Phase 1, Single-Ascending Dose Results from the PHIN-001* Study of PHIN-214 in Compensated and Decompensated Patients with Cirrhosis.

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PHARMAIN

BACKGROUND

Portal hypertension is a major driver of decompensation in patients with cirrhosis, yet effective long-term pharmacologic options remain limited.

PHIN-214 is a novel vasopressin analogue with partial V1a receptor agonism, reduced V2 activity, and a wide therapeutic index. It is being developed as a once-daily, subcutaneous self-injection for outpatient management of portal hypertension and its complications.

PHIN-001 (NCT05490888) is an ongoing phase 1 dose-optimization study evaluating single and multiple doses of PHIN-214 in adults with Child-Pugh class A and B cirrhosis. The objectives are to assess safety, tolerability, pharmacokinetics, and pharmacodynamics.

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

PATIENT CHARACTERISTICS

The single ascending dose phase of the study is complete. 15 subjects were treated across 8 single-ascending dose levels. 1 subject was treated twice, at dose level 1 and dose level 2.

Table 1: Baseline demographics and subject characteristics – Part 1 (SAD) (n=15)

Demographic/Baseline Characteristic	n=15 subjects
Age in years, mean (range)	56 (42 - 72)
Body Mass Index in Kg/m^2, mean (range)	31.6 (24.1 - 39.7)
Sex, number (%)	
Male	8 (53)
Female	7 (47)
Race, number (%)	
White	13 (87)
Black or African American	1 (7)
American Indian or Alaskan Native	1 (7)
Ethnicity, number (%)	
Hispanic or Latino	2 (13)
Not Hispanic or Latino	13 (87)
Child-Pugh (CP) class, number (%)	
A	11 (73)
B	4 (27)
MELD-Na score, mean (range)	10 (6 - 14)

Table 2: Relevant Concomitant Medications – Part 1 (SAD) (n=15)

Medication Class	Number (%)
Any diuretics	9 (60)
Furosemide	9 (60)
Spironolactone	8 (53)
Eplerenone	1 (7)
Beta Blockers	8 (53)
Lactulose	1 (7)
Rifaximin	1 (7)

SAFETY

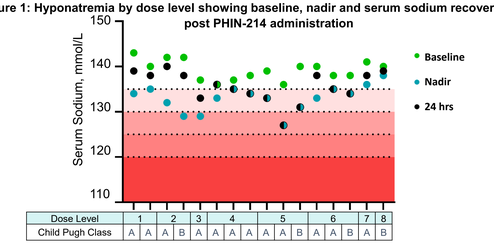
PHIN-214 was generally well tolerated with a safety profile consistent with on-target V1a engagement. 4 of the 15 total subjects treated experienced AEs considered possibly or likely drug-related adverse events. No AEs were reported in subjects treated at dose levels 1-3. A dose limiting toxicity (DLT) (hypertension) occurred at dose level 8, at which point enrollment into SAD ceased and the study transitioned to part 2 (MAD), per protocol.

Table 3: Reported AEs possibly/probably/definitely related to PHIN-214 administration

Dose Level	Subject	AE (verbatim term)	CTCAE Grade	DLT
4	106-028	Injection Site Reaction-Blanching	1	No
5	107-032	Acid Reflux	2	No
		Abdominal pain	1	No
		Diarrhea	1	No
6	100-027	Diarrhea	2	No
8	105-037	**Increased systolic blood pressure**	**3**	**YES**
		Blood in stool	2	No
		Abdominal cramping	2	No
		Weight loss	1	No
		Nausea	1	No
		Headache	1	No
		Abdominal distension	1	No
		Irregular, frequent bowel movements	1	No

An asymptomatic decrease in serum sodium was observed in all cases with a mean decrease of 6.2 mmol/L (95% CI: 4.6-7.8) and mean minimum of 133 mmol/L (95% CI: 131.6-134.4). At 24 hrs. serum sodium recovered to a mean of 135.5 mmol/L (95% CI: 133.8-137.2). Serum sodium changes did not differ between Child Pugh A and B subjects nor between subjects with and without diuretics.

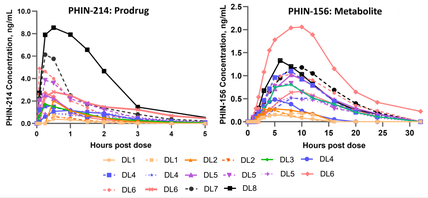
Figure 1: Hyponatremia by dose level showing baseline, nadir and serum sodium recovery at 24 hrs. post PHIN-214 administration



PHARMACOKINETICS

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). PHIN-214 and its active metabolite PHIN-156 demonstrate dose-proportional pharmacokinetics consistent with preclinical observations.

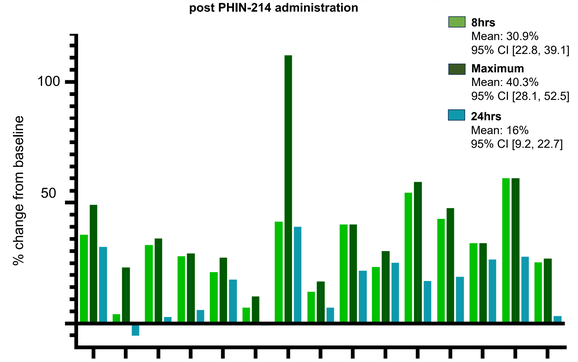
Figure 2: PHIN-214 (parent) and PHIN-156 (active metabolite) pharmacokinetics



EVIDENCE OF CLINICAL ACTIVITY

Evidence of improved renal function was observed with improved eGFR (CKD-EPI Cystatin C) in all subjects, irrespective of Child-Pugh classification or baseline eGFR. Improvements in eGFR persisted until at least 24 hours following PHIN-214 dosing in most subjects. Note: Due to missing data in 1 subject at DL5 only 15 data points are included.

