Weekly Subcutaneous Doses of [redacted] (PB1023) a Novel GLP-1 Analogue Reduce Glucose Exposure Dose Dependently

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ABSTRACT

[redacted] (PB1023) is a 636 amino acid polypeptide comprised of GLP-1 genetically fused to a physiologically inert repeating polymeric elastin-like peptide expressed in E.coli. [redacted] retains potency similar to native peptide and is formulated as a liquid for sc administration. This study assessed multiple 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 2 week run-in period. 56 subjects were randomized to weekly double blind injections of either placebo or [redacted] for 4 weeks. Subjects were dosed after a liquid mixed meal tolerance test (MMTT). Safety, PK and PD were reviewed before escalation to the next dose of 0.3, 0.6, 0.9, and 1.35 mg/kg, respectively. PK exhibited slow absorption with sustained duration of exposure and minimal accumulation. Dose-response was evident for FPG, MMTT AUC glucose and average glucose (AG) assessed by continuous glucose monitoring (CGM). At the 1.35 mg/kg dose, placebo-adjusted AG change from baseline was -50 mg/dL (≈ -1.8% A1C) (p<0.0001). AG showed minimal loss of efficacy 7 days after the prior dose. CL/F indicated no correlation of clearance to body weight supporting transition to fixed instead of weight-based dosing. The dose and AG data fit an Emax model with Emax of -48 mg/dL compared to placebo, and 80% of that effect (ED80) at a dose of 63 mg. [redacted] was well tolerated. The only dose related trend in adverse events (AE) was nausea at the highest doses. 3 subjects experienced mild or moderate injection site erythema that resolved spontaneously. 1 of these received subsequent doses that did not result in exacerbation or recurrent erythema. This subject and 1 other developed low titer non-neutralizing antibodies. There was no indication of adverse effects on any other safety parameters and no serious AEs reported. Conclusion: [redacted] has properties that support development of 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.

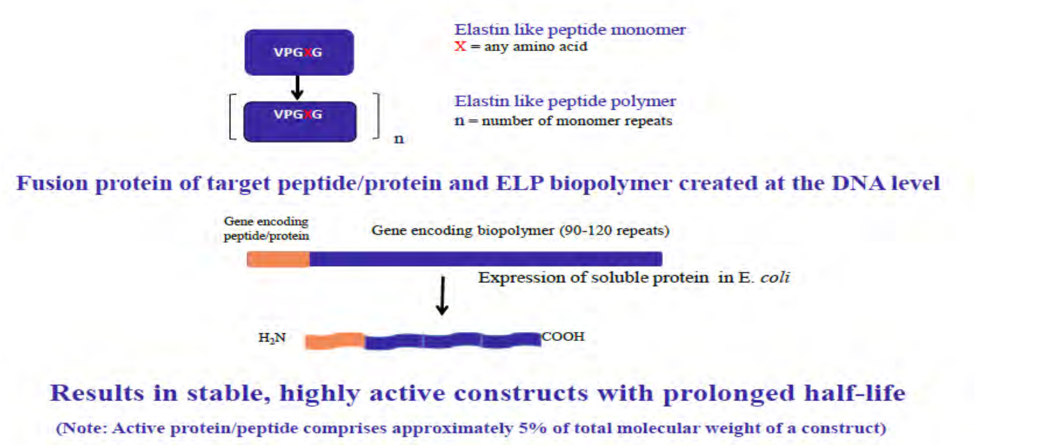

Figure 1: ELP Fusion Technology Platform

ELPs can be engineered to form a more compact highly ordered hydrogen bonded structure as a result of excluding its water shell. The hydrogen bonding, or phase transitioning, a highly reversible process 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 resulting in a controlled drug release from the site of administration (Figure 2). The controlled rate of absorption in addition to the prolonged half-life results in the optimal drug exposure seen in PhaseBio's preclinical and clinical studies.

