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Non-alcoholic Steatohepatitis (NASH): UK Treatment Outlook

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Key points

01 Three disease-modifying NASH treatments are currently in phase III trials with the **potential for the first FDA approval in Q2 2024**: Madrigal's resmetirom[1]

02 **NASH represents a significant unmet medical need;** from no approved treatments currently it is expected to grow to a USD14bn market globally by 2032[1]

03 However, **there are factors that would limit access to any launched treatment** including low awareness of NASH, a lack of convenient diagnostic options, and complex care pathways

04 There may be **opportunities for manufacturers to support health systems** in reforming NASH care pathways such as helping to highlight and standardize referral best practices and raise awareness among key HCPs

Non-alcoholic steatohepatitis (NASH) diagnosis and care pathways in the UK are sub-optimally prepared for potential new treatments.

Mid-to-late-phase trial results in 2023 have increased the likelihood of the first approval of a disease-modifying treatment for non-alcoholic steatohepatitis (NASH) [1]. Healthcare providers (HCPs) and patients have voiced the need for new treatment options as NASH associated unmet medical need continues to increase in line with lifestyle related diseases such as diabetes and obesity. NASH is estimated to affect up to 5% of the UK population[4], therefore, a safe and effective treatment, that is appropriately priced, also represents a significant market opportunity.

However, there remain barriers to the uptake of a NASH therapeutic, even one that meets the criteria above. NASH is a complex disease that often presents with no, minimal, or under-recognised symptoms until the later stages of disease progression [5] , as a result, awareness of the disease is low, even among HCPs in related specialties [6]. A biopsy is considered the diagnostic standard for diagnosing NASH, presenting risks for patients and costs for healthcare systems [7][8] . These awareness and diagnosis challenges exacerbate uncertainty in referral pathways for NASH patients who often have multiple co-morbidities [6][9]. To deliver broad access to a long-awaited NASH therapeutic, manufacturers have already begun to work towards addressing some of these barriers, however, step changes are still required in the identification, referral, and diagnosis of NASH patients, as highlighted by the British Liver Trust [5] .

The first disease-modifying NASH treatment is likely to be approved by the FDA in 2024, UK approval could be expected sometime after this. Developers of NASH treatments have faced challenges in clinical trial design due to requirements for biopsy-related endpoints (discussed below), a lack of validated biomarkers, and heterogeneity in the genetic drivers of NASH. Despite these challenges, there are three promising candidates in Phase III trials and a further 44 candidates in Phase II [1][10]. Among those in Phase III, Madrigal's resmetirom could be the first approved disease-modifying NASH treatment having submitted for regulatory approval in the US in July 2023 with accelerated review and a PDUFA date of 14th March 2024 [9]. The EMA is also considering accelerated approval, meaning that resmetirom could be approved for use in the EU from as soon as early 2025. The other Phase III candidates include Inventiva's lanifibranor and Novo Nordisk's semaglutide (the same active ingredient as its GLP-1 diabetes and obesity treatments). We note a range of mechanisms of action across these candidates and those that follow in early and mid-stage development.[1]

Resmetirom expected to be first-to-market NASH treatment

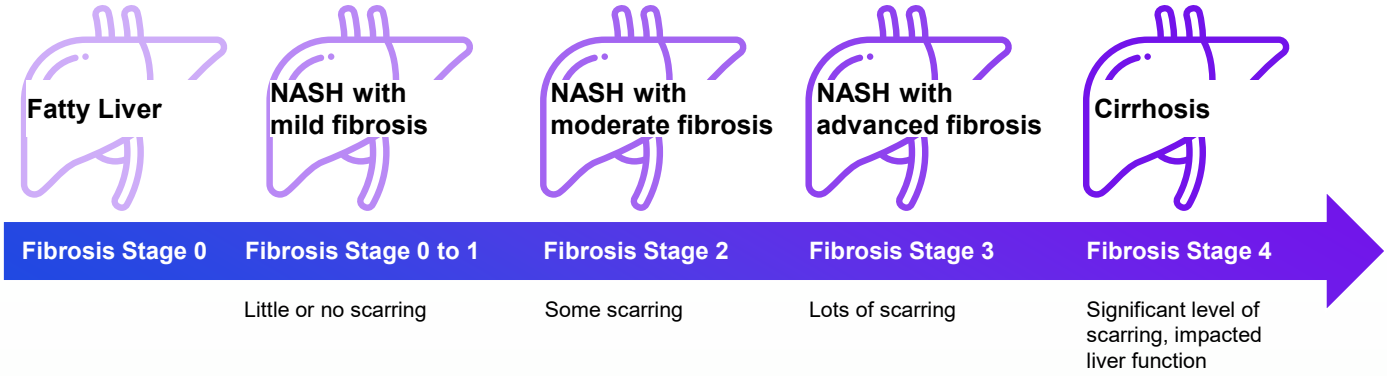
Source: Biomedtracker, KPMG

Company	Candidate	Trial Phase	Expected FDA approval	Expected EMA approval
Madrigal Pharmaceuticals	Resmetirom	3	Apr-24	Feb-25
Novo Nordisk	Semaglutide	3	Jan-26	Sep-27
Inventiva	Lanifibranor	3	Feb-27	Oct-27

