TAYLOR COLLISON

Sharebrokers and Investment Advisers
www.taylorcollison.com.au

30 November, 2016

Pharmaxis (PXS)

Outperform

Initiating: A Partnership Play with Effective Risk-Mitigation

Price Target: $0.35

Elyse Shapiro
eshapiro@taylorcollison.com.au
+61 4 9126 7142

Summary (AUD)

Market Capitalisation	**$82.85**
Share Price	**$0.26**
52 week low	$0.42
52 week high	$0.22
Ave Monthly Vol (year rolling)	236.35K

Key Financials (A$ million)

Year End	FY16 Act.	FY17 Est.	FY18 Est.
Revenue ($m)	**19.0**	**31.1**	**18.6**
EBITDA ($m)	17.8	24.1	29.9
NPAT ($m)	**9.0**	**13.5**	**18.0**
EPS (c)	-5	-3	-4
EPS Growth (%)	-188%	39%	-32%
PE (x)	**-5**	**-8**	**-6**
EV ($M)	53.37	53.37	53.37
EV/EBITDA (x)	**16.2x**	**11.9x**	**9.6x**
ROE	na	na	na
EBITDA Margin	-71%	-11%	-44%

Share Price Graph (AUD)

The Taylor Collison Insight

We are initiating on Pharmaxis with an Outperform and $0.35 target. We think the company's robust amine oxidase platform can produce novel clinical assets for various disease targets in inflammation. The company has generated a successful partnership with Boehringer Ingelheim (BI), and we think an additional partnership, especially in non-alcoholic steatohepatitis (NASH), could generate near-and-long term value.

PXS's novel pipeline in NASH could be widely used.
PXS developed 2 drug candidates for the treatment of non-alcoholic steatohepatitis (NASH), a disease which affects 3-5% of the US population, for which there are no treatments currently approved. The LOXL2 and SSAO inhibitor show promising, albeit early, data suggesting potential clinically meaningful efficacy around the mechanism of action and NASH resolution. While PXS's compounds would, if approved, enter the market after the first FDA approvals for NASH, we note that PXS has two NASH candidates which are designed to treat NASH patients with both early stage (SSAO inhibitor) disease, as well as later-stage diseases (LOXL2 inhibitor). Additionally, given the differences between the mechanisms of the compounds likely to earn regulatory approval in the next 1-3 years, the PXS compounds are well suited as combination therapies. In a heterogeneous and chronic disease like NASH, physicians will likely need to use multiple treatments in an approach to control the metabolic burden, inflammation, and fibrosis associated with disease progression.

BI Partnership bolsters credibility, shows potential for more partnerships.
PXS partnered their SSAO inhibitor (PXS-4728A) with BI for NASH for an upfront payment of A$39M, in a deal worth potentially A$750M. We see the partnership with a reputable large pharma as one that builds credibility for PXS, and helps reposition the company to one targeting fibrosis, after the Bronchitol FDA rejection in 2013. Upfront payments for NASH compounds fall into the $50-400M range, with total deal sizes varying, potentially reaching just over $1B. In addition to the upfront payment from BI for the Ph2 initiation of the SSAO inhibitor, BI may elect to further investigate the SSAO inhibitor in other indications. If the PXS asset generates meaningful antifibrotic data, we see significant potential associated with a respiratory indication such as COPD. Potentially partnering the LOXL2 candidate post Phase 1 (pending data), could also generate significant value for PXS, especially at the current valuation. Even if the asset is acquired at a steep discount, an upfront payment in the range of $50M would generate meaningful upside for PXS, given its market cap of ~$83M. We look forward to PXS announcing a lead LOXL2 candidate before the end of 2016, and expect potential partnership after Phase 1 trials (potentially in the 2018 timeframe).

Good balance of near and long-term catalysts, value inflection points.
We anticipate constant news flow from PXS in the near-term, and like the short-term potential for reliable growth, while at the same time, preserving a value proposition for the stock for the next 2-3 years. We most look forward to 2016 catalysts such as the nomination of a LOXL2 NASH drug candidate, and the initiation of preclinical candidates, as well as the commencement of a LOXL2 IPF candidate. In 1H17, we look forward to the ~A$25M milestone from BI for initiation of the Phase 2 NASH program.

Pharmaxis - Summary of Forecasts PXS $0.26

PROFIT & LOSS SUMMARY (A$m)

Year end June	FY15A	FY16A	FY17E	FY18E	FY19E
Total Revenue	**59.2**	**19.0**	**31.1**	**18.6**	**50.8**
EBITDA	**21.9**	**(13.4)**	**(3.3)**	**(8.3)**	**15.4**
D&A	(1.0)	(1.0)	(3.8)	(4.3)	(5.0)
EBIT	**20.9**	**(14.4)**	**(7.1)**	**(12.6)**	**10.4**
Net Interest	0.0	0.0	0.0	0.0	1.0
Pre-Tax Profit	18.5	(16.5)	(10.1)	(13.4)	16.4
Tax Expense	(0.0)	(0.0)	0.0	0.0	4.9
NPAT Adj	**18.5**	**(16.5)**	**(10.1)**	**(13.4)**	**11.5**
Abnormals	0.0	0.0	0.0	0.0	0.0
Reported Profit	18.5	(16.5)	(10.1)	(13.4)	11.5
Margins on Sales Rev					
EBITDA	37.0%	-70.6%	-10.7%	-44.4%	30.3%
EBIT	35.3%	-75.9%	-22.8%	-67.6%	20.5%
NPAT Adj	31.2%	-86.6%	-32.6%	-72.0%	22.6%
Change on pcp					
Total Revenue	465.0%	-67.9%	63.6%	-40.2%	173.3%
EBITDA	-146.1%	-161.3%	-75.2%	148.1%	-286.6%
EBIT	-140.2%	-169.0%	-50.9%	77.5%	-183.0%
NPAT Adj.	-135.6%	-189.2%	-38.4%	32.1%	-185.8%

BALANCE SHEET SUMMARY

Year end June	FY15A	FY16A	FY17E	FY18E	FY19E
Cash	54.1	39.2	34.8	9.3	37.0
Receivables	1.0	1.3	1.0	1.0	1.0
Other	0.0	0.0	0.0	0.0	1.0
Total Current Assets	61.5	46.4	41.8	16.3	44.0
Property Plan	19.6	17.8	18.0	18.0	18.0
Intangibles	0.4	0.1	0.3	0.3	0.3
Other	0.0	0.0	0.0	0.0	1.0
Total Non-Current Assets	21.0	19.2	19.3	19.3	19.3
TOTAL ASSETS	**82.6**	**65.7**	**61.1**	**35.6**	**63.2**
Accounts Pay	5.8	5.0	5.0	5.0	5.0
Tax Liabilities	0.0	0.0	0.0	0.0	0.0
Provisions	0.5	0.5	0.5	0.5	0.5
Deferred Con	0.0	5.7	0.0	0.0	1.0
Borrowings	0.8	0.9	0.9	1.0	1.0
Total Current Liab	6.5	15.9	17.9	22.3	23.3
Provisions	0.3	0.3	0.3	0.3	0.3
Borrowings	10.121	9.258	10	10	10
Other	0.1	0.2	0.2	0.2	1.2
Total Non-Current Liab	38.1	33.7	35.3	35.3	35.3
TOTAL LIABILITIES	**48.7**	**46.2**	**44.7**	**42.7**	**42.7**
TOTAL EQUITY	**18.1**	**36.3**	**20.9**	**18.4**	**(7.2)**

