*PHIN-214: Phase 1 Study in Compensated and Decompensated Cirrhotic Patients - A Novel Treatment to Manage Complications of Portal Hypertension with Subcutaneous, Once-daily Self-administration

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INTRODUCTION

Portal hypertension drives disease progression and decompensation in liver cirrhosis. Treatment of decompensated cirrhosis is largely palliative and there are no approved directed pharmacologic therapies for long-term management of portal hypertension.

Terlipressin, a vasopressin-analog recently approved by FDA, reduces portal pressure, however, its potential to elicit ischemia mandates inpatient venous infusion and stringent safety monitoring.

PHIN-214 is a proprietary, structurally optimized derivative of terlipressin designed to exhibit partial V1a receptor agonism with a reduced V2 receptor affinity, and a 10-fold broader therapeutic index than terlipressin. **PHIN-214 was engineered to manage portal hypertension and associated complications, as a self-administered, subcutaneous (SC), once-daily (QD) injection in an outpatient setting.**

PHIN-001 is an on-going Phase 1 dose-optimization study comprising both single and multi-ascending dose assessments of SC PHIN-214 in patients with cirrhosis. The primary objectives of the PHIN-001 study are to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) properties of PHIN-214, and to establish the recommended Phase 2 dose for further development.

BACKGROUND

PHIN-214 is a small peptide prodrug that is metabolized rapidly post-administration into the pharmacologically active metabolite PHIN-156 **(Fig 1)**. PHIN-156 activates V1a receptors on arterial smooth muscle causing mesenteric arterial vasoconstriction, reducing splanchnic blood flow and reducing portal pressure. Vasoconstriction also increases systemic arterial pressure preventing activation of the renin-angiotensin-aldosterone system (RAAS) and sodium retention. Moreover, increased systemic and renal arterial pressure improves kidney perfusion, glomerular filtration rate (GFR) and creatinine clearance.

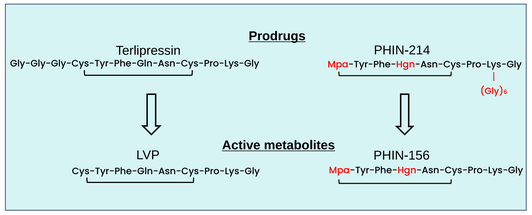


Figure 1: Amino acid sequence of PHIN-214 and its active metabolite, PHIN-156 (right) compared to terlipressin and its active metabolite, lysine vasopressin (LVP, left).

Metabolism of PHIN-214 and PHIN-156 are thought to be mediated by peripheral peptidases, and exposure is not anticipated to increase as a function of hepatic impairment. However, in this first-in-human study, Child-Pugh grade A (CP-A) subjects with less advanced cirrhosis were enrolled before Child-Pugh grade B (CP-B) subjects, to explore any association between disease severity and drug metabolism.

STUDY OVERVIEW

PHIN-001: Phase 1 open label, single-arm, dose optimization study

Part 1 – Single-Ascending Dose (SAD)
- Single dose
- 24-hour observation period, PK/PD assessments

Part 2 – Multiple-Ascending Dose (MAD)
- 28-days of single, daily administration
  - Days 1-4, 7, 14, 21 & 28 clinic visits for observation, PK/PD assessments
  - Days 4-28 daily self-administration at home

Option for SAD patients to roll into MAD study

To date, a total of 6 single ascending dose levels of PHIN-214 have been administered in a total of n=13 subjects

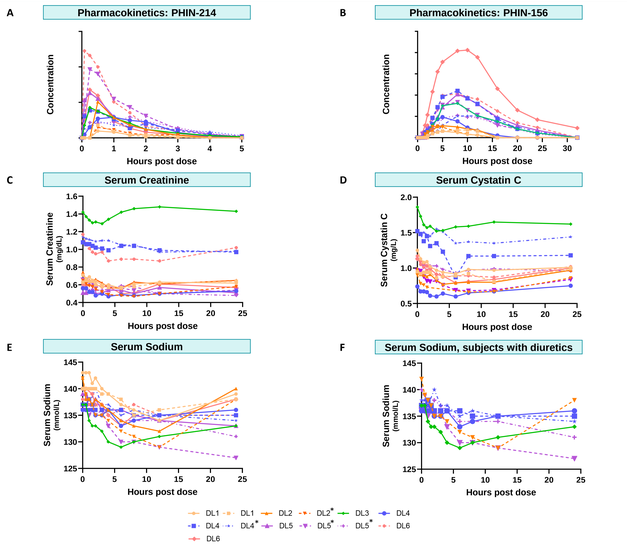
Table 1: Summary of study population demographics and baseline characteristics (n=13)

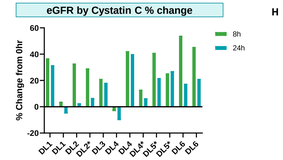
Demographic/Baseline Characteristic (n=13)	Value
Average age	55.5 (range: 43-72)
Average BMI	33.1 (range: 26-38)
Female (n)	8
Ascites (n)	4
NSBB (n)	8
Diuretic use (n)	7
Disease etiology	
Alcohol (n)	6
NASH (n)	3
HCV (n)	2
Alcohol & HCV (n)	2

Table 2: Summary of individual subject characteristics (n=13)

