PRE-RELEASE RESOURCE FOR SNACK FOUR OF FOUR
RELEASING 9/18/26

Reaching the Shoreline

Emerging Amylin-Based Therapies and Trial Signals

THE CLOSER: WHAT'S IN DEVELOPMENT, WHAT THE EARLY DATA SHOW & HOW TO READ IT

CME OUTFITTERS

Why do we need yet another gut hormone? In this final CME Snack, **W. Timothy Garvey, MD**, joins series chair **Robert F. Kushner, MD**, to bring the series ashore — from biology to the pipeline itself. The aim isn't more weight loss for its own sake: it's to **moderate weight loss that patients can tolerate and stay on**. Here's what's in development, the early signals, and the lens to read them through. All agents are investigational.

THE PIPELINE — FIVE AGENTS, THREE DEVELOPMENT PATHS

monoagonist · fixed-dose combination · unimolecular co-agonist

AGENT (DEVELOPER)	CLASS	STAGE	SIGNAL TO DATE
Cagrilintide (Novo)	Long-acting amylin / DACRA	Ph 3 program	**~11.5%** as monotherapy at 68 wk • REDEFINE 1
Petrelintide (Zealand/Roche)	Long-acting amylin analog	Ph 3 starting 2H 2026	**~10.7%** at 42 wk; tolerability ≈ placebo • ZUPREME-1 Ph 2
Eloralintide (Lilly)	Selective amylin receptor agonist	Ph 3 recruiting	up to **~20.1%** at 48 wk • Ph 2
CagriSema (Novo)	Amylin + GLP-1, fixed-dose	Ph 3 / NDA filed	**20.4%** treatment-policy • **22.7%** adherence, 68 wk • REDEFINE 1
Zenagamtide [amycretin] (Novo)	Unimolecular GLP-1 / amylin	Ph 3 underway	**~24.3%** at 36 wk • Ph 1b/2a

Not head-to-head — separate trials differing in phase, duration, dose ladder, and population; read as directional, not comparative. Classes are as each developer describes its own molecule

TOLERABILITY — THE REAL DIFFERENTIATOR

AGENT	NAUSEA	VOMITING	D/C FOR AE
Petrelintide selective • monotherapy	**19.6%** vs 6.2	**3.0%** vs 6.2%	**4.8%** vs 4.9%
Eloralintide selective • monotherapy	**32.7%** vs 13.5%	**8.2%** vs 0%	**10%** vs 8%
Cagrilintide amylin analog • monotherapy	**23.8%** vs 12.6%	**7.0%** vs 4.1%	**2.6%** vs 3.5%
CagriSema amylin + GLP-1 • combination	**55.0%** vs 12.6%	**26.1%** vs 4.1%	**5.9%** vs 3.5%
Zenagamtide GLP-1 + amylin • unimolecular	GI mostly mild–moderate		

The one within-trial comparison. All four REDEFINE 1 arms, 68 wk — nausea: **55.0%** CagriSema · **43.7%** semaglutide · **23.8%** cagrilintide alone · **12.6%** placebo (all GI events 79.6 / 73.8 / 54.0 / 39.9%). Amylin alone runs **about half the nausea of semaglutide**, and discontinued **below placebo**. **Eloralintide is the exception** — pooled nausea 32.7% but 64% in the no-titration arm, fatigue 26.9% vs 11.5%, AE discontinuation 21% in the fixed-dose 6 mg arm, which used no titration.

BEYOND %TBWL — FOUR SIGNALS TO READ

1. **Trajectory & durability.** Not just the endpoint — the shape of the curve. Where does it plateau, and does it hold at 68 weeks?
2. **Tolerability & persistence.** Many stop after year one — multifactorial, with side effects a driver in up to ~20% in some studies. Weight, and the benefit, come back.
3. **Complementary mechanism.** Amylin and GLP-1 hit overlapping brain regions but different cells, so weight loss *appears* additive, though less than the sum of the single agents. Does efficacy add without proportionally adding side-effect burden?
4. **Who responds, and what else moves.** Response is heterogeneous, not average — watch subgroup and sex signals, plus muscle, bone, resting energy expenditure, and cardiometabolic markers.

