

# OPINIONS

## Structure of Proof of Concept Studies That Precede a Nonalcoholic Steatohepatitis Development Program

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**Surrogate endpoints for clinical proof of concept (POC) trials in nonalcoholic steatohepatitis (NASH) are based upon expert pathological review of liver biopsies. During early development, these long-term POC studies ( $\geq 48$  weeks) add cost and time to the “Go/No Go” decision process. However, it is possible to conduct short-term noninvasive POC studies utilizing biomarkers and magnetic resonance imaging. Here, we discuss the use of shorter noninvasive POC studies relative to biopsy-driven studies for drug development in NASH.**

Nonalcoholic steatohepatitis (NASH) is approaching epidemic proportions with a high prevalence in obese, insulin-resistant subjects, and patients with type 2 diabetes mellitus. In the United States, the prevalence of NASH among patients with non-alcoholic fatty liver disease, as determined with imaging techniques, has been reported to be  $\sim 60\%$ , with similar or higher rates in Europe and Japan (the prevalence of nonalcoholic fatty liver disease being  $\sim 24\%$  of the population).<sup>1</sup> The features of NASH include fat accumulation in the liver, inflammation, and various degrees of cellular damage and fibrosis, leading to liver-related outcomes and mortality. Diagnosis and disease staging of NASH requires liver biopsies and expert pathological review. Currently, there are no drugs approved for the treatment of NASH although the

multiple pathogenic steps implicated in the development of NASH provide a broad spectrum of potential, and differing, pharmacological targets.<sup>2</sup> For example, targets already being investigated in clinical trials include such mechanistically diverse pathways as proliferator-activated receptor-related signaling, galectin inhibition, and farnesoid receptor activation. With at least two drugs in phase III development, we can expect to see continued interest in the development of drugs to treat NASH, and continued interest for assessing the value of various phase II proof-of-concept (POC) study designs for this complex metabolic disease.

Definitive phase II POC studies in NASH often require a sufficient duration ( $\geq 48$  weeks) to demonstrate liver improvements through the evaluation of tissue

biopsies. From a drug development perspective there are many disadvantages for stakeholders when conducting such long POC studies involving an invasive procedure, such as a liver biopsy: (1) patients might be exposed to ineffective investigational drugs with potentially unknown side effects for relatively long periods of time; (2) enrollment challenges from reluctance by patients and caregivers to participate due to repeated liver biopsies; and (3) long-term POC studies incur substantive cost burdens on the sponsor. These issues become magnified when considering dose response studies with inclusion of several experimental arms, or when the sponsor is considering exploring the pharmacological activity of several potentially effective drugs within their portfolio.

To establish a more streamlined and affordable approach for drug development in NASH, we and others have considered an alternative strategy of utilizing early phase II POC noninvasive study designs lasting  $\leq 28$  weeks. These short-term phase II POC studies provide composite biomarker endpoints that incorporate a variety of noninvasive measures. Although noninvasive measures have not been clinically validated for use in NASH, they can provide a degree of confidence strong enough for all stakeholders to further invest in the development of the product, patients, sponsors, and regulators. Such noninvasive measures include scanning technologies (e.g., magnetic resonance imaging, magnetic resonance elastography) and various biochemical markers (e.g., markers of insulin resistance, liver inflammation, and fibrosis).<sup>3,4</sup> Although none of these biomarkers taken in isolation can fully replace a liver biopsy in terms of NASH progression, they do provide information about pathogenic factors associated with NASH as well as drug-induced changes in morphology

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**Table 1 Key differentiators between noninvasive and invasive biopsy-driven nonalcoholic steatohepatitis proof of concept studies**