Lack of symptoms will continue to lead to under-diagnosis. NASH often progresses slowly from non-alcoholic fatty liver disease (NAFLD) which is characterised by the building up of fat in the liver; once there are also signs of inflammation and fibrosis the condition is then defined as NASH [5]. NASH progresses through four stages of increasing fibrosis (F1-F4) leading eventually to cirrhosis (F4) (see graphic below). This process which can occur over decades (taking an average of seven years to progress one fibrosis stage), however, the patient in most cases will exhibit no or minimal symptoms [5][12]. When symptoms do occur, they are often non-specific. This lack of easily characterizable symptoms translates to suboptimal recognition of NASH by patients and HCPs and therefore acts as a first barrier to referral, diagnosis, and treatment.

Stages of NASH progression

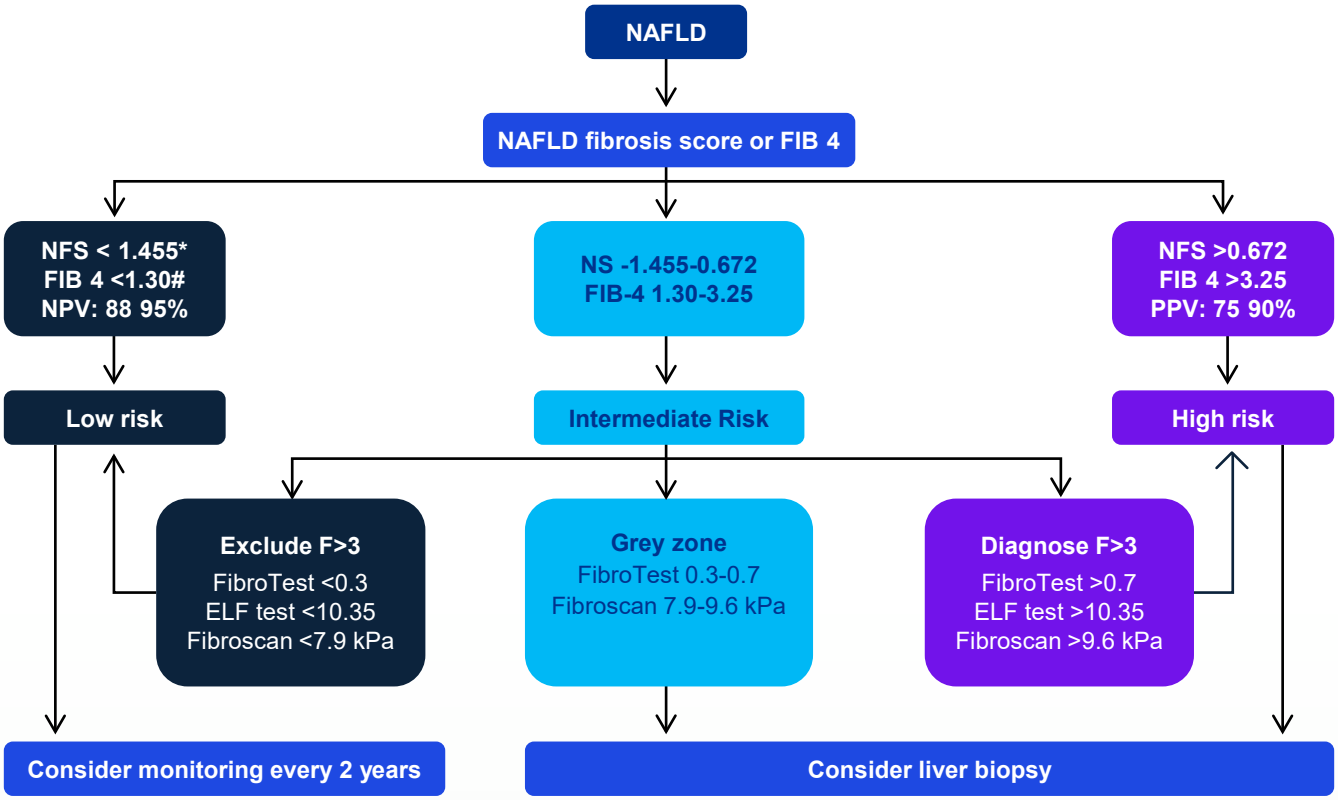
Source: British Liver Trust



Lack of simple diagnostic tools acts as a second barrier to diagnosis. A range of non-invasive tests are used to estimate the risk of liver fibrosis in NAFLD and NASH patients. These can be broadly grouped into 1) serology tests such as FIB-4 and enhanced liver fibrosis (ELF) tests and 2) imaging tests such as elastography and magnetic imaging resonance (MRI). Risk scores yielded by non-invasive tests used in combination can help to estimate fibrosis stage, however, if risk scores indicate a possibility of advanced fibrosis, a biopsy remains the standard of care at this point to confirm NASH [13] [14] (see pathway on following page). Biopsies carry costs for healthcare systems and risks for patients such as pain, bleeding, and the risk of infection [8]. These costs and risks must be weighed against the asymptomatic nature and slow progression of NASH, meaning that biopsies are utilised sparingly in practice. However, regulators currently require liver biopsy as a condition to enrolment in NASH trials as well has biopsy confirmation of NASH severity as part of clinical endpoints [13]. Treatments nearing approval may therefore face a label that requires biopsy confirmation, which would act as a further barrier to uptake [1].

Proposed algorithm for diagnosis of NAFLD and non-invasive assessment of liver fibrosis

Source: British Society of Gastroenterology



Therefore, there remains an unmet need for non-invasive tests to better stratify NAFLD patients and to diagnose NASH. Indeed, NICE's guidelines on NAFLD include a research recommendation to identify which non-invasive tests most accurately identify NASH in people with NAFLD [15]. We note that there has been progress in this area including the development of a diagnostic tool for NASH by researchers at King's College London. This test utilises protein biomarkers PLIN2 and RAB 14 to achieve sensitivity of 88-95%, a specificity of 90%-100%, and an overall accuracy of 92-93% for NASH [14].The company commercialising this technology, Metadeq, is currently seeking FDA approval via a 510(k)-breakthrough device designation [17].
The availability of testing to bypass the need for a biopsy would be an important change for the ease of patients accessing NASH treatments.

Healthcare systems will need to optimise NASH pathways and referral practice to ensure efficient patient access to approved treatments. Given its association with diabetes and obesity, NASH requires a joined-up approach between different HCP types including primary care physicians and specialist physicians [18]. GPs manage care for earlier stage NASH when there is limited scarring or long-term damage to the liver, with checks performed every three years. If the disease progresses to include moderate or advanced fibrosis, care is transferred to hospital specialist hepatologists or gastroenterologists as part of a multidisciplinary care team. Checks on liver function are increased at this point from once every three years to once every 6 months [5].

