

3 ORIGINAL ARTICLE

4 Clinical development landscape of THR- β 5 agonists in MASLD/MASH: an analysis of 6 clinical trials registered on ClinicalTrials.gov

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12 ABSTRACT

13 **Background:** Metabolic dysfunction-associated steatohepatitis (MASH), the progressive inflammatory form of
14 metabolic dysfunction-associated steatotic liver disease (MASLD), is associated with substantial risks of fibro-
15 sis progression, cirrhosis, and liver-related morbidity and mortality. The increasing burden of MASLD/MASH
16 has accelerated the development of targeted pharmacological therapies, including thyroid hormone receptor
17 beta (THR- β) agonists. However, the overall clinical development landscape of this therapeutic class has not
18 been comprehensively characterized. This study aimed to characterize the registered clinical trial landscape of
19 THR- β agonists for MASLD/MASH and identify major development trends and evidence gaps.

20 **Methods:** A descriptive analysis of clinical trials registered in ClinicalTrials.gov was conducted. Thirty-two
21 records were initially identified and manually screened for eligibility. Eighteen interventional trials involving
22 disease populations within the MASLD/MASH spectrum were included after exclusion of healthy-volunteer
23 clinical pharmacology studies, non-liver indications, observational studies, and unrelated records. Included
24 trials were characterized according to study status, start date period, mapped clinical phase, drug family, ther-
25 apeutic strategy, clinical focus, sponsorship, geographic distribution, and registry results posting. Categorical
26 variables were summarized using frequencies and percentages, and Fisher's exact test was used to assess the
27 association between study status and registry results posting. The small sample limited the robustness and
28 generalizability of the findings.

29 **Results:** Among the 18 included trials, resmetirom/MGL-3196 was the most frequently investigated THR- β
30 agonist, accounting for 9 studies (50.0%), followed by ASC41/ASC43F with 4 studies (22.2%). Ten trials (55.6%)
31 were phase 2, phase 2a, or phase 2b studies. Most trials were industry-sponsored (17/18, 94.4%), and 15
32 studies (83.3%) evaluated single-agent THR- β strategies. Eight trials (44.4%) were completed, while 5 (27.8%)
33 were recruiting and 4 (22.2%) were active but not recruiting. Only 2 trials (11.1%) had posted results on
34 ClinicalTrials.gov. The association between study status and registry results posting was not statistically signif-
35 icant (Fisher's exact test, $p = 0.531$).

Continued

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ABSTRACT

Conclusion: The clinical development landscape of THR- β agonists for MASLD/MASH is active and includes several agents, with resmetirom/MGL-3196 representing the largest development program. However, registry results posting was infrequent; dissemination through publications and other sources was not systematically assessed. More complete registry results posting, broader geographic and academic participation, continued evaluation of combination strategies, and longer-term assessment of efficacy and safety may strengthen the evidence base for this emerging therapeutic class.

Keywords: Metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction-associated steatohepatitis, thyroid hormone receptor beta, THR- β agonists, ClinicalTrials.gov, clinical trials.

Introduction

Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), represents the progressive inflammatory form of metabolic dysfunction-associated steatotic liver disease (MASLD) and is associated with substantial risks of fibrosis progression, cirrhosis, hepatic decompensation, hepatocellular carcinoma, liver transplantation, and premature death. Under the 2023 multisociety nomenclature, MASLD is defined by hepatic steatosis together with at least one cardiometabolic risk factor, whereas MASH is characterized histologically by steatosis, hepatocellular ballooning, and lobular inflammation, with or without fibrosis [1]. This updated terminology emphasizes the metabolic drivers of the disease and its close association with obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension. The risk of liver-related outcomes increases substantially with advancing fibrosis [2].

MASLD has become the most prevalent chronic liver disease worldwide. Contemporary estimates suggest that approximately 38% of adults globally have MASLD, and its prevalence may continue to increase substantially over the coming decades if current metabolic trends persist [3]. The burden is particularly high among individuals with type 2 diabetes mellitus, in whom pooled prevalence approaches two-thirds [4]. Estimating MASH prevalence remains challenging because definitive diagnosis has historically relied on liver biopsy; nevertheless, modelling studies estimate a substantial and increasing burden of MASH among adults [5]. These trends underscore the need for effective pharmacological therapies capable of improving steatohepatitis and fibrosis while addressing the metabolic mechanisms underlying disease progression.

The therapeutic landscape of MASLD/MASH has evolved substantially in recent years. In March 2024, resmetirom became the first liver-directed thyroid hormone receptor beta (THR- β) agonist approved by the U.S. Food and Drug Administration for adults with noncirrhotic MASH and moderate-to-advanced fibrosis, following the results of the phase 3 MAESTRO-NASH trial [6,7]. THR- β agonists have attracted particular interest because THR- β is the predominant thyroid hormone receptor subtype in the liver and plays an important role in hepatic lipid metabolism, fatty acid oxidation, and

cholesterol homeostasis. Selective activation of hepatic THR- β is intended to reproduce beneficial hepatic effects of thyroid hormone while minimizing systemic effects associated with THR- α activation [8,9]. The emergence of resmetirom has therefore provided clinical validation for THR- β agonism as a therapeutic strategy and has been followed by continued development of other agents within the same class.

Although recent reviews have summarized emerging pharmacotherapies for MASLD/MASH according to individual agents or therapeutic classes, the broader clinical development landscape of THR- β agonists has not been comprehensively characterized [10]. In particular, the distribution of registered trials across development phases, study status, sponsorship, geographic location, therapeutic strategies, clinical focus, and results reporting has not been systematically described. A registry-based analysis can provide a complementary perspective by capturing both completed and ongoing studies and by identifying areas in which clinical development is expanding or where publicly available evidence remains limited.

Accordingly, this study aimed to characterize the clinical development landscape of THR- β agonists for MASLD/MASH using registered clinical trials in the ClinicalTrials.gov database, with emphasis on trial characteristics, development phases, therapeutic strategies, sponsorship, geographic distribution, and results posting on ClinicalTrials.gov.

Study Design and Methods

Clinical trials data acquisition and preprocessing

This study was designed as a registry-based cross-sectional descriptive analysis of clinical trials registered in the ClinicalTrials.gov database. This website is an online registry of clinical studies in various medical areas that presents structured data on clinical trial start and end dates, recruitment status, study design, intervention type, clinical phase, outcome, registry results posting status, inclusion criteria, and sponsor data.

Our analysis started with a search of all the ClinicalTrials.gov studies related to THR- β agonists and metabolic liver disease using the uploaded registry dataset through July 2026. For reproducibility, the search strategy was

reconstructed using the following disease-related terms: (“MASLD” OR “NAFLD” OR “MASH” OR “NASH” OR “hepatic steatosis” OR “metabolic liver disease”) AND the following THR-β-related terms: (“THR-beta” OR “thyroid hormone receptor beta” OR “resmetirom” OR “MGL-3196” OR “ASC41” OR “ASC43F” OR “VK2809” OR “TERN-501” OR “ECC4703” OR “CS060380”). No restrictions were initially applied according to study status or study type to allow broad retrieval of potentially eligible records. At first, we had 32 records in our dataset. All of them were screened manually for relevance to THR-β agonist therapy in MASLD, NAFLD, MASH, or NASH patients. As a result of manual screening, 18 relevant interventional disease population records remained in our analysis. They were sorted in tables by start date period, status of the study, mapped clinical phase, drug family, therapeutic approach, clinical focus, and results posting status. Clinical phase was mapped from registry titles and descriptions of the trials because there was no phase field in the uploaded dataset.

