

# Intracystic Injection of Large Surface Area Microparticle Paclitaxel for Chemoablation of Intraductal Papillary Mucinous Neoplasms: Insights from an Expanded Access Protocol

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## BACKGROUND and AIMS

Branch duct (BD) – Intraductal Papillary Mucinous Neoplasms (IPMNs) represent 80% of incidentally identified pancreatic cystic lesions (PCLs). Guideline-directed risk assessment is suboptimal and about 60% patients undergo unnecessary surgical resection. Thus, minimally invasive treatments are increasingly being utilized.

A phase 1 clinical trial evaluated the safety, tolerability, and preliminary efficacy of EUS-guided fine needle injection (EUS-FNI) with novel particle-engineered form of paclitaxel with large surface area microparticles (LSAM-PTX, NanoPac®, CritiTech, Lawrence, KS) in mucinous PCLs.

We prospectively evaluated the safety and response of EUS-FNI of LSAM-PTX to chemoablate BD-IPMNs in an expanded access protocol (EAP).

## METHODS

Subjects diagnosed with BD-IPMNs and deemed non-surgical received up to two doses of LSAM-PTX (15mg/mL; 12 weeks apart) by EUS-FNI as part of a multicenter clinical trial (NCT03188991). Subjects at our center were subsequently enrolled into an EAP where additional doses of LSAM-PTX were administered by EUS-FNI on similar schedules (Figure 1).

## RESULTS

Six BD-IPMNs measuring (mean ± standard deviation (SD)) 3.18 ± 0.76 cm in diameter among 5 subjects (mean age: 66 years) were treated by EUS-FNI of LSAM-PTX. Two to six doses of LSAM-PTX (mean dose/cyst: 73 ± 31 mg) were administered, and subjects were followed for up to 32 months.

