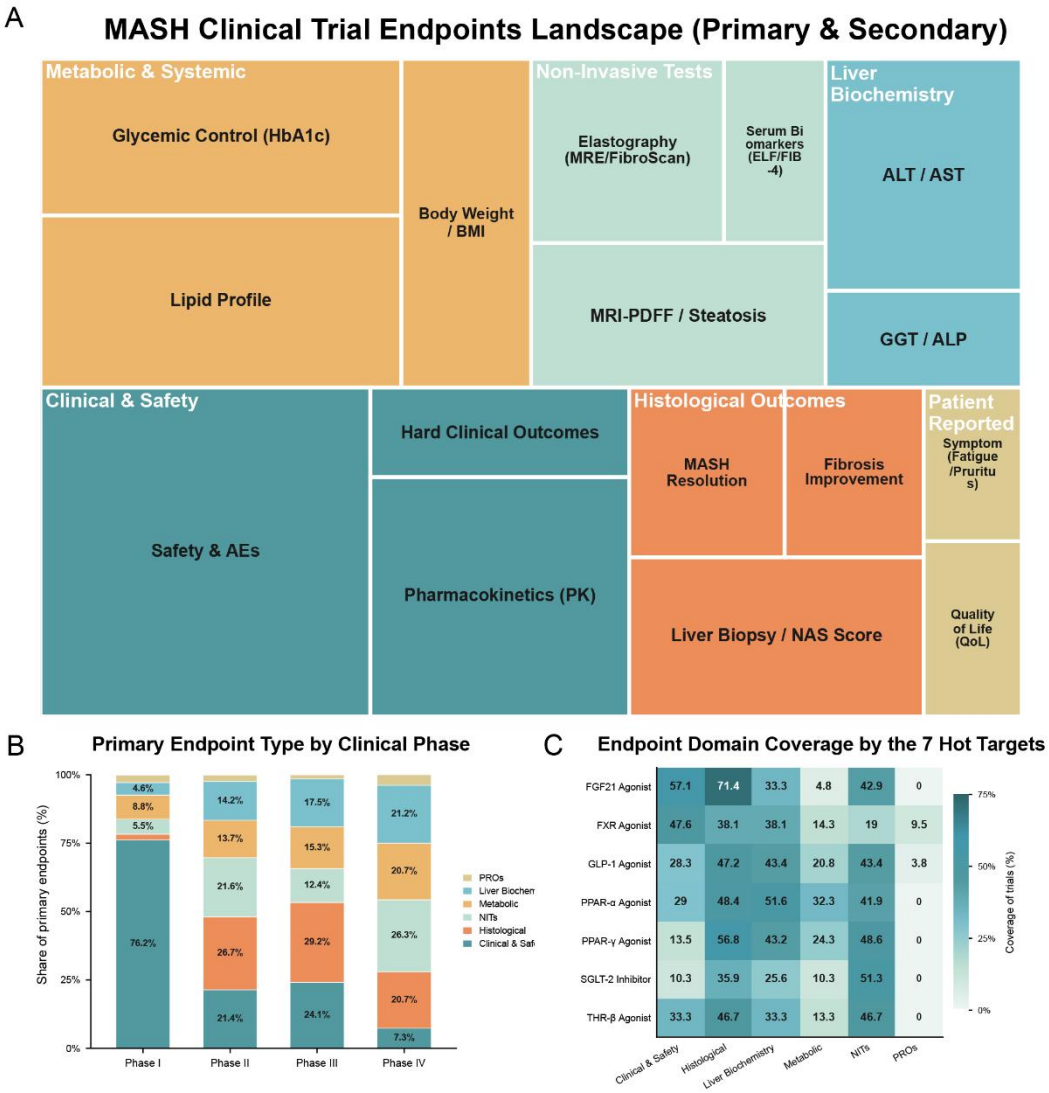
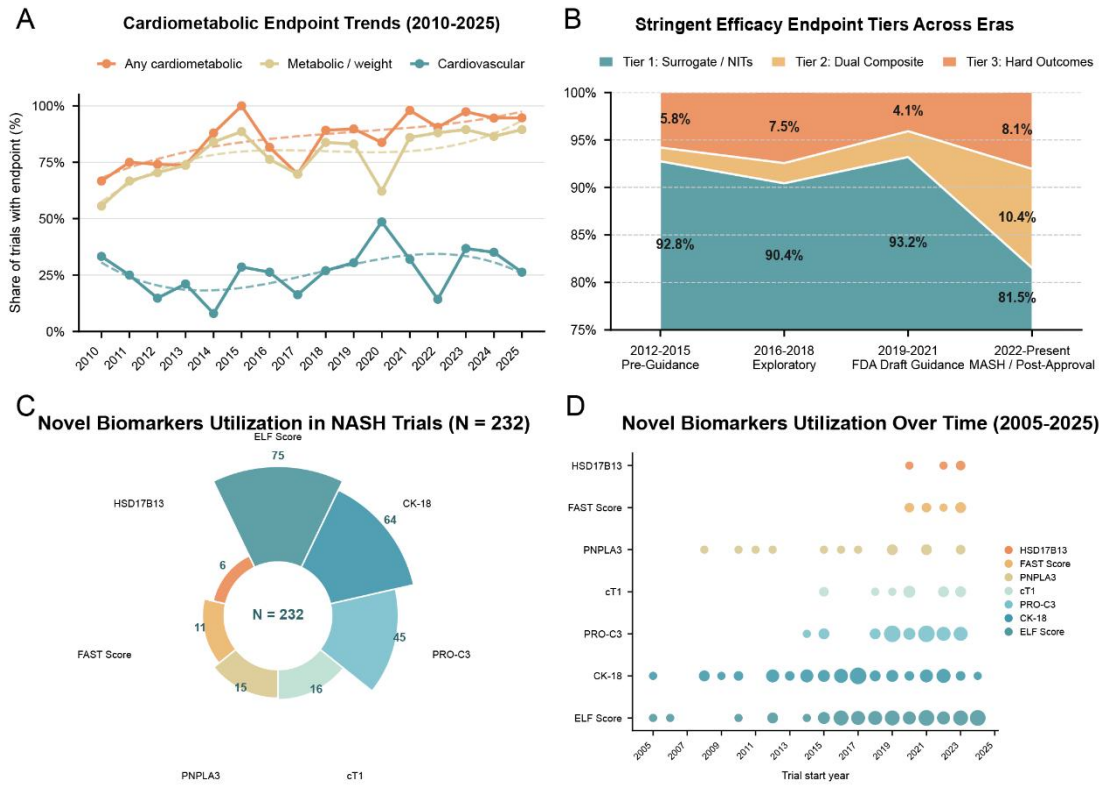

