White Paper

Insights into MASH Clinical Research

Enrollment amid increasing access to GLP-1 agonists

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are growing public health concerns characterized by liver steatosis (fat build-up), inflammation and fibrosis due to metabolic dysfunction. Around one-fifth of MASLD patients have MASH, a major cause of liver fibrosis and cirrhosis. Clinical development in MASH faces challenges, with an 83% decrease in median recruitment rates for Phase IIb and III clinical trials in the United States between 2012-15 and 2020-23.[1]

Participant enrollment in a MASH trial almost always includes a restriction on glucagon-like peptide-1 (GLP-1) agonist medications, with inclusion criteria specifying that study participants must have stopped taking these medications or have been on a stable dose for a number of months. Recent enrollment declines in the U.S. have been largely driven by increased access to GLP-1 agonists and glucose-dependent insulinotropic polypeptides (GIPs) combined with GLP-1s. The GLP-1s have demonstrated efficacy in the treatment of type 2 diabetes and obesity, which are risk factors in patients targeted for MASH trials. Unit sales of GLP-1s increased in the U.S. by 1,265% from the last quarter of 2015 to the last quarter 2023 due to the launch of new GLP-1s, insurer coverage, and unconventional distribution channels for patients willing to pay out of pocket for these medications.

While the U.S. is often an attractive country for sponsors to conduct clinical trials, increased access to GLP-1s has made it more difficult to enroll patients in MASH trials. Based on this experience, GLP-1s can be expected to have a similar impact on clinical trials in other countries as patients gain access to these medications. To reduce the risk of enrollment delays, it may be necessary to reduce dependence on the U.S., further diversifying operational strategies to include less traditional countries with more favorable environments for MASH enrollment.

To create the right balance of countries and sites, feasibility could be improved by focusing on key country-selection criteria, including GLP-1 saturation, competition from trials testing GLP-1s in type 2 diabetes and obesity (in addition to MASH), and the availability of qualified sites. IQVIA's MIDAS® database provides insights into the use of GLP-1s within targeted countries, while IQVIA's MASH Site Network database houses intelligence on >760 investigators in 61 countries which informs country and site feasibility.

Authored by experts from IQVIA, this white paper presents the relationship between MASH enrollment and GLP-1 sales in the U.S. as a driver of slowed enrollment and suggests an approach to future feasibility in MASH to address this trend as it unfolds around the world.

MASH clinical trials: Historical trends

Metabolic dysfunction-associated steatotic liver disease (MASLD, previously known as nonalcoholic fatty liver disease [NAFLD][2]) is the most common liver disease worldwide, the fastest growing indication for liver transplant in Western countries,[3] and a leading cause of liver-related morbidity and mortality.[4] MASLD has a global prevalence of around 32.4%.[5] Metabolic dysfunction-associated steatohepatitis (MASH, previously known as non-alcoholic steatohepatitis [NASH][6]) has a global prevalence of 3% to 5%.[5] MASH is associated with liver fibrosis (abnormal amounts of scar tissue in the liver) and cirrhosis (liver damage and scarring). About 100 million people (some 25%) in the United States are estimated to have MASLD;[7] of these, around 20% have MASH (or some 5% of adults in the U.S.).[8]

There is currently only one U.S. Food and Drug Administration (FDA) approved therapy for MASH, resmetirom (Rezdiffra™), an oral THR-β agonist designed to target the underlying causes of MASH.[9]

Enrollment trends of MASH trials conducted in the U.S.

There has been a sharp decrease in enrollment rates in Phase IIb and III MASH trials conducted in the U.S., starting from a median rate of 0.41 patients per site per month for MASH trials completed between 2012 and 2015, when clinical development for this therapeutic area began.[1] For MASH trials completing enrollment between 2020 and 2023, the median enrollment rate decreased to 0.07 per site per month, a decline of 83%.

This fall in enrollment rates in the U.S. reflects increased access to GLP-1 agonists (which target areas of the brain that regulate appetite and food intake[10]) and GIPs combined with GLP-1s. Both drug categories are included when GLP-1s are referenced throughout this white paper.

