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Clarivate Analytics

Monograph

Efpeglenatide

Rec INN

Glucagon-like peptide 1 (GLP-1) receptor agonist
Treatment for type 2 diabetes

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Contents

Summary

Diabetes mellitus is a chronic disease in which the body presents with numerous pathophysiological defects, some of which have to do with glucagon-like peptide 1 (GLP-1). GLP-1 is a gastrointestinal peptide that stimulates glucose-dependent insulin release from pancreatic islets, slows gastric emptying time, inhibits inappropriate post-meal glucagon release, and ultimately reduces food intake. These mechanisms together allow for significant blood glucose control and meaningful weight loss. GLP-1 receptor agonists (GLP-1RAs) are a class of medications that are currently approved for the treatment of diabetes mellitus and obesity. Efpeglenatide is a novel investigational GLP-1RA that is currently being studied in phase III clinical trials. Efpeglenatide's extended duration of action is its most promising advantage above the other GLP-1RAs, which is due to the unique composition of the compound. Efpeglenatide is chemically conjugated to recombinant human immunoglobulin G4 Fc fragment through a nonpeptidyl linker to CA-Exendin-4 and has the potential for once-monthly dosing, which would be advantageous over the currently available twice-daily, once-daily and once-weekly GLP-1RAs on the market.

Key words: Diabetes – Efpeglenatide – HM-11260C – LAPS-Exd4 – LAPS-Exendin – LAPS-exendin-4 analogue – LAPS-Exendin4 – LAPS-CA-Exendin-4 – SAR-439977 – GLP-1 receptor agonist – Antidiabetic agents

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HM-11260C
Langlenatide (former INN)
LAPS-CA-Exendin 4
LAPS-Exendin4
SAR-439977

Exenatide derivative linked to human IgG4 Fc dimer via a polyethylene glycol derivative

N6.27,N.1′-[omega-(oxypropane-1,3-diyl)-α-(propane-1,3-diyl)poly(oxyethylene)] [1-(imidazol-4-ylacetic acid)] exendin-4 *Heloderma suspectum* (Gila monster), human immunoglobulin G4 Fc fragment-(9′-229′)-peptide dimer (3′-3″)-disulfide

Long-acting exenatide analogue by conjugating the exendin-4 analogue CA exendin-4 and the constant region of human immunoglobulin fragment (Fc) via a flexible nonpeptidyl linker

Integrity Entry Number: 476350

Background

The prevalence of diabetes mellitus (DM) worldwide is drastically rising, with a predicted 366 million diagnosed in the year 2030 due to contributing factors such as obesity, inactivity, aging and hormonal disorders (1-3). Over the last 9 years, the Ominous Octet theory has detailed the various pathophysiological defects of DM, including increased hepatic glucose production, neurotransmitter dysfunction, increased glucagon secretion by the islet alpha cells, impaired insulin secretion by the islet beta cells, decreased incretin effect, increased lipolysis, decreased glucose uptake and increased glucose reabsorption (4). While there are many available treatment regimens for type 2 DM (T2DM), some of the older therapies present with undesirable adverse events (AEs), including hypoglycemia, hunger and weight gain. The latter is particularly problematic as insulin resistance is strongly correlated with obesity, having numerous metabolic complications such as T2DM, cardiovascular disease and dyslipidemia, all resulting in an increased risk of mortality (2, 5).

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a preferred treatment option in T2DM due to their ability to decrease blood glucose levels while having a neutral effect on weight or resulting in weight loss. These agents function by delaying gastric emptying time, which slows carbohydrate absorption consumed with meals, leading to increased satiety, reduced food intake and ultimately potential weight reduction (5, 6). Furthermore, since these medications are subcutaneous injections, they have the ability to bypass the first-pass effect allowing a greater concentration of drug to reach systemic circulation instead of being reduced by absorption into the liver or gut wall (7).