A
MASH Clinical Trial Endpoints Landscape (Primary & Secondary)
Metabolic & Systemic
Glycemic Control (HbA1c)
Lipid Profile
Body Weight / BMI
Non-Invasive Tests
Elastography (MRE/FibroScan)
Serum Biomarkers (ELF/FIB-4)
MRI-PDFF / Steatosis
Liver Biochemistry
ALT / AST
GGT / ALP
Clinical & Safety
Safety & AEs
Hard Clinical Outcomes
Pharmacokinetics (PK)
Histological Outcomes
MASH Resolution
Fibrosis Improvement
Liver Biopsy / NAS Score
Patient Reported
Symptom (Fatigue /Pruritus)
Quality of Life (QoL)
B
Primary Endpoint Type by Clinical Phase
Share of primary endpoints (%)
100%
75%
50%
25%
0%
Phase I
Phase II
Phase III
Phase IV
4.6%
8.8%
5.5%
76.2%
14.2%
13.7%
21.6%
26.7%
21.4%
17.5%
15.3%
12.4%
29.2%
24.1%
21.2%
20.7%
26.3%
20.7%
7.3%
PROs
Liver Biochem
Metabolic
NITs
Histological
Clinical & Safe
C
Endpoint Domain Coverage by the 7 Hot Targets
FGF21 Agonist 57.1 71.4 33.3 4.8 42.9 0
FXR Agonist 47.6 38.1 38.1 14.3 19 9.5
GLP-1 Agonist 28.3 47.2 43.4 20.8 43.4 3.8
PPAR-α Agonist 29 48.4 51.6 32.3 41.9 0
PPAR-γ Agonist 13.5 56.8 43.2 24.3 48.6 0
SGLT-2 Inhibitor 10.3 35.9 25.6 10.3 51.3 0
THR-β Agonist 33.3 46.7 33.3 13.3 46.7 0
Clinical & Safety
Histological
Liver Biochemistry
Metabolic
NITs
PROs
75%
50%
25%
0%
Coverage of trials (%)