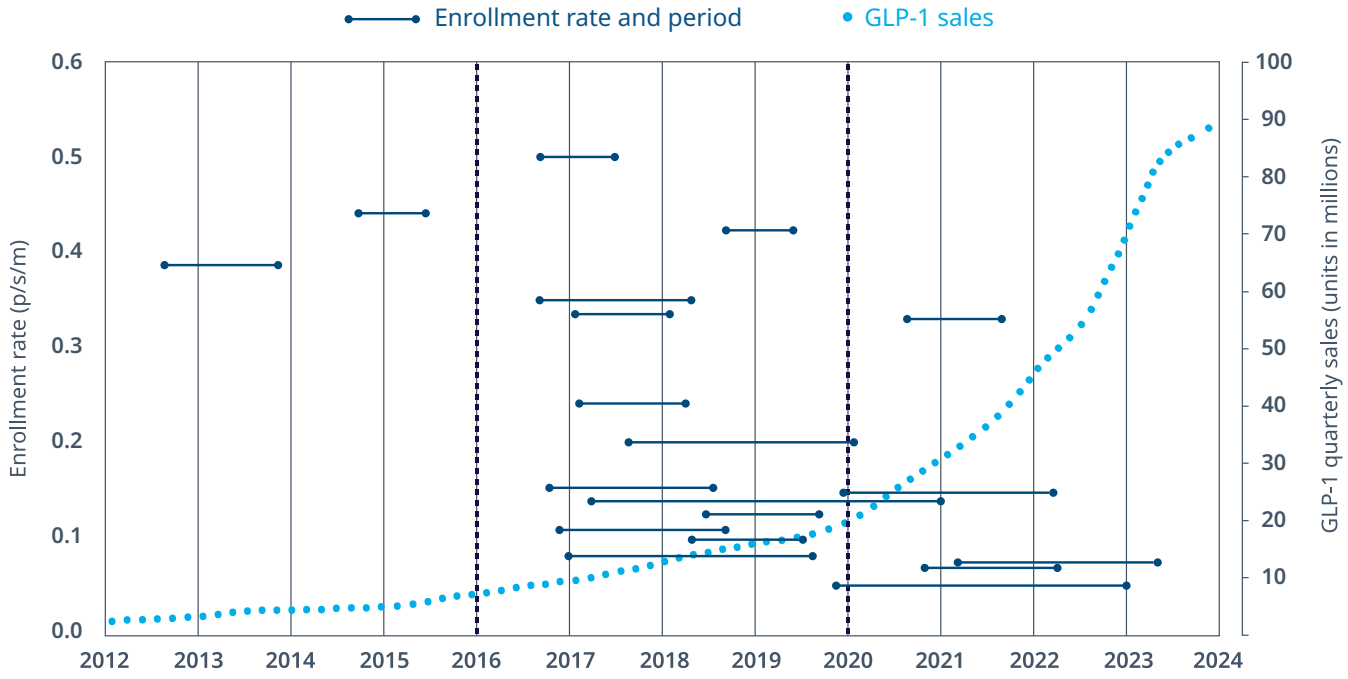
GLP-1s are an effective treatment for both T2DM and obesity. While there are now nine GLP-1s approved in the U.S., the most recent increase in sales was primarily driven by the launches of semaglutide (Ozempic®) in 2018 and tirzepatide (Mounjaro®) in 2022 for T2DM. Semaglutide (Wegovy®) was approved for obesity in 2021 and tirzepatide (Zepbound®) was approved for obesity in 2023. The market success of these treatment options has encouraged more sponsors to enter the obesity market. As a result, patients with type 2 diabetes mellitus (T2DM) and obesity have more treatment options today and often prefer obesity or T2DM clinical trials offering GLP-1s to MASH trials which often involve liver biopsies.