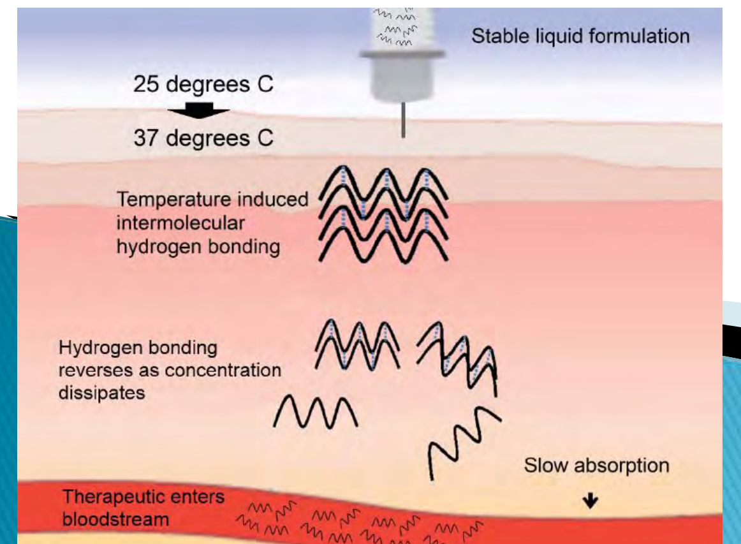

Figure 2: Cartoon Representation of Controlled Release of ELP Fusion Following SC Injection

STUDY DESIGN AND OBJECTIVES

This Phase 1/2a study (NCT 01236404) was a multicenter randomized, double-blind, placebo-controlled study that was conducted in two parts; Part A as a single ascending dose (SAD) study (results reported at the Annual Diabetes Technology Society Meeting 2011) and Part B as a 4–week multiple (once weekly dosing) ascending dose (MAD) study (topic of this presentation). 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/m^2. 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 MAD portion of the study underwent assessment of daily fasting glucose monitoring, liquid meal challenge (pre- and ~ 24 hours following the 4th dose), and continuous glucose monitoring (CGMS® iPro™, Medtronic, Inc.) for 7 days prior to the first dose and following the 4th dose. Key study activities are described below. A centralized laboratory was used for all analysis of glucose data.

ACTIVITY / STUDY DAY	SCR	D-14^3	D-7	D-4	D-1	D0	D1	D2	D3	D5	D7	D14	D21	D22	D23	D26	D28	D35	D42	D49
Wash Off OAD Therapy		←															→			
Confinement					X	X	X	X					X	X						
Dosing						X					X	X	X							
Safety Labs/ECG	X			X^7	X^8		X			X	$X^{1,6,7}$	$X^{1,6,7}$	$X^{1,6}$				X			X
AE and Injection Site Assessment						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	$X^{1,6}$	X	X	X	X	$X^{1,6}$	$X^{1,6}$	$X^{1,6}$	X	X	X	X	X	X	X
Pharmacokinetics						X^4		X	X	X	X^1	X^1	X^4	X	X	X	X	X	X	X
Immunogenicity						X^1						X^1					X			X
Mixed Meal Tolerance Test (MMTT)^2						X^1								X						
Fasting Plasma Glucose (FPG)	X	X	X	X	X	X^1		X	X	X	X^1	X^1	$X^{1,4}$	X	X	X	X	X	X	X
Continuous Glucose Monitoring (CGM)			X	X	X	X							X	X	X	X	X			

1= Pre-dose
2 = Boost® (16 ounces), Nestle Nutrition. Measure insulin, C-peptide and Glucose at -30, -15, 0, 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes
3 = Phone Visit
4 = Pre-dose and 1,4,8 and 12 hours post-dose
5 = CGMS IPro® inserted every 3 days. Calibrated with finger stick glucose 4 times per day
6 = Various post dose assessments
7 = Labs only
8 = ECG only

SUBJECT DEMOGRAPHICS AND DISPOSITION

A total of 56 subjects were enrolled (refer to Table 2) and 53 completed the study as planned.

