NANOPAC-2017-01 MID-STUDY REPORT: SAFETY, TOLERABILITY AND PRELIMINARY EFFICACY OF INTRACYSTIC SUBMICRON PARTICLE PACLITAXEL (SPP) FOR THE TREATMENT OF PANCREATIC MUCINOUS CYSTS

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Abstract (#705555) - Updated

Introduction

Pancreatic mucinous cystic lesions have significant potential for malignant transformation[1]; delivery of SPP as a direct intratumoral injection confirmed SPP present at the delivery site for at least 100 days in a prior study; intracystic therapy with SPP may prevent progression to cancer without corresponding systemic toxicities.

Aim

To determine safety and preliminary efficacy of SPP for treatment of pancreatic mucinous cystic lesions using endoscopic ultrasound fine needle Injection (EUS-FNI).

Materials and Methods

Subjects with confirmed mucinous cystic lesions, based on elevated intracystic CEA and cytology, received intracystic SPP via EUS FNI at volumes equal to the aspirated cyst fluid volume in sequential cohorts at 6, 10, and 15 mg/mL in a standard '3+3' dose-escalation protocol. The highest dose with acceptable safety and tolerability profile, as determined by a DSMB, proceeded into the double-injection phase of the study; 9 additional subjects received two injections of SPP at the same concentration, 12 weeks apart. Subjects were followed for 6 months for clinical endpoints including: safety and tolerability evaluations, physical examination findings and vital signs; pharmacokinetic analysis of systemic paclitaxel drug levels; and cyst volume response was reported by imaging at 3 and 6 months.

Results

Fifteen subjects have been enrolled to date; 8 completed the study (1 injection). Imaging (EUS, CT, MRI), cyst fluid CEA and amylase concentrations were consistent with branched duct IPMN cysts (BD-IPMN) or MCNs (Table 1).

No dose limiting toxicities, or clinically significant changes in blood work (chemistry; hematology; coagulation) or urinalysis have been reported. Adverse events have been mainly transient in nature, with one serious event considered probably related to the Investigational Product (see Safety).

Plasma paclitaxel concentrations did not exceed 1 ng/mL and were undetectable at 2 weeks supporting retention of SPP at delivery site.

In dose-escalation subjects, treated cysts had reduced volumes at study completion in comparison to screening; one subject's cyst was increasing volume after Month 3, but remained below baseline at Month 6 (Figure 1a).

Discussion

Intracystic SPP appears safe and tolerable when administered at 6, 10, and 15 mg/mL in a volume equal to that of aspirated cyst fluid. Minimal systemic study drug exposure has been experienced. No pancreatitis has been reported. Intracystic SPP appears to prevent continued growth of the cysts and may reduce total cyst volume. Subject enrollment in the double-injection phase is underway at 15 mg/mL.

Trial Design

Dose-Escalation Phase: Subjects were enrolled in sequential, escalating cohorts of SPP at concentrations of 6, 10, or 15 mg/mL injected directly into the cyst within the pancreas at a volume sufficient to fill the cyst, at least equivalent to the amount of fluid removed from the cyst (single injection); Safety and tolerability parameters were used to determine whether escalation could proceed by DSMB review.

Double-Injection Phase: Once the dose deemed appropriate for further evaluation was determined by the DSMB, an additional 9 subjects will be enrolled at that dose level. Subjects in this phase will also receive a second SPP injection to their cyst (at the same concentration) 12 weeks after the first SPP injection.

Objectives & Endpoints

Primary Objective/Endpoint:

- Safety and tolerability, as assessed by AEs, changes in vital signs, laboratory results, and physical examinations.

Secondary Objective/Endpoint:

- Concentration of paclitaxel in systemic circulation post-injection.
- Cyst volume response.

Inclusion Criteria

- Signed informed consent
- Age ≥18 years
- Recently confirmed mucinous cystic pancreatic neoplasm; may be confirmed by presence of mucin, cyst fluid carcinoembryonic antigen (CEA) above 192 U/L, or other reliable diagnostic means such as endomicroscopy; KRAS analysis may also be performed at the discretion of the Investigator
- Unilocular cyst with diameter of at least 1.5 cm and no more than 4 cm
- Subjects of child-bearing potential must follow adequate contraceptive measures

Exclusion Criteria

- Positive cytology indicating malignancy
- Thrombotic or embolic events
- Absolute neutrophil count ≤1.5 x 10^9/L and platelets ≤100 x 10^9/L
- Total bilirubin >3x ULN
- GGT, AST, and ALP >1.5x ULN
- Creatinine clearance < 60 mL/min/1.73 m^2
- Elevated serum lipase
- Hepatobiliary dysfunction within 3 months
- Interventions of the upper gastrointestinal tract (i.e. Endoscopic Retrograde Cholangiopancreatography [ERCP] or EUS) within 1 month
- Known hypersensitivity to study agent
- Known drug or alcohol abuse
- Pregnant or breastfeeding women

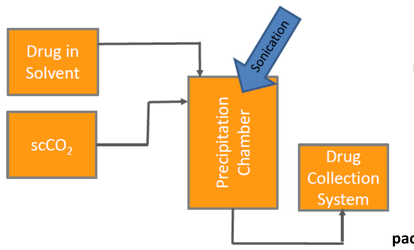
Investigational Product – Submicron Particle Paclitaxel (SPP; NanoPac®)

Technology

Unique non-mechanical process using supercritical CO_2 and sonication to precipitate submicron particle paclitaxel (SPP) in a GMP production environment (CritiTech, Inc.; Lawrence, KA).