This trend is likely to continue in the U.S., with Medicare spending on GLP-1s 'skyrocketing,' according to the Kaiser Family Foundation; the recent FDA approval for a new use for semaglutide (Wegovy®) to lower the risk of heart attacks and stroke in people with cardiovascular disease who are overweight or obese has expanded access to this drug.[11] The June 2024 U.S. launch of the first generic GLP-1, a formulation of liraglutide (Victoza®) for the treatment of T2DM, will further increase access.[12] Other generics are expected as other novel therapies reach patent expiry. Patients with T2DM and/or obesity may also elect to participate in clinical trials offering GLP-1s.

An analysis of Phase IIb and III MASH enrollment rates in the U.S.

The following analysis examines median enrollment rates relative to GLP-1 sales across three time periods: 2012-2015, 2016-2019, and 2020-2023.[1] *Figure 1* illustrates enrollment rates in the U.S. on the left axis for 19 Phase IIb and III MASH trials (3 U.S.-only and 16 global trials), represented by blue bars. All studies have been completed and meet the criteria for a Phase IIb or III MASH trial (i.e., two liver biopsies, histology-based primary endpoint, and >100 patients). The length of each bar represents the enrollment period for that trial. Yellow data points represent quarterly GLP-1 sales in standard units per the right axis. A standard unit refers to the smallest common dose of a product form as defined by IQVIA. Sales include all GLP-1s (including GIPs) sold in the U.S. for T2DM and obesity.

Figure 1: MASH study enrollment rates and quarterly GLP-1 sales in the U.S.



*Includes GLP-1s and GIPs

Sources[1]: MIDAS Quarterly Sales (2024); the Clinical Trials Gov data bank; and the EU Clinical Trials Register

The data shows that competition amongst MASH trials has significantly increased over time in the U.S.[1] *(Figure 2)*. While only two trials completed enrollment between 2012 and 2015, this count increased five-fold between 2016 and 2019, to a total of 12 trials. While only five trials were completed between 2020 and 2023, more than 20 additional trials were enrolling patients during this time.

Median enrollment rates of completed trials in the U.S. declined by 83% from 2012-2015 to 2020-2023.[1] Between 2012 and 2015, the median enrollment rate was 0.41 patients per site per month *(Figure 2)*. Between 2016 and 2019, the median rate declined by 56% to 0.18 patients per site per month. Between 2020 and 2023, this figure declined by another 61% to 0.07 patients per site per month. Respectively, the median number of patients enrolled per site in the U.S. declined 61% from 2012-2015 to 2020-2023. Between 2012 and 2015, sites enrolled 4.92 patients per site. Between 2016-2019, the median declined 28% to 3.55 patients per site. Between 2020 and 2023, it declined another 46% to 1.93 patients per site.

During the same time frame, the market experienced a significant increase in GLP-1 sales in the U.S. for T2DM and obesity, which are risk factors for MASH. Sales increased by 1,265% from the last quarter of 2015 to the last quarter 2023. During the last quarter of 2015, GLP-1 sales were 6.6 million units. During the last quarter of 2019, sales increased by 185% to 18.9 million units. During the last quarter of 2023, sales increased by another 377% to 90.1 million.

