[redacted] (PB1023) a Novel GLP-1 Analogue Dose Dependently Reduces Meal Challenge Induced Glucose Exposure Following a Single Subcutaneous Dose

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ABSTRACT

[redacted] PB1023) is a 636 amino acid polypeptide of GLP-1 (~5% of molecular weight) genetically fused to a physiologically inert repeating peptide polymeric expressed in *E.coli*. [redacted] retains potency similar to native peptide and is formulated as a liquid for SC administration. This study assessed single dose safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in adults with T2DM.

Subjects treated with 1 or 2 oral anti-diabetic drugs (OAD) discontinued their OADs during a minimum 2 week run-in period. Subjects were randomized (double-blind) to either placebo or PB1023 (1:3) in each cohort. Following a baseline liquid mixed meal tolerance test (MMTT), subjects were dosed. Cohorts were staggered in time and safety, PK and PD was reviewed before escalation through doses 0.1, 0.3, 0.9, 1.35 and 2.0 mg/kg.

[redacted] was well tolerated with no dose related trends in the type and severity of reported adverse events at escalating doses. Two subjects (9%) treated with active study drug reported mild nausea with one event of vomiting at exposures approximately 2-3 fold higher than what is needed to elicit a significant pharmacodynamic effect.

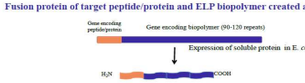
PK parameters showed [redacted] to have a slow flat absorption profile with a sustained duration of exposure in a therapeutic range to support once weekly dosing. FPG average days 1-7 change from baseline days at -2-0 showed dose response with a difference from placebo of -53 mg/dL at the dose 0.9 mg/kg close to maximal effect. Day 2 MMTT Glucose $AUC_{(0\text{-}240\ min)}$ demonstrated a consistent dose response with an ED50 at 0.35 mg/kg in Emax modeli

In conclusion [redacted] has properties that support further development as a once weekly dose.

BACKGROUND AND TECHNOLOGY

PhaseBio's proprietary technology (Figure 1) is based on recombinant biopolymers, called ELPs. The individual subunit or building blocks of ELPs are derived from the five amino acid motif VPGXG where "X" is a guest amino acid. Fusion to ELPs improves significantly the solubility and bioavailability of peptides and proteins, and the fusion protein retains almost identical activity to the native peptide or protein. Modifying the sequence of the individual subunits of the ELP and its length is used to optimize the physical and chemical properties of each ELP-fusion protein or biopolymer-drug conjugate. ELPs can be engineered to form a more compact highly ordered hydrogen bonded structure as a result of excluding its water shell, a highly reversible process. The hydrogen bonding, or phase transitioning, process (Figure 2) can be engineered to occur upon an increase in temperature such as the temperature increase from a room temperature formulation in a syringe to drug delivery at body temperature. Biophysical studies at body temperature indicate that the consequence of this phenomenon would be controlled drug release from the site of administration as the concentration of drug dissipates and the process of hydrogen bonding reverses. The controlled rate of absorption into the circulation may account for the smooth (lack of "burst") and slow absorption in addition to the prolonged half-life, resulting in the optimal drug exposure seen in PhaseBio's preclinical and clinical studies.

Fusion protein of target peptide/protein and ELP biopolymer created at the DNA level



Results in stable, highly active constructs with prolonged half-life

(Note: Active protein/peptide comprises approximately 5% of total molecular weight of a construct)

Figure 1: ELP Fusion Technology Platform

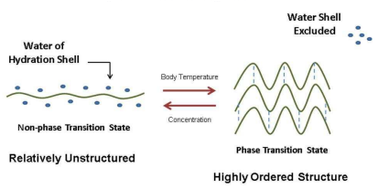
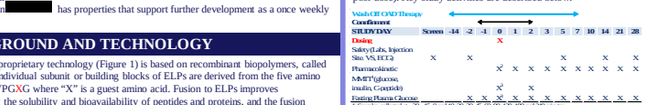