PER SHARE DATA

Year end June	FY15A	FY16A	FY17E	FY18E	FY19E
EPS Adj. (c)	**0.06**	**(0.05)**	**(0.03)**	**(0.04)**	**0.05**
Growth (pcp)	-65%	-188%	-39%	32%	-223%
Dividend (c)	0.0	0.0	0.0	0.0	0.0
Franking	0%	0%	0%	0%	0%
Gross CF per share (c)	0.24	0.05	0.07	(0.05)	0.13
NTA per share (c)	0.1	0.1	0.1	(0.0)	0.1

CASH FLOW SUMMARY

Year end June	FY15A	FY16A	FY17E	FY18E	FY19E
EBITDA	**21.9**	**(13.4)**	**(3.3)**	**(8.3)**	**15.4**
Tax	(0.0)	(0.0)	0.0	0.0	4.9
Interest	0.0	0.0	0.0	0.0	1.0
Working Capital	55.0	30.5	24.0	(6.0)	20.6
Other	0.0	0.0	0.0	0.0	0.0
Operating Cash Flow	**76.9**	**17.1**	**20.6**	**(14.3)**	**42.0**
Capex	20.7	(13.9)	(0.4)	(25.6)	27.6
Free Cash Flow	**(55.8)**	**(32.1)**	**(34.4)**	**14.8**	**(42.8)**
Issues of Shares	0.0	0.0	0.0	0.0	0.0
Net Borrowings	0.8	0.9	0.0	0.0	0.0
Acquisition related	0.0	0.0	0.0	0.0	0.0
Dividends	0.0	0.0	0.0	0.0	0.0
Net cash Flow	**20.0**	**(14.9)**	**(4.4)**	**(25.5)**	**27.7**

KEY RATIOS

Year end June	FY15A	FY16A	FY17E	FY18E	FY19E
Net Debt / EBITDA (x)	na	na	na	na	na
Net Debt : Equity (%)	na	na	na	na	na
EBIT Interest cover (x)	na	na	na	na	na
Free CF / NPAT (5 yr avg	4112.7%	1696.3%	8937.7%	4599.0%	2302.1%
Current ratio (x)	9.4	2.9	2.3	0.7	1.9
ROE (%)	102.2%	-45.3%	-48.4%	-72.7%	-160.7%
ROIC (%)	27.7%	-19.9%	-15.4%	-21.9%	32.3%
Dividend Payout Ratio	na	na	na	na	na

VALUATION

Year end June	FY15A	FY16A	FY17E	FY18E	FY19E
PE Ratio (x)	**4.4**	**(5.0)**	**(8.1)**	**(6.2)**	**5.0**
FCF Yield (%)	-214.5%	-123.4%	-132.1%	56.8%	-164.5%
EV/EBITDA (x)	**2.4**	**-4.0**	**-16.0**	**-6.5**	**3.5**
EV/EBIT (x)	151.2	-70.4	-234.3	-78.9	259.9

INVESTMENT THESIS

Pharmaxis aims to be a market leader in early-stage inflammation compounds. PXS is building a streamlined, early stage inflammation portfolio which is conducive to sustainable growth. PXS is developing PXS4728A (SSAO inhibitor), a LOXL2 inhibitor (for NASH and other inflammatory diseases), and a variety of other products targeting inflammation. The company will likely partner with larger biotech or pharma companies with the financial capacity and regulatory experience to conduct high quality, sufficiently powered clinical trials. Early stage development has worked for Pharmaxis in the recent past with the most recent NASH asset acquisition by large-pharma Boehringer Ingelheim (BI) for A$39M upfront. Management seems to recognize inherent limitations associated with its current status as a turn-around, early stage, mid-cap biotech company, and is taking an appropriate level of clinical and financial risk. While the focus on early stage compounds may optically limit optimal value creation, additional significant clinical risk is associated with later stage development. We like management's focus on early-stage development, which creates a mid and long term growth potential. Investors will also likely appreciate a lower-risk development pathway which offsets a significant portion of clinical risk.

Stable growth, with cheap upside optionality, price target of A$0.35. We reach a price target of $0.35 with a pNPV analysis. This represents almost 40% growth opportunity, which could further grow if PXS shows more proof of concept clinical data with their LOXL2 drug candidate. The current BI deal supports most of the current valuation, which we think adds a nice "floor" to downside. We look forward to target identification and preliminary data for the LOXL2 small molecule in the next 6 months. If positive, we expect a Phase 1 trial to potentially be complete by the end of 2017, and, pending data, could generate substantial upside for shareholders in the late 2017 to early 2018 timeframe.

Inflammation, especially NASH, is a well-validated, high-value therapeutic area to pursue. PXS is pursuing drug candidates in the therapeutic area of inflammation. A variety of diseases with unmet-need fall into the therapeutic category of inflammatory diseases, and most have well-validated biomarkers and a clear understanding of FDA's expectations, allowing for a clear path to approval (pending positive data). NASH (nonalcoholic steatohepatitis) is an emerging field, with no available treatment, high patient numbers, and significant unmet need. While the first wave of registrational regulatory interactions are underway with Intercept's obeticholic acid (OCA) and Genfit's Elafibronor, the NASH market is large, and there could be a strong opportunity for PXS's compounds to work as complementary treatments. PXS's therapeutic candidates have different mechanisms which allow for a broad potential patient market. Phase-2 ready SSAO inhibitor, '4728A is designed to treat earlier stage NASH patients, and the second, a LOXL2 inhibitor, will be targeted at higher risk, later-stage patients. Additionally, given the PXS drug candidates have unique mechanisms of actions compared to OCA and elafibronor (which will likely be on the market before the PXS candidates reach advanced clinical trials), we think they could potentially be marketed as co-therapies.