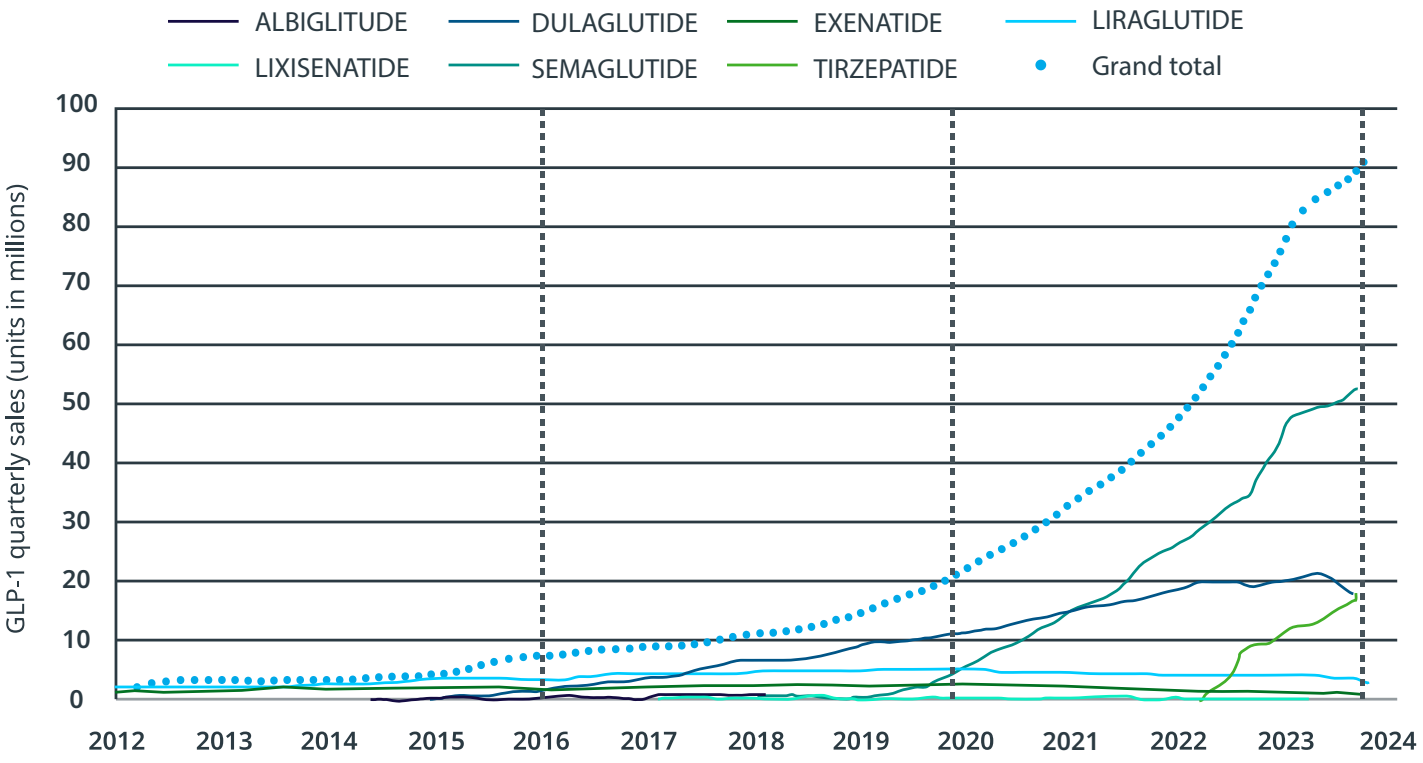
"Competition among MASH trials has increased in the U.S., with median enrollment rates declining by 83% from 2012-2015 to 2020-2023. During that time, the U.S. saw a significant increase in GLP-1 sales for Type 2 diabetes and obesity, which are risk factors for MASH."

Figure 2: Phase IIb and III MASH enrollment rates and GLP-1 sales (millions of units; 2012-23)[1]

PERIOD	NUMBER OF TRIALS	ENROLLMENT RATE (PATIENTS PER SITE PER MONTH)	PATIENTS PER SITE	GLP-1 QUARTERLY SALES (UNITS IN MILLIONS)	
Years	Count	Median	Median	Range	Last quarter
2012 - 2015	2	0.41	4.92	2.2 - 6.6	6.6
2016 - 2019	12	0.18	3.55	7.0 - 18.9	18.9
2020 - 2023	5	0.07	1.93	22.5 - 90.1	90.1

Quarterly sales of GLP-1s by molecule are illustrated in *Figure 3*

Figure 3: Quarterly GLP-1 sales by molecule (in millions of units)



*Includes GLP-1s and GIPs
Source: MIDAS Quarterly Sales (May 2024)

Insurers in the U.S. have provided improved access to these medications for T2DM but have restricted access for obesity. Insurers will typically follow the lead of Medicare, which is now covering the cost of GLP-1s for T2DM but requires patients with obesity to also have established cardiovascular disease to qualify. Patients can still obtain GLP-1s for weight loss through self-pay, though the cost may be prohibitive for many.

