WORLDWIDE CLINICAL TRIALS

A TALE OF TWO AGENCIES: FDA AND EMA REGULATORY GUIDANCE FOR NASH AND THE IMPACT ON PROGRAM DESIGN

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver condition in the United States, affecting some 25% of adults.[1] Typically, NAFLD by itself does not lead to liver damage. However, a more severe form of NAFLD called nonalcoholic steatohepatitis (NASH) affects approximately 20% of NAFLD patients (5% of U.S. adults), and NASH can, over the course of years, lead to cirrhosis and hepatocellular carcinoma (HCC).[1, 2] There is no universally endorsed standard of care for NASH, and why some individuals affected by NAFLD progress to NASH remains unknown.[1, 3]

Nor is this solely an American problem. Studies cited by the European Medicines Agency (EMA) note that prevalence rate of NAFLD (25% of the general population) and NASH (5% of the general population) are the same across the entirety of the Western world, mirroring the epidemiological data within the U.S..[4] In Europe, NASH is particularly found in Ireland, Hungary, Luxembourg, and the United Kingdom.[5]

Of concern in both the U.S. and Europe are studies projecting that the incidence of NAFLD and NASH will increase significantly in the next decade. One projection shows new NASH cases in the US increasing from 16.25M in 2015 to 27M in 2030.[2] That reflects a 3.33% year-over-year growth rate. Moreover, NASH cases will constitute, proportionately, 27% of NAFLD cases in the U.S. by 2030. This same study projects that incidence of decompensated cirrhosis will increase 168% to 105,430 cases by 2030, while incidence of associated morbidity such as HCC will increase by 137% to 12,240 cases. Given the morbidity of NASH and the absence of a cure for the condition, these projected increases prompt concerns about the impact that will be placed on families, local economies, and health care systems.[6] As an example, NASH is expected to become the leading cause of liver transplantation in the United States between 2020-2025.[7-9] Between 2017 and 2060, the total healthcare burden of NASH in the U.S. is projected to be $359 billion dollars.[10] At the same time, it is acknowledged that the availability of donors for organ transplantation is limited.[3, 11, 12]

Both the EMA and U.S. Food and Drug Administration (FDA) agree that identifying therapies to slow the progress of, halt, or reverse NASH and NAFLD will address a significant unmet clinical need.[3, 4] Clear guidance exists from both regulatory authorities on the structure of a clinical development program and the range of study designs for potentially pivotal trials, including patient eligibility criteria, endpoints, and safety assessments for NASH clinical trials. However, as is frequently the case in an international clinical development program, guidance and recommendations may not be fully concordant, and these apparent differences in regulatory standards for a market authorization application (MAA) or new drug application (NDA) raise questions regarding the strategic design of registration programs. These differences can be anticipated and preemptively addressed, and the exploration of similarities and differences across regulated jurisdictions — and their impact on program and protocol design — warrants review.

PARSING THE EMA AND FDA GUIDANCE

The major areas where the FDA and EMA guidance documents converge are notable:

- Both agencies agree that the ultimate goal of a NASH treatment is to slow the progress of, halt, or reverse disease progression and improve clinical outcomes.
- Both have developed highly codified preclinical and clinical requirements for the NASH indication. In particular, the recommendations for trial designs after preclinical enabling studies are specific.
- Both call for interventional studies to include patient populations with specific and common

comorbidities associated with NASH (e.g., obesity, diabetes, possibly cardiovascular disease).

- For Stage 2 or 3 fibrosis patients, both agencies recognize the primacy of a composite endpoint that includes all-cause mortality, liver transplantation, a manifestation of decompensation, a histological diagnosis of liver cirrhosis, and a score of >14 on the Model for End-Stage Liver Disease (MELD) assessment.
- Both agencies require adjudication committees for outcomes related to liver pathology and cardiovascular safety, and both project that programs will continue for at least five years when efficacy and safety requirements are fully considered.

The FDA and EMA also diverge in design and operational areas, as **Table 1** illustrates. An examination of these differences follows.