For descriptive summaries, mapped phase 2, 2a, and 2b studies were combined into one category; phase 1, phase 3, and phase 4 were retained separately. Separate pre-consensus phase ratings and external validation records were not available for this analysis, so inter-rater agreement could not be quantified, and phase assignments should be interpreted cautiously.

Selection criteria

The objective of our study was to provide an updated review on the current therapeutic arena of THR-β agonists in MASLD/MASH. Consequently, eligible studies were identified from the initial list of 32 studies using predetermined inclusion and exclusion criteria. The screening process was performed independently by two reviewers. Any disagreements regarding study eligibility were resolved through discussion and, when necessary, by consultation with a third reviewer.

Inclusion criteria

The study included all interventional clinical trials registered in the ClinicalTrials.gov database investigating THR-β agonists for the treatment of MASLD or MASH. Eligible studies included trials of any recruitment status (e.g., recruiting, active, completed, or terminated) and any phase of clinical development (Phase I–IV), provided sufficient trial information was available within the registry.

Exclusion criteria

Observational studies, expanded-access programs, compassionate-use protocols, duplicate records, withdrawn studies, and trials unrelated to THR-β agonists or not involving patients with MASLD/MASH were excluded. Studies with incomplete registry information that precluded data extraction were also excluded.

Outcomes of interest

The key outcome variables of interest included details of the registered THR-β/MASLD-MASH clinical trials, such as study status, start date range, mapped clinical phase, drug class, therapeutic approach, clinical focus, and posting of results on ClinicalTrials.gov. These variables were selected to characterize the current clinical development landscape of THR-β agonists. Data were independently extracted by two reviewers using a standardized data extraction form. Any discrepancies in data extraction were resolved through discussion and, when necessary, by consultation with a third reviewer. Drug classes included resmetirom/MGL-3196, ASC41/ASC43F, VK2809, ECC4703, TERN-501, and CS060380. The therapeutic approaches were subdivided into single THR-β agent, single THR-β agent and pharmacokinetics, single THR-β agent and pharmacokinetic drug–drug interaction, and combination. Clinical focus was subdivided into MASH/NASH therapy or special population, NAFLD/CVD/pharmacokinetics, and hepatic impairment/pharmacokinetics. Results posting referred specifically to registry summary results and was not a measure of publication status or overall dissemination.

The included studies were further described in terms of NCT number, study title, drug/intervention, objective of study, current interpretation, date started, date completed, mapped phase.

Statistical analysis

The categorical variables were analyzed based on frequency and percentage. Descriptive statistics were conducted for characteristics of the trial according to the start date periods, the status category of the study, phase category, drug family, therapeutic approach, clinical emphasis, and result reporting status. With only 18 trials and sparse categories, the robustness and generalizability of comparisons were limited. Inferential analyses were restricted to the reported exploratory exact tests; the dataset was not sufficient for reliable multivariable modeling of results posting, given only two posting events. An additional descriptive cross-tabulation summarized therapeutic strategy by sponsorship, with counts and within-sponsor percentages. Single-agent strategies were grouped for this comparison, including pharmacokinetic and drug–drug interaction studies. Start-period patterns were described without formal trend testing.

To examine the association between the status of the study and results reporting, Fisher’s exact test was carried out because of the relatively small sample size and low expected cell counts. Another sensitivity test was performed by grouping the study status into completed studies vs non-completed studies. Statistical significance was set at $p < 0.05$. The results were presented in tables and figures.

This registry-based cross-sectional descriptive study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guideline.

252 **Ethical considerations**

253 This study utilized publicly available information from
254 the ClinicalTrials.gov database and did not involve
255 direct interaction with human participants or access to
256 identifiable patient-level data. Therefore, no individual
257 informed consent was required. The study was conducted
258 in accordance with applicable ethical principles and
259 institutional requirements.

260 **Results**

261 ***An overview of the clinical trial features related*** 262 ***to THR- β agonists in MASLD/MASH registered*** 263 ***in ClinicalTrials.gov***

264 In the current analysis, 32 ClinicalTrials.gov entries
265 were identified in the registry dataset and manually
266 screened. The entries that did not meet the criteria were
267 healthy-only clinical pharmacology studies, non-liver
268 indications, observational records, and irrelevant studies.
269 Consequently, 18 interventional MASLD/MASH studies
270 that met the inclusion criteria were used for further
271 descriptive analysis. The screening and selection process
272 is summarized in Figure 3.

273 Only 2 of the 18 included studies (11.1%) had posted
274 results on ClinicalTrials.gov. Regarding the drug family
275 used in the studies, resmetirom/MGL-3196 accounted for
276 9 trials (50.0%) being the highest. The next drug family
277 after resmetirom/MGL-3196 is ASC41/ASC43F with 4
278 trials (22.2%). Thereafter comes the drug VK2809 with
279 2 trials (11.1%). ECC4703, TERN-501, and CS060380
280 each accounted for 1 trial (5.6%).

281 In terms of drug type administration, single-agent
282 treatment accounted for 13 trials (72.2%), while
283 combination therapy involved 3 trials (16.7%).

284 Second, we organized our findings based on their
285 sponsor type and geographical locations, as shown in
286 Supplementary Table 1 and Supplementary Table 2.
287 Analysis based on the type of sponsor revealed that
288 most of the clinical trials for THR- β /MASLD-MASH
289 were industry-sponsored. Industry/pharmaceutical was
290 the type of sponsor of 17 out of the 18 selected studies
291 (94.4%), whereas only 1 study (5.6%) had the sponsor
292 as academic/university. There were no trials sponsored
293 by hospitals/medical centers, research foundations/
294 organizations, or any other type of sponsor. All the time
295 periods of the start dates of industry-sponsored trials
296 covered all the completed trials, active-but-not-recruiting
297 trials, the withdrawn trial, and 2 posted trials. The only
298 academic/university sponsored trial had a start date from
299 2023 and onward, was recruiting, and studied resmetirom/
300 MGL-3196 as a single-agent THR- β approach in the
301 MASH/NASH therapeutic or special population. No
302 sponsor-group significance test was added because
303 the academic category contained only one trial. Using
304 the broader single-agent grouping, industry-sponsored
305 trials included 14 single-agent studies (82.4%) and 3
306 combination studies (17.6%), while the sole academic-
307 sponsored trial evaluated a single-agent strategy (Table
308 1). This comparison is descriptive and does not establish
309 an association between sponsorship and therapeutic
310 strategy.