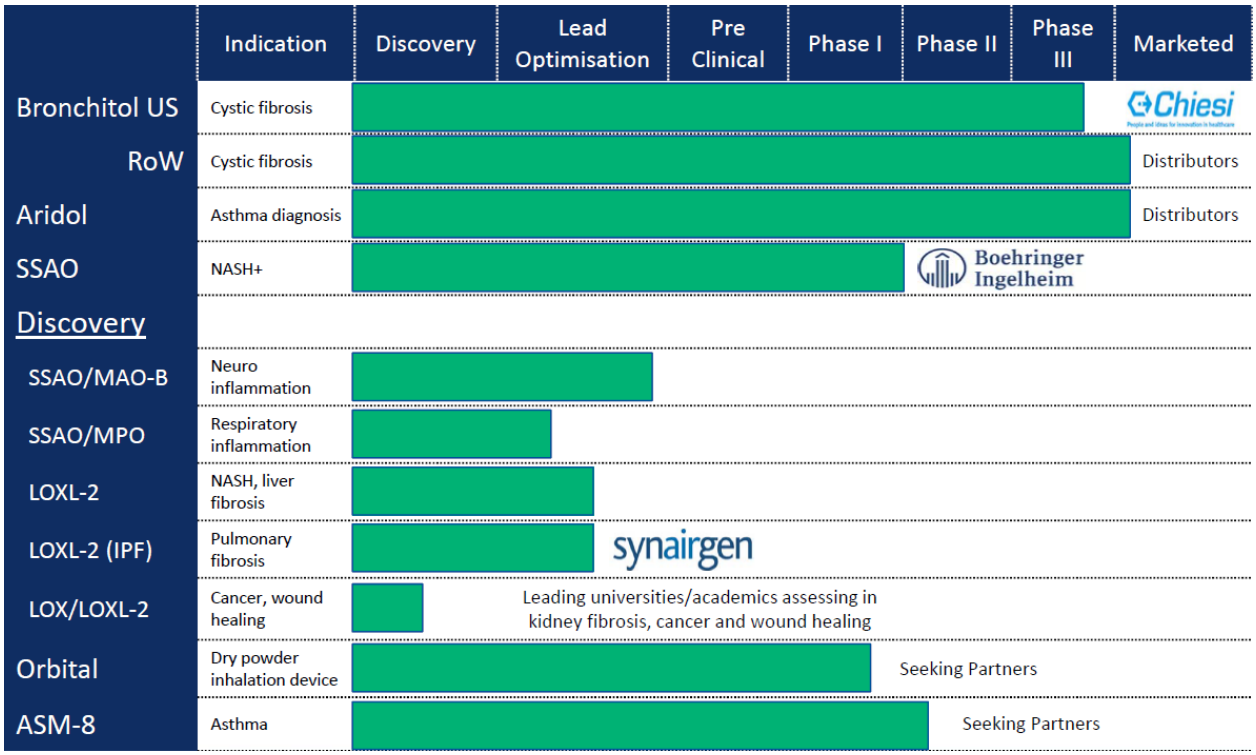
Eventually, we would like to see PXS retaining value. We think PXS may have the potential to develop its own clinical assets in the longer term. This would enable more value-retention of the more developed assets instead of early-stage partnerships that tend to lower value (which force PXS to partner at a discount, especially in NASH, receiving some cash and royalties, but not necessarily the full earning potential of a clinical asset). PXS has a comfortable cash position of $32M, and we think after the near-term $25M payment from BI and a potential partnership of the LOXL2 program in either pulmonary fibrosis or NASH, PXS should have the resources and bandwidth to discover and develop another therapeutic candidate, at least until after Phase 1. We are very confident in the upcoming BI payment, and view trial-start as more of a "when" than an "if", especially because BI does not have another NASH compound in development.

Early stage opportunity in respiratory indications potentially promising. We think the LOXL2 asset in IPF could potentially form the base of a successful partnership. In June 2016, BI entered a collaboration and licensing agreement with Inventiva, a French biopharma with an early-stage IPF candidate, for €170M (A$252M). In 2014, Roche acquired US biotech InterMune, which was already marketing Esbriet (pirfenidone) for $8.3B, a 63% premium to the share price prior to M&A rumors. There remains significant unmet need in respiratory indications with a fibrotic disease pathology, and we think the mechanism supports potential efficacy in diseases like COPD and IPF. Partnering an early-stage respiratory asset could earn PXS in the range of $25-50M upfront, with a more sizeable deal pending successful milestones and royalties.

COMPANY DESCRIPTION

Pharmaxis is a Sydney-based pharmaceutical company which was founded in 1998 and listed on the ASX in 2003. PXS boasts two commercialized products in the respiratory area, Bronchitol and Aridol. The company's research pipeline is focused on areas of high unmet clinical need in the therapeutic area of inflammation, with semicarbazide-sensitive amine oxidase inhibitors (SSAO) for non-alcoholic steatohepatitis (NASH) and other inflammatory diseases, as well as Lysl Oxidase Inhibitors (LOX), targeting fibrotic diseases including NASH, pulmonary fibrosis, and some cancers. The company's platform has been well validated, with one asset-acquisition by Boehringer Ingelheim, and one collaboration agreement with Synairgen.

Figure 1



Source: PXS

FINANCIALS

We reach our price target of A$0.35 based on a pNPV analysis that considers the likely upcoming milestone payments for PXS4728A NASH program, a potential new indication, and potential partnerships for both the LOXL2 NASH and idiopathic pulmonary fibrosis (IPF) partnerships. After the BI payment for NASH, we see the stock getting closer to the $0.40 range. Following LOXL2 target identification and more data, we would potentially begin to attribute more value to the LOXL2 platform, especially given its broad applicability in NASH, IPF, and wound/scar healing.

We think PXS provides a steady opportunity for almost 40% upside in a 2-year timeframe, which may seem lower than potential blockbuster therapeutic companies. However, we like the stability associated with the BI program, and look forward to additional asset acquisitions in the next few years, pending clinical data.

Our model does not account for a Phase 3 start or potential royalties from the SSAO NASH program because we think the program is too early-stage to include in the valuation, and would like to see more data before assigning more value to the program. A Phase 3 trial would likely not start until mid 2018 or 2019, depending on recruitment rates. We have also not included sales revenues from Bronchitol in our model. Nonetheless, we think the current collaboration with Chiesi allows PXS to retain upside if Bronchitol is approved by the FDA, while limiting downside clinical and capital risk.

Figure 2

Assumptions / Results	
Total NPV	**0.35**
Number of Shares (m)	317.0
Implied Upside	36%
Pharma PE	11.5x
Discount rate	25%
Current year	2016.75

Product Development

Drug name	Indication	Status	Launch	Years to Launch	Years to Launch plus 6	Success	Sales (US$m)	Probability weighted Peak Sales (US$m)	Royalty	Profitability	Probability weighted Peak Profit (US$m)	Discount Factor	NPV (US$)
SSAO Milestone	NASH	Phase 2	2017.5	1	7	90%	25.0	22.5	100%	100%	22.50	4.51	0.18
SSAO New Indication	Resp.	Phase 2	2018	1	7	50%	18.0	9.0	100%	100%	9.00	5.04	0.06
LOXL2 Partner (upfront)	NASH	Lead opt.	2019	2	8	25%	50.0	12.5	100%	100%	12.50	6.30	0.07
LOXL 2 Additional Indications (upfront)	Respiratory	Lead opt.	2020	3	9	20%	40.0	8.0	100%	100%	8.00	7.88	0.04
										Total			**0.35**

Source: Taylor Collison estimates

PXS has a comfortable cash position of A$32M, and we do not think the company will need to raise capital for the next estimated 2-3 years, based on the current burn rate and our expectation of the upcoming $25M cash payment from the BI NASH partnership, as well as potential future partnerships. The company plans to spend existing cash on development, but we would not rule out inorganic growth, and we think PXS may look to in-license new assets. Early stage development of the LOXL2 program is relatively cheap. Early toxicology models should cost around $750K and each Phase 1 trial would likely cost in the range of $2. Chiesi is absorbing the bulk of the costs for the Phase 3 Bronchitol trial, and PXS would likely only pay out around $4M for the trial. As such, we forecast relatively low expenditures for PXS going forward.