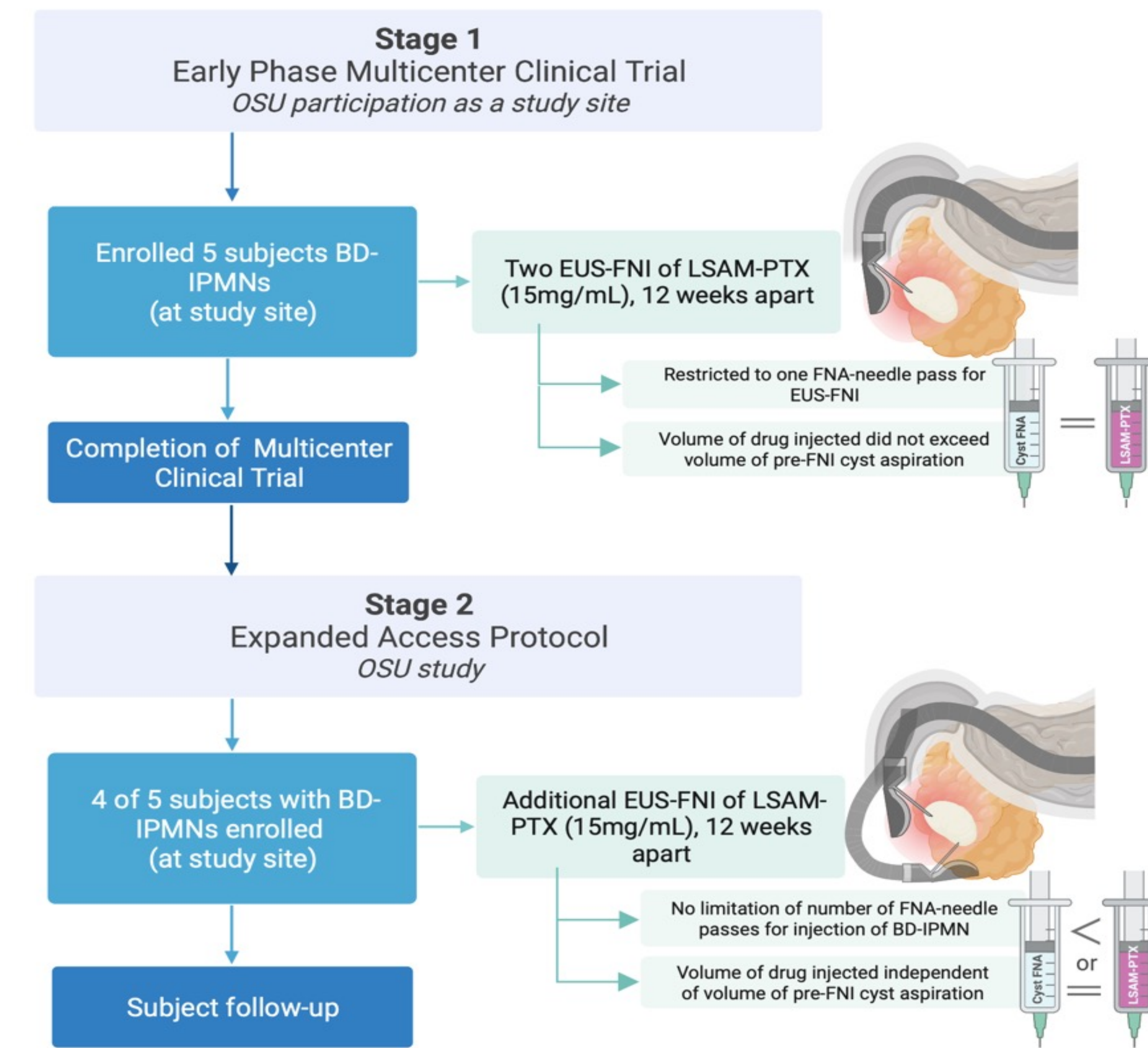


Figure 1. Study flow chart

The mean volume reduction of the treated cysts was 42-89% (absolute volume change from 9.58 ± 5.1ml to 2.2 ± 1.1ml (p=0.016)), Figure 2. The mean surface area was reduced from 31-83% (absolute reduction from 21.9 ± 8.7cm<sup>2</sup> to 5.7 ± 2.5cm<sup>2</sup> (p=0.009)), Figure 2.

Higher dosing-frequency of EUS-FNI of LSAM-PTX significantly correlated with a reduction in cyst volume (R<sup>2</sup>=0.87, p=0.03) and surface area (R<sup>2</sup>=0.83, p=0.04), Figure 3.

Comparing pre-and-post ablation, molecular analysis of the cyst fluid demonstrated loss of the cyst-associated mutations in 5 (83.3%) with reemergence in 1 and persistence in 1, and intracystic changes of fibrosis or calcification were observed in 83.3% (n=5) BD-IPMNs (Figure 4).

