Table 1 (abstract 189):
Order and test adherence rates according to gender, race, age range, and age group

Table 1: Outcomes Before and After ELX/TEZ/IVA (N=8)				
Outcome measure	**Visit 1**	**Visit 2**	**Difference**	**P-value**
Weight z-score	-0.52 (-1.51, -0.31)	0.18 (-1.27, 0.66)	0.52 (0.27, 1.09)	**0.014**
BMI z-score	-0.11 (-0.69, 0.86)	0.89 (0.06, 1.46)	0.35 (0.21, 1.11)	0.18
FEV1 % predicted	79 (5, 101.75)	86 (57.5, 102.25)	3 (1, 8)	**0.076**
FVC % predicted	80 (62, 104.25)	88.5 (73.5, 104.5)	6 (0.5, 14.5)	0.09
% fat mass	19.9 (17.6, 28.57)	25.7 (19.52, 28.95)	4.75 (0.92, 5.77)	**0.03**
% fat free mass	0.8 (0.71, 0.82)	0.74 (0.71, 0.81)	-0.048 (-0.05, -0.01)	**0.03**
Fat mass index	4.12 (3.07, 6.67)	6.29 (4.08, 7.49)	1.55 (0.48, 2.11)	**0.014**
Fat free mass index	17.4 (15.73, 17.77)	17.71 (16.53, 18.01)	0.43 (0.05, 1.008)	**0.14**
Glucose iAUC	6668.8 (4850.7, 8548.8)	5760.7 (4269.6, 8459.2)	-1021.3 (-2935.1, -244.0)	**0.23**
Insulin iAUC	701.37(198.1, 2103.1)	1652.1 (929.8, 3228.5)	962.5 (522.3, 2217.5)	**0.021**
Cpeptide iAUC	46537.65 (36232.73, 62363.49)	83660.81 (66735.62, 121036.69)	36330.73 (25330.39, 46849.99)	**0.021**
HOMA2 IR	0.73 (0.61, 0.78)	1.25 (0.83, 1.61)	0.46 (0.35, 0.92)	**0.014**
*Data presented as median (IQR)				

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Hyperosmolar salt concentrations slow digestion of milk and meconium by pancreatic enzymes

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Background: Meconium ileus (MI) is a life-threatening presentation of cystic fibrosis (CF) that occurs in approximately 20% of newborns with CF [1]. Current treatments with hyperosmolar or N-acetylcysteine (NAC) enemas often fail to relieve MI. Approximately 75% of newborns with MI ultimately require surgery [2]. Most newborns with MI have pancreatic insufficiency, indicating a possible role for pancreatic enzymes in the pathogenesis and treatment of MI. We find that meconium from CF pigs is digestible with pancreatic enzymes, but it does not break down in NAC or hypertonic solutions. Because hypertonic solutions are often used to treat MI, our goal was to determine how salt concentration affects pancreatic enzyme function using milk and meconium as substrates.

Methods: To compare digestion kinetics at different salt concentrations, we used powdered milk in water at 31.9 g/L. We added different NaCl concentrations over a range of doses with a maximum range of 333 mM. Because pH influences pancreatic enzyme function, we buffered the solutions at pH = 7.0 with 3.3 mM piperazine-N, N′-bis. We added 4.2 units of lipase/mL of mixed pancreatic enzymes (Epizyme) and then assessed the digestion of milk at 37°C kinetically by measuring absorbance at 600 nm every 5 minutes with a plate reader. In ongoing studies, we are digesting 0.7-g pieces of CF pig meconium with 10 mg/mL of mixed pancreatic enzymes in different NaCl concentrations at 37°C with constant agitation. We measure meconium digestion at 16 hours by comparing release of pigments (A_{405}) and residual weight of meconium solids.

Results: In the absence of added salt, pancreatic enzymes rapidly clarified powdered milk, decreasing the A_{600}. Increasing NaCl concentrations at doses above 0.0833 M decreased the rate of enzymatic digestion in a dose-dependent manner. At 0.166 M NaCl, enzymatic digestion of milk was approximately half as fast as the samples without added salt (Figure 1). We compared digestion of CF meconium pieces by pancreatic enzymes in normal saline (0.15 M) and 7% NaCl (1.1 M) and found that residual meconium was lower in normal saline.

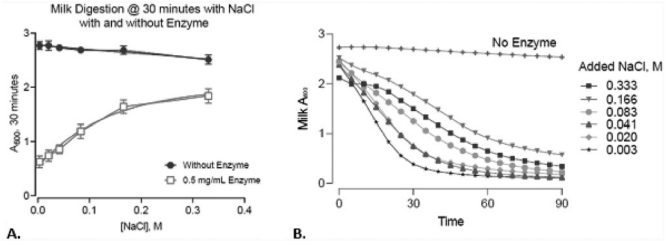

Figure 1. Pancreatic enzyme function is optimal in low salt. Dry powdered milk was dissolved in different [NaCl]. We measured milk digestion by decreasing absorbance at 600 nm using a plate reader at 37°C. Epizyme 4.2 units of lipase/mL was added to wells unless indicated. A. Residual milk signal at 30 minutes was lowest with low NaCl concentrations. Symbols represent means and standard deviations for three experiments. B. Milk digestion kinetics were faster at lower NaCl concentrations. Representative experiment, symbols are the mean from three wells.

