

Review

Once-Monthly and Extended-Interval Incretin-, Amylin-, and THR β -Targeting Therapies for Type 2 Diabetes and Obesity: Clinical Evidence and Development Pipelines

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Abstract

Once-monthly injectable therapies targeting glucagon-like peptide-1 (GLP-1), glucose-dependent insulintropic polypeptide (GIP), and adjacent metabolic pathways are moving from a conceptual goal to a plausible next step for type 2 diabetes (T2D) and obesity. The most clinically advanced program is maridebart cafraglutide (MariTide), a long-acting GLP-1 receptor agonist conjugated to an Fc-containing scaffold that also mediates sustained GIP receptor antagonism. Across phase 2 trials, once-monthly maridebart has produced clinically meaningful weight loss (~12–16% in adults without diabetes; ~8–12% in those with T2D), together with HbA1c reductions of ~1.2–1.6 percentage points, with a safety profile broadly consistent with GLP-1-based therapy. An exploratory every-8-weeks regimen showed attenuated efficacy, suggesting that monthly dosing may represent a practical lower boundary for maintaining therapeutic exposure and metabolic effect in this format. Beyond maridebart, a rapidly expanding pipeline—including ultra-long-acting GLP-1 analogs, dual GLP-1/GIP agonists, long-acting GIPR antagonists, amylin receptor agonists, and emerging thyroid hormone receptor beta (THR β) agonists—is actively testing monthly regimens or induction-to-monthly maintenance strategies; however, most readouts remain early and are frequently limited to conference presentations or sponsor communications. Accordingly, much of the pipeline evidence should be interpreted as early-phase and non-peer-reviewed, and therefore hypothesis-generating. Key uncertainties include long-term durability, cardiometabolic outcomes, immunogenicity, and interindividual variability in response, which will ultimately determine how once-monthly regimens integrate with established weekly standards in routine care.



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1. Introduction

The evolution of incretin-based pharmacotherapy reflects a two-decade trajectory of innovation in both molecular engineering and dosing convenience. The first-generation

glucagon-like peptide-1 receptor agonists (GLP-1 RAs), exemplified by twice-daily exenatide, established proof-of-principle that pharmacologic incretin enhancement could achieve clinically meaningful improvements in glycemic control with modest weight reduction [1]. Long-acting analogs such as liraglutide (once-daily) and, subsequently, once-weekly formulations including dulaglutide and semaglutide shifted the therapeutic paradigm, offering sustained receptor engagement with simplified regimens [2–4]. Beyond glycemic control, cardiovascular outcome trials such as LEADER, SUSTAIN-6 and REWIND demonstrated cardioprotection, consolidating GLP-1-based therapy as a cornerstone of type 2 diabetes (T2D) care and, more recently, as a central strategy in obesity management [5–7].

While the glycemic benefits of GLP-1 RAs are driven largely by incretin-mediated enhancement of glucose-dependent insulin secretion, their effects on body weight arise primarily from central modulation of appetite, satiety and energy intake [8,9]. This duality in mechanism, together with robust cardiometabolic outcome data, has contributed to unprecedented global uptake of once-weekly GLP-1-based therapies for both T2D and obesity [10]. However, the rapid expansion in clinical use has also exposed practical limitations, including recent supply constraints, treatment costs and variability in patient expectations regarding the need for long-term pharmacotherapy in obesity [11–13]. These challenges have intensified interest in ultra-long-acting formulations capable of maintaining therapeutic potency while reducing injection burden, setting the stage for the development of once-monthly injectable agents targeting GLP-1, glucose-dependent insulintropic polypeptide (GIP) and related metabolic pathways [14–16].

Against this background, a natural next step in metabolic peptide pharmacotherapy has been to extend dosing intervals beyond the once-weekly standard while preserving the metabolic benefits that made these agents transformative. Pharmacokinetic (PK) and pharmacodynamic (PD) modeling, together with exploratory clinical data, suggest that substantial weight-loss efficacy can be maintained even when dosing is less frequent, if receptor engagement remains above a critical threshold over time [17,18]. Earlier attempts, such as efpeglenatide, an exendin-based GLP-1 analog evaluated in once-monthly regimens, demonstrated that once-monthly administration is technically feasible, although efficacy and tolerability appeared constrained by trough exposures at the end of the dosing interval [19]. Maridebart cafraglutide (MariTide, Amgen Inc., Thousand Oaks, CA, USA) is a long-acting peptide–antibody conjugate that combines GLP-1 RA with glucose-dependent insulintropic polypeptide (GIP) receptor antagonism and is being developed for the treatment of obesity and T2D [14,20]. In phase 2 trials, once-monthly subcutaneous administration of maridebart cafraglutide has produced clinically meaningful weight loss and improvements in glycemic control in adults with obesity, with and without T2D, with a safety profile broadly consistent with GLP-1-based therapies [14,20].

Alongside maridebart, an emerging pipeline of ultra-long-acting therapies—including albumin-binding GLP-1 analogs, dual GLP-1/GIP agonists, long-acting GIP receptor antagonists, and amylin receptor agonists—is now explicitly testing extended-interval regimens as alternatives or complements to weekly standards [21–25]. This shift raises practical questions that are not simply incremental, including what PK/PD thresholds are required to avoid end-of-interval loss of effect, how titration should be engineered when “turning off” exposure is slow, and which patients or care settings stand to benefit most from extended-interval strategies. For clarity, we use “once-monthly” to denote fixed regimens administered approximately every 4 weeks (~28–30 days). We use “extended-interval” as an umbrella term for dosing intervals ≥ 4 weeks (including exploratory every-8-week schedules). “Induction-to-monthly maintenance” refers to programs that begin with a more frequent initiation phase (e.g., weekly or biweekly titration) followed by a transition to monthly administration once tolerability and effective exposure are established. In this

review, we summarize the pharmacologic design principles, available clinical efficacy and safety signals, and the development landscape of once-monthly injectable therapies for T2D and obesity, highlighting the uncertainties that will determine their role in routine metabolic care.

Methods: Evidence Identification and Selection

This manuscript is a narrative (non-systematic) review designed to synthesize the clinical evidence and development landscape of extended-interval injectable pharmacotherapies targeting incretin, amylin, and thyroid hormone receptor beta (THR β) pathways for obesity and type 2 diabetes (T2D). Evidence was identified through (i) targeted searches of biomedical literature databases (e.g., PubMed/MEDLINE) using combinations of terms related to “once-monthly”, “extended-interval”, “long-acting injectables”, “GLP-1”, “GIP”, “amylin”, “THR β ”, and individual asset names/codes; (ii) trial registry searches (e.g., ClinicalTrials.gov) to capture ongoing and completed studies, dosing schedules, and primary endpoints; and (iii) review of publicly available scientific disclosures from major international meetings where early-stage metabolic pipelines are commonly presented (e.g., ADA, EASD, ObesityWeek), alongside sponsor materials when peer-reviewed publications were not yet available.

Assets were included if they met at least one of the following criteria: (1) peer-reviewed human clinical data supporting an extended-interval (≥ 4 -week) dosing regimen; (2) human PK profiles plausibly enabling monthly dosing (e.g., terminal half-life and exposure persistence compatible with ≥ 4 -week intervals), accompanied by clearly disclosed clinical development intent for monthly dosing; or (3) clinical trial programs explicitly incorporating induction-to-monthly maintenance strategies. Foundational weekly comparators were included selectively to contextualize pharmacologic design principles and expected efficacy/safety boundaries.

Because many emerging programs remain in early development, a substantial portion of available information for pipeline assets derives from conference presentations, sponsor communications, or preliminary disclosures rather than fully peer-reviewed articles. Throughout the manuscript, the evidentiary level is explicitly signaled where applicable (peer-reviewed publication vs. conference/sponsor disclosure vs. preclinical/hypothesis-generating evidence), and conclusions regarding investigational assets are framed as provisional. The search and screening process was completed by December 2025. No formal risk-of-bias tool or quantitative meta-analysis was performed, consistent with the narrative scope of the review; accordingly, completeness and interpretability are constrained by the evolving and non-uniform evidence base.

2. Pharmacologic Principles of Extended-Interval Injectable Therapies

2.1. Rationale for Extending Dosing Intervals

The rapid uptake of once-weekly GLP-1 receptor agonists and dual GLP-1/GIP agonists in T2D and obesity has highlighted a persistent gap between trial efficacy and real-world treatment persistence. Despite robust effects on HbA1c and body weight, observational cohorts consistently report high discontinuation rates within the first year, driven by gastrointestinal adverse events, treatment fatigue, perceived regimen complexity, evolving expectations regarding the duration of pharmacotherapy, and—in many health systems—intermittent drug shortages that disrupt otherwise stable treatment courses [26–28]. Recurrent supply constraints and high out-of-pocket costs further challenge long-term use, particularly in obesity care, where treatment is often perceived as discretionary rather than essential [29,30]. In this context, extended-interval formulations should be considered not

only through the lens of individual adherence but also within supply-chain frameworks capable of reliably delivering each scheduled dose.

Reducing injection frequency from weekly to once-monthly is an intuitive strategy to lower treatment burden while preserving metabolic control. Fewer injections may reduce psychological load, simplify routines, and better align therapy with common chronic-care rhythms (e.g., monthly refills and periodic monitoring) [31,32]. From a logistical perspective, extended intervals may also reduce the number of injection devices and needles used per patient-year; the environmental implications of this potential reduction, however, remain insufficiently characterized. Convenience alone is insufficient: less frequent dosing narrows the margin for missed or delayed injections, reduces flexibility for rapid dose adjustment, and amplifies the consequences of any disruption in drug availability. Extending dosing intervals therefore requires PK/PD designs that maintain stable receptor engagement across a 4-week cycle, with predictable safety despite prolonged drug persistence [18,31–35], and must be embedded within health systems that can ensure timely and continuous access to therapy.

