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Perspective

Long-Acting, Longer-Acting, and Ultralong-Acting Antiobesity Peptides

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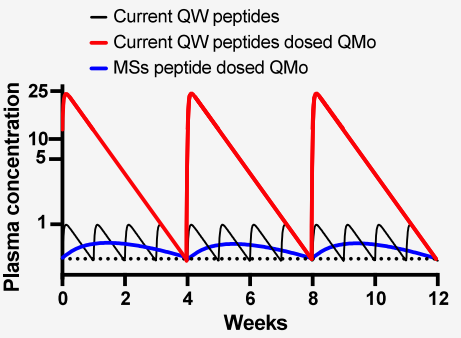
ABSTRACT: This perspective describes the current status and future prospects of developing long- to ultralong-acting anti-obesity peptides. First, we discuss the current status of lipidation, PEGylation, and Fc fusion technologies to obtain long-acting peptides administered once weekly, and we critique their proposed use for longer dosing intervals. Next, we describe the approach and current results of using macromolecular peptide prodrugs with preprogrammed releasable linkers to achieve longer-acting peptides that can be administered weekly or monthly. Finally, we posit novel modifications of the latter technology that could provide ultralong half-lives of over one month by advantageously exploiting the clearance rates of released peptides. As examples, we posit that prodrugs of low-clearance GLP-1 agonists derived from peptides already modified by lipidation, PEGylation, and Fc fusion could produce ultralong-acting agonists with dosing intervals reaching 3 to even 6 months.



INTRODUCTION

There is a renaissance of interest in incretin-based peptides as treatments for obesity and other conditions. As an example, peptidic GLP-1 receptor agonists (GLP-1RAs) are mainstays of treatments for T2D and obesity, and are potential therapies for MAFLD and age-related diseases such as Parkinson's and Alzheimer's. However, a problem is that therapeutic peptides have short in vivo half-lives of minutes to hours and require some form of half-life extension to make them practical for use as therapeutics. The most common half-life extension technologies used for peptides include lipidation, PEGylation, and Fc fusions, all of which require weekly administration.[1] Since the half-life is limited by the technology's mechanism of half-life extension, it is unlikely that longer-acting peptides can be achieved using these approaches per se.[1]

It has been well established that persistence and adherence in GLP-1 agonist use are low and is a very large problem.[2−4] In part, this is caused by the adverse GI effects that are so common with GLP-1 receptor agonists. Persistence and compliance in anti-obesity drug use can be significantly increased by reducing the dosing frequency.[4,5] Also, the GI toxicity of GLP-1 agonists is related to dosing frequencies in the order twice daily (BID) > once-daily (QD) > once-weekly (QW), which is thought to reflect the higher C_{max} or C_{max}/C_{min} of BID and QD drugs.[5] Hence, GI effects are less common with long-acting than short-acting compounds, and the earlier shorter-acting peptide agonists have been displaced by those that can be administered weekly. For the future, it would be beneficial to obtain peptides that have optimized pharmacokinetic profiles that allow dosing intervals longer than 1 week, such as once-monthly (QMo) and perhaps even longer than one month.

Achieving an optimal pharmacokinetic profile requires a balance between half-life and dosing. To keep a peptide above its minimal therapeutic level, C_{min}, the optimal half-life is about equal to the dosing interval, and the optimal dose is the minimum dose that maintains plasma concentrations above the therapeutic C_{min} for the dosing interval. With peptides having a shorter half-life than dosing interval, it is often common practice to maintain the concentration above C_{min} by increasing its dose and risking C_{max}-related toxicities. For example, AMG133—a GLP-1 agonist/GIP antagonist mAb—has a half-life of 14 days yet is dosed every month;[6] here, administering sufficient drug to maintain C_{min} for two half-lives does not cause adverse effects. However, at some point, increasing the dose and C_{max} to achieve longer-acting agents will undoubtedly cause toxicities.

