The most often utilized clinical endpoints for assessing treatment efficacy in non-alcoholic fatty liver or non-alcoholic steatohepatitis

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BACKGROUND

- Non-alcoholic fatty liver disease (NAFLD) is characterized by the deposition of fat in the liver (hepatic steatosis) in absence of any identifiable secondary causes of hepatic fat accumulation[1].
- NAFLD consists of various liver conditions, including non-alcoholic fatty liver (NAFL) or hepatic steatosis, and non-alcoholic steatohepatitis (NASH) or steatohepatitis[1,2].
- The worldwide prevalence of NAFLD was estimated at 30.2%. Men have a higher prevalence compared to woman, 36.6% and 25.5%, respectively[2].
- Although treatment options are currently limited, a broad range of promising drugs is now undergoing clinical trials to expand available therapies.

OBJECTIVES

- The aim of this study was to determine the most often utilized clinical endpoints for assessing treatment efficacy in NAFL or NASH in phase 2 trials and to compare them with those obtained in our previous analysis focusing on the phase 3 and phase 4 studies[3].
- Additional objective was to compare the results with the outcomes considered in economic models recently developed in NASH[4,5].

METHODS

- The analysis of clinical trials targeting NAFL/NASH was conducted using data from ClinicalTrials.gov[6].
- Trials in the second phase with a minimum of 50 participants were included, but those focused on device testing, dietary restrictions, surgeries, or diagnostic evaluation were excluded (Table 1).
- Trials were tagged and classified according to the outcome measures, and the most frequent primary and secondary outcomes across all trial were determined.

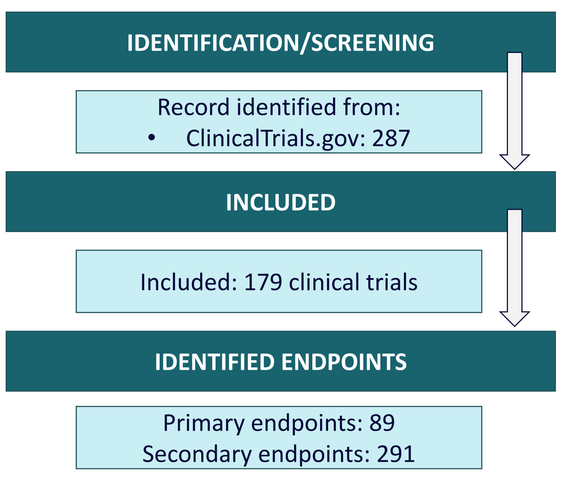

Figure 1. Flowchart of the literature analysis.

Table 1. PICOS criteria.

	Inclusion	Exclusion
Population	Patients with NAFL/NASH	Less than 50 participants
Intervention & comparator	Any pharmaceutical intervention	Device testing, diet restriction, surgeries and diagnostic intervention
Outcomes	No restrictions	
Study design	Phase 2	Phase 1, 3, 4, or "not applicable"

- The eight most common primary and secondary endpoints identified in phase 2 trials were compared with the most common primary and secondary endpoints observed in phase 3 and 4[3].
- Identified endpoints were afterwards compared with the outcomes considered in economic models recently developed in NASH – based on literature review it was mostly fibrosis and liver transplantation[4,5].

RESULTS

- The initial search returned 287 trials for pre-screening. The application of the inclusion criteria reduced the number of trials to 179.
- Following the review process, a total of 83 primary and 291 secondary distinct endpoints were identified.
- The primary endpoints most commonly observed were liver fat, MRI-PDFF, adverse events, ALT and NAS (Figure 2).
- Among secondary endpoints, ALT appeared most commonly, followed by fibrosis, AST, adverse events, and liver fat (Figure 3).
- Additional endpoints identified were adverse events and insulin resistance.
- Among the top 8 the primary endpoints, five were common to the phase 2 studies and to the phases 3 and 4 studies: liver fat, ALT, NAS, improvement of fibrosis, and steatosis (Table 2).

Table 2. Most common clinical endpoints.

	Primary endpoints	Secondary endpoints
Phase 2	• liver fat • MRI-PDFF • adverse events • ALT • NAS • NASH resolution • improvement of fibrosis • steatosis	• ALT • fibrosis • AST • adverse events • liver fat • triglycerides • body weight • HbA1C
Phase 3 and 4	• liver fat • ALT • NAS • AST • CAP • improvement of fibrosis • steatosis • fibrosis	• ALT • AST • triglycerides • body weight • HbA1C • LDL-C • total cholesterol • BMI

