

Special Article - Complications of Diabetes

Efpeglenatide: A Once Monthly GLP-1 RA in the Pipeline

Davies ML^{1*}, Thiman ML² and Kugler AJ¹¹Department of Pharmacy Practice and Administration, Western University of Health Sciences College of Pharmacy, USA²Department of Clinical & Administrative Pharmacy, University of Georgia College of Pharmacy, USA***Corresponding author:** Davies ML, Department of Pharmacy Practice and Administration, Western University of Health Sciences College of Pharmacy, 309 E. Second Street, Pomona, USA**Received:** October 06, 2016; **Accepted:** November 08, 2016; **Published:** November 15, 2016**Abstract**

Efpeglenatide is a potential once-monthly, subcutaneous Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) and is currently being studied as a treatment option for patients with Type 2 Diabetes (T2DM). Its novel mechanism utilizes a long acting protein technology, where the modified Exendin-4, GLP-1 RA, molecule is attached to a flexible linker to the Fc fragment of IgG, allowing for a longer half-life and monthly administration. In phase II trials, efpeglenatide weekly demonstrated a reduction in A1C of 1.24-1.61% and monthly administration reduced A1C 0.7-1.2%, with most doses producing significant A1C lowering when compared to placebo. Additionally, efpeglenatide resulted in weight loss of ~2-3.5 kg in trials including patients with T2DM and greater weight reduction in one trial of obese patients without diabetes. Efpeglenatide has also been shown to target fasting plasma glucose, an effect seen previously with other long-acting GLP-1 RAs. Although gastrointestinal events were as high as 67%, nausea, the main side effect of GLP-1 RAs, was similar when efpeglenatide weekly was compared to liraglutide in one of the trials (33% in each group). The potential for increased adherence with monthly administration and the positive effects of glycemic control and weight loss may make this up-and-coming GLP-1RA a promising option.

Keywords: Efpeglenatide; Glucagon-like peptide-1 receptor agonist; GLP-1; GLP-1 RA

Abbreviations

GLP-1 Ras: Glucagon-Like Peptide-1 Receptor Agonists; T2DM: Type 2 Diabetes Mellitus; GI: Gastrointestinal; IR: Immediate-Release; ER: Extended-Release; GLP-1R: Glucagon-Like Peptide-1 Receptor; DPP-IV: Dipeptidyl Peptidase-IV; LAPSCOVERY: Long Acting Protein / Peptide Discovery Platform Technology; t1/2: Half-Life; QW: Weekly; Q2W: Every Other Week; FPG: Fasting Plasma Glucose; PPG: Post-Prandial Glucose

Introduction

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) have proven to be an effective drug class at improving glycemic control in patients with Type 2 Diabetes Mellitus (T2DM) [1]. This class has been shown to reduce A1C in ranges of 1-1.5% in addition to standard of care [2]. Furthermore, GLP-1 RAs delay gastric emptying time, which slows carbohydrate absorption and increases satiety, often reducing overall food intake and resulting in weight reduction [1,3]. Unfortunately, the delay in gastric emptying also leads to the main adverse events seen in this class, Gastrointestinal (GI) events, especially nausea which can be seen in up to 30% of patients [1,4].

It has been over a decade since the first GLP-1 RA, exenatide, was approved by the FDA [4]. There are now 6 GLP-1 RAs available in the US, including exenatide Immediate-Release (IR) (Byetta), liraglutide (Victoza), lixisenatide (Adlyxin), dulaglutide (Trulicity), albiglutide (Tanzeum), and exenatide Extended-Release (ER) (Bydureon). Exenatide IR is administered twice daily by subcutaneous injection, liraglutide and lixisenatide offer a once daily injection, and dulaglutide, albiglutide, and exenatide ER are once weekly medications, lessening injection burden, and potentially improving patient adherence. The move to weekly GLP-1 RA administration not only has the potential to

improve adherence, but also mechanistically, with an extended-release function, decreases the incidence of nausea and vomiting commonly seen with the class [5,6]. Efpeglenatide is a potential monthly GLP-1 RA in the pipeline, which may offer additional administration and side-effect profile benefits. The purpose of this review is to evaluate the pharmacologic design, efficacy, and tolerability of efpeglenatide, a potential once-monthly GLP-1 RA currently under investigation.

