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

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Abstract

Ultra long-acting basal insulins may lead to improved glycemic control with less weight gain and fewer injections, thereby optimizing initiation of and adherence to an insulin regimen. AB101 is a microsphere formulation (MS-form) of a 5 KDa PEGylated human recombinant insulin (peginsulin) and is being developed as a once weekly basal insulin. We previously reported results showing that the in vitro pharmacology of this peginsulin is comparable to native insulin, while the MS-form administered SC resulted in a slow onset and sustained increase in insulin levels with glucose reduction over an extended 5 to 10 day period 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 pharmacology of potential therapies (Larsen and Rolin, 2004; Lin et al, 1998). Presently, we report the PK and PD of AB101 administered as a single SC dose (7 mg/kg) to alloxan-induced diabetic Yucatan miniature swine (n=4) not controlled on an existing insulin regimen (baseline glucose 310 ± 27 mg/dL). Fasting peginsulin (ELISA) and glucose (glucometer) were measured at baseline and repeatedly over a 14 day period after dosing. Results demonstrated a slow onset and sustained increase in peginsulin, and corresponding sustained glucose reductions to near normal levels over a duration of ~ 1 week. Concomitant to the onset and duration of action of AB101, background insulin was able to be weaned off. AB101 was safe and well-tolerated. In summary, in a human relevant diabetes model at clinically applicable doses, AB101 produced sustained insulin increases without acute release, and clinically significant glucose lowering over the extended period of the study, making it feasible to administer AB101 as a weekly SC basal insulin in patients with diabetes mellitus. Clinical trials of AB101 are planned.

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Introduction and Background

Diabetes, Insulin Management, and Unmet Need

- Earlier use of insulin, particularly basal insulin, is increasingly recognized for its importance in restoring endogenous insulin-glucose homeostasis, leading to better glycemic control and potentially improved outcomes.[1,2,3]
- Barriers to insulin use include prescribing aversions, needle or insulin averse patients, and concerns over weight gain and hypoglycemia.[4,5]
- An ultra-long acting basal insulin could lead to improved glycemic control with less weight gain and hypoglycemia, potentially offering a safer, more effective, more convenient treatment option.
- There are no approved insulins with a duration of action > 24-36 hours.

AB101 is Being Developed as a Once Weekly Basal SC Insulin

- AB101 is pegylated (5 kDa PEG) native human recombinant insulin, encapsulated into microspheres for SC injection.
- In contrast to currently available basal insulin analogs, AB101 requires no modification to the native recombinant insulin structure.
- The extended duration time-action profile is conferred by the depot release properties, not by reduced peginsulin clearance.
- Peginsulin (drug substance) exhibits comparable pharmacologic activity to human insulin, *in vitro* (Figure 1).
- AB101 (drug product) administered SC resulted in a slow onset and sustained increase in insulin levels with glucose reduction over an extended 5 to 10 day period in normal rats and dogs (Figure 2).

Figure 1: Activity in Cell-Based Signal Transduction (left) and Functional Assays (right)

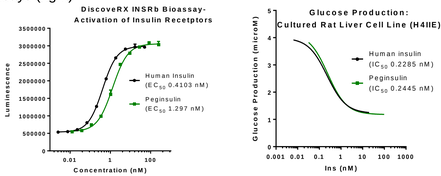
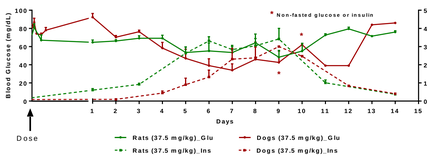


Figure 2: Slow Onset and Sustained Pharmacology of AB101 Administered as a Single SC Dose in Normal Sprague Dawley Rats and Beagle Dogs



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 potential therapies.[6,7]
- The objective of this study was to determine the PK/PD profile of AB101 after single dose SC administration to alloxan-induced diabetic Yucatan miniature swine ('mini-pig') not controlled on existing insulin therapy.

Methods

Study Population and Design

- 4 male diabetic Yucatan mini-pigs ≥ 3 mo. old and ≥ 20 kg in weight
- Indwelling vascular access ports and induction of diabetes with alloxan were per CRO standard procedure
- During a study run-in period, animals were switched from their usual insulin to a regimen of NPH (QAM) and Glargine (QPM), titrated to achieve glucose stability to a target blood glucose (BG) value of 250-400 mg/dL. After AB101 dosing, further insulin increases were not permitted, but reductions could be made to avoid hypoglycemia
- Animals received a single dose of AB101 (7 mg/kg) on Study Day 0.
- After an overnight fast, food was provided 2x/day after dosing and blood sampling.

Assessments and Endpoints

- Serial 2x/day BG measurement (~ 8 am and ~ 5 pm) from baseline through Day 14, using an AlphaTrax® glucometer.
- Fasting peginsulin was performed using a peginsulin-specific ELISA at baseline and at Days 0 (2 hour), 1, 3, 5, 7, 8, 9, 10, 12, and 14 post-dose.
- Background insulin needs were assessed and recorded on a daily basis as an additional surrogate of the time-action effect of AB101.
- Animal health and injection sites were observed daily.
- Concentration-time profiles were constructed to characterize the AB101 single dose PK (peginsulin), PD (glucose), and time action profile.
- Repeat dose concentration-time curves were generated using modeling of the observed single dose PK profile, to simulate time to steady-state and peak to trough ratio with once weekly dosing of AB101.
- No formal analytical methods were used, and all results are presented descriptively.
- For unclear reasons, peginsulin levels were not detected in one animal who was injected with investigational product which was labeled AB101. This animal was nevertheless included in the primary PK-PD data summary, but was excluded from the repeat dose simulations, to give a more accurate representation of the likely repeat dose kinetics.