TABLE 1: THE MAJOR DIFFERENCES BETWEEN THE REGULATORY GUIDANCE FROM THE FDA AND EMA FOR THE DEVELOPMENT OF A DRUG THERAPY IN NASH.

POINTS OF DIVERGENCE - FDA	POINTS OF DIVERGENCE - EMA
• Phase 2 trials are formally divided into "Early Phase 2 Trials" and "Late Phase 2 Trials," reflecting a tiered approach in program development. • Baseline histologic documentation of NASH is not always needed for early Phase 2 trials, though patients should have a histological diagnosis for a Phase 3 trial proximal to study enrollment. • Phase 2 designs must examine a potential dose-response relationship, but demonstration of a dose-response based upon observed data may not be mandated for approval. • Biomarker "signatures" serve a strategic objective and are explicitly requested. • Phase 3 should be a double-blind, placebo-controlled, parallel group study of sufficient duration and size given clinical endpoints. The explicit description suggests relative lack of flexibility in alternative study options. • Multiple and precise eligibility criteria or characteristic. • Decompensated cirrhotic (stage 4 fibrosis) patients are excluded. • Stopping rules on a patient and study level are clearly defined.	• Primary endpoints based on repeated biopsy results for early Phase investigations, and throughout the program. • Combination products explicitly recognized within NASH guidance - properties of single substances explored and described before or during development of combination treatment. • Compensated and decompensated cirrhotic (stage 4 fibrosis) patients are permitted.

EARLY AND LATE PHASE 2 TRIALS

The FDA recommends dividing NASH Phase 2 trials into "early" and "late" Phase 2 trials. The EMA does not mandate this distinction, but neither does it explicitly reject a trial design that incorporates an early and late Phase 2 staging. In an early Phase 2 trial, the FDA recommends that a sponsor seek proof-of-concept (POC) validation with respect to improvement on markers of steatohepatitis, fibrosis, or both.[3] Acceptable POC study endpoints could include noninvasive disease-specific biomarkers, standard measures of liver injury (AST and ALT), as well as imaging modalities that assess liver stiffness or hepatic fat content.[3] Many imaging modalities are being explored for NASH, including ultrasonography, ultrasound elastography (USE), two-dimensional SWE (2D-SWE), fibroscan, and others.[13] The FDA also recommends an early Phase 2 trial as an opportunity to evaluate multiple dose levels of a test substance in an examination of dose–exposure–response and to evaluate histological and biochemical markers for use as non-invasive biomarkers. The "late" Phase 2 trials should build on the insights from the "early" Phase 2 trials and focus on the treatment effect as manifest in histological endpoints such as the reduction of inflammatory changes, improvement in fibrosis, or both.[3]

EARLY AND LATE PHASE 2 TRIALS

Depending on endpoints selected, the FDA may not require baseline histologic documentation of NASH in either the early or late Phase 2 studies. In some cases, patients can be enrolled based on "a combination of biochemical criteria and/or imaging evidence of steatosis/steatohepatitis/fibrosis in addition to known risk factors for NASH."[3] However, the EMA requires baseline histological documentation even where the FDA does not, so capturing baseline histologic data during Phase 2 would be a prudent step, duly satisfying criteria under both regulatory umbrellas (particularly because the FDA does require patients to have a histological diagnosis of NASH proximate to enrollment in a Phase 3 trial).

DOSE-RESPONSE RELATIONSHIP

The FDA recommends that early Phase 2 trials be designed to facilitate the examination of a dose-response relationship. No similar recommendations are found in the EMA guidance on NASH.[4] However, a 2015 report from an EMA workshop on dose finding, which is generally applicable across multiple therapeutic areas, emphasizes the importance of dose-exposure-response relationships to assist in an overall interpretation of drug effect.[14, 15] Differences in how demonstration of that effect may occur are also highlighted in that guidance. An example of particular note, given its ubiquitous presence in parallel group dose-ranging studies, is the observation that "traditional statistical pairwise comparisons in Phase 2 trials to support dose selection, by testing for statistically significant differences between the groups … is suboptimal in terms of dose selection."[14] This same workshop champions dose-ranging using model-based estimation rather than hypothesis testing via pairwise comparisons.[14]

