# A Phase 1, Multi-center, Randomized, Double-blind, Placebo Controlled Study to Evaluate the Safety/Tolerability, Pharmacokinetic and Hemodynamic Response Following Single Ascending Subcutaneous Doses of PB1046 (Vasomera™) in Subjects with Essential Hypertension (Trial Registry No. NCT01523067)


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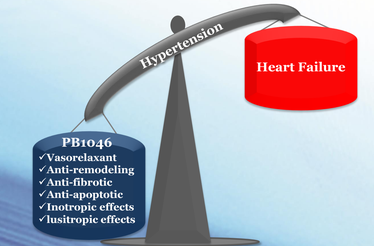
## ABSTRACT


Introduction: Vasoactive intestinal peptide (VIP) is involved in regulation of the cardiopulmonary system. PB1046, a first-in-class VIP receptor agonist with slow absorption and a long half-life, has been shown in animal models of hypertension (HTN) and heart failure to improve hemodynamic function. This study investigated the safety and pharmacokinetics, and hemodynamic response based on changes in blood pressure (BP) following single subcutaneous (SC) doses of PB1046 in subjects with HTN. Methods: Five dose levels (0.05 to 0.8 mg/kg) of PB1046 injected SC were evaluated sequentially in groups of 8 subjects randomized to PB1046 (n=6) or placebo (n=2). Antihypertensive therapy was withheld for at least 14 days prior and 7 days post dosing unless diastolic BP (DBP) >109 or systolic (SBP) >169. BP and heart rate (HR) were monitored using standardized methodology; Omron Model BP785 (triplicate seated BP) and Spacelabs Healthcare Model 90207 (ambulatory blood pressure monitor). Cardiac safety evaluated using telemetry and serial electrocardiograms. Results: All 40 subjects completed the study. There was a dose-related but less than dose proportional increase in mean serum concentrations and exposure (AUC). Maximum concentrations were reached between 24 and 72 hours (median 48) and the terminal half-life was approximately 60 hours. PB1046 significantly ($p=<0.05$) decreased both office/subject self-monitored seated SBP and DBP in a dose/exposure dependent manner relative to placebo over 7 days following dosing. At 0.8 mg/kg, the placebo adjusted 7 day average change from baseline in SBP and DBP were -7.1 mmHg and -6.0 mmHg, respectively with an associated average change in HR of -0.7 beats per minute. There were no serious adverse events or dose limiting toxicities. Dose dependent adverse events (AEs) occurring in ≥ 5% subjects were confined to injection site reactions: mild/moderate erythema (local vasodilation), mild pain, pruritus, induration/swelling. Additional AEs not dose dependent include mild/moderate nausea, headache, and mild fatigue. Conclusions: PB1046 significantly decreased both SBP and DBP in a dose dependent manner with no clinically relevant dose dependent increases in HR. At the doses tested, PB1046 was generally well tolerated.


## BACKGROUND

Hypertension remains a major public health problem associated with considerable morbidity and mortality. Chronically elevated blood pressure can lead to hypertensive heart disease, a constellation of abnormalities that include left ventricular hypertrophy (LVH) and systolic and diastolic dysfunction resulting in symptomatic heart failure. Vasoactive intestinal peptide (VIP) is a neuropeptide and its biological effects are mediated by two receptors, $VPAC_1$ and $VPAC_2$, that belong to the family B of G protein-coupled receptors (GPCRs). VIP fibers are distributed throughout the heart and coronary vasculature and VPAC receptors are found on vascular smooth muscle cells within the systemic circulation as well as coronary and myocardial arteries, cardiac myocytes and various immune cells. Several cardiovascular diseases, such as myocardial fibrosis, heart failure, cardiomyopathy and pulmonary hypertension, have been found to be associated with changes in myocardial VIP concentration or with alteration of affinity, density and physiological responsiveness of the VIP receptors. Many studies have proven the therapeutic potential of VIP, but the poor stability after systemic administration has limited its clinical application. PhaseBio has successfully created a stable long-acting VIP analogue that is active at the VPAC1 receptor but has much greater activity at the VPAC2 receptor. This profile elicits the desired cardiovascular effects (see below) but without the negative gastrointestinal effects (GI) associated with over activation of VPAC1 (e.g. profuse watery diarrhea).