Results

Table 1: Baseline Characteristics

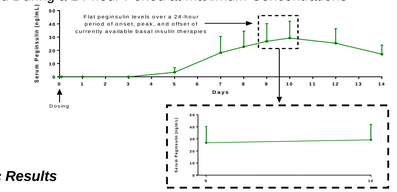
	Pig #1	Pig #2	Pig #3	Pig #4	Mean
Age (months)	50	50	54	52	----
Weight (kg)	55.4	58.9	51.2	57.8	----
Glucose (mg/dL)					310
Fasting	429	319	391	341	370
PM	262	189	276	272	250
Daily Background Insulin (units)					
NPH	7	6	7	6	----
Lantus	12	12	7	9	----
Total	19	18	14	15	16.5

Results (cont.)

Single Dose PK (Peginsulin Concentration-Time Profile)

- AB101 administered as a single subcutaneous dose produced a slow onset and sustained increase in peginsulin levels over a total duration of approximately one week, without acute or delayed burst (Figure 3).

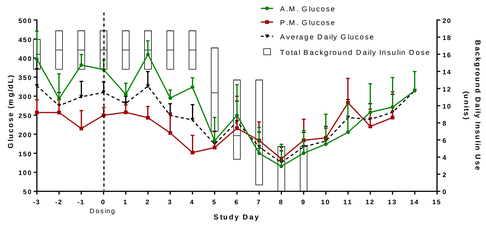
Figure 3: Mean (± SEM) Peginsulin Levels in Alloxan-Induced Diabetic Mini-Swine Over a 14 Day Period After Administration of a Single SC Dose of AB101 and During a 24-hour Period at Maximum Concentrations



Glycemic Results

- Glycemic stability within the target range and stable background insulin doses were achieved during the run-in period, in the days leading up to and including AB101 dosing.
- AB101 produced slow onset and sustained reductions in glucose over a total duration of approximately one week, which corresponded qualitatively to the observed peginsulin time-action profile (Figure 4). Additionally:
  - Concomitant to the onset and duration of action of AB101, background insulin administration was slowly weaned then stopped;
  - Improvement in glucose was noted overall and at the individual a.m. and p.m. measurements; and
  - Less intra-day (a.m. to p.m.) variability in glycemic control was observed after AB101 injection compared to existing insulin therapy.

Figure 4: Mean (± SEM) Glucose Levels and Median (Min,Max) Total Daily Insulin Requirements in Alloxan-Induced Diabetic Mini-Swine Over a 14 Day Period After Administration of a Single SC Dose of AB101

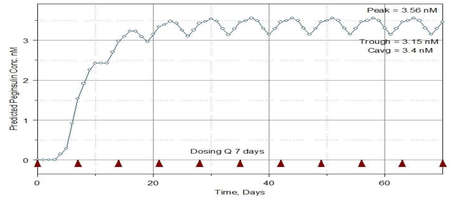


Simulated Repeat (Weekly) Dose Pharmacokinetics (Shown in Figure 5)

- Steady-state achieved after 2 to 3 weekly doses;
- Approximately a 2-fold accumulation in peginsulin levels with once weekly repeat dosing; and
- A nearly flat or continuous insulin profile as suggested by a peginsulin peak to trough ratio of 1.1.

Results (cont.)

Figure 5: Simulated Peginsulin Concentration-Time Profile of Repeat (Weekly) SC Dosing of AB101 in Alloxan-Induced Diabetic Miniature Swine



Safety and Tolerability

- Increases in food consumption and minimal increases in body weight were observed, in conjunction with an increase in frequency and size of food offering as preventive measures against hypoglycemia.
- AB101 was safe and well tolerated, with no clinically apparent hypoglycemia.

Conclusions and Discussion

- A single SC dose of AB101 in Alloxan-induced diabetic mini-pigs resulted in a slow onset and sustained PK-PD effect over the duration of ~ 1 week, with near normalization of glucose and the ability to stop other insulins.
- Glucose control improved at both the morning and evening measurements with less intra-day variability between these measurements, in the setting of stopping both a.m. NPH and p.m. Glargine.
- Repeat dose simulations predict a nearly flat or peakless steady state insulin profile over the entire weekly dosing interval.
- Taken together, actual and simulated results may reasonably predict that an ultra long-acting insulin such as AB101 could stabilize endogenous insulin-glucose homeostasis, reduce glycemic variability, and decrease the incidence of hypoglycemia.
- In multiple non-clinical development studies, no acute or delayed sudden insulin release has occurred.
- Clinically relevant human doses are readily predicted from usual insulin needs and animal studies, and can be delivered via acceptable volumes and needle gauge.
- To our knowledge, AB101 is the only non-analog (native human insulin) to have an extended duration of action.
- AB101 is being developed as a once weekly basal insulin for subcutaneous injection; Clinical trials are planned.

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