Table 2: Subject Demographics and Disposition

		Glymera (mg/kg)			
Subject Characteristic	**Placebo**	**0.3**	**0.6**	**0.9**	**1.35**
Sex					
N	14	6	12	12	12
Male	11	3	8	6	9
Female	3	3	4	6	3
Race					
N	14	6	12	12	12
White	10	6	7	9	8
Asian	1	0	1	3	3
Black	3	0	2	0	1
American Indian or Alaska Native	0	0	1	0	0
Other	0	0	1	0	0
Ethnicity					
N	14	6	12	12	12
Hispanic or Latino	1	2	0	1	0
Not Hispanic or Latino	13	4	12	11	12
Age					
N	14	6	12	12	12
Mean Years	59	56.2	57.8	62	64
Disposition					
N	14	6	12	12	12
Completed	13	6	11	12	11
Premature Discontinuation	1	0	1	0	1
Subject Request	0	0	1	0	0
Adverse Event	0	0	0	0	1
Hyperglycemia	1	0	0	0	0

Source: T14.1.1.1 Demographics – simple 02-01-2012 and T14.1.2 Subject Disposition 02-01-2012

RESULTS – PHARMACOKINETICS

The pharmacokinetic (PK) analysis population consisted of all subjects dosed and who had sufficient data for PK analysis. 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. PK showed a combination of a slow absorption and long half-life [flip-flop kinetics] (Figure 3) following once weekly subcutaneous dosing with [redacted] Steady state is reached after the second dose with minimal accumulation (~ 5%) with repeated administration. Area under the curve AUC showed dose-proportionality (Figure 4) when plotted versus total dose administered. There are no apparent relationships between clearance (CL/F), body weight and BMI (data not shown). Based on these data, dosing of [redacted] is amenable to a once weekly fixed dose regimen.

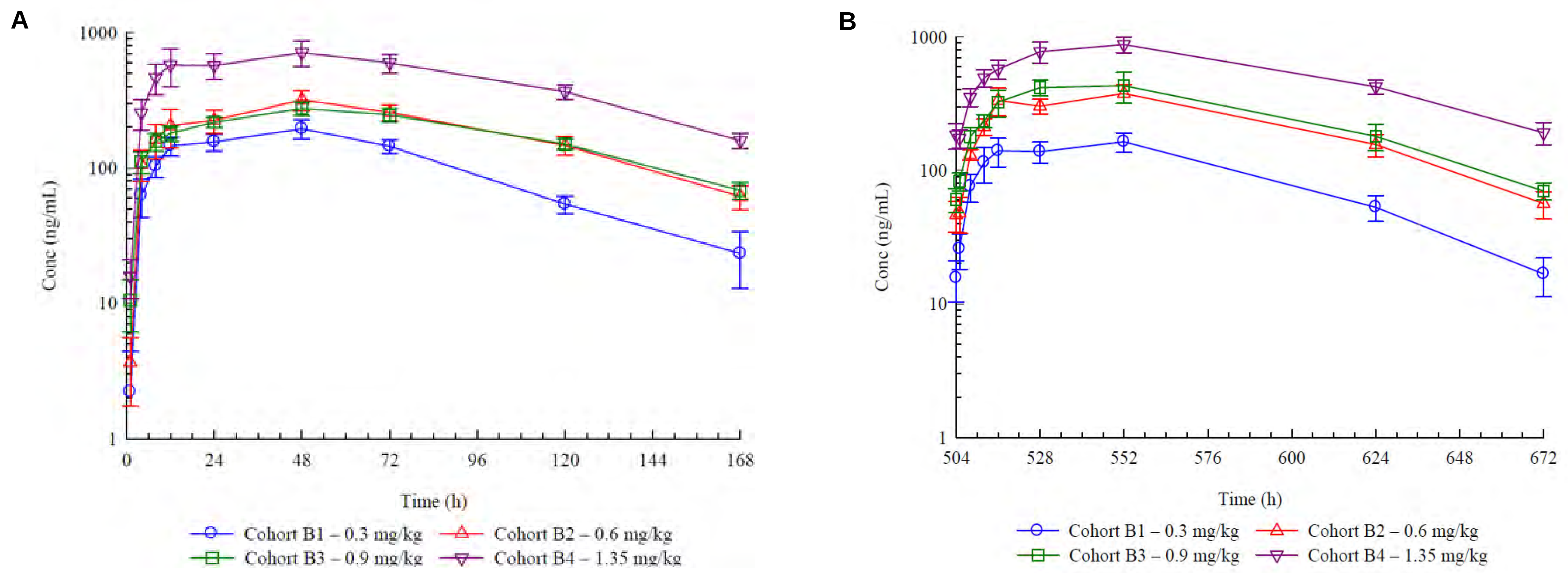

Figure 3: Arithmetic Mean Serum Concentrations of [redacted] Following the First (Panel A) and Fourth (Panel B) Once Weekly Subcutaneous Dose of 0.3, 0.6, 0.9, 1.35 mg/kg (6,12,18 and 27 nmol/kg respectively) to Adult Subjects with Type 2 Diabetes Mellitus — semi-logarithmic axes