311 In terms of geographical distribution, the largest number
312 of trials was in North America, where 7 of 18 studies

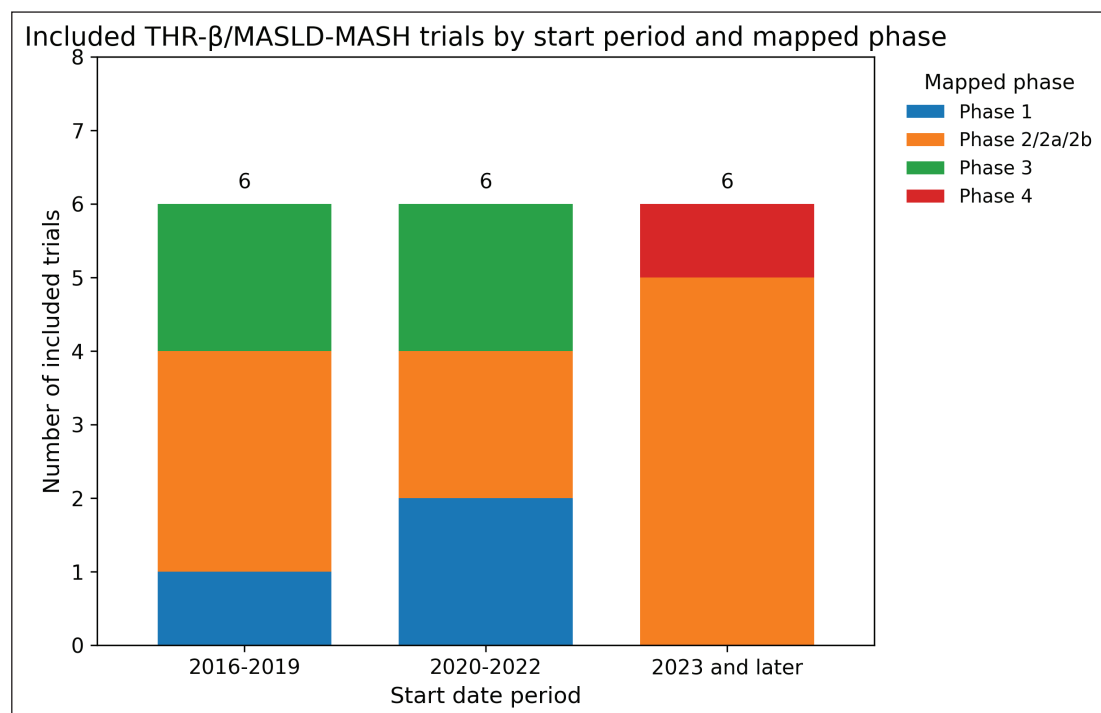


Figure 1. Number of included THR- β /MASLD-MASH clinical studies by start date period and mapped clinical phase (N = 18). Phase was mapped from registry titles/summaries because the uploaded CSV did not include a phase field.

Table 1. Clinical trial characteristics by start date period.

Characteristic	Category	2016-2019 n (%)	2020-2022 n (%)	2023 and later n (%)	Total n (%)
Total	All included records	6 (33.3%)	6 (33.3%)	6 (33.3%)	18 (100.0%)
Study status	Completed	5 (83.3%)	3 (50.0%)	0 (0.0%)	8 (44.4%)
Study status	Active not recruiting	1 (16.7%)	3 (50.0%)	0 (0.0%)	4 (22.2%)
Study status	Recruiting	0 (0.0%)	0 (0.0%)	5 (83.3%)	5 (27.8%)
Study status	Withdrawn	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (5.6%)
Drug family	Resmetirom / MGL-3196	4 (66.7%)	2 (33.3%)	3 (50.0%)	9 (50.0%)
Drug family	ASC41 / ASC43F	0 (0.0%)	3 (50.0%)	1 (16.7%)	4 (22.2%)
Drug family	VK2809	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
Drug family	ECC4703	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (5.6%)
Drug family	TERN-501	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (5.6%)
Drug family	CS060380	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (5.6%)
Therapeutic strategy	Single THR-β agent	5 (83.3%)	4 (66.7%)	4 (66.7%)	13 (72.2%)
Therapeutic strategy	Single THR-β agent / PK	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Therapeutic strategy	Single THR-β agent / PK-DDI	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (5.6%)
Therapeutic strategy	Combination therapy	0 (0.0%)	1 (16.7%)	2 (33.3%)	3 (16.7%)
Clinical focus	MASH/NASH therapeutic or special population	3 (50.0%)	3 (50.0%)	6 (100.0%)	12 (66.7%)
Clinical focus	NAFLD/cardiometabolic/PK	2 (33.3%)	3 (50.0%)	0 (0.0%)	5 (27.8%)
Clinical focus	Hepatic impairment/PK	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Results posted	Yes	1 (16.7%)	1 (16.7%)	0 (0.0%)	2 (11.1%)
Results posted	No	5 (83.3%)	5 (83.3%)	6 (100.0%)	16 (88.9%)

Note: Descriptive counts and percentages are calculated from the 18 included THR-β/MASLD-MASH records in the uploaded ClinicalTrials.gov CSV. P-values are intentionally not calculated because the sample is small and sparse.

(38.9%) took place, followed by multiregional trials (6 studies; 33.3%) and Asian trials (4 studies; 22.2%) (Supplementary Table 2). No trials were solely done in Europe, and 1 study (5.6%) belonged to other/no geographical area. The number of completed trials was the largest in North America, where, out of 7 studies from North America, 5 were completed, while Asia and multiregional areas gave the greatest contribution to the ongoing trial landscape. Resmetirom/MGL-3196 trials were mostly performed in North America and multiregional areas, while ASC41/ASC43F trials were performed in Asia. Registry results were posted for trials in two geographical categories only: 1 trial in North America and 1 in a multiregional area. Therefore, the main focus of THR-β agonist research in MASLD/MASH appears to be industry-supported and done mostly in North America, Asia, and multinational trial areas.

Depiction of THR-β/MASLD-MASH clinical trials based on phase, study status, study type, and drug family

As can be seen from Figure 1, phase 2, phase 2a, and phase 2b trials comprised the major proportion of the included clinical development programs. In total, 10 phase 2/2a/2b trials, 4 phase 3 trials, 3 phase 1 trials, and 1 phase 4 trial were included. Hence, the current THR-β agonist pipeline focuses mainly on proof-of-concept and efficacy studies, while also including pivotal phase 3 trials and post-approval studies.

From Table 2 and Figure 2, the most common status was completed, accounting for 8 studies (44.4%). There were also 5 recruiting trials (27.8%), 4 active-not-recruiting trials (22.2%), and 1 withdrawn trial (5.6%). Out of all retrieved records before conducting manual screening, the majority of the studies were interventional (30 out of 32 studies or 93.8%), while only 2 records (6.2%) were observational, as presented in Figure 4a. As a result of manual screening, the included studies were mainly focused on interventional pharmacotherapy. Moreover, Figure 4b shows that resmetirom/MGL-3196 dominated the included trial landscape, followed by ASC41/ASC43F and VK2809.

Study results' distribution by key characteristics

As shown in Table 3, results posting was not common. Of the 18 studies included in the review, only 2 of them (11.1%) had posted their results. The remaining 16 (88.9%) studies had no posted results. Upon further analysis of the relationship between study status and results posting, it was found out that the 2 studies with posted results were completed studies. On the other hand, in the completed studies, there were only 2 of 8 trials (25.0%) that had posted results, and the rest of the recruiting, active-not-recruiting, and withdrawn trials did not post any results. Fisher's exact test result showed no significant association between study status and results posting in Table 3 ($p = 0.531$).