The market has responded to the demand for GLP-1s for weight loss at a reduced cost. Physicians are prescribing GLP-1s approved for T2DM off-label for weight loss. Weight loss programs (e.g., Noom® and WeightWatchers®[12]) have expanded their services to prescribe GLP-1s at reduced prices.

Implications for future enrollment of MASH trials

The pool of potential patients for MASH trials in the United States will likely continue to decline due to:

- Reduced interest in study participation if patients with T2DM and/or obesity have access to GLP-1s
- Ineligibility if patients taking GLP-1 medications are not on a stable dose
- Patient preference to participate in clinical trials for obesity and T2DM offering GLP-1s where liver biopsies are not required.

As GLP-1s gain approval in other countries, enrollment is likely to be impacted accordingly. To develop the most effective and realistic strategies to conduct Phase IIb and III trials moving forward, there is a need to holistically evaluate the current and future enrollment potential of other countries. This evaluation should focus on three primary factors – GLP-1 saturation, competition from trials testing GLP-1s in T2DM and obesity (in addition to MASH), and the availability of qualified sites – and should take account of any likely changes during the planned study enrollment period.

GLP-1 saturation

Utilization of GLP-1s should be assessed at the country level via an index for objective comparison of the levels of saturation. IQVIA has developed such an index for GLP-1 saturation utilizing pharmaceutical sales data from IQVIA MIDAS®. This index is calculated by dividing total unit sales of GLP-1s by the total adult population (>18 years of age). Sample data is shown for five countries in *Figure 4.*

Figure 4: IQVIA's GLP-1 index to compare saturation across countries

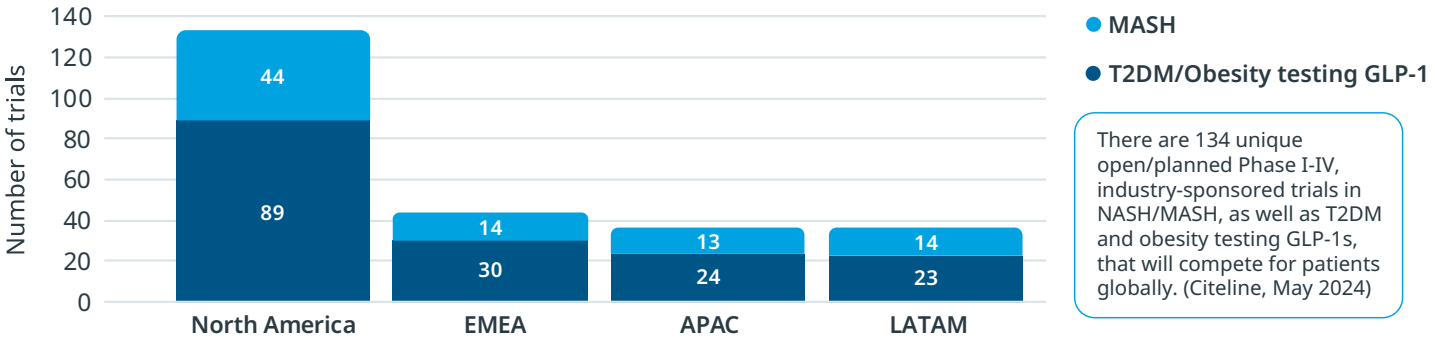
COUNTRY	GLP-1 UNITS SOLD	ADULT POPULATION	GLP-1 INDEX
United States	310,991,681	339,665,118	0.91
Poland	14,212,171	39,142,267	0.36
United Kingdom	22,958,857	68,138,484	0.33
Brazil	22,440,212	218,689,757	0.10
South Korea	2,127,972	51,966,948	0.04

Source: IQVIA MIDAS (2023); United States Census Bureau (2023)

Competing trials

A holistic analysis of the competitive trial landscape should include all phases of MASH trials and trials offering GLP-1s for patients with T2DM and/or obesity. More than 100 Phase I-IV studies are estimated to be planned and ongoing in MASH *(Figure 5)*. In addition to T2DM and obesity studies of GLP-1s, these will compete for patients globally.