Pharmacology of Efpeglenatide

Mechanistically, the GLP-1 RAs have the ability to suppress glucagon release and enhance insulin secretion in a glucose-dependent manner, by binding to the GLP-1 Receptor (GLP-1R) on the beta cells of the pancreas [7,8]. Unfortunately, endogenous GLP-1 is degraded within 1-2 minutes by Dipeptidyl Peptidase-IV (DPP-IV) [7]. Compounds have been discovered and synthesized that mitigate this degradation. Exenatide IR (also known as Exendin-4) is a GLP-1 discovered from saliva of the Gila monster, a venomous lizard. This compound does not have the DPP-IV cleavage site, which increases the GLP-1 RA half-life [7]. Weekly GLP-1 RAs, albiglutide and dulaglutide also have been synthetically modified with DPP-IV resistance. In addition, albiglutide is attached to human serum albumin protein to decrease elimination and extend the half-life (t1/2) to 6-7 days [9]. Dulaglutide is fused with the Fc region of IgG4 to prolong t1/2 and decrease immunogenicity via antibody formation [9]. Immunogenicity is a concern, as low titer anti-exenatide antibodies have been shown in up to 45% of patients treated with exenatide [10]. In an analysis of 17 trials, low titers of anti-exenatide antibodies did not result in reduced efficacy; however, higher titers, seen in 12% of patients on exenatide ER, did result in reduced efficacy [10].

Efpeglenatide (HM-11260C or LAPSCA-Exendin 4) is a GLP-1 RA that has been synthetically modified for a potential once-monthly injection. CA-Exendin 4 has a single amino acid modification, decreasing its degradation by DPP-IV [11]. Additionally, the Long Acting Protein / Peptide Discovery Platform Technology (LAPSCOVERY) developed by Hanmi Pharmaceuticals allows for an extended t_{1/2}. The LAPSCOVERY system conjugates the IgG4 Fc fragment with a flexible linker to the middle of the CA-Exendin 4 peptide to potentially decrease loss of activity from anti-drug antibodies [9,12,13]. The increased size resulting from the conjugation decreases renal clearance, and preclinical studies have shown efpeglenatide results in decreased GLP-1R internalization and degradation, another mechanism of clearance and shortened half-life of the GLP-1 Ras [11].

Clinical Trials Reviewed

In a 12-week dose ranging study, subjects with T2DM were randomized to one of 7 arms – a placebo control, an active control of liraglutide dosed daily (titrated to 1.8 mg), or efpeglenatide 0.3 mg, 1 mg, 2 mg, 3 mg, or 4 mg dosed weekly [14]. The study was double-blinded with the exception of those in the active control arm. Variations in metformin use were accounted for in the randomization process. On average, subjects (n=254) had T2DM for 73.08 months, were 55.3 years old, had a baseline weight of 86-95 kg, BMI of 31.76 kg/m², and a baseline A1C ranging from 7.7-8.0%. Fifty-three percent of subjects were male. All active arms showed a statistically significant (p<0.05) reduction in A1C from baseline at week 13, with the largest decrease in the efpeglenatide 4 mg group (-1.61%). Approximately 83.3% and 80.6% of subjects reached an A1C of ≤7% at 12 weeks with efpeglenatide 3 mg and 4 mg respectively compared to only 27% of subjects receiving placebo (p<0.0001 for both) and 61.1% of subjects receiving liraglutide 1.8 mg daily. Reduction in Fasting Plasma Glucose (FPG) from baseline to week 13 was 2.19 mmol/L (39.4 mg/dL), 2.44 mmol/L (43.9 mg/dL), and 1.46 mmol/L (26.3 mg/dL) in the efpeglenatide 3 mg, efpeglenatide 4 mg, and liraglutide groups respectively, which were all statistically significant compared to placebo (p<0.05). Statistically significant weight loss of 2.73 kg (p<0.05), 3.31 kg (p<0.05), and 3.21 kg was reported in the 3 mg efpeglenatide, 4 mg efpeglenatide, and liraglutide arms respectively, as compared to 1.29 kg of weight loss in the placebo group. GI disorders occurred in 51-73% of efpeglenatide groups, the highest occurrence being in the 3 mg arm, compared to 81% in the liraglutide group and 62% in placebo. Of note, daily liraglutide doses were titrated, whereas weekly efpeglenatide doses were not. Injection site reactions were more common in the liraglutide arm, occurring in 36% of subjects, as opposed to 3-24% in the efpeglenatide arms (Table 1).