2.2. Molecular Design Strategies for Ultra-Long-Acting Injectables

Several structural approaches are being used to achieve PK profiles compatible with extended-interval dosing. Fc-fusion and peptide–antibody conjugates, exemplified by maridebart cafraglutide, prolong half-life by engaging neonatal Fc receptor (FcRn) recycling and reducing renal clearance, enabling sustained GLP-1 receptor activation with infrequent injections [14,20,36–38]. Similar concepts underpin long-acting strategies targeting the GIP receptor (GIPR), including programs designed to sustain GIPR antagonism, an approach supported by human genetic and physiological data linking reduced GIP signaling to lower adiposity [20,39–43].

A second strategy is albumin binding and lipidation. Fatty acid-modified GLP-1 analogs or albumin-binding constructs extend circulation time through high-affinity interaction with plasma proteins and altered tissue distribution, as has been characterized for currently approved long-acting GLP-1 RAs [38,44–46]. Platforms such as Metsera’s MET-097i apply these principles to generate ultra-long-acting GLP-1 RA, while complementary amylin receptor agonists such as MET-233i are being developed with half-lives compatible with less frequent dosing, either as monotherapy or in fixed-ratio combinations (for example, MET-097i plus MET-233i) [22,23,47–49]. Collectively, Fc-fusion, albumin binding and receptor-selective antibodies provide a modular toolkit for constructing ultra-long-acting metabolic agents tailored to specific mechanistic targets and dosing intervals.

2.3. PK/PD Requirements for Once-Monthly Regimens

Effective once-monthly therapy depends on tight PK/PD alignment. Agents must achieve a half-life and minimum concentration ($C_{\min}$) sufficient to sustain receptor engagement throughout a 4-week interval, avoiding troughs that erode effects on appetite, body weight and glycemic control. Data from existing GLP-1 RA and dual GLP-1/GIP agonists indicate that cumulative exposure and stable signaling, rather than high transient peaks, best predict HbA1c and weight responses [50–52]. Ultra-long-acting constructs therefore aim to minimize peak–trough fluctuation while maintaining PD activity across the entire dosing cycle [18,38].

Transitioning from weekly to monthly regimens raises practical issues of dose selection, titration and accumulation. Longer half-lives slow the approach to steady state and increase the risk of overexposure if doses are escalated too aggressively, yet underdosing may lead to a perceptible loss of benefit before the next injection [34,53,54]. Thus, PK/PD requirements for monthly dosing extend beyond simply lengthening half-life; they demand

dosing schemes that balance durability of action, tolerability and operational flexibility in routine care.

2.4. Safety Considerations for Monthly Dosing

Ultra-long-acting injectables introduce safety nuances that are less pronounced with shorter-acting formulations. Gastrointestinal adverse events remain the dominant side effects of GLP-1-based therapies and are closely related to dose and speed of titration [33,55,56]. With once-monthly dosing, an excessive initial dose or rapid uptitration may result in more prolonged or severe symptoms because drug clearance is slow and the ability to rapidly “switch off” effective exposure is limited. Careful titration and proactive counseling are therefore critical [34,57].

Prolonged systemic exposure also raises theoretical concerns about accumulation-related toxicity, off-target effects and immunogenicity, particularly at doses used for obesity [58–61]. Managing adverse events is more challenging when pharmacologic effects persist for weeks, especially in older adults or those with significant comorbidities. Finally, once-monthly regimens will often be combined with other antidiabetic or anti-obesity drugs, potentially modifying hypoglycemia risk (for example, when used with insulin) and compounding gastrointestinal or gallbladder events [5,62]. Robust pharmacovigilance and real-world data will be essential to define the safety profile of these agents and to guide their integration into complex treatment regimens.

While the discussion below uses once-monthly dosing as the reference case, several management considerations generalize to extended-interval regimens beyond 4 weeks. Beyond tolerability and accumulation considerations, extended-interval exposure introduces practical safety-management challenges that are uncommon with weekly agents. Because PD effects cannot be rapidly attenuated once a dose is administered, “limited reversibility” increases the importance of conservative dose escalation, clear discontinuation guidance, and careful switching strategies that avoid overlapping long-acting exposures (“stacking”) when transitioning between agents. Extended-interval incretin-based therapies may also require explicit planning for acute illness, prolonged fasting, and peri-procedural care. In patients with reduced oral intake, persistent nausea/vomiting, or dehydration risk, prolonged exposure may complicate symptom control and fluid management. In the perioperative setting, delayed gastric emptying associated with GLP-1-based therapies has anesthesia implications; therefore, elective procedures may require individualized planning, while urgent/emergent procedures may necessitate heightened aspiration-risk mitigation. These considerations underscore the need for pragmatic, half-life-informed clinical guidance as ultra-long-acting regimens move into routine practice (Table 1).

3. Maridebart Cafraglutide (MariTide): Lead Once-Monthly GLP-1 RA Plus GIPR Antagonist

3.1. Mechanistic Rationale: GLP-1 RA Plus GIPR Antagonism

Maridebart cafraglutide (MariTide or AMG133; Amgen) is a long-acting conjugate that combines GLP-1 RA activity with GIPR antagonism in a single molecule. The construct consists of a fully human IgG1 monoclonal antibody directed against GIPR, covalently linked to two GLP-1 analog peptides [20]. This design leverages high-affinity GLP-1R agonism to drive weight loss and glycemic improvement, while sustained GIPR blockade is expected to counteract GIP-mediated adipogenesis and postprandial lipid storage [63]. The rationale for targeting GIPR antagonism is supported by human genetic and experimental data [43]. Loss-of-function variants in GIPR have been associated with lower BMI and improved adiposity profiles, and preclinical studies with GIPR antagonists show reductions in body weight and fat mass [42]. In this context, MariTide provides a “dual-lever” approach

distinct from GLP-1/GIP co-agonists: rather than potentiating both incretin pathways, it amplifies GLP-1 signaling while chronically suppressing GIP signaling. Whether this strategy yields advantages over dual agonism remains an open question, but phase 1–2 data indicate that combined GLP-1 agonism with GIPR antagonism can achieve clinically meaningful reductions in body weight and improvements in glycemic control in the populations studied [14,20].

3.2. Preclinical and Early Clinical Development

In preclinical models, maridebart cafraglutide showed marked anti-obesity and metabolic effects. In diet-induced obese mice and cynomolgus monkeys, repeated administration produced marked and sustained reductions in body weight, accompanied by improvements in glycemia and lipid parameters without evidence of off-target toxicity [14,20,64]. In vitro, the molecule behaved as intended, demonstrating potent GLP-1R agonism and GIPR antagonism in cell-based functional assays [20]. A first-in-human, randomized, double-blind, placebo-controlled phase 1 study in adults with obesity evaluated single and multiple ascending subcutaneous doses of maridebart cafraglutide, with the multiple-dose cohorts receiving injections every 4 weeks [20]. In the once-monthly multiple-ascending-dose cohorts, maridebart cafraglutide produced dose-dependent weight loss, with mean reductions of about 7% at 140 mg and up to approximately 14–15% at the highest 420 mg regimen after 12 weeks of treatment [20].

3.3. Phase 2 Trials in Obesity Without T2D

At week 52, mean percentage body-weight reductions in the non-diabetes cohort were approximately 12–16% across the monthly regimens, compared with ~2–3% with placebo [14]. A high proportion of participants achieved $\geq 10\%$ and $\geq 15\%$ weight loss, and weight trajectories generally continued downward through week 52, suggesting that a clear plateau had not yet been reached [14]. In contrast, the every-8-week (q8w) arm showed attenuated efficacy, with smaller absolute and relative weight reductions than the q4w regimens [14]. This pattern supports the concept that once-monthly dosing may represent the lower practical limit for maintaining near-maximal efficacy within this pharmacologic class. Beyond weight, maridebart cafraglutide improved multiple cardiometabolic risk markers in participants without diabetes, including modest reductions in blood pressure, triglycerides and high-sensitivity C-reactive protein, consistent with the magnitude of weight loss [14].

3.4. Phase 2 Trials in T2D with Obesity

A parallel cohort of adults with T2D and obesity or overweight was included in the same phase 2 program [14]. Participants (baseline BMI ≈ 36 kg/m², established T2D on stable background therapy) were randomized to once-monthly maridebart cafraglutide at 140, 280 or 420 mg, or placebo, for 52 weeks [14]. As typically observed with incretin-based therapies, absolute weight loss was somewhat smaller in the diabetes cohort but remained clinically significant. At week 52, mean weight reductions with maridebart cafraglutide ranged from approximately 8–12%, compared with ~2% in the placebo group [14]. Importantly, these weight effects were accompanied by robust improvements in glycemic control. Across doses, HbA1c decreased by roughly 1.2–1.6 percentage points versus minimal change or slight increases with placebo [14]. A substantial proportion of participants achieved guideline HbA1c targets despite background therapy [14]. Together, these data indicate that once-monthly maridebart cafraglutide can deliver dual efficacy in weight and glycemia in people living with T2D and obesity, with effect sizes that are directionally consistent with those reported for potent once-weekly GLP-1-based regimens

in broadly similar populations, acknowledging that cross-trial comparisons are inherently limited [2–4,8–10,14].