Figure 2: Phase Transition for Controlled Drug Release and Prolonged Half-Life

STUDY DESIGN

This Phase 1/2a study (NCT 01236404) was a randomized, double-blind, placebo-controlled study that was conducted in two parts; Part A as a single ascending dose (SAD) study (topic of this presentation) and Part B as a 4–week multiple (once weekly dosing) ascending dose (MAD) study. The subjects enrolled were males and females 18-75 years of age with Type 2 Diabetes Mellitus requiring treatment with oral antidiabetic agents (OAD) who were in otherwise stable health. Subjects on a background of one OAD were required to have a screening HbA1c between 6-9% and between 6-8.5% when taking up to two oral agents. All subjects were required to have a fasting C-peptide of ≥ 0.8 ng/mL, and Body Mass Index (BMI) ≤ 40 kg/m². Subjects were washed-off from background therapy for a minimum of 14 days prior to dosing with study drug and remained off therapy for 7 days following dosing with study drug. The purpose of the study was to assess safety and tolerability as well as to assess the pharmacokinetic and pharmacodynamic profile of various subcutaneous (SC) doses of [redacted]. Subjects participating in the SAD portion of the study underwent assessment of daily fasting glucose monitoring and liquid meal challenge (pre- and ~ 44 hours post-dose). Key study activities are described below.



DEMOGRAPHICS/SUBJECT DISPOSITION

A total of 24 subjects were enrolled and dosed (refer to Table 1) in the SAD portion of the study . All subjects completed the study as planned.

Table 1: SAD Demographics

Factor	Placebo	[redacted] (PB1023) (mg/kg)				
		0.10	0.30	0.90	1.35	2.00
N	6	3	3	6	3	3
Sex						
Male	5	2	3	4	3	3
Female	1	1	0	2	0	0
Race						
White	5	3	2	3	3	3
Black	1	0	0	3	0	0
Other	0	0	1	0	0	0
Ethnic						
Not Hispanic or Latino	6	3	3	6	3	3
Age(Years)						
Mean	59.0	60.0	52.0	54.3	53.7	56.0

RESULTS - SAFETY

No serious adverse events (SAEs) or dose limiting toxicities were reported. There were no dose related trends in changes in laboratory parameters (chem-12, LFTs, amylase/lipase, CBC, or UA/Micro), VS (HR, BP, RR and temperature), or ECGs that would indicate a safety concern. Table 2 is a summary of adverse events occurring in 2 or more subjects receiving Glymera™ or placebo.

Table 2: **Adverse Events Reported in ≥ 2 Subjects Receiving a Single Subcutaneous Dose of [redacted] (PB1023) or Placebo**

Adverse Event	Placebo	[redacted] (PB1023)				
		Subjects (%) [No of Events] 0.1mg/kg	Subjects (%) [No of Events] 0.2mg/kg	Subjects (%) [No of Events] 0.9 mg/kg	Subjects (%) [No of Events] 1.35 mg/kg	Subjects (%) [No of Events] 2.0 mg/kg
N	6	3	3	6	3	3
Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%) 1 †	0 (0.0%)	1 (33.3%) 1 †
Chills	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%) 2	0 (0.0%)	0 (0.0%)
Injection Site Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (50%) 4**	0 (0.0%)	2 (66.7%) 2*
Upper Respiratory Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%) 1	1 (33.3%) 1	0 (0.0%)
Headache	1 (16.7%) 1	0 (0.0%)	0 (0.0%)	2 (33.3%) 2	0 (0.0%)	1 (33.3%) 1

* Pain reported in the first three subjects dosed with hypotonic formulations. Formulation subsequently adjusted with sodium chloride to render formulation nearly isotonic for subsequently dosed subjects.
† Events of interest reported as mild.

RESULTS - PHARMACOKINETICS

The pharmacokinetic (PK) analysis population consisted of all subjects dosed and who had sufficient data for PK analysis. PK showed a combination of a slow absorption and long half-life [flip-flop kinetics] (Figure 3) following single subcutaneous doses of [redacted]. All subjects were dosed in the abdomen. Depending on the dose level, subjects received between 1 and 9 injections in close proximity in order to deliver a complete dose. Calculations were based on non-compartmental analysis. Serum concentrations less than the validated lower limit of the bioanalytical method were taken as zero for calculation of descriptive statistics at all sampling time-points. Area under the curve (AUC) and maximum concentration (C_{max}) showed dose-proportionality (Figure 4). There are no apparent relationships between clearance (CL/F), body weight (Figure 5) and BMI (data not shown). Based on these data, dosing of [redacted] is amenable to a fixed dose regimen.