A 20-week randomized, double-blind, placebo-controlled, parallel group study evaluated the impact of four efpeglenatide doses on body weight in obese patients without diabetes [15]. A total of 297 patients were randomized to efpeglenatide 4mg or 6mg once Weekly (QW), 6mg or 8mg every other week (Q2W), or placebo. At baseline, participants' average age was 43 years, weight was 95.6-101.7kg, BMI was 35 kg/m², and waist circumference was 108.9-111.9cm. Treatment groups ranged from 69.5-87.9% female. A significant reduction in weight was demonstrated in all efpeglenatide treatment groups at follow-up (week 21) compared to placebo, with average weight loss of

6.7kg, 7.3kg, 6.7kg, and 7.4kg in the 4mg QW, 6mg QW, 6mg Q2W, and 8mg Q2W treatment groups respectively (p<0.0001). Likewise a significant reduction in BMI compared to placebo was demonstrated at week 21, with average reductions of 2.4kg/m², 2.6kg/m², 2.3kg/m², and 2.6 kg/m² in the 4mg QW, 6mg QW, 6mg Q2W, and 8mg Q2W treatment groups respectively (p<0.0001). A significantly greater proportion of participants assigned to efpeglenatide achieved 5% weight loss and 10% weight loss at week 21 when compared to placebo (p<0.0001 and p<0.01 respectively). Lastly, the decrease in waist circumference was significantly greater in all efpeglenatide treatment groups when compared to placebo at week 21, with an average reduction of 5.2cm, 6.7cm, 6.2cm, and 8.3cm in the 4mg QW, 6mg QW, 6mg Q2W, and 8mg Q2W treatment groups respectively (p<0.01 for 4mg QW and 6mg Q2W, p<0.0001 for 6mg QW and 8mg Q2W). GI events were the most common adverse effect, occurring in up to 83.1% of patients in the QW groups and up to 75.9% in the Q2W groups. GI events were noted to have occurred most often early in therapy with improvement over time.

In a randomized, double-blind, placebo-controlled phase IIa study, 6 different efpeglenatide doses (3 weekly and 3 monthly) were compared to placebo in subjects with T2DM on stable metformin and with a baseline A1C of 7-10% [16]. Subjects were randomized to efpeglenatide 1 mg, 2 mg, 4 mg, or placebo weekly for 8 weeks, or 8 mg, 12 mg, 16 mg, or placebo monthly for 3 months (n=51 in efpeglenatide groups and n=17 in placebo). Subjects were on average 52 years old, approximately 50% were female, average weight was 97kg, and average duration of diabetes was 58 months. The efpeglenatide 1mg, 2mg, and 4mg weekly doses, as well as the 8 mg and 12 mg monthly doses significantly reduced A1C at follow-up compared to placebo (p<0.05). The greatest change in A1C was seen with the efpeglenatide 8 mg monthly dose, which reduced A1C 1.36% when added to stable metformin. Efpeglenatide reduced FPG from baseline by 3.65 mmol/L (65.7 mg/dL) in the 4 mg QW group, 1.75 mmol/L (31.5 mg/dL) in the 8 mg monthly group, and 1.9 mmol/L (34.2 mg/dL) in the 16mg monthly group (p<0.001, p<0.05, p<0.05 respectively). Significant weight loss compared to placebo was seen with efpeglenatide 4 mg QW (-2.63 +/- 1.16 kg; p=0.029) and 16 mg monthly (-2.82 +/- 1.23 kg; p=0.031). Nausea occurred in up to 67% of subjects in the monthly groups and 33% in the QW groups; however, there were no discontinuations due to GI events. Efpeglenatide plasma concentrations demonstrated a t_{1/2} of 153-171 hours in all doses.