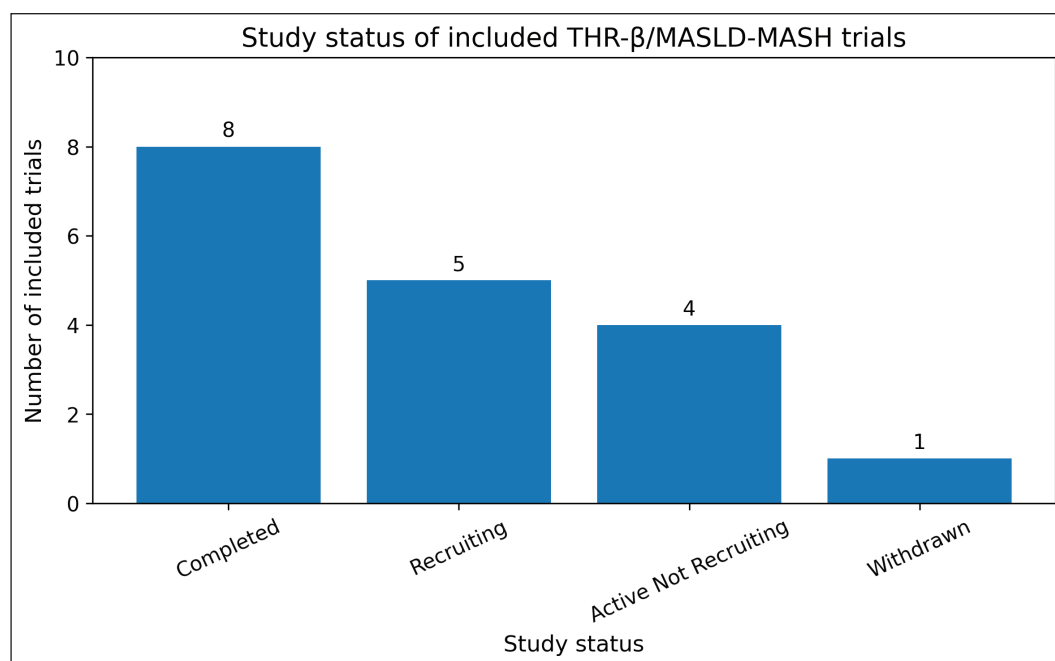


Figure 2. Study status distribution of included THR-β/MASLD-MASH clinical studies (N = 18).

Table 2. Clinical trial characteristics by study status distribution.

Study status	Count	Percentage
Completed	8	44.4%
Recruiting	5	27.8%
Active not recruiting	4	22.2%
Withdrawn	1	5.6%
Total	18	100.0%

Note: Status categories are taken directly from the uploaded ClinicalTrials.gov CSV after manual inclusion screening.

Table 3. Study results distribution.

Results status	Count	Percentage
Results available (yes)	2	11.1%
No results available (no)	16	88.9%
Total	18	100.0%

Note: Results posted is based on the Results First Posted field in the uploaded CSV.

Table 4. Relationship between study status and results reporting.

Study status	Has results n	No results n	Total	Fisher's exact p-value
Completed	2	6	8	$p = 0.531$
Active not recruiting	0	4	4	-
Recruiting	0	5	5	-
Withdrawn	0	1	1	-
Total	2	16	18	-

Note: Cross-tabulation of Study Status by Results First Posted. Fisher's exact test was applied to the full 4×2 table because several expected cell counts were <5 . The association between study status and results reporting was not statistically significant ($p = 0.531$). As an exploratory sensitivity check, collapsing status into completed versus non-completed studies gave Fisher's exact $p = 0.183$.

From Table 4, it can be seen that only trials that were conducted from 2016 to 2019 and from 2020 to 2022 have posted results, with one trial in each start-period category. There is no result posted from a trial that started in 2023 or thereafter. By phase, only phase 2/2a/2b studies posted results, with 2 of 10 trials (20.0%). No results were posted from phase 1, phase 3, or phase 4 studies. For drug families, only 1 resmetirom/MGL-3196 and 1 TERN-501 trial posted results. Supplementary Figure 1 further demonstrates that results reporting was restricted to completed trials. Together, these findings showed that the majority of registered studies have not yet posted their results, suggesting an important knowledge gap in the publicly available registry data. Each start-period category contained 6 trials: 1 of 6 (16.7%) in 2016-2019, 1 of 6 (16.7%) in 2020-2022, and 0 of 6 (0%) from 2023 onward had posted registry results. The equal trial counts across periods do not demonstrate an increasing initiation rate, particularly because the periods differ in duration. More recent trials had less time to complete and disseminate results; these figures should not be interpreted as evidence of worsening reporting.

In addition, Table 5 illustrates the distribution of results reporting by interventions/drugs family. Resmetirom/MGL-3196 constituted the largest group of interventions, consisting of 9 studies (50.0%), but only one of them (11.1%) posted registry results. ASC41/ASC43F covered 4 studies (22.2%), VK2809 covered 2 studies (11.1%), and ECC4703, TERN-501, and CS060380 covered 1 study each (5.6%). Among these other drug families, the single TERN-501 trial had posted registry results; this isolated observation does not support a drug-family comparison. In terms of therapeutic approach, single-agent THR-β therapy was prevalent among all trials analyzed, which amounted to 15 trials (83.3%); however, just one study (6.7%) had posted its results. Combination therapies were less represented, including 3 studies (16.7%), with

Table 5. Distribution of posted study results by key study characteristics.

Variable	Category	Total <i>n</i>	Results reported <i>n</i> (%)	No results <i>n</i> (%)
Study status group	Completed	8	2 (25.0%)	6 (75.0%)
Study status group	Ongoing	9	0 (0.0%)	9 (100.0%)
Study status group	Other	1	0 (0.0%)	1 (100.0%)
Start period	2016-2019	6	1 (16.7%)	5 (83.3%)
Start period	2020-2022	6	1 (16.7%)	5 (83.3%)
Start period	2023 and later	6	0 (0.0%)	6 (100.0%)
Phase group	Phase 1	3	0 (0.0%)	3 (100.0%)
Phase group	Phase 2 / 2a / 2b	10	2 (20.0%)	8 (80.0%)
Phase group	Phase 3	4	0 (0.0%)	4 (100.0%)
Phase group	Phase 4	1	0 (0.0%)	1 (100.0%)
Drug family	Resmetirom / MGL-3196	9	1 (11.1%)	8 (88.9%)
Drug family	ASC41 / ASC43F	4	0 (0.0%)	4 (100.0%)
Drug family	VK2809	2	0 (0.0%)	2 (100.0%)
Drug family	ECC4703	1	0 (0.0%)	1 (100.0%)
Drug family	TERN-501	1	1 (100.0%)	0 (0.0%)
Drug family	CS060380	1	0 (0.0%)	1 (100.0%)
Therapeutic strategy	Single THR- β agent	13	1 (7.7%)	12 (92.3%)
Therapeutic strategy	Single THR- β agent / PK	1	0 (0.0%)	1 (100.0%)
Therapeutic strategy	Single THR- β agent / PK-DDI	1	0 (0.0%)	1 (100.0%)
Therapeutic strategy	Combination therapy	3	1 (33.3%)	2 (66.7%)
Clinical focus	MASH/NASH therapeutic or special population	12	2 (16.7%)	10 (83.3%)
Clinical focus	NAFLD/cardiometabolic/PK	5	0 (0.0%)	5 (100.0%)
Clinical focus	Hepatic impairment/PK	1	0 (0.0%)	1 (100.0%)

Note: This table mirrors the results-reporting analysis in the example paper but adapts the features to THR- β /MASLD-MASH trials.