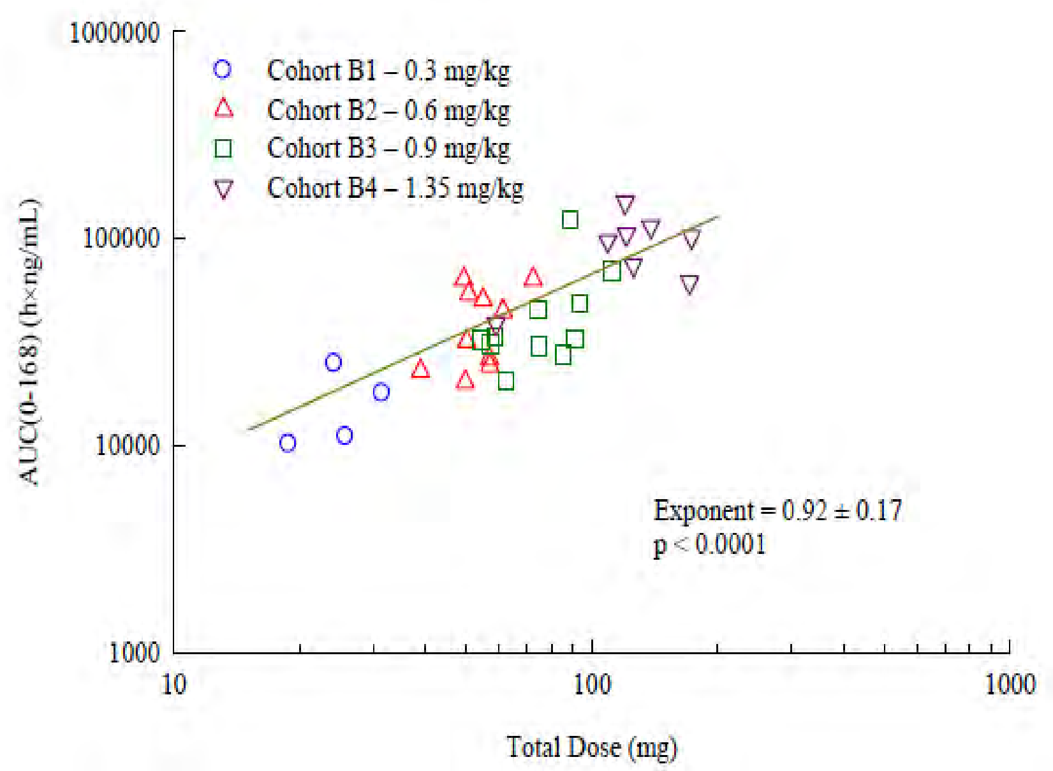

Figure 4: Relationship Between Individual Subject AUC (inf) and Total Dose Following the Fourth Subcutaneous Dose of [redacted]

RESULTS – PHARMACODYNAMICS

The pharmacodynamic analysis consisted of all subjects dosed who had sufficient data for PD analysis. [redacted] displayed a clinically significant dose dependent effect on reduction in fasting plasma glucose (Figure 5) and attenuation of glucose following a liquid meal challenge (Figure 6) after 4 once weekly subcutaneous injections of [redacted] at doses ranging from 0.6 to 1.35 mg/kg. Additionally, following multiple doses ranging from 0.6 to 1.35 mg/kg, [redacted] was able to significantly reduce mean average daily glucose over the 7 day period following the fourth dose of study drug as measured by continuous glucose monitoring (CGM) (Figure 7) which translates into a clinically meaningful reduction in imputed A1c of between -1.0% to -1.8% (placebo adjusted). [redacted] effects appear to be more pronounced during the morning hours as displayed in Figure 8.