In a 16-week study of once monthly efpeglenatide, 209 subjects with T2DM on stable doses of metformin were randomly assigned to one of 4 arms [17]. For the interim analysis presented, 86 subjects were included and were randomized to: efpeglenatide 8 mg (n=22), efpeglenatide 12 mg (n=21), efpeglenatide 16 mg (n=22) or placebo (n=21) once monthly. Subjects randomized to efpeglenatide were titrated for the first 4 weeks by 4mg every week, then 8 mg monthly for 1 month, then continued 8 mg or increased to 12 mg or 16 mg for the remaining 2 months of the study. At baseline, average age was 56 years, weight was 91-95.2kg, duration of T2DM was 95.4 months, A1C was 7.8%, and 60% of the participants were male. The primary endpoint, change in A1C over the 16 weeks, was -0.3%, -1.2%, -0.7%, and -1.1% for the placebo, efpeglenatide 8 mg, 12 mg, and 16 mg groups respectively. Compared to placebo, the efpeglenatide 8 mg group had

Table 1: Summary of clinical outcomes from efpeglenatide phase II clinical trials.

Study Design	Study arms	A1C	Weight	Nausea
12-week study of 254 T2DM subjects [14]	LIRA 1.8 mg daily, or EFP 0.3mg, 1mg, 2mg, 3mg, 4mg, or P QW	EFP 4mg QW: -1.61%* LIRA 1.8mg Qday: -1.38%* P: -0.4%	EFP 4mg QW: -3.31 kg* LIRA 1.8mg Qday: -3.21kg P: -1.29 kg	EFP 4mg QW: 33% LIRA 1.8mg Qday: 33% P: 16%
20-week of 297 obese subjects [15]	EFP 4mg QW, 6mgQW, 6mg Q2W, 8mg Q2W, or P	Not reported in weight loss study	EFP 4 mg QW: -6.7 kg* EFP 6 mg QW: -7.3 kg* EFP 6 mg Q2W: -6.7 kg* EFP 8mg Q2W: -7.4 kg* P: + 0.1 kg	EFP 4 mg QW: 54% EFP 6 mg QW: 59% EFP 6 mg Q2W: 48% EFP 8mg Q2W: 62% P: 18%
8-12 weeks of 68 T2DM subjects [16]	EFP 1 mg, 2 mg, 4 mg, or P QW x 8 wks, or EFP 8 mg, 12 mg, 16 mg, or P QMo x 3mos	EFP 4mg QW: -1.24%* P QW: -0.09% EFP 8 mg QMo: -1.36%* EFP 16 mg QMo: -0.99% P QMo: -0.14%	EFP 4mg QW: -2.38kg* P QW: +0.25 kg EFP 16 mg QMo: -2.68* P QMo: +0.15 kg	QW regimens: 0-33% QMo regimens: 44-67%
16-week of 86 T2DM subjects [17]	EFP 8 mg, 12 mg, 16 mg, or P QMo	EFP 8mg QMo: -1.2%* EFP 12mg QMo: -0.7% EFP 16mg QMo: -1.1% P QMo: -0.3%	EFP 8mg QMo: -2.3kg EFP 12mg QMo: -2.2kg EFP 16mg QMo: -2.8kg P QMo: -1.2kg	EFP 16mg QMo: ~30% P QMo: ~5%