3.5. Safety and Tolerability Profile

Across phase 1–2, the safety profile of maridebart cafraglutide has been broadly consistent with that of GLP-1 RAs. The most frequent adverse events were GI symptoms—principally nausea, vomiting and constipation—which were generally mild to moderate, occurred predominantly during the early treatment period, and tended to resolve spontaneously [14]. Incidence and severity of GI events were higher with rapid initiation of high doses and mitigated by gradual dose escalation, supporting the use of titration schemes in later-phase trials [14]. Discontinuation due to GI adverse events occurred in a minority of patients, particularly in titration arms [14]. No new safety signals specific to GIPR antagonism or the antibody–peptide format have been identified to date. In phase 2, there was no excess of serious cardiovascular events, and maridebart cafraglutide was associated with favorable changes in blood pressure and inflammatory markers [14]. No adjudicated cases of acute pancreatitis were observed in the phase 2 program, and no imbalance in pancreatic events was detected relative to placebo. Likewise, no consistent signal for gallbladder disease has emerged to date in the available datasets; however, systematic adjudication and longer-term exposure will be important, and gallstone formation remains a theoretical consideration with any therapy that induces rapid and sustained weight loss [14]. Hypoglycemia rates were low and comparable to placebo when maridebart cafraglutide was used without insulin or sulfonylureas, reflecting the glucose-dependent nature of GLP-1-mediated insulin secretion [14]. Immunogenicity appears limited so far: development of anti-drug antibodies has been infrequent and without clear impact on PK or efficacy in the timeframe studied [14,20]. Overall, maridebart cafraglutide currently appears to have a manageable tolerability profile, dominated by class-typical GI effects, with no overt safety penalty relative to weekly GLP-1 RAs [14,20].

3.6. Key Lessons from Maridebart Cafraglutide for Monthly Therapies

Finally, maridebart cafraglutide illustrates practical considerations that will likely apply to other monthly agents: the need for careful titration to balance efficacy with GI tolerability; reduced flexibility to rapidly down-titrate in the event of adverse effects due to prolonged drug persistence; and the importance of understanding how monthly regimens will interface with existing weekly incretin therapies in terms of switching, sequencing or combination use [14–16,20]. Ongoing phase 3 outcome trials will be crucial to clarify the durability of weight loss, effects on cardiovascular and heart-failure endpoints, and the real-world role of once-monthly incretin-based therapies within the broader landscape of obesity and T2D management. Building on phase 2, Amgen initiated the MARITIME phase 3 program across obesity and T2D (e.g., MARITIME-1, -2, -CV, and -HF), with additional studies announced in other comorbidity areas; timelines and final protocols should be interpreted as subject to change as programs mature.

4. Beyond Maridebart: Emerging Extended-Interval Pipelines

The development of maridebart cafraglutide has redefined the therapeutic boundaries of long-acting metabolic pharmacotherapy and catalyzed a new generation of extended-interval agents. Although maridebart remains the only once-monthly incretin-based therapy supported by peer-reviewed phase 2 data, several emerging programs seek to approach its efficacy, PK stability, and durability of effect [14]. As summarized in Figure 1, the once-monthly pipeline now spans ultra-long-acting GLP-1 RAs, dual GLP-1/GIP agonists, amylin receptor agonists, long-acting GIPR antagonists, and selected non-incretin

metabolic targets, including thyroid hormone receptor beta agonist strategies (THR β -RAs). However, the evidentiary base is uneven: most available data for these agents come from sponsor-released summaries, conference presentations, or early-phase trials, and formal peer-reviewed publications remain scarce. The following narrative synthesizes the mechanistic rationale, developmental progress, and translational potential of these programs, while emphasizing the provisional nature of the available evidence. Throughout Section 4, evidence level is indicated explicitly (peer-reviewed clinical data vs. sponsor/conference disclosure vs. preclinical/hypothesis-generating evidence).

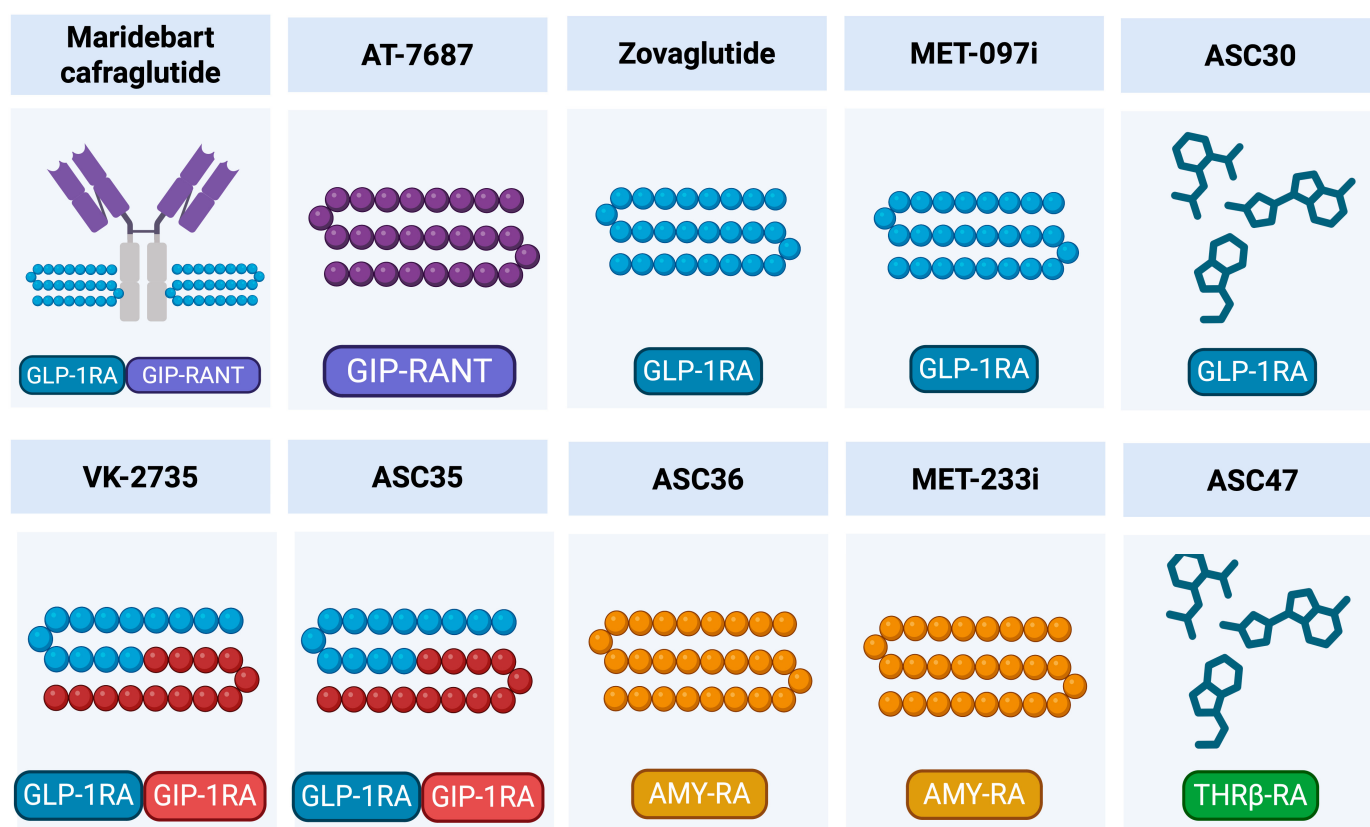


Figure 1. Mechanistic landscape of emerging extended-interval metabolic candidates discussed in this review. Programs are grouped by pharmacologic class as indicated by the colored labels: GLP-1RA (blue), GIP-1RA (red), GIPR-ANT (purple), AMY-RA (orange), and THR β -RA (green). Maridebart cafraglutide (MariTide; AMG 133) is depicted as a peptide–antibody conjugate combining GLP-1RA activity with sustained GIPR antagonism. Asset names are shown as development codes; icons are schematic and intended to illustrate mechanistic classification rather than molecular structure or comparative efficacy.

4.1. MET-097i: Ultra-Long-Acting GLP-1 RA (NuSH Platform)

Metsera, a clinical-stage biotech that Pfizer has agreed to acquire as part of its obesity strategy [65], is developing an ultra-long-acting “nutrient-stimulated hormone” (NuSH) platform centered on two injectable peptides engineered for extended dosing intervals: the fully biased GLP-1 RA MET-097i and the ultra-long-acting amylin analog MET-233i [66]. Both candidates are designed as next-generation NuSH analogs with closely aligned PK profiles intended to support once-monthly dosing and, ultimately, fixed-ratio co-formulation. MET-097i uses Metsera’s HALO™ peptide lipidation technology to enhance albumin binding and prolong systemic exposure, whereas MET-233i incorporates dual fatty-acid modifications to extend its half-life; together, they are being developed to provide comple-

mentary control of appetite, gastric emptying, and postprandial metabolism in people with overweight or obesity, with or without T2D [22,23,66–68].

MET-097i is a fully biased, subcutaneously administered GLP-1 RA with a sponsor-reported human half-life of approximately 380 h (~16 days), providing a strong PK rationale for exploring once-monthly maintenance regimens [66,68]. To date, however, all efficacy data have been generated under once-weekly schedules. In an early-phase 1/2 study in adults with overweight or obesity without diabetes, five once-weekly injections of MET-097i (up to 1.2 mg) given without dose titration produced dose-dependent weight loss, with mean reductions of approximately 7–8% by day 36 and about 8.1% by day 57—four weeks after the last injection—indicating sustained PD activity beyond the formal dosing period [66,68,69]. This continued weight loss after treatment cessation is a key argument supporting the feasibility of extended-interval dosing. Building on these findings, the randomized, placebo-controlled VESPER-1 phase 2b trial evaluated 28 weeks of once-weekly MET-097i (0.4–1.2 mg) in adults with overweight or obesity without diabetes, reporting placebo-subtracted mean weight loss of up to 14.1% at the highest dose, individual reductions as high as 26.5%, a total study discontinuation rate of 2.9%, and a gastrointestinal tolerability profile that appears manageable in the context of GLP-1-based therapies [47,66,68,70]. In parallel, the VESPER-3 program and a dedicated phase 2b study (NCT06973720) are evaluating multiple once-monthly MET-097i regimens, generally following an initial weekly induction phase, with the aim of characterizing the durability, safety, and tolerability of true monthly maintenance dosing [47,71].

