ACC 2025: Clarivate's take on the five key presentations

Market Event Summary

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SOUL: oral semaglutide slashes cardiovascular risks in T2D patients

Background and study design

- Novo Nordisk's Rybelsus (oral semaglutide), a GLP-1 receptor agonist (RA), is an FDA-approved therapy to improve glycemic control in adults with type 2 diabetes.
- SOUL is a placebo-controlled, Phase 3 study that evaluated the effects of Rybelsus versus placebo on CV outcomes in participants aged 50 or older with T2D, atherosclerotic cardiovascular disease (ASCVD), and/or chronic kidney disease (CKD).
- The study randomized 9,650 patients to receive either placebo or once-daily Rybelsus (maximal dose 14 mg) in addition to SOC.

Top-line results

- On March 29, 2025, Novo Nordisk presented data at ACC 2025 demonstrating Rybelsus's ability to reduce the risk of MACE by 14% compared with placebo after nearly four years of treatment.

Key endpoints (percentage of participants with event)	Rybelsus (n=4,825)	Placebo (n=4,825)
MACE-3 events (composite of CV death, non-fatal MI, or non-fatal stroke)	12%	13.8%
Major kidney disease events	8.4%	9.0%
Death from cardiovascular causes	6.2%	6.6%
MACE-5 events (composite of CV death, non-fatal MI, or non-fatal stroke, coronary revascularization, HF-related hospitalization)	13.9%	16.1%

Clarivate's takeaways

Label expansion: The SOUL clinical trial is the first to demonstrate CV benefits of an oral GLP-1 RA agent. Based on the trial outcomes, we expect Rybelsus to receive a label expansion to reduce CV risks in patients with high-risk T2D. With its proven CV benefits, Rybelsus may influence prescribing trends for T2D patients with CV risks, positioning it ahead of other oral T2D agents such as DPP-4 inhibitors and metformin.

Market driver: All GLP-1 RA agents that have demonstrated CV risk reduction are injectable formulations, requiring daily or weekly self-injections. This has created a barrier for patients who are resistant to injections and prefer an oral agent. Rybelsus offers these patients the clinical benefits of semaglutide in the form of a tablet.

Study limitations: The SOUL clinical trial confirms Rybelsus's CV-related benefits but had limitations, including low enrollment of women and Black patients, which may have led to biased outcomes. T2D is more prevalent among Black individuals than white individuals, and CV-related risk is higher among women than men. Additional limitations include the absence of an active comparator and lack of renal-related outcomes. These limitations may impact physician confidence in prescribing Rybelsus.

Overall uptake: Despite positive CV-related outcomes, we do not expect significant uptake for Rybelsus. Market growth will be restricted by several factors, including modest CV risk reduction, less convenient daily dosing, and lower compliance rates compared with injectable GLP-1 RA agents. Additionally, the high price and challenging dosing conditions relative to other available oral agents for T2D will further limit market growth.

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STRIDE: semaglutide's impact on patients with PAD and T2D

Background and study design

- Novo Nordisk's Ozempic (SC semaglutide), a GLP-1 RA, is an FDA-approved therapy to improve glycemic control in type 2 diabetes patients. Additionally, it is approved to reduce the risk of MACE in adults with T2D and kidney failure in adults with T2D and CKD.
- STRIDE is a placebo-controlled, Phase 3 study that evaluated the effects of Ozempic versus placebo on walking capacity and QOL in participants with early-stage, symptomatic peripheral artery disease (PAD) and T2D.
- The study randomized 792 patients to receive either placebo or once-weekly SC semaglutide (maximal dose 1.0 mg) in addition to SOC.

Top-line results

- On March 29, 2025, Novo Nordisk presented data at ACC 2025 demonstrating Ozempic's ability to increase maximum walking distance by 13% compared with placebo after one year of treatment.

Key endpoints (median at 52 weeks, ratio to baseline)	Ozempic (n=396)	Placebo (n=396)
Maximum walking distance	1.21	1.08
VascuQOL-6 total score	2.0	1.0
Pain-free walking distance	1.21	1.10

Clarivate's takeaways

Label expansion: Based on the positive outcomes from the STRIDE study, we expect Ozempic to gain a label expansion to encompass the treatment of symptomatic PAD patients with T2D. Ozempic will be the first GLP-1 RA agent to receive authorization for this patient population, giving it a first-mover advantage.

High unmet need: PAD is the most prevalent CV comorbidity among T2D patients, leading to a high risk of severe complications like acute limb ischemia. However, treatment options are limited to antiplatelet and lipid-lowering therapies, underscoring the substantial unmet need. Ozempic is the first medication in over two decades to demonstrate meaningful improvements in functional capacity and QOL, potentially addressing this critical unmet need for patients with PAD and T2D influencing future treatment guidelines for PAD.

Market adoption: Given Ozempic's robust clinical data, strong physician familiarity, and anticipated first-in-class entry for this patient population, it is poised to achieve substantial market uptake.