*p<0.05 when compared to placebo

EFP: Efpeglenatide; P: Placebo; LIRA: Liraglutide; QW: Every Week; Qday: Daily; Q2W: Every Other Week; Qmo: Every Month; mos: Months

significantly greater reductions in A1C ($p < 0.0035$). In addition 61.9-63.6% of subjects in the efpeglenatide arms were able to achieve A1C goal of $< 7\%$ versus only 19% in the placebo group. Weight loss was observed in all arms: 1.2 kg, 2.3 kg, 2.2 kg, and 2.8 kg for the placebo, efpeglenatide 8 mg, 12 mg, and 16 mg groups respectively. Nausea and vomiting, as expected, were the most common adverse effects, occurring in 15-20% of subjects treated with efpeglenatide 4mg in the first week (part of dose titration). In addition, approximately 30% of subjects in the efpeglenatide 16 mg group experienced GI-related events when titrating from 8 mg monthly to 16 mg monthly for the last 2 months at the 2-month mark. There were also more discontinuations in the efpeglenatide arms compared to the placebo arm (19 (30%) versus 4 (18%).

Discussion

Efpeglenatide resulted in favorable effects in glycemic control in phase II studies. A1C reduction was up to 1.61% for efpeglenatide 4mg weekly compared to 1.38% for liraglutide 1.8 mg daily, with 89% of patients on metformin prior to the addition of GLP-1 RA [14]. Furthermore, efpeglenatide 8mg monthly significantly decreased A1C 1.2% compared to 0.3% for placebo, with all patients on stable doses of metformin prior to addition of GLP-1 RA [17]. Efpeglenatide resulted in a reduction of 34.2-43.9 mg/dL in FPG with weekly-monthly dosing, whereas liraglutide only reduced FPG by 26.3 mg/dL [14,17]. Endogenous GLP-1 is secreted after a meal, which assists in reducing Post-Prandial Glucose (PPG); however, previous literature suggests longer-acting GLP-1 RAs reduce FPG in addition to PPG, which appears to be similar for long-acting efpeglenatide [14,17,18].

Weight loss of ~2-3.5kg was seen in all the studies of subjects with T2DM [14,16,17]. The most pronounced weight loss was seen in the study of obese patients without diabetes where subjects lost

7.3 kg with efpeglenatide 6mg weekly and 7.1 kg with efpeglenatide 8mg every 2 weeks [15]. This is higher than commonly reported with the approved GLP-1 RAs, even liraglutide (Saxenda), the approved product for weight loss [19]. This marked reduction may be due to exercise or nutrition confounding variables in this study, but needs to be explored in phase III trials.

The longer duration of efpeglenatide and novel monthly administration may reduce common adverse effects. Not only does monthly administration have the potential to improve adherence, but also reduce injection burden and injection site reactions [14,15]. In addition, the long-acting GLP-1 RA may result in fewer GI events. In a phase I study, efpeglenatide 16mg monthly had less effect on gastric emptying compared to liraglutide [20]. This may lead to a less pronounced impact on PPG control, but could lead to less nausea. When used weekly there were similar rates of nausea with efpeglenatide 4mg and liraglutide 1.8mg daily (33%), so further investigation on a larger scale will be important to identify frequency [14]. Although the studies presented in this review do show GI events reduced over time, there were inconsistencies in GLP-1 RA dose titration. Lastly, immunogenicity, as mentioned previously with regards to pharmacologic design, was not observed. The studies presented here showed there were no subjects who developed neutralizing antibodies to efpeglenatide [14-16].

Several limitations of the currently available data for efpeglenatide must be noted, primarily that data is limited to phase II studies presented at professional meetings and peer-reviewed abstracts at this time. Additionally, there is limited data regarding clinical results of once-monthly dosing of efpeglenatide. Lastly, most of these studies are small-scale and potentially underpowered to detect significant differences in some of the doses and/or secondary outcomes.

The use of efpeglenatide, thus far, has demonstrated some potential benefits over the currently marketed GLP-1 RAs. Efficacy was seen in glycemic control and weight loss in phase II studies. The potential for lower adverse events is yet to be elucidated in phase III studies.