It would be timely and impactful to develop approaches to obtain longer-acting and ultralong-acting peptides that allow less frequent dosing. As examples, longer acting GLP-1 agonists should increase convenience and decrease some toxicities. Advanced systems for drug delivery would also mitigate many common impediments to adherence,[7] which is a major problem with GLP-1RAs.[3]

Here, we discuss the technologies to obtain long-acting peptides that are administered once weekly, our approach to

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Table 1. GLP-1 Receptor Agonists That Have Been Proposed to Be Suitable for QMo Dosing[12]

Product	Company	Receptor target	Drug type	Half-life, day[b]	Current dosing interval, week	Dose and C_{max} increase to maintain C_{min} over 1 mo[c]	
						based on dosing interval = half-life	based on current dosing interval used
PG-102	Progen	GLP-1/GLP-2	Fc fusion	5.0	1	24	18
efpeglenatide	Hanmi	GLP-1/GLP-2	Fc fusion	6.5	1	10	10
MBX4291	MBX	GLP-1/GIPR	acyl-peptide[a]	6.0	1	13	11
VK2735	Viking	GLP-1/GIPR	acyl-peptide[a]	8.8	1	5	5
ZT002	QL Bio	GLP-1	acyl-peptide[a]	11	1	3	4
AMG133	Amgen	GIP(ant)/GLP-1	mAb	14	4	2	1

[a]Lipidated peptide. [b]Half-lives as reported or estimated from available data;[12] median $t_{1/2}$, if range is reported; [c]Calculated as dose increase = $D\tau_2/D\tau_1 = e^{-\ln 2/t_{1/2}(\tau_1-\tau_2)}$, where τ_1 and τ_2 are the dose intervals compared and $D\tau$ is the dose for a specified dose interval.

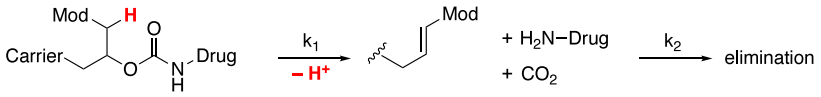

Figure 1. β-Eliminative release of a drug from a carrier–linker–drug conjugate.

create longer-acting peptides administered once monthly, and a new approach we posit will allow ultralong-acting peptides that can be administered at even less frequent intervals of 3 months or maybe even 6 months.

Long-Acting Peptides: Lipidation, PEGylation, and Fc Fusions. Following are brief descriptions of the three major technologies currently used for half-life extension of peptides that allow QW administration—lipidation, PEGylation and Fc fusion. First, lipidation covalently connects a fatty acid to a peptide. The fatty acid moiety tightly and reversibly binds to serum albumin, and converts the parent peptide's half-life ($t_{1/2}$) from about 1 h to about 1 week by piggybacking on the long-lived albumin.[8,9] The intense efforts of pharmaceutical companies have achieved enormous success in optimizing lipidation for half-life extension of peptides.[8] But, the price paid for half-life extension by lipidation is the high dose of peptide needed to bind the albumin sink yet provide a sufficient amount of active free lipidated peptide to exert its intended activity. Second, PEGylation permanently connects a high molecular weight PEG polymer—optimal at about 40 kDa—to the peptide to retard renal filtration. However, 40 kDa PEG itself has an elimination half-life of about 6 days in humans, limiting half-life extension so PEGylated peptides and proteins require at least QW administration.[1,10] Finally, fusions of peptides to the Fc fragment of an IgG show a longer half-life because of the approximately 50 kDa increase in size and Fc recycling.[11] Many scientists unfamiliar with specifics of the technology assume Fc fusions have half-lives similar to IgG or therapeutic antibodies; however, the average half-life of Fc fusions is just 4 to 5 days, which best supports QW administration.[11] It is likely that some agonists may not have a tight PK/PD relationship so the PD effect may be longer than the PK might predict. For example, a single dose of AMG133 caused weight loss at day 150, at which time the drug was long-gone. In summary, the three most frequently used technologies for half-life extension of peptides seem to be best suited for QW administration.

Regardless, longer-acting peptides are highly sought after and it is asserted that many such agonists can be used for QMo administration. Except for agonists having uncoupled PK/PD, the most common way to achieve this is by increasing the dose to maintain the therapeutic C_{min} over an extended interval.

An example of this approach is AMG 133, which has a $t_{1/2}$ of 14 days, but can be dosed in an amount 2-fold higher than its $t_{1/2}$ that keeps the concentration above C_{min} for a month without adverse effects (Table 1). Another example is VX2735—the tirzepatide parent peptide with a different lipid—which would require a 5-fold increase in dose to keep it above C_{min} for a month. Clearly, at some point, the increase in C_{max}/C_{min} needed to maintain therapeutic C_{min} for dosing intervals much longer than the half-life of a peptide will become problematic.