Growth constraints: While the STRIDE trial confirms Ozempic's benefits for PAD and T2D patients, the trial had limitations, including the absence of an active comparator and the exclusion of patients without T2D. Further head-to-head studies with other agents, such as cilostazol, that have shown meaningful improvements against these endpoints, are necessary to boost physician confidence. Additionally, studies including PAD without T2D are required to demonstrate its efficacy among the larger PAD population.

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SCORE: Wegovy lowered CV risks in the real-world setting

Background and study design

- Novo Nordisk's Wegovy (SC semaglutide 2.4 mg), a GLP-1 RA, is an FDA-approved therapy for the management of obesity and overweight.
- SCORE is a real-world, observational study that evaluated the effects of Wegovy on CV outcomes in participants aged 45 or older with overweight / obesity and ASCVD without T2D.
- According to the trial's inclusion criteria, the study included 27,963 patients who were either Wegovy users or non-users as per pharmacy or medical claims databases.

Top-line results

- On March 29, 2025, Novo Nordisk presented data at ACC 2025 demonstrating that Wegovy use was associated with a 45% lower risk of revised MACE-5 events compared with Wegovy non-users.

Key endpoints **Median follow-up (months):** **Users: 7.1 and non-users: 6.4**	**Wegovy users (n=9,321)**	**Wegovy non-users (n=18,642)**
Revised MACE-5 events (all-cause mortality, non-fatal MI, non-fatal stroke, coronary revascularization, HF-related hospitalization)	0.94%	1.54%
Revised MACE-3 events (composite of all-cause mortality, non-fatal MI, or non-fatal stroke)	0.45%	0.94%
Death from cardiovascular causes	0.06%	0.21%

Clarivate's takeaways

Strategic positioning: Wegovy is the first antiobesity agent to demonstrate positive CV-related outcomes in a real-world study in obese patients with high risk of CV events. These benefits are poised to strengthen physicians', regulators', and payers' confidence in Wegovy.

Impact on payer coverage: The demonstrated CV benefits of Wegovy could influence insurance providers. These providers typically cover GLP-1 RAs when obese patients also have comorbid conditions, such as ASCVD and T2D. Broader insurance coverage and favorable reimbursement policies may enhance patient access to Wegovy.

Study limitations: While the SCORE trial confirms Wegovy's CV benefits in obese patients, the study had limitations, including a shorter follow-up duration that restricts the assessment of long-term outcomes and the use of retrospective claims data, which may exclude patients with intermittent coverage or those from underserved populations, potentially limiting the generalizability of the findings.

Overall uptake: Despite positive outcomes from the SCORE trial, we do not anticipate a significant impact on Wegovy's uptake, primarily owing to its key competitor Zepbound's (tirzepatide) superior weight-loss efficacy and lower price compared with Wegovy, as well as the forthcoming launch of CagriSema. While Wegovy has demonstrated CV efficacy in the SELECT trial for secondary prevention, Zepbound's CVOT (SURMOUNT-MMO) includes primary prevention patients. If successful, this will further limit Wegovy's uptake.

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SUMMIT: the impact of CKD on tirzepatide's efficacy in HFpEF

Background and study design

- Eli Lilly's Zepbound (tirzepatide), a dual GIP / GLP-1 RA, is an FDA-approved therapy for the management of obesity and overweight. Additionally, it is indicated for the treatment of moderate to severe obstructive sleep apnea (OSA) in adults with obesity.
- SUMMIT is a placebo-controlled, Phase 3 trial that evaluated the influence of CKD on the clinical responses to Zepbound versus placebo in patients with obesity-related HFpEF and investigated the complexity of tirzepatide-related changes in renal function.
- The study randomized 731 patients to receive placebo or tirzepatide 2.5 mg/week subcutaneously, in addition to their usual therapy.

Top-line results

- On March 31, 2025, Eli Lilly presented data at ACC 2025 indicating that the severity of heart failure was greater in those with CKD, including a twofold increase in the risk of worsening HF events.

Outcomes at week 52	Patients with CKD (Zepbound vs. placebo)	Patients without CKD (Zepbound vs. placebo)
HF-related outcomes: CV death or worsening HF events	27 (13%) vs.43 (19%)	9 (6%) vs. 13 (10%)
Renal outcomes: Change in eGFR (mL/min/1.73 m^2)	Creatinine-based: +1.9 ± 1.0 vs. –1.8 ± 1.0 Cystatin C-based: +2.1 ± 0.9 vs. –1.1 ± 1.0	Creatinine-based: –2.1 ± 0.8 vs. –2.43 ± 1.0 Cystatin C-based: +2.5 ± 1.3 vs. –0.8 ± 1.5

Clarivate's takeaways

HF-related outcomes: Additional analysis of data from the SUMMIT trial indicated that patients with obesity and HFpEF with CKD experienced more severe HF-specific outcomes compared with those without CKD. This is likely because patients with CKD are more prone to having NYHA class III or IV HF, elevated NT-proBNP levels, and poorer performance in the 6-minute walk test. Furthermore, the sample sizes in each cohort were relatively small, emphasizing the need for further research to validate Zepbound's efficacy in a larger population.

Renal outcomes: Zepbound demonstrated improvements in renal function during long-term treatment, although the results varied over time and among different patient groups. These findings highlight the limitations of current methods for estimating kidney function and support the consideration of directly measuring GFR in clinical trials.