BIOMARKER SIGNATURES

The FDA and the EMA both acknowledge that a reliable diagnosis of NASH can only be obtained through a histopathological examination of a tissue specimen obtained through a liver biopsy.[3, 4] Both guidance documents also acknowledge that liver biopsies are burdensome, invasive, and carry their own risk of morbidity. For these reasons, both agencies encourage the development of strategies that will lead to the identification of biomarkers that can provide non-invasive insights into the state and

stage of NASH in a patient and that could serve as a proxy to indicate the efficacy of a therapy in development.

Where the EMA and FDA differ on the matter of biomarkers is this: The FDA actively encourages inclusion of a biomarker signature strategy in Phase 2 of a trial. The EMA does not discourage the inclusion of such a strategy during Phase 2, but neither does it require the formal inclusion of such a strategy in Phase 2. For this reason, interventional trialists referencing the EMA guidance as a template may find themselves unprepared for regulatory submission in the U.S. unless they actively incorporate a biomarker signature stratagy in Phase 2.

While both the FDA and EMA acknowledge the burden, complexity, and risks associated with liver biopsies, they both also require such biopsies within the context of a NASH trial. However, they require them at different times. The EMA requires a histological diagnosis of state and stage of NASH before an individual can be included in a Phase 2 trial[4]; in contrast, the FDA mandates histological insight into the state and stage of NASH only when a patient enrolls in a Phase 3 trial.[3] It may be argued that this is a distinction without substantive difference, but nevertheless the criterion may materially affect patient eligibility and thus accrual depending on the stage of clinical development.

Finally, on the subject of biomarkers, biopsies, and analysis, it is important to note that EMA guidance requires primary endpoints, even in Phase 2 trials, based on histologic results. In contrast, the FDA allows the use of non-invasive endpoints in some trial scenarios (such as early Phase 2 POC studies, in which an imaging study may provide suitable insight into liver stiffness or fat content).[3] Sponsors should be aware that such endpoints may prove to be unacceptable and are unpersuasive under an and EMA framework for product evaluation. One stratagy to be considered would be the use of dual primary endpoints (not co-primaries) but separate endpoints as appropriate within these investigations, emphasizing the primacy of one over the other contingent upon the jurisdiction in which the study is conducted. Both endpoints would require suitable powering given this stated objective, with attention to details regarding data acquisition and analysis appropriate to each endpoint.

PHASE 3 TRIAL DESIGNS

The FDA guidance specifically recommends that a Phase 3 NASH trial be undertaken as a double-blind, placebo-controlled group study of sufficient duration and size given clinical endpoints. The explicit description suggests a relative lack of flexibility regarding alternative trial designs, in spite of regulatory guidance accepting (in principle) alternative approaches under the adaptive trial concept.[16] Conversely, EMA guidance is less prescriptive. Sponsors considering a common application that will be reviewed by both regulatory bodies should be aware of the potential limitations of the FDA's recommendation and design their potentially pivotal trials conservatively subject to regulatory review.

TRIALS INVOLVING PRODUCT COMBINATIONS

The EMA guidance formally recognizes value in studying combinations of products in the search for an efficacious NASH therapy. In contrast, the FDA guidance on NASH is silent regarding product combinations explicitly in reference to NASH. Worldwide notes that other FDA guidelines do address the study of product combinations (e.g., the combination rule) and that, even though these guidelines do not specifically reference NASH, it is understood that the existing guidance may also apply to NASH.[17]

CLINICAL ELIGIBILITY CRITERIA

Both the FDA and EMA specify multiple and precise eligibility criteria for NASH trial Phases. As noted above, the EMA requires histological validation of the state and stage of NASH within each trial Phase involving human subjects with a diagnosis of NASH. In contrast, the FDA guidance indicates participants who may simply present as likely NASH patients because of insights gleaned from non-invasive imaging technologies or other biochemical criteria may represent suitable trial candidates, particularly for earlier Phase investigations.

