EMERGING SAFETY, PHARMACOKINETIC, AND PHARMACODYNAMIC RESULTS OF THE FIRST MULTIPLE-ASCENDING DOSE COHORT FROM THE PHASE 1 PHIN-001 STUDY OF PHIN-214 IN ADULTS WITH DECOMPENSATED CIRRHOSIS.

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BACKGROUND

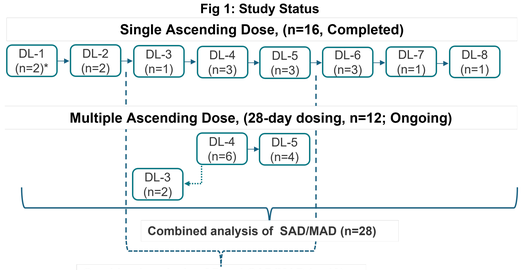
Portal hypertension drives cirrhosis decompensation, but long-term drug options are limited. PHIN-214 is a self-administered subcutaneous vasopressin analogue with partial V1a agonism, reduced V2 activity, and a wide therapeutic index, designed to increase splanchnic vasoconstriction and effective arterial volume.

The ongoing Phase 1 PHIN-001 study (NCT05490888) evaluates safety, tolerability, pharmacokinetics, and pharmacodynamics in adults with cirrhosis; single-ascending-dose (SAD) is complete, and multiple-ascending-doses (MAD) enrollment continues.

STUDY STATUS OVERVIEW

Fifteen subjects received PHIN-214 across eight SAD dose levels, with preliminary clinical activity observed at each dose. MAD began at DL4, prioritizing dose escalation while allowing simultaneous enrollment at lower dose levels (Fig. 1). Participants received 28 days of treatment; at this data cut, six DL4, four DL5 and two DL3 participants had received treatment.

Fig 1: Study Status



One SAD participant received a single dose at DL1 and later re-enrolled at DL2; this participant is counted twice in the figure. All 12 MAD participants were included in safety analyses. Pooled SAD/MAD Day 1 data (n=28) were used to assess eGFR, MAP, and HR; the DL3–5 eGFR analysis included 19 participants. Longitudinal eGFR analysis included four DL5 participants, selected because of more complete sampling.
Source Data: SAD locked data 23Sep2025, MAD database snapshot 02Oct2026

PATIENT CHARACTERISTICS

Table 1: Baseline Patient Characteristics

		SAD (n=15)	MAD (n=12)	Overall (n=27)	DL3-5 SAD+MAD (n=19)
Age (years), median		56	48	54	54
Sex, n (%)	**Male**	8 (53)	8 (67)	16 (59)	12 (79)
	Female	7 (47)	4 (33)	11 (41)	7 (21)
Race, n (%)	**White**	13 (87)	10 (83)	23 (85)	16 (84)
	Non-white	2 (13)	2 (17)	4 (15)	3 (16)
BMI (kg/m^2)		30.9	30.9	30.9	30.8
Child-Pugh Class, n (%)	**Class A**	9 (60)	0	9 (33)	5 (26)
	Class B	6 (40)	12 (100)	18 (67)	14 (74)
Albumin (g/dL), median		3.7	3.9	3.8	3.6
Platelets (10^3/µL), median		110	92.5	94	84
Total bilirubin (mg/dL), median		0.82	1.05	0.83	1.19
MELD 3.0, median (range)		10 (7-15)	9.5 (7-19)	10 (7-19)	10 (7-19)
Diuretic use at baseline, n (%)		9 (60)	12 (100)	21 (78)	18 (95)
Beta Blocker Use On Study, n (%)		8 (53)	5 (42)	13 (48)	10 (53)
Baseline eGFR CKD-EPI cystatin C (mL/min/1.73m^2), median		65.8	70.8	67.2	67.4
Baseline MAP (mmHg), median		86.7	90.9	87.9	88.7

SAFETY

SAD safety findings were reported previously (Simonetto et al., AASLD 2025; abstract 2404). This current analysis includes 12 MAD participants with Child-Pugh class B cirrhosis: six in DL4, four in DL5, and two in DL3. The first participant, treated with daily dosing, developed Grade 4 hyponatremia after four doses. Subsequent participants received every-other-day dosing on Days 1–14 while serum sodium stabilized, followed by daily dosing on Days 15–28. All participants were receiving diuretics before enrollment. Except for the first participant, diuretics were discontinued on or before Day 1. There were no consistent progressive increases in body weight or abdominal circumference; one participant restarted diuretics at the investigator's discretion. Among the 11 participants who received the modified regimen, 3 had Grade 2 hyponatremia, 4 had Grade 1, and 4 had no hyponatremia (Table 2). The hyponatremia may be compatible with residual V2-mediated antidiuresis, although the available data do not establish this as the sole mechanism.