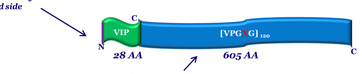



## ELASTIN-LIKE POLYPEPTIDE TECHNOLOGY

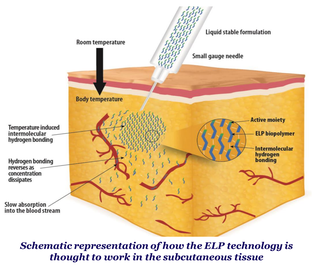
- ***Native vasoactive intestinal peptide sequence***
- ***One additional amino acid renders greater selectivity to VPAC2 compared to VPAC1 thus reducing the potential for GI receptor-mediated side effects***

***PB1046 (Vasomera)***

- ***Recombinant fusion protein expressed in soluble fraction of Escherichia coli***
- ***Total molecular mass of 50.95 kDa***




- ***Elastin like peptide 5 amino acid monomer with X as guest residue designed to achieve desired transition (temperature induced) properties for absorption profile***
- ***Repeated 120 times to achieve desired half-life extension***




***Schematic representation of how the ELP technology is thought to work in the subcutaneous tissue***

## STUDY DESIGN AND OBJECTIVES

**Study Design**:

First-in-human, multi-center, randomized, double-blind (Investigator, subject and efficacy/safety assessor), placebo controlled, single ascending (sequentially) dose study

**Objectives:**

Primary: Evaluate safety and tolerability of single ascending doses of PB1046 given as a subcutaneous (SC) injection

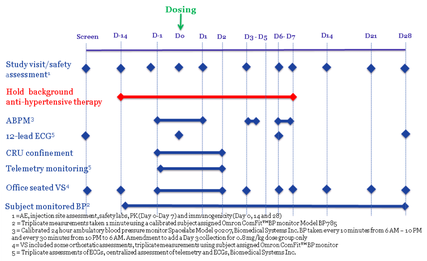
Secondary : Characterize the relationship between the pharmacokinetic profile and hemodynamic response (e.g. change in systolic and diastolic blood pressure)

**Subject Population:**

Adult male and females 18 – 70 years of age (inclusive) diagnosed with Stage 1 or Stage 2 uncomplicated essential hypertension

a. If not treated, had seated mean systolic blood pressure (SBP) between 140-169 mmHg (between 130-169 mmHg if diabetic) or mean diastolic blood pressure (DBP) 90-109 mmHg (between 85 - 109 if diabetic)
b. Treated with no more than two (2) antihypertensive agents in combination and can tolerate being tapered background therapy

The difference (highest to lowest mean values) in mean seated SBP (triplicate measurements at 1-2 minute interval) measured on three separate occasions between Day -4 and Day 0 (pre-dose) was within 14 mmHg and DPB was within 8mmHg




1 =AE, injection site assessment, safety labs, PK (Day 0-Day 7) and immunogenicity (Day 0, 14 and 28)
2 = Triplicate measurement taken 1 minute using a calibrated subject assigned Omron ComFit™BP monitor Model BP785
3 = Calibrated 24 hour ambulatory blood pressure monitor Spacelabs Model 90207, Biomedical Systems Inc. BP taken every 1 minute from 6 AM – 10 PM and every 30 minutes from 10 PM to 6 AM. Amendment to add a Day 3 collection for 0.8mg/kg dose group only
4 = VS included some orthostatic assessments, triplicate measurements using subject assigned Omron ComFit™BP monitor
5 = Triplicate assessments of ECGs, centralized assessment of telemetry and ECGs, Biomedical Systems Inc.

**Figure 1: Study Schematic**

## RESULTS – DEMOGRAPHICS and SAFETY

Study population characteristics are described in Table 1. No serious adverse events (SAEs) or dose limiting toxicities were reported, and no subject required rescue therapy. No systematic changes in heart rate (HR) or rhythm were noted during the 24-hour telemetry monitoring and no clinically relevant trends with respect to change from baseline in ECG parameters (HR, PR interval, QRS duration, QT interval or QTcF duration) were observed following dosing. The most frequent treatment emergent adverse events are shown in Table 2. Overall, injection site reactions were the most frequently (97%) reported AE and exhibited an apparent dose dependency following subcutaneous (SC) injection and were reported as mild or moderate in severity. The erythema, pain or itching reported at the site of injection were not considered to be an allergic response but rather associated with activation of the VPAC2 receptors in the skin (known to be localized around hair follicles). Events were not considered concerning either by the investigator or study subject.