Due to the challenges outlined above in terms of a lack of easily recognisable symptoms and simple diagnostic options, there remain areas for improvement in NASH care pathways. GPs have reported uncertainty with respect to referral practice, particularly when it comes to borderline liver function results. Both GPs and specialists also highlight some ambiguity over which activities (such as diagnostic testing) should be conducted by primary care versus specialist services [9]. Echoing these challenges, the British Liver Trust published a consensus statement in March 2023 that highlighted that there is "widespread variation" in diagnosis practice across different regions of the UK. The same document calls for six key actions to improve pathways and thereby the standard of care for patients, three of these actions are directly related to the organization of primary and secondary services towards the improvement of treatment pathways [19].

There may be opportunities for manufacturers of NASH treatments to support across these activities. The British Liver Trust's recommendations point towards significant work required by local health authorities and therefore also represent opportunities for manufacturers to support and take a leading role in shaping the care pathway for NASH:

The British Liver Trust calls for:

01 **A prompt and comprehensive review of adult liver services** that would assess number of patients engaged by services, regional differences in care, availability of relevant HCPs, interactions between primary and secondary services, and treatment outcomes.

02 **Development of a national pathology pathway** for the early detection of liver disease that would inform and empower GPs to make greater use of intelligent liver function tests (iLFTs) and other non-invasive tests for at-risk populations to fast-track referrals to secondary care.

03 **Ways to drive greater multidisciplinary team working** between the different HCPs involved in NAFLD and co-morbidity care to coordinate joined-up care for patients and ensure that patients are managed in the most appropriate setting.

Opportunities for manufacturers to support:

01 **Helping to build the picture of regional disparities and highlighting best practices:** primary research involving HCPs across the pathways in different regions could help to build the picture of pain points, best practices, and regions which may be lagging in NASH care.

02 **Supporting the awareness of GPs of non-invasive tests and referral pathways:** manufacturers can help to build GPs' understanding of NASH and the key watchouts in NASH diagnosis and referral practice.

03 **Identification of referral practice across analogues in other therapy areas:** an analogue assessment could help to identify learnings from treatments across other disease areas that have faced similar challenges e.g., silent diseases, unclear referral pathways, and a lack of non-invasive diagnostic options.

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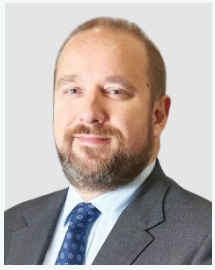

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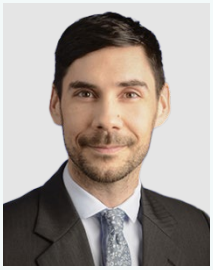

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