Table 6. Proportion of results reporting by intervention/drug family.

Intervention / drug family	Total <i>n</i> (%)	Results reported <i>n</i> (%)	No results <i>n</i> (%)
Resmetirom / MGL-3196	9 (50.0%)	1 (11.1%)	8 (88.9%)
ASC41 / ASC43F	4 (22.2%)	0 (0.0%)	4 (100.0%)
VK2809	2 (11.1%)	0 (0.0%)	2 (100.0%)
ECC4703	1 (5.6%)	0 (0.0%)	1 (100.0%)
TERN-501	1 (5.6%)	1 (100.0%)	0 (0.0%)
CS060380	1 (5.6%)	0 (0.0%)	1 (100.0%)
Single-agent THR- β strategy	15 (83.3%)	1 (6.7%)	14 (93.3%)
Combination therapy strategy	3 (16.7%)	1 (33.3%)	2 (66.7%)

Note: Drug-family and strategy categories are manually mapped from study titles/interventions in the CSV.

1 (33.3%) of them posting their results. The posting proportions of 1/15 for single-agent strategies and 1/3 for combination strategies are descriptive only; one posting event in each group is insufficient to infer a difference between strategies.

Identification of eligible therapeutic interventional clinical studies for THR- β agonists in MASLD/MASH

As a result of the prior results, it can be noted that the majority of records obtained were interventional studies; therefore, it was decided to use the uploaded ClinicalTrials.gov database and conduct manual filtering of eligible THR- β agonist studies within the context of the MASLD/MASH continuum, as shown in Figure 3.

Initially 32 records were identified, which were then filtered out. The application of the exclusion criteria resulted in the exclusion of 14 records, including healthy-only clinical pharmacology studies ($n = 10$), indications other than liver ($n = 2$), and unrelated studies ($n = 2$). Consequently, there were 18 interventional studies of the disease population selected for further analysis. They were then classified based on the status of the study, mapped clinical phase, drug family, therapeutic approach, and reporting status of results.

Table 6 presents the 18 studies in the interventional category based on objective, drug/intervention used, phases, start and completion dates, and posting of results Table 7. The resmetirom/MGL-3196 regimen was the most extensive development strategy, involving phase 2 proof-of-concept trials, phase 3 trials in NASH

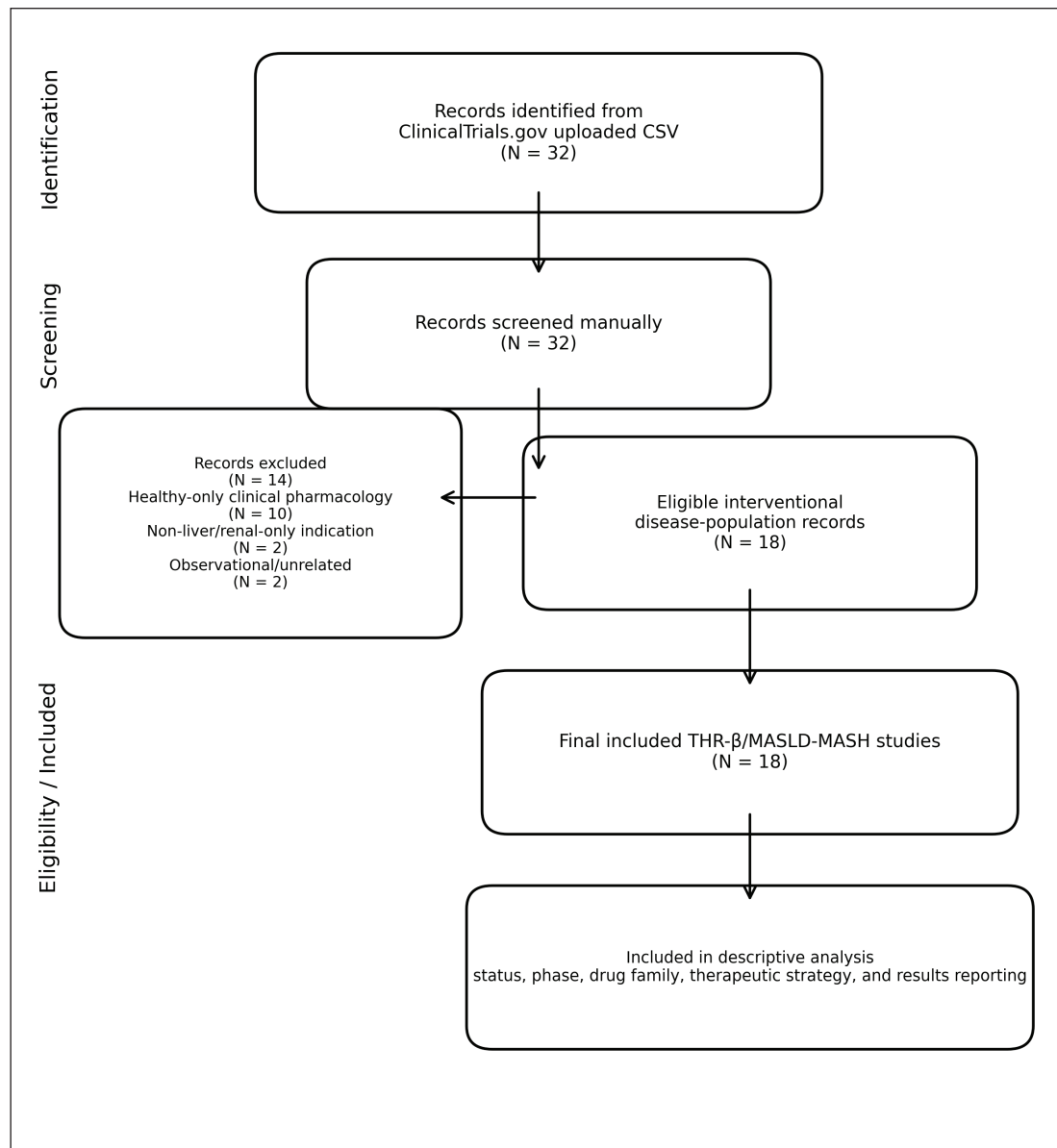


Figure 3. Flowchart of the screening and selection strategy used to identify included THR- β /MASLD-MASH studies from the uploaded ClinicalTrials.gov CSV.

