Real World Semaglutide Dose-Escalation and Persistence among Patients with MASLD

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INTRODUCTION

- Metabolic dysfunction-associated steatohepatitis (MASH), a progressive subtype of metabolic dysfunction-associated steatotic liver disease (MASLD), is estimated to affect over 115 million people globally.[1-4]
- Semaglutide 2.4 mg was recently granted accelerated approval for the treatment of noncirrhotic MASH, with full approval pending completion of the ongoing phase 3 ESSENCE trial.
- At 72-weeks of trial follow-up, 88% of participants followed the 16-week dose-escalation schedule and maintained a 2.4 mg dose.[5]
- While interim results are promising, existing evidence indicates the potential for an efficacy-effectiveness gap due to lower rates of dose-escalation and persistence observed in real-world populations.

OBJECTIVES

- To evaluate real-world compliance with the ESSENCE trial protocol among MASLD patients starting semaglutide 2.4 mg for an approved indication.

METHODS

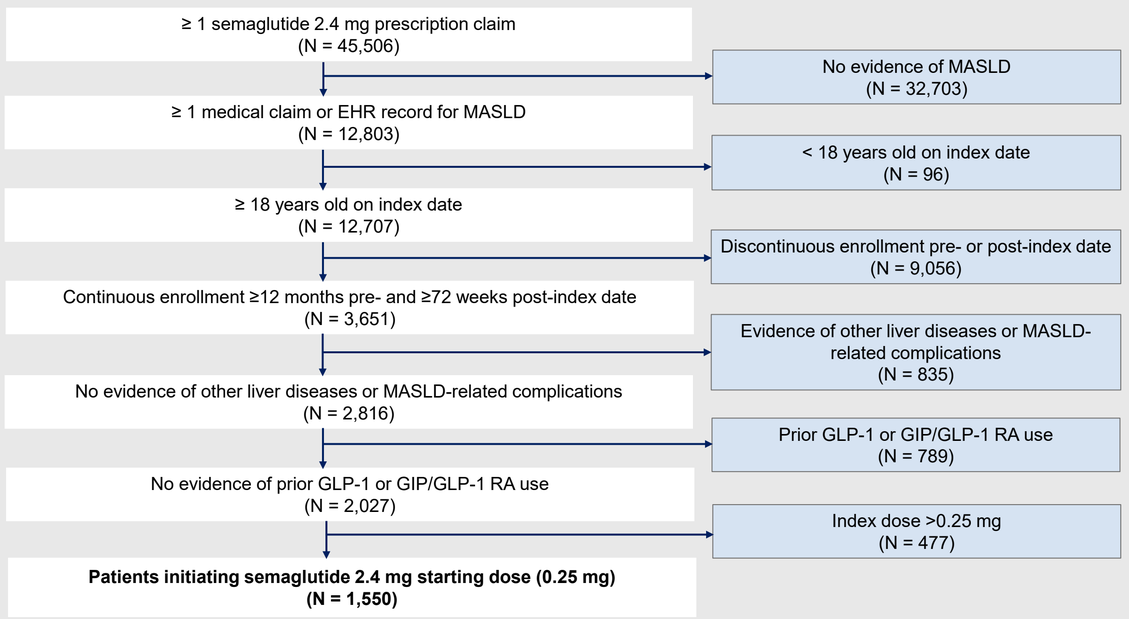
Study Design and Setting

- A descriptive analysis was conducted using Optum Market Clarity data from June 4, 2021, through December 31, 2024.
- Patients with MASLD initiating semaglutide 2.4 mg were included, with the study period consisting of the time from first observed dispensation (index date) through 72 weeks of follow-up.
- The 12-month interval preceding the index date was used for sample selection (Figure 1) and covariate measurement.

