CLOSER LOOK

MEMORANDUM

Roche announces positive topline phase 2 results of CT-388 dual GLP-1/GIP RA for obesity – January 27, 2026

Highest dose of CT-388 (24 mg) conferred body weight reduction of up to 22.5% and resolved obesity in more than half of the participants at 48 weeks

Roche just announced positive topline results from the phase 2 trial (n=469) of CT-388, its once-weekly dual GLP-1/GIP agonist for obesity. CT-388 demonstrated up to 22.5% weight loss at 48 weeks with no plateau. Nearly all participants on the 24 mg dose lost at least 5% of their weight, and almost half lost 20% or more. The therapy also showed meaningful metabolic benefits: 73% of participants with prediabetes returned to normal glucose levels, far outperforming the placebo (7.5%). The drug's safety profile was consistent with that of the incretin class, with most adverse events being mild-to-moderate GI events.

Roche plans to launch phase 3 trials for CT-388 in 1Q26. An additional phase 2 trial (n=360) for CT-388 is underway in people with obesity and T2D, with expected completion in August 2026. A phase 2 trial of fixed-dose combination of Zealand-partnered long-acting amylin agonist petrelintide and CT-388 is also expected to launch in 2026.

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Topline results demonstrate 73% of patients with prediabetes returning to normoglycemia

CT-388 demonstrated durable weight loss across all doses, with the highest dose (24 mg) achieving 22.5% placebo-adjusted weight loss at 48 weeks and no evidence of plateau.[1] In addition, 96% of participants on the 24 mg dose lost at least 5% of their body weight and 48% lost ≥20% of their body weight. On the highest dose, 54% of participants on the 24 mg dose demonstrated resolution of obesity, defined as BMI <30 kg/m^2. Metabolic benefits were also notable, with nearly three-quarters (73%) of participants with prediabetes returning to normoglycemia, compared to only 7.5% on placebo.

Safety was consistent with other therapies among the incretin class, with mostly mild-to-moderate gastrointestinal events and a discontinuation rate of 5.9% vs. 1.3% in placebo due to adverse events. While no new or unexpected safety signals were observed, which was very good news, we would love to get a better sense of how "mild" is characterized and what mild *really means* compared to "moderate".

Roche's cardiometabolic pipeline continues to grow

One of the best moments of JP Morgan this year in our view happened when Roche Pharmaceuticals CEO Ms. Teresa Graham said that Roche is committed to being a *top three* player in obesity. That a company of this strength and scale would commit to helping so many people globally with the biggest public health problem of our time was simply stirring to hear. Roche *especially* aims to address gaps in the obesity therapeutic landscape, namely tolerability (see questions above), suboptimal responses in about a fifth (~ 20%) of patients, lean muscle loss, a "ceiling effect" on weight loss (23% is a big percentage!), weight maintenance challenges (the biggest gap in our view), and comorbidities (we need more specificity here). Candidates in its obesity pipeline include the following:

- **CT-868,** a once-daily dual GLP-1/GIP RA, for people with T1D and BMI 25 kg/m^2 will enter phase 3 in 2026, following phase 2 results expected this year.
- **CT-996,** a once-daily oral GLP-1 candidate continues in phase 2 development and is expected to complete in July 2026, following results from the phase 1 trial, where CT-996 demonstrated ~7% weight loss at four weeks.
- **Petrelintide,** a Zealand-partnered long-acting amylin analog, is in two phase 2 trials, including: (i) the 42-week phase 2b ZUPREME-1 trial (n=494) for people with overweight or obesity, expected to complete in March 2026; and (ii) the 28-week phase 2 ZUPREME-2 trial (n=216) in people with overweight or obesity and T2D, expected to complete in June 2026.
- **Emugrobart (GYM329),** anti-latent myostatin antibody, co-developed with Roche-owned Japanese drug developer Chugai, is designed to preserve muscle mass and prevent post-treatment weight regain, addressing a key limitation of GLP-1 RA therapies. The GYMINDA trial (n=234) evaluating GYM329 in combination with tirzepatide is expected to be completed in September 2027. Roche plans to seek approval as early as 2028.

Interview with Dr. Chakravarthy on Roche's R&D focus on CVRM

In May 2025, our team had a chance to interview with Roche's Senior VP and Global Head of cardiovascular-renal-metabolic (CVRM) Product Development, Dr. Manu Chakravarthy. He said that the $2.7 billion acquisition of Carmot Therapeutics in December 2023 catalyzed Roche's momentum in the CVRM field, with the inclusion of CT-388, CT-868, and CT-996 in the pipeline. Moreover, the $5.3 billion partnership with Zealand in March 2025 allows Roche to advance long-acting amylin agonist petrelintide, a complementary hormone to GLP-1, that has the potential to bring additive – or even synergistic – benefits. Dr. Chakravarthy believes that these candidates are equipped to address the heterogeneity of obesity and patients' different needs, whether it be greater weight loss, improved tolerability profile, lean mass preservation, cardiorenal risk reduction, or treatment for Alzheimer's and Parkinson's via combination therapy with Roche's anti-amyloid candidate. See select sections of the interview about CVRM in the appendix below and see the entire interview here.

