Clinical safety and pharmacodynamics of VLX103, a new orally administered pentamidine formulation, in cirrhotic patients with early stage hepatocellular carcinoma

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VERLYX
TREATING LIVER DISEASE

1. ABSTRACT

VLX103 is the first oral pentamidine isethionate formulation ever administered to humans. Pentamidine has been historically administered parenterally to treat P. Carinii infection in AIDS patients, and has been associated with well-described adverse events. Because VLX103 is hepatoselective in humans, it is expected to be safer due to its limited systemic exposure, sparing usual target organs of toxicity. Moreover, animal studies have shown that pentamidine is anti-inflammatory and hepatoprotective through lipopolysaccharide (LPS) neutralization and prevention of the hepatic TLR4-mediated signaling pathways, suggesting a good therapeutic potential in liver disease. To translate these findings clinically, the safety and pharmacodynamics of VLX103 were assessed in a clinical Phase I study.

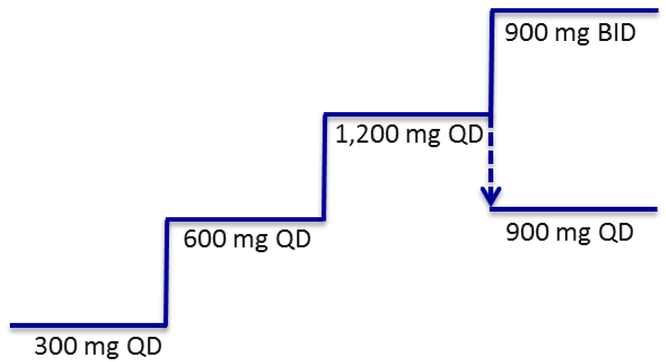
Methods: Four ascending doses of VLX103 or placebo (300, 600, 900 and 1,200 mg) were sequentially administered daily over three days to cohorts (N:8) of adult cirrhotic patients with early stage hepatocellular carcinoma scheduled to undergo thermal ablation of their liver tumor post VLX103 treatment. Safety was assessed through a comprehensive battery of clinical chemistry and hematology tests as well as physical assessments. Adverse events (AEs) were reported. Plasma ALT and AST activity was used as a marker of hepatoprotection for preliminary efficacy assessment.

Results: Among the 28 patients randomized, the three lowest doses were well tolerated. Most AEs reported were mild, of a GI nature, considered unrelated to VLX103 and resolved completely without any sequelae. The 1,200 mg QD regimen was poorly tolerated, with more severe GI AEs. Nonetheless, no clinically significant safety lab abnormality was reported at all four doses tested, including liver function tests. No VLX103-related SAE was reported. Only two subjects had significantly elevated ALT-AST values at baseline, i.e. one placebo (2x ULN) and one on 600 mg of active drug (4 x ULN). While a non-significant ALT-AST plasma activity reduction was observed with placebo, the VLX103 subject fully normalized ALT-AST after only three days of treatment. No other cause for transaminase normalization could be identified.

Conclusions: These results show that 1) VLX103 is safe and well tolerated at the 300-900 mg QD doses studied and 2) a possible hepatoprotective effect may be associated with short-term VLX103 therapy, in patients with liver disease and high ALT-AST.

2. STUDY DESIGN

Figure 1. Phase 1 Study Design: Randomized, double-blind, placebo controlled, dose ascending with distinct patients cohorts (n=8/cohort; 6 active, 2 placebo)



Study Patient Population

- Male or female subjects
- 18 years of age or older
- Radiologically established diagnosis of hepatocellular carcinoma (HCC) with tumor diameter ≤ 5 cm
- Suitable for and scheduled to undergo thermal ablation or partial hepatectomy as treatment
- HCC with a Barcelona score of 0 or A
- Cirrhosis with a Child Pugh score of A or B

Safety & Pharmacodynamic Endpoints

- Safety as assessed by adverse events (AE) occurence, vital signs, laboratory parameters (clinical chemistry & hematology) and physical exams including EKG.
- Plasma pharmacodynamic markers of efficacy: plasma ALT and AST activity.

3. DEMOGRAPHICS

Table 1. Patient Demographics

Gender	**97 % male**
Race	79 % Caucasian
HCC stage	75 % Barcelona 0
Cirrhosis stage	75 % Child-Pugh A

4. RESULTS

Safety: Adverse Events

A total of 114 Non-Serious Adverse Events (NSAE) occurred during the study, being Treatment Emergent (the majority) or not. The majority of AEs reported were mild, of a non-probable or definitive relationship with the study drug, did not require any particular action and resolved completely at the end of treatment of before. Doses between 300 and 900 mg QD were safe and well tolerated. However, 1,200 mg QD was associated with significant incidence of GI adverse events, which were manageable through dose reduction or splitting. The MTD was 900 mg QD.