Study Measures

- Adherence: Proportion of days covered (PDC) by a semaglutide 2.4 mg fill over the 72-week follow-up period, capped at 100% with overlapping fills carried forward.
- Discontinuation: Presence of a gap in treatment coverage of ≥45 days from the last day of medication availability using fill dates and days of medication supplied to account for excess (carryover) medication from previous fills. Switching between branded versions of semaglutide was allowed.
- Dose escalation and persistence: Patients were grouped into the following categories based on adherence to the ESSENCE trial protocol:
  - Group 1: Failure to complete the 16-week dose-escalation schedule to 2.4 mg (assessed at week 17)
  - Group 2: Dose-escalation schedule completion with subsequent discontinuation
  - Group 3: Dose-escalation schedule completion with persistence (no discontinuation) through the end of the 72-week follow-up period

FIGURE 1. Sample Selection Diagram



RESULTS

- The majority (85.7%; n = 1,328) of the 1,550 patients in the final sample failed to complete a 16-week dose-escalation schedule (Group 1), with 6.9% (n = 107) completing dose escalation but subsequently discontinuing (Group 2) and 7.4% (n = 115) remaining fully compliant with the ESSENCE trial protocol (Group 3).
- Among patients in Group 1, over 60% did not reach a 2.4 mg target dose at 17 weeks due to prior treatment discontinuation (Figure 2). While 33.5% did eventually reach a 2.4 mg dose, fewer than 14% of patients were persistent at any dose by the end of the 72-week follow-up period.
- Mean (standard deviation) PDC for the 72-week follow-up period was 42.2% (32.5). PDC in Groups 1, 2, and 3 was 36.7% (30.4), 54.3% (18.3), and 94.7% (6.2), respectively.
- Patients across all three groups were predominantly Caucasian (>70%), covered by commercial insurance (>70%), and had an average out-of-pocket payment for their first semaglutide 2.4 mg fill between $115 and $130 (Table 1).
- The occurrence of moderate/severe GI adverse events during follow-up varied by group membership, with patients in Group 1 almost three times more likely than those in Group 3 to experience a GI adverse event (11.3% vs 4.3%).

