Pharmacokinetic Properties and Effects of PT302 After Repeated Oral Glucose Loading Tests in a Dose-Escalating Study

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ABSTRACT

Background: PT302 is a sustained-release exenatide under clinical development for the treatment of type 2 diabetes mellitus.

Objective: The aim of this study was to evaluate the pharmacokinetic properties, pharmacodynamic properties, and tolerability of PT302 after a single subcutaneous injection in healthy individuals.

Methods: A dose-block randomized, double-blind, placebo-controlled, dose-escalating study (0.5, 1, 2, and 4 mg) was performed in 34 healthy individuals. The plasma concentrations of exenatide in serial blood samples were quantified for 56 days after dosing with an exendin-4 fluorescent immunoassay kit. Noncompartmental analysis was performed to assess the pharmacokinetic characteristics of PT302. Oral glucose tolerance tests were repeated weekly until day 42; the concentrations of serum glucose, serum C-peptide, plasma insulin, and plasma glucagon were measured for 2 hours to evaluate the pharmacodynamic characteristics of PT302. Clinical laboratory tests, vital signs, physical examinations, 12-lead ECGs, and adverse events were monitored to evaluate the safety profile and tolerability.

Results: PT302 exhibits a biphasic pharmacokinetic profile, with the initial peak occurring 2 hours after administration. PT302 was quantifiable in the plasma until days 23, 30, 32, and 55 (median) in the 0.5-mg, 1-mg, 2-mg, and 4-mg dosage groups of PT302, respectively. Systemic exposure increased proportionally to the dose during the entire dose range investigated. The pharmacodynamic effect of PT302 on the postprandial response of insulin and C-peptide was significant on days 21 to 28 at the 4-mg dose and was positively correlated with plasma exenatide concentrations, whereas the correlations with glucose and glucagon were not significant. The fasting levels of these pharmacodynamic biomarkers were not altered by PT302. The most common adverse events were injection site induration and pruritus related to inflammatory foreign body reaction, which were mild and spontaneously resolved within several weeks.

Conclusion: The pharmacokinetic characteristics of PT302 were biphasic and dose proportional. A single 4-mg dose of PT302 significantly increased the insulin and C-peptide response to oral glucose loading and was well tolerated in healthy individuals. ClinicalTrials.gov identifier: NCT00964262. (*Clin Ther*. 2014;36:101–114)

Key words: exenatide, pharmacodynamic properties, pharmacokinetic properties, sustained release, tolerability.

INTRODUCTION

Type 2 diabetes mellitus is a progressive disease characterized by peripheral insulin resistance, pancreatic β-cell dysfunction, and subsequent insufficient insulin secretion, resulting in the failure of homeostatic glycemic regulation. Because the pathophysiology of type 2 diabetes is complex and the control of circulating glucose levels is sometimes restrictive, new classes of antidiabetic agents have recently been developed.[1]

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Glucagon-like peptide 1 (GLP-1) agonists are a new class of antidiabetic agents. GLP-1 is an incretin hormone secreted from enteroendocrine L-cells in the intestinal mucosae, which are stimulated by food intake.[2] After reaching the liver and pancreas through the mesenteric capillaries and portal vein, GLP-1 stimulates insulin secretion and reduces glucagon secretion by binding to its specific receptors on pancreatic cells and increases β-cell mass by enhancing cell proliferation and inhibiting apoptosis. It has also been reported that GLP-1 is synthesized in certain areas of the brain, such as the nucleus of the tractus solitarius and the area postrema. Its receptor is distributed among the pancreatic islets, brain, heart, kidney, and gastrointestinal tract.[3] GLP-1 regulates blood glucose levels, appetite, food intake, and weight directly via its specific receptors or indirectly via gut-brain and brain-periphery pathways in response to blood glucose levels. The concentration of GLP-1 in the blood has been reported as one of the hormones responsible for the incretin effect, which is significantly reduced in those with type 2 diabetes.[4,5] GLP-1 regulates blood glucose levels, appetite, food intake, and weight through the gut-brain axis by increasing postprandial insulin release, reducing glucagon secretion, and delaying gastric emptying in response to blood glucose levels. The concentration of GLP-1 in the blood has been reported to be responsible for the incretin effect, which is significantly reduced in those with type 2 diabetes.[4,5] The incretin effect is the augmentation of insulin secretion in response to oral glucose loading relative to intravenous glucose infusion.[6] In vitro and in vivo studies have found that GLP-1 regulates the expression and apoptosis of β-cells and improves β-cell function.[7–9] For these reasons, various GLP-1 agonists were developed as treatments for type 2 diabetes.

Exenatide is the first GLP-1 agonist to be marketed as a treatment for type 2 diabetes. A 1-year randomized controlled trial found that treatment with exenatide induced a 2.46-fold higher C-peptide response to combined glucose and arginine stimulation with weight reduction compared with insulin glargine treatment in metformin-treated type 2 diabetic patients.[10] Because exenatide is resistant to rapid degradation by dipeptidyl peptidase IV (unlike endogenous GLP-1), the half-life of the drug is 2.5 hours, much longer than the 1- to 2-minute half-life of endogenous GLP-1, with the clinical effect of exenatide lasting up to 8 hours.[11,12] Therefore, exenatide is recommended to be administered twice daily via subcutaneous injection.

An extended-release formulation of exenatide* with a once-weekly regimen has been developed for a more favorable, less frequent treatment regimen. This formulation was approved for marketing in Europe in 2011 and the United States in 2012.[13] The release control agent of this formulation is a D,L-lactide-co-glycolide (PLGA), which has been used in encapsulation of macromolecular groups, such as proteins, peptides, genes, and vaccines.[14,15]

PT302 is also a sustained-release (SR) exenatide that uses PLGA microparticles and is under clinical development by Peptron Inc (Daejeon, Republic of Korea); PT302 is manufactured through an ultrasonic spraying drying process using SMARTDEPOT technology (Peptron Inc, Daejeon, Korea), endowing it with several advantages over exenatide. Exenatide is composed of large polymers to minimize the initial burst-related adverse effects. Large polymers are responsible for a number of drawbacks, such as low bioavailability, large dosage deviation, and higher injection site toxic effects. However, the proprietary technology that Peptron uses to coat microparticles with L-lysine allows PT302 to suppress the initial burst and overcome the disadvantages of large polymers. In addition, the smaller particle size of PT302 makes it possible to reduce the needle size (25 vs 23 G for exenatide) and the pain of injection. The primary aim of this study was to investigate the pharmacokinetic properties and tolerability of a single dose of PT302 in healthy individuals to meet the regulatory requirements for drug labeling and marketing in Korea. The secondary aim of the study was to explore its effect on the intact glucoregulatory system during 6 weeks.

MATERIALS AND METHODS

This study was a Phase I first-in-human study designed as a dose-block randomized, double-blind, placebo-controlled, parallel-group, single-dose, dose-escalating clinical trial to assess the pharmacokinetic, pharmacodynamic, and safety profiles of PT302, a long-acting exenatide. The protocol was approved by the Korean Food and Drug Administration and the institutional review board of Seoul National University Hospital

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