Table 1 shows GLP-1RA-containing anti-obesity agents with half-lives of 5 to 14 days that have been **proposed** as suitable for QMo dosing. Also shown are the estimated dose and relative C_{max} increases necessary to keep the drug above a therapeutic C_{min} for one month compared to (a) the dose needed and resultant C_{max} for dosing intervals equal to the half-life and (b) the dose and C_{max} for currently used dosing intervals, typically 1 week.

It can be seen that the monthly doses are inversely related to the half-life of the drug: the shorter the half-life, the higher the dose, and the greater the risk for C_{max}-related toxicities. While AMG133 appears effective and safe with QMo dosing, data are unavailable to assess the other peptides. Hence, while some peptides might tolerate higher dosing and C_{max} to achieve QMo dosing intervals, many would likely breach their tolerance barrier and cause unacceptable toxicities. A more promising approach would be to develop technologies that could overcome the barriers to QMo administration.

Longer-Acting Peptides: Prolonged Drug Release from Microsphere (MS)–Peptide Prodrugs. We have developed a general approach for half-life extension of therapeutics that theoretically allows the achievement of any desirable half-life.[13,14] Practically, peptide half-lives of over 2 months have been achieved, and achieving temporal drug exposure is not the limitation of the technology.[15,16] Rather, the limitation is imposed by the stability of the peptide and the dose needed to supply sufficient drug over the desired dosing interval. In our approach, a drug is covalently tethered to a long-lived carrier by a linker that cleaves in a base-catalyzed β-elimination rate-determining step, k_1 (Figure 1).[17] All subsequent steps are faster, so the rate of drug release directly reflects that of this first step. The cleavage rate of the linker is controlled by the nature of an electron-withdrawing "modu-

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lator" (Mod) which regulates the acidity of an adjacent carbon−hydrogen bond. Since the in vitro and in vivo cleavage rates follow a tight structure−activity relationship with the electron-withdrawing ability of the modulator, cleavage rates are predictable and tunable, and the in vitro−in vivo correlation is high.[18] After release of the active drug, the drug is cleared from the system by elimination rate k_2 which, by design, is faster than cleavage k_1. Also, the releasable linkers are not affected by enzymes and are extraordinarily stable when stored at lower pH and temperature.[13,19]

With this system, the pharmacokinetics can be easily and accurately simulated and modeled.[15,18] This is because there are only two relevant processes that define the pharmacokinetics: k_1, the slow cleavage rate of the linker, and k_2, the faster elimination rate of the released drug. The rate-determining linker cleavage manifests as the in vivo half-life of the released drug, $t_{1/2,1}$, but—perhaps unintuitively—the elimination half-life, $t_{1/2,2}$, of the released drug manifests in the steady-state concentration of the drug.

An important differentiating feature of this half-life extension technology from others is that drug release is chemically controlled, so in vivo half-lives are species-independent;[13,15,20] they can be determined in the mouse and be translated to man. In contrast, half-lives of lipidated, PEGylated and Fc fusion peptides, are species-dependent and have shorter half-lives in rodents than humans; translation from preclinical models to humans requires oft-risky allometric scaling.

One carrier we use is a mesoporous tetra-PEG hydrogel to which a drug can be tethered via a releasable linker.[14,21] These hydrogels—fabricated as uniform ∼50 μm microspheres (MS)[22,23]—are injected subcutaneously (SC) through a small-bore 29G needle—similar to what is used with lipidated peptides—where they sit at the injection site as a stationary SC depot and slowly release the drug to the systemic circulation. These MSs show no adverse injection site reactions or potential safety issues in preclinical models. We also incorporate slower-cleaving β-eliminative linkers in cross-links of these polymers with half-lives longer than the linker used for drug release, so programmed gel degradation occurs in vivo after drug release.[22]

Proofs of concept for the effectiveness of the technology for peptides reside in its success in providing longer-acting MS prodrugs of [Gln^{28}]exenatide[15] and semaglutide[24] that show ≥30 day half-lives. Since GLP-1 agonists like AMG133 can be safely dosed at least 2-fold higher than needed to maintain C_{min} over one-half-life,[6] the same should be true with these GLP-1 agonists. Hence, with the ∼30 day half-life of [Gln^{28}]exenatide when released from microspheres, it should be possible to achieve Q2Mo or longer dosing by administering 2-fold more drug than needed to maintain C_{min} over one-half-life. To our knowledge, other than a few peptides delivered from polymeric depots and devices, [Gln^{28}]exenatide[15] and semaglutide[24] when released from microspheres are the only peptides thus far reported with half-lives of 1 month that can be dosed at 1 month or longer intervals.

