A Phase 1b Study of PHIN-214, a Subcutaneous Peptide Derivative of Terlipressin, for At Home Therapy of Refractory Ascites

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Introduction

- PHIN-214 is a peptide derivative of terlipressin
- PHIN-214 and its pharmacologically active metabolite, PHIN-156, are partial agonists of the vasopressin receptor V1a
- Therapeutic Goals of PHIN-214 Treatment:
  - Expected to have a broader therapeutic index compared to IV terlipressin, resulting in an improved safety profile, with reduced risk of ischemia, and more comfort for the patient
  - Long term therapy at home
  - Decreases ascites formation via reduction of portal pressure
  - Reduces the need for large volume paracenteses, TIPS or peritoneovenous shunts
  - Delays progression to HRS via slowing the hemodynamic deterioration towards loss of kidney perfusion
  - Reduces risks and increases quality of life

Mechanism of Action

1. Binds to V1a receptors in the arterial smooth muscle causing mesenteric arterial vasoconstriction
2. Results in reduced blood flow to the splanchnic artery
3. Reduces portal hypertension
4. Increases systemic arterial pressure preventing activation of the renin-angiotensin-aldosterone system (RAAS) in the kidney and salt and water accumulation
5. The increase in systemic pressure and renal arterial pressure increases kidney perfusion as measured by creatinine and GFR
6. Collectively these changes result in reduced portal hypertension, improved renal blood flow and subsequent diuresis and natriuresis

Objectives

- To investigate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of PHIN-214 in patients with Child-Pugh A or B cirrhosis in this single ascending dose / multiple ascending dose study.
- To establish the maximum tolerated dose of PHIN-214 in both single and multiple (daily) doses.

Key Eligibility Criteria

Key Inclusion Criteria

- Child-Pugh A and B patients (based on histology or a combination of clinical, imaging, or biochemical)
- Males & Females, ages 18-75, BMI 18-40
- eGFR by CKD-Epi > 60 ml/min/1.73 m^2
- Resting heart rate 60-100 bpm
- SBP 90-140 mmHg; DBP 60-90 mmHg

Key Exclusion Criteria

- Uncontrolled hypertension and anti-HTN medications (beta-blockers are not exclusionary)
- Uncontrolled respiratory disease requiring oxygen
- Medications that could cause QTc prolongation

Currently enrolling at:
- Arizona Liver Health, Chandler AZ
- Mayo Clinic, Rochester MN

Treatment

- Open label, no placebo
- Single ascending dosing (SAD, part 1):
  - Dosing on Day 1, 24-hour observation period (vital signs, injection site, SpO2, 12-lead ECG)
- Multiple ascending dosing (MAD, part 2)
  - 28-day daily dosing
  - Extended observation period
  - Option for SAD patients to roll to MAD study

Advantages over Terlipressin

Parameter	Terlipressin	PHIN-214
Administration	IV, bolus or infusion	Subcutaneous
Location	Clinical setting, acute care setting	Home
Half-life	Short: 26 minutes	Long: 4-5 hours
V1a Agonist	Full	Partial
Ischemia	High risk	Low risk

Conclusions

- The mechanism of action is similar to terlipressin but, as a V1a partial agonist, PHIN-214 is expected to have a broader therapeutic index providing a higher safety margin and better quality of life for the patient.
- The subcutaneous daily administration at home would allow long-term benefit.

ClinicalTrials.gov
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