When assessing GLP-1RAs, one can see that some require daily subcutaneous injections, while others only require once-weekly subcutaneous injections. Although these injections are typically painless, daily injections can be burdensome which may affect patient compliance. A long-acting weekly or monthly injection has the potential to improve patient adherence and compliance by decreasing injection burden especially for those patients who are also on insulin therapy (6, 8). When added to standard of care, GLP-1RAs have been shown to reduce HbA_{1c} in the range of 1-1.5% and to reduce body weight in the range of 2-3.5 kg (6). U.S. Food and Drug Administration (FDA)-approved medications in this drug class include exenatide twice-daily (Byetta), exenatide once-weekly (Bydureon), liraglutide once-daily (Victoza, Saxenda), lixisenatide once-daily (Adlyxin), albiglutide once-weekly (Tanzeum), dulaglutide once-weekly (Trulicity) and semaglutide once-weekly (Ozempic) (Table I) (6, 9-16). Furthermore, Sanofi and Hanmi Pharmaceutical are currently conducting clinical trials on efpeglenatide, a GLP-1RA being studied as a once-weekly or once-monthly treatment option for patients with T2DM (6).

This article aims to discuss the role of GLP-1RAs in T2DM and obesity, while evaluating the efficacy and safety of efpeglenatide, a novel drug within the class of GLP-1RAs.

Preclinical Pharmacology

In patients with poorly controlled T2DM, it was recognized that a single exogenous infusion of GLP-1 increased insulin levels in a glucose-dependent manner. This in turn normalized fasting hyperglycemia which led to current therapeutic approaches with GLP-1 (17). The mechanism of GLP-1RAs was also identified with a deletion of the GLP-1 receptor in mice that presented with impaired glucose tolerance (5). Furthermore, through central nervous system-mediated mechanisms, it was demonstrated that GLP-1 also has the ability to suppress food intake (18, 19). In rodents, monkeys and humans, GLP-1RAs have been found to improve glucose homeostasis and promote weight loss (5, 20).

Compared to other GLP-1RAs, efpeglenatide has several modifications that increase its half-life and allow the potential of once-monthly s.c. dosing (6). Efpeglenatide, or LAPS-Exendin-4, is a novel long-acting form of CA-Exendin-4 which has decreased renal clearance and slow vascular endothelial clearance (21). In addition, efpeglenatide has a single amino acid modification which decreases its degradation by dipeptidyl peptidase 4 (DPP-4) (6). The long-acting protein/peptide discovery platform technology (LAPSCOVERY) allows the molecule to have an extended half-life, which also potentially decreases the loss of activity as a result of antidrug antibodies (6). Furthermore, due to conjugation, the increased size of the molecule decreases renal clearance and has resulted in decreased GLP-1 receptor internalization and degradation (6).

Pharmacokinetics and Metabolism

A preclinical study in male Sprague-Dawley rats, examined a single s.c. injection of efpeglenatide 2.1 nmol/kg at a target dose level of 24 nmol/kg. In this study, the greatest maximum concentration (C_{max}) was observed in the kidney cortex (C_{max} = 1246 nMeq), with the second and third highest C_{max} demonstrated in the lungs and blood (C_{max} = 66 and 58 nMeq, respectively). Park et al. determined the time to C_{max} (t_{max}) was 48 h in the liver, intestinal content, lung, myocardium, pancreas, pituitary and the spleen, while the blood and kidney cortex had a t_{max} of 24 and 144 h, respectively. Furthermore, the area under the curve (AUC) was highest in the kidney cortex and the lungs, with below quantifiable levels found in the intestines, cerebellum and cerebrum (10).

LAPSCOVERY technology developed by Hanmi Pharmaceutical introduced efpeglenatide as a new long-acting GLP-1RA. The technology allowed decreased structural hindrance and increased pharmacological activity of the exendin-4 analogue which is conjugated to a nonglycosylated human Fc fragment through a nonpeptidyl linker (11). Efpeglenatide plasma concentrations demonstrated a half-life of 153-171 h at all doses (6).

