EPH161

Estimation of the Size of the Eligible Population in the United States for Resmetirom, a Novel Investigational Therapy for NASH

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BACKGROUND

- Nonalcoholic Steatohepatitis (NASH), also known as Metabolic Dysfunction-Associated Steatohepatitis (MASH), is a subset of Nonalcoholic Fatty Liver Disease (NAFLD), also known as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).
- NASH, characterized by hepatic fat accumulation alongside inflammation, is often associated with an accelerated progression towards cirrhotic NASH and advanced liver diseases, such as decompensation (i.e., liver failure), hepatocellular carcinoma, and the necessity for liver transplant. Additionally, individuals with NASH face elevated mortality risks. [1, 2]
- Resmetirom, as of March 2024, is the first and only therapy available in the United States (US) that is conditionally approved, in conjunction with diet and exercise, for the treatment of adults (aged 18+) with NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) [3] - henceforth: "NASH with significant fibrosis".
- Despite the clinical significance of NASH and its considerable healthcare burden, current estimates of prevalent and incident cases in the US often vary in published literature.

OBJECTIVES

- A dynamic population calculator was developed to estimate the number of US adults who are resmetirom treatment-eligible – i.e., adults with diagnosed NASH with significant liver fibrosis (consistent with stages F2 to F3 fibrosis).

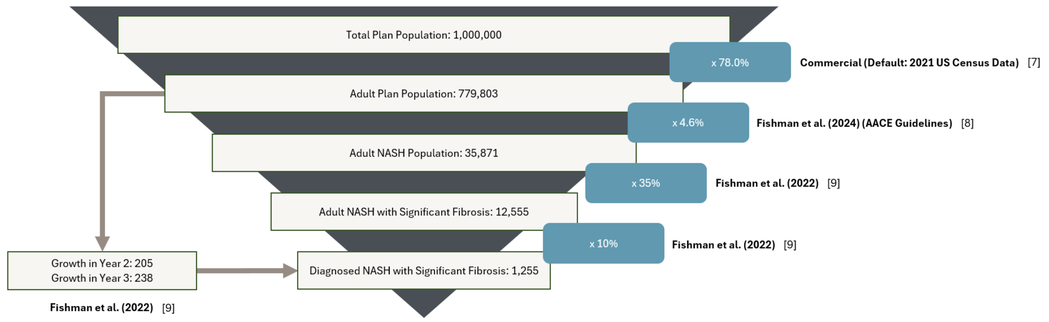
METHODS

- The population calculator is intended to support resmetirom treatment-eligible patient count estimates, which may be used to inform future budget impact analysis (BIA). BIAs are developed with time horizons that align with payer needs, with US-based BIAs typically spanning 3-5 years. [4, 5]
- Over a three-year time horizon, the population calculator estimates resmetirom treatment-eligible prevalent (year 1) and incident (years 2 and 3) patients.
- Calculations are performed as follows:
  - Step 1: Identify the number of adult members in a representative US commercial, Medicare, or Medicaid health plan.
  - Step 2: Estimate the prevalence of NASH in US adults.
    - The likely range for NASH prevalence among US adults was found to be between 1% and 6%. [8,13,14]
  - Step 3: Estimate the fraction of NASH patients who have significant fibrosis.
    - This excludes individuals with NASH stages F0–F1 or cirrhosis (F4+) to align with resmetirom's indication per its USPI and the eligibility criteria of the Phase 3 MAESTRO-NASH trial (NCT03900429). [3,6] In our model, we assumed that F1B is similar to F2.
  - Step 4: Identify those who have NASH with significant liver fibrosis who have received an official diagnosis from a healthcare provider.
    - This yields an estimate for the prevalent resmetirom treatment-eligible population in year 1.
  - Step 5: A year-over-year growth rate is applied to project the expected increase in size of the treatment eligible population for years 2 and 3.
    - This yields estimates for the incident resmetirom treatment-eligible populations in years 2 and 3.
- An additional annual growth rate can be applied to account for the potential increase in treated patients over time resulting from the introduction of an approved therapy - which may increase disease screening/demand. [17]
- For each step of the population calculator, multiple sources were provided from contemporary databases and literature to mitigate the uncertainty associated with estimating adults with diagnosed NASH with significant liver fibrosis prevalent and incident patient counts.

RESULTS

Base-case

Figure 1: Base-case resmetirom treatment-eligible population estimates



- In a hypothetical 1 million-member US representative commercial health plan, the estimated prevalent patient count of adults with diagnosed NASH with significant liver fibrosis in Year 1 was 1,255.
- In years 2 and 3, the estimated incident patient counts of adults with diagnosed NASH with significant liver fibrosis were 205 and 238, respectively.
- Therefore, the estimated base-case total patient counts – i.e., prevalent + incident - for years 1, 2, and 3 were 1,255; 1,460; and 1,699; respectively.

Scenario Analyses

Table 1: Alternative sources for resmetirom treatment-eligible patient count estimates[a]