Benefits

- Stable submicron particles without need for additives or coatings.
- Submicron particles with narrow particle size distribution (0.8 µm mean) with a large surface area to size ratio.
- SPP has shown sustained drug release and preliminary efficacy in preclinical[2,3] and clinical studies[4-6].



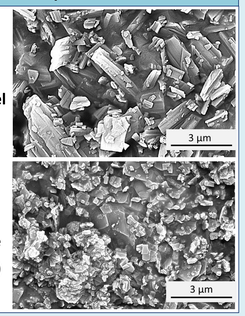


Table 1. Demographics

	Screening – mean [range]			
	Age	Largest Cyst Diameter (cm)	Cyst Fluid CEA Levels (ng/ml)	Cyst Fluid Amylase Levels (U/L)
Cohort 1 (6 mg/ml)	66.3 [57-73]	2.76 [2.7-2.8]	485.3 [317-732]	4398 [25-13108]
Cohort 2 (10 mg/ml)	73.6 [62-85]	2.16 [1.6-2.8]	1410.3 [595-2870.4]	8739.7 [3-13108]
Cohort 3 (15 mg/ml)	59.6 [53-70]	3.3 [2.4-3.9]	14771.5 [380.3-43343]	5140.3 [45-13108]
Double-Injection Phase (2x15 mg/ml)	67.5 [59-83]	3.29 [1.3-4.6]	917.6 [299-3101]	6664 [184-13108] (n=3)

Safety

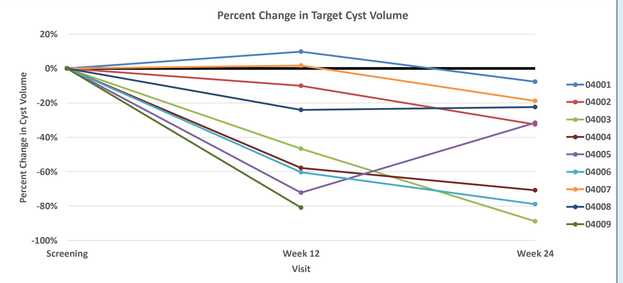
The double-injection phase of the study is actively enrolling at the highest dose level (15 mg/mL).

- There have been no SAEs considered related to the study drug in the dose escalation cohorts.
- In the double-injection phase of the study, one moderately severe SAE of Gastric Outlet Obstruction was experienced (06001) and was deemed probably related to SPP; the subject had elevated serum lipase and hepatobiliary dysfunction at the time of screening and had undergone ERCP two weeks prior to administration (eligibility criteria added following this event).
- Adverse events across all cohorts possibly related to SPP include mild, transient abdominal pain/discomfort in 4 subjects and nausea in 2 subjects.
- No events of pancreatitis have been reported.

Figure 1a. Dose-Escalation Single-Injection Cyst Volume Response

	Subject	Total Drug Given (mg)	Cyst Volume (cc)			
			Screening	Day 1[a]	Week 12	Week 24
Cohort 1 (6 mg/mL)	04001	21	N/A	9.2	10.1	8.5
	04002	15	4.0	8.2	3.6	2.7
	04003	24	N/A	10.3	5.5	1.15
Cohort 2 (10 mg/mL)	04004	50	N/A	14.1	5.96	4.13
	04005	30	7.23	3.05	2.01	4.95
	04006	50	18.9	38.78	7.5	4.0
Cohort 3 (15 mg/mL)	04007	105	18.98	31.06	19.3	15.4
	04008	112.5	11.6	9.95	8.8	9
	04009	75	2.2	4.19	0.8	Nov 2019

[a]Volume not reported by EUS imaging; volume calculated by V = π/6•l^3 if one dimension reported or by V = π/6•l•w^2 if two dimensions reported.



Percent change calculated from Day 1 volume if Screening volume not available

Figure 1b. Double-Injection Cyst Volume Response

	Subject	Total Drug Given (mg)		Cyst Volume (cc)			
		Injection 1	Injection 2	Screening	Day 1	Week 12	Week 24
Double-Injection Phase (2 x 15 mg/mL)	04010	105	60	8.3	4.07	6.03	Dec 2019
	04011	45	37.5	1.08	1.13	1.0	Dec 2019
	06001	75	N/A	27.2	29.76	Nov 2019	Jan 2020
	04012	255	Nov 2019	15.58	11.45	Nov 2019	Feb 2020
	07001	120	Nov 2019	16.76[a]	14.78[a]	Nov 2019	Feb 2020
	07002	15	Dec 2019	1	3.97[a]	Dec 2019	Mar 2020

[a]Volume not provided in imaging report; volume calculated by V = π/6•l•w^2 if two dimensions reported or by V = π/6•l•w•h if three dimensions reported.

Pharmacokinetic Data

Plasma paclitaxel is assessed at one and two hours post SPP administration and at each study follow-up visit.

- In Cohorts 1 and 2, the maximum systemic paclitaxel concentration did not exceed 1 ng/mL and is undetectable at 2 weeks.
- Cohort 3 and Double-Injection Phase PK samples are awaiting batched-sample analysis.

Cyst fluid aspirated at Week 12, prior to SPP administration in the Double-Injection phase, will be assessed for paclitaxel.

Conclusion

- Safety and tolerability were established in the dose-escalation phase allowing the double-injection phase to proceed at the highest-dose concentration (15 mg/mL).
- Maximum systemic paclitaxel levels did not exceed 1 ng/mL.
- No pancreatitis has been reported.
- Adverse events occurring on study were generally mild and self-limiting.
- Reduction of cysts volume was noted during the 6-months follow up period.

Preliminary results of the use of SPP (NanoPac) in the management of pancreatic mucinous cysts are promising and warrant further evaluation.

References

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