Expectedly, there is a strong preference among patients for longer-acting agonists, but since there are no approved incretin-based agonists with half-lives longer than ∼1 week, there are no real-world data on benefits or detriments of longer-acting peptides. However, if advantages of longer-acting agonists mirror those of QD vs QW agonists,[7] we project positive effects on patients' preference, persistence, and compliance. Also, QW dosing of GLP-1RAs gives lower side effects than BID and QD dosing due to C_{max} effects.[5] Once-monthly or longer dosing intervals using the optimal half-life will give even lower C_{max} and C_{max}/C_{min} values and could lower associated toxicities even more. This is nicely exemplified by comparing the concentration vs time profiles of released, unmodified semaglutide after multiple dosing of QW semaglutide to a simulation of the QMo MS∼semaglutide that has been fit to the therapeutic window of QW semaglutide (Figure 2).[24,25] Here, QMo MS∼semaglutide maintains the

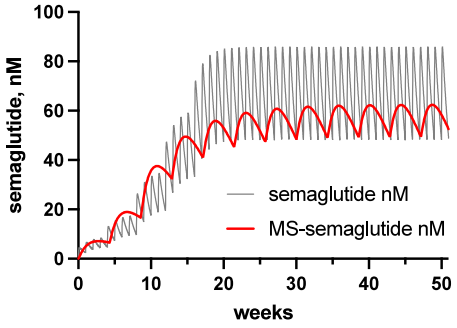

Figure 2. Simulated concentration vs time of semaglutide vs QMo MS∼semaglutide in humans. QW semaglutide dose escalation uses pharmacokinetic data for the recommended 4 weeks each of 0.25 mg, 0.5 mg, 1 mg, and 1.7 mg followed by 2.4 mg per week.[25] QMo MS∼semaglutide shows drug concentrations for single doses of 2.5 mg, 5 mg over two months followed by 9 mg/month. Modeling of SC semaglutide and MS∼semaglutide was performed using two and three sequential first-order reactions, respectively, as described.[26]

therapeutic C_{min} of QW semaglutide with only 75% of the C_{max}, and a lower C_{max}/C_{min}. Hence, we posit that compared to QD or QW dosing, a QMo peptide should improve tolerability—e.g. reduce GI side effects—and/or allow higher dosing.

Ultralong-Acting Peptides: Using Drug Clearance (CL) to Increase Peptide Concentration and Dosing Interval. Since the technology described here can confer almost any half-life to a drug, it should be able to achieve dosing intervals for peptides of even longer than one month—"ultralong-acting" peptides. However, delivering the amount of drug needed for longer periods in a suitable dosing volume can be a major impediment. For example, MS conjugates of the same peptide, e.g., [Gln^{28}]exenatide, with half-lives optimized to 1 and 3 months could be problematic in a dose-limiting situation since the Q3Mo conjugate would require ∼3-fold increase in dose. We recently recognized that an approach to over-ride this problem and achieve blood concentrations that mitigate problematic dose limitations is simply to use an agonist with decreased drug clearance, CL (k_2V_d/F; where V_d is the volume of distribution and F is the subcutaneous bioavailability). While the half-life is governed by the release rate, k_1, the plasma concentration of the released peptide is governed by the balance between the slow rate of peptide released into the circulation (k_1) and the rate it is cleared from the circulation (k_2). So, all else constant, the CL is inversely proportional to the peptide concentration (eq 1); hence, lowering the CL has the effect of increasing the plasma concentration.

$$C_t = \text{dose}(k_1/\text{CL})e^{-k_1 t} \quad (1)$$

From eq 1, when the release half-life is adjusted to equal the dosing interval, τ, the dose required to maintain plasma levels

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above C_{min} is given as eq 2, and the comparative doses of two different MS~peptide conjugates, A and B, is given by eq 3 where τ is the dosing interval:

$$\text{dose} = 2C_{min}(\text{CL}/k_1) \quad (2)$$

$$\text{dose}_B/\text{dose}_A = (C_{min,B}/C_{min,A})(\text{CL}_B/\text{CL}_A)(\tau_B/\tau_A) \quad (3)$$

A plentiful source of peptide agonists with reduced clearance is the collection already modified to provide QW dosing; we posit that many of these can be converted from long-acting to ultralong-acting therapeutics. As examples of how lowered clearance can alleviate dose limitations and be used to obtain effective ultralong-acting drugs, we compare simulations of the pharmacokinetics of MS conjugates of unmodified peptides with MS conjugates of peptides modified by lipidation, PEGylation, or Fc fusion.