At present, these phase 2 results are available mainly through sponsor materials and conference disclosures, and detailed peer-reviewed reports on glycemic outcomes, body-composition changes, and long-term durability remain limited. Consequently, positioning MET-097i as a once-monthly therapy is currently supported primarily by its PK profile, the observation of continued weight loss after weekly dosing is stopped, and the design of ongoing trials, rather than by fully adjudicated clinical data.

4.2. MET-233i: Ultra-Long-Acting Amylin Analog

MET-233i is Metsera's ultra-long-acting, subcutaneously administered amylin analog, developed within its next-generation nutrient-stimulated hormone (NuSH) portfolio and specifically engineered for potential once-monthly dosing [22,48,66]. Amylin receptor agonism complements GLP-1 signaling by reducing appetite, slowing gastric emptying and enhancing postprandial satiety, providing a mechanistically distinct but synergistic axis within NuSH-based weight-loss strategies [22,67]. MET-233i is the lead next-generation NuSH peptide designed for combination and co-formulation with the fully biased GLP-1 RA MET-097i; both molecules were engineered using Metsera's HALO™ peptide stabilization and lipidation platform, yielding matched solubility profiles and extended half-lives compatible with monthly regimens [48,66]. In a randomized, double-blind, placebo-controlled phase 1 trial in 80 adults with overweight or obesity without T2D, MET-233i was evaluated as single ascending doses (0.15–2.4 mg) and multiple ascending doses (0.15–1.2 mg) administered once weekly over five weeks, without titration [48,66,72].

MET-233i showed dose-linear PK with an observed half-life of approximately 19 days—among the longest sponsor-reported profiles to date for an amylin analog—which, together with an exposure pattern that closely matched MET-097i after multiple doses, supports the feasibility of once-monthly dosing and fixed-ratio co-formulation. In the multiple-dose cohorts, five weekly injections of 1.2 mg produced placebo-subtracted mean weight loss of up to 8.4% at day 36, with individual reductions approaching 10% [48,66,72]. In the single-dose cohorts, a single injection produced clinically meaningful weight loss that was maintained for more than four weeks, consistent with the ultra-long PK profile [48,66,72].

Tolerability in phase 1 was reported as favorable: GI adverse events in the multiple-dose portion were mild, dose-dependent and largely confined to the first week of treatment, despite roughly three-fold accumulation of exposure over five weeks, and no severe or serious adverse events or concerning safety signals were reported [48,66,72]. Anticipated starting doses of 0.15–0.3 mg showed placebo-like tolerability. This profile, aligned with the historically lower GI burden reported with amylin analogs relative to GLP-1 RAs, supports the use of MET-233i as a tolerable backbone for chronic, high-exposure regimens and combination therapy. MET-233i is now being investigated in a 12-week monotherapy study employing weekly titration followed by an exposure-matched once-monthly dose at week 13, designed to characterize the maintenance potential, safety and tolerability of true monthly administration, and to inform dose selection for later-phase development [48,66,72].

4.3. MET-233i + MET-097i: First-in-Class Monthly Multi-NuSH Combination

A central element of Metsera's development strategy is the co-formulation of the ultra-long-acting amylin analog MET-233i with the fully biased GLP-1 RA MET-097i as a potential once-monthly multi-nutrient-stimulated hormone (NuSH) injectable therapy for chronic weight management. Both peptides were deliberately engineered using Metsera's proprietary HALO™ lipidation platform to achieve compatible solubility characteristics and closely aligned PK profiles, with observed terminal half-lives of approximately 19 days for MET-233i and ~380 h (~16 days) for MET-097i [48,66]. This alignment is intended to enable coordinated exposure over a multi-week dosing interval and supports their development as a co-formulated injectable combination [48,66].

The mechanistic rationale for this dual-NuSH approach lies in the complementary metabolic actions of GLP-1 and amylin signaling. GLP-1 RA activity provides potent incretin-mediated effects on glycemic control and central appetite suppression, while amylin agonism reinforces satiety, slows gastric emptying and modulates postprandial nutrient handling. In combination, these mechanisms may offer additive or synergistic effects on body-weight reduction and metabolic regulation, with the potential for dose-sparing and possibly improved GI tolerability relative to escalation of a single pathway [48,66]. Evidence supporting the combination remains early but has been substantiated by multiple sponsor-reported sources [72]. Phase 1 data indicate that MET-233i achieves placebo-adjusted mean weight loss of up to 8.4% at day 36 following five weekly doses, with individual responses approaching 10%, and demonstrates an observed half-life compatible with extended-interval dosing [72]. Importantly, sponsor-reported PK analyses suggest that exposure profiles of MET-233i after multiple doses closely match those of MET-097i, supporting practical co-formulation [72]. GI adverse events observed to date have been predominantly mild, dose-dependent and largely confined to the initial dosing period, with no severe or serious adverse events reported in early studies [72].

The co-administration strategy is currently being evaluated in a randomized, double-blind, placebo-controlled phase 1 trial (NCT06924320) enrolling adults with overweight or obesity, including a cohort with T2D [73]. This study incorporates single- and multiple-ascending-dose cohorts with extended safety follow-up and is designed to characterize safety, tolerability, PK, PD and preliminary weight-loss effects of MET-233i administered together with MET-097i [73]. In parallel, Metsera has disclosed plans to explore regimens that transition from an induction phase to exposure-matched monthly maintenance dosing, aiming to balance rapid onset of weight loss with long-term convenience and scalability. From a regulatory perspective, the sponsor has indicated an intent to advance the MET-233i/MET-097i combination through the U.S. FDA biologics pathway, targeting eventual submission under a biologics license application framework. While the pharmacological

rationale and early clinical signals are encouraging, positioning this combination as a leading monthly therapy remains provisional [48,66]. Robust phase 2 and phase 3 trials will be required to define incremental efficacy over single-mechanism NuSH agents, long-term safety, and effects on body-composition endpoints, metabolic risk factors and treatment persistence relative to established weekly GLP-1-based regimens.

4.4. Zovaglutide (ZT002): A Once-Monthly Long-Acting GLP-1 RA

Zovaglutide (ZT002; QL Biopharmaceutical) is an ultra-long-acting GLP-1 RA being developed for true once-monthly subcutaneous administration. The molecule incorporates a dual fatty-acid chain modification strategy that markedly enhances albumin binding, thereby extending systemic exposure and enabling prolonged PK durability. This structural design differentiates zovaglutide from earlier acylated GLP-1 analogs and supports a terminal half-life in the range of approximately 260–273 h, consistent with its intended four-week dosing interval [74]. The clinical development of zovaglutide is led by Beijing QL Biopharmaceutical Co., Ltd., reportedly founded by former Novo Nordisk scientists, with integrated capabilities spanning peptide discovery, recombinant E. coli-based manufacturing, and GMP-scale production [74]. Zovaglutide is described as a selective GLP-1 RA with no reported activity on GIP or glucagon receptors, exerting its metabolic effects through established central and peripheral GLP-1 pathways that promote satiety, reduce caloric intake, and enhance glucose-dependent insulin secretion [74].

Phase 2 efficacy data were presented at the European Association for the Study of Diabetes (EASD) Annual Meeting in 2025 from a randomized, double-blind, placebo-controlled, multicenter trial enrolling 303 adults with overweight or obesity [75]. Participants received zovaglutide at doses of 80 mg or 160 mg administered either once monthly (Q4W) or every two weeks (Q2W) for 24 weeks. Mean placebo-subtracted body-weight reductions ranged from 10.6% to 14.4% at week 24, with the 160 mg Q4W regimen achieving a mean reduction of 13.8%, closely comparable to the 160 mg Q2W regimen (14.4%) [75]. No plateau in weight loss was observed at the end of the treatment period, suggesting ongoing efficacy beyond six months [75]. A high proportion of participants achieved clinically meaningful weight loss, with approximately 90–97% reaching $\geq 5\%$ weight reduction and 77–85% achieving $\geq 10\%$ weight loss across active treatment arms, compared with 13% and $\sim 5\%$, respectively, in the placebo group [75]. These effect sizes are notable for a 24-week dataset; however, cross-trial comparisons with weekly semaglutide (including differences in duration, populations, and titration) should be interpreted cautiously until peer-reviewed reports and longer-term phase 3 results are available.

Zovaglutide demonstrated a safety and tolerability profile consistent with the GLP-1 RA class. GI adverse events, primarily nausea, vomiting, and diarrhea, were the most commonly reported events and occurred predominantly during the dose-escalation phase. Treatment discontinuation due to GI adverse events was low (approximately 1.3%) in this trial [75]. The once-monthly 160 mg regimen was associated with fewer GI events during maintenance compared with bi-weekly dosing, suggesting that extended dosing intervals may mitigate peak-related tolerability in some settings [75]. Based on these findings, zovaglutide has advanced into a pivotal phase 3 program. The ongoing HORIZON-1 trial (NCT07230119) is a randomized, double-blind, placebo-controlled phase 3 study enrolling approximately 620 adults with overweight or obesity, evaluating the efficacy and safety of once-monthly zovaglutide over 52 weeks, with primary endpoints including percent change in body weight and the proportion of participants achieving $\geq 5\%$ weight loss [76]. The results of this study will be critical in determining long-term durability, safety, and regulatory viability of zovaglutide as a monthly GLP-1 RA.