## Immediate and Sustained Response

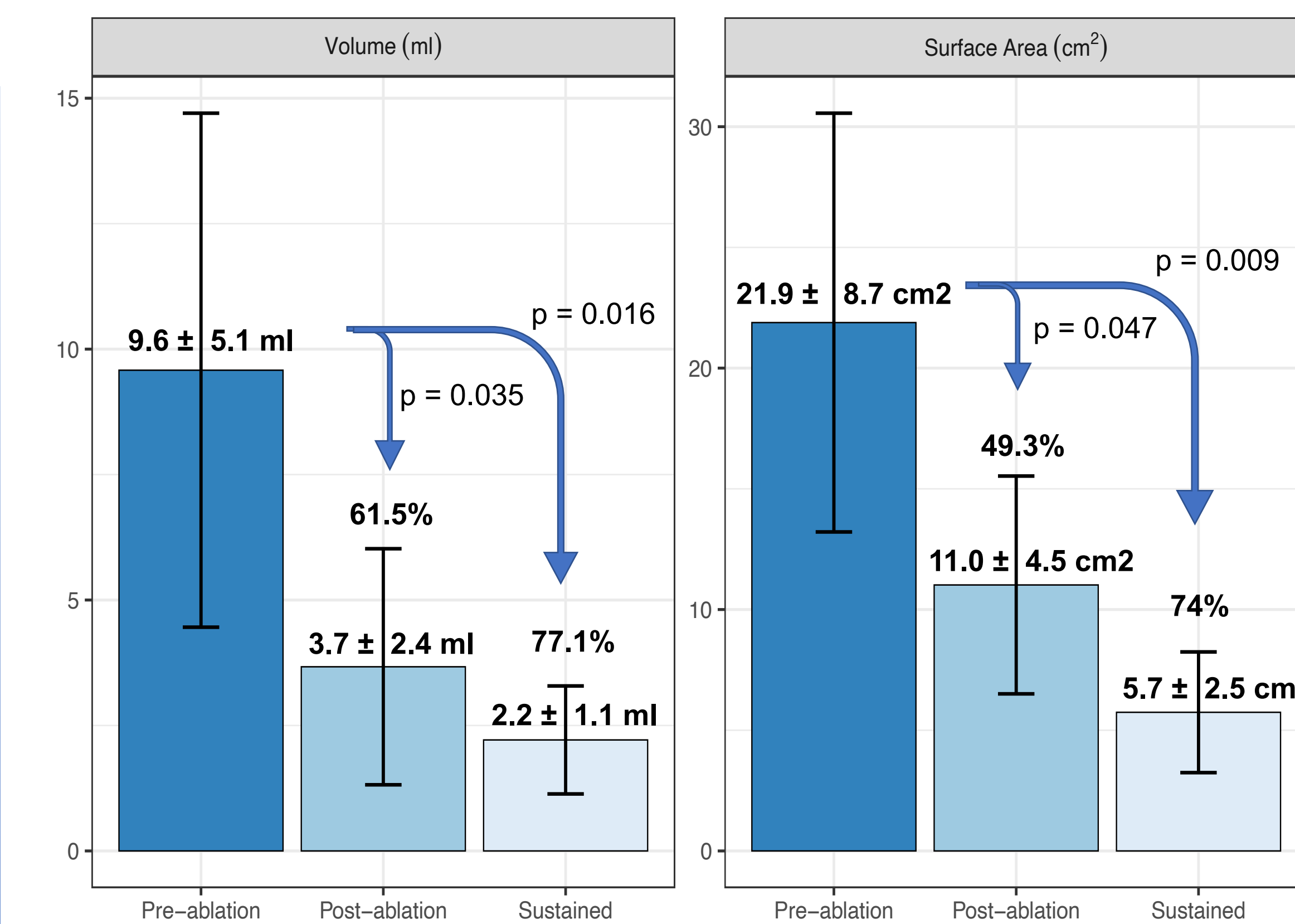


Figure 2. Changes in BD-IPMN volume and surface comparing pre-ablation, immediate and sustained response; box-plot with 95% CI.