Baseline	Dose Level												
	1	1	2	2	3	4	4	4	5	5	5	6	6
CTP class	A	A	A	B	A	A	A	B	A	B	B	A	A
MELD-Na	7	6	6	12	14	14	14	9	11	9	11	7	8
Albumin (g/dL)	4.4	3.8	4.1	4.1	3.6	3.3	4.0	3.5	3.4	3.6	2.7	3.7	4.6
Creatinine (mg/dL)	0.7	0.6	0.7	0.6	1.4	0.6	1.1	1.1	0.5	0.7	0.6	0.6	0.9
eGFR-Cr (mL/min)	100	98	89	109	49	118	76	72	113	103	111	102	103
Total Bilirubin (mg/dL)	0.7	0.4	0.4	2.0	0.6	2.7	2.2	1.2	1.4	0.5	0.8	0.7	0.7
Sodium (mmol/L)	143	140	142	142	137	136	137	138	139	136	140	140	138
Hemoglobin (g/dL)	14	13	13	13	12	13	13	13	14	12	12	10	18
Platelets ($x10^9$/L)	124	137	156	128	56	79	61	110	144	82	56	227	135
INR	1.1	1.0	1.0	1.3	1.4	1.3	1.4	1.1	1.5	1.2	1.5	1.1	1.2

PK & PD OBSERVATIONS





H

eGFR (n=13) Change from baseline (calculated with cystatin C)		
	8 hr	24 hr
Delta %	28.5 CI 95% [18.7, 38.3]	14.8 CI 95% [6.4, 23.3]

Figure 2: Pharmacokinetic plots of PHIN-214 (A) and PHIN-156 (B); serum creatinine (C); serum cystatin C (D); serum sodium for the whole population (E); and for subjects taking concomitant diuretics (F); eGFR calculated based on cystatin C (F); with % change from baseline at 8 and 24 hours (H); * indicates a CP-B subject

The clinical PK profile of both PHIN-214 and PHIN-156 are consistent with preclinical observations[1] **(Fig 2A, B)**, with overall exposure being more comparable to dogs than rats. PHIN-214 is absorbed and metabolized rapidly (median T_{max} = 0.5 hrs; median half life = 0.9 hrs) to the active metabolite PHIN-156 which persists longer (median T_{max} = 8 hrs; median half life = 5.2 hrs). Overall, exposure to PHIN-214 and PHIN-156 appears dose-proportional. All subjects dosed to date demonstrate a drop in serum concentrations of sodium **(Fig. 2E, F)**, creatinine **(Fig. 2C)** and cystatin C **(Fig. 2D)** with creatinine and cystatin C appearing concentration-dependent. Subjects on concomitant diuretic therapy tend to exhibit more pronounced hyponatremia **(Fig. 2F).**

Pseudo-hyponatremia was evident in some patients with elevated baseline hyperglycemia. Of note, an improvement in eGFR was observed in the majority of subjects (**Fig. 2G, H**), with a median 28.5% improvement at 8 hours being sustained at 14.8% by 24 hours following a single dose of PHIN-214. The emerging PK profile of PHIN-156 supports QD dosing with little predicted accumulation.

SAFETY OBSERVATIONS

No treatment-emergent dose-limiting toxicities, serious adverse events (SAEs) or incidents of peripheral or central ischemia have occurred to date.

Adverse events (AEs) reported as related to PHIN-214 include:
- One CP-B subject (DL4) experienced a Grade 1 transient injection site reaction (blanching of skin)
- One CP-B subject (DL5) experienced acid reflux (Grade 2); abdominal pain & diarrhea (Grade1).
- One CP-A subject (DL6) experienced Grade 2 diarrhea with onset at 5 hours post dose which resolved by 21 hours post dose.
- Additional adverse events include transient Grade 2 asymptomatic hypo-natremia (3 subjects), which were coincident with concomitant diuretic therapy.

AEs reported as unrelated to PHIN-214 include:
- One incidence of hypotension (Grade 1)

CONCLUSIONS

Single, SC injection of PHIN-214 is well tolerated in compensated and decompensated cirrhosis, and yielded preliminary evidence of clinical activity at all dose levels administered

These emerging data support further development of PHIN-214 as a self-administered, SC, QD injection for treatment of complications of portal hypertension in patients with decompensated cirrhosis.

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AUTHOR DISCLOSURES

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[3]EW: **Consultant:** PharmaIN, BioVie, Novo Nordisk, Sequana, Astra Zeneca, Kezar

[4]PS: **Consultant:** PharmaIN. **Travel support:** Falk Pharma

[5]AK: Madrigal, Gilead

[6]MP: **Consultant:** PharmaIN, BioVie and River2Renal.

[7]EL: **Research:** 89Bio Inc., Akero Therapeutics, Alnylam Pharmaceuticals Inc., Amgen, Astrazeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cour Pharmaceuticals, Cymabay Therapeutics, Eli Lilly and Company, Enanta Pharmaceuticals, Enyo Pharma, Evidera Bioscience, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead Sciences, GlaxoSmithKline, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Ipsen, Janssen Pharmaceuticals, Madrigal Pharmaceuticals, Merck & Co., NGM Biopharmaceuticals Inc., Northsea Therapeutics, Novartis, Novo Nordisk Inc., Organovo, Poxel Co., Regeneron, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics, Zydus Pharmaceuticals. **Speaker:** Abbvie, Gilead Sciences, Intercept, Madrigal. **Consultant:** 89Bio Inc, Astrazeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck & Co, Novo Nordisk Inc, Organovo, Regeneron, Sagimet Biosciences

Reference:
[1]Biomedicine & Pharmacotherapy 2024 (171) 116068. (https://doi.org/10.1016/j.biopha.2023.116068)