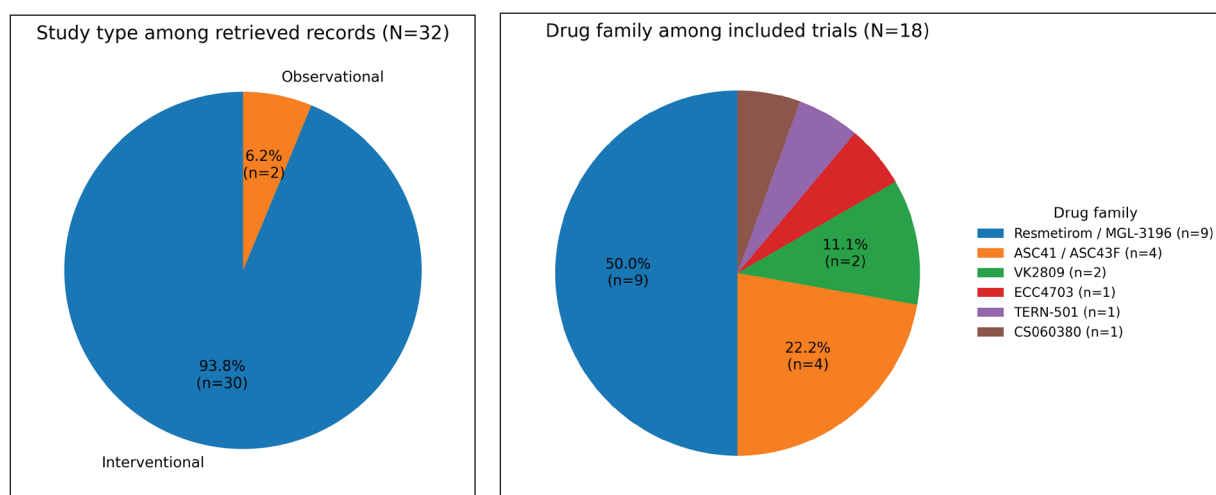


Figure 4. A. Study type distribution among all retrieved ClinicalTrials.gov records before manual screening (N = 32). B. Drug family distribution among included THR- β /MASLD-MASH clinical studies (N = 18).

Table 7. Interventional clinical trials organized by objectives, interpretation, and start date.

NCT number	Study title	Drug/intervention	Objective of the study and current interpretation	Start date - completion date	Mapped phase	Posted results	Source URL
NCT02912260	Phase 2 Study of MGL-3196 in Patients With Non-Alcoholic Steatohepatitis (NASH)	MGL-3196 (Resmetrom)	Determine the effect of once-daily MGL-3196/resmetrom on hepatic fat fraction in NASH and assess downstream histologic/metabolic effects. Current interpretation/conclusion: Completed with posted results. This phase 2 trial supports proof-of-concept for resmetrom by hepatic fat reduction and NASH-related endpoints.	2016-10-18 to 2021-11-23	Phase 2	Yes	ClinicalTrials.gov
NCT02927184	Safety and Tolerability of VK2809 in Patients With Primary Hypercholesterolemia and Non-Alcoholic Fatty Liver Disease	VK2809	Assess efficacy, safety, and tolerability of VK2809 in primary hypercholesterolemia with NAFLD, with LDL-C change as primary outcome. Current interpretation/conclusion: Completed; no posted results in CSV. Clinical-development relevance is cardiometabolic overlap: LDL-C and NAFLD/liver fat outcomes.	2016-09-28 to 2019-03-26	Phase 2	No	ClinicalTrials.gov
NCT04643795	Phase 1 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Multiple Oral Doses of MGL-3196 in Subjects With Varying Degrees of Hepatic Impairment and Healthy Matched Control Subjects	MGL-3196 (Resmetrom)	Evaluate multiple-dose resmetrom pharmacokinetics, safety, and tolerability in hepatic impairment and matched controls, relevant to NASH/cirrhosis populations. Current interpretation/conclusion: Completed; no posted results in CSV. Relevant for dose/safety considerations in hepatic impairment.	2018-10-25 to 2021-08-04	Phase 1	No	ClinicalTrials.gov
NCT03900429	A Phase 3 Study to Evaluate the Efficacy and Safety of MGL-3196 (Resmetrom) in Patients With NASH and Fibrosis	Resmetrom (MGL-3196)	Evaluate resmetrom efficacy and safety in NASH with fibrosis, including NASH resolution and fibrosis improvement/progression outcomes. Current interpretation/conclusion: Active not recruiting; no posted results in CSV. Central phase 3 resmetrom efficacy trial for NASH with fibrosis.	2019-03-28 to 2028-01	Phase 3	No	ClinicalTrials.gov
NCT04173065	A Study to Assess the Efficacy and Safety of VK2809 for 52 Weeks in Subjects With Biopsy Proven NASH	VK2809	Assess VK2809 efficacy and safety over 52 weeks in biopsy-proven NASH, including liver fat and histologic outcomes. Current interpretation/conclusion: Completed; no posted results in CSV. Relevant phase 2b evidence stream for next-generation THR-β agonists in biopsy-proven NASH.	2019-11-15 to 2024-01-26	Phase 2b	No	ClinicalTrials.gov
NCT04197479	A Phase 3 Study to Evaluate Safety and Biomarkers of Resmetrom (MGL-3196) in Non Alcoholic Fatty Liver Disease Patients	Resmetrom (MGL-3196)	Evaluate resmetrom safety, tolerability, and biomarkers in NAFLD/presumed NASH as part of the MAESTRO program. Current interpretation/conclusion: Completed; no posted results in CSV. Phase 3 safety/biomarker study supporting the resmetrom program.	2019-12-16 to 2023-01-06	Phase 3	No	ClinicalTrials.gov
NCT04686994	Study to Evaluate the Safety and Efficacy of ASC41 in Overweight and Obese Subjects	ASC41	Evaluate safety and efficacy of ASC41 tablets in overweight/obese subjects with metabolic risk features relevant to NAFLD/NASH development. Current interpretation/conclusion: Completed; no posted results in CSV. Relevant as early metabolic safety/efficacy support for ASC41 advancement.	2020-12-22 to 2021-02-07	Phase 1	No	ClinicalTrials.gov
NCT04845646	DDI Study of ASC41 in HV and the PK, Safety and Tolerability in Subjects With NAFLD.	ASC41	Assess ASC41 drug-drug interaction with itraconazole/phenytoin and characterize ASC41 PK, safety, and tolerability in healthy volunteers and NAFLD subjects. Current interpretation/conclusion: Completed; no posted results in CSV. Best interpreted as supportive early clinical pharmacology evidence, not a definitive efficacy trial.	2021-03-16 to 2021-06-10	Phase 1	No	ClinicalTrials.gov
NCT04951219	A Phase 3 Study to Evaluate Safety and Biomarkers of Resmetrom (MGL-3196) in Patients With Non-alcoholic Fatty Liver Disease (NAFLD), MAESTRO-NAFLD-Open-Label-Extension (MAESTRO-NAFLD-OLE)	Resmetrom (MGL-3196)	Evaluate longer-term safety and biomarker effects of open-label resmetrom in NAFLD after prior MAESTRO participation. Current interpretation/conclusion: Active not recruiting; no posted results in CSV. Useful for long-term safety and extension evidence once complete.	2021-07-09 to 2027-04	Phase 3	No	ClinicalTrials.gov