Figure 5: The competitive trial landscape for MASH



EMEA includes Europe, Africa and Middle East countries; APAC region includes Asia and Oceania countries; LATAM includes Mexico, Central and South America countries
Sources[1]: (May 2024)

Availability of qualified study sites per IQVIA's global MASH site network

In 2023, IQVIA developed a dynamic clinical trial site database to maintain current intelligence about sites interested in MASH clinical trials, allowing the evolving global landscape to be tracked. This database houses intelligence on >760 investigators in 61 countries, expanding sponsors' ability to enroll patients in countries with the required capabilities and enrollment potential (see *Sidebar*). Over 90% of investigators in the database have clinical trial experience in MASH and/or other metabolic disorders. These investigators form the basis for the following analysis.

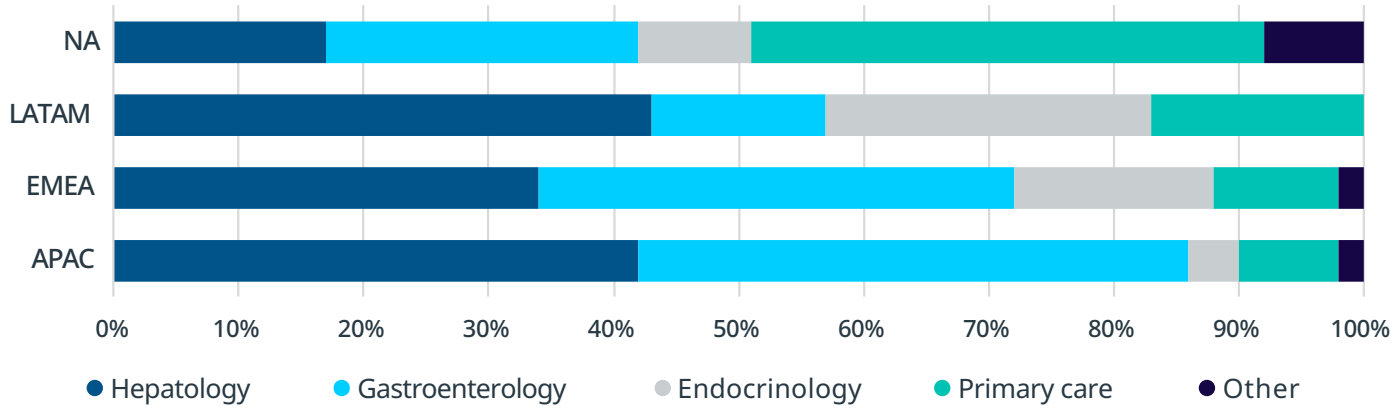
IQVIA'S GLOBAL MASH SITE NETWORK AND CAPABILITY ASSESSMENT

IQVIA's database provides current intelligence on over 760 investigators across 61 countries, including relevant clinical trial experience, access to diagnostic technologies and procedures, characteristics of their local patient population, standard of care, and recruitment practices to inform country and site feasibility for MASH trials. Local insights enable us to consider less traditional countries that may offer more favorable MASH enrollment potential.

Investigator specialties by region

The specialties of investigators who are capable of conducting MASH studies are expanding from hepatology and gastroenterology to include endocrinologists/diabetologists and primary care physicians who provide routine care for patients with metabolic disorders. This evolution takes clinical trials to the point of care and expands enrollment potential within each region as shown in *Figure 6.*