Figure 4


A
Cardiometabolic Endpoint Trends (2010-2025)
Any cardiometabolic
Metabolic / weight
Cardiovascular
Share of trials with endpoint (%)
100%
75%
50%
25%
0%
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
B
Stringent Efficacy Endpoint Tiers Across Eras
Tier 1: Surrogate / NITs
Tier 2: Dual Composite
Tier 3: Hard Outcomes
100%
95%
90%
85%
80%
75%
5.8%
7.5%
4.1%
8.1%
10.4%
92.8%
90.4%
93.2%
81.5%
2012-2015
Pre-Guidance
2016-2018
Exploratory
2019-2021
FDA Draft Guidance
2022-Present
MASH / Post-Approval
C
Novel Biomarkers Utilization in NASH Trials (N = 232)
ELF Score
75
HSD17B13
CK-18
64
6
N = 232
11
45
FAST Score
PRO-C3
15
16
PNPLA3
cT1
D
Novel Biomarkers Utilization Over Time (2005-2025)
HSD17B13
FAST Score
PNPLA3
cT1
PRO-C3
CK-18
ELF Score
2005
2007
2009
2011
2013
2015
2017
2019
2021
2023
2025
Trial start year

References

1 Ho, G. J. K. et al. High Global Prevalence of Steatotic Liver Disease and Associated Subtypes: A Meta-analysis. Clin Gastroenterol Hepatol 23, 2423-2432.e2421, doi:10.1016/j.cgh.2025.02.006 (2025).

2 Diehl, A. M. & Day, C. Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis. N Engl J Med 377, 2063-2072, doi:10.1056/NEJMra1503519 (2017).

3 Kisseleva, T. & Brenner, D. Molecular and cellular mechanisms of liver fibrosis and its regression. Nat Rev Gastroenterol Hepatol 18, 151-166, doi:10.1038/s41575-020-00372-7 (2021).

4 Sanyal, A. J. et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med 392, 2089-2099, doi:10.1056/NEJMoa2413258 (2025).

5 Agha RA, M. G., Rashid R, Kerwan A, Al-Jabir A, Sohrabi C, Franchi T, Nicola M, Agha M, TITAN Group. Transparency In The reporting of Artificial INtelligence – the TITAN guideline. Premier Journal of Science 10, 100082 (2025).

6 Feng, G. et al. Recompensation in cirrhosis: unravelling the evolving natural history of nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 21, 46-56, doi:10.1038/s41575-023-00846-4 (2024).

7 Harrison, S. A. et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med 390, 497-509, doi:10.1056/NEJMoa2309000 (2024).

8 Loomba, R. et al. Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH. N Engl J Med 389, 998-1008, doi:10.1056/NEJMoa2304286 (2023).

9 Gawrieh, S. et al. Saroglitazar, a PPAR-α/γ Agonist, for Treatment of NAFLD: A Randomized Controlled Double-Blind Phase 2 Trial. Hepatology 74, 1809-1824, doi:10.1002/hep.31843 (2021).

10 Tacke, F., Puengel, T., Loomba, R. & Friedman, S. L. An integrated view of anti-inflammatory and antifibrotic targets for the treatment of NASH. J Hepatol 79, 552-566, doi:10.1016/j.jhep.2023.03.038 (2023).