Comparative parameter	Phase II POC studies $\geq 48$ weeks incorporating invasive liver biopsies as clinical endpoints	Phase II POC studies $\leq 28$ weeks incorporating noninvasive liver measures as clinical endpoints
Ease of patient enrollment	Reluctance of patients to undergo multiple biopsies	Larger pool of subjects for clinical studies
Data acquisition logistics	Challenges for accurate pathological quantification of serial liver biopsies	Quantification of multiple biomarkers relatively straightforward
Cost	\$\$\$	\$
Duration of trial	Years	Months
Applicability of results	Gold-standard for drug effect on NASH	Not definitive, but provides confidence for further investment/development
Combination therapy assessment	Unlikely to be applicable to drug combinations without information from short-term studies	Applicable to early combination therapy POC studies
Enrichment strategy	Requires time to determine specific advantages of enrichment	Provides for rapid evaluation of enrichment strategy
Stand-alone study	Yes	Yes
Potential to incorporate into adaptive designs	Yes	Yes
Additional studies for registration	Registration study(s)	Biopsy-driven phase II POC study <sup>a</sup> plus registration study(s)

NASH, nonalcoholic steatohepatitis; POC, proof of concept.

<sup>a</sup>Given the chronic nature of NASH, a biopsy-driven POC study ( $\geq 48$  weeks) would still be required before larger phase III registration studies (even with a positive noninvasive short-term POC study). The noninvasive short-term POC study remains essentially a tool for early “Go/No Go” decisions.

and liver function. Furthermore, based upon the mechanism of action of the drug, specific biomarkers can be preselected based on the mechanism of action of a new drug to best determine if an experimental agent is having the positive impact expected on histological outcomes. Given these short-term noninvasive studies can offer a signal of pharmacological activity, and at less cost than biopsy-driven studies, they can offer a more attractive option for patients, and certainly provide a more sustainable financial model for drugs in early clinical development (Table 1). Nevertheless, there is no one “ideal” biomarker that demonstrates specificity for NASH and development decisions will have to be made using a composite evaluation of both chemical biomarkers and appropriate scanning technologies. Eventually, a proven composite of biomarkers might emerge, but for now, “Go/No Go” decisions for each molecule in development will have to be reasoned on a case-by-case basis.

Enrollment of patients into clinical studies is likely to be challenging when they are expected to undertake multiple liver biopsies. However, most patients will require a biopsy to confirm the diagnosis of NASH. Consequently, patients can be enrolled

into short-term noninvasive POC studies within a period of time following their confirmed diagnosis without undergoing further biopsies. Of course, another intriguing possibility for noninvasive short-term POC studies is to enroll patients with no liver biopsy, but with a high risk of developing or already having NASH (if a baseline biopsy is not available). However, as of today, the drug development utility of this approach remains open to debate. The presence of a baseline biopsy-driven diagnosis also provides an opportunity to enrich the patient cohort in a manner that will tailor the results toward the mechanism of action of the drug. For example, drugs acting on fibrosis can be directed toward patients with high fibrosis scores as opposed to other drugs that are more likely to influence glucose or lipid metabolism and impact necroinflammation (in any case, long-term studies will have to prove an impact on fibrosis as well). Other enrichment strategies might involve genetic variations or a variety of baseline pathologies. Enrichment strategies have proven useful in phase II oncology studies and it seems reasonable to assume they will also prove to be very effective in short-term noninvasive NASH studies. Similarly, given

the multiple pharmacological targets in NASH, it is likely that combination therapy might afford the best option for treatment; short-term noninvasive POC studies with a combination of investigational products would surely prove an attractive alternative relative to more expensive long-term phase II studies.

An analysis of phase II POC studies listed on clinical trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) over the last 6 years suggest that sponsors are using both biopsy-driven and shorter noninvasive phase II POC studies (Table 2). It does seem that over the past 2 years there has been an increase in the use of short-term noninvasive POC studies, whereas the number of long-term POC studies seems relatively constant over the last 6 years. Given the chronic nature of NASH, and the relatively slow ability of the liver to repair after reaching advanced fibrosis, it is possible that studies of short duration ( $\sim 12$  weeks) will have an inherent risk for false-negative outcomes. This risk has to be weighed against the advantages of confirming pharmacological activity at multiple doses over a short period of time, and for much less cost than larger biopsy-driven studies ( $\geq 48$  weeks), which incorporate only a few doses of drug.