First, we compare the pharmacokinetics of a MS conjugate of an unmodified GLP-1 peptide to MS~semaglutide, which releases the lipidated peptide with a lowered CL (Figure 3).

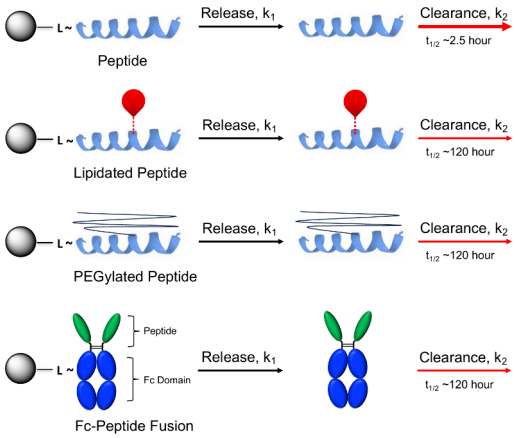

Figure 3. Depiction of the cleavage of MS prodrugs and clearance of released drugs. A β-eliminative relesable linker (L) covalently tethers the drug to MSs. The plasma concentration of the released drug is governed by the balance between k_1 and k_2, where k_1 is the rate of β-elimination and k_2 is the elimination rate.

PLX039 is a MS~[Gln^{28}]exenatide that confers a 30-day half-life to the released peptide in multiple species.[15,20] In humans, exenatide has a rapid elimination $t_{1/2,2}$ of 2.5 h and CL of 9.1 L/h, whereas semaglutide has a much lower CL of 0.05 L/h. For the same linker release rate k_1 and dose, the plasma concentrations reflect $\text{CL}_{Ex}/\text{CL}_{Sema}$ (eq 3), and the semaglutide concentration should be 180-fold higher than exenatide (Supporting Information Figure S1). However, because of the albumin sink for the lipidated peptide the effective C_{min} of semaglutide is ~500-fold higher than that of exenatide. Nevertheless, the effective molar dose of QMo semaglutide is only ~3-fold higher than that for MS~[Gln^{28}]exenatide and MS~semaglutide should be—and has recently been shown to be[24]—sufficient to prolong the dosing interval to at least 1 month (Figure S2 and S3). Hence, the decreased CL of lipidated peptides due to albumin binding enables longer half-lives, but the price paid is a requisite higher dose. The high ~50 nM C_{min} required to satisfy albumin binding makes achieving longer dosing intervals challenging, but dosing intervals up to 3 months may be possible with an increased dose or dosing volume

Similarly, we compare MS~exenatide to a MS~PEGylated exenatide (Figure 3). Pegloxenatide is a PEGylated exenatide[27] with a therapeutic target concentration, C_{min}, similar to exenatide, but a much lower CL of 0.014 L/h vs 9.1 L/h.[28] The difference in CL values means that—all else being equal—the plasma concentrations reflect $\text{CL}_{Ex}/\text{CL}_{PEGlox}$ (eq 2), and the Pegloxenatide concentration will be 650-fold higher than exenatide (Figure S1). Thus, it is estimated that the effective molar dose of a QMo MS~Pegloxenatide would be ~140-fold lower than MS~exenatide. Further, with an optimized dose and linker it should be possible to produce a much longer acting conjugate of Pegloxenatide than with exenatide. Indeed, pharmacokinetic simulations (Figure S4) indicate a MS~Pegloxenatide conjugate having a linker with a $t_{1/2,1}$ similar to the dosing interval would allow Q3Mo, and maybe even Q6Mo dosing in an injection volume of less than 1 mL.

Finally, ultralong dosing frequencies could be achieved with other peptidic drugs that are sufficiently potent and have low CL, such as Fc fusions (Figure 3). Fc fusions typically have half-lives of 4 to 5 days,[11] which, assuming similar V_ds, reflect CL. Thus, when attached to MSs the conjugates should provide higher concentrations of the fused than the nonfused peptide. And, if not too extreme, reduced potencies of Fc fusions compared to nonfused peptides can be overcome by their lower CL (eq 3). For example, the potent Fc GLP-1 fusion, dulaglutide, with a $t_{1/2,2}$ of 5 days and CL of 0.11 L/h, has an ~1 nM C_{min} that is about 10-fold higher than exenatide.[29] The difference in CL values means the released dulaglutide concentration will be 80-fold higher than the same dose of exenatide (Figure S1). This translates to either a ~100-fold lower molar dose for QMo administration, or to a longer-acting GLP-1 agonist. Our simulations (Figure S5) indicate that a MS~dulaglutide conjugate having a linker with a release half-life similar to the dosing interval would allow at least Q3Mo, and maybe even Q6Mo dosing in an injection volume of less than 1 mL.

