PharmaIN

Proprietary Peptide Drugs for In-Home Therapy

PHIN -214
Non-Confidential Presentation
November 2022

Key points

- Developing In-Home Therapy
- Two lead programs:
  - PHIN-214
    - SC drug for Refractory Ascites
    - Phase 1b Clinical Trial in US in cirrhotic patients
  - PHIN-1314
    - SC Immuno-Oncology drug for Solid Tumors
    - Aim to submit IND in 2023

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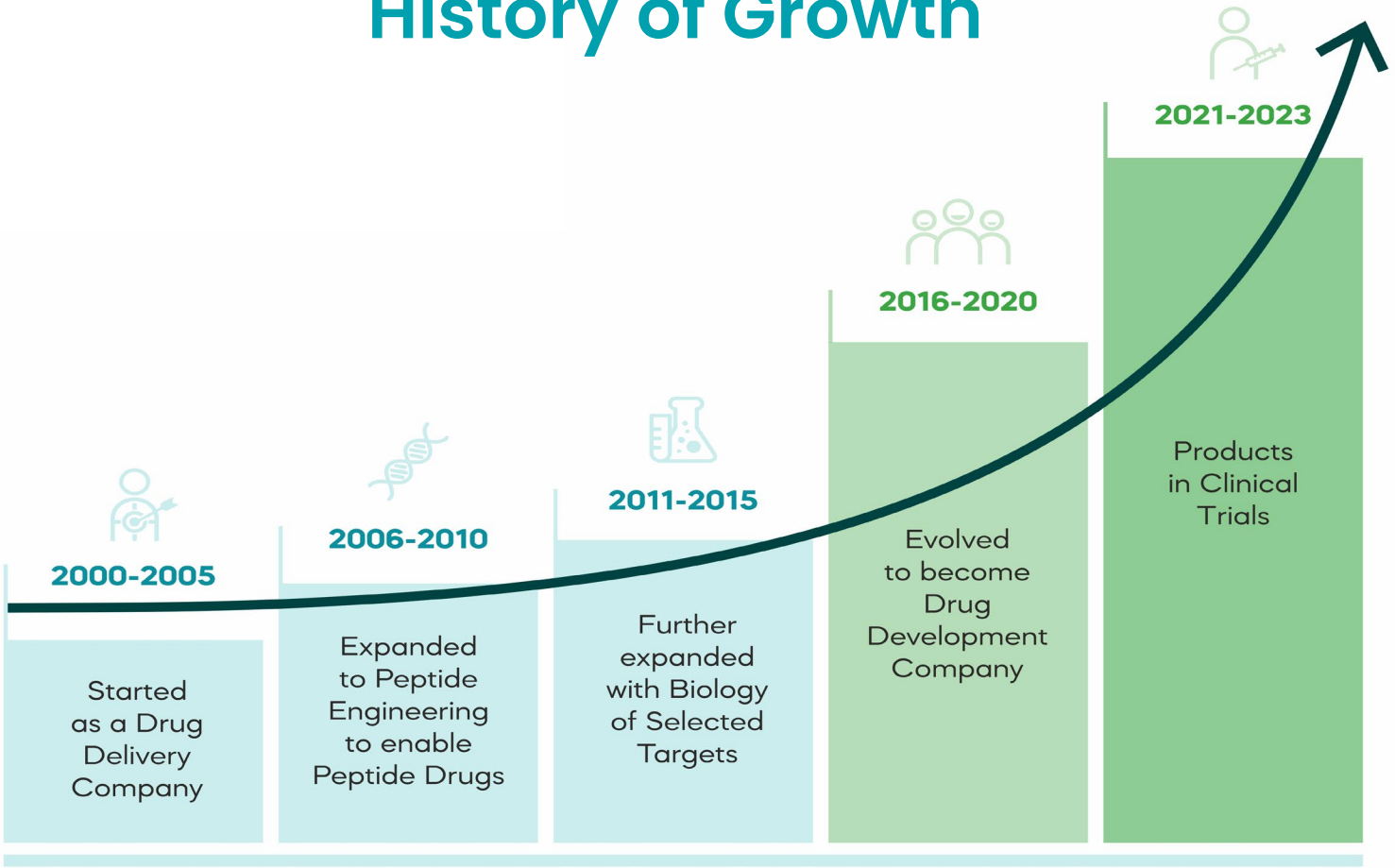
Two Products with 6+ Indications