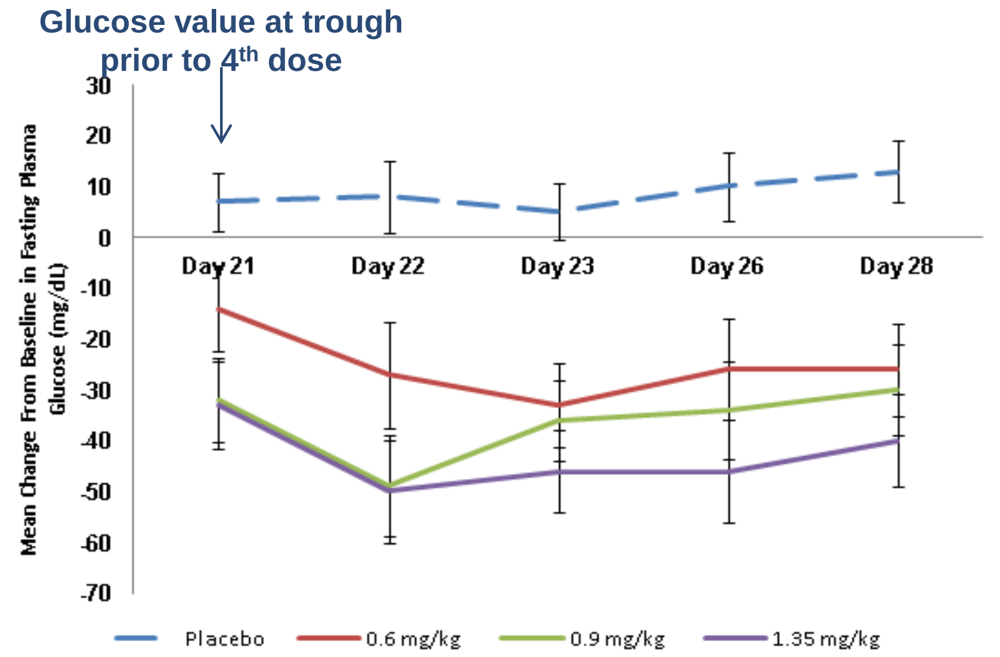

Figure 5: Mean (SEM) Change From Baseline in Fasting Plasma Glucose Over 7 Days Following the 4th SC Dose of [redacted] (Placebo Adjusted)

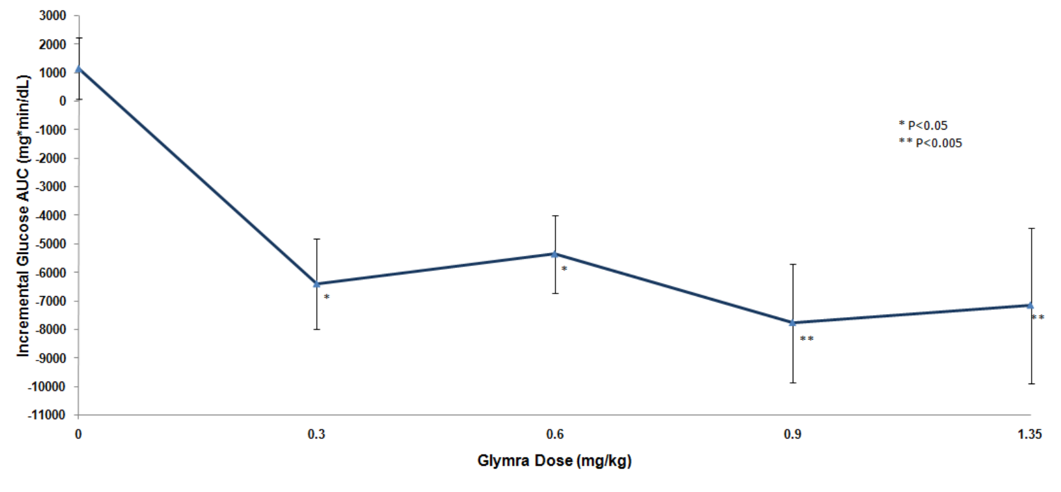

Figure 6: Mean (SEM) Change From Baseline in Glucose $AUC_{0\text{-}240\ minutes}$ (Baseline Adjusted at 0 minutes) Following Liquid Meal Challenge 24 Hours Following the 4th SC Dose of [redacted]

