



# GLP-1 Safety Signal Analysis

Thyroid Cancer & Gastroparesis - Signal vs Noise

Position Sizing Meeting - February 2026

- Presenter: Investment Research Team

# EXECUTIVE SUMMARY

## Key Findings from GLP-1 Safety Analysis



### THYROID: Volume Growth Only

- Proportion stable at 0.5%
- Tracks with usage ( $p=0.087$  NS)



### GASTROPARESIS: TRUE Acceleration

- Proportion significantly increasing
- $p=0.001$
- Emerging signal



### INVESTMENT IMPLICATION

Gastroparesis is the real story, not thyroid.

# THE GLP-1 SAFETY DEBATE

Market concerns and safety analysis of leading GLP-1 receptor agonists.



## THYROID BLACK BOX WARNING

- Media focus on long-standing warning (since 2010).
- Is this the most critical risk?



## GASTROPARESIS & LAWSUITS

- Recent cases and lawsuits emerging.
- FDA review initiated.



## POSITION SIZING: NOISE OR SIGNAL?

- Market concern vs. actual signal.
- Sell-side focus vs. real risk.

# RESEARCH QUESTIONS

Market concerns and safety analysis of leading GLP-1 receptor agonists.



## ACTUAL ACCELERATION?

- Are adverse event reports **ACTUALLY** accelerating? (or just tracking with usage growth)



## WITHIN-CLASS COMPARISON

- Is one GLP-1 drug riskier than others? (within-class comparison)



## HIDDEN SIGNALS

- What's **NOT** in the sell-side notes? (hidden signals)

# METHODOLOGY



## DATA SOURCE

- FDA FAERS via OpenFDA API



## TARGET DRUGS

- Semaglutide Ozempic/Wegovy
- Tirzepatide Mounjaro
- Liraglutide Victoza
- Dulaglutide Trulicity
- Exenatide Byetta