FIGURE 2. ESSENCE Trial Compliance

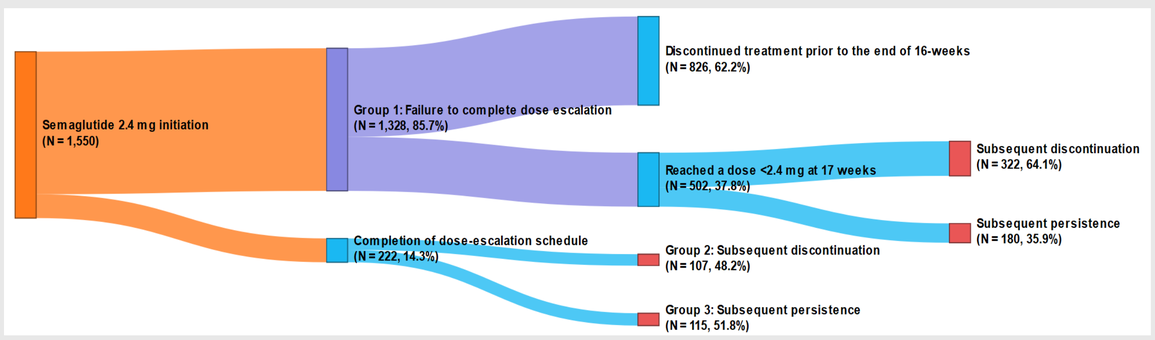


TABLE 1. Patient Characteristics

	Overall (N = 1,550	Group 1 (N = 1,328)	Group 2 (N = 107)	Group 3 (N = 115)
Age				
Mean (SD)	47.3 (10.7)	47.3 (10.8)	47.5 (9.4)	47.7 (10.0)
Median (IQR)	48.0 (40.0, 55.0)	49.0 (40.0, 56.0)	48.0 (41.0, 55.0)	48.0 (41.0, 55.0)
Gender				
Female	1,056 (68.1)	923 (69.5)	66 (61.7)	67 (58.3)
Male	493 (31.8)	404 (30.4)	41 (38.3)	48 (41.7)
Unknown	1 (0.1)	1 (0.1)	0 (0.0)	0. (0.0)
Race				
African American	110 (7.1)	87 (6.6)	13 (12.1)	10 (8.7)
Asian	23 (1.5)	20 (1.5)	2 (1.9)	1 (0.9)
Caucasian	1,119 (72.2)	957 (72.1)	76 (71.0)	86 (74.8)
Other/Unknown	298 (19.2)	264 (19.9)	16 (15.0)	18 (15.7)
Ethnicity				
Hispanic	143 (9.2)	134 (10.1)	3 (2.8)	6 (5.2)
Not Hispanic	1,074 (69.3)	903 (68.0)	83 (77.6)	88 (76.5)
Unknown	333 (21.5)	291 (21.9)	21 (19.6)	21 (18.3)
Region				
Midwest	429 (27.7)	348 (26.2)	43 (40.2)	38 (33.0)
Northeast	615 (39.7)	541 (40.7)	30 (28.0)	44 (38.3)
South	299 (19.3)	254 (19.1)	25 (23.4)	20 (17.4)
West	132 (8.5)	120 (9.0)	5 (4.7)	7 (6.1)
Other/Unknown	75 (4.8)	65 (4.9)	4 (3.7)	6 (5.2)
Insurance Type				
Commercial	1,292 (83.4)	1,097 (82.6)	94 (87.9)	101 (87.8)
Medicaid	192 (12.4)	172 (13.0)	13 (12.1)	7 (6.1)
Medicare	65 (4.2)	59 (4.4)	0 (0.0)	6 (5.2)
Unknown	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.9)
Out-of-Pocket Payment				
Mean (SD)	124.0 (389.2)	124.0 (332.1)	118.3 (315.2)	128.7 (814.5)
Median (IQR)	25.0 (25.0, 60.0)	25.0 (24.0, 60.0)	25.0 (20.0, 45.5)	25.0 (25.0, 55.0)
GI Adverse Events*				
Yes	162 (10.5)	150 (11.3)	7 (6.5)	5 (4.3)
No	1,388 (89.5)	1,178 (88.7)	100 (93.5)	110 (95.7)
Obesity				
Yes	1,413 (91.2)	1,208 (91.0)	100 (93.5)	105 (91.3)
No	137 (8.8)	120 (9.0)	7 (6.5)	10 (8.7)
T2D				
Yes	184 (11.9)	158 (11.9)	14 (13.1)	12 (10.4)
No	1,366 (88.1)	1,170 (88.1)	93 (86.9)	103 (89.6)

**Presence of one or more of the following moderate/severe GI adverse events during the follow-up period: bowel obstruction, cholecystitis, cholelithiasis, gastroenteritis, gastroparesis, or pancreatitis.*

CONCLUSION

- **In this real-world study, fewer than 8% of patients with MASLD initiating semaglutide 2.4 mg followed the ESSENCE dose-escalation schedule and remained persistent over the 72-week follow-up period.**
- **Findings suggest a lack of alignment between semaglutide 2.4 mg use in the ESSENCE trial and that observed for currently approved indications in the real world.**

LIMITATIONS

- Key limitations include a reliance on pharmacy claims to measure medication use, limited generalizability to the Optum population, inability to capture compounded semaglutide or fills outside insurance coverage, lack of data on semaglutide 2.4 mg use specifically for MASH, and an inability to differentiate between patient-driven non-adherence versus that due to semaglutide 2.4 mg supply shortages.

ABBREVIATIONS

GI: Gastrointestinal; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1; IQR: Interquartile range; MASH: Metabolic dysfunction-associated steatohepatitis; MASLD: Metabolic dysfunction-associated steatotic liver disease; PDC: Proportion of days covered; SD: Standard deviation; T2D: Type 2 diabetes

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- AC, AM, DN, SC and MD are all employees of Medicus Economics, LLC
- NA, BT and FL are all employees of Madrigal Pharmaceuticals

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REFERENCES

1. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell. 2021 May 13;184(10):2537–64; **2.** British Liver Trust. International NASH Day. Available at: https://britishlivertrust.org.uk/nashday/. Last accessed: August 2025; **3.** Tesfay M, Goldkamp WJ, Neuschwander-Tetri BA. NASH: The Emerging Most Common Form of Chronic Liver Disease. Mo Med. 2018;115(3):225–9; **4.** Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatol Baltim Md. 2018 Jan;67(1):123–33; **5.** Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025;392(21):2089-2099