PHIN-214	Refractory Ascites P1 is ongoing	Hepatorenal Syndrome	Undisclosed
PHIN-1314	Oncology Solid Tumors IND in 2023	Oncology Combination with Checkpoint Inhibitors	Inflammation and Fibrosis

History of Growth



Clinical Goals for the Use of PHIN-214

- Long term SC therapy at home
- Delay progression to HRS via slowing the hemodynamic deterioration towards loss of kidney perfusion
- Decrease ascites formation via reduction of portal pressure that drives ascites formation
- Reduce risks and increase quality of life by reduction in clinical visits and the need for paracentesis procedure

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PHIN-214 for Portal Hypertension with Refractory Ascites

▶ **PHIN-214** is a derivative of Terlipressin, effective at controlling hemodynamic imbalance

- New Chemical Entity with a broader therapeutic index providing higher safety
  - Partial V1a agonist providing milder vasopressor activity allowing for subcutaneous administration with reduced risk of ischemia or injection site reaction
- Longer acting than Terlipressin*
  - Single subcutaneous injection provides a sustained PK, and will enable long term therapy at home instead of IV infusion

▶ **PHIN-156** is an active metabolite of PHIN-214, also a partial V1a agonist

*Terlipressin is an IV therapy for bleeding esophageal varices and HRS in EU and Asia, and for HRS in US

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Target Indication(s)

Compensated Cirrhosis (~1-1.5 M in US)

↓

Decompensated Cirrhosis

↓

Ascites
(~500K patients)

↓

Refractory Ascites
(Current Clinical Trial Indication)

↓

Hepatorenal Syndrome (HRS-CKD)

↓

HRS-AKI (or Esophageal Variceal Bleed)

↓

Reversal, Liver Transplant, or Death

PHIN-214
(V1a Partial Agonist)

Hospitalized
I.V. Terlipressin
V1a Full agonist, In US, EU & Asia

Mechanism of Action

Liver Cirrhosis

↓

↑ Hepatic Resistance

↓

x↑ Portal Hypertension

↓

x↑Splanchnic Blood Pooling

↓

x↓ Arterial blood pressure

↓

x↑ Activation of RAAS x

↓

x↑Retention of Na + water

↓

x↑ Ascites formation

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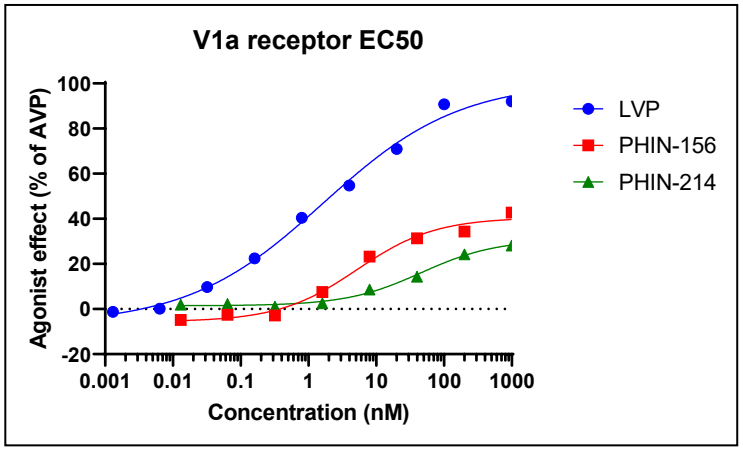
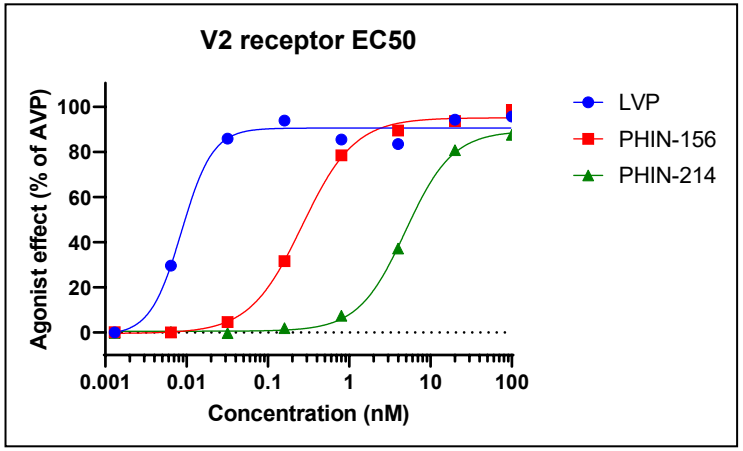
PHIN-214 and PHIN-156 are both partial V1a agonists while Terlipressin is a full V1a agonist through Lysine Vasopressin (LVP)

