A Phase 1 Safety Study of SBP-101, a Polyamine Metabolic Inhibitor, for Pancreatic Ductal Adenocarcinoma

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Abstract

Background: SBP-101 (diethyl dihydroxyhomospermine), a polyamine (PA) analogue of spermine, inhibited growth in 6 human pancreatic ductal adenocarcinoma (PDA) cell lines and 3 murine xenograft tumor models. A Phase 1 dose escalation study assessed the safety, tolerability and pharmacokinetics (PK) of SBP-101 in previously treated patients with locally advanced or metastatic PDA. Methods: In a modified 3+3 dose escalation scheme, daily subcutaneous injections of SBP-101 were dosed at 0.05, 0.1, 0.2, 0.4 or 0.8 mg/kg, Monday-Friday for 3 weeks, followed by 5 weeks of observation (1cycle), for 1 or 2 cycles. Safety and tolerability were evaluated by clinical and laboratory assessments. PK was evaluated on Days 1 and 18 of cycle 1. Efficacy was assessed by RECIST criteria and overall survival. Results: Twenty-nine patients were enrolled in 5 cohorts: (1: N=3; 2: N=5; 3: N=4; 4: N=7; 5: N=10). Twenty-six had ≥2 prior chemotherapy regimens. Drug-related toxicity in cohorts 1-4 was minimal, although one patient in cohort 4 developed focal pancreatitis at the site of the tumor at 2.3 months. Most common adverse events (AEs) were abdominal pain, constipation, decreased appetite, dehydration, diarrhea, fatigue, nausea and vomiting. Most were grades 1 or 2 or considered unlikely or not related. No drug-related bone marrow suppression or peripheral neuropathy was seen at any dose. No DLTs occurred in cohorts 1-4. Three patients in cohort 5 developed serious adverse events considered dose limiting toxicities: bacterial sepsis with metabolic acidosis (N=1), hepatic and renal failure with elevated lipase (N=1) and superior mesenteric vein thrombosis with metabolic acidosis (N=1). Plasma C_{max} and AUC_{0-t} increased linearly with dose. Stable disease occurred in 2 patients each in cohorts 3 and 4, and in 4 patients in cohort 5. Median survival in cohort 3 was 5.9 months. Conclusions: SBP-101 was well tolerated in this study at dose levels 1-4; 0.8 mg/kg exceeded the maximum tolerated dose (MTD). Best tumor response and survival occurred with 0.2 mg/kg/day. The low incidence of AEs below the MTD and absence of bone marrow toxicity or peripheral neuropathy suggest the potential for SBP-101 as an addition to front line treatment for PDA and justify a combination study.
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Introduction

- PA concentrations are elevated in a number of neoplasms, including PDA, suggesting a promising therapeutic target.
- To exploit this observation, several synthetic PA analogues have been synthesized and tested as anti-neoplastic agents.
- SBP-101 is a synthetic analogue of spermine that inhibits PA metabolism *in vitro* and *in vivo*.
- This Phase-1 first-in-human safety study was conducted to evaluate safety, tolerability, and PK in previously treated patients with locally advanced or metastatic PDA.

Methods

- 29 patients were enrolled in a modified 3+3 dose-escalation protocol.
- 5 sites: 3 in Australia, 2 in the US.
- SBP-101 was administered subcutaneously daily Monday through Friday for 3 weeks followed by 5 weeks observation (=1 cycle).
- One to two cycles of 8 weeks each was administered.
- Five dose-level cohorts: 0.05, 0.1, 0.2, 0.4 and 0.8 mg/kg/dose.
- Safety and tolerability evaluated by clinical observations and laboratory tests.
- PK measurements performed on days 1 and 18 of cycle 1.
- Efficacy by RECIST criteria and overall survival were secondary endpoints.