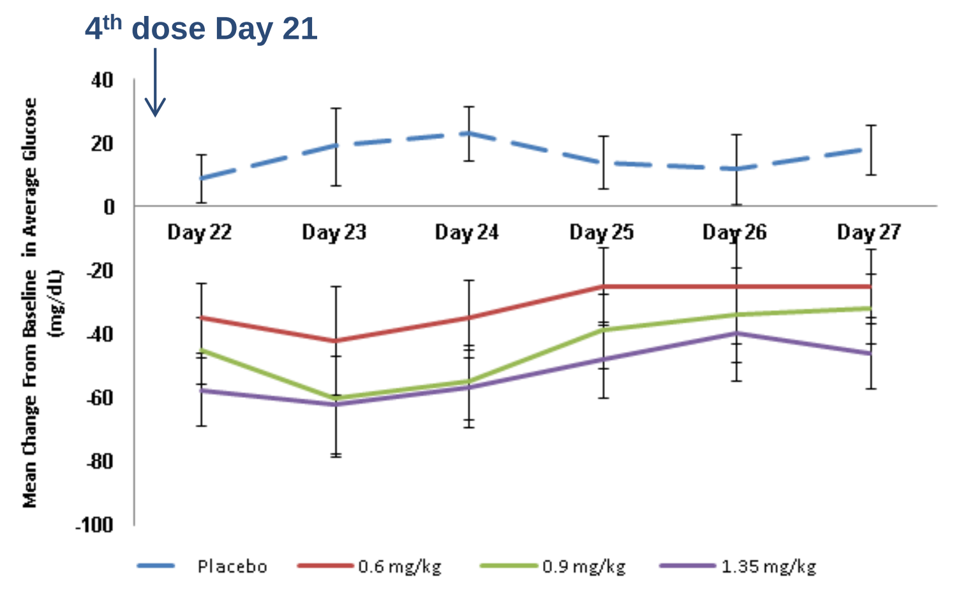

Figure 7: Mean (SEM) Change From Baseline in Average Glucose Measured by CGM Over 7 Days Following the 4th SC Dose of [redacted] (Placebo Adjusted)

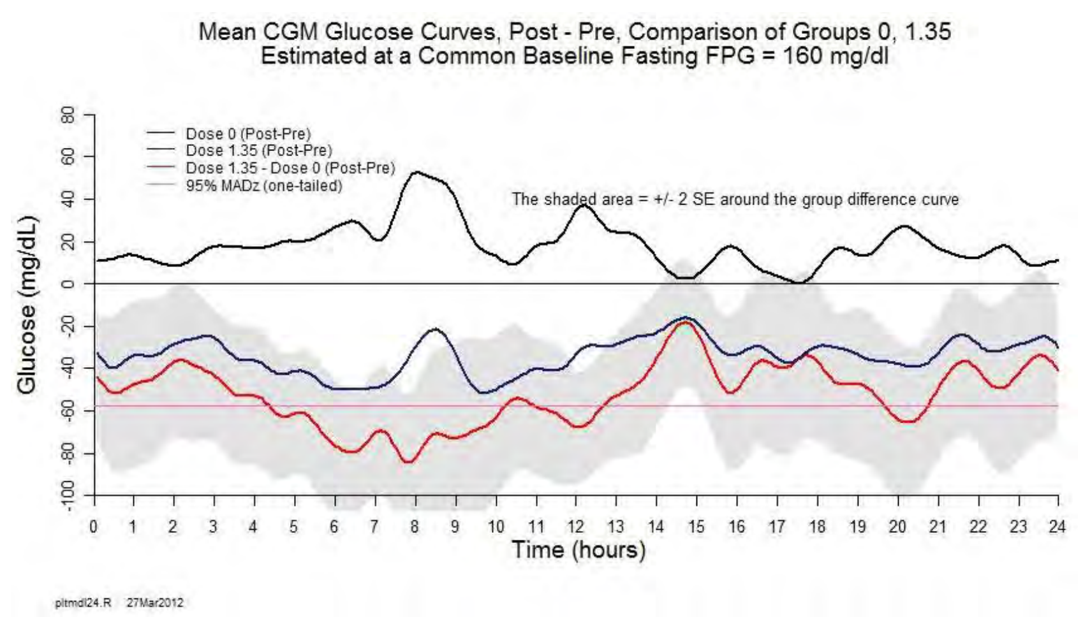

Figure 8: Mean 24 Hour CGM Curves, Post (Following 4th Dose) and Pre Comparisons Between Placebo and 1.35 mg/kg of [redacted]

The dose and AG data fit an Emax model with Emax of -51 mg/dL, and 80% of that effect (ED80) at a dose of 0.85 mg/kg as displayed below in Figure 9.