Table 2: Worst hyponatremia following PHIN-214 administration in MAD subjects

Worst hyponatremia following PHIN-214 administration, n (%)	DL3 (n=2)	DL4 (n=6)	DL5 (n=4)	All subjects (n=12)
Grade 0	1 (50)	2 (33.3)	1 (25)	4 (33.3)
Grade 1	1 (50)	2 (33.3)	1 (25)	4 (33.3)
Grade 2		1 (16.7)	2 (50)	3 (25)
Grade 3				
Grade 4		1 (16.7)		1 (8.3)

Grade 0: >=135, Grade 1: 130 mmol/L - <135, Grade 2: 125 - <130 mmol/L, Grade 3: 120 - <125 mmol/L, Grade 4: <120 mmol/L

Two of 12 participants discontinued PHIN-214 due to DLTs: Grade 4 hyponatremia (DL4) as described above and an asymptomatic Grade 3 lipase increase (DL5). Among the 10 subjects who completed the 28-day treatment period, doses were withheld for hyponatremia in four participants—two per protocol and two at the investigator's discretion.

PHIN-214 was generally well tolerated. Aside from the DLTs, treatment-related adverse events were Grade 1 or 2 and generally resolved within the first week. The MAD safety profile was consistent with the SAD experience and on-target V1a activity (Table 3).

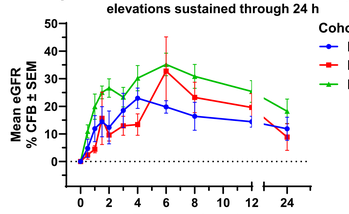
Table 3: Treatment related AEs following PHIN-214 administration in MAD subjects

Preferred Term	DL 3 (n=2)	DL 4 (n=6)	DL 5 (n=4)	All Subjects (n=12)
Any Treatment Related AE	1 (50.0)	4 (66.7)	3 (75.0)	8 (66.7)
Any grade ≥3 Treatment Related AE	-	1 (16.7)	1 (25.0)	2 (16.7)
Any DLT leading to dose discontinuation	-	1 (16.7)	1 (25.0)	2 (16.7)
Hyponatraemia	1 (50.0)	3 (50.0)	1 (25.0)	5 (41.7)
Hypokalaemia	-	1 (16.7)	1 (25.0)	2 (16.7)
Abdominal discomfort	-	1 (16.7)	-	1 (8.3)
Abdominal pain	-	-	1 (25.0)	1 (8.3)
Anaemia	1 (50.0)	-	-	1 (8.3)
Bradycardia	-	-	1 (25.0)	1 (8.3)
Brain natriuretic peptide increased	1 (50.0)	-	-	1 (8.3)
Diarrhoea	-	1 (16.7)	-	1 (8.3)
Erythema	-	1 (16.7)	-	1 (8.3)
Feeling of body temperature change	-	1 (16.7)	-	1 (8.3)
Hypertension	-	1 (16.7)	-	1 (8.3)
Hypophosphataemia	-	-	1 (25.0)	1 (8.3)
Injection site reaction	-	-	1 (25.0)	1 (8.3)
Lipase increased	-	-	1 (25.0)	1 (8.3)
Nausea	-	-	1 (25.0)	1 (8.3)
Pallor	-	1 (16.7)	-	1 (8.3)
Peripheral swelling	-	1 (16.7)	-	1 (8.3)
Procedural headache	-	1 (16.7)	-	1 (8.3)
Vomiting	-	1 (16.7)	-	1 (8.3)

EVIDENCE OF CLINICAL ACTIVITY

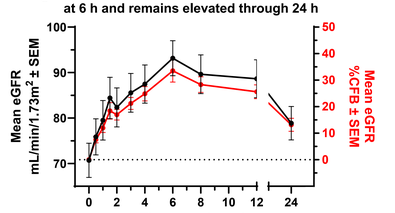
Exploratory analyses assessed PHIN-214's pharmacodynamic effects on renal function (Fig. 2). In pooled SAD and MAD data, participants at DL3–5 (n=18) had peak mean (± SEM) percent changes from baseline (CFB) in eGFR CKD-EPI cystatin C of 23.0 ± 3.7%, 32.8 ± 12.4%, and 35.2 ± 4.1%, at DL3, DL4 and DL5 respectively, with elevations persisting through 24 h postdose (Fig. 2A). Across all available Day 1 SAD and MAD data (n=27), eGFR %CFB peaked at 33.5 ± 4.3% at 6 h and remained elevated through 24 h. (Fig. 2B).

