

Summary

An estimated 280 million people have diabetes worldwide and the long-term consequences include blindness, kidney failure, coronary artery disease and lower limb amputation. Global expenditures on diabetes were estimated to be at least \$418 billion in 2010 and are projected to be at least \$561 billion by 2030. Most pharmaceutical treatments for diabetes have an increased risk of hypoglycemia and weight gain. These adverse effects often limit their usefulness and, in the case of weight gain, may add to the progressive nature of the disease. Thus, safe and effective therapies for diabetes that result in weight loss could have a major impact on long-term health outcomes.

One such treatment is exenatide. Exenatide is a peptide that was identified from the saliva of the gila monster, a lizard native to the southwestern United States and northwestern Mexico. Unlike most diabetes treatments, exenatide lowers blood glucose during hyperglycemia, but not during hypoglycemia. In addition, exenatide reduces appetite, often leading to weight loss with long-term use. Exenatide was one of the first glucagon-like peptide-1 (GLP-1) receptor (GLP 1R) agonists to be identified and to progress through clinical development. It shares 53% sequence identity with human GLP-1, a hormone secreted by intestinal L cells in response to nutrients and is equipotent at the GLP-1 receptor. This thesis describes the development of exenatide as a treatment for diabetes. The original formulation is injected twice a day prior to the morning and evening meals. A second formulation is also described that uses an extended-release technology to provide continuous exposure with only once a week administration.

This thesis manuscript focuses on specific components of that clinical development plan that helped to make exenatide-based therapies available to patients. While native exenatide has a high potential as a therapeutic based on its pharmacokinetic and pharmacodynamic properties, the clinical development plan needed to determine 1) the dose(s) that provided an optimal balance between tolerability and effect size and 2) the optimal dose timing and dose frequency that provided a balance between patient convenience and overall effect. Additionally, as there is a strong dose-dependence to nausea and vomiting, strategies to reduce gastrointestinal adverse effects needed to be considered.

Chapter 2 describes the first 28-day clinical study of this class of type 2 diabetes therapies (GLP-1 receptor antagonists) and was designed to study the effects of twice-daily (BID) injections of exenatide at breakfast and dinner or breakfast and bedtime and three times a day (TID) injections at breakfast, dinner, and bedtime. Lunch injections were not studied as compliance for mid-day administration is typically poor. The bedtime injection was studied to determine if night-time exenatide exposure could improve the fasting glucose level the next day despite the relatively short (6-7 hour) pharmacokinetic profile of exenatide.

Chapter 3 describes a clinical study designed to determine if dose titration can be used to induce tolerance to the gastrointestinal side effects observed with high doses of exenatide. Results from the study described in Chapter 3 were used to design the drug initiation strategy for Phase 3 studies and ultimately for commercial use.

Chapter 4 describes the single dose and multiple dose clinical studies of the exenatide extended-release formulation. These studies were designed to determine the optimal dose regimen that would provide continuous exenatide exposure in the therapeutic range as defined in the exenatide BID development program. The chapter also includes an assessment of the plasma concentrations of exenatide necessary to achieve a postprandial glucose lowering effect compared to a fasting glucose lowering effect.

Chapter 5 provides a review of the differential effects of GLP-1 mediated therapies (DPP- 4s, short-acting GLP-1R agonists and GLP-1R agonists that provide continuous exposure) on fasting and postprandial glucose. The chapter also provides support for the hypothesis that continuous GLP-1 receptor activation results in tachyphylaxis of the gastric emptying effect, thus reducing the effect on postprandial glucose. The clinical implications of this hypothesis are also discussed.

Lastly, peptide and protein therapeutics have the potential to induce an immune response even when the drug is identical to the endogenous human peptide, as reported for exogenously administered human insulins. The consequences of such a response vary widely and include possible effects on efficacy, safety, and on endogenous systems if the antibody cross-reacts with an endogenous peptide. Chapter 6 provides an extensive characterization of the incidence, time course, and clinical consequence of anti-exenatide antibodies resulting from chronic administration of exenatide BID and exenatide once weekly. Throughout this manuscript, the terms exenatide, exendin-4, and AC2993 (the chemical compound number for exenatide) are used interchangeably.