Demographics

	Cohort 1 (0.05 mg/kg) (N=3)	Cohort 2 (0.10 mg/kg) (N=5)	Cohort 3 (0.20 mg/kg) (N=4)	Cohort 4 (0.40 mg/kg) (N=7)	Cohort 5 (0.80 mg/kg) (N=10)	All Cohorts (N=29)
Age (years)						
n	3	5	4	7	10	29
Mean	61.3	68.0	61.8	67.6	67.1	66.0
SD	4.93	9.27	7.89	7.35	9.76	8.34
Median	59.0	70.0	61.0	67.0	67.5	67.0
Minimum	58	55	55	56	53	53
Maximum	67	79	70	79	79	79
Gender n (%)						
Male	2 (66.7%)	4 (80.0%)	3 (75.0%)	2 (28.6%)	4 (40.0%)	15 (51.7%)
Female	1 (33.3%)	1 (20.0%)	1 (25.0%)	5 (71.4%)	6 (60.0%)	14 (48.3%)
Race n (%)						
Caucasian	3 (100.0%)	4 (80.0%)	3 (75.0%)	6 (85.7%)	8 (80.0%)	24 (82.8%)
Black African	0	1 (20.0%)	0	0	0	1 (3.4%)
Asian	0	0	1 (25.0%)	1 (14.3%)	1 (10.0%)	3 (10.3%)
Other	0	0	0	0	1 (10.0%)	1 (3.4%)

Table 1. Age, gender, and race for each cohort and all cohorts. There were no significant differences between cohorts in age, gender, or race, nor for height, weight or body mass index (BMI). (Data on file)

Treatment Exposure

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	All Cohorts
≥ 2 Prior Chemotherapy Regimens	3/3	3/5	4/4	2/7	8/10	20/29

Table 2. Previous Chemotherapy Exposure. Number of patients and total in cohort that received ≥ 2 chemotherapy regimens for metastatic disease.

Number of Doses	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	All Cohorts
Mean	14.0	17.4	21.3	18.4	13.5	16.5
SD	1.00	7.70	7.97	6.68	3.37	6.06
Median	14.0	15.0	20.5	15.0	15.0	15.0
Minimum	13	11	14	13	5	5
Maximum	15	30	30	30	15	30
Cumulative Dose (mg/kg)						
Mean	0.700	1.738	4.214	7.358	10.814	6.458
SD	0.0500	0.7685	1.5422	2.6405	2.7207	4.4091
Median	0.701	1.500	4.105	6.000	11.996	6.000
Minimum	0.65	1.11	2.80	5.20	3.99	0.65
Maximum	0.75	2.99	5.85	11.94	12.50	12.50

Table 3. SBP-101 Exposure. Amount of study drug administered by number of doses and by total mg/kg for each cohort and all patients in the study.

Disposition

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	All Cohorts
Adverse Event or DLT	0	0	0	2 (28.6%)	2 (20.0%)	4 (13.8%)
Investigator's/(IRB/EC) decision	0	0	0	0	1 (10.0%)	1 (3.4%)
Radiological progression	2 (66.7%)	2 (40.0%)	2 (50.0%)	3 (42.9%)	2 (20.0%)	11 (37.9%)
Clinical progression	1 (33.3%)	2 (40.0%)	2 (50.0%)	2 (28.6%)	3 (30.0%)	10 (34.5%)
Death	0	1 (20.0%)	0	0	1 (10.0%)	2 (6.9%)
Other (Subject decision)	0	0	0	0	1 (10.0%)	1 (3.4%)

Table 4. Disposition. Reasons for study termination in each cohort

Adverse Events

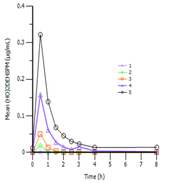
	All Grades		Related*		Grades 3-5**	
Nausea	18/29	62.1%	10/29	34.5%	2	6.8%
Fatigue	17/29	58.6%			1	3.4%
Abdominal Pain	13/29	44.8%	6/29	20.7%	1	3.4%
Constipation	13/29	44.8%			1	3.4%
Vomiting	11/29	37.9%	7/29	24.1%	1	3.4%
Decreased appetite	10/29	34.5%			1	3.4%
Dehydration	8/29	27.6%			2	6.8%
Diarrhea	8/29	27.6%	6/29	20.7%	0	--
Disease Progression	8/29	27.6%			8	27.6%
Injection site pain	6/29	20.7%	6/29	20.7%	0	--

Table 5. Adverse events. Adverse events occurring in >20% of patients of all grades, those that were related, and those that were Grade 3, 4 or 5, whether related or not related to study drug.
- A total of 155 adverse events occurred in 29 subjects.
- Most AEs were Grade 1 or 2 and/or considered unlikely or not related to the investigational product.
- The only Grade 3, Grade 4, or Grade 5 adverse event occurring in more than 20% of subjects was disease progression.
- No drug-related bone marrow suppression or peripheral neuropathy was seen at any dose and diarrhea was only Grade 1.
- Injection site pain (Grade 1) was only seen in Cohort 5