Figure 6: MASH investigator specialty by region



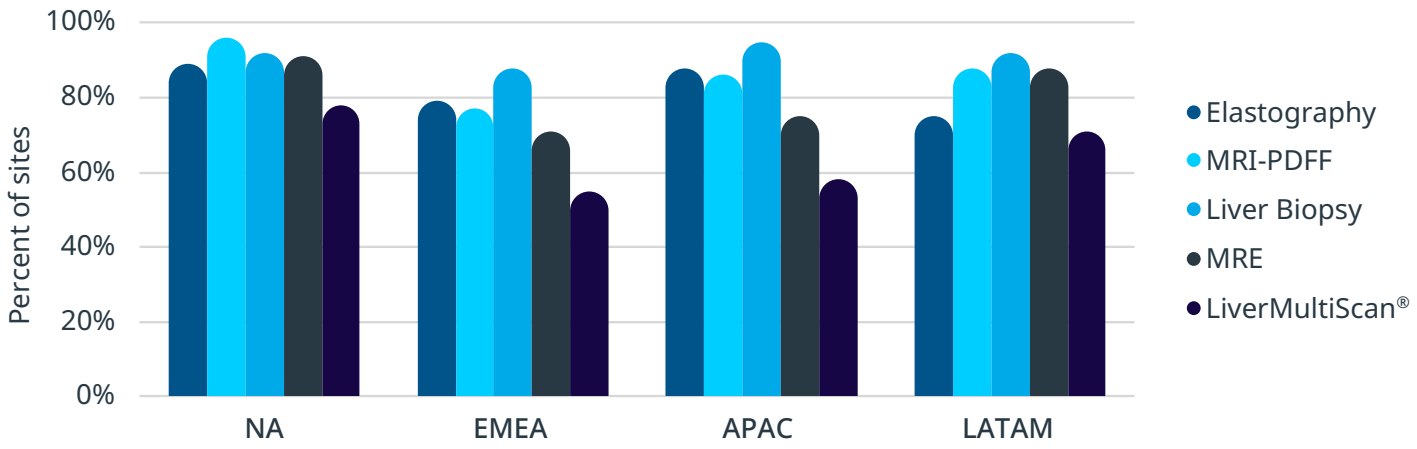
Key site capabilities: Elastography, MRI-PDFF, liver biopsy, MRE and LiverMultiScan®

A key criterion for site qualification for a MASH trial is access to the technology and procedures used for diagnosis and treatment evaluation. These may include:

- Elastography, which is typically needed across Phases I-III of clinical trials due to the need to identify and qualify patients at risk of MASH
- MRI-PDFF, which is commonly used in Phase IIa to measure the primary endpoint
- Liver biopsy, a procedure that is often limited to Phase IIb and III as a primary endpoint
- Magnetic resonance enterography (MRE) and LiverMultiScan®, which are not typically used for primary outcomes, but are increasingly being used as secondary or exploratory endpoints for efficacy in recent and planned MASH studies

Awareness of MASH among investigators has increased since clinical trials began in this indication, along with interest in participating in MASH trials. Access to commonly-used technology and procedures for MASH trials is advancing globally, further expanding sponsor opportunities in less traditional, less competitive countries. *Figure 7* shows the percentage of sites with access to each technology and procedure by region: North America (NA), Europe Middle East & Africa (EMEA), Asia and Oceania (APAC), and South America (LATAM).

Figure 7: Percentage of sites with access to capabilities by region



While protocols vary based on sponsor objectives, the most typical capabilities needed by phase are shown in *Figure 8*.

Figure 8: Capabilities typically needed for MASH trial phases

CAPABILITY	PHASE 1B	PHASE 2A	PHASE 2B/3
Elastography	●	●	●
MRI-PDFF		●	●
Liver biopsy			●

Using IQVIA's site intelligence database, country feasibility was assessed based on site capabilities by phase and region. Using the defined capabilities by phase shown in *Figure 8*, the percentage of sites that meet these criteria was determined *(see Figure 9)*.

Figure 9: Percentage of sites with capabilities by phase and region

REGION	PHASE 1B	PHASE 2A	PHASE 2B/3
NA	89%	87%	83%
EMEA	79%	63%	60%
APAC	88%	79%	77%
LATAM	75%	70%	65%

Additional considerations

While key considerations for country selection focus on GLP-1 saturation, competition from trials testing GLP-1s in T2DM and obesity (in addition to MASH), and the availability of qualified sites, additional factors need to be considered. These include access to medical records, use of transient elastography, and conduct of liver biopsies.