**Table 1: Study Population Characteristics and Disposition**

| Population Characteristic | Placebo | PB1046 (mg/kg) 0.05 | 0.1 | 0.2 | 0.4 | 0.8 |
|---|---|---|---|---|---|---|
| N | 10 | 6 | 6 | 6 | 6 | 6 |
| **Sex (N/group)** | | | | | | |
| Male | 6 | 5 | 3 | 3 | 1 | 3 |
| Female | 4 | 1 | 3 | 3 | 5 | 3 |
| **Race (N/group)** | | | | | | |
| White | 7 | 4 | 6 | 1 | 3 | 6 |
| Black | 3 | 1 | 0 | 2 | 1 | 0 |
| Asian | 0 | 0 | 0 | 2 | 1 | 0 |
| American Indian/Alaskan Native | 0 | 1 | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 1 | 0 |
| Other | 0 | 0 | 0 | 1 | 0 | 0 |
| **Ethnicity (N/group)** | | | | | | |
| Hispanic or Latino | 0 | 1 | 0 | 0 | 0 | 0 |
| Not Hispanic or Latino | 10 | 5 | 6 | 6 | 6 | 6 |
| **Age (Years)** | | | | | | |
| Mean (SD) | 49.8 (9.7) | 58.5 (6.9) | 55.0 (8.3) | 50.3 (10.7) | 58.2 (5.9) | 54.7 (10) |
| Range | 35-63 | 48-69 | 46-66 | 35-63 | 51-67 | 43-69 |
| **Body Mass Index (BMI) (kg/m²)** | | | | | | |
| Mean (SD) | 33.8 (4.5) | 30.3 (3.8) | 32.7 (4.4) | 32.9 (3.7) | 33.0 (4.6) | 32.3 (3.4) |
| Range | 26.4-39.4 | 25.9-35.9 | 24.6-37.2 | 27.7-37.2 | 24.3-38.0 | 28.8-35.9 |
| **Hypertension Duration (N/group)** | | | | | | |
| < 1 year | 1 | 0 | 0 | 1 | 0 | 0 |
| 1-10 years | 5 | 6 | 3 | 3 | 3 | 6 |
| > 10 years | 4 | 0 | 3 | 2 | 3 | 0 |
| **Background Antihypertensive Therapy (N/group)** | | | | | | |
| 1 Agent | 6 | 3 | 4 | 3 | 4 | 5 |
| 2 Agents | 3 | 0 | 1 | 1 | 2 | 1 |
| Treatment naïve | 1 | 1 | 1 | 0 | 0 | 0 |
| **Disposition (N/group)** | | | | | | |
| Completed Study as Planned | 10 | 6 | 6 | 6 | 6 | 6 |