Both regulatory bodies emphasize the importance of populating NASH trials with individuals who also suffer from comorbidities often accompanying NASH (such as obesity and type 2 diabetes mellitus [T2DM]). As patients with NASH and significant comorbidities represent a subgroup with significant healthcare utilization, including these patients within potentially pivotal studies additionally has value in discussions regarding formulary placement and methods of reimbursement, which occur outside of a regulatory discussion prompting approval.

A specific area of divergence, though, has to do with patients indicating advanced decompensated cirrhosis. The 2018 FDA guidance expressly excludes from trial participation any patient with a NASH Clinical Research Network (CRN) fibrosis score indicating greater than 3.[3] In contrast, the EMA guidance expressly permits the inclusion of NASH patients with a CRN fibrosis score of 4, allowing for the inclusion of patients with decompensated cirrhosis.[4] The 2019 FDA guidance permits the inclusion of patients with compensated cirrhosis in Phase 3 trials, though not decompensated cirrhosis.[18] The FDA guidance also indicates that sponsors should be careful to enroll patients whose cirrhosis is secondary to NASH.[18]

SUMMARY OF PROGRAM OPTIONS

The commonalities linking the FDA and EMA guidelines for NASH studies outweigh the differences, and the differences that do exist largely can be accommodated effectively through careful planning.

- Both agencies require a rationale for NASH, accompanied by primary pharmacology data derived (generally) from in vivo preclinical paradigms that have demonstrable heuristic value and potentially some predictive utility in determining the propriety of a NASH clinical development program.[19, 20] They both require essentially the same preclinical safety, toxicology, and biodisposition data as well, as would be consistent with ICH conventions.
- Both agencies require Phase 1 trial data from normal volunteers to validate liver safety and additional endpoints (i.e., general safety, tolerability, and exposure) prior to embarking on a Phase 2 trial involving patients with NASH.
- Both agencies mandate Phase 2 investigations, though the FDA requires biomarker data as a criterion for admission and the EMA requires biopsy results for admission. Under EMA guidance, an additional biopsy at endpoint for Phase 2 would be scheduled only if there is likelihood of a cirrhotic process based upon noninvasive methods such as fibroscan.
- The FDA and the EMA both recognize the importance of dose ranging data emerging during Phase 2 trials, and the method of analysis in both jurisdictions suggest flexibility in the approach.
- The trial protocol for the potentially pivotal study supporting either MAA or NDA must adhere to the guidance provided by both agencies, but there are features within that study design that create a framework for accommodations that may be acceptable to both agencies. For example, discrepancies in emphasis could be

accommodated by the use of dual endpoints in which two different outcomes are appropriately powered, to yield statistically significant differences between treatment group, but the primacy of one over the other is contingent upon the jurisdiction (FDA vs. EMA) where the study has occurred. Precedent examples in other indications exist, admittedly in orphan indications where there is unsettled clinical trial methodology, and the topic is one that may be explored.

- Patient eligibility requirements mandated by each agency are largely interchangeable, except where the inclusion of decompensated cirrhotic patients is concerned. Inclusion of both compensated and decompensated cirrhotic patients is permitted, but not mandated, in the EMA guidelines. Compensated cirrhotic patients are permitted in Phase 3 trials under FDA guidelines, provided their cirrhosis is secondary to NASH; however, decompensated cirrhotic patients are excluded.
- Adjudication committees and stopping rules are required by both agencies, and the emphasis placed on appropriate biostatistical analyses is comparable between both reviewing divisions.

As highlighted above, the differences in FDA and EMA guidelines principally involve patient phenotype (e.g., patients with cirrhosis vs. those without) or methods of assessment (e.g., the EMA's requirement for access to repetitive biopsy results for all Phases). With experienced trial designers, these differences can be addressed without undue burden, ensuring that a sponsor can conduct a single (rather than duplicate) series of NASH trials that comply with both FDA and EMA guidelines.

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