Clinical Studies

A phase Ib, randomized, placebo- and open-label controlled study evaluated the effect of efpeglenatide on the insulin secretion rate (ISR) and beta-cell responsiveness in subjects with T2DM, aged 18-70 years, on a stable dose of metformin (no changes for > 3 months) and HbA_{1c} between 6.5% and 10% compared to placebo and liraglutide. Subjects were divided into three cohorts: cohort A (efpeglenatide 6 mg s.c. weekly [n = 13]), cohort B (efpeglenatide 16 mg s.c. monthly [n = 13]) and cohort C (liraglutide 1.8 mg s.c. daily [n = 13]). Subjects in cohorts A and B were randomized 3:1 to receive efpeglenatide or placebo. Islet beta-cell function was assessed after a mixed meal tolerance test, during an intravenous graded glucose infusion (GGI), which consisted of infusion steps with 2, 4, 6, 8,

Table I. *Current glucagon-like protein 1 (GLP-1) receptor agonists.*

Generic name	Brand name	Indication	Frequency of administration	Half-life	Time to peak, plasma	Metabolism	Chemical nature
Exenatide	Byetta	Diabetes mellitus	Twice daily	2.4 h	2.1 h	Degradation proteolytically may occur	Synthetic exendin-4 analogue
Exenatide	Bydureon	Diabetes mellitus	Once weekly	~2 weeks	2 weeks after single dose; steady state achieved after 6 to 7 weeks	Degradation proteolytically may occur	Synthetic exendin-4 analogue
Liraglutide	Victoza	Diabetes mellitus	Once daily	~13 h	8 to 12 h	Endogenously by DPP-4 and endopeptidases	GLP-1 with palmitic acid attachment
Liraglutide	Saxenda	Chronic weight management	Once daily	~13 h	8 to 12 h	Endogenously by DPP-4 and endopeptidases	GLP-1 with palmitic acid attachment
Lixisenatide	Adlyxin	Diabetes mellitus	Once daily	~3 h	1 to 3.5 h	Proteolytic degradation presumed	Exendin-4 analogue with an addition of six lysines and a deletion of a proline at the C-terminus (12)
Albiglutide	Tanzeum	Diabetes mellitus	Once weekly	~5 days	3 to 5 days	Proteolytic enzymes degrade to small peptides and individual amino acids	GLP-1 dimer fused to recombinant human albumin (13)
Dulaglutide	Trulicity	Diabetes mellitus	Once weekly	~5 days	24 to 72 h	Protein catabolism pathways degrade to amino acids	GLP-1 analogue covalently linked to a human IgG4-Fc (14)
Semaglutide	Ozempic	Diabetes mellitus	Once weekly	~1 week	1 to 3 days after a single dose; steady state achieved after 4 to 5 weeks	Cleavage of the peptide backbone (proteolytic) with β-oxidation of the fatty acid sidechain	GLP-1 molecule with amino acid substitutions and a large fatty acid-derived chemical moiety attached (15)
Efpeglenatide		Diabetes mellitus*	Once weekly ~monthly	153-171 h (6, 11)	24 h (10)		Exendin-4 analogue and human Fc fragment conjugated via nonpeptidyl linker (9)
Efpeglenatide		Obesity*	Once weekly ~monthly	153-171 h (6, 11)	24 h (10)		Exendin-4 analogue and human Fc fragment conjugated via nonpeptidyl linker (9)

*Indications not yet approved by the U.S. Food and Drug Administration (FDA) or any other regulatory agency. DPP-4, dipeptidyl peptidase 4.

12 mg/kg/min of 20% i.v. glucose for 30 min each. At each GGI step, ISR, plasma glucose response and C-peptide levels were measured. Cohorts A and C were evaluated at baseline and steady state while cohort B was evaluated at trough and peak drug concentration. All active treatments showed increased ISR compared to placebo. Mean ISR by C-peptide convolution for cohort A reached about 18 pmol/kg/min at 150 min versus about 24 pmol/kg/min on day 90 at 150 min and about 9 pmol/kg/min on day 83 at 150 min for cohort B (21). During the GGI, the AUC-insulin and AUC-C-peptide were statistically larger in cohort A compared to cohort C ($P < 0.05$) showing improved measures of beta-cell function compared to placebo. Mean insulin concentrations reached about 210 mU/L for cohort B at 150 min on day 90, about 50 mU/L at 150 min on day 83 and 190 mU/L at 150 min for cohort A. Insulin secretion for all efpeglenatide treatment arms was increased significantly compared to placebo over the range of blood glucose concentrations ($P < 0.0001$) (21). The monthly efpeglenatide dose showed a significant diminution of effect on ISR at PK trough (day 82). However, there was a significant treatment effect relative to placebo/baseline in a comparison of the relationship between plasma glucose and ISR using mixed effects modeling ($P < 0.0001$), which was not different among the treatment groups (21).