**Table 2: Screening and Baseline Office Seated[1] Blood Pressure**

| Study Time Point | All Placebo (N = 10) | PB1046 (mg/kg) 0.05 (N = 6) | 0.1 (N = 6) | 0.2 (N = 6) | 0.4 (N = 6) | 0.8 (N = 6) |
|---|---|---|---|---|---|---|
| | mean median (SD) (range) | mean median (SD) (range) | mean median (SD) (range) | mean median (SD) (range) | mean median (SD) (range) | mean median (SD) (range) |
| **SCREENING - SYSTOLIC** | | | | | | |
| Observed | 135.4 (11.4) 138.4 (10.6) | 138.2 (13.4) | 127.5 (8.8) | 134.0 (10.8) | 141.8 (10.3) | |
| | 134.5 (113, 154) 131 (130, 151) | 144 (116, 151) | 130 (111, 137) | 133.5 (118, 146) | 142.5 (130, 153) | |
| **BASELINE SYSTOLIC (Day 0 pre-dose)** | | | | | | |
| Observed | 140.4 (8.2) 143.0 (8.8) | 138.0 (3.3) | 139.0 (9.4) | 132.3 (8.2) | 144.8 (5.2) | |
| | 142.0 (124, 152) 139.5 (135, 156) | 139.0 (132, 142) | 137.0 (129, 153) | 131.0 (145, 160) | 146.0 (135, 150) | |
| % Change from Screening | 4.2 (5.6) 2.2 (5.4) | 0.6 (9.6) | 9.2 (6.8) | 13.8 (13.2) | 2.6 (9.2) | |
| | 2.3 (-8, 27) 4.6 (-7, 6) | -3.5 (-8, 14) | 8.8 (-2, 19) | 12.5 (0, 31) | 4.7 (-11, 11) | |
| **SCREENING - DIASTOLIC** | | | | | | |
| Observed | 90.9 (6.5) 88.8 (5.2) | 93.3 (11.0) | 81.3 (6.3) | 84.0 (6.1) | 90.8 (7.2) | |
| | 89.0 (84, 105) 90.0 (83, 94) | 95.0 (73, 106) | 81.5 (74, 89) | 84.0 (76, 93) | 89.5 (83, 100) | |
| **BASELINE DIASTOLIC (Day 0 pre-dose)** | | | | | | |
| Observed | 90.9 (5.7) 91.5 (4.9) | 92.2 (5.5) | 90.8 (3.2) | 94.3 (5.8) | 96.2 (5.6) | |
| | 90.5 (81, 100) 91 (86, 98) | 93.5 (85, 98) | 90.5 (87, 95) | 94.5 (86, 102) | 97.5 (86, 103) | |
| % Change from Screening | 0.2 (4.9) 4.2 (2.6) | -0.2 (12.1) | 12.0 (5.6) | 12.7 (9.2) | 6.2 (7.3) | |
| | 2.2 (-7, 7) 4.3 (0, 7) | -4.8 (-11, 18) | 13.0 (5, 18) | 12.1 (2, 18) | 4.7 (-5, 15) | |

[1]Mean triplicate measurements taken 1 minute apart for each subject at each time-point using a calibrated Omron ComFit™ Blood Pressure Cuff Model BP785.

**Table 3: Most Frequent (≥ 5%) Treatment Emergent[1]Adverse Events Related (Possibly, Probably or Definitely) to Study Drug**

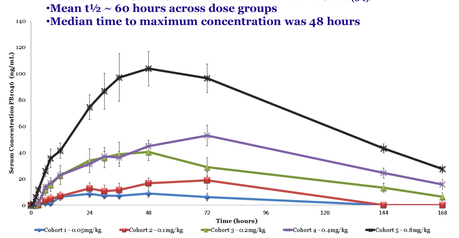
| Adverse Event Body System/ Preferred Term | Placebo Subjects (%) | PB1046 (mg/kg) Subjects (%) 0.05 | Subjects (%) 0.1 | Subjects (%) 0.2 | Subjects (%) 0.4 | Subjects (%) 0.8 | Subjects (%) OVERALL |
|---|---|---|---|---|---|---|---|
| N | 10 | 6 | 6 | 6 | 6 | 6 | 30 |
| **Cardiac Disorders** | | | | | | | |
| Ventricular tachycardia | 0 (0) | 0 (0) | 1 (16.7)[2] | 0 (0) | 0 (0) | 0 (0) | 1 (3.3) |
| **Gastrointestinal Disorders** | | | | | | | |
| Nausea | 0 (0) | 0 (0) | 1 (16.7) | 1 (16.7) | 1 (16.7) | 1 (16.7) | 4 (13.3) |
| Vomiting | 0 (0) | 0 (0) | 0 (0) | 1 (16.7) | 0 (0) | 0 (0) | 0 (0) |
| **General Disorders and Administration Site Conditions** | | | | | | | |
| Fatigue | 0 (0) | 0 (0) | 1 (16.7) | 0 (0) | 0 (0) | 0 (0) | 1 (3.3) |
| Injection site discoloration | 0 (0) | 0 (0) | 1 (16.7) | 0 (0) | 0 (0) | 0 (0) | 1 (3.3) |
| Injection site erythema | 0 (0) | 4 (66.7) | 6 (100.0) | 5 (83.3) | 6 (100.0) | 6 (100.0) | 27 (90.0) |
| Injection site induration | 0 (0) | 1 (16.7) | 0 (0) | 0 (0) | 2 (33.3) | 2 (33.3) | 5 (16.7) |
| Injection site macule | 0 (0) | 1 (16.7) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (3.3) |
| Injection site pain | 0 (0) | 1 (16.7) | 6 (100.0) | 6 (100.0) | 6 (100.0) | 5 (83.3) | 24 (80.0) |
| Injection site papule | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (16.7) | 1 (3.3) |
| Injection site pruritus | 0 (0) | 2 (33.3) | 3 (50.0) | 1 (16.7) | 4 (66.7) | 0 (0) | 10 (33.3) |
| Injection site swelling | 0 (0) | 1 (16.7) | 1 (16.7) | 0 (0) | 3 (50.0) | 0 (0) | 5 (16.7) |
| Injection site warmth | 0 (0) | 1 (16.7) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (3.3) |
| **Nervous System Disorders** | | | | | | | |
| Headache | 0 (0) | 0 (0) | 0 (0) | 1 (16.7) | 0 (0) | 1 (16.7) | 2 (6.7) |