SUMMARY

Currently, three technologies are commonly used to convert short-acting peptides to long-acting peptides that can be administered once weekly—lipidation, PEGylation, and Fc fusions. However, other than increasing doses, options to use these technologies per se to increase dosing intervals beyond 1 week are limited and would risk C_{max}-related toxicities. Using MS carriers and β-eliminative cleavable linkers, active peptides with in vivo half-lives of over one-month can be achieved. And, through fortuitous unconnected PK/PD relationships or modest ~2-fold dose increases, it should be possible to increase dosing intervals of GLP-1 agonists at least 2-fold. Furthermore, there could be huge practical impacts of using MS conjugates of potent peptides/proteins with low clearance. As examples, MS~conjugates of potent lipidated, PEGylated and Fc fusion peptides with moderate half-lives of ~5 to 7 days and low clearance could be converted to ultralong-acting peptides that could maintain therapeutic levels for up to 3 or even 6 months. Additionally, there are over 50 lipidated peptides, 100 PEGylated drugs and a similar number of Fc fusions that are approved or in clinical trials;[30] it is likely that some significant number of these would be suitable for developing biobetter longer- or ultralong-acting therapeutics.

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MATERIALS AND METHODS

Pharmacokinetic simulations were performed as reported[18] and are provided in the Supporting Information.

ASSOCIATED CONTENT

Data Availability Statement

All data are available in the main text or the Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.4c02647.

Simulation of C vs t curves and simulation results of MS∼GLP-1 agonists (PDF)

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Author Contributions

E.L.S., J.A.H., and G.W.A. designed/performed research; D.V.S. designed research/wrote the manuscript.

Notes

The authors declare the following competing financial interest(s): All authors have ProLynx shares and/or options.

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ABBREVIATIONS

BID, twice daily; CL, drug clearance; C_{max}, maximum blood plasma concentration; C_{min}, minimum blood plasma concentration; F, subcutaneous bioavailability; GLP-1RA, GLP-1 receptor agonist; MAFLD, metabolic dysfunction-associated fatty liver disease; Mod, modulator; MS, microsphere; QD, once daily; QMo, once a month; Q2Mo, once every two months; Q3Mo, once every three months; Q6Mo, once every six months; QW, once every week; Vd, volume of distribution

REFERENCES

(1) Yu, M.; Benjamin, M. M.; Srinivasan, S.; Morin, E. E.; Shishatskaya, E. I.; Schwendeman, S. P.; Schwendeman, A. Battle of GLP-1 delivery technologies. *Adv. Drug Deliv Rev.* **2018**, *130*, 113−130.

(2) Gasoyan, H.; Pfoh, E. R.; Schulte, R.; Le, P.; Rothberg, M. B. Early- and later-stage persistence with antiobesity medications: A retrospective cohort study. *Obesity (Silver Spring)* **2024**, *32* (3), 486−493.

(3) Palanca, A.; Ampudia-Blasco, F. J.; Calderon, J. M.; Sauri, I.; Martinez-Hervas, S.; Trillo, J. L.; Redon, J.; Real, J. T. Real-World Evaluation of GLP-1 Receptor Agonist Therapy Persistence, Adherence and Therapeutic Inertia Among Obese Adults with Type 2 Diabetes. *Diabetes Ther* **2023**, *14* (4), 723−736.

(4) Kassem, S.; Khalaila, B.; Stein, N.; Saliba, W.; Zaina, A. Efficacy, adherence and persistence of various glucagon-like peptide-1 agonists: nationwide real-life data. *Diabetes Obes Metab* **2024**, *26* (10), 4646−4652.

(5) Filippatos, T. D.; Panagiotopoulou, T. V.; Elisaf, M. S. Adverse Effects of GLP-1 Receptor Agonists. *Rev. Diabet Stud* **2014**, *11* (3−4), 202−30.