1. Top Takeaways
2. Interview with Roche's SVP and Global Head of CVRM Product Development, Dr. Manu Chakravarthy
    - On his professional background and Roche's recent integration with Carmot
    - On the upcoming integration of Roche's Innovation Center with Harvard's research ecosystem
    - On the pipeline for Roche and Genentech's Cardiovascular, Renal, and Metabolism (CVRM) hub
    - On Roche's partnership with Zealand to co-develop obesity therapies
    - On the "war on hyperglycemia"
    - On Roche's focus on digitalization and AI
    - On Roche's future

Close Concerns' Questions

1. Given the normalization of glucose in 73% of participants with prediabetes, does Roche see a regulatory path for a future T2D prediabetes indication?
2. How has CT-388 impacted cardiometabolic markers, such as LDL-cholesterol, triglycerides, and blood pressure?
3. Given GYM329's muscle-preservation mechanism, which of Roche's incretin or amylin candidates does the company envision pairing it with in future combination strategies?
4. How is Roche approaching patient segmentation across its broader obesity and cardiometabolic pipeline, particularly in determining which populations are best suited for CT-388, CT-868, CT-996, petrelintide, or future combination approaches?

--by Kayla Mathieu, Kat Moon, Monica Oxenreiter, and Kelly Close

Appendix. Select interview with Roche's SVP and Global Head of CVRM Product Development Dr. Manu Chakravarthy

Monica Oxenreiter: Hello, Dr. Chakravarthy, it's incredible to have some time with you today. Congratulations on the very exciting Roche and Genentech Innovation Center that will be launching in Boston soon! As a Boston resident, I was particularly thrilled to hear this news.

Dr. Manu Chakravarthy: I'm always happy for the chance to talk about this exciting announcement, and it is great to see all of you again.

On his professional background and Roche's recent integration with Carmot

Esther Min: Once again, Dr. Chakravarthy, all of our thanks for your time! As Monica mentioned, we're very excited to hear more about the new Innovation Center that you will be leading in Boston. As the head of the site, how do you plan to bring your previous leadership positions at Merck, Lilly, and Carmot to the forefront, as you plan Roche's re-entry into metabolic diseases?

Dr. Chakravarthy: To start, I want to reflect on Carmot's acquisition by Roche, which really catalyzed Roche's momentum in the therapeutic area and it also re-energized the entire field. The fact that we have great data has been the driving force in kickstarting Roche's re-entry into metabolic disease. Roche clearly has a long history of diabetes care and diagnostic expertise, as well as in the therapeutics space, the latter more than a decade ago. But, what ambition do we have here at Roche today? What do we really want to do in cardiometabolic disease?

We obviously have two very strong, entrenched players, and having worked in one of them, I can tell you that it is formidable competition. But we are taking a very patient-centered approach, and when you look at it from a patient perspective, the key questions are: How and what are you doing for them? Are you focused on meeting their core unmet needs? In that sense, I am trying to focus our efforts in CVRM on how can we bend the trajectory of health outcomes with our current and prospective assets.

Taking what I' ve learned as a physician-scientist at both Merck and Lilly, and how we ran Carmot, the best way I believe to energize CVRM within Roche is to have a fully integrated, end-to-end approach. In my mind, it's impossible to separate the science from the medicine or the patients, as it's all one continuum. That integrated approach is what we'd like to bring into the Boston Innovation Center.

On the pipeline for Roche and Genentech's Cardiovascular, Renal, and Metabolism (CVRM) hub

Esther: That's really terrific, and it's great to hear about Cardiovascular, Renal, and Metabolism hub. To dive into that a little bit more, Roche has a plethora of drug candidates in its pipeline, including several dual GLP-1 RAs, oral GLP-1 RAs, anti-myostatic antibodies, therapies for MASH, and the development of AI-powered compound identification – the list goes on. You mentioned an end-to-end approach, and are there some other

themes that you expect this innovation center to more specifically focus on?

Dr. Chakravarthy: Overall, the innovation center is going to focus on making sure that the drug candidates we discussed above are developed and brought to patients. We will be augmenting the footprint that already exists for Roche/Genentech, which includes Genentech's South San Francisco campus and Roche's Basel campus in Europe. In that sense, this is a critical piece between those two geographies by having a strong East Coast presence. We're not trying to replicate or duplicate all the great capability that already exists at those sites. We're bringing one more piece into our capability set, primarily focused on that core mission of CVRM.

The Carmot acquisition has helped kickstart the metabolic pipeline right away. We have CT-388, the once-weekly dual GLP-1-GIP receptor agonist with broad indications that include obesity, many of its comorbidities, and type 2 diabetes.