4.5. VK-2735: Dual GLP-1/GIP Receptor Agonist with a Maintenance-Oriented Path Toward Monthly Dosing

VK-2735 (Viking Therapeutics, San Diego, CA, USA) is a peptide-based dual agonist of the GLP-1 and GIP receptors developed for metabolic disease, conceptually aligned with the central premise of this review: that pharmacologic engineering can shift incretin therapy from weekly standards toward longer dosing intervals without surrendering clinically meaningful efficacy [61]. By co-activating GLP-1R and GIPR, VK-2735 is positioned to couple established GLP-1-mediated satiety and glucose-dependent insulin secretion with a complementary incretin axis that may further modulate nutrient handling and adiposity-related biology, consistent with mechanistic work across the dual-agonist class [77]. A key feature relevant to extended-interval development is VK-2735's predictable and prolonged exposure profile in humans. In early clinical development, Viking reported a terminal half-life of ~170–250 h (≈ 7 –10 days) and a $t_{\max}$ of ~75–90 h, consistent with a gradual rise in systemic exposure and a PK profile described as amenable to extended dosing strategies [78,79].

Clinically, VK-2735 has demonstrated robust short-term efficacy with once-weekly subcutaneous dosing. In the phase 2 VENTURE trial, weekly VK-2735 administered for 13 weeks resulted in mean weight loss of up to 14.7% from baseline, with placebo-adjusted reductions reaching 13.1%, and with up to 88% of treated participants achieving $\geq 10\%$ weight loss [80]. Weight reduction was progressive throughout the treatment period, with no clear plateau at week 13 [80]. Treatment was generally well tolerated, with GI adverse events predominating and largely mild to moderate in severity, low discontinuation rates, and no unexpected safety signals [80]. Data presented at ObesityWeek 2024 provided additional insight relevant to maintenance strategies. In a PK subset of VENTURE participants, most of the weight loss was maintained four weeks after the final weekly dose, including 98% maintenance at the lowest evaluated dose, with continued maintenance observed up to seven weeks post-dose in combined analyses [81]. These findings support the biological plausibility of once-monthly dosing in a maintenance setting, provided that substantial weight loss is first achieved during a weekly induction phase.

This concept has now been operationalized within Viking's development program. In October 2025, the company initiated an exploratory maintenance-dosing trial in adults with obesity, in which all participants received weekly subcutaneous VK-2735 for 19 weeks before transitioning to maintenance regimens that included monthly subcutaneous dosing, alongside oral weekly or daily schedules [82]. Importantly, Viking's pivotal phase 3 program (VANQUISH-1 and VANQUISH-2) continues to advance VK-2735 on a weekly injectable schedule, underscoring that monthly dosing remains investigational and positioned as a potential persistence-enhancing strategy rather than a primary therapeutic paradigm [21,82–84]. VK-2735 therefore represents an induction-to-monthly maintenance development strategy rather than a true once-monthly agent at present. Its human PK, durable PD effects after dose cessation, and explicit maintenance-focused clinical strategy make it highly relevant to the discussion of extended-interval incretin therapy [21,82]. However, whether monthly maintenance can reliably preserve weight loss trajectories and glycemic control comparable to weekly dosing—without compromising tolerability or increasing interindividual variability in response—remains a central unanswered question that ongoing studies are designed to address.

4.6. ASC30: Ultra-Long-Acting Small-Molecule GLP-1 RA with Monthly and Quarterly Injectable Potential

ASC30 is Ascleptis' lead incretin program and represents a distinctive approach within the GLP-1 RA landscape as a fully biased small-molecule GLP-1R agonist being developed for both oral once-daily administration and ultra-long-acting subcutaneous depot formula-

tions designed for once-monthly treatment and once-quarterly maintenance [85]. ASC30 was discovered and developed in-house using Ascleitis' AI-Assisted Structure-Based Drug Discovery (AISBDD) platform and advanced through proprietary drug-delivery technologies that differentiate it from peptide-based incretin therapies [85]. Mechanistically, ASC30 is characterized by potent cAMP signaling with minimal β -arrestin recruitment, a signaling bias proposed to preserve metabolic efficacy while potentially improving tolerability and durability of response [85]. While this property is relevant across both oral and injectable programs, it is particularly consequential for extended-interval regimens, where excessive peak-related adverse events or receptor desensitization could undermine feasibility [85].

The injectable formulation of ASC30 leverages Ascleitis' Ultra-Long-Acting Platform (ULAP) to generate slow-release subcutaneous depots with tunable release kinetics [85]. In a randomized, double-blind, placebo-controlled phase Ib study conducted in the United States, ASC30 subcutaneous injection was evaluated in adults with obesity following a single 100 mg dose administered as either a treatment formulation or a maintenance formulation. PK analyses reported exceptionally prolonged apparent half-lives, reaching approximately 46 days (~1100 h) for the treatment formulation and 75 days (~1810 h) for the maintenance formulation [85]. These exposure profiles support once-monthly dosing for active treatment and once-quarterly dosing for maintenance, investigational with favorable peak-to-trough ratios ($C_{\max}$ -to- $C_{\text{day}29}$ ratio of 1.5:1 for monthly treatment; $C_{\max}$ -to- $C_{\text{day}85}$ ratio of 2.5:1 for quarterly maintenance) [85].

Safety and tolerability findings from the phase Ib subcutaneous study were encouraging and relevant to extended-interval dosing. No serious adverse events or grade ≥ 3 adverse events were reported [85]. GI events—including nausea, vomiting, diarrhea, and constipation—were mild to moderate in severity, with no treatment discontinuations. Laboratory parameters, vital signs, electrocardiograms (including QTc), and physical examinations revealed no hepatic or cardiovascular safety signals, supporting the translational plausibility of chronic ultra-long-acting exposure [85]. Parallel clinical development includes an oral formulation enabled by Ascleitis' POTENT platform, which has progressed through phase I and completed a 13-week phase II study in obesity, reporting placebo-adjusted weight loss up to ~7.7%, favorable cardiometabolic effects, and a low discontinuation rate driven primarily by mild GI events [85,86]. While the oral program provides important evidence of pharmacologic activity and tolerability, the injectable ASC30 platform is strategically positioned as a long-interval therapy intended to address adherence and persistence challenges that remain unmet even with weekly GLP-1 RAs [86].

At the time of writing, ASC30 subcutaneous injection is advancing through phase II clinical development for once-monthly administration, while a separate ultra-long-acting quarterly injectable formulation is being evaluated in phase I clinical studies [87]. If replicated in larger and longer trials, ASC30 would represent a small-molecule GLP-1 RA capable of sustaining meaningful metabolic effects over multi-month dosing intervals. The ASC30 program therefore exemplifies a next-generation incretin strategy in which signaling bias, depot engineering, and ultra-long PK converge, offering a credible path toward reducing injection burden while preserving efficacy and safety in chronic weight management.

4.7. ASC35: Once-Monthly Subcutaneous GLP-1R/GIPR Dual Peptide Agonist

ASC35, previously referred to as ASC31 in early preclinical disclosures, is Ascleitis' once-monthly subcutaneous dual peptide agonist of GLP-1R and GIPR, discovered and developed in-house using the company's AISBDD platform and ULAP [88–90]. ASC35 is engineered to combine high intrinsic potency at both incretin receptors with extended apparent half-life and high bioavailability per milligram of peptide, enabling a low-volume (≤ 1 mL) once-monthly injection strategy [88–90]. The preclinical characterization dis-

closed by Ascletis is unusually quantitative for a pre-IND incretin asset. In head-to-head non-human primate studies, ASC35 demonstrated an average observed half-life of approximately 14 days, described as roughly six-fold longer than that of subcutaneously administered tirzepatide [88–90]. Systemic drug exposure, assessed by area under the curve, was reported to be approximately 80% higher following intravenous administration and 70% higher following subcutaneous administration compared with tirzepatide [88–90]. Using cross-species PK scaling anchored to published tirzepatide absorption, distribution, metabolism, and excretion data, Ascletis projects that ASC35 could plausibly achieve a human half-life approaching or exceeding 30 days, supporting a once-monthly dosing paradigm [88–90]. In vitro, ASC35 is described as approximately four-fold more potent than tirzepatide at both GLP-1R and GIPR [88–90].

These potency and PK properties translated into marked efficacy signals in vivo. In a 14-day diet-induced obese mouse study using equal molar dosing, ASC35 produced a –33.6% change in body weight compared with –19.6% for tirzepatide, corresponding to a 71% greater relative weight reduction [88–90]. While short-duration rodent studies require cautious interpretation given species differences and dosing intensity, these head-to-head preclinical findings are consistent with a high-potency dual incretin agonist profile; however, clinical positioning as a monthly therapy remains provisional and will depend on first-in-human PK/PD and dose-ranging studies [88–90]. Regulatory intent is explicitly stated, with Ascletis planning to submit an Investigational New Drug application to the U.S. FDA in the second quarter of 2026 for the treatment of obesity [88–90]. Beyond monotherapy, the company has articulated a broader strategic vision in which ASC35 serves as a backbone component of once-monthly combination regimens, most notably with ASC36, a long-acting amylin receptor agonist, and potentially with ASC47, an adipose-targeted thyroid hormone receptor beta agonist. This positioning reflects an effort to construct integrated monthly metabolic interventions that align incretin signaling, amylin-mediated satiety, and THR β biology [88–90]. The central translational question for ASC35 remains whether the apparent advantages in potency and PK will translate into clinically meaningful incremental weight loss and improved tolerability compared with established weekly incretin therapies. These hypotheses are mechanistically plausible and testable, but definitive validation awaits first-in-human PK/PD and dose-ranging studies [88–90].

4.8. ASC36: Once-Monthly Subcutaneous Amylin Receptor Peptide Agonist

ASC36 is Ascletis' once-monthly subcutaneous amylin receptor peptide agonist selected for clinical development as a high-potency amylin-pathway candidate and a foundational component for combination regimens in obesity [90,91]. Like ASC35, ASC36 was discovered and engineered in-house using Ascletis' AI-assisted structure-based drug discovery platform and its ultra-long-acting formulation technology, with explicit design objectives that include extended apparent half-life, high subcutaneous bioavailability, low injection volume (≤ 1 mL), and manufacturing scalability [90,91]. The principal differentiators disclosed for ASC36 relate to both PK behavior and formulation stability. In head-to-head non-human primate studies, slow-release subcutaneous depot formulations of ASC36 exhibited an average observed half-life of approximately 15 days, described as roughly threefold longer than petrelintide [90,91]. Based on established cross-species PK relationships for peptide hormones, these data support the feasibility of once-monthly subcutaneous dosing in humans.