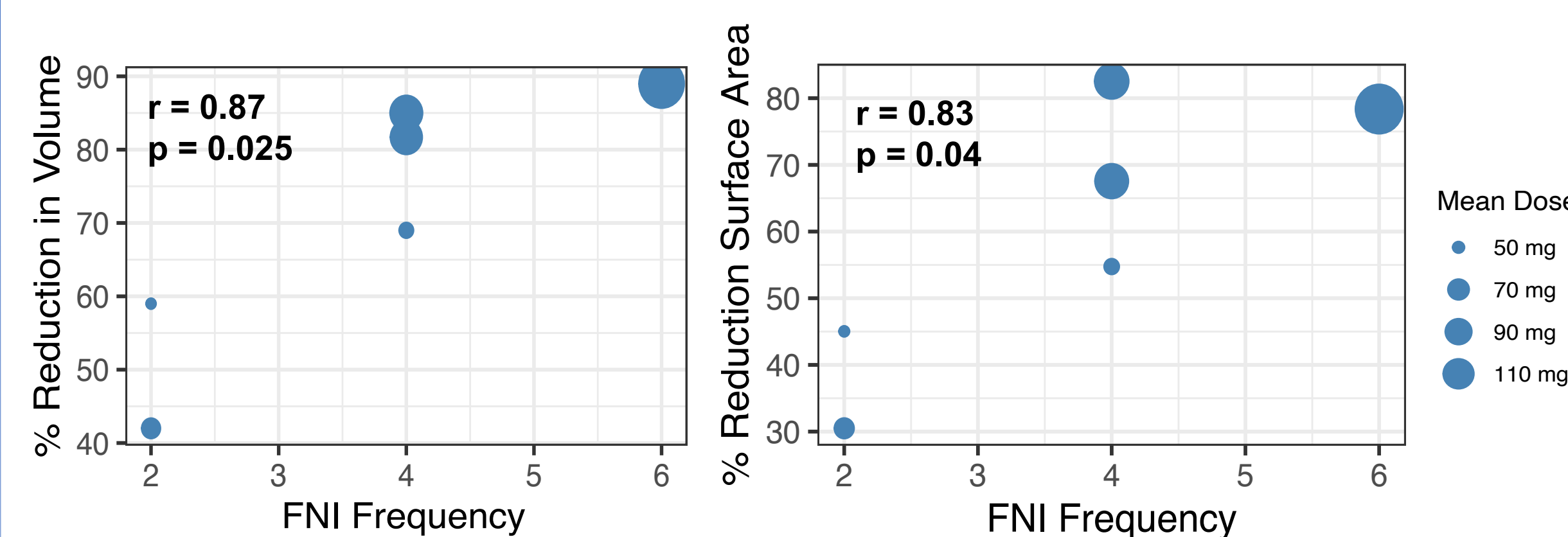


Figure 3. Reduction in BD-IPMN volume and surface and correlation with frequency and dosing of LSAM-PTX

## ADVERSE EVENTS

One subject developed mild acute pancreatitis following EUS-FNI (5th dose) of LSAM-PTX in a fibrotic BD-IPMN.

Phase	CT and/or MRI changes	EUS morphology	Cyst fluid molecular analysis	
BD-IPMN #1	Pre-ablation	Septations, septal and wall enhancement, focal dilation of PD	Multilobulated, thick wall and septations	KRAS (p.G12V) GNAS (p.R201H)
	Post-ablation	Small to characterize, fibrosis, decrease in focal dilation of PD	Increase in size, inflammatory debris no septations, thick wall	No mutations
	Sustained			No mutations
BD-IPMN #2	Pre-ablation	Septations, septal enhancement	Multilobulated, thin septations, thin wall	KRAS (p.G12V) GNAS (p.R201C)
	Post-ablation	New calcifications, decrease in size	Reduced size, thick septations, thick wall, fibrosis	KRAS (p.G12V) GNAS (p.R201C)
	Sustained			
BD-IPMN #3	Pre-ablation	Uniform thin wall, no septations	Single compartment, thin wall	GNAS (p.R202C) BRAF (p.V600_S605delinsD)
	Post-ablation	Decrease in size, new septations	Decrease in size, subtle septations vs. fibrosis	No mutations
	Sustained			
BD-IPMN #4	Pre-ablation	Dense septations, thin wall	Multilobulated, thin septations, thin wall	KRAS (p.Q61H) GNAS (p.R202C)
	Post-ablation	Prominent septations, fibrotic changes, decrease in size	Reduced size, multilobulated, thick septations, thick wall	KRAS (p.Q61H) GNAS (p.R202C)
	Sustained			
BD-IPMN #5	Pre-ablation	Lobulated, thin septations, thin wall	Multilobulated, thin septations, thin wall	KRAS (p.G12V) GNAS (p.R202H)
	Post-ablation	Decrease in size, thick septations, fibrotic changes	Reduced size, multilobulated, thin septations, thin wall	No mutations
	Sustained			
BD-IPMN #6	Pre-ablation	Enhancement of smooth cyst wall	Single compartment, thick wall	KRAS, p.G12R
	Post-ablation	Thick wall, fibrosis, calcification	Inflammatory debris, thickening of wall	No mutations
	Sustained			

Figure 4. Morphological changes observed in cross-sectional imaging and EUS after EUS-guided chemoablation with LSAM-PTX

## CONCLUSION

In this extended access protocol, EUS-FNI of LSAM-PTX into BD-IPMNs was safe and resulted in volume and surface area reduction, morphological changes, and loss of pathogenic mutations.