Conclusions: We found that digestion of powdered milk and CF meconium by pancreatic enzymes was faster with lower salt concentrations. Endogenous pancreatic enzymes are insufficient in patients with MI, and hyperosmolar solutions could slow meconium digestion. Future studies are needed to establish ideal conditions for dissolving obstructive meconium in animal models, with the goal of relieving intestinal obstruction in newborns with MI.

Acknowledgements: Anthony Fischer, Christian Zirbes.

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Cystic fibrosis transmembrane conductance regulator potentiator (ivacaftor) has minimal effects on gut microbiome composition in people with cystic fibrosis and gating mutations

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Background: Cystic fibrosis (CF) is associated with gut microbiota dysbiosis. It is likely that the etiology of microbiota differences in CF is multifactorial and includes impaired bicarbonate secretion, low pH, abnormal gastrointestinal motility, inspissated intestinal stool and mucous, fat malabsorption, lack of endogenous pancreatic enzymes, high fat diet, and frequent antibiotic use. Prior studies have demonstrated altered microbiota composition in individuals with CF. The impact of highly effective CF transmembrane conductance regulator (CFTR) modulator therapy on the microbiota is largely unknown. We compare microbiota composition in individuals with CF and gating mutations at baseline and 3 months after initiation of the CFTR potentiator ivacaftor with that in healthy controls.
Methods: Subjects with gating mutations were recruited from CF centers in the United States and Italy. Stool samples were collected at baseline and 3 months after initiation of ivacaftor treatment. Age-matched healthy subjects were included from two previously published cohorts [1,2]. Microbiome composition was assessed using shotgun metagenomic sequencing with the DNeasy PowerSoil Kit (Qiagen, Germantown, MD) for extraction, the NexteraXT DNA Library Preparation Kit (Illumina, San Diego, CA), and an Illumina HiSeq 2500 using 2 × 125 base pair chemistry. Data were processed using the Sunbeam, abundance of bacteria was estimated using Kraken, and analysis was conducted in R. Dysbiosis score was calculated as the median Bray-Curtis distance to healthy participants.
Results: Eighteen individuals with CF (7 male, 11 female, median age 15.3), 13 of whom had exocrine pancreatic insufficiency and five of whom had pancreatic sufficiency, completed the study. There were no differences in alpha diversity between healthy and CF subjects using richness or Shannon's index, but CF subjects had higher dysbiosis scores ($p < 0.001$) and a different microbiota composition (beta diversity) than healthy controls (Figure 1, permutational multivariate analysis of variance $p < 0.01$). These differences in composition corresponded to a greater relative abundance of *Enterobacteriaceae*, *Escherichia coli*, and *Veillonella parvula* in subjects with CF and a smaller relative abundance in ten *Bacteroidetes* taxa, *Eubacterium rectale, Faecalibacterium prausnitzii,* and *Akkermansia muciniphila* (all false discovery rate < 0.05). By contrast, treatment with ivacaftor for 3 months did not lead to statistically significant differences in alpha diversity (richness or Shannon's diversity index), beta diversity (Bray-Curtis distances), or relative abundance of specific bacterial taxa.
Conclusions: Different microbiome composition was found in subjects with CF than in healthy participants, consistent with previously reported results. We observed no statistically significant effects of ivacaftor treatment on gut microbiota composition, although this was a small cohort with multiple confounders, including antibiotics use and differences in exocrine pancreatic function.

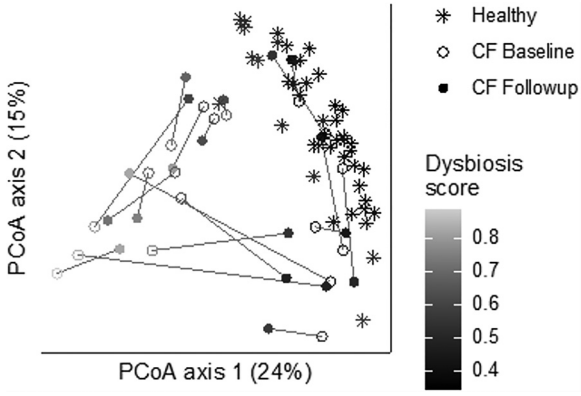

Figure 1. Principal coordinate analysis plot of microbiome composition (Bray-Curtis distance) in people with cystic fibrosis (CF) and healthy controls

Acknowledgements: This work was supported by the Penn Center for Nutritional Science and Medicine, Vertex Pharmaceuticals, and National Institutes of Health, National Center for Advancing Translational Sciences (UL1TR001878, UL1RR024134, UL1TR000003). The authors acknowledge JN Brownell for his contributions.

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Gastrointestinal symptoms in a cystic fibrosis transmembrane conductance regulator modulator era—an international survey

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Background: How to relieve gastrointestinal (GI) symptoms in people with cystic fibrosis (CF) was identified as a research priority and explored through an international qualitative survey in the CF community in 2018 [1]. After introduction of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in 2019, many more people with CF (PwCF) are able to access CF transmembrane conductance regulator (CFTR) modulator therapy. Although the respiratory benefits of ELX/TEZ/IVA are well documented, effects on the GI tract are not well understood. The aim of this study was to characterize GI symptoms in the CF population and ascertain whether the introduction of modulators affected them.
Methods: PwCF, families, and health care professionals (HCPs) completed electronic surveys over a 1-month period. The survey was promoted