References

- American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care*. 2016; 39: 1-119.
- Reid TS. Practical use of glucagon-like peptide-1 receptor agonist therapy in primary care. *Clin Diab*. 2013; 31: 148-157.
- Apovian CM, Aron-ne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015; 100: 342-362.
- Prescribing information. Byetta (exenatide). San Diego CA. Amylin Pharmaceuticals Inc. 2015.
- Prescribing information. Bydureon (exenatide extended-release). Wilmington DE: AstraZeneca Pharmaceuticals LP. 2015.
- Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009; 374: 39-47.
- Doyle ME, Egan JM. Mechanisms of Action of GLP-1 in the Pancreas. *Pharmacol Ther*. 2007; 113: 546-593.
- Nielsen LL, Young AA, Parkes DG. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. *Regul Pept*. 2004; 117: 77-88.
- Kaspar AA, Reichert JM. Future directions for peptide therapeutics development. *Drug Discov Today*. 2013; 18: 807-817.
- Fineman MS, Mace KF, Diamant M, Darso T, Cirincione BB, Booker Porter TK, et al. Clinical relevance of anti-exenatide antibodies: safety, efficacy and cross-reactivity with long-term treatment. *Diabetes Obes Metab*. 2012; 14: 546-554.
- Choi IY, Park SH, Trautmann M, Hwang SY, Kim JY, Bae SM, et al. Superagonistic mechanism of increased glucodynamic and weight loss effects of lapsca-exendin-4 (HM11260C). Poster presentation of 51st European Association for the Study of Diabetes (EASD) Annual Meeting. September 14-18. Stockholm. 2015.
- Hanmi Pharmaceutical. Hanmi presented the research results of long acting diabetes-obesity medicines at ADA. 2016.
- Choi IY, Park SH, Lee GH, Choi SM, Kim SJ, Kang JH, et al. A Long-Acting Exendin-4 Analog Conjugate to the Human Fc Fragment Reveals Low Immunogenic Potential. Poster presentation of 74th ADA Scientific Sessions. 2014.
- Yoon KH, Kang JH, Han OP, Gee KH, Choi IY, Kwon SC, et al. Once weekly HM11260C (efpeglenatide) significantly improves glycemic control and reduced body weight in patients with type 2 diabetes: A phase II dose finding study. Poster presentation of 51st European Association for the Study of Diabetes (EASD). 2015.
- Pratley RE, Kang JH, Kim PK, Kwak EH, Han OP, Gee KH, et al. Significant effects of HM11260C (efpeglenatide) on body weight over 20 weeks in obese subjects without diabetes: A randomised, double-blind, placebo controlled study. Poster presentation of 51st European Association for the Study of Diabetes (EASD). 2015.
- Kang J, Choi S, Choi IY, Kwon SC, Trautmann M, Hompesch M, et al. HM11260C, a New Generation Long Acting Super GLP-1R Agonist with a unique Pharmacokinetic Profile Improves Glucose Control and GI tolerability; a Phase IIa Clinical Trial in T2DM. Poster presentation of 49th European Association for the Study of Diabetes (EASD) Annual Meeting; 2013.
- Del Prato S, Kang JH., Choi SM, Lee WH, Han OP, Kil SY, et al. Once a month treatment with HM11260C improves glycaemic control in type 2 diabetes mellitus: Interim data from a 16-week study. Poster presentation of 75th American Diabetes Association (ADA) Scientific Sessions. 2015.
- Uccellatore A, Genovese S, Dicembrini I, Mannucci E, Ceriello A. Comparison Review of Short-Acting and Long-Acting Glucagon-like Peptide-1 Receptor Agonists. *Diabetes Ther*. 2015; 6: 239-256.
- Three-year data show early response to Saxenda[®] resulted in improvements in weight loss and cardiometabolic risk factors. Saxenda (liraglutidine). Bagsvaerd, Novo Nordisk. 2016.
- Watkins E., Kang J., Trautmann M, Choi S, Han O, Hompesch M. LAPS-Exendin-4 (HM11260C) enhances insulin secretion and beta cell responsiveness in subjects with type 2 diabetes. *Diabetologia*. 2015.