Percent	Year 1	Year 3	Sources
Step 1: Identify the number of adults in the plan population			
99.4%	1,600	2,165	Medicare (2021 US Census Data) [7]
55.3%	890	1,205	Medicaid (2021 US Census Data) [7]
75.0%	1,208	1,634	Commercial (SHADA) [10]
100.0%	1,610	2,178	Medicare (CMS Snapshot) [11]
Step 2: Estimate the prevalence of NASH in the adult plan population			
3.0%	819	1,262	NHANES (FAST Cutoff ≥ 0.48) [8]
4.8%	1,310	1,753	NHANES (FAST Cutoff ≥ 0.35) [8]
1.3%	355	798	NHANES (FAST Cutoff ≥ 0.67) [8]
5.0%	1,365	1,808	NHANES (MAESTRO: Healthcare Restricted) [8]
6.3%	1,719	2,162	NHANES (MAESTRO: Healthcare Unrestricted) [8]
4.0%	1,085	1,528	Younossi et al. (2016) [12]
4.0%	1,092	1,535	Loomba et al. (2020) [13]
14.2%	3,885	4,328	Younossi et al. (2022) [14]
Step 3: Identify NASH patients with significant fibrosis without cirrhosis			
N/A	N/A	N/A	N/A
Step 4: Identify patients with diagnosed NASH and significant fibrosis			
14.3%	1,795	2,238	NHANES Extended Analysis [8]
3.3%	409	852	Tapper et al. (2023) [15]
Step 5: Specify the year-over-year growth in the treatment-eligible patient population			
Annual percentage growth of treatable population (diagnosed NASH with significant fibrosis)			
4.3%	1,255	1,367	Rochon et al. (2023) (Low) [16]
13.1%	1,255	1,605	Rochon et al. (2023) (High) [16]
2.0%	1,255	1,306	Younossi et al. (2019) [2]
Additional annual growth after introduction of resmetirom			
3.2%	1,255	1,793	Oka et al. (2023) [17]

Abbreviations: CAP, Controlled Attenuation Parameter; CMS, Centers for Medicare & Medicaid Services; FAST, FibroScan-AST; NASH, Nonalcoholic Steatohepatitis; NHANES, National Health and Nutrition Examination Survey; NIT, noninvasive tests; SHADA, State Health Access Data Assistance.
Notes: a) The total population counts for Year 1 and Year 3 are calculated under the assumption that all other parameters are set to their respective base case settings.

- In the alternative scenarios tested, year 1 counts of adults with diagnosed NASH with significant liver fibrosis patients per 1 million members ranged from 355 to 3,885 and year 3 counts ranged from 798 to 4,328.
- Growth of treated patients over time may increase upon introduction of an approved therapy due to increased screening/demand. Utilizing base-case estimates with a 3.175% growth factor per Oka et al. (2023) [17], the projected number of resmetirom treatment-eligible patients by year 3 was estimated to be 1,793.
- An additional scenario evaluated resmetirom's treatment eligibility for the entire US adult population. With an estimated US adult population of 257,279,447 [18], we assumed a 3.5% prevalence of NASH – i.e., the midpoint of likely range of 1-6%. [8,13,14] Employing the same methodology as the base-case for model steps 3 through 5, we projected 315,167 NASH patients with significant fibrosis in year 1. Using Fishman et al. (2022), we calculated an annual growth rate of 21.0%, resulting in 66,144 new patients in year 2 and 80,026 in year 3. [9] Consequently, a cumulative resmetirom treatment-eligible population of 461,337 was estimated over the three years post-FDA approval.

STRENGTHS & LIMITATIONS

- The model integrated multiple recent data sources throughout the identification process of the target population. Specifically, it utilized a nationally representative US sample from the National Health and Nutrition Examination Survey (NHANES) 2017-March 2020 cycle, employing noninvasive tests (NIT) screening techniques for default NASH prevalence and in five additional scenario analyses. [8]
  - Utilizing NIT screening within NHANES enabled the capture of both diagnosed and undiagnosed prevalent NASH patients, potentially yielding a more precise representation of real-world patient counts, given the common underdiagnosis of the disease.
  - Nevertheless, inputs derived from NHANES 2017-March 2020 using NITs for NASH and fibrosis estimation carry inherent uncertainties. Consequently, the application of various NIT criteria in the NHANES analysis produced a range of prevalence estimates, reflecting differences in their predictive performance.
- The analysis further enhanced robustness by incorporating three large national contemporary datasets following the implementation of ICD-10-CM codes for diagnosed NASH classification – i.e., post-October 1st, 2015. [9,16]
- Prevalence estimates for NASH derived from the literature exhibit significant variability due to several factors, including the methodologies used for case identification and the populations under assessment.
  - Prevalence estimates relying on liver biopsy (the reference standard for diagnosis) are difficult to obtain due to the invasive and expensive nature of the procedure and may suffer from selection bias, as typically only patients with other risk factors/evidence of disease are recommended for biopsy screening. [12]
- The model's projections for population growth, based on retrospective estimates for disease incidence, do not encompass changes in disease screening protocol's post-introduction of a first in class approved therapy.
  - However, to address this uncertainty, a scenario is incorporated that offers an evidence-based estimate for the anticipated growth following the introduction of an innovative therapy into a specific disease space. [17]

CONCLUSIONS

- **Given the FDA conditional approval of resmetirom for treating NASH with moderate to advanced, or significant, liver fibrosis (consistent with stages F2-F3) in adults and the uncertainty in NIT-based prevalence estimates, it is important to provide healthcare decision makers with contemporary estimates of the treatment-eligible population for resmetirom.**
- **For a hypothetical 1-million-member commercial health plan, the conceptual framework combining novel analyses of NHANES 2017-March 2020 cycle survey data and a range of published sources estimated that 1,255 patients will be eligible for treatment with resmetirom in year 1 of product availability, increasing to 1,699 in year 3 in the base case; These estimates correspond to 0.13% and 0.17% of the health plan's population being identified as treatment eligible for years 1 and 3, respectively.**

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DISCLOSURES

JF and YK are employees of Madrigal Pharmaceuticals and may own stocks/and or options from Madrigal Pharmaceuticals. EB and TO are employees of Medicus Economics, LLC. Medicus Economics, LLC received consulting fees for research from Madrigal Pharmaceuticals. ZS was an employee of Medicus Economics, LLC at the time of development of this manuscript. Medicus Economics, LLC received consulting fees for research from Madrigal Pharmaceuticals