Figure 3

PXS Income Statement (in $M)											
	FY2014	**FY2015**	**FY2016**	**Sep-16**	**Dec-16**	**Mar-17**	**Jun-17**	**FY2017E**	**FY2018E**	**FY2019E**	**FY2020E**
Sales revenues	5.04	6.00	6.14	0.90	0.90	0.10	0.10	2.00	0.59	0.80	1.03
Other revenues	1.74	52.46	9.41	4.03		25.00		29.03	18.00	50.00	0.00
Other income	3.72	0.79	3.47	0.09				0.09	0.00	0.00	0.00
Total Income	10.49	59.25	19.02	5.01	0.90	25.10	0.10	31.11	18.59	50.80	1.03
Expenses											
Employee Costs	-19.38	-14.11	-10.53	-2.89	-2.50	-2.50	-2.50	-10.39	-10.91	-11.46	-12.03
Admin+Corporate	-3.38	-3.32	-2.08	-0.54	-0.50	-0.50	-0.50	-2.04	-2.14	-2.24	-2.36
Rent/Occupancy	-1.77	-1.59	-1.30	-0.24	-0.45	-0.40	-0.40	-1.49	-1.64	-1.81	-1.99
Clinical Trials	-6.22	-11.32	-11.96	-3.77	-3.50	-4.00	-4.50	-15.77	-4.00	-4.00	-4.00
Drug Development	-1.26	-1.70	-2.91	-0.73	-1.00	-1.00	-1.00	-3.73	-4.00	-4.50	-5.00
Sales, Marketing, Distro	-3.38	-1.96	-1.10	-0.21	-0.30	-0.30	-0.30	-1.11	-1.22	-1.34	-1.47
Safety, medical, reg affa	-1.85	-1.72	-1.71	-0.38	-0.50	-0.50	-0.50	-1.88	-2.06	-2.27	-2.50
Manufacturing	-2.14	-1.74	-1.93	-0.31	-0.60	-0.70	-0.80	-2.41	-2.66	-2.92	-3.21
Other	-1.77	-2.30	-0.38	0.31	-0.25	-0.25	-0.25	-0.44	-0.50	-0.50	-0.50
D&A	-5.13	-3.41	-3.03	-0.76	-1.00	-1.00	-1.00	-3.76	-4.32	-4.97	-5.72
Finance	-7.15	2.70	1.62	-0.16	0.50	0.50	0.50	1.34	1.47	1.62	1.78
Impairment	-8.78	-0.28	-0.17	0.58	-0.05	-0.05	-0.05	0.43	0.00	0.00	0.00
Total expenses	**-62.20**	**-40.74**	**-35.48**	**-9.10**	**-10.15**	**-10.70**	**-11.30**	**-41.25**	**-31.98**	**-34.39**	**-36.99**
Profit before tax	-51.72	18.51	-16.46	-4.09	-9.25	14.40	-11.20	-10.13	-13.39	16.41	-35.96
Income tax expense	-0.10	-0.04	-0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Profit/loss	-51.82	18.47	-16.46	-4.09	-9.25	14.40	-11.20	-10.13	-13.39	16.41	-35.96
NoSH	305	313	317	319	320	322	323	321	324	327	331
EPS	-$0.17	$0.06	$0.05	-$0.01	-$0.03	$0.05	-$0.04	-$0.03	-$0.04	$0.05	-$0.11

Source: Taylor Collison estimates, Company Reports

NASH MARKET IS SIGNIFICANT

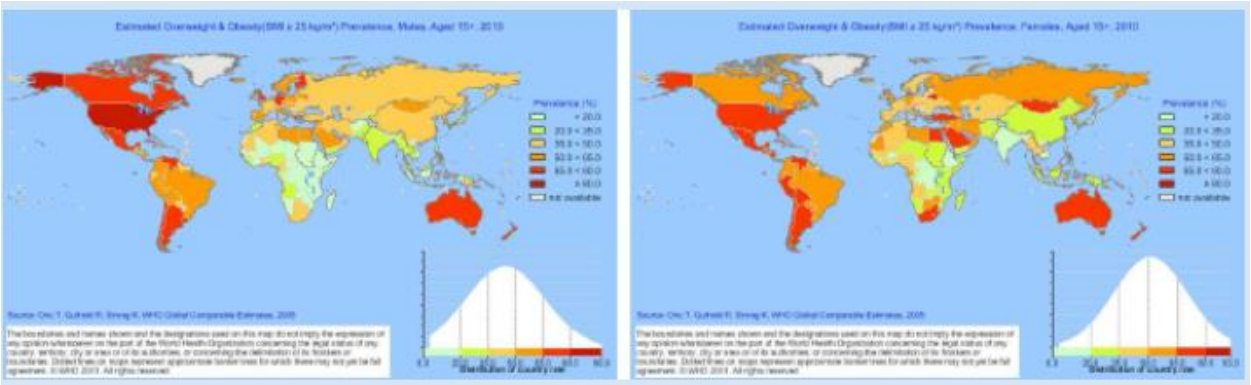
Nonalcoholic Steatohepatitis (NASH) Background

NASH is caused by excessive fat accumulation in the liver, also known as steatosis. Steatosis is associated with liver inflammation, which leads to progressive fibrosis (the thickening and scarring of connective tissue), and then cirrhosis (chronic liver damage). NASH affects 70-90% of obese or diabetic populations, and overall, 3-5% of Americans. Another 10-20% of Americans have "fatty liver" indicating fat in the liver without inflammation. NASH is the third most common reason for liver transplants in the US, and is thought rise to be the most common in a few years, given the increasing prevalence of obesity. NASH could overtake chronic Hep C infection and alcoholic liver disease as the primary cause for liver transplant. The most common causes of death in NASH are cancer, cardiovascular disease, and liver failure. Over 20% of NASH patients progress to cirrhosis in a 10-year timeframe. 25% develop major complications of portal hypertension, such as hepatic encephalopathy and esophageal varices.

NASH Epidemiology

The prevalence of NASH in the US is about 3-5% of the general population. A significant proportion of NASH patients (likely around 5 million patients in the US, 5 million in the EU) have either severe disease or are at a high risk of progressing to cirrhosis, liver cancer, or liver failure. About 2.5% of NASH adult patients with advanced fibrosis and cirrhosis are thought to be irreversible. The disease pathology of NASH is associated with metabolic dysfunction is exacerbated by diseases such as diabetes and obesity. Given the significant growth in the obese and diabetic population, we expect the co-morbid NASH population to also grow. A large proportion of NASH patients who need treatment are undiagnosed.