A phase II, randomized, double-blind, open-label, placebo- and active-controlled study evaluated the efficacy, safety and tolerability of once-weekly doses of efpeglenatide compared to once-daily liraglutide. In this 12-week dose-ranging study, 254 adults with T2DM on diet and exercise or metformin ≥ 1500 mg daily were randomized to either placebo, liraglutide s.c. daily (titrated to 1.8 mg), or efpeglenatide 0.3, 1, 2, 3 or 4 mg s.c. weekly. The subjects were 18 to 75 years of age with an HbA_{1c} of 7.0% to 10.0% and a body mass index (BMI) < 40 kg/m^2. At the end of the trial (week 13), all subjects randomized to an efpeglenatide arm had statistically significant reductions in HbA_{1c} from baseline. The reductions for placebo s.c. weekly, liraglutide s.c. daily (titrated to 1.8 mg), efpeglenatide 0.3, 1, 2, 3 or 4 mg s.c. weekly were −0.40%, −1.38%, −0.56%, −0.95%, −1.19%, −1.41% and −1.61%, respectively; ($P < 0.05$). In addition, efpeglenatide 0.3, 1, 2, 3 or 4 mg s.c. weekly demonstrated reductions in mean fasting plasma glucose (FPG) of −0.48, −1.31, −1.27, −2.19 and −2.44 mg/dL, respectively ($P < 0.05$) with reduction of −0.49 mg/dL in placebo and −1.46 mg/dL in the liraglutide arm, from baseline to week 13. Regarding the effects on weight, efpeglenatide 3 mg (2.73 kg; $P < 0.05$), efpeglenatide 4 mg (3.31 kg; $P < 0.05$) and liraglutide (3.21 kg; $P < 0.05$) all showed statistically significant weight reduction compared to the placebo group (1.29 kg; $P < 0.05$), demonstrating the lower doses of efpeglenatide (0.3, 1 and 2 mg) did not have a significant impact on body weight reduction (6, 22).

Pratley et al. conducted a phase II randomized, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy, safety and tolerability of efpeglenatide (23). This study examined 297 obese subjects without DM who were between 18 to 65 years of age, with a stable body weight (< 5% change) for at least 3 months, and with a BMI ≥ 30 kg/m^2 or a BMI of ≥ 27 kg/m^2 with treated or untreated comorbidities (23). In this 20-week study, efpeglenatide 4 mg s.c. weekly, efpeglenatide 6 mg s.c. weekly, efpeglenatide 6 mg s.c. every other week, and efpeglenatide 8 mg s.c. every other week all showed significant reductions in body weight and BMI at follow-up (20 weeks) compared to placebo s.c. weekly (P value < 0.0001) with changes in body weight of −6.6, −7.3, −6.4, −7.1 and 0 kg, respectively, and changes in BMI from baseline of −2.4, −2.6, −2.3, −2.6 and 0.0, respectively (6, 23). Furthermore, in an analysis of waist circumference, efpeglenatide 4 mg s.c. weekly, efpeglenatide 6 mg s.c. weekly, efpeglenatide 6 mg s.c. every other week, efpeglenatide 8 mg s.c. every other week, and placebo s.c. weekly showed reductions from baseline of −5.2 cm ($P < 0.01$), −6.7 cm ($P < 0.0001$), −6.2 cm ($P < 0.01$), −8.3 cm ($P < 0.0001$) and −0.9 cm, respectively (23).