We also know that injectables alone may not be sufficient, because while some people like injectables, others hate needles. Having an oral option became equally important, which is why we have a molecule called CT-996, a once-daily oral GLP-1 RA pill. This candidate has really exciting phase 1 data, and we are now in phase 2.

Furthermore, we have another candidate that we hope to bring as an on-label adjunctive treatment to insulin for people living with type 1 diabetes. I say "on-label" because of course people use incretins off-label for type 1 diabetes, and patients have a hard time accessing therapies that are not on-label. This candidate is CT-868, a once daily dual GLP-1/GIP receptor agonist. We're very excited about this, as our preliminary studies have indicated potent reductions in blood glucose while sparing insulin.[3] This approach means that we hope to titrate insulin requirements down dramatically and lower the burden of hypoglycemia, a common fear in nearly all patients living with type 1 diabetes. Given the mechanism of action, we would also expect to see clinically meaningful weight loss and cardiovascular risk reduction. We're currently in the midst of a phase 2 trial, and we can't wait to see data in the second half of 2025. If all goes well, we can formalize phase 3 initiation in 2026.

We are also excited about GYM329, our anti latent myostatin antibody because preserving lean mass is very important for long term weight maintenance. Having sufficient lean mass can buffer many other comorbidities, because the more lean mass people lose, the more they become susceptible to other diseases.

Esther: How are you looking at any of these candidates as a component of a combination therapy, for any range of diseases?

Dr. Chakravarthy: Great question! You hit right on another important pillar of our strategy in CVRM, which is to adequately address the co-morbidities of obesity with combination therapies. Heart and kidney disease are naturally front-and-center, but Roche's broader pipeline extends beyond the cardiorenal or metabolic spaces to include neurodegeneration – a complication that many GLP-1 RAs are trying to tackle now. For example, we have some very interesting assets positioned to treat Alzheimer's and Parkinson's. Can we actually combine CT-388 with our novel brain shuttle-enabled anti-amyloid plaque reducing agents for Alzheimer's? It will certainly be interesting to see. When you put it all together, there's indeed a lot to do, and no one or twocompanies can possibly handle the incredible complexity and the heterogeneity of obesity and its many co-morbidities.

On Roche's partnership with Zealand to co-develop obesity therapies

Jeremy: Thank you for that thorough review, Dr. Chakravarthy. I also wanted to ask about Roche partnering with Zealand to co-develop petrelintide for obesity, including as a combination therapy with CT-388. Could you talk more about Roche's expectations for that partnership?

Dr. Chakravarthy: Of course, I'd be remiss not to round out my overview of our pipeline without discussing our recent partnership with Zealand. As bullish as I am about our portfolio, I'm also aware that in order to really compete, we must have more than incretins. That's one of the core reasons we did that deal with Zealand, a co-development and a collaborative partnership.

Amylin is a complementary hormone to GLP-1. We know from preclinical and clinical studies that when you combine an amylin with a GLP-1 RA, you have this very nice additive, and possibly, synergistic response. We expect to see that with petrelintide too, which is a long-acting amylin analogue.

We are in the amylin space to ensure that we have the right mechanisms to adequately address the heterogeneity of

obesity and consequently, address patients' different needs. We can envision the use of petrelintide in a couple of different ways. One is as a monotherapy, and the other is in combination with CT-388. For those patients that might be looking to lose say 10-15% of their body weight, a monotherapy option with amylin alone might be sufficient to get them there with excellent tolerability. But if people need to lose say 25% or more of their body weight and they already have type 2 diabetes or other obesity-related comorbidities, combining amylin with our dual GLP-1/GIP receptor agonist can be a fantastic combination.

There are two phase 2 trials with petrelintide underway, and we are eagerly looking forward to seeing that data in the coming months and then to initiate phase 3 studies in 2026. We are doing everything we can to bring these medicines to patients living with obesity as quickly as possible.

On the “war on hyperglycemia”

Kelly Close: We’re only in the very low numbers of millions of people being served right now, in terms of GLP-1 based therapies and we're thrilled that you're working on type 1 diabetes. We also love the idea of medicines reflecting a specific cardio- and kidney protection, and love some focus on a “war on hyperglycemia,” so we’re happy that you're taking on that field as well.

Dr. Chakravarthy: Thank you, and let me add that you're absolutely correct. Getting the majority of people living with diabetes to their treatment goals and targets remains a challenge. There is still a need for effective medicines and approaches that can do that. The current focus of our interactions with both Breakthrough T1D and other health agencies has been on safety. And appropriately so, because hypoglycemia is an important consideration. We are ensuring that with our trial designs we are minimizing the risk for both hypoglycemia as well as for DKA. To add to that, I would say one of our other points of emphasis has been end-organ protection, particularly the kidney. I'm very glad to hear that you guys also feel that our approach is in the right direction.

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[1]For reference, at Week 176, Lilly’s tirzepatide demonstrated 23% weight loss in the SURMOUNT-1 trial.