PHIN-214 , a Subcutaneous Peptide Derivative of Terlipressin, for At Home Therapy of Refractory Ascites
- Preclinical Results -

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Objective

- To evaluate PHIN-214 for safety and efficacy as proof of mechanism

Introduction

- PHIN-214 is a derivative of terlipressin
- PHIN-214 can be administered subcutaneously (SC) because the derivative avoids the skin necrosis associated with SC terlipressin

Discussion

- PHIN-214 showed a dose dependent diuretic and sodium excretion effect in rats, more effect at a lower dose than terlipressin
- PHIN-214 is a partial V1a agonist, compared to the full V1a agonist terlipressin
- PHIN-214 increases systemic pressure in dogs which should increase kidney perfusion
- PHIN-214 is more effective in reducing portal vein pressure in BDL rats than terlipressin

GLP Toxicity Studies

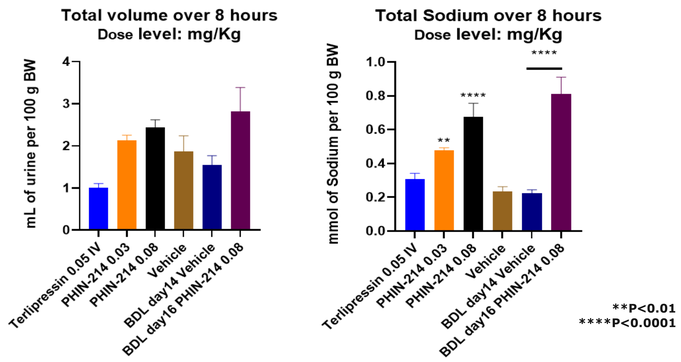
- PHIN-214 was evaluated in GLP and non-GLP studies including 28 day repeat dosing in dogs and rats
- PHIN-214 was also evaluated in cardiovascular (dog), and neurobehavioral and respiratory (rat) studies.

Pre-clinical Results

This work was funded by NIH grant DK103553

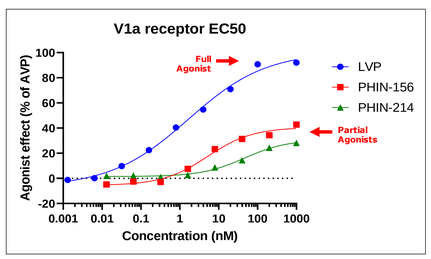
Diuresis & Sodium Excretion (Rats)

- Bile Duct Ligated (BDL) rats are more responsive at the same dose, compared to healthy rats
- Cumulative dose dependent increase in urine volume and sodium excretion observed at 8 hours after single dose
- Higher urine volume and sodium excretion than terlipressin at a higher dose



PHIN-214 is a Partial V1a Agonist

- PHIN-214 and its active metabolite (PHIN-156) are partial V1a agonists
- Terlipressin's active metabolite (Lysine Vasopressin, LVP) is a full V1a agonist



Pre-clinical Results (cont.)

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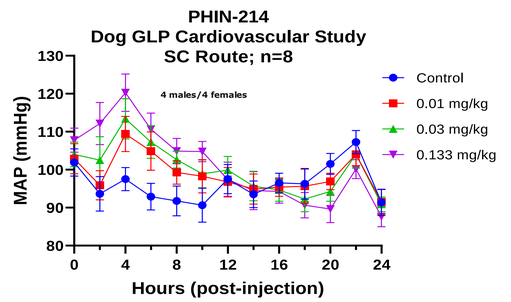
Increases MAP (Dogs)

- PHIN-214 increases mean arterial pressure (MAP)
- Increasing PHIN-214 dose results in lower, and potentially safer, non-proportional increase in MAP



Reduces Portal Vein Pressure (BDL Rats)

- PHIN-214 is more effective in reducing Mean Portal Vein Pressure (PVP) than terlipressin in BDL rats, for longer, and at a lower dose

Percent Change (%) in Mean PVP from baseline

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)

Conclusions

- These preclinical results support the study of PHIN-214 in humans
- Now recruiting in first-in-human Phase 1 study