NCT number	Study title	Drug/intervention	Objective of the study and current interpretation	Start date - completion date	Mapped phase	Posted results	Source URL
NCT05415722	DUET Study: A Clinical Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Orally Administered TERN-501 as Monotherapy and in Combination With TERN-101 in Noncirrhotic Adults With Presumed Non-Alcoholic Steatohepatitis	TERN-501 + TERN-101	Evaluate TERN-501 monotherapy and TERN-501 plus TERN-101 for safety, efficacy, PK, and PD in noncirrhotic presumed NASH. Current interpretation/conclusion: Completed with posted results. Supports emerging combination/monotherapy development of TERN-501 with noninvasive liver endpoints.	2022-06-28 to 2023-07-10	Phase 2a	Yes	ClinicalTrials.gov
NCT05462353	Study to Evaluate the Safety, Tolerability, and Efficacy of ASC41 Tablets in Adult Patients With NASH	ASC41	Evaluate ASC41 tablets in adults with NASH, including histologic response, safety/tolerability, and MRI-PDFF hepatic fat change. Current interpretation/conclusion: Active not recruiting; no posted results in CSV. Final conclusions require trial completion/results posting.	2022-09-30 to 2025-06-10	Phase 2	No	ClinicalTrials.gov
NCT05500222	A Phase 3 Study to Evaluate the Effect of Resmetirom on Clinical Outcomes in Patients With Well-compensated NASH Cirrhosis (MAESTRO-NASH-OUTCOMES)	Resmetirom	Evaluate whether resmetirom improves clinical outcomes in well-compensated NASH cirrhosis. Current interpretation/conclusion: Active not recruiting; no posted results in CSV. Important because it uses clinical outcomes in compensated cirrhosis rather than only surrogate endpoints.	2022-08-26 to 2027-01	Phase 3	No	ClinicalTrials.gov
NCT05118360	Study to Evaluate the Safety, Tolerability, and Efficacy of ASC41 in Adults With NASH	ASC41	Evaluate ASC41 safety, tolerability, and efficacy in adults with biopsy-confirmed NASH using histologic NAS improvement and fibrosis safety endpoints. Current interpretation/conclusion: Withdrawn; no efficacy conclusion can be drawn. Still relevant for landscape analysis because it reflects planned ASC41 NASH development.	2023-12-01 to 2025-01-09	Phase 2	No	ClinicalTrials.gov
NCT07249788	Resmetirom Efficacy & Safety in Patients With MASH	Resmetirom	Further evaluate resmetirom efficacy and safety in patients with fibrosclerotic proven MASH in a real-world/regional post-approval setting. Current interpretation/conclusion: Recruiting; no conclusion yet. Post-approval phase 4 evidence may support external validity and regional effectiveness/safety.	2025-10-17 to 2026-12-31	Phase 4	No	ClinicalTrials.gov
NCT07288138	A Study of a Thyroid Hormone Receptor Beta Isoform (THRβ) Agonist and an Semicarbazide Sensitive Amine Oxidase (SSAO) Inhibitor, Alone and in Combination, in Adults With Presumed Metabolic Dysfunction-associated Steatohepatitis (MASH)	ECC4703 + ECC0509	Evaluate ECC4703 and ECC0509 alone and in combination for hepatic fat reduction in presumed MASH by MRI-PDFF. Current interpretation/conclusion: Recruiting; no conclusion yet. Indicates movement toward combination therapy and dual-mechanism MASH pharmacotherapy.	2025-12-15 to 2027-09-29	Phase 2a	No	ClinicalTrials.gov
NCT07335601	Study to Evaluate Resmetirom in Post-Liver Transplant Patients With MASH	Resmetirom	Evaluate resmetirom in post-liver transplant patients with recurrent or de novo MASH and moderate-to-advanced fibrosis. Current interpretation/conclusion: Recruiting; no conclusion yet. Expands THR-β therapy into post-transplant MASH, a special internal-medicine/hepatology population.	2025-12-29 to 2029-03	Phase 2	No	ClinicalTrials.gov
NCT07143968	A Study to Evaluate the Use of Resmetirom in Participants With MASLD and HIV	Resmetirom	Evaluate resmetirom safety and efficacy in participants with MASLD and HIV. Current interpretation/conclusion: Recruiting; no conclusion yet. Addresses MASLD in HIV, a clinically important comorbidity population.	2026-04-23 to 2027-11	Phase 2	No	ClinicalTrials.gov
NCT07466017	A Study of CS060380 Tablets in Patients With MASH and Obesity	CS060380 + Semaglutide	Evaluate CS060380 tablets in combination with semaglutide in adults with MASH and obesity. Current interpretation/conclusion: Recruiting; no conclusion yet. Reflects movement toward MASH-obesity combination pharmacotherapy with GLP-1 overlap.	2026-04-02 to 2027-07-30	Phase 2	No	ClinicalTrials.gov

Note: The phase column is manually mapped from trial titles/registry snippets where the uploaded CSV did not include a Phase field. Verify by re-downloading ClinicalTrials.gov with the Phase field before journal submission.

fibrosis patients, an extension trial, clinical outcome trials in well-compensated NASH cirrhosis, as well as newer studies involving special populations like post-liver transplantation MASH and MASLD with HIV. The other interventions include agents like VK2809, ASC41/ASC43F, TERN-501, ECC4703, and CS060380, representing the development of next-generation THR- β agonists.

Overall, it can be said that the THR β agonists for MASLD/MASH are in a very active state and constantly developing. Resmetirom/MGL-3196 stands out as currently being the major program. Nevertheless, the low number of posted registry results indicates limited reporting within ClinicalTrials.gov; it does not establish a lack of published evidence.

Discussion

This study characterized the clinical development landscape of THR- β agonists for MASLD/MASH using ClinicalTrials.gov. Of 32 identified records, 18 eligible interventional trials were included. The landscape was marked by continued development, predominance of mid-stage studies, extensive industry sponsorship, and a leading role for resmetirom/MGL-3196. Resmetirom accounted for 9 of 18 trials (50.0%), phase 2/2a/2b studies represented 10 of 18 (55.6%), and 17 of 18 trials (94.4%) were industry-sponsored. Despite this active pipeline, only 2 of 18 trials (11.1%) had posted results.

These findings are clinically relevant given the growing burden of fatty liver disease. The multisociety Delphi consensus replaced NAFLD/NASH with MASLD/MASH to better reflect the metabolic basis of the disease [1]. MASLD is strongly associated with obesity, insulin resistance, type 2 diabetes, and cardiometabolic risk. A global meta-analysis estimated NAFLD prevalence at approximately 30%, emphasizing the need for effective pharmacological therapies [11]. Fibrosis stage is also a major predictor of liver-related outcomes and mortality [2,12]. Therefore, continued development of THR- β agonists is particularly relevant for patients with MASH and fibrosis.