Fig. 2A: PHIN-214 increases eGFR across DL3-5, with elevations sustained through 24 h



eGFR CKD-EPI cystatin C (mL/min/1.73m^2); Day 1; pooled SAD/MAD participants at DL3–DL5 (n=18, 1 SAD subject at DL5 missing day 1 cystatin C data)

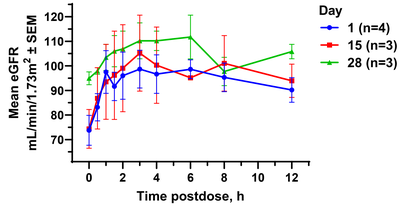
Fig. 2B: Across SAD and MAD cohorts, eGFR peaks at 6 h and remains elevated through 24 h



eGFR CKD-EPI cystatin C (mL/min/1.73m^2); Day 1; all SAD/MAD participants (n=27)

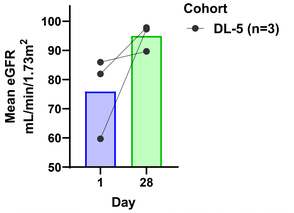
In MAD DL5, eGFR increases were observed after dosing on Days 1, 15 (after the every-other-day lead-in), and 28 (after transition to daily dosing), with peak mean increases of approximately 35%, 32%, and 19% from pre-dose baseline, respectively (Fig. 3A). DL5 was selected for its more complete longitudinal sampling. Across MAD DL3–5, mean predose eGFR increased from 74.6 ± 5.9 on Day 1 to 84.6 ± 6.4 mL/min/1.73 m² on Day 28 (mean ± SEM; data not shown); the largest paired increase was in DL5 (+19 mL/min/1.73 m²; n=3) (Fig. 3B). These findings are consistent with improved renal function over the 28-day dosing period.

Fig. 3A: eGFR increases recurred after dosing through Day 28



eGFR CKD-EPI cystatin C (mL/min/1.73m^2); Days 1, 15 and 28; MAD DL5

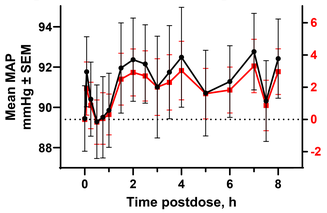
Fig. 3B: Predose eGFR increased over 28 days, with the largest paired increase in DL5



Pre-dose eGFR CKD-EPI cystatin C (mL/min/1.73m^2); Days 1 and 28; MAD DL5

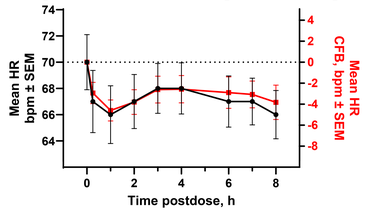
In pooled SAD and MAD subjects (n=28), mean arterial pressure (MAP) increased after PHIN-214, peaking at 3.32 ± 1.66 mmHg above baseline at 7 h. (Fig. 4A) before trending toward baseline by 12 h (data not shown). The increase was greater in subjects with lower baseline MAP (data not shown). Heart rate (HR) generally decreased over a similar timeframe (Fig. 4B). Together with the eGFR increases, these findings are consistent with the anticipated pharmacodynamic effects of V1a receptor agonism.

Fig. 4A: MAP increased following PHIN-214 dosing



MAP (mmHg); Day 1; all SAD/MAD participants (n=28)

Fig. 4B: HR decreased following PHIN-214 dosing



HR (bpm); Day 1; all SAD/MAD participants (n=28)

PHARMACOKINETICS

Following subcutaneous administration, PHIN-214 was rapidly absorbed and converted to the active metabolite, PHIN-156. On Day 1 (MAD DL3–5), PHIN-214 exhibited a median T_{max} of 0.25–0.75 h and half-life (t½) of 0.73–0.86 h, compared with 6–7 h and 4.8–5.7 h, respectively, for PHIN-156.

PHIN-214 exhibited approximately dose-proportional PK across DL3–5. Further analysis after cohort completion is warranted.

Both analytes showed negligible overall accumulation over 28 days (geometric mean accumulation ratios: 1.01–1.58), despite individual variability.

Prolonged PHIN-156 exposure coincided with postdose increases in eGFR CKD-EPI cystatin C, consistent with a temporal PK/PD relationship.

CONCLUSIONS

In decompensated cirrhotic subjects, 28 days of subcutaneous PHIN 214 with an every-other-day lead-in was well tolerated and produced rapid, exposure dependent improvements in eGFR consistent with selective V1a engagement. Changes in eGFR were accompanied by increased MAP and decreased heart rate.

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

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AUTHOR DISCLOSURES

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