(6) Veniant, M. M.; Lu, S. C.; Atangan, L.; Komorowski, R.; Stanislaus, S.; Cheng, Y.; Wu, B.; Falsey, J. R.; Hager, T.; Thomas, V. A.; Ambhaikar, M.; Sharpsten, L.; Zhu, Y.; Kurra, V.; Jeswani, R.; Oberoi, R. K.; Parnes, J. R.; Honarpour, N.; Neutel, J.; Strande, J. L. A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings. *Nat. Metab* **2024**, *6* (2), 290−303.

(7) Baryakova, T. H.; Pogostin, B. H.; Langer, R.; McHugh, K. J. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. *Nat. Rev. Drug Discov* **2023**, *22* (5), 387−409.

(8) Knudsen, L. B.; Lau, J. The Discovery and Development of Liraglutide and Semaglutide. *Front. Endocrinol.* **2019**, *10*, 155.

(9) Hijazi, Y. Prediction of Half-Life Extension of Peptides via Serum Albumin Binding: Current Challenges. *Eur. J. Drug Metab Pharmacokinet* **2021**, *46* (2), 163−172.
(10) Sharda, N.; Khandelwal, P.; Zhang, L.; Caceres-Cortes, J.; Marathe, P.; Chimalakonda, A. Pharmacokinetics of 40 kDa Polyethylene glycol (PEG) in mice, rats, cynomolgus monkeys and predicted pharmacokinetics in humans. *Eur. J. Pharm. Sci.* **2021**, *165*, No. 105928.
(11) Strohl, W. R. Fusion Proteins for Half-Life Extension of Biologics as a Strategy to Make Biobetters. *BioDrugs* **2015**, *29* (4), 215−39.
(12) Data sources: (Progen) Han, S.; Han, S.; Son, K.-H.; Sung, Y. PG-102, a Novel Bispecific GLP-1R/GLP-2R Fc-Fused Agonist—Data on Safety, Tolerability, and Pharmacokinetics (PK) in Single Ascending Dose Trial in Healthy Subjects and Preliminary Population PK Modeling. *Diabetes* **2024**, *73* (Suppl 1), 1859-LB. (Hanmi) Frias, J. P.; Choi, J.; Rosenstock, J.; Popescu, L.; Niemoeller, E.; Muehlen-Bartmer, I.; Baek, S. Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE-M Randomized Controlled Trial. *Diabetes Care* **2022**, *45* (7), 1592−1600. (MBX) *MBX Biosciences Inc. U.S. Securities and Exchange Commission Form S-1*, August 23, 2024. (Viking) Gatlin, A.; *Viking Therapeutics Unveils Monthly Weight-loss shot, rocking Eli LillyInvestor's Business Daily*, July 25, 2024. (QL Bio) Zhang, Y.; Xu, X.; Mclendon, K.; Wong, A. H. L.; Zhang, Y.; Zhang, X. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Novel Ultra-Long-Acting GLP-1 Receptor Agonist (ZT002) in Healthy Subjects. *Diabetes* **2024**, *73* (Suppl 1), 119-OR. (Amgen) Veniant, M. M.; Lu, S.-C.; Atangan, L.; Komorowski, R.; Stanislaus, S.; Cheng, Y.; Wu, B.; Falsey, J. R.; Hager, T.; Thomas, V. A.; et al. A GIPR Antagonist Conjugated to GLP-1 Analogues Promotes Weight Loss with Improved Matabolic Parameters in Preclinical and Phase 1 Settings. *Nat. Metab.* **2024**, *6*, 290−303.
(13) Santi, D. V.; Schneider, E. L.; Reid, R.; Robinson, L.; Ashley, G. W. Predictable and tunable half-life extension of therapeutic agents by controlled chemical release from macromolecular conjugates. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109* (16), 6211−6.
(14) Ashley, G. W.; Henise, J.; Reid, R.; Santi, D. V. Hydrogel drug delivery system with predictable and tunable drug release and degradation rates. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110* (6), 2318−23.
(15) Schneider, E. L.; Hearn, B. R.; Pfaff, S. J.; Reid, R.; Parkes, D. G.; Vrang, N.; Ashley, G. W.; Santi, D. V. A Hydrogel-Microsphere Drug Delivery System That Supports Once-Monthly Administration of a GLP-1 Receptor Agonist. *ACS Chem. Biol.* **2017**, *12* (8), 2107−2116.