In a head-to-head diet-induced obese rat study using equal molar dosing, ASC36 reduced body weight by 10.01% after 7 days, compared with 5.25% for petrelintide, corresponding to an approximately 91% greater relative weight reduction [90,91]. While short-duration preclinical studies may overestimate clinical separation, the magnitude

and head-to-head nature of these data support ASC36's positioning as an amylin agonist optimized for long-interval administration [90,91]. A particularly consequential attribute of ASC36 is its reported chemical and physical stability at near-neutral pH, with sponsor-reported absence of fibrillation or aggregation under the tested conditions [90,91]. This feature is positioned to enable co-formulation with other peptide agents, including the once-monthly GLP-1R/GIPR dual agonist ASC35, without reliance on acidic formulations [90,91]. Given the historical challenges of amylin aggregation and device compatibility, this stability profile—if confirmed under formal stability programs—could reduce formulation, device, and immunogenicity risks for fixed-dose or co-formulated monthly products [90,91].

Ascleitis has stated its intention to submit an investigational new drug application to the U.S. FDA in the second quarter of 2026 for ASC36 in obesity [90,91]. The company positions ASC36 both as a monotherapy candidate and as a central platform for combination strategies in cardiometabolic disease, with explicit plans to pursue co-development with ASC35 [90,91]. Key translational uncertainties remain those inherent to amylin biology: whether extended-interval exposure can preserve or improve tolerability—particularly GI adverse effects—and whether hypothesized benefits of exposure smoothing translate into superior clinical persistence [90,91]. Nonetheless, among early-stage once-monthly amylin programs, ASC36 stands out for the granularity of its disclosed PK, efficacy, and formulation data as it advances toward first-in-human evaluation [90,91].

4.9. ASC47: Adipose-Targeted, Once-Monthly Subcutaneous THR β Agonist as a Muscle-Preserving Adjunct to Incretin Therapy

ASC47 is Ascleitis' adipose-targeted, once-monthly subcutaneous small-molecule agonist of thyroid hormone receptor beta (THR β), positioned as a “muscle-preserving” adjunct to incretin therapy rather than a stand-alone competitor to high-efficacy GLP-1-based regimens [92]. Conceptually, ASC47 extends the company's monthly dosing thesis beyond gut-brain hormones toward metabolic remodeling: THR β engagement is framed as a lever to enhance lipid handling and energy expenditure while incretins primarily suppress intake, creating a rationale for combination regimens that could improve weight-loss trajectory, mitigate rebound after discontinuation, and potentially enable lower incretin exposure with improved tolerability [92,93].

The most mature human signal disclosed to date comes from ASC47-103 (NCT06972992), a randomized, double-blind, placebo-controlled U.S. study in adults with obesity evaluating a single ultra-long-acting ASC47 depot dose combined with four weekly doses of semaglutide 0.5 mg, versus placebo plus the same semaglutide schedule, over a 4-week treatment period with 6-week follow-up ($n = 28$) [94]. Given the short duration, the primary translational value is proof-of-concept for add-on efficacy, tolerability, and pharmacology rather than definitive body-composition outcomes (fat versus lean mass was explicitly not an objective over 28 days) [94]. These short-duration, small-cohort data have been reported by the sponsor and should be interpreted as exploratory. At day 29, the semaglutide-only arm achieved ~2.5% weight reduction from baseline, while ASC47 add-on effects were dose-dependent: 30 mg ASC47 plus semaglutide ($n = 6$) was reported to produce a 56.2% greater relative reduction in body weight compared with semaglutide alone ($n = 7$); 60 mg ASC47 plus semaglutide ($n = 9$) produced a 15.1% greater relative reduction; and 10 mg did not add benefit, consistent with sponsor-reported biomarker evidence of insufficient target engagement at that dose [94]. Mechanistically, Ascleitis used sex hormone-binding globulin (SHBG) as a PD readout for THR β engagement, reporting that SHBG responses at 10 mg were below the threshold required for clinical effect, whereas both 30 mg and 60 mg showed target engagement [94]. Cardiometabolic directionality was also emphasized: LDL-C reductions were reported as significant in

the 30 mg and 60 mg groups versus semaglutide monotherapy, again suggesting that the 10 mg dose was sub-therapeutic [94].

A distinctive element relevant to a “monthly maintenance” narrative is the sponsor-reported rebound signal after discontinuation. In ASC47-103, the ultra-long-acting ASC47 depot was reported to have an observed half-life of up to ~30 days, accompanied by less post-treatment rebound versus semaglutide alone [94]. Four weeks after discontinuation (day 57), the semaglutide-only arm’s initial day-29 weight loss was reported to rebound by 68% (to ~0.8% below baseline) [94]. In contrast, the 30 mg ASC47 arm was reported to show a 157.1% greater relative reduction in body weight versus semaglutide alone at day 57, and the 60 mg arm a 110.4% greater relative reduction; pooled (30 + 60 mg) analysis was described as a 129.9% greater relative reduction [94]. These relative metrics require cautious interpretation in small cohorts and short trials; nonetheless, the pattern is directionally consistent with the company’s hypothesis that a long-acting THR β component could serve as a “maintenance scaffold” when incretin exposure stops or is interrupted [94].

Tolerability signals—if reproducible—are among the most differentiating sponsor-reported claims. Under the study’s non-titrated semaglutide schedule, vomiting incidence was reported as 6.7% with ASC47 add-on versus 57.1% in the semaglutide-only group [94]. The sponsor also reported no thyroid-related adverse events; thyroid function tests within normal limits (TSH, FT3/TT3, FT4/TT4); normal telemetry and ECGs; and no increases in heart rate or QTc—points directly relevant to historic regulatory sensitivities around thyroid-axis pharmacology [94]. If sustained in larger studies, this combination profile would support ASC47’s most plausible clinical role: not as a high-efficacy monotherapy, but as a monthly add-on aimed at improving tolerability and persistence while preserving (or extending) weight-loss effects across dosing gaps [94].

Finally, ASC47’s positioning is tightly linked to Ascletis’ broader once-monthly metabolic strategy, but combination claims must be interpreted within the limits of current evidence. To date, combinations of ASC47 with a GLP-1R/GIPR dual agonist (ASC35) have been demonstrated only in preclinical diet-induced obese mouse models, where ASC47 plus the dual incretin peptide reportedly outperformed ASC47 combined with tirzepatide [88]. In contrast, human combination data exist only for ASC47 with semaglutide, as shown in ASC47-103 [94]. Accordingly, ASC47 should presently be viewed as an early clinically supported adjunct to incretin therapy via semaglutide, while ASC35-based combinations remain preclinical and hypothesis-generating [88,94]. ASC47 therefore represents one of the first attempts to integrate monthly metabolic remodeling with satiety-based pharmacology within a single long-interval therapeutic framework.

4.10. AT-7687: GIPR Peptide Antagonist with Extended-Interval Development Intent

AT-7687 is Antag Therapeutics’ peptide-based antagonist of GIPR, developed as a complementary strategy to incretin agonism rather than as a stand-alone weight-loss agent. The program targets suppression of GIP signaling, a pathway genetically and pharmacologically linked to adiposity, insulin resistance, and dyslipidemia, while remaining compatible with GLP-1-based therapies [24,25]. Preclinical data provide the primary rationale for its development. In non-human primates, AT-7687 showed high antagonistic potency at GIPR (pK_B $\approx$ 9.5), an observed half-life of ~27 h, and favorable metabolic effects without reported GI adverse events [25]. In these models, AT-7687 prevented weight gain as monotherapy and enhanced weight loss when combined with a GLP-1 RA, alongside improvements in glucose and lipid parameters [25]. Collectively, these findings position AT-7687 as a potential tolerability- and durability-enabling adjunct rather than a maximal-efficacy monotherapy [25].

In 2025, Antag initiated a first-in-human, randomized, double-blind, placebo-controlled phase 1a study to assess safety, tolerability, and PK in healthy individuals and participants with obesity [95]. While efficacy data remain pending, the development strategy explicitly prioritizes future combination studies with GLP-1 RAs, particularly for patients who are inadequate responders or intolerant to incretin-associated GI effects [95]. AT-7687 is currently being evaluated as a once-weekly injectable, and the sponsor has stated that a once-monthly formulation is under development [95]. Within the context of extended-interval obesity pharmacotherapy, AT-7687 represents a mechanistically orthogonal approach aimed at improving the durability and tolerability of incretin-based regimens rather than competing directly on maximal weight-loss efficacy.

5. Clinical Positioning and Future Role of Extended-Interval Therapies

The emergence of once-monthly injectable incretin-, amylin-, and THR β -based agents is not merely a formulation upgrade; it is a deliberate attempt to reframe chronic metabolic pharmacotherapy around persistence. Weekly GLP-1-based regimens demonstrate that sustained receptor engagement can transform weight and glycemic trajectories, yet real-world discontinuation, intermittent access, and treatment fatigue remain major frictions in long-term care [11,12,29,30]. Once-monthly dosing should therefore be viewed as a strategy to reduce regimen burden while preserving durable PD coverage—an objective that is technically feasible but clinically non-trivial, because longer intervals narrow the margin for missed doses, limit titration flexibility, and prolong exposure when adverse effects occur [18,53–57]. In this context, the pivotal question is not whether monthly dosing is possible (it is, as shown by maridebart cafraglutide), but where it adds incremental clinical value relative to established weekly standards, and for whom [14]. The developmental maturity of these programs is highly heterogeneous, with maridebart cafraglutide currently representing the most advanced clinical example of true once-monthly dosing, while most other candidates remain in early clinical or preclinical stages (Figure 2).