Figure 3: Changes in eGFR (CKD-EPI Cystatin C); Maximum change and change at 8 hrs. and 24 hrs. post PHIN-214 administration



Dose Level	1		2		3	4			5		6			7	8
CP class	A	A	A	B	A	A	A	A	A	B	A	A	B	A	B
Baseline eGFR	57	78	74	90	33	107	45	46	78	60	63	67	87	65	67
Maximum eGFR	85	96	100	116	43	119	95	54	110	78	100	99	116	104	85
eGFR at 24hrs	75	74	76	95	39	106	63	49	95	75	74	80	110	83	69

Improvements in eGFR were correlated with PHIN-156 exposure (active metabolite), particularly at higher dose levels. A statistically significant & strong positive correlation was observed in all patients for which sufficient data points were available (Figure 4). Moreover, PHIN-214 treatment resulted in greater decrease in cystatin C than albumin in all subjects (Table 4) and there was no statistically significant correlation between serum albumin and PHIN-156 PK in any subject supporting a true improvement in eGFR mediated by PHIN-214.

Figure 4: Correlation between PHIN-214 PK and eGFR (CKD-EPI Cystatin C)

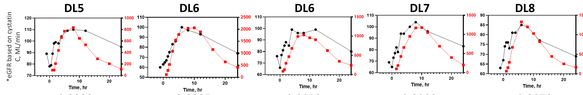
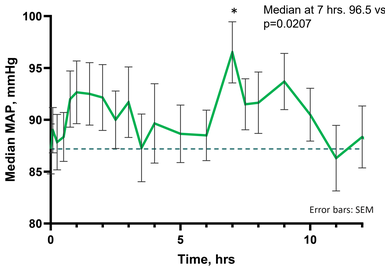


Table 4: Comparison of changes in cystatin C vs Albumin at 8hrs post PHIN-214 administration

% change at 8 hrs.	Dose Level 1	2	3	4		5		6		7	8	Average [95% CI]
Cystatin C	-21.6	-3.2	-19.2	-26.7	-14.5	-12.2	-23.0	-9.9	-29.9	-14.9	-28.3	-23.9	-25.3	-29.6	-15.6	-19.8 [-23.9, -15.8]
Albumin	-13.6	+2.6	-7.3	-9.8	-5.6	-6.1	-5.0	-5.7	0	-7.4	+2.7	-4.3	-7.9	-9.3	0	-5.1 [-7.5, -2.7]

PHIN-214 treatment resulted in a median Mean Arterial Pressure (MAP) increase of 3.24mmHg over the first 12 hours following PHIN-214 treatment and the median MAP was significantly increased at 7hrs following PHIN-214 administration.

Figure 5: Median Mean Arterial Pressure (MAP) post PHIN-214 administration



CONCLUSIONS

Single, SC injection of PHIN-214 is well tolerated and 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 injection for treatment of complications of portal hypertension in patients with decompensated cirrhosis.** Enrollment into part 2 - multiple ascending dose - is ongoing.

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AUTHOR DISCLOSURES

[1]DS: **Consultant/Advisor:** Mallinckrodt, BioVie, Resolution Therapeutics, Evive and Iota.
[2]NA: **Speaking and Teaching:** Echosens, Intercept, Ipsen, Gilead, Madrigal; **Consultant/Advisor:** 89Bio, Boehringer Ingelheim, Cima, Fibronostics, Gilead, Ipsen, Madrigal, Novo Nordisk, Perspectum; **Grants/Research Support:** 89Bio, Akero, Arbutus, AstraZeneca, Boehringer Ingelheim, Boston Pharma, Corcept, Eli Lilly, Galectin, Gilead, GSK, Inventiva, Ipsen, Madrigal, Merck, Novo Nordisk, Perspectum, Pfizer, Regeneron.
[3]EW: **Consultant/Advisor:** Biovie, Amgen, Astra Zeneca, Kezar, Mallinkrodt, Novo Nordisk, PharmaIN, Sequana.
[4]CL: Nothing to disclose
[5]GR: Nothing to disclose
[6]EL: **Speaking and Teaching:** AbbVie, Gilead Sciences, Intercept, Madrigal Pharmaceuticals; **Grants/Research Support:** 89Bio, Akero Therapeutics, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Corcept Therapeutics, Cour Pharmaceuticals, Cymabay Therapeutics, Eli Lilly and Company, Galectin Therapeutics, Gilead Sciences, GlaxoSmithKline, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Ipsen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Regeneron, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics, Zydus Pharmaceuticals; **Consultant/Advisor**: 89Bio, AstraZeneca, Boehringer Ingelheim, Corcept Therapeutics, Inventiva, Merck, Novo Nordisk, Organovo, Sagimet.