Unit (nM)	Human V1a EC50	Human V1a Highest agonist effect (% of AVP)	Human V2 EC50	Human V2 Highest agonist effect (% of AVP)	**Ratio of EC50 of V1a to V2 (i.e., preference for V2)**
LVP	1.65	92.09	0.01	96.16	**165 fold**
PHIN-156	2.05	41.02	0.26	98.69	**~8 fold**
PHIN-214	45.89	28.18	4.93	87.66	**~9 fold**





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PHIN-214 has 10X higher therapeutic index than Terlipressin based on observations in SD Rats

	Terlipressin mg/Kg i.v.*	PHIN-214 mg/Kg s.c.
NOEL Highest dose with no observable paleness effect or vasoconstriction	0.005 (N/A)	0.0015 (N/A)
NOAEL Highest Dose with no observable adverse effect or lethargy but with paleness or vasoconstriction (paleness duration, hrs +/- SD)	0.05 (1.3 ± 0.05 hrs, n=3)	0.15 (5.79 ± 0.08 hrs; n=3)
Therapeutic Index NOAEL/NOEL	**~10**	**~100**
* Note: Terlipressin is currently administered i.v. since s.c. administration causes local vasoconstriction and necrosis whereas PHIN-214, a partial agonist, does not cause local vasoconstriction even if administered s.c.		

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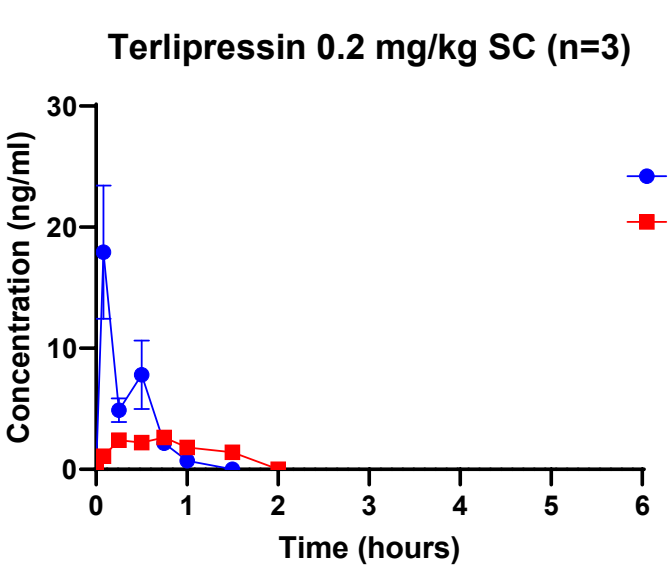
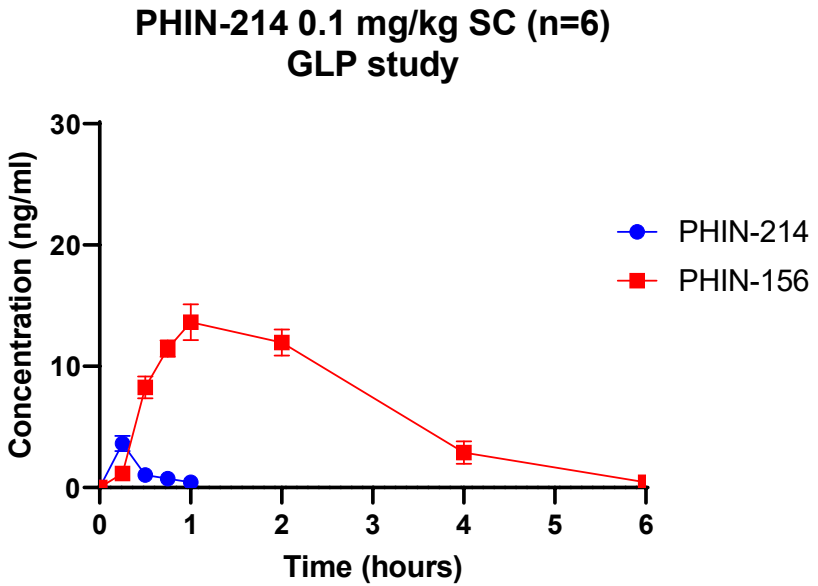
PHIN-156 has longer presence in the blood than LVP based on PK study in Rats



