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The Development Landscape for Non-Alcoholic Steatohepatitis

by

Two NASH experts discuss critical challenges, biomarkers and insights from scientific and regulatory perspectives. *Content paid for by Covance*.

Dr. Claudia Filozof, senior medical director in the Phase II-IV cardiovascular/metabolic group at Covance, and Dr. Richard Williams, executive strategist, global regulatory affairs at Covance, give their insights on the latest changes in NASH.

Q **Is this a good time to develop a NASH drug, and if so, why?**

A Claudia: Yes, it's a very good time. There are multiple companies starting NASH development, and there is a huge unmet medical need with no treatment approved so far. Health authorities also have shown a lot of interest in supporting companies to speed up development. If you have the right compound, there are multiple advantages to starting a NASH program.
Richard: The cost to society will be enormous if we can't treat this disease. I think most pharmaceutical companies, big and small, see this as a substantial unmet medical need. With this unmet medical need, regulatory agencies can grant conditional approval (accelerated approval in the US), where the drug is approved for marketing with the condition that the company later shows it has a clinical benefit based on clinical outcomes.

Q **What do you see as the most critical challenges in NASH development?**

A Claudia: Companies still need to use an invasive method for the primary and many

secondary endpoints, but patients may not be willing to have multiple liver biopsies. Also, completing a clinical outcomes study requires at least five or six years. Another important challenge is the natural history of the disease: many patients spontaneously regress, which makes the placebo behavior, in some cases, difficult to predict.

Richard: One risk involves reimbursement. Companies have to consider whether health authorities in other countries would be willing to pay for this drug and what evidence they would want to see. The best strategy is to have dialogues with health technology assessment groups early in the process, then incorporate clinical endpoints to demonstrate that the treatment has a real benefit for patients in the eyes of the payers.

Q **Should companies consider repurposing existing drugs for NASH?**

A Richard: Since this is an unmet medical need with no approved treatments, companies can be quite creative in repurposing drugs. For instance, weight loss may be effective for NASH patients. If a company has a drug that causes weight loss, that may be an interesting avenue to pursue. The safety profile is already known, so that takes away some of the risk of developing those products.

Q **What is the ideal target population for a trial in early stage disease?**

A Claudia: We know that some patients may regress, so companies should not include patients in the very early phases of the disease. If they select patients based on liver biopsy, they may want to enroll patients with non-alcoholic steatohepatitis with an NAFLD activity score of at least 4. Since liver fibrosis is the main driver of progression, a subgroup of patients with fibrosis must be enrolled.

Q **How can companies ensure that they're selecting the right biomarkers?**

A Claudia: The most accepted biomarkers are changes in liver enzymes such as alanine aminotransferase (ALT). But ALT has limitations as a biomarker for NASH. Levels can be normal in many stages of the disease, and only one-third of NASH patients have high ALT. Companies need to consider the compound's mode of action, as well as the

sensitivity and specificity of the biomarker. Insulin resistance is a key component in the development and perpetuation of the disease. In general, improvement in insulin resistance is associated with improvement in NASH. Biomarkers of inflammation, apoptosis, oxidative stress and fibrosis should also be considered.

Q **What future changes do you anticipate in NASH development?**

A Richard: It's a rapidly changing field, and we're waiting to see if better, non-invasive endpoints emerge. If so, that will lead to faster registration. Patients will probably show biochemical changes long before histological changes, so there's the potential to accelerate development.

Claudia: I think the number of patients with confirmed NASH will increase in the near future. We will likely end up with multiple compounds, and the final treatment will probably be a combination of different modes of action. In the mid-term, a non-invasive marker is expected to be validated.

Q **What capabilities does Covance offer in this area?**

A Richard: We're one of the few CROs that offer support throughout the entire drug development process, from pre-clinical to Phase IV. We have liver disease experts who can help refine various aspects of the trial design, whether it's reducing costs or using biomarkers to make clinical decisions. Our clients also work with our drug development experts who can address market access and regulatory issues that are critical to a product's success. So we can offer a full range of services to a company that wants to bring a NASH treatment to market.