(16) Schneider, E. L.; Henise, J.; Reid, R.; Ashley, G. W.; Santi, D. V. Subcutaneously Administered Self-Cleaving Hydrogel-Octreotide Conjugates Provide Very Long-Acting Octreotide. *Bioconjug Chem.* **2016**, *27* (7), 1638−44.
(17) Hearn, B. R.; Fontaine, S. D.; Pfaff, S. J.; Schneider, E. L.; Henise, J.; Ashley, G. W.; Santi, D. V. Primary deuterium kinetic isotope effects prolong drug release and polymer biodegradation in a drug delivery system. *J. Controlled Release* **2018**, *278*, 74−79.
(18) Schneider, E. L.; Henise, J.; Reid, R.; Ashley, G. W.; Santi, D. V. Hydrogel Drug Delivery System Using Self-Cleaving Covalent Linkers for Once-a-Week Administration of Exenatide. *Bioconjug Chem.* **2016**, *27* (5), 1210−5.
(19) Henise, J.; Yao, B.; Ashley, G. W.; Santi, D. V. Autoclave sterilization of tetra-polyethylene glycol hydrogel biomaterials with β-eliminative crosslinks. *Eng. Rep.* **2020**, *2* (1), No. e12091.
(20) Schneider, E. L.; Reid, R.; Parkes, D. G.; Lutz, T. A.; Ashley, G. W.; Santi, D. V. A once-monthly GLP-1 receptor agonist for treatment of diabetic cats. *Domest Anim Endocrinol* **2020**, *70*, No. 106373.
(21) Henise, J.; Hearn, B. R.; Ashley, G. W.; Santi, D. V. Biodegradable tetra-PEG hydrogels as carriers for a releasable drug delivery system. *Bioconjug Chem.* **2015**, *26* (2), 270−8.
(22) Henise, J.; Yao, B.; Hearn, B. R.; Schneider, E. L.; Ashley, G. W.; Santi, D. V. High-throughput, aseptic production of injectable Tetra-PEG hydrogel microspheres for delivery of releasable covalently bound drugs. *Eng. Rep.* **2020**, *2* (8), No. e12213.
(23) Henise, J.; Yao, B.; Ashley, G. W.; Santi, D. V. Facile preparation of tetra-polyethylene glycol hydrogel microspheres for drug delivery by cross-flow membrane emulsification. *Eng. Rep.* **2021**, *3* (11), No. e12412.
(24) Schneider, E. L.; Hangasky, J. A.; Fernandez, R. d. V.; Ashley, G. W.; Santi, D. V. The limitation of lipidation: Conversion of semaglutide from once-weekly to once-monthly dosing. *Proc. Natl. Acad. Sci. U. S. A.* **2024**, *121* (47), No. e2415815121.
(25) NovoNordisk. Wegovy (semaglutide) [package insert]. U.S. Food and Drug Administration website, revised March 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215256s011lbl.pdf (accessed October 2024).
(26) Westman, A. E. R.; DeLury, D. B. The differential equations of consecutive reactions. *Can. J. Chem.* **1956**, *34*, 1134−1138.
(27) Cai, H.; Chen, Q.; Duan, Y.; Zhao, Y.; Zhang, X. Short-term effect of polyethylene glycol loxenatide on weight loss in overweight or obese patients with type 2 diabetes: An open-label, parallel-arm, randomized, metformin-controlled trial. *Front. Endocrinol.* **2023**, *14*, No. 1106868.
(28) Wang, J.; Huang, J.; Li, W.; Tang, S.; Sun, J.; Zhang, X.; Liu, J.; Yi, B.; Liu, J.; Zhang, X.; Yang, Q.; Yang, X.; Yang, S.; Yang, G.; Zhang, H. Polyethylene glycol loxenatide (PEX168) in subjects with renal impairment: A pharmacokinetic study. *Br. J. Clin. Pharmacol.* **2019**, *85* (12), 2714−2720.
(29) Geiser, J. S.; Heathman, M. A.; Cui, X.; Martin, J.; Loghin, C.; Chien, J. Y.; de la Pena, A. Clinical Pharmacokinetics of Dulaglutide in Patients with Type 2 Diabetes: Analyses of Data from Clinical Trials. *Clin Pharmacokinet* **2016**, *55* (5), 625−34.
(30) *Global Data*, Accessed September 2, 2024. https://www.pharma.globaldata.com/.

https://doi.org/10.1021/acs.jmedchem.4c02647
J. Med. Chem. 2025, 68, 2301−2306