The biological basis of this class of drugs is clear and solid. The THR- β subtype receptors are predominant in the liver, and they mediate the metabolism of lipids, cholesterol homeostasis, mitochondria, and fatty acid oxidation [8,9]. Thus, selective THR- β agonists try to achieve beneficial effects at the level of liver metabolism while minimizing other potential harmful effects on the heart and bones through THR- α [9].

The temporal allocation of the trials shows that trials were initiated across all three periods. The 18 trials were equally divided into three time periods by their initial dates. However, their current recruitment status varies over time, with earlier trials being more likely to have been completed, while those initiated from 2023 onward are mostly recruiting or ongoing. Most trials were phase 2, 2a, and 2b, but there were also 4 phase 3 and 1 phase 4 study. This fits with the MASH drug development scheme with an emphasis on histological parameters like MASH resolution and fibrosis improvement [13,14]. However,

the number of trials and their phase cannot be taken as evidence of the effectiveness of this approach.

Resmetirom/MGL-3196 was the most common agent, representing half of all the trials in this review. A significant reduction in hepatic fat was reported with resmetirom in a randomized phase 2 trial by Harrison et al. [15], whereas extension data confirmed its safety and impact on non-invasive measurements. Phase 3 MAESTRO-NAFLD-1 trial investigated its safety and tolerability [16]. However, most importantly, the MAESTRO-NASH study has shown superior results compared with placebo concerning MASH resolution without increasing fibrosis and improvement in fibrosis without MASH worsening [6]. These results contribute to the extensive development program of resmetirom.

Other THR- β agonists were also represented. Four trials (22.2%) were performed using ASC41/ASC43F; 2 (11.1%) used VK2809, and each of TERN-501, ECC4703, and CS060380 was tested individually in clinical trials. Thus, this shows that the development is expanding beyond one drug but is limited in number to make any statements concerning their efficacy or safety. Phase 2a DUET trial of TERN-501 showed a dose-dependent decrease in MRI-PDFF compared with placebo. It was investigated both as monotherapy and in combination with TERN-101 [17]. It is worth noting that monotherapy is much more common than combinations in current studies.

Sponsorship and geography had distinct trends as well. Industry sponsorship was reported in 17 out of 18 trials (94.4%), and only one study (5.6%) had academic sponsorship. While high involvement of industry in pharmaceutical research is anticipated, more investigator-initiated research might contribute to additional evidence on comparative effectiveness, safety, and usage. Seven trials (38.9%) were conducted in North America, six (33.3%) were multiregional, and four (22.2%) - were conducted in Asia; none of the studied trials was conducted exclusively in Europe. Increased geographic variation might be beneficial to generalizability.

For clinical practice, this registry analysis describes where evidence is being developed rather than which THR- β agonist or combination should be selected for an individual patient. Treatment decisions require evidence on efficacy, safety, and the applicable indication, not trial counts or registry posting rates. For drug development, the predominance of phase 2 studies and the small number of combination trials identify areas for further evaluation rather than demonstrating superiority of any strategy. Adequately designed comparative and combination studies, longer-term clinical outcomes, and broader population representation could address these gaps. Any proposed advantage of combination therapy remains a question for prospective testing.

Registry results posting was infrequent, but this endpoint did not measure the total availability of trial findings. Of 18 trials, only two (11.1%) had posted results on ClinicalTrials.gov, and only two out of eight finished trials (25.0%). All trials that posted registry results were completed, and Fisher's exact test found no significant correlation between the status of the study and registry

673	results posting ($p = 0.531$); thus, this trend should be	not systematically assessed outside the registry. The	733
674	interpreted descriptively. The creation of ClinicalTrials.	next studies should focus on transparent and timely	734
675	gov was partially motivated by the need for increased	results reporting, geographical diversification, academic	735
676	access to clinical trials data [18]; however, several studies	research, combination research, and long-term efficacy	736
677	found that reporting guidelines were not followed fully	and safety evaluation.	737
678	[19,20]. It is worth noting that a lack of posted registry		
679	results does not mean that findings are not available		
680	through other means, since results can be published in		
681	journals or elsewhere. Similarly, no trials initiated from		
682	2023 onward had posted registry results, but some of		
683	them are ongoing at the moment.		
684	The study has several strengths, such as the use of a clinical		
685	trials registry, manual screening, and consideration of		
686	phase, status, drug class, therapeutic approach, sponsor,		
687	geography, and results posting. However, several		
688	limitations should be noted. For instance, ClinicalTrials.		
689	gov was the only website that was used for searching,		
690	so some trials that were registered elsewhere may be		
691	missed. The second limitation is that registry information		
692	may be incomplete, out-of-date, or inconsistent. Third,		
693	the absence of systematic trial-level linkage to journal		
694	publications, conference abstracts, and other sources is a		
695	major limitation. No supplementary dissemination search		
696	was performed for the 16 trials without posted registry		
697	results; consequently, registry non-posting cannot be		
698	interpreted as non-publication, non-dissemination, or		
699	noncompliance with reporting requirements. Ongoing		
700	trials may not yet have reached an applicable reporting		
701	deadline. Fourth, manual phase mapping may have		
702	introduced misclassification; independent phase-rating		
703	records and external validation were unavailable for		
704	assessment, precluding an inter-rater agreement estimate.		
705	Finally, the small sample of 18 trials, including several		
706	single-trial categories and only two results-posting		
707	events, limits the robustness and generalizability of the		
708	findings. Category percentages may be unstable, and		
709	the nonsignificant exact test should not be interpreted as		
710	evidence of no association. Therefore, the results should		
711	be considered as a descriptive analysis of the field of		
712	development of THR- β agonists, not as a comparison of		
713	treatment effectiveness.		
714	In summary, THR- β agonists comprise a developing		
715	therapeutic area for MASLD/MASH, led by resmetirom,		
716	but with other potential drugs under development.		
717	Priorities for the future include reporting of results,		
718	involvement of academia, representation from different		
719	geographic regions, more combination approaches, and		
720	evaluation of long-term effectiveness, fibrosis outcomes,		
721	and safety.		
722	Conclusion		
723	THR- β agonists are being investigated across several		
724	stages of clinical development for MASLD/MASH.		
725	The drug resmetirom/MGL-3196 currently leads the		
726	registered trials and possesses the most solid published		
727	clinical data, while other drugs such as ASC41/ASC43F,		
728	VK2809, TERN-501, ECC4703, and CS060380 are also		
729	represented in the pipeline. However, only 2 of the 18		
730	included studies (11.1%) had posted results, indicating		
731	limited results posting within ClinicalTrials.gov. This		
732	does not quantify overall dissemination, which was		
		Acknowledgments	738
		None.	739
		List of Abbreviations	740
		CVD Cardiovascular disease	741
		DDI Drug–drug interaction	742
		FDA U.S. Food and Drug Administration	743
		HIV Human immunodeficiency virus	744
		LDL-C Low-density lipoprotein cholesterol	745
		MASH Metabolic dysfunction	746
		Conflict of interest	747
		The authors declare that there is no conflict of interest	748
		regarding the publication of this article.	749
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		Ethical approval	754
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		available ClinicalTrials.gov trial-level information and did not	756
		involve direct interaction with human participants or access	757
		to identifiable patient-level data.	758
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		<i>Supplementary content (If any) is available online.</i>	781
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