[1]Treatment-emergent = began or worsened in severity within 7 days of dosing. Subjects counted only once per row.
[2]One single event of a 5 - beat run (average rate 146 beats per minute) of ventricular tachycardia observed on telemetry monitoring, asymptomatic and mild in severity. No treatment required.

## PHARMACOKINETICS

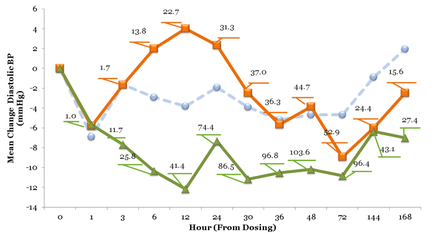
**Key Findings:**

- **Dose related but less than dose-proportional increase in maximum concentration (Cmax) and area under the curve ($AUC_{(0-t)}$)**
- **Mean t½ ~ 60 hours across dose groups**
- **Median time to maximum concentration was 48 hours**




Pharmacokinetic parameters calculated using non-compartmental analysis. Only those serum concentrations equal or greater than the LOQ (7.8 ng/mL) were used in the analysis

**Figure 2: Mean ± Standard Error (SE) Serum Concentrations of PB1046 Following a Single SC Dose to Adults with Stage 1 or 2 Essential Hypertension – linear axes**




[1]Mean triplicate measurements taken 1 minute apart for each subject at each time-point using a calibrated Omron ComFit™ Blood Pressure Cuff Model BP785. The arm used for the pre dose evaluation was used to evaluate post dose changes. Placebo (pooled) N = 10 with baseline DBP 91.2 mmHg (±6.3) ; N = 6 per 0.4 mg/kg of PB1046 with baseline DBP 92.2 mmHg (± 5.96) N = 6 per 0.8 mg/kg of PB1046 with baseline DBP 96.2 mmHg (± 5.88)

**Figure 3: Observed Mean ± Standard Error (SE) Change From Baseline (Day 0 Pre-dose) in Office Seated[1] Diastolic BP (mmHg) and Corresponding PB1046 Serum Concentrations (ng/mL) Following a Single SC Dose in Adults with Stage 1 or 2 Essential Hypertension**

**Table 4: Categorical Analysis of 24-Hour ABPM**

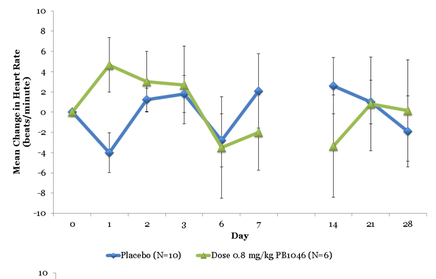
| Dose (mg/kg) PB1046 | Day -1 (24 hour period prior to dosing) Systolic Subjects/Group (%) with SBP ≥140 mmHg | Day -1 Diastolic Subjects/Group (%) with DPB ≥90 mmHg | Day 3 Systolic Subjects/Group (%) with SBP ≥140 mmHg | Day 3 Diastolic Subjects/Group (%) with DPB ≥90 mmHg | Day 6 Systolic Subjects/Group (%) with SBP ≥140 mmHg | Day 6 Diastolic Subjects/Group (%) with DPB ≥90 mmHg |
|---|---|---|---|---|---|---|
| 0 (Placebo) | 5/10 (50.0) | 3/10 (30.0) | 0/2 (0.0) | 1/2 (50.0) | 6/10 (60.0) | 5/10 (50.0) |
| 0.05 | 4/6 (66.7) | 0/6 (0.0) | NA | NA | 3/6 (50.0) | 1/6 (16.7) |
| 0.1 | 6/6 (100.0) | 4/6 (66.7) | NA | NA | 3/6 (50.0) | 2/6 (33.3) |
| 0.2 | 3/6 (50.0) | 2/6 (33.3) | NA | NA | 4/6 (66.7) | 2/6 (33.3) |
| 0.4 | 4/6 (66.7) | 1/6 (16.7) | NA | NA | 3/6 (50.0) | 1/6 (16.7) |
| 0.8 | 5/6 (83.3) | 3/6 (50.0) | 3/6 (50.0) | 3/6 (50.0) | 4/6 (66.7) | 1/6 (16.7) |