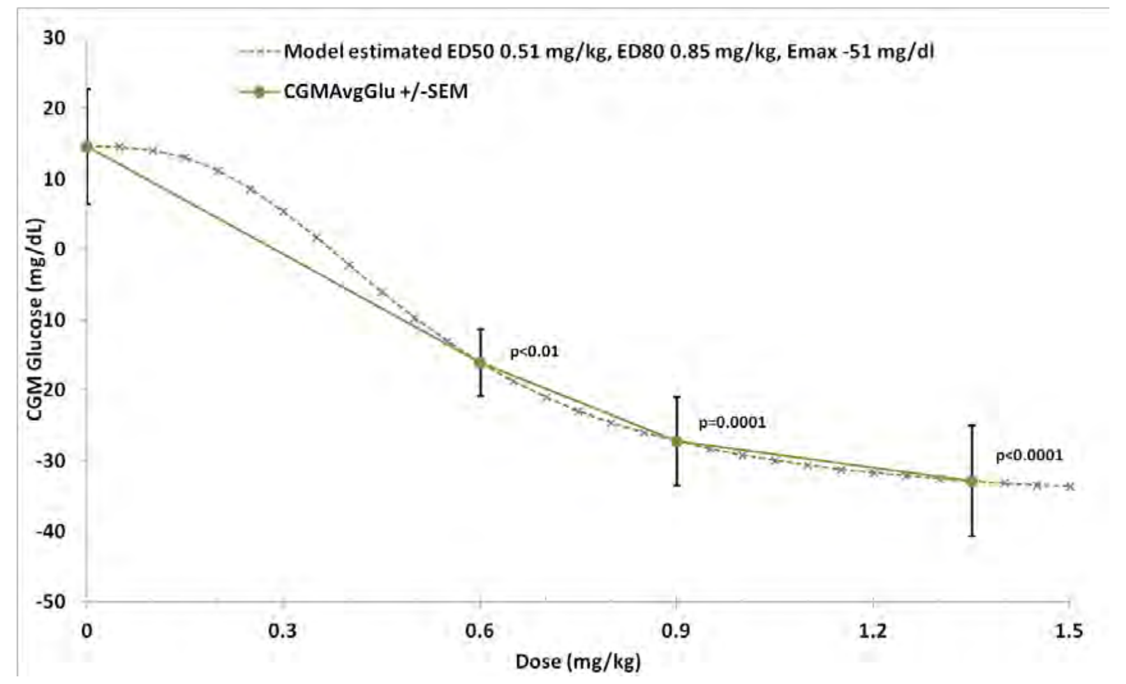

Figure 9: Average CGM Glucose Response by [redacted] Dose Group with Emax Model

RESULTS – SAFETY

No SAEs or dose limiting toxicities were reported. All adverse events were mild or moderate in severity. There were no dose related abnormal trends in change in laboratory parameters (Chem-12, CBC, LFTs, amylase/lipase, Lipids or Calcitonin), vital signs or ECGs that would indicate a safety concern. The most common reported adverse events (whether or not considered related to study drug) are listed below. One subject reported symptoms of hypoglycemia (plasma glucose 71 mg/dl) at about 6 hours after dosing which was self treated with oral carbohydrates.

Of the 42 subjects who received more than one dose of active study drug, one subject developed a low level non-neutralizing antibody response to [redacted] with no associated injection site reactions. One subject developed a low level non-neutralizing antibody response to native GLP-1. This subject reported mild injection site erythema following the second dose that did not proliferate with subsequent injections.