Figure 4

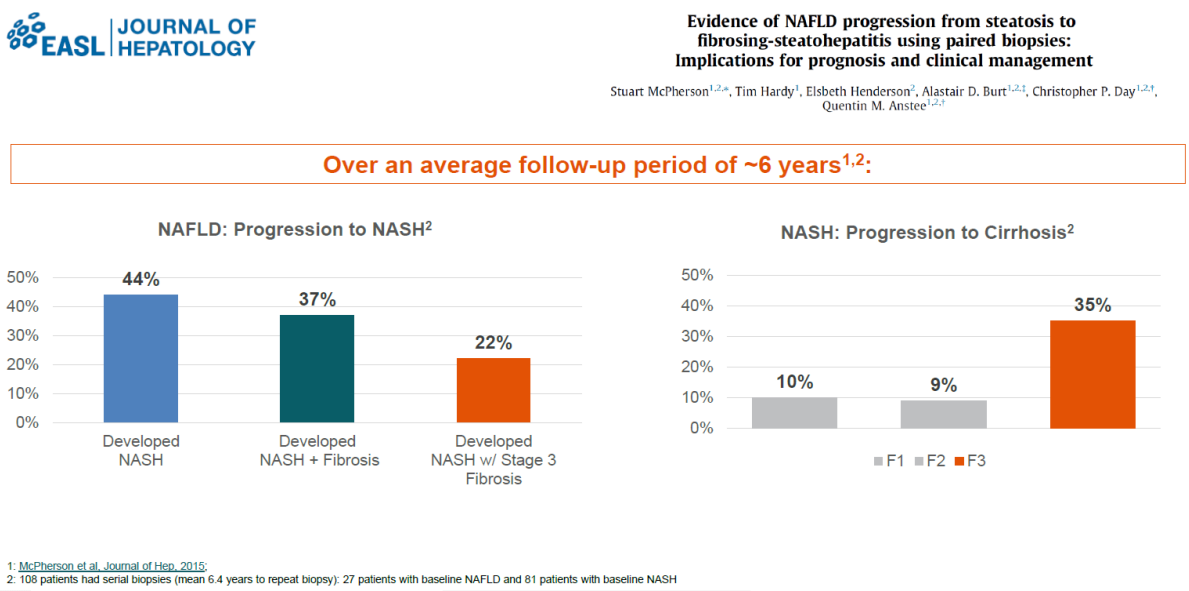


Source: WHO InfoBase.

NASH Disease Progression

If fat makes up over 5-10% of a patient's liver weight, the individual may have NAFLD, or nonalcoholic fatty liver disease. NAFLD is marked by the appearance of triglyceride accumulation in the liver, also known as steatosis. Triglycerides are stored in adipose tissue and newly made fatty tissues within the liver. Steatosis alone is known as NAFLD, but it may not be harmful to the liver and may not result in inflammation. One third of NAFLD patients develop NASH. Hepatocyte injury from fat accumulation and other causes can lead to an immune and inflammatory response. Macrophages in the liver can initiate the inflammatory response, which activate stellate cells to differentiate into myofibroblasts. These, in turn, synthesize excess collagen leading to fibrosis. About 15-25% of NASH cases progress to liver cirrhosis. Continued progression of the disease can lead to liver failure, hepatocellular carcinoma, and death. NASH is the second leading cause of liver cancer. It could develop in the liver prior to being cirrhotic. While NASH is defined by inflammation, the trigger is unknown. The figure below highlights the significant proportion of patients who progress from relatively benign NAFLD to NASH patients with significant physiological complications attributed to the disease.

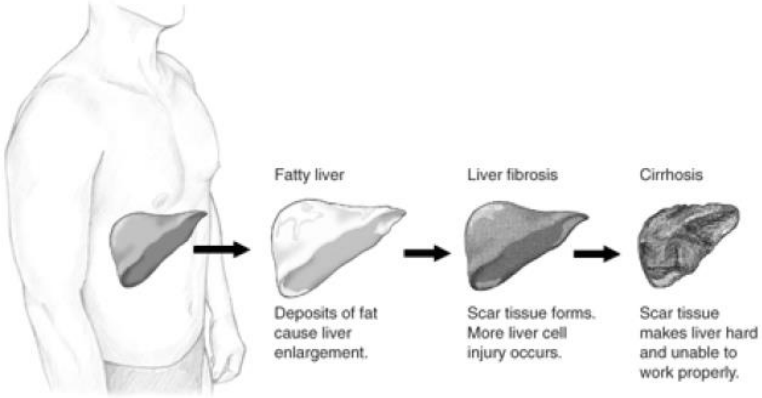
Figure 5



Source: Intercept Corporate Presentation

The disease pathology of NASH can be heterogeneous, with more than one cause. For example, insulin resistance can play a role in the development of hepatic steatosis, and is observed in non-obese NASH patients. Additionally, oxidative injury is also correlated with a NASH diagnosis. Leaky gut syndrome may play a role in NASH.

Figure 6



Source: https://www.niddk.nih.gov/health-information/health-topics/liver-disease/nonalcoholic-steatohepatitis/PublishingImages/liver_damage.gif

NASH Diagnosis

The only means of proving a diagnosis for NASH and ruling out NAFLD is a liver biopsy. NASH is usually diagnosed in a patient whose liver enzyme tests ALT (alanine aminotransferase) and AST (aspartate aminotransferase) are elevated. X rays or imaging shows fat in liver, which can be used to diagnose NASH when a patient evaluation shows no other clear reason (medications, excessive alcohol consumption, viral hepatitis) for the development of liver disease.

The NAS (the NAFLD activity score) measures changes in NAFLD and NASH trials, and patients can receive a score between 0 and 8. It is calculated with a sum of steatosis (0-3), lobular inflammation (0-3), and hepatocyte ballooning (0-2).

NASH resolution is defined by the NAS Clinical Research Network as reaching a NAS score of 0 on all three histological components. Nonetheless, some trials define NASH resolution as reaching a NAS score of zero on any one of the three histological components.

Fibrosis can also be measured to assess a patient's disease progression. A normal liver is at a stage between F0 and F1. F2 indicates light fibrosis, F3 is severe fibrosis, and F4 is cirrhosis, where scar tissue exists in the liver.

Other forms of assessing the extent of a patient's liver scarring and the extent of fibrosis include the Fib4 (Fibrosis 4), APRI (AST to platelet ratio index), and elastography (performed using a FibroScan device).

Figure 7

Test	Sensitivity	Specificity	Remarks
Histology, liver biopsy	The gold standard	Cannot reliably distinguish between ASH and NASH	Significant variability between pathologists' reading of the same sample; a highly experienced hepatopathologist is best
Liver enzymes	Low	Low	AST/ALT usually < 1.0; values may be normal
Imaging			
Ultrasound	Limited	Limited	Insensitive unless steatosis > 33%; operator-dependent
MRI, MRS, CT scan ± contrast enhancement	Results are variable and not well verified		Test are costly, less available, cannot distinguish steatosis and fibrosis or NASH/ASH or stage disease, and are insensitive if there is < 33% steatosis; see reference list and extended reference list

ALT, alanine aminotransferase; ASH, alcoholic steatohepatitis; AST, aspartate aminotransferase; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NASH, nonalcoholic steatohepatitis.

