Transdermal Exenatide Delivery in Patients with Type 2 Diabetes: Pharmacokinetic and Pharmacodynamic Evaluation

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Abstract

Objective Exenatide, a GLP-1 receptor agonist administered twice daily (BID) via subcutaneous (SC) injection, improves glycemic control when added to standard of care therapy for patients with type 2 diabetes. The Exenatide PassPort® System is a drug-device combination product designed to be used by patients with type 2 diabetes (see Fig 1).

Introduction

Exenatide, a GLP-1 receptor agonist administered twice daily (BID) via subcutaneous (SC) injection, has been demonstrated to improve glycemic control, often with associated weight reduction.

A once-daily transdermal exenatide patch is designed to provide sustained exenatide concentrations in patients with type 2 diabetes.

The exenatide patch utilizes the microporation technology developed by Altea Therapeutics (PassPort® System) that enables transdermal delivery by creating aqueous microchannels through the stratum corneum into the viable epidermis.

The Exenatide PassPort® System is a drug-device combination product designed to be used by patients with type 2 diabetes (see Fig 1).

Objective

This double-blind, placebo controlled, 3-period, 3-treatment study evaluated the pharmacokinetic/pharmacodynamics (PK/PD) and safety of the exenatide transdermal patch (TDP) in subjects with type 2 diabetes.

Methods

This Phase 1 study was a PK/PD study involving three treatments: an active exenatide patch, a placebo patch, and a subcutaneous injection (SC) in a 3-way crossover study.

Subjects were randomly assigned to one of three treatment sequences (Table 1).

Eleven patients with type 2 diabetes were enrolled and 9 subjects completed the study (Table 2).

On separate days, subjects received a single dose of exenatide TDP (1.9 mcg exenatide, 3 cm²), placebo TDP (3 cm²), or exenatide SC (10 mcg BID by SC injection).

The investigator and subject were blinded to exenatide/placebo TDP content. The placebo TDP had the same excipient composition as the exenatide TDP and did not contain exenatide. The placebo TDP was used as a control to assess skin responses to the patch independent of exenatide exposure.

A standardized breakfast, lunch and dinner meal were provided. For TDP, meals were given after application (3, 7, 13 h) and the patch was removed after 24 h. For SC, meals were given at 0, 5, 10 h and injections were administered just prior to breakfast and dinner. The washout prior to subsequent treatments was 24 h after patch removal and 14 h after the last SC injection.

The skin response to the patch was evaluated by visual scoring (modified Draize scale) and transepidermal water loss (TEWL) measurements.

Blood samples were collected for determination of plasma exenatide and glucose concentrations throughout the study. Exenatide concentrations were determined by a proprietary Enzyme-Linked Immunosorbent Assay (ELISA) (LLOQ 10 pg/mL) and TEWL was determined by assay on a Roche Modular Analyser (keratinase enzymatic method).

Pharmacokinetic parameter estimates for exenatide and glucose concentrations were calculated by standard noncompartmental methods of analysis using WinNonlin Enterprise 5.0.1

Results & Discussion

• A single dose exenatide patch application, plasma exenatide concentrations increased gradually for 10 hours reaching a Cmax of 301 pg/mL. On average, plasma concentrations were sustained at approximately 250 pg/mL until the patch was removed at 24 hours (Fig 2).

• Plasma exenatide concentrations were maintained above 50 pg/mL for 21 hours (median) with a range of 14-25 h (Fig 2). A The minimum effective plasma exenatide concentration required for a glucose lowering effect is 50 pg/mL.

PassPort® Patch

Exenatide Transdermal

500 g

400 g

800 g

Fig. 1 Exenatide PassPort® Transdermal Delivery System

Fig. 2 Transdermal exenatide (mean +SD) vs. SC exenatide (mean –SD) clinical PK

Fig. 3 Transdermal exenatide clinical pharmacodynamics (mean plasma glucose concentration). Meals marked for breakfast (B), lunch (L), dinner (D) and SC injections marked (SC).

• The relative bioavailability of the exenatide patch compared to the 10 mcg SC injection was approximately 3% using a patch formulation that was not optimized for bioavailability.

• Single transdermal doses of exenatide were safe and generally well tolerated by subjects with type 2 diabetes when administered for 24 hours in this study. The most frequently reported drug-related adverse events were nausea, headache and vomiting with exenatide TDP demonstrating a higher incidence than SC injection due to the higher plasma exenatide concentrations achieved. In some subjects, there was mild transient erythema at the application site seen after patch removal.

• The skin response as measured on a modified Draize scale and skin barrier function as measured by TEWL were similar between the sites treated with placebo and exenatide TDP indicating that the mild erythema was primarily due to the process of creating micropores in the stratum corneum.

Conclusion

This study showed that exenatide can be administered by the transdermal route resulting in sustained therapeutic plasma exenatide concentrations and postprandial glucose lowering in patients with type 2 diabetes.

References

1. Bystedt et al., http://pubs.acs.org/doi/abs/10.1021/b800965g