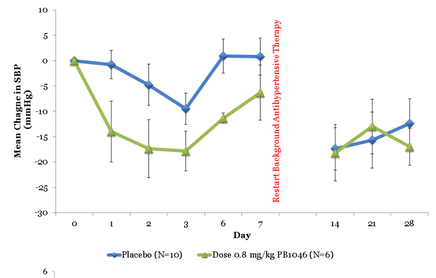
Note: The average of multiple values at each time point was used for analyses. A subject is counted only once if the subject had more than one value over the threshold (> 140 mmHg for SBP or >90 mmHg for DBP) during a study day.

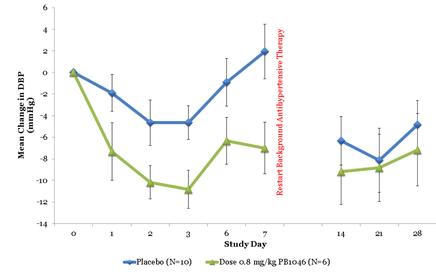
## CONCLUSIONS

- ❖ Single SC doses of PB1046 up to 0.8 mg/kg were safe and well tolerated.
- ❖PB1046 exhibited the anticipated (by design) slow absorption and extended half-life providing a VIP analogue that is suitable as a therapeutic agent.
- ❖The current study demonstrates that the modified form of VIP linked to ELP (PB1046) retains the inherent vasodilatory effects of VIP as measured by reductions in office seated SBP and DBP.
- ❖PB1046 produced a statistically significant and sustained (7 day dosing interval) decrease in blood pressure at the highest dose tested but with no significant increase in HR.
- ❖The same or smaller proportion of subjects treated with PB1046 had SBP or DBP values over pressure threshold limits during a study day as measured by ABPM.
- ❖These findings support further investigation of PB1046 as a potential therapy for hypertension and heart failure.

## PHARMACODYNAMICS




[1]Mean triplicate measurements taken 1 minute apart for each subject at each time-point using a calibrated Omron ComFit™ Blood Pressure Cuff Model BP785. The arm used for the pre dose evaluation was used to evaluate post dose changes. Placebo (pooled) N = 10 with baseline SBP (mean ± SD) of 139.6 mmHg (±7.7), DBP 91.2 mmHg (±6.3) and HR 74.4 (± 11.7) bpm, ; N = 6 per 0.8 mg/kg of PB1046 with baseline SBP (mean ± SD) of 146.0 mmHg (± 3.86), DBP 96.2 mmHg (± 5.88) and HR 76.4 (± 14.0) bpm

**Figure 4: Observed Mean ± Standard Error (SE) Change From Baseline (Day 0 Pre-dose) in Office Seated[1] Heart Rate (top) Systolic BP (middle), Diastolic BP (bottom) Following a Single SC in Adults with Stage 1 or 2 Essential Hypertension**

## DISCLOSURES


•A. Free, M. Matson, R. Brazg, W. Smith and L. Chuck: Principal Investigators. Compensation paid to Clinical Research Unit for study costs/services. Investigators have received no other compensation from PhaseBio nor do they have ownership interest in PhaseBio.
•L. Georgopoulos, S. Arnold and J. Malatesta: PhaseBio employees with ownership interest in PhaseBio.
•P. Strange: Consultant/Advisory Board with ownership interest in PhaseBio.
•L. Shi, W. Kramer and J Gwynne: Paid consultant, no ownership interest in PhaseBio.



**SPONSOR CONTACT INFORMATION**

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PhaseBio Pharmaceuticals, Inc.


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