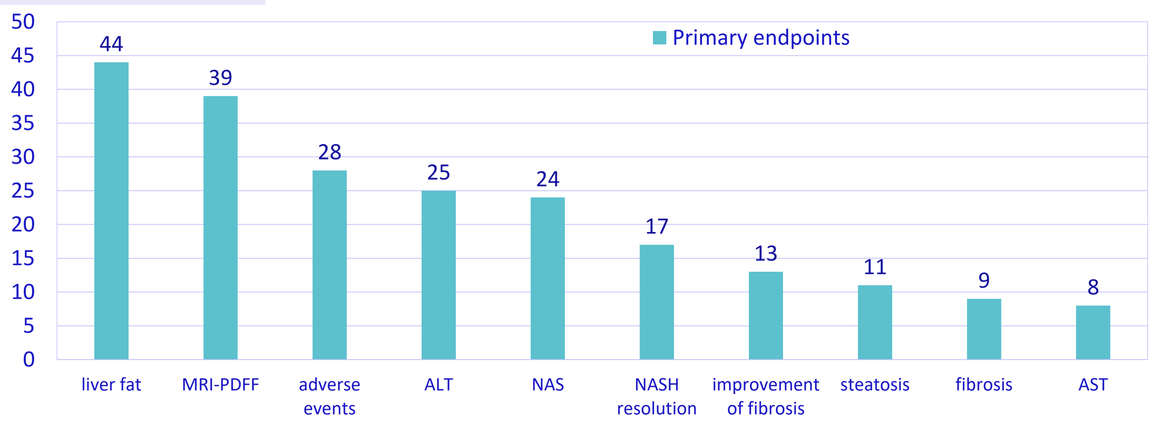

Figure 2. Number of studies by primary endpoints in phase 2.

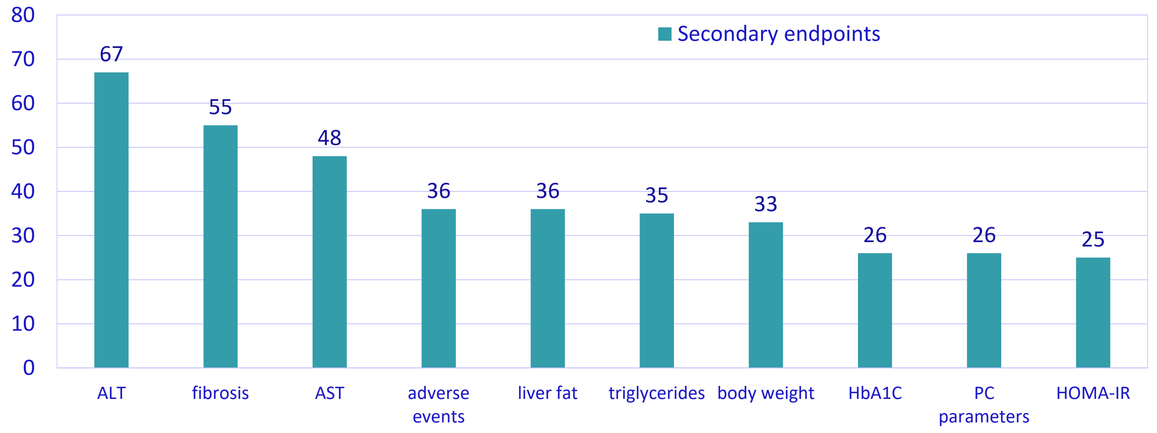

Figure 3. Number of studies by secondary endpoints in phase 2.

- Five secondary endpoints were common to the phase 2 and phases 3 and 4 among the top 8 secondary outcomes: ALT, AST, triglycerides, body weight, and HbA1C (Table 2).
- As expected, adverse events were included as an endpoint in phase 2 trials.
- Most endpoints were surrogates and did not directly measure patient-relevant outcomes. In contrast, the economic models used fibrosis and liver transplant as key outcomes.

Abbreviations
- ALT – alanine aminotransferase
- AST – aspartate aminotransferase
- CAP – controlled attenuation parameter
- HbA1C – glycated hemoglobin
- LDL-C – low-density lipoprotein-cholesterol
- MRI-PDFF – magnetic resonance imaging-derived proton density fat fraction
- NAFL – non-alcoholic fatty liver
- NAFLD – non-alcoholic fatty liver disease
- NAS – NAFLD activity score
- NASH – non-alcoholic steatohepatitis
- PC – pharmacokinetics

CONCLUSIONS

- **Numerous clinical trials are currently underway to explore different treatments for NASH, each with its own set of outcomes under consideration.**
- **Recognizing the diversity of outcome sets and understanding the most prevalent endpoints will enable more effective comparisons between clinical studies.**
- **Common endpoints across phases indicate that early models based on phase 2 can be aligned with results from phases 3 and 4.**
- **Validated risk equations are needed to predict how treatment effects on surrogate endpoints affect outcomes that are meaningful to patients.**

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