5.1. Who Benefits Most from Monthly Dosing?

In routine practice, the most compelling candidates for monthly regimens may not be those seeking maximal short-term weight loss, but those in whom persistence is the limiting factor. Patients who have already demonstrated benefit from incretin therapy yet struggle with weekly injection routines, device fatigue, or recurrent disruptions in access may derive disproportionate value from a monthly schedule—if efficacy and tolerability are maintained across the full dosing cycle [11,12,31,32,35]. The value proposition is strongest when monthly dosing converts intermittent, stop–start use into stable longitudinal treatment, particularly in obesity care where pharmacotherapy is frequently perceived as optional despite the chronicity of the disease [29,30]. At the same time, extended intervals create a paradox: fewer injections may improve acceptability, but any missed or delayed administration can carry larger clinical consequences if trough exposure at the end of the interval permits appetite or glycemic rebound [18,53–57]. As such, monthly regimens will likely require explicit adherence scaffolding (structured follow-up, reminder systems, proactive refills) to prevent “silent discontinuation” that becomes apparent only after weight regain or glycemic drift. In practical terms, the earliest and most realistic use case is likely maintenance after response induction in obesity care and in T2D patients already stabilized on incretin therapy, rather than de novo initiation in highly symptomatic or medically complex presentations.

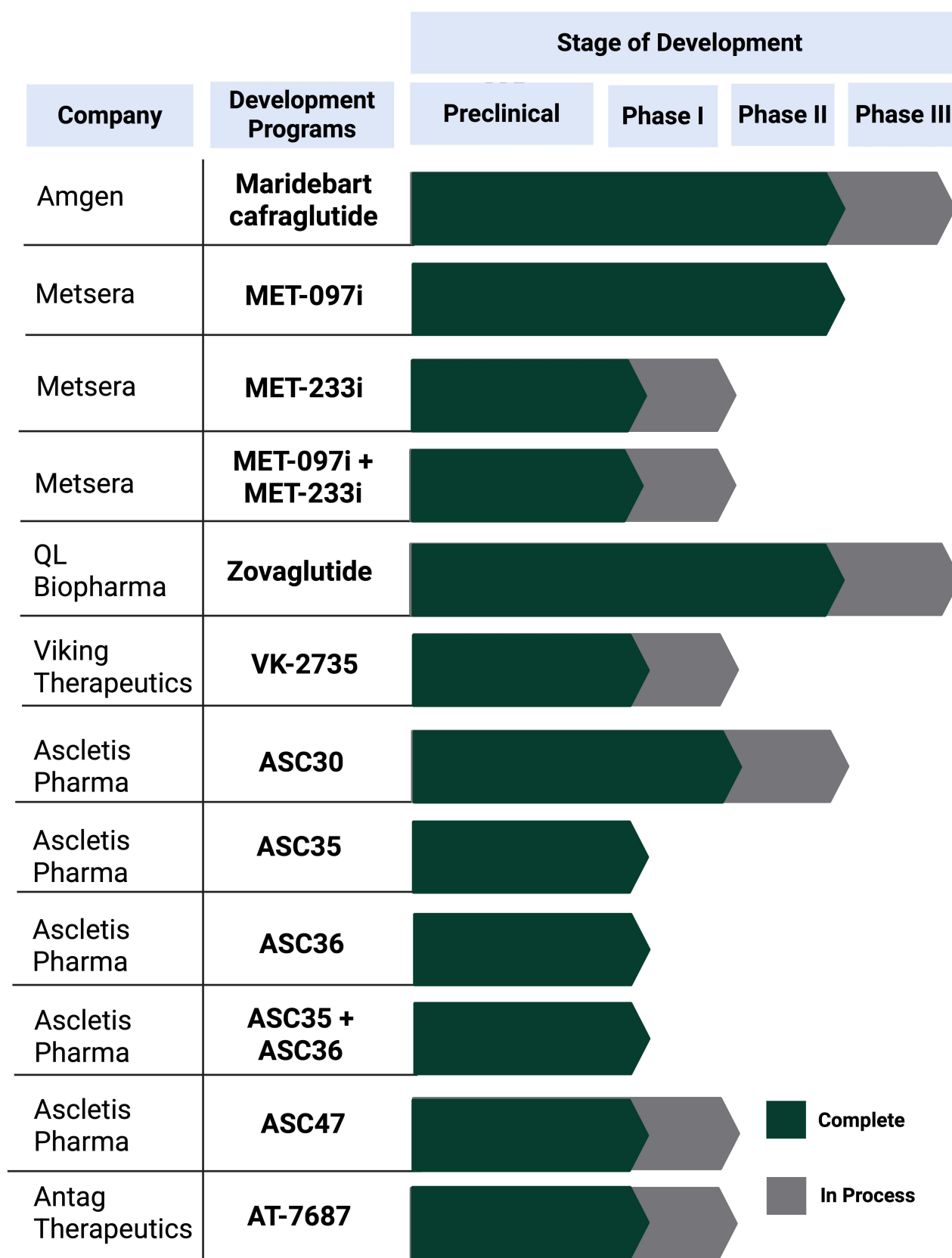


Figure 2. Clinical development status of extended-interval injectable therapies (monthly or longer) and induction-to-monthly maintenance programs for obesity and T2D. Dark green bars indicate development stages completed, and gray bars indicate stages ongoing at the time of writing. Program stage is based on publicly available sponsor disclosures and trial registries and may change as studies progress.

5.2. Induction-to-Monthly Maintenance and Switching Strategies

A central practical insight from current pipelines is that “true once-monthly from day 1” may not be the dominant use case. Several programs implicitly support an induction-to-maintenance paradigm: initial weekly titration to establish early momentum and tolerability, followed by exposure-matched monthly maintenance once a stable response is achieved [14,70–72,84]. This is aligned with PK/PD realities—ultra-long-acting agents approach steady state slowly, and overly rapid escalation can amplify GI adverse events that may then persist for weeks [18,53–57]. MariTide also provides an important boundary condition: extending intervals beyond monthly (e.g., every 8 weeks) appears to attenuate benefit, consistent with a threshold model in which receptor engagement must remain above a critical minimum across the dosing cycle to preserve metabolic effects [14]. Switching from weekly incretin therapy to a monthly agent similarly raises understudied practical questions. Ultra-long-acting exposure limits rapid reversibility; overlap during switching could prolong intolerance, while excessive washout could permit symptomatic rebound. Until formal switching studies exist, transitions should prioritize tolerability, avoid unnecessary exposure stacking, particularly when transitioning from agents with long terminal half-lives or depot formulations, and allow longer observation windows before concluding that a stable monthly “maintenance equilibrium” has been reached [18,53–57].

5.3. Practical Constraints: Tolerability, Safety Monitoring, Access and Cost

Monthly regimens magnify a core feature of long-acting incretin pharmacology: adverse effects can last longer because clearance is slow [18,53–57]. GI symptoms remain class-defining and are strongly influenced by dose and titration speed; therefore, monthly products will require disciplined titration frameworks and proactive counseling to prevent early discontinuation [18,53–57]. In parallel, rapid and sustained weight loss increases the background risk of gallbladder events, and while no consistent unexpected pancreatic or biliary signals have dominated leading programs to date, long-term surveillance and outcomes-grade evidence remain decisive for definitive clinical positioning [5–7,60–62]. Access and economics may ultimately be as determinative as biology. Monthly dosing could simplify distribution and reduce device count per patient-year, but it also concentrates therapeutic value into fewer administrations—meaning supply interruptions may be more clinically disruptive if a scheduled monthly dose is missed [11,12]. Cost-effectiveness will depend on whether monthly regimens measurably improve persistence and long-term outcomes relative to weekly comparators, not merely whether they reduce injection frequency [29,30]. Finally, the pipeline’s move beyond incretins toward amylin and THR β suggests that once-monthly therapy may evolve primarily as combination architecture rather than as a single-mechanism alternative. For monthly dosing to become a new standard rather than a niche convenience, later-phase trials must demonstrate durable maintenance, acceptable long-term safety, and real-world persistence advantages that withstand cost, access, and behavioral constraints [14,18,53–57]. Clinical implementation will also require pragmatic guidance for acute illness, prolonged fasting, and peri-procedural management, given delayed gastric emptying and limited reversibility with ultra-long-acting exposure.

6. Discussion

The transition from once-weekly to once-monthly injectable therapies in obesity and T2D is being driven by a clinically credible premise: durable metabolic benefit requires sustained pharmacologic coverage, yet sustained coverage in real-world care is frequently constrained by persistence, access, and treatment fatigue. Extended-interval dosing should therefore not be framed as a purely cosmetic convenience upgrade but rather as a deliberate redesign of chronic metabolic pharmacotherapy around continuity of exposure—an

objective that is technically feasible but clinically demanding, as longer dosing intervals inherently reduce flexibility for rapid dose adjustment and prolong exposure when adverse effects occur. Within this evolving landscape, maridebart cafraglutide (MariTide) currently represents the clearest proof-of-concept that clinically meaningful metabolic efficacy can be achieved with a true once-monthly regimen. In a phase 2 trial, once-monthly maridebart produced substantial weight reduction in adults with obesity with or without T2D, with mean weight loss in the obesity cohort in the ~12–16% range and in the obesity–T2D cohort in the ~8–12% range at 52 weeks, accompanied by clinically relevant HbA1c reductions in the T2D cohort. Importantly, exploratory every-8-week regimens demonstrated attenuated efficacy relative to monthly dosing, supporting a threshold model in which receptor engagement must remain above a critical minimum across the entire dosing interval to preserve appetite and glycemic effects [1–4,14,18].