Table 3: Adverse Events Reported in ≥ 2 Subjects Receiving Multiple Doses of [redacted] or ≥ 2 Subjects Receiving Placebo

	Placebo	Glymera				
Adverse Event Body System/ Preferred Term	**Subjects (%) [No of Events]**	**Subjects (%) [No of Events] 0.3 mg/kg**	**Subjects (%) [No of Events] 0.6 mg/kg**	**Subjects (%) [No of Events] 0.9 mg/kg**	**Subjects (%) [No of Events] 1.35 mg/kg**	**Subjects (%) [No of Events] OVERALL**
N	**14**	**6**	**12**	**12**	**12**	**42**
Gastrointestinal Disorders						
Constipation	1 (7.1%) 1	0 (0.0%)	1 (8.3%) 1	0 (0.0%)	1 (8.3%) 1	2 (4.8%) 2
Dyspepsia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%) 1	1 (8.3%) 1	2(4.8%) 2
Nausea	1 (7.1%) 1	1(16.7%)1‡	1(8.3%) 1‡	1 (8.3%) 3‡	7 (58.3%) 14†	10 (24%) 19
Vomiting	1 (7.1%) 2*	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (25.0%) 6*	3 (7.1%) 6
General Disorders and Administration Site Conditions						
Catheter site pain	2 (14.3%) 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatigue	0 (0.0%)	0 (0.0%)	1 (8.3%) 1	1 (8.3%) 1	2 (16.7%) 2	4 (9.5%) 4
Injection site pain	1 (7.1%) 2	0 (0.0%)	0 (0.0%)	1 (8.3%) 2‡	3 (25.0%) 3‡	4 (9.5%) 5
Injection site erythema	0 (0.0%)	0 (0.0%)	0 (0.0%)	1(8.3%) 1‡	2 (16.7%) 4‡	3 (7.1%) 5
Injection site parasthesia	0 (0.0%)	0 (0.0%)	1 (8.3%) 1‡	0 (0.0%)	1 (8.3%) 1‡	2 (4.8%) 2
Musculoskeletal and Connective Tissue Disorders						
Myalgia	2 (14.3%) 2	1 (16.7%) 1	0 (0.0%)	1 (8.3%) 1	0 (0.0%)	2 (4.8%) 2
Nervous System Disorders						
Dizziness	1 (7.1%) 1	1 (16.7%) 1	0 (0.0%)	0 (0.0%)	2 (16.7%) 2	3 (7.1%) 3
Headache	3 (21.4%) 3	0 (0.0%)	0 (0.0%)	1 (8.3%) 1	2 (16.7%) 2	3 (7.1%) 3
Injury, Poisoning and Procedural Complications						
Muscle strain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%) 1	1(8.3%) 1	2(4.8%) 2

Date Source: Table 14.3.1.1: Adverse Events (Overall) - After Injection 02-01-2012
‡ Events reported as mild with event lasting less than 1 day.
* Two/six occurrences of vomiting reported as moderate in active group and two/two occurrence of vomiting in placebo reported as moderate.
† All events of nausea reported were considered mild and lasted between 1-2 days. Of the seven (7) subjects who reported nausea in the 1.35 mg/kg dose, three (3) experienced only 1 event of nausea. Two (2) subjects reported nausea with 2/4 doses, one (1) subject reported nausea with 3/4 doses and one (1) subject reported nausea with all four doses.

SUMMARY AND CONCLUSIONS

Following 4 weeks of once weekly SC doses ranging from 0.6 to 1.35 mg/kg, [redacted] displayed a clinically significant dose dependent effect on reduction in fasting plasma glucose and was able to significantly reduce mean average daily glucose over the 7 day dosing interval with minimal loss of glycemic control. This translates into a clinically meaningful reduction in imputed A1c of between -1.0% and -1.8% (placebo adjusted). Furthermore [redacted] was capable of attenuating the rise in glucose ($AUC_{0\text{-}240\ minutes}$) following a liquid meal challenge.

The rate-controlled exposure as a consequence of slow absorption from the site of injection, consistent with the ability of the ELP technology to control drug release at the site of injection, may enhance the overall gastrointestinal tolerability with maximal efficacy. There was minimal accumulation with repeated administration consistent with the half-life and once weekly dosing frequency.

[redacted] was generally well tolerated with no clinically relevant safety signals that would preclude further development as a once weekly treatment for hyperglycemia in patients with type 2 diabetes.

INFORMATION

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