*Related AEs include definite, probable, possible, unlikely, missing and insufficient data to assess.
**Additionally, 1 patient each had a Grade 3, 4, or 5: anemia, hematemesis, pancreatitis, mesenteric vein thrombosis, pyrexia, hepatic failure, pneumonia, sepsis, multi-organ failure, urinary tract infection, spinal fracture, spinal cord compression, large bowel obstruction, elevated alkaline phosphatase, gamma-glutamyl transferase, hypoglycemia, hypophosphatemia, syncope, renal failure, pulmonary edema, pleural effusion, hypertension, and/or hypotension. Two patients each had grade 3, 4, or 5: small bowel obstruction, metabolic acidosis, hyponatremia, or increased aspartate aminotransferase, alanine aminotransferase, bilirubin, and/or lipase.

Pharmacokinetics

A. Mean Plasma Concentration vs. Time



B. SBP-101 PK Parameters

Dose (mg/kg)		Cmax (µg/mL)	Tmax (hr)	AUC_{0-t} (µg·hr/mL)	CL/F (mL/hr/kg)	T1/2 (hr)	R AUC
0.4 N=7	Mean	0.158	0.49	0.172	1945	2.24	1.29
	CV (%)	(44.5)	(7.0)	(50.4)	(55.1)	(133)	(43.1)
	GM	0.147	--	0.152	--	--	--
0.8 N=7	Mean	0.322	0.5	0.618	1132	12.1	2.19
	CV(%)	(21.2)	(6.2)	(61.4)	(49.0)	(122)	(40.7)
	GM	0.315	--	0.533	--	--	--

N=number of subjects, AUC=Area Under Curve, CL/F= Clearance
R=Accumulation ratio, GM=Geometric mean, CV=Coefficient of Variation

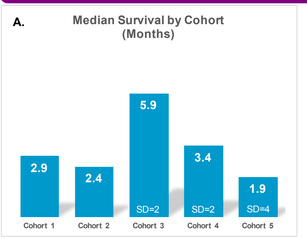
Figure 1. Pharmacokinetic Parameters on Day 18 (Fifteenth scheduled dose).
- **A. Mean plasma concentration of SBP-101 over time by cohort.** SBP-101 was rapidly absorbed with the time to reach Cmax (Tmax) occurring at approximately 0.5 hr. Cmax and AUC_{0-t} increased linearly with dose.
- **B. Comparison of PK parameters for the two highest dose levels**. Cmax, but not Tmax increased proportionately to the dose. AUC_{0-t} and $T_{1/2}$ increased as the CL/F decreased. CV% indicated moderate to high variation in the systemic exposure to SBP-101.

Dose Limiting Toxicities

- No SUSARs or DLTs in Cohorts 1-3.
- One patient in Cohort 4 developed Grade 3 focal pancreatitis at the tumor site during cycle 2 (2.3 months).
- Three patients in Cohort 5 developed serious adverse events considered dose limiting toxicities:
  - Bacterial sepsis with metabolic acidosis (N=1).
  - Hepatic and renal failure with Grade 4 elevated lipase (N=1).
  - Superior mesenteric vein thrombosis with metabolic acidosis (N=1).

Efficacy and Survival

A. Median Survival by Cohort (Months)



B.

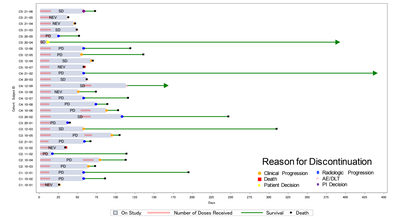


Figure 2. Survival by Cohort and Swim Lane Plot by Patient.
- **A.** Median survival in Cohort 3 was 5.9 months. Stable disease (SD) occurred in 2 patients each in Cohorts 3 and 4, and in 4 patients in Cohort 5.
- **B.** Time on study, dose administered, survival and reason for discontinuation from study.

CONCLUSIONS

- SBP-101 was well tolerated in this study at dose levels 1-4.
- Dose level 5 (0.8 mg/kg) exceeded the MTD.
- Best tumor response and survival occurred with 0.2 mg/kg/day (Cohort 3).
- The low incidence of AEs below the MTD and absence of drug-related bone marrow toxicity and peripheral neuropathy suggest the potential for SBP-101 as an addition to front line treatment for PDA and justify a combination study.