ACCESS TO MEDICAL RECORDS

Due to underdiagnosis, identifying and qualifying patients at high risk of MASH before screening them for a clinical trial is essential to manage screen failure rates. To do this effectively, sites need access to each potential study participant's medical records to review their history for key MASH indicators. Sites that are integrated into or aligned with a clinical practice or health system are best positioned to identify patients that meet eligibility criteria and determine if they are a good fit for a MASH trial.

Having access to electronic medical records (EMRs) or a clinical trial management system (CTMS) to query the database for patients makes this process more efficient than a manual search of paper-based records. The following percentage of investigators in each region report having a searchable EMR or CTMS system: 83% in NA, 46% in EMEA, 54% in APAC, and 55% in LATAM.

TRANSIENT ELASTOGRAPHY

Transient elastography (TE) is not standard of care for assessing liver health in all countries, which poses a challenge to MASH recruitment. Due to underdiagnosis, sites typically need to identify a large volume of patients at high risk of MASH and utilize TE to assess liver health. Where this technology is standard of care, a TE device would be located on site and used in routine clinical practice. Results would be recorded with each patient's consent to search their health data for future clinical trial consideration.

At locations where this technology is not standard of care nor reimbursed, the study sponsor would likely need to provide a device and training to establish a process to qualify patients within each practice setting. While this approach would involve additional cost, it could be a worthwhile investment to accelerate enrollment in countries with strong enrollment potential.

Currently, the following percentage of investigators in each region report having access to transient elastography on a regular basis: 89% in NA, 79% in EMEA, 88% in APAC, and 75% in LATAM. Of these investigators, the following percentage report that their site routinely pre-screens patients with risk factors for NASH using transient elastography: 81% in NA, 85% in EMEA, 84% in APAC, and 71% in LATAM.

LIVER BIOPSY

A vast majority of investigators across all regions (89% in NA, 78% in EMEA, 85% in APAC, and 86% in LATAM) report a willingness to participate in a MASH study requiring two liver biopsies 48 weeks apart. The majority of sites report that the required observation period for patients following this procedure is less than 24 hours. Sites requiring longer observation periods (ranging up to 4 days) would have cost implications relating to multiple overnight stays.

Confirming enrollment potential at the site level

To select high-quality sites with the greatest enrollment potential, a thorough understanding of the current situation regarding patient access to GLP-1s is needed at the local level, as this can vary widely within regions and communities. Access for various diseases will be determined by payors (i.e., T2DM and/or obesity), the qualification requirements, prescriber limitations, duration of use, and amount of patient copay. Patients with obesity who do not qualify for GLP-1 coverage are often motivated to pay out-of-pocket, so it is also important to assess general affordability of these medications and access via alternative weight loss providers.

It will also be important to understand the number of trials each site will be conducting in MASH, as well as trials offering GLP-1s to patients with type 2 diabetes and obesity.

Conclusions

Developing a predictable approach for the successful delivery of Phase IIb and III MASH trials is becoming increasingly complex. In the U.S., enrollment rates have steadily declined primarily due to increased access to GLP-1s. As other countries gain access to these medications, a similarly negative impact on enrollment rates can be anticipated. Conduct of MASH trials will continue in the U.S. but will be based on realistic enrollment expectations and scrutiny of each site's enrollment potential from the local perspective.

To develop the most effective and realistic strategies to conduct Phase IIb and III MASH trials moving forward, a tailored approach to feasibility is needed to evaluate the current enrollment potential of each country. Criteria for country selection should focus on GLP-1 saturation, competition from trials testing GLP-1s in type 2 diabetes and obesity (in addition to MASH), and the availability of qualified sites. While the U.S. and other MASH-experienced countries will continue to be included in MASH studies, consideration should be given to including less traditional, less competitive countries with favorable enrollment potential to ensure continued progress in this important area.

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