11 Zhou, X. D. et al. Combination therapies for metabolic dysfunction-associated steatohepatitis: challenges and opportunities. Gut 75, 815-825, doi:10.1136/gutjnl-2025-337431 (2026).

12 Loomba, R. et al. Combination Therapies Including Cilofexor and Firsocostat for Bridging Fibrosis and Cirrhosis Attributable to NASH. Hepatology 73, 625-643, doi:10.1002/hep.31622 (2021).

13 Rinella, M. E. et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 78, 1966-1986, doi:10.1097/hep.0000000000000520 (2023).

14 Munk Lauridsen, M., Ravnskjaer, K., Gluud, L. L. & Sanyal, A. J. Disease classification, diagnostic challenges, and evolving clinical trial design in

MASLD. J Clin Invest 135, doi:10.1172/jci189953 (2025).
15 Zannad, F. et al. MASLD, MASH, and the CKM Spectrum: A Roadmap for Multiorgan Clinical Trial Design. J Am Coll Cardiol 87, 2006-2033, doi:10.1016/j.jacc.2025.12.015 (2026).
16 Taylor, R. S. et al. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology 158, 1611-1625.e1612, doi:10.1053/j.gastro.2020.01.043 (2020).
17 U.S. Food and Drug Administration. Nonalcoholic Steatohepatitis With Compensated Cirrhosis: Developing Drugs for Treatment: Guidance for Industry. FDA-2019-D-1516, https://www.regulations.gov/docket/FDA-2019-D-1516 (2019).
18 European Medicines Agency. Reflection Paper on Regulatory Requirements for the Development of Medicinal Products for Non-Alcoholic Steatohepatitis (NASH). EMA/CHMP/111529/2024, https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-development-medicinal-products-non-alcoholic-steatohepatitis-nash_en.pdf (2024).
19 Pericàs, J. M. et al. A roadmap for clinical trials in MASH-related compensated cirrhosis. Nat Rev Gastroenterol Hepatol 21, 809-823, doi:10.1038/s41575-024-00955-8 (2024).
20 Boursier, J. et al. A stepwise algorithm using an at-a-glance first-line test for the non-invasive diagnosis of advanced liver fibrosis and cirrhosis. J Hepatol 66, 1158-1165, doi:10.1016/j.jhep.2017.01.003 (2017).
21 Tiniakos, D. G. et al. The Elucidating Pathways of Steatohepatitis (EPoS) staging system: A reproducible 7-tiered fibrosis scoring system in MASLD. JHEP Rep 8, 101737, doi:10.1016/j.jhepr.2026.101737 (2026).
22 Angelini, G. et al. Performance of Noninvasive Tests for Metabolic Dysfunction-Associated Steatohepatitis and Liver Fibrosis Resolution after Bariatric Surgery. Clin Chem 71, 406-417, doi:10.1093/clinchem/hvae208 (2025).
23 Daniels, S. J. et al. ADAPT: An Algorithm Incorporating PRO-C3 Accurately Identifies Patients With NAFLD and Advanced Fibrosis. Hepatology 69, 1075-1086, doi:10.1002/hep.30163 (2019).
24 Pavlides, M. et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. J Hepatol 64, 308-315, doi:10.1016/j.jhep.2015.10.009 (2016).
25 Kanda, T. et al. Polygenic Risk Score for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis: A Narrative Review. Int J Mol Sci 26, doi:10.3390/ijms26115164 (2025).
26 Pulaski, H. et al. Clinical validation of an AI-based pathology tool for scoring of metabolic dysfunction-associated steatohepatitis. Nat Med 31, 315-322, doi:10.1038/s41591-024-03301-2 (2025).
27 Zeng, R. Q. et al. Drug Development for MASH-Related Compensated

Cirrhosis: Past, Present and Future. Liver Int 46, e70784, doi:10.1111/liv.70784 (2026).