Source: http://www.worldgastroenterology.org/guidelines/global-guidelines/nafld-nash/nafld-nash-english

There are No Currently Approved NASH Treatments

NASH is an emerging field, and no treatments are currently approved. NASH is treated today with lifestyle modification. Adherence, however, tends to be poor. Diabetic patients can add metformin to their treatment regime, if they are not already treated with and/or have not developed a resistance to it. Non-diabetic patients can supplement with Vitamin E, although the literature around Vitamin E efficacy in NASH is mixed.

Figure 8

Level 1—extensive resources		Availability	Feasibility	Remarks
1	Weight loss diet (individually planned diet, based on measurements of total and resting energy expenditures), exercise, education	Well-trained health-care providers available	Well-trained doctors, nurses, dietitians, exercise/physiotherapy providers available	*Lifestyle changes are the single most effective weapon in treating NASH; an* enthusiastic support group is very helpful
2	Diabetes control	One of the key risk factors; well-recognized health problem	Physicians, nurses, dietitians readily available with appropriate training	Essential to control if present
3	Lipid-lowering agents	Readily available; dietary changes also essential	Physicians, nurses, dietitians readily available with appropriate training	Essential to control if present
4	Weight loss—bariatric surgery	Widely, although not universally available	Major surgery; still requires extensive lifestyle changes; likely not available if the patient is already cirrhotic or has portal hypertension	Should be considered early, before the patient has cirrhosis/portal hypertension; has been shown to reverse many of the problems of NASH/metabolic syndrome
5	Liver transplantation	Generally available in high-resource countries, but not in all centers or cities	Generally not available to patients with BMI > 45 (> 35 in some centers)	NASH may recur or develop de novo in the transplanted liver

http://www.worldgastroenterology.org/guidelines/global-guidelines/nafld-nash/nafld-nash-english

NASH Treatments in the Clinic

The companies Intercept (NASDAQ: ICPT) and Genfit (NASDAQ: GFIT) have led the field in potential treatments for NASH, and were the first to have registrational regulatory interactions with FDA. ICPT's OCA will likely be the first to market approved treatment for NASH. The treatments that are closest in progression through trials may be used as combination therapies because their mechanism would allow for them to be used as such. Trial design and regulatory interactions from both these trials will be helpful when evaluating future NASH trials, and insights can be derived from regulatory interactions with regard to what FDA may consider acceptable endpoints and metrics for approval.

Figure 9

Metabolic modifier

Company	Drug	Mode of action	Highest Phase
Intercept	Obeticholic acid	FXR agonist	Phase III
GFT-505	Elafibranor	PPAR α/δ agonist	Phase III
Galmed	Aramchol	Synthetic fatty acid bile conjugate	Phase II/III
Islet Sciences	Remogliflozin	SGLT2 inhibitor	Type 2 Diab
Novo Nordisk	Liraglitude	GLP1R agonist	Type 2 Diab
Allergan	Evogliptin	DPP-4 inhibitor	Type 2 Diab
Gilead	GS-9674	FXR agonist	Phase II
Gilead	GS-0976	ACC inhibitor	Phase II
Bristol-Myers Squibb	BMS-986036	FGF21 agonist	Phase II
Shire	Volixibat (SHP626)	ASBT inhibitor	Phase II
Arisaph Pharmaceuticals	ARI3037MO	Niacin analogue	Phase II

Anti-fibrotic

Company	Drug	Mode of action	Highest Phase
Gilead	Simtuzumab	LOXL2 inhibitor	Phase II
Galectin	GR-MD-02	Galectin-3 inhibitor	Phase II
Bristol-Myers Squibb	ND-L02-s0201	Hsp47 inhibitor	Phase Ib

Anti-inflammatory

Company	Drug	Mode of action	Highest Phase
Conatus	Emricasan	Pan caspase protease inhibitor	Phase II
Allergan	Cenicriviroc	CCR2 and CCR5 inhibitor	Phase II
Gilead	Selonsertib (GS-4997)	MAPK5 inhibitor	Phase II
MediciNova	Tipelukast (MN-001)	LTD4 receptor antagonist	Phase II
Immuron	IMM 124E	Immunomodulator	Phase II
Cempra	Solithromycin	Macrolide antibiotic	Phase II
Boehringer Ingelheim	PXS-4728A	SSAO inhibitor	Phase I

Source: Pharmaxis Investor Presentationn

Regulatory Landscape for NASH

FDA involvement in NASH accentuates the significant level of unmet clinical need and the urgency to develop safe, effective treatments for the disease. The FDA has co-sponsored multiple workshops to develop guidance on NASH therapies. As previously mentioned, 15-20% of NASH patients develop cirrhosis over many years. Cirrhosis is the primary cause of liver related deaths, and has a mortality rate of 4%.

Companies investigating NASH compounds can apply for a Subpart H approval, which is an accelerated approval pathway with FDA. Subpart H is intended for drugs which treat serious and life threatening illnesses providing therapeutic benefit over existing treatments. The accelerated approval is based on a surrogate or intermediate endpoint that is reasonably likely to predict mortality. Progression to cirrhosis is considered to be a definitive NASH approval endpoint.

Measuring improvement in mortality rates in a trial including early stage NASH patients is unfeasible and would require a trial longer than 10-15 years. There would be significant costs associated with such a trial, and the end-point of all cause mortality is almost prohibitive. Noninvasive biomarkers may also predict mortality such as FIB4, CK18, and HVPG. Elastography has proven more helpful for HCV than NASH because it identifies later stage disease.

NASH M&A SPACE

The mergers and acquisitions and asset acquisition space in NASH has been active, with companies receiving relatively lucrative structures for their clinical stage. The premium associated with NASH may, however, decrease, as clear leaders have already emerged in the NASH space, and followers will miss the first-to-market opportunity. However, there may be sufficient need for additional therapies for NASH patients at different disease stages, as well as for add-on therapies.

Compared to other M&A deals in the NASH space, we think the deal between PXS and BI was on the low end, although at the time, the size of the deal was close to the company's market cap, making it a good strategic decision for PXS. After PXS establishes more credibility in the NASH space, we think the size of the next NASH acquisition will be larger than the first. While we do not anticipate deals the size if the Arresto or Lumena deals, we think an upfront payment in the line of A$50M would be reasonable, depending on the Phase 1 dataset.