AUC (ng/ml*h) @ 0.1 mg/kg dose
Terlipressin: 4.4
LVP: 2.5



AUC (ng.ml*h) @ 0.1 mg/kg dose
PHIN-214: 1.34
PHIN-156: 34.8

Note: PHIN-156 has over 10-fold higher plasma bioavailability than LVP (active metabolite of terlipressin)

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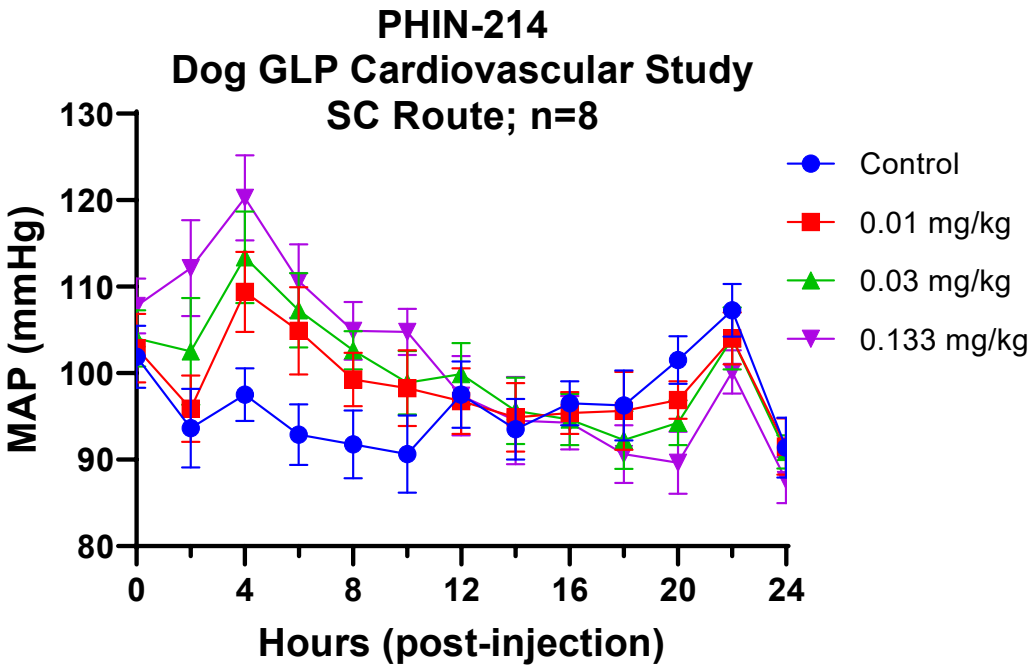
PHIN-214 increases MAP in a dose response manner that is needed to increase Kidney perfusion



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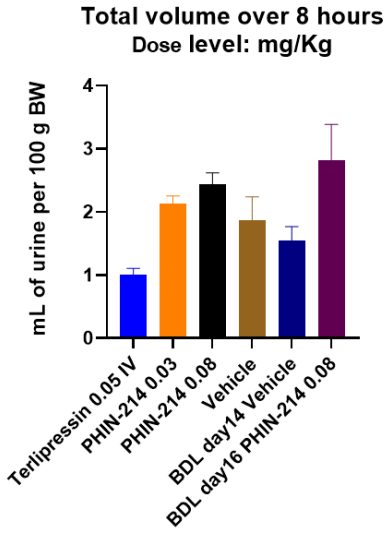
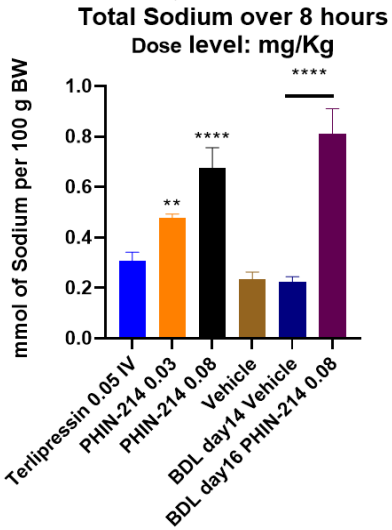
PHIN-214 showed dose dependent diuretic and sodium excretion effect in rats Superior to that of Terlipressin