## ANALYSIS

- Disproportionality (ROR/PRR) with within-class comparator



## TIME-SERIES

- Mann-Kendall trend test
- Linear regression on proportions

# DATA SUMMARY



**TOTAL REPORTS:**  
**20,307**  
unique reports

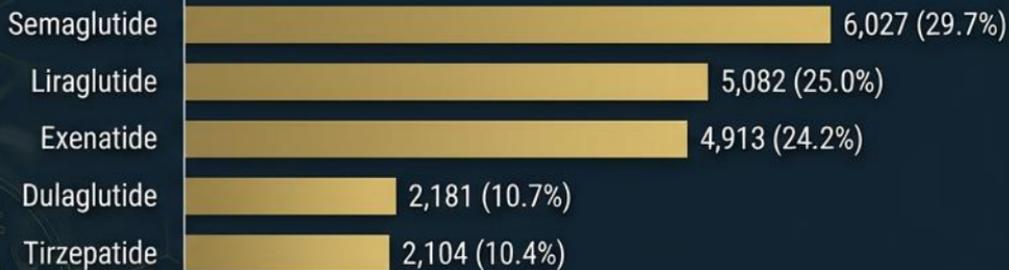


**DATE RANGE:**  
**2004-2025**  
(21 years)



**FLATTENED  
OBSERVATIONS:**  
**87,154**  
AE records

## BREAKDOWN BY DRUG



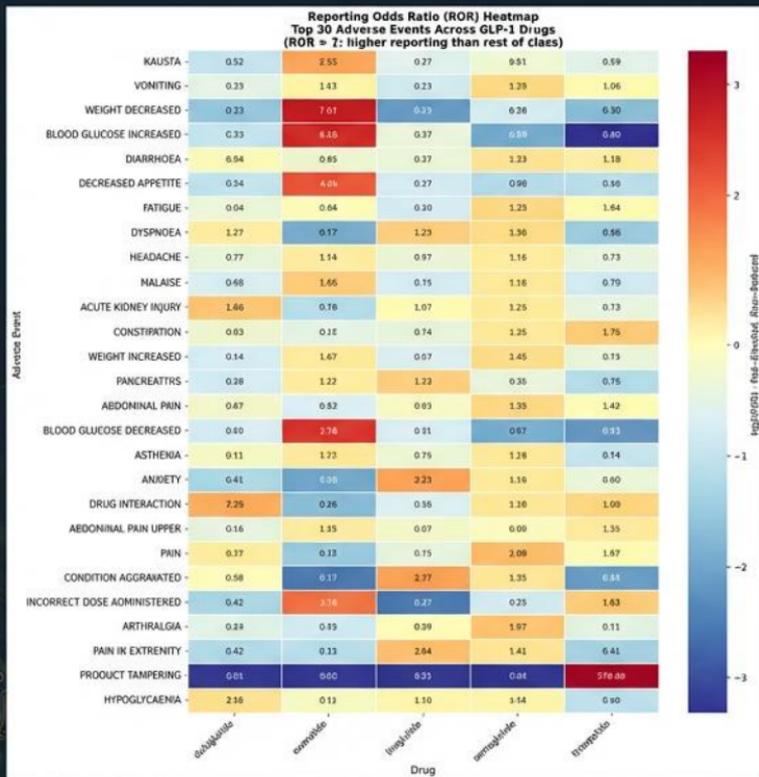
**SERIOUSNESS**

**60%**

serious events  
(12,233 reports)

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# ADVERSE EVENT PROFILES



## KEY INSIGHTS

- Interpretation: Red = elevated ROR (higher reporting vs other GLP-1s), Blue = reduced ROR
- Top 30 most frequent adverse events analyzed across the class
- GI effects common across the entire GLP-1 class
- Drug-specific fingerprints identified, showing unique AE profiles

# Disproportionality Analysis: Target Signals

## THYROID CANCER GROUP (66 total reports)

**Liraglutide**  
ROR=1.52 (95% CI: 0.91-2.52, NS)   **NS**

**Exenatide**  
ROR=1.29 (95% CI: 0.76-2.18, NS)   **NS**

**Tirzepatide**  
ROR=0.93 (95% CI: 0.41-2.09, NS)   **NS**

**Semaglutide**  
ROR=0.71 (95% CI: 0.40-1.26, NS)   **NS**

**Dulaglutide**  
ROR=0.60 (95% CI: 0.23-1.56, NS)   **NS**

## GASTROPARESIS (3 total reports)

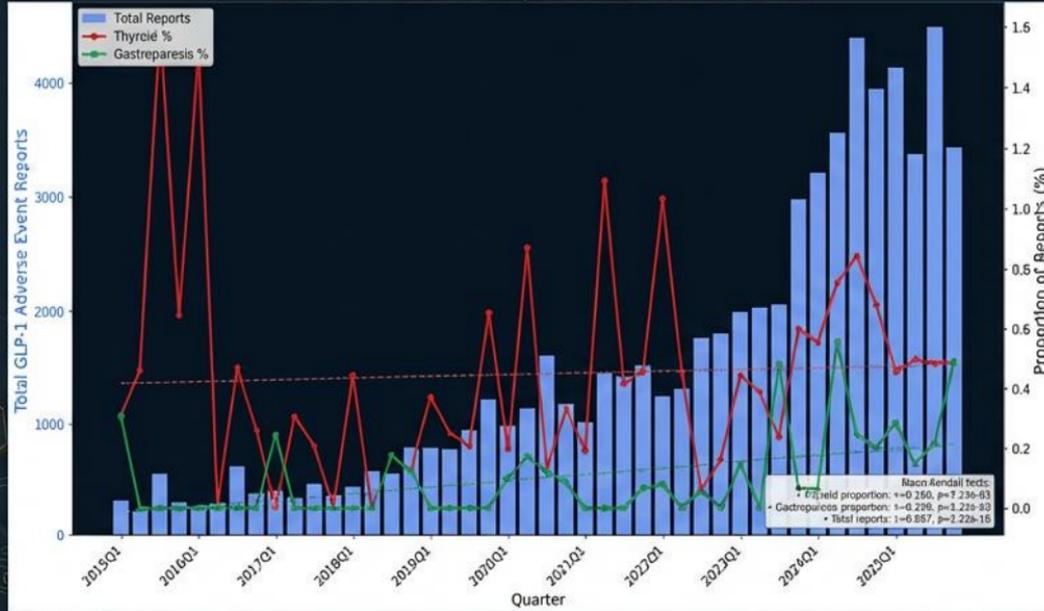
Insufficient data.