Partnering deals in NASH

Figure 10

Company	Asset	Acquirer	Stage	Upfront ($M)	Potential ($M)
Nimbus	Partnership	Gilead	Phase 1	400	1200
Tobira	Acquisition	Allergan	Phase 2	400	800
Promedior	Acquisition	BMS	Phase 2	150	1250
Phenex	Asset acquisition	Gilead	Phase 2	Undisclosed	470
NGM	License	Merck	Phase 2	94+15% stock	250
Galecto	License	Gilead	Phase 1	Undisclosed	444
Arresto	Acquisition	Gilead	Phase 1	225	225
Lumena	License	Shire	Phase 1	260	Undisclosed
Akarna	Acquisition	Allergan	Preclinical	50	Undisclosed
Regulus	License	AstraZeneca	Preclinical	Undisclosed	500
PXS	Asset acquisition	BI	Phase 1	A$39	A$750

Source: PXS, Taylor Collison

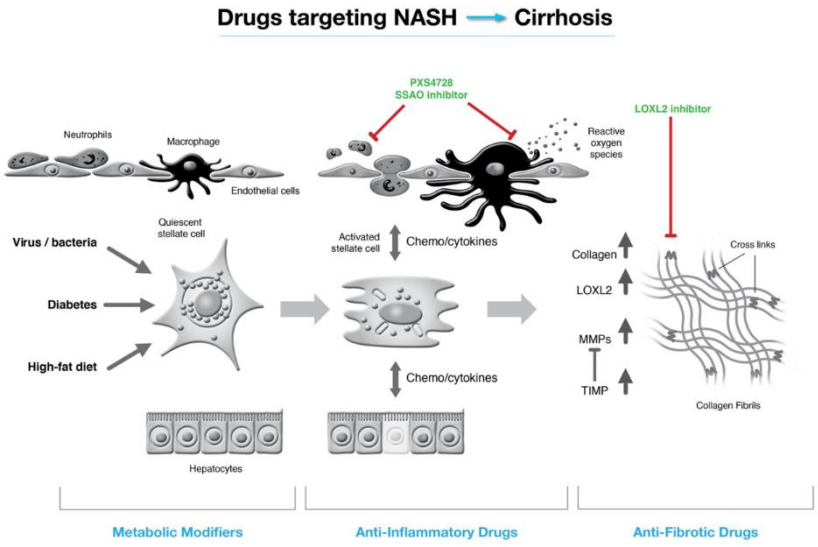
PXS4728A

PXS's SSAO inhibitor, '4728A has shown efficacy in preclinical models of NASH and airway inflammation. Phase 1 data in NASH shows promising, albeit early, indication of potential efficacy, with good PK data, progressive dose response, and long-lasting enzyme inhibition after a single dose. '4728A will be most effective in earlier-stage NASH patients. The drug candidate was acquired by BI at Phase 1 for A$39MM upfront in, with a total of ~A$750M milestone payments. The next milestone of ~A$25M is due upon Phase 2 initiation, which is likely to occur in 1Q17. BI is also looking to develop '4728A in other indications (kidney fibrosis, COPD), and the addition of new indications will also spur-on additional milestone payments, likely in the $15-20M range upon initiation of another Phase 2.

PXS's SSAO Inhibitor: Mechanism of Action

We think the SSAO/VAP-1 mechanism of action is well-validated, and has a good scientific rationale based on human data and animal models. SSAO/VAP-1 is an ectoenzyme. The enzyme is found on endothelial cells, adipocytes, and smooth muscle cells. It allows for the migration of leukocytes and lymphocytes to inflammation sites, which cause inflammation, and also induce oxidative stress. SSAO/VAP-1 can be shed from the hepatic endothelium into general circulation. The concentration of SSAO/VAP-1 is correlated with liver fibrosis and cirrhosis, so inhibiting SSAO/VAP-1 could help treat liver diseases, especially those related with inflammation and cirrhosis. VAP-1 plays an important role in the progression of NAFLD into chronic liver disease. VAP-1 deficiency hinders CCL4-induced hepatic fibrosis. Additionally, VAP-1 deficiency hinders leukocyte infiltration into the liver during fibrogenisis. The image below shows where in the disease pathway both PXS NASH assets combat the disease mechanism.

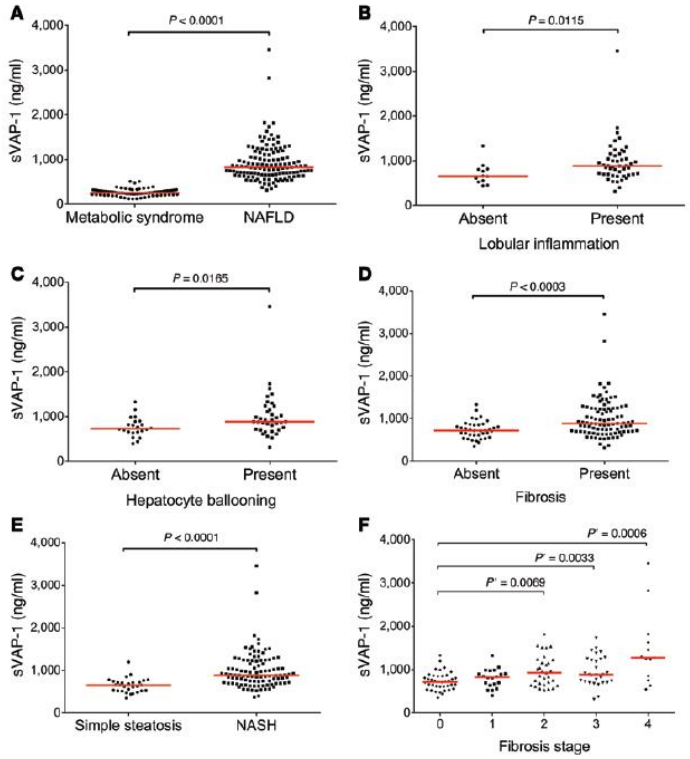
Figure 11



Source: PXS

The image below (from a preclinical study) shows that serum sVAP-1 is elevated in patients with NAFLD, and that it is correlated with the histological markers of liver injury.

Figure 12

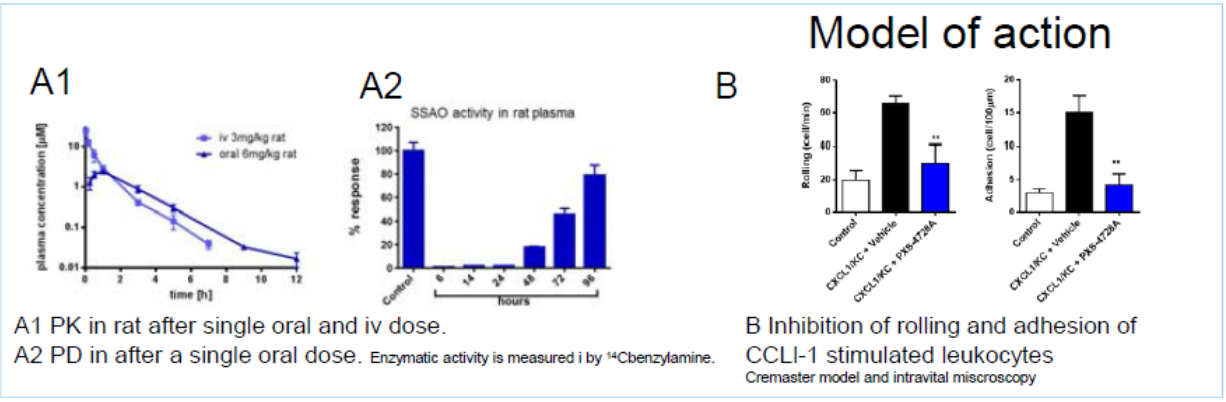


Source: doi: 10.1111/bph.13573

Preclinical Data

Preclinical data validates the mechanism of '4728A and indicated early signals of potential safety and efficacy in CCL4 and NASH models of liver fibrosis. The figures below show the early stage, animal model, oral availability of '4728 as well as the promising, lasting reduction in SSAO activity after oral dosing.