SELECTIVE VS DACRA — WHY IT MIGHT MATTER

No one yet knows which is better. Roughly **2–3% of bone mass** goes with 20% weight loss and salmon calcitonin still treats osteoporosis, so a DACRA *could* be bone-protective. Pulling the other way, preclinical data hint **selective amylins may be more effective for weight loss**.

PRECLINICAL · HUMAN DATA NEEDED

> *"What we're looking for right now is a drug that gives us moderate levels of weight loss, approaching 15% on average ... that's well tolerated ... that can be taken long-term ... I think the early data indicate that long-acting amylins may fill that bill."*
>
> — **W. Timothy Garvey, MD, MACE**
> CHARLES E. BUTTERWORTH, JR. PROFESSOR & UNIVERSITY PROFESSOR
> UNIVERSITY OF ALABAMA AT BIRMINGHAM

CARDIOMETABOLIC DIRECTION · NO CVOT YET

- ↓ Pulse **3.31 bpm** (semaglutide ↑1.17)
- ↓ Blood pressure
- ↓ CRP
- Lipids & glycemia improve
- ↓ Fasting insulin (↑ sensitivity)

Heart rate from REDEFINE 1; CVOTs have not reported. **Directional; not proof of benefit.**

CARDIOMETABOLIC DIRECTION · NO CVOT YET

BMI ≥40 ± MOBILITY	Especially with mobility limits — go for magnitude with **dual or triple agonists**; some are surgical candidates.
COMPLICATION-DRIVE	CV secondary prevention, MASH, OSA, T2D — use the **GLP-1-based agent with outcome data** for it.
EVERYONE ELSE	Most patients have none of those complications. A well-tolerated **long-acting amylin first-line** is reasonable; add a GLP-1 if goals aren't met.

HYPOTHESIS · NOT A GUIDELINE RECOMMENDATION

PROGRAM COMING YOUR WAY...

FORMAT	~30 min video CME "Snack" — a moderated expert conversation
FACULTY	W. Timothy Garvey, MD, with chair Robert F. Kushner, MD
AUDIENCE	Obesity-medicine, endocrinology, primary care & cardiometabolic clinicians (MD, NP, PA, PharmD)
OBJECTIVES	Assess emerging amylin-based therapeutic strategies in obesity management • Differentiate key trial signals that inform interpretation of investigational data

THE SERIES AHEAD — FOUR SNACKS, ONE ARC

SNACK ONE
The multi-pathway rationale
Lee M. Kaplan, MD, PhD

SNACK TWO
The biology of amylin
Matthew R. Hayes, PhD

SNACK THREE
Phenotypes & who benefits
Andres Acosta, MD, PhD

SNACK FOUR (NOW)
Emerging therapies & the data
W. Timothy Garvey, MD

Chaired throughout by **Robert F. Kushner, MD** *— Northwestern University Feinberg School of Medicine. Emerging amylin agents are investigational.*

In support of improving patient care, CME Outfitters, LLC, is jointly accredited by the ACCME, ACPE, and ANCC to provide continuing education for the healthcare team. Supported by an independent educational grant from Novo Nordisk, Inc. Content is independent, evidence-based, and fair-balanced; emerging amylin agents are investigational. **Key references:** Garvey WT, et al. *N Engl J Med*. 2025;393(7):635-647. · Billings LK, et al. *Lancet*. 2025;406(10520):2631-2643. · Dahl K, et al. *Lancet*. 2025;406(10499):149-162. · ClinicalTrials.gov. Identifier: NCT06662539. **Acronyms:** AE = adverse event; BMI = body mass index; CRP = c-reactive protein; CV = cardiovascular; CVOTs = cardiovascular outcomes trials; DACRA = dual amylin and calcitonin receptor agonist; D/C = discontinued; GI = gastrointestinal; GLP-1 = glucagon-like peoptide-1; MASH = metabolic dysfunction-associated steatohepatitis; NP = nurse practitioner; OSA = obstructive sleep apnea; PA = physician associate; Ph = phase; T2D = type 2 diabetes.; TBWL = total body weight loss.