**KEY FINDING:** NO drug shows significantly elevated risk vs other GLP-1s. All 95% CIs include 1.

 **NO SIGNAL**

# Time-Series Analysis: Are Reports Accelerating?

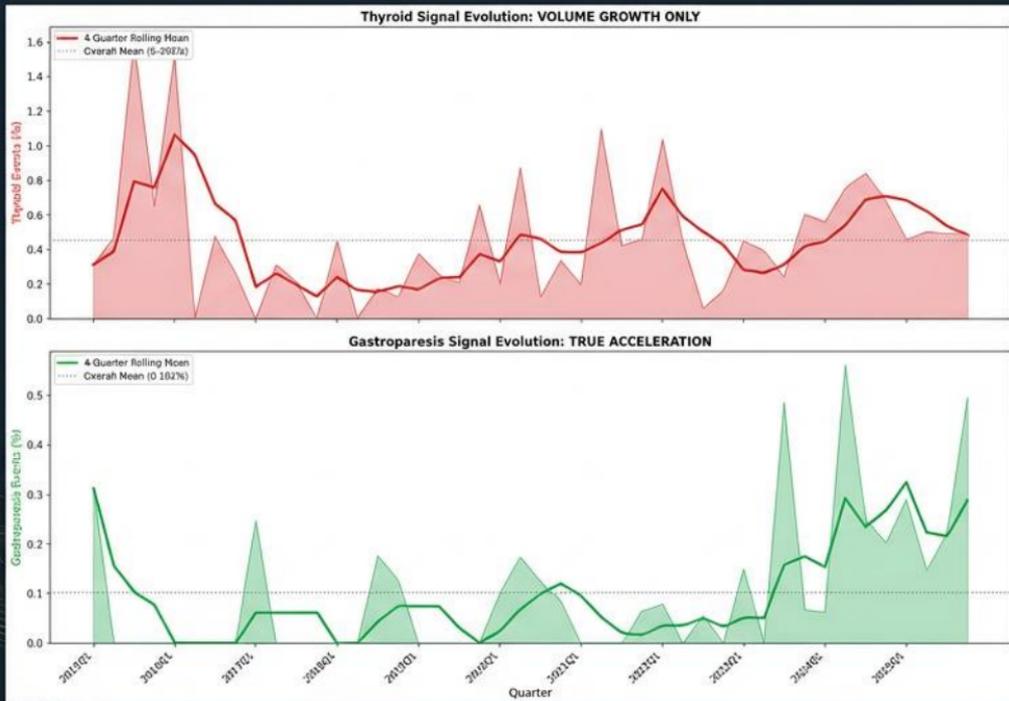
GLP-1 Adverse Event Reporting Trends (2015-2025)  
Thyroid: VOLUME GROWTH ONLY | Gastroparesis: TRUE ACCELERATION



**KEY INSIGHT:** Total reporting is growing massively, but need to look at PROPORTIONS to see true signal.

- Blue Bars: Total GLP-1 reports per quarter (SIGNIFICANT INCREASE,  $\tau=0.87$ ,  $p<0.001$ )
- Red Line: Thyroid proportion over time (STABLE at  $\sim 0.5\%$ )
- Green Line: Gastroparesis proportion over time (INCREASING,  $p=0.001$ )

# Signal Evolution Over Time



## KEY INTERPRETATION:

- **TOP PANEL:** Thyroid signal trajectory is relatively FLAT. 4-quarter rolling mean hovers around overall mean (STABLE) – suggests NOISE.
- **BOTTOM PANEL:** Gastroparesis signal trajectory shows clear UPWARD TREND. Rolling mean consistently ABOVE overall mean especially post-2022 (ACCELERATING) – confirms SIGNAL.