However, MariTide establishes feasibility rather than definitive clinical positioning. Several uncertainties remain central. First, durability beyond one year is unresolved, particularly in obesity, where long-term maintenance and relapse prevention ultimately determine clinical value. Second, comparative advantage over best-in-class once-weekly GLP-1 RA-based regimens cannot be inferred from separate trials and will require either direct head-to-head studies or robust comparative-effectiveness analyses. Third, ultra-long-acting exposure alters the practical management calculus: titration discipline, anticipatory tolerability counseling, and conservative dose escalation become more consequential, as adverse effects may persist longer and rapid PD de-escalation is inherently limited.

A second defining feature of the once-monthly field is that pipeline expansion is currently outpacing the peer-reviewed evidence base. Beyond MariTide, many extended-interval-intent programs rely predominantly on sponsor communications, conference disclosures, or early-phase trial descriptions rather than fully adjudicated publications. This evidentiary asymmetry is particularly consequential for ultra-long-acting agents, as short-term tolerability snapshots may fail to capture prolonged symptom burden, accumulation dynamics, delayed-onset events, or the clinical consequences of missed or delayed doses within a long-interval schedule. If monthly dosing requires clinicians and patients to accept fewer administrations with greater pharmacologic commitment per dose, transparency regarding dose selection, titration logic, immunogenicity, and discontinuation management must be at least as rigorous as that established during the once-weekly GLP-1 RA era [18,33–35,55–58].

A key limitation of this narrative review is that the evidence base for many extended-interval metabolic programs is early and heterogeneous. With the exception of maridebart cafraglutide (peer-reviewed phase 2), multiple pipeline assets are supported largely by sponsor and conference disclosures rather than full peer-reviewed publications, which limits methodological granularity, reproducibility, and clinical extrapolation and may be subject to selective reporting. Accordingly, quantitative estimates for investigational assets should be interpreted as provisional and hypothesis-generating; longer-term durability, uncommon adverse events, and heterogeneity of response remain incompletely characterized, particularly for ultra-long-acting agents with limited reversibility.

Biological heterogeneity in treatment response represents a third axis that may ultimately determine whether once-monthly therapies become broadly transformative or selectively useful. The marked interindividual variability observed with GLP-1 RAs and GLP-1/GIPR dual agonists reinforces that obesity is not a physiologically homogeneous condition. A plausible explanatory framework positions individuals along a secretion-responsiveness spectrum of incretin effectiveness, ranging from relative hyposecretion to functional forms of incretin resistance, in which circulating incretin levels may be preserved or elevated but downstream insulinotropic and metabolic effects are attenuated—classically

reflected in an impaired incretin effect involving both secretion and β -cell responsiveness [5–9,59,64]. Monthly dosing may amplify this heterogeneity: individuals near the exposure threshold required for stable appetite suppression may be more vulnerable to end-of-interval troughs, whereas others with prolonged PD carryover may maintain benefit with lower-frequency maintenance once a new weight equilibrium is achieved.

This variability reframes why “monthly” may matter most as a platform for mechanistic diversification rather than as a simple alternative to once-weekly incretin therapy. MariTide itself already exemplifies a qualitative shift within the incretin axis—GLP-1 RA biology combined with sustained GIPR antagonism—underscoring that altering pathway biology, not merely dosing frequency, can be clinically meaningful [1–3,20]. In parallel, long-acting amylin analogs, THR β agonists, and non-peptide or biased small-molecule GLP-1 RAs expand beyond classical incretin biology, raising the possibility that some patients with attenuated incretin responsiveness may preferentially benefit from therapies that engage satiety, energy handling, or adipose-selective pathways through complementary mechanisms [22–24,40,96,97]. As monthly regimens mature, the most clinically informative trials may therefore be those that move beyond mean efficacy and incorporate response-dispersion metrics, end-of-interval stability, body-composition outcomes, and biomarker-enabled stratification strategies that support mechanism-matched therapy selection.

Ultimately, several inflection points will determine whether once-monthly therapies redefine routine metabolic care or remain a niche convenience layer. The first is durability and maintenance: sustained efficacy beyond one year, accompanied by clear guidance on missed doses and discontinuation in long half-life contexts. The second is long-term safety and outcomes: extended surveillance and, where appropriate, outcomes programs capable of establishing benefit–risk profiles comparable in credibility to the evidence that legitimized once-weekly GLP-1 RA standards in T2D. The third is real-world value: demonstration that monthly schedules meaningfully improve persistence and effectiveness relative to weekly comparators, sufficiently to justify likely premium pricing and to withstand access and supply constraints that have challenged the current incretin era [11,26–30,96]. Until these conditions are met, once-monthly therapies should be viewed as a promising, mechanistically expanding platform—anchored by MariTide proof-of-concept—but still in the process of earning their definitive clinical role.

Table 1. Pharmacologic and molecular design features of established weekly incretin therapies and emerging ultra-long-acting injectables enabling once-monthly dosing in T2D and obesity.

Asset	Primary Target	Secondary Target	Reported Half-Life *	Dominant Half-Life Extension Strategy	References
Native GLP-1	GLP-1R	—	~1.5–2 min	Rapid DPP-4 degradation and renal clearance (no protection)	[8]
Native GIP	GIPR	—	~5–7 min	Rapid DPP-4 degradation and renal clearance (no protection)	[9]
Liraglutide	GLP-1R	—	~13 h (~0.5 days)	Fatty-acylation → high albumin binding, reduced clearance	[45]

Table 1. Cont.

Asset	Primary Target	Secondary Target	Reported Half-Life *	Dominant Half-Life Extension Strategy	References
AT-7687	GIPR antagonism	—	~27.4 h (~1.1 days)	Long-acting peptide engineering (program-specific)	[25]
Tirzepatide	GIPR	GLP-1R	~120 h (~5 days)	Albumin binding via fatty-acid moiety	[52,56,61]
Semaglutide	GLP-1R	—	~168 h (~7 days)	Albumin binding via fatty-acid moiety	[50,55,60]
VK-2735	GLP-1R	GIPR	~170–250 h (~7–10 days)	Long-acting peptide scaffold (program-specific)	[21,80–86]
Zovaglutide	GLP-1R	—	~260–273 h (~11 days)	Extended half-life GLP-1 analog (likely acylation/albumin-binding based)	[76–78]
MariTide (maridebart cafraglutide)	GLP-1R	GIPR antagonism	~343–396 h (~14–16 days)	Peptide–antibody conjugate with FcRn recycling; markedly reduced clearance	[14,20]
MET-097i	GLP-1R	—	~15–16 days	NuSH™ HALO proprietary ultra-long-acting engineering (controlled release + reduced clearance)	[47–49,69–72]
ASC36	Amylin receptor	—	~15 days	ULAP depot exposure + high intrinsic potency (AISBDD/POTENT)	[92,93]
MET-233i	Amylin receptor	—	~19 days	NuSH™ HALO proprietary ultra-long-acting engineering	[22,73–75]
ASC35	GLP-1R	GIPR	$t_{1/2} \geq 30$ days	ULAP ultra-long-acting peptide engineering (with AISBDD-guided potency optimization; POTENT)	[91,92]
ASC47-103	THR β	—	~26–40 days	ULAP long-acting depot exposure (with AISBDD-driven adipose-selective THR β agonism; POTENT)	[94–96]
ASC30	GLP-1R	—	~36 days	AISBDD-derived potent small-molecule GLP-1RA formulated via ULAP subcutaneous depot	[87–89]

* Half-life values are approximate and reflect reported or inferred terminal elimination half-life where available. For assets in early development, estimates may derive from conference or sponsor disclosures and may represent observed human data, projected human half-life based on translational modeling/cross-species scaling, or program-level targets rather than fully peer-reviewed clinical pharmacokinetic reports. The em dash (—) indicates “not applicable” (i.e., no secondary target). AISBDD, AI-assisted structure-based drug design; ULAP, Ultra-Long-Acting Platform; POTENT, Peptide Oral Transport Enhancement Technology.

7. Conclusions

Once-monthly injectable therapies are emerging as a credible next step in chronic pharmacologic management of obesity and T2D, aiming to reduce injection burden while preserving sustained metabolic efficacy. Maridebart cafraglutide currently provides the strongest proof-of-concept, demonstrating clinically meaningful improvements in body weight and glycemic control with monthly dosing, while also suggesting that extending dosing intervals beyond monthly may attenuate efficacy in this format.

Beyond this lead program, the pipeline is rapidly expanding across incretin-, amylin-, and THR β -based platforms, but definitive clinical positioning will depend on evidence that monthly regimens deliver durable long-term maintenance, acceptable safety under prolonged exposure, and real-world persistence advantages that justify cost and access constraints. As these programs mature, physiology-informed stratification and response-stability metrics—particularly end-of-interval control—may be essential to match extended-interval therapies to the biological heterogeneity that underlies variable treatment response in obesity and T2D.

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Abbreviations

The following abbreviations are used in this manuscript:

AI	Artificial intelligence
AISBDD	AI-Assisted Structure-Based Drug Discovery
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
GI	Gastrointestinal
GIP	Glucose-dependent insulintropic polypeptide
GIPR	Glucose-dependent insulintropic polypeptide receptor
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated hemoglobin
IND	Investigational New Drug
LDL-C	Low-density lipoprotein cholesterol
NCT	ClinicalTrials.gov identifier
NuSH	Nutrient-stimulated hormone
PD	Pharmacodynamics

PK	Pharmacokinetics
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
QTc	Corrected QT interval
SHBG	Sex hormone-binding globulin
SQ	Subcutaneous
T2D	Type 2 diabetes
THR β	Thyroid hormone receptor beta
TSH	Thyroid-stimulating hormone
ULAP	Ultra-Long-Acting Platform

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