Incretins and eGFR measurements: GLP-1 RAs reduce the number of adipocytes, thereby decreasing the production of cystatin C independently of kidney function. Consequently, when eGFR is measured using cystatin C, GLP-1 RAs show improvement regardless of the presence of CKD. However, when eGFR is measured using creatinine, GLP-1 RAs demonstrate improvement only in individuals with CKD, as creatinine levels are not influenced by adipocytes.

Unmet need: The interplay of obesity, HFpEF, and CKD, which share common root causes and are associated with poor outcomes, creates a significant unmet need. This presents a substantial opportunity for companies aiming to address these unmet needs.

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ZENITH: sotatercept's success in high-risk PAH patients

Background and study design

- Merck & Co.'s Winrevair (sotatercept-csrk) is an FDA-approved therapy for the treatment of adults with pulmonary arterial hypertension (PAH) (WHO group-1) who are receiving background PAH therapy. It is the first PAH therapy with a non-vasodilatory MOA; it instead targets the BMP pathway.
- ZENITH is a placebo-controlled, Phase 3 study that evaluated the effects of Winrevair on time to first event of all-cause death, lung transplantation, or PAH worsening-related hospitalization of ≥24 hours in participants with NYHA FC III or IV PAH at high risk of mortality.
- The study randomized 172 patients to receive either placebo or sotatercept (0.3 mg to 0.7 mg per kg) every three weeks.

Top-line results

- On March 31, 2025, Merck & Co. presented data at ACC 2025 demonstrating that Winrevair reduced the risk of a composite outcome of all-cause death, lung transplantation, and PAH-related hospitalization by 76% compared with placebo.

Key endpoints	Winrevair (n=86)	Placebo (n=86)
All-cause death	8%	15%
Lung transplantation	1%	7%
PAH-related hospitalizations	9%	50%
Deaths due to AEs	6%	14%

Clarivate's takeaways

Market uptake: The success of the ZENITH trial is expected to boost confidence among physicians to drive broader adoption of Winrevair in the treatment of advanced PAH (NYHA FC III or IV) in patients at high risk of mortality, potentially increasing its market share.

Unmet need: Despite a vast array of treatment options, mortality rates in advanced PAH remain high, highlighting a significant unmet need. Winrevair's robust efficacy in reducing mortality risk in this population will substantially address this critical need.

Early discontinuation: The ZENITH trial was halted early following the reporting of strong efficacy data during an interim analysis in November 2024. As a result, the trial lacks statistical data for secondary endpoints and long-term safety data, which may influence physicians' perceptions and potentially hinder the growth of Winrevair in high-risk patients. However, Merck & Co. is conducting a follow-up study, SOTERIA, to evaluate the long-term outcomes of Winrevair in patients who have completed their respective PAH Winrevair clinical studies, including ZENITH.

Treatment burden: In the United States, Winrevair was launched at a WAC price of $14,420 per vial, administered once every three weeks, resulting in an annual cost of approximately $250,000. The requirement to administer Winrevair on top of standard PAH therapy will lead to increased economic and dosing burdens, possibly limiting the uptake of Winrevair in early lines of treatment.

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Clarivate coverage of relevant indications

Type 2 diabetes (T2D) and GLP-1-related products

- Disease Landscape & Forecast | G7 countries, providing comprehensive market intelligence insights
- Current Treatment: Physician Insights (US) | GLP-1 receptor agonists
- Current Treatment: Physician Insights | T2D (US)
- Treatment Algorithms | Claims Data Analysis - US
- Unmet Need | US and EU
- Epidemiology | Global markets including G7 countries
- Access & Reimbursement | US
- China In-Depth | T2D

Pulmonary arterial hypertension (PAH)

- Disease Landscape & Forecast | G7 countries, providing comprehensive market intelligence insights
- Treatment Algorithms | Claims Data Analysis - US
- Unmet Need | US and EU
- Epidemiology | Global markets including G7 countries

Obesity / overweight

- Disease Landscape & Forecast | G7 countries, providing comprehensive market intelligence insights
- Treatment Algorithms | Claims Data Analysis - US
- Unmet Need | US and EU
- Epidemiology | G7 countries.
- Access and Reimbursement | US
- China In-Depth | Obesity / Overweight

Heart failure (HF)

- Disease Landscape & Forecast | G7 countries, providing comprehensive market intelligence insights
- Treatment Algorithms (CHF, HFpEF, and HFrEF) | Claims Data Analysis - US
- Unmet Need | Heart Failure with Preserved Ejection Fraction | US and EU
- China In-Depth | Heart Failure

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Tej has authored several reports focusing on cardiovascular, metabolic, and renal indications. Previously, he was an analyst at IQVIA and at Smart Analyst Inc., where he worked closely with top pharmaceutical companies on commercial and technical ad-hoc requests. During his tenure there, he delivered competitive landscape and market insight projects on various oncology indications. He holds a master's degree in pharmacy with a specialization in pharmaceutical chemistry from the Delhi Institute of Pharmaceutical Sciences and Research in New Delhi, India.

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