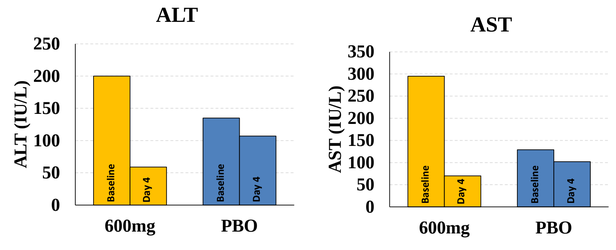
Table 2. ALT (IU/L); Normal Values: 10-50 IU/L

		Randomized Treatment Cohorts				
Variables	**Statistics**	**300 mg (N=6)**	**600 mg (N=6)**	**900 mg (N=6)**	**1200 mg (N=4)**	**Placebo (N=7)**
Screening	N	6	6	6	4	7
	Mean	44.5	77.8	51.7	72.8	48.9
	Std	27.19	73.64	28.47	47.95	39.91
Day-01	N	6	5	6	4	7
	Mean	45.8	36.4	50.3	70.3	44.1
	Std	31.02	17.31	24.65	53.38	28.19
Day-04	N	6	5	6	3	7
	Mean	47.8	38	49.5	82	44.6
	Std	26.51	16.39	26.96	64.86	29.9
Day-12	N	6	5	6	3	7
	Mean	49.5	90.8	59.5	74	95.3
	Std	15.4	64.93	32.44	43.41	79.45

Table 3. AST (IU/L); Normal Values: 10-70 IU/L

		Randomized Treatment Cohorts				
Variables	**Statistics**	**300 mg (N=6)**	**600 mg (N=6)**	**900 mg (N=6)**	**1200 mg (N=4)**	**Placebo (N=7)**
Screening	N	6	6	6	4	7
	Mean	46.3	96.8	53.7	75.5	58.6
	Std	24.65	109.47	21.38	38.51	42.81
Day-01	N	6	5	6	4	7
	Mean	45.7	40.8	51	79	53.3
	Std	29.4	28.19	23.58	46.53	36.91
Day-04	N	6	5	6	3	7
	Mean	46.2	38.6	49.5	84.3	54.1
	Std	22.98	23.2	22.11	57.66	37.27
Day-12	N	6	5	6	3	7
	Mean	42	58.2	45.8	68.7	60
	Std	20.07	41.36	19.03	35.22	30.19

Figure 2. Pharmacodynamics: full normalization in 1 patient on active drug



5. SUMMARY

In the context of this Phase I study in cirrhotic patients, VLX103 was safe and well tolerated at doses up to 900 mg QD during 3 days. The high dose (1200 mg) was associated with an increased prevalence of GI adverse events, but was otherwise safe from a biochemical, hematological and physical point of view. The only patient who had significantly elevated transaminases at baseline and receiving VLX103 was fully normalized after only 3 days of therapy, suggesting a hepatoprotective effect of the compound.

In conclusion, the results of this study show that VLX103 is safe and well tolerated within a 300-900 mg QD dose range, and could be hepatoprotective in liver disease patients showing significantly elevated transaminases.

6. REFERENCES

1. Szabo G *et al.* Gut-liver axis and sensing microbes. Dig Dis., 2010;28(6):737-44. doi: 10.1159/000324281. Epub 2011 Apr 27, (pc-29).
2. John G. *et al.* A 5-Year Retrospective Review of Adverse Drug Reactions and Their Risk Factors in HIV-Infected Patients Who Were Receiving Intravenous Pentamidine Therapy for PCP. Clinic Infect Dis 1997; 24:854-9.
3. David, SA. Towards a rational development of anti-endotoxin agents: novel approaches to sequestration of bacterial endotoxins with small molecules. J. Mol. Recognit. 2001; 14: 370–387.
4. Pentam 300. APP Pharmaceuticals, LLC | Last revised: 7 March 2012.
5. Johnston DE *et al.* Special considerations in interpreting liver function tests. Am. Fam. Physician. 1999 Apr 15;59(8):2223-2230.

6. DISCLOSURES

- Patrick Colin & François Ravenelle are employees of Verlyx Pharma Inc.
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