**Table 2** Patterns of short-term and long-term phase II proof of concept clinical studies in nonalcoholic steatohepatitis over 6 years

2-year periods in which phase II studies were initiated in NASH (www.clinicaltrials.gov)	Phase II POC studies $\geq 48$ weeks incorporating invasive liver biopsies as clinical endpoints	Phase II POC studies $\leq 28$ weeks incorporating noninvasive liver measures as clinical endpoints <sup>a</sup>
June 2010 – May 2012	3	1
June 2012 – May 2014	4	3
June 2014 – May 2016	5 <sup>b</sup>	10

NASH, nonalcoholic steatohepatitis; POC, proof of concept.

Notes: No drugs have been approved for the treatment of NASH. As yet, it is not possible to calculate the relative success of different POC study designs for predicting overall development success.

Search terms: nonalcoholic steatohepatitis, NASH |Phase 2 | NIH, Industry | Studies received from 06/01/yyyy to 05/31/yyyy.

<sup>a</sup>Range 4–28 weeks; mean 16 weeks. <sup>b</sup>Includes one study that was 13 weeks in duration. Source Data: www.clinicaltrials.gov.

Indeed, short-term noninvasive studies with multiple doses can be used not only for “Go/No Go” decisions, but they can also be used as an aid to refine the choices for selecting both the registration and minimally effective doses. An optimum duration for these short-term noninvasive POC studies has yet to be determined, and no consensus has emerged. For example, over the last 6 years the 14 short-term noninvasive POC studies shown in **Table 2** (completed or in progress) have ranged from 4–28 weeks in length. On the other hand, because of the multiple pharmacological targets available to treat NASH, and potential differences in inclusion/exclusion criteria based on the stages of the disease, it should not be surprising that there is variation in the duration of noninvasive POC studies.

The use of noninvasive measures to assess NASH progression, and the effect of experimental drugs, has recently been suggested as a means to gain marketing approval.<sup>5</sup> However, because there are no validated biomarkers for NASH at the present time, the applicability of short-term noninvasive studies remains essentially a cost-effective tool directed at accelerating “Go/No Go” decisions. With time, it may be expected that noninvasive endpoints for NASH will be developed, but for now, the gold standard remains to be invasive (i.e., liver biopsy-driven endpoints). The importance of biopsy-derived data is reflected in the apparent path to marketing approval, in which accelerated approval in the United States, and conditional approval in the European Union, are based wholly on

endpoints from liver biopsies (full marketing approval would then be granted with completion of a clinical outcomes trial).<sup>2</sup> Of course, short-term noninvasive phase II POC studies do not necessarily need to be stand-alone studies, they can also be incorporated as early futility enabling events for longer phase II biopsy-driven studies, or even incorporated into adaptive phase II/III designs for registration studies.

In summary, the decision whether to initially develop a drug for NASH through a short-term noninvasive phase II POC study, or move forward with development through a long-term biopsy-driven phase II POC study (or a combination of both), will continue to be actively discussed. Fortunately, for patients with NASH, options for trial designs are now becoming available to streamline the development process. Clearly, whether used as stand-alone studies or as part of longer-term studies, the use of noninvasive short-term phase II POC NASH studies has the potential to refine which drugs should, or should not, be selected for further development early in the process. This approach may also support POC testing for various drug combinations. It seems reasonable to assume that, in the future, drugs for NASH will be developed and approved based upon the validation of appropriate biomarkers, and that the use of noninvasive measures will continue to evolve for noninvasive phase II POC studies. Consequently, while development of drugs for NASH will, at least in the near term, continue to rely on liver biopsies for gaining marketing approval, the day of using noninvasive surrogate endpoints

might perhaps arrive sooner than we currently envision.

#### CONFLICT OF INTEREST

The authors declared no conflict of interest.

Additional Supporting Information may be found in the online version of this article.

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