The Extended Duration Single Dose Pharmacokinetics (PK) and Pharmacodynamics (PD) of AB101, a Potential Once Weekly Basal Subcutaneous (SC) Insulin, in Diabetic Minicathe Mouse

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ABSTRACT

Ultra-long-acting basal insulins may lead to improved glycemic control with less weight gain and fewer hypoglycemic episodes compared to currently available insulin regimens. AB101 is a microsphere-based extended action insulin analog (PEGylated human recombinant insulin) showing unique pharmacokinetic and pharmacodynamic profiles compared to currently available basal insulins, resulting in a slow onset and sustained increase in insulin levels with reduction over an extended duration of 5 to 10 days in normal rats and dogs. Due to similarities in anatomy and metabolism, pigs are a useful animal model for the study of human diabetes, and are highly predictive of the SC absorption, PK, and pharmacodynamics of current insulins in diabetes therapies (Larsen and pollen, 2004, Lin et al., 1999). Previously, we reported on the PK and PD of AB101 administered as a single SC dose (7 mg/kg) in rats and dogs (Figure 1). The PEGylated human recombinant insulin encased in microspheres for SC injection. The extended duration time-action profile is consistent with the depot release properties, not by reduced peak insulin clearance. Peg insulin dose exhibits comparative pharmacological activity to human insulin, in vivo (Figure 1). AB101 is a single dose SC regimen that results in a slow onset and sustained increase in insulin levels with reduction over an extended duration of 5 to 10 days in normal rat and dog models (Figure 2). AB101 was well tolerated and had no clinically apparent hypoglycemic episodes.

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INRODUCTION AND BACKGROUND

Diabetes, Insulin Management, and Unmet Need

Earlier use of insulin, particularly basal insulin, is increasingly recognized as an important therapeutic modification to the native recombinant insulin structure. Although the current insulin market is highly competitive, multiple opportunities for novel insulin therapies exist. For unclear reasons, there is no clinically applicable method to provide insulin delivery over a total duration of approximately one week, without acute or delayed hypoglycemia. AB101 was developed to fill this unmet need.

METHOds

Study Population and Design

In multiple nonclinical studies, once on stable dose for approximately 10 days, daily fasting and P.M. glucose levels were obtained in unanesthetized rats and dogs (Figure 3). The same animals were then dosed once a week with AB101 and daily P.M. glucose levels were obtained (Figure 4). Results demonstrated a slow onset and sustained increase in insulin levels and corresponding sustained glucose reductions to near normal levels over a duration of ~ 1 week. Consistent to the onset and duration of action of AB101, background hypoglycemia was able to be avoided off. AB101 was well tolerated and well tolerated. In summary, in a human relevant diabetic model at clinically applicable doses, AB101 produced sustained insulin increases without release, and clinically significant glucose lowering over the extended period of injection. These results make it feasible to administer AB101 as a weekly SC basal insulin in patients with diabetes mellitus, Clinical Trials of AB101 are planned.

RESULTS

Study Objectives: AB101 in a Human-Relevant Diabetes-Insulin Model

Pigs are a useful animal model for the study of human diabetes, and are highly predictive of therapeutic potential of chemical modification to the native recombinant insulin structure. The objective of this study was to determine the PKPD profile of AB101 after a single dose SC administration to albino rabbit diabetic minicatheter (mini-pig) not considered on existing insulin therapy. AB101 achieved systemic exposure of a single SC dose of AB101 and showed substantial increase in insulin levels with reduction over 14 days in rats and dogs. Abnormal fasting blood glucose levels were observed, in conjunction with an increase in frequency and size of food. The extended duration time-action profile is consistent with the depot release properties, not by reduced peak insulin clearance. Peg insulin dose exhibits comparative pharmacological activity to human insulin, in vivo (Figure 1). AB101 is a single dose SC regimen that results in a slow onset and sustained increase in insulin levels with reduction over an extended duration of 5 to 10 days in normal rat and dog models (Figure 2). AB101 was well tolerated and had no clinically apparent hypoglycemic episodes.

RESULTS (CONT.)

Simulated Repeat (Weekly) Dose Pharmacokinetics of AB101 in Albino-Diabetic Minicatheter Rats (Figure 5)

Sustained plasma Peginsulin concentrations were achieved during the run-in period, in the days leading up to and during the study. This was achieved without any overt changes in food, the observed single dose PK profile, to simulate time to steady state and intermittent feeding treatment options. Animals received a single dose of AB101 (7 mg/kg) on Study Day 0. After an overnight fast, food was provided 24hours after dosing and blood sampling.

CONCLUSIONS AND DISCUSSION

A single SC dose of AB101 in Albino-diabetic mini-pigs resulted in sustained plasma Peginsulin-PK and pharmacodynamic effects over the dosing interval, with near normalization of glucose and the ability to stop other insulins. Glycemic control improved at both the morning and evening measurement with less intra-day variability between these measurements, in the setting of stopping both a) NPH and b) Glucophage. Repeat dose simulations predict a nearly flat or continuous insulin profile as suggested by a nearly flat or continuous glucose profile over the entire dosing interval. Taken together, actual and simulated results may reasonably predict that an ultra-long acting insulin such as AB101 could establish endogenous insulin-glucose homeostasis, reduce glycemic variability, and decrease the incidence of hypoglycemia. In multiple nonclinical development studies, no acute or delayed hypoglycemia was observed, in conjunction with an increase in frequency and size of food. The extended duration time-action profile is consistent with the depot release properties, not by reduced peak insulin clearance. Peg insulin dose exhibits comparative pharmacological activity to human insulin, in vivo (Figure 1). AB101 is a single dose SC regimen that results in a slow onset and sustained increase in insulin levels with reduction over an extended duration of approximately 1 week, without acute or delayed hypoglycemia (Figure 3). AB101 administered as a single subcutaneous dose produced a slow onset and sustained increase in total body glucose over a total duration of approximately one week, without acute or delayed hypoglycemia. AB101 dose, further insulin increases were not permitted. The observed single dose PK profile, to simulate time to steady state and intermittent feeding treatment options. Animals received a single dose of AB101 (7 mg/kg) on Study Day 0. After an overnight fast, food was provided 24hours after dosing and blood sampling.

安全性和可接受性

在负荷后，模型预测的总周间血糖减少率与实际观察的周间血糖减少率相符。在负荷后，模型预测的总周间血糖减少率与实际观察的周间血糖减少率相符。在负荷后，模型预测的总周间血糖减少率与实际观察的周间血糖减少率相符。在负荷后，模型预测的总周间血糖减少率与实际观察的周间血糖减少率相符。在负荷后，模型预测的总周间血糖减少率与实际观察的周间血糖减少率相符。