A phase II, randomized, double-blind, parallel-group, placebo-controlled study completed by Kang et al. evaluated the tolerability, pharmacokinetics, and pharmacodynamics of efpeglenatide compared to placebo. Seventy-two adults with T2DM on stable metformin monotherapy (for at least 3 months) with baseline HbA_{1c} values of 7% to 10% were randomized to 8 efpeglenatide weekly doses of 1, 2 and 4 mg or 3 efpeglenatide monthly doses of 8, 12 and 16 mg (24). The three weekly dosing regimens of efpeglenatide 1 mg ($P < 0.05$) and efpeglenatide 2 and 4 mg ($P < 0.01$) and the two lower doses of the monthly regimen (efpeglenatide 8 mg [$P < 0.05$] and 12 mg [$P < 0.01$]) showed significant reductions in HbA_{1c} at follow-up compared to placebo (6). The weekly efpeglenatide groups showed reductions in HbA_{1c} from baseline of −0.92 ($P < 0.05$), −1.02 ($P < 0.01$) and −1.24 ($P < 0.01$) for the 1-, 2- and 4-mg arms, respectively. The 8-, 12- and 16-mg monthly efpeglenatide groups resulted in HbA_{1c} changes from baseline of −1.36 ($P < 0.01$), −1.07 ($P < 0.05$) and −0.99, respectively (24). Change from baseline in FPG was −2.01 mmol/L ($P < 0.05$), −1.47 mmol/L and −3.65 mmol/L ($P < 0.001$) for the weekly efpeglenatide doses of 1, 2 and 4 mg, respectively, versus 0.09 mmol/L in the placebo weekly group. In the monthly dosed efpeglenatide groups of 8, 12 and 16 mg, there were FPG changes of −1.75 mmol/L ($P < 0.05$), −1.09 mmol/L and −1.90 mmol/L ($P < 0.05$) from baseline, respectively, versus −0.10 mmol/L in the placebo monthly group. Compared with placebo, a statistically significant change in body weight was seen in patients receiving the highest dose of each efpeglenatide weekly and monthly regimen, 4 and 16 mg with −2.38 kg ($P = 0.029$) and −2.68 kg ($P = 0.031$), respectively (24). While the monthly doses showed extended half-lives and t_{max} values compared with the weekly doses of efpeglenatide, the accumulation ratio for plasma concentrations was reduced in the monthly doses (24).

Sanofi is currently conducting phase III clinical trials worldwide. One study currently enrolling patients is a 56-week, multicenter, double-blind, placebo-controlled, randomized study to evaluate the efficacy and safety of efpeglenatide once weekly in patients with T2DM inadequately controlled with diet and exercise (AMPLITUDE-M). This study plans to evaluate the safety of once-weekly efpeglenatide injections in addition to demonstrating superiority in comparison to placebo on glycemic control and body weight in patients with T2DM treated with diet and exercise and HbA_{1c} between 7.0% and 10.0% (25). Another study currently being conducted is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effect of efpeglenatide on cardiovascular outcomes in T2DM patients at high cardiovascular risk (AMPLITUDE-O) (26). This trial intends to demonstrate that efpeglenatide at two different doses is noninferior to placebo on 3-point major adverse cardiac event (MACE) in patients with HbA_{1c} greater than 7% and age 18 years or older with established cardiovascular disease or age 50 years (male), 55 years (female) or older with estimated glomerular filtration rate ≥ 25 and < 60 mL/min and at least one cardiovascular risk factor (26).

Sanofi released plans to conduct a trial studying the efficacy and safety of efpeglenatide versus dulaglutide in patients with T2DM inadequately controlled with metformin (AMPLITUDE-D) (27). This study will enroll patients with T2DM on stable dose of at least 1500 mg/day of metformin or maximum tolerated dose for at least 3 months and HbA_{1c} between 7.0% and 10.0% to evaluate change from baseline to week 56 in HbA_{1c} (27). In addition, a study of the efficacy and safety of efpeglenatide versus placebo in patients with T2DM inadequately controlled with basal insulin alone or in combination with oral antidiabetic drug(s) (AMPLITUDE-L) will begin in the near future (28). This trial will enroll patients with T2DM on basal insulin regimen alone or in combination with oral antidiabetic drugs for at least 6 months with HbA_{1c} between 7.0% and 10.0% to evaluate change in HbA_{1c} from baseline to week 30 (28).

