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Translating Science to Medicine

The ABC's of NASH

Key NASH Terms for Clinical Drug Development

Nonalcoholic steatohepatitis (NASH) is a chronic liver disease characterized by steatosis, hepatic inflammation and injury. As a relatively new indication for disease treatment, the FDA and EMA have issued draft guidance for clinical drug development.

The following is a set of key NASH terms related to inclusion criteria, clinical endpoints, biomarkers and outcome measures.

Anti-fibrotic: Fibrosis is the scarring of tissue. Anti-fibrotic properties are desirable attributes for NASH drugs to reverse fibrosis staging and prevent cirrhosis progression.

Ballooning injury: Also referred to as hepatocyte injury and a component of NASH disease activity. Ballooning injury results in enlarged vacuolated liver cells that classically contain histological features such as Mallory Denk Bodies inclusions. Histologically graded from 0-2 as part of NAS, indicating none, few or many ballooned cells respectively.

Cytokeratin 18: An intermediate filament and part of the cytoskeleton. Serum caspase-cleaved fragment of CK-18 (DiaPharma, OH) is a marker of apoptosis and reflects hepatocyte ballooning in NASH. Currently, CK-18 is undergoing development as a diagnostic and treatment response biomarker of NASH.

Disease activity (NAS): The NAFLD Activity Score (NAS) is a composite histological grading of the disease which includes steatosis (0-3), ballooning injury (0-2) and inflammation (0-3), reflecting features of active disease. A NAS of 4 or more is indicative of NASH and often used as inclusion criteria for late phase clinical trials.

Endpoints: The primary outcomes of a clinical trial. Current accepted endpoints for conditional approval include resolution of NASH without worsening of fibrosis and/or improvement in fibrosis without worsening of NASH by liver histology.

FibroScan®: A noninvasive imaging technique used to simultaneously assess liver stiffness and hepatic fat through vibration controlled transient elastography and controlled attenuation parameter respectively. The FibroScan (Echosens, France) is a point-of-care system and available at Celerion clinics.

Genetic polymorphism: A variation in a gene that results in a specific phenotype and inherited trait. The patatin-like phospholipase 3 gene (PNPLA3) encodes the enzyme adiponutrin, a regulator of hepatic fat content and lipid secretion. The PNPLA3 variant I148M is suspected of being a predictor of and implicated in NAFLD/NASH.

Hepatic impairment PK studies: The liver is a main site of drug metabolism. Dose adjustment may be required for patients with hepatic impairment as the excretion and/or absorption of a drug can be adversely altered. The FDA recommends conducting a pharmacokinetic (PK) hepatic impairment study early in NASH drug development.

Inflammation: A component of NAS, inflammation is graded (0-3) reflecting neutrophil infiltration in the liver. Hepatic inflammation is also characterized by Kupffer cell activation and a systemic upregulation of cytokines and chemokines.

Jaundice: A medical condition caused by the obstruction of the bile duct, by liver disease or by the excessive breakdown of red blood cells, due to excess bilirubin and characterized by yellowing of the skin or whites of the eyes. Jaundice can be a symptom of advanced NASH cirrhosis.

Kupffer cells: Specialized, resident liver macrophages lining the walls of the sinusoids. They play a role in the pathogenesis of various liver disease and ultimately are involved in the liver's response to infection, inflammation, toxins, ischemia, resection and other stressors.

Liver disease: Is defined as any condition that damages the liver and negatively affects the normal healthy functioning of the organ. There are several types of liver disease including NASH, Hepatitis A, Hepatitis B, Hepatitis C, cirrhosis and alcoholic hepatitis. Liver disease is the 3rd leading cause of death in patients with NAFLD, followed by cardiovascular disease and malignancy.

MRI-PDFF/MRE: Magnetic resonance imaging (MRI) noninvasively quantifies liver fat content by an analysis called proton density fat fraction (PDFF) and liver stiffness by elastography (MRE). Both tests perform very well against liver biopsy results, provide full coverage of the liver, and are often used as inclusion criteria for early phase clinical studies.

Nonalcoholic steatohepatitis: Histologically defined as the presence of more than 5% hepatic steatosis with inflammation and hepatocyte injury (ballooning) with or without fibrosis. NASH can progress to cirrhosis, liver failure requiring a transplant and even cancer.

Outcomes (clinical): Measurable action reflecting how a patient feels, functions or survives. For NASH, clinical outcomes may include cirrhosis progression, time to liver transplant, varices, mortality (liver related or all-cause).

Pro-C3: A serum biomarker of type III collagen formation (Nordic Biosciences, Denmark). Collagen is a component of fibrosis, and Pro-C3 reflects hepatic fibrosis staging of the disease. Pro-C3 is currently being developed as a diagnostic and treatment response biomarker.

Qualified biomarkers: A biomarker is an indicator of normal or pathogenic processes. Biomarkers can be molecular, histological, radiographic or physiological in nature. Qualified biomarkers undergo analytical validation and formal regulatory validation for a given context of use.

Resolution of NASH: A primary endpoint for NASH Phase III clinical trials. Resolution of NASH is defined as ballooning injury score of 0, inflammation of 0-1 and any stage of steatosis using the NAS grading system.

Steatosis: Accumulation of fat in the liver often related to insulin resistance and obesity. Steatosis results from hepatic uptake of excess lipids derived adipose tissue, intake of high fructose diet and de novo lipogenesis. Steatosis is histologically defined as >5% lipid droplets distributed on liver biopsy slide, MRI-PDFF value ≥5% or CAP value of ≥260 dB/m.

Transplantation: An operation that replaces a diseased liver with a whole or partial healthy liver from a donor. NASH is anticipated to become the primary etiology for liver transplant. Currently there is no FDA approved treatments for NASH.

Ultrasound: The size and shape of the liver can be determined through sounds waves. Ultrasound can detect hepatic steatosis, though only when liver fat is >30%. Currently it is not considered a validated tool for drug development.

Vibration-controlled transient elastography: A measure of liver stiffness determined by the FibroScan® (Echosens, France). Values range from 2-75 kPa and a VCTE value of ≥7kPa suggests the presences of liver stiffness and fibrosis.

Worsening of NASH: Determined by increased NAS (ballooning injury, inflammation, steatosis). No worsening of NASH is a component of Phase III primary endpoints for NASH studies.

Farnesoid X receptor: A target of interest for treating NASH. FXR is a nuclear receptor expressed in liver and intestinal cells. FXR agonists reduce hepatic steatosis, inflammation and fibrosis.

Roux-en-Y gastric bypass: Gastric bypass surgery is indicated for morbidly obese NASH patients. The surgery resolves the features of NASH and fibrosis within the first year of surgery.

Zucker rat: The leptin deficient fa/fa obese rat is a genetic preclinical model of NASH. Other models include dietary interventions such as high-fat, fructose and cholesterol or methionine and choline deficient diets. The STAM mouse, DIAMOND mouse, Western diet plus CCl4 supplementation are generated with chemical and dietary interventions.

Links to Guidance Documents:

FDA NASH draft Guidance

FDA Hepatic Impairment PK Guidance

EMA Reflection paper on NASH

AASLD Diagnosis and Management of NAFLD

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