# Key Finding #1: THYROID - Volume Growth Only



## NOISE

Visual Verdict

Mann-Kendall  $\tau=0.18$ ,  $p=0.087$  (NOT SIGNIFICANT)

Linear slope= $0.000014/\text{quarter}$  (essentially flat)

Proportion stable at  $\sim 0.5\%$  of total reports

### INTERPRETATION:

- Thyroid reports ARE increasing in raw numbers, but only because overall GLP-1 usage is exploding. The RATE is not changing.
- This is EXPECTED based on the black box warning since 2010. NOT a new or emerging signal - it's proportional to usage growth.

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## Key Finding #2: GASTROPARESIS - TRUE Acceleration



**EMERGING  
SAFETY  
SIGNAL**

Mann-Kendall  $\tau=0.34$ ,  $p=0.001$  (SIGNIFICANT)

Linear slope= $0.000054/\text{quarter}$  ( $R^2=0.23$ , clear trend)

Proportion **INCREASING** over time

### INTERPRETATION:

- The proportion of gastroparesis events is **SIGNIFICANTLY** increasing beyond just usage growth.
- This is an **EMERGING SAFETY** that warrants close monitoring. Recent lawsuits and FDA interest are tracking real signal. **THIS** is what's **NOT** in the sell-side notes.

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# What's Not in the Sell-Side Notes

## **ON THE LABEL / KNOWN**

- Thyroid C-cell tumors black box warning (since 2010)
- GI side effects (nausea, vomiting, diarrhea)
- Pancreatitis risk

## **EMERGING / WATCH LIST**

- Gastroparesis acceleration ( $p=0.001$ )
- Product tampering signal for Tirzepatide (ROR=574)
- Counterfeit concerns for Semaglutide (ROR=37)

**KEY INSIGHT:** Sell-side focuses on thyroid because it's on the label. Gastroparesis is the emerging story with real trend acceleration. Product quality issues are drug-specific.

# Investment Implications

## Strategic Implications for Position Sizing



### **THYROID RISK -** Priced In

- Black box warning since 2010
- Stable reporting proportion
- No surprise factor for market



### **GASTROPARESIS -** Watch Closely

- Accelerating signal ( $p=0.001$ )
- FDA could require additional warnings
- Litigation trajectory uncertain



### **DRUG-SPECIFIC** **CONSIDERATIONS**

- Tirzepatide has product tampering signal (supply chain?)
- Semaglutide has counterfeit concerns (brand integrity?)
- Demographic differences complicate direct comparison

**KEY INSIGHT:** The risk everyone's focused on (thyroid) is noise. The risk accelerating (gastroparesis) is under-discussed.

# Important Caveats



- FAERS is VOLUNTARY reporting - cannot establish causality, only detect signals
- Within-class comparison only - all GLP-1s may share class-wide risks not detectable here
- Weber effect - newer drugs (tirzepatide, semaglutide) may have stimulated reporting
- Media attention bias - recent news coverage may inflate gastroparesis reports
- No denominator - cannot calculate true incidence rates (only reporting rates)

**KEY INSIGHT:** This analysis is hypothesis-generating, not confirmatory. Use with appropriate epistemic humility.

# Conclusions

1



**THYROID:**  
It's **NOISE**

- Reports increasing with usage, proportion **STABLE** ( $p=0.087$ )
- Priced in since 2010 black box warning

1

2



**GASTROPARESIS:**  
It's **SIGNAL**

- Proportion **SIGNIFICANTLY ACCELERATING** ( $p=0.001$ )
- Emerging safety concern, under-discussed vs thyroid

2

3



**POSITION**  
**SIZING**

- Factor gastroparesis trajectory into risk assessment
- Don't over-weight thyroid concerns

3

**KEY INSIGHT:** Visual summary with checkmark for 'noise' and warning for 'signal'.

# Questions? / Discussion

1



**DATA  
SOURCE**



- FDA Adverse Event Reporting System (FAERS) via OpenFDA API
- 20,307 unique reports analyzed (2004-2025)

2



**ANALYSIS  
METHODOLOGY**



- Disproportionality (ROR/PRR)
- Mann-Kendall trend test
- Within-class comparator methodology

3



**CONTACT  
& MEETING**



- Investment Research Team
- Position Sizing Meeting February 2026