Safety

Among the GLP-1RA drug class, the most noted AE is gastrointestinal (GI) events, which has been consistent with efpeglenatide. Throughout the efpeglenatide trials, it was noted that GI events occur most frequently early in therapy initiation and improve over time (6). These GI events (i.e., nausea, vomiting and diarrhea) are presumed to occur due to the mechanism of the medication, including the delay of gastric emptying or involving the central nervous system (17). Since these potential AEs are well known, it is important to counsel patients at the time of therapy initiation about the potential effects of the medication, such as decreased appetite, weight loss and GI symptoms, to reduce discontinuation rates of the medication (17).

In a 16-week study evaluating 209 patients with efpeglenatide 8, 12 and 16 mg monthly, the most reported AEs were GI disorders (mild to moderate in severity) and some recurrence of GI events was observed during monthly dosing. Both blood pressure and heart rate (HR) profiles remained within the expected range and no specific findings in clinical laboratory results (amylase, lipase, calcitonin, AST and ALT) were found (29). In the 12-week dose-ranging study, injection-site reactions occurred in 3-24% of the subjects in the efpeglenatide arms compared to 36% of subjects in the liraglutide arm. An AE occurred in 51-73% of subjects in the efpeglenatide groups, compared to 81% in the liraglutide group and 62% in placebo (6, 22). Of the GI AEs reported, the highest occurrence was in the efpeglenatide groups, with the 3-mg dose at 53% compared with 44% in the liraglutide group and 30% in placebo (22).

In a 20-week study with obese patients without diabetes, GI disorders were reported as 64.4% to 83.1% in the various efpeglenatide groups compared to 46.7% in placebo groups. Most of the reported nausea and vomiting occurred with the first few injections and subsided over time (23). In addition, injection-site reactions were reported in 21.7% of patients on placebo compared to 8.5% to 18.6% in efpeglenatide groups. Most importantly, treatment-emergent AEs leading to discontinuation of therapy consisted of 4 patients in the placebo arm, 3 patients in the efpeglenatide 4 mg weekly arm, 11 patients in the efpeglenatide 6 mg weekly arm, 7 patients in the efpeglenatide 6 mg every 2 weeks group, and 10 patients on the efpeglenatide 8 mg every 2 weeks dose (23). At week 21 (during the post-treatment follow-up visit), HR and blood pressure change from baseline were calculated showing statistically significant increases in HR with values of 4.7, 6.2, 5.2, 3.6 and 0.5 bpm, respectively, which are within the expected range for GLP-1RAs (23). Treatment-emergent anti-efpeglenatide antibodies were detected in 20.0% of the subjects taking efpeglenatide (47 out of 235 patients) with the highest occurrence with the 8-mg biweekly dose. However, it is important to note that none of the patients with positive drug antibodies showed neutralizing antibody against efpeglenatide and there was no effect on efpeglenatide efficacy (23).

Conclusions

Efpeglenatide, a novel investigational GLP-1RA, has demonstrated positive effects on beta-cell function, HbA_{1c}, FPG and weight throughout completed clinical trials. Its effects on numerous components of the Ominous Octet secure its value in decreasing blood glucose concentrations, aiding in the management of DM. Efpeglenatide's long-acting effect through the LAPSCOVERY technology presents an advantage of once-weekly or once-monthly dosing compared to other medications in the GLP-1 class. The extended half-life

establishes a benefit to patient adherence and quality of life. Similarly to other GLP-1RAs, efpeglenatide has shown to be consistent with GI side effects. However, the slow titration of this medication may prove beneficial in decreasing this effect which diminishes over time. Phase III clinical trials are currently being conducted with efpeglenatide and the results are expected to further establish its potential benefit in the class of GLP-1RAs.

Disclosures

The authors state no conflict of interests.

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