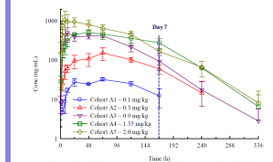


Figure 3: Arithmetic [redacted]erum Concentrations Following Single SC Dose of [redacted] – Semi-logarithmic Axis

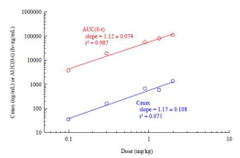


Figure 4: Relationship Betw[redacted]max and AUC(0-t) Following Single SC Dose of [redacted]

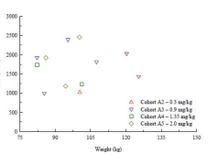


Figure 5: Relationship of Individual Subj[redacted]nd Body Weight Following Single SC Dose of [redacted]

RESULTS - PHARMACODYNAMICS

The pharmacodynamic (PD) analysis population consisted of all subjects dosed and who had sufficient data for PD analysis.

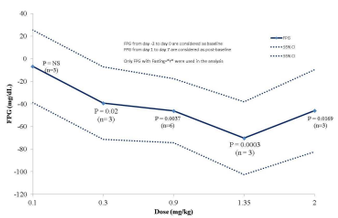


Figure 6: Mixed Model Estimate, Average Change (Days 1, 2, 3, 5 and 7) Fasting Plasma Glucose (FPG) From Baseline - Placebo Adjusted Values

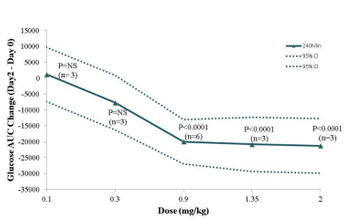


Figure 7: Mixed Model Estimate, Liquid Mixed Meal Mean Glucose AUC (0-240 minutes) (Days 1, 2, 3, 5 and 7) Change From Baseline - Placebo Adjusted Values

The observed model–predicted relationship between change in glucose $AUC_{0\text{-}4\ h}$ following liquid meal challenge on Day 2 (~ 48 hours post –dose which was anticipated to be the mean time to Cmax), and concentration of [redacted] (PB1023) at 48 hours and [redacted] exposure ($AUC_{(0\text{-}48)}$) are displayed below in Figures 8 and 9 respectively. Note: E_{max} modeling was based on a maximum change in glucose AUC following meal challenge of -33,340 ± 8,015 min*mg/dL and the serum concentration at 48 hours as well as maximum AUC change of -28,313 ± 5,359 min*mg/dL and AUC(0-48). The estimated EC_{50} (drug concentration) at 48 hours is 373 ± 185 ng/mL and exposure ($AUC_{(0\text{-}48)}$) is 10,905 ± 5,008 min*ng/mL.

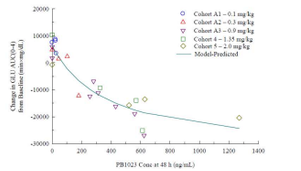


Figure 8: Observed and [redacted]cted Relationship Between Change in Glucose $AUC_{(0\text{-}4\ hours)}$ and [redacted] (PB1023) Concentration at 48 hours

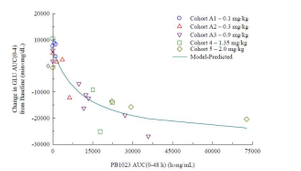


Figure 9: Observed and Mo[redacted]d Relationship Between Change in Glucose $AUC_{(0\text{-}4\ hours)}$ and [redacted] (PB1023) $AUC_{(0\text{-}48)}$

SUMMARY AND CONCLUSIONS

[redacted] is a recombinant glucagon-like peptide-1 (GLP-1) analogue that has been genetically fused to an ELP biopolymer and is manufactured in *E.coli* and is being developed with the intent of once weekly dosing. Single subcutaneous doses of [redacted] in the dose range of 0.1 to 2.0 mg/kg (2 nmol/kg to 39 nmol/kg of active GLP-1 peptide) were well tolerated. The PK profile displayed a smooth slow absorption profile cons[redacted] the predicted mechanism of absorption/long half life of the ELP biopolymer technology. AUC and C[redacted] showed dose-proportionality, and clearance does not appear to be dependent on weight or BMI, which allows for transition to a fixed dose regimen for future clinical trials.[redacted] demonstrated a dose dependent glucose lowering effect consistent between fasting plasma glucose (FPG) and liquid mixed meal AUC glucose. Emax modeling indicates final doses may be found in the dose range studied. The MAD study results will be available in Q4 2011.