- BDL rats are more responsive at the same dose (80 µg/kg), compared to healthy rats
- V1a receptor response to PHIN-214 overwhelms V2 receptor antidiuretic response.
  - i.e., V1a overwhelm V2 effect as dose increases without causing skin necrosis (from Tox. Study).
  - V2 is mainly in kidney and has limited response capacity whereas V1a is in the entire vasculature and has higher capacity to respond to PHIN-214





**P<0.01
****P<0.0001

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PHIN-214 is more effective in reducing Portal Vein Pressure than Terlipressin

PHIN-214 at 12 ug/kg S.C. is more effective than Terlipressin at 41 ug/kg I.V. in providing a sustained decrease in portal pressure in Bile Duct Ligated Rats

Percent decrease (%) in Mean Portal Vein Pressure (MPVP) from BDL baseline prior to treatment

Test Article	Dosing (µg/kg)	Time (hr)				
		0	1	4	7	20
BDL PHIN-214 n=4	12	0	5 (7.39)	-30.5 (7.12)	-10.5 (14.79)	-29.75 (5.0)
BDL Terlipressin n=4	41	0	-23 (21.0)	11.3 (20.3)	10.8 (7.7)	7.3 (13.03)

Data Displayed as Percent Change (SEM)
Day 13 MPVP: BDL = 22.2 mmHg (SEM:6.45); Sham = 14.08 mmHg (SEM:1.51)

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PHIN-214 Potential Advantages over Terlipressin

Parameter	Terlipressin/LVP	PHIN-214/156
Administration	IV, bolus or infusion	Subcutaneous
Location	Clinical setting	Home
Half-life	Short: minutes	Long: hours
Therapeutic index	Narrow	Broad
Receptor	Full V1a agonist	Partial V1a agonist
Ischemia	High risk	Low risk

Single Ascending Dose (SAD) Study, Phase 1

- Child-Pugh A and B patients
- Primary objective: safety & tolerability, Maximum tolerated dose (MTD)
- Secondary objective: pharmacokinetics (PK)
- Exploratory objectives: MAP, urine output, sodium excretion
- Two sites currently recruiting:
  - Arizona Liver Health, Phoenix
  - Mayo Clinic, Rochester MN

Phase 1 Study: Inclusion Criteria

Type of Participant and Disease Characteristics

- Males & Females, Ages 18-70
- BMI 18-40
- eGFR by CKD-Epi > 60 ml/min/1.73 m^2
- Cardiovascular
  - Resting heart rate 60-100 bpm
  - SBP 90-140 mmHg; DBP 60-90 mmHg
- Cirrhosis: Child-Pugh A or B
  - Biopsy or Fibroscan
  - Etiologies of cirrhosis include:
    - Alcohol, NASH, hepatitis B, hepatitis C
    - Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC)

Phase 1 Study: Exclusion Criteria

Barriers to Recruitment To Date

- Previously limited to Child-Pugh A patients
- Hypertension and anti-HTN medications (beta blockers ok)
- Platelet count $<50x10^9/L$ (was $100x10^9/L$)
- Hepatic encephalopathy ≥ grade 1
- Respiratory disease: asthma, COPD
- Anti-depression medications (Zoloft/Sertraline ok)
- Fecal occult blood

Note: this list is a subset of the Exclusion Criteria

We look forward to working with you!

Thank you!

ContactUs@pharmain.com | +1 206 568 1450

Akiko Nishimoto-Ashfield (西本晶子), Associate Director, BD

Elijah Bolotin, President/CEO