Figure 13



A1 PK in rat after single oral and iv dose.
A2 PD in after a single oral dose. Enzymatic activity is measured i by ^{14}Cbenzylamine.

B Inhibition of rolling and adhesion of CCLI-1 stimulated leukocytes
Cremaster model and intravital miscroscopy

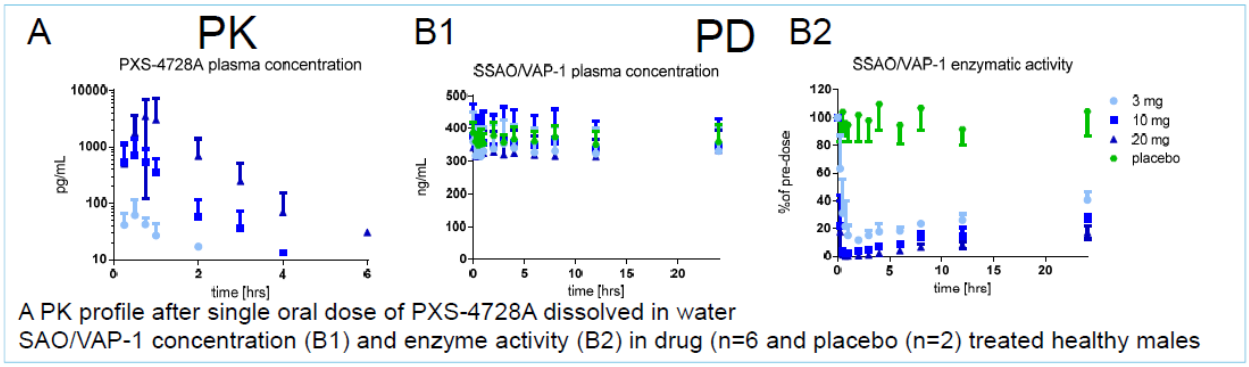
Source: PXS

'4728A Phase 1

Phase 1 data presented at EASL in April 2015 showed that PXS-4728A was safe and well tolerated, is orally available and has a short half-life (which is good when considering safety outcomes). Treatment resulted in a long-lasting SSAO-VAP-1 enzyme inhibition after one dose without a change in SSAO concentration.

The image below shows data from the SAD (single ascending dose) Phase 1 study. We are further encouraged early indicators of a clear dose response, with the 20mg dose correlating with the greatest inhibition of SSAO/VAP-1 enzymatic activity over 24 hours.

Figure 10



A PK profile after single oral dose of PXS-4728A dissolved in water
SAO/VAP-1 concentration (B1) and enzyme activity (B2) in drug (n=6 and placebo (n=2) treated healthy males

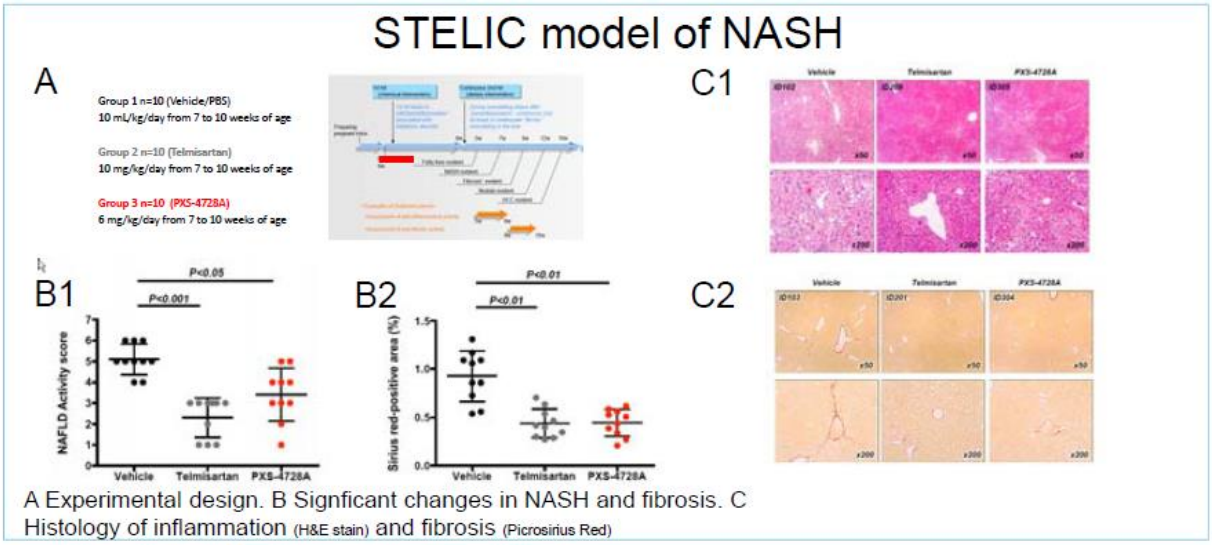
Source: PXS

Phase 2 Outlook

We look forward to more patient data in a Phase 2 study, to provide further clinical validation of '4728A. Based on previous trials and FDA precedent, we think the primary endpoint will be improvement in NAS score vs placebo. Secondary endpoints could include any combination of the following: NASH diagnosis, fibrosis score, hepatocellular ballooning score, hepatic fat fraction, insulin resistance, GGT, cholesterol and triglyceride levels.

If data from the Phase 2 shows similar patient improvement to that from the Phase 2 FLINT trial, or the Phase 2 GFIT trial, we would be exponentially more confident in the potential success of '4728A, especially if '4728A has a positive safety profile with a minimal effect on initiation of statin treatment and cholesterol levels. (as a reminder 46% of the treated patients in the flint Phase 2 met the histological endpoint, vs 21% in placebo ($p<0.001$). A numerically higher response rate was seen in OCA-treated patients who were diagnosed with more advanced NASH prognosis, and the response was also numerically higher for OCA-treated patients in the moderate to severe patients with fibrosis or comorbid with type 2 diabetes.

Figure 11



Recruitment for a Phase 2 in NASH could potentially be slower than expected once ICPT's and GFIT's compounds for NASH are approved (both of which we think are fairly likely). This is because concurrent treatment for NASH will likely serve as an exclusion criteria given concomitant therapies could confound efficacy.

Potential Market

We conservatively model $2B in peak global sales for '4728A in the US and EU population. Our model assumes a $6,000/yr price, given the high prevalence of low-risk NASH patients, and lower, $4000/yr pricing in the EU. Our model is very conservative, and assumes 5% peak penetration for moderate patients in the US, and 3% peak penetration in the EU. Discounts to our market model include the low formal diagnosis rate of NASH, which is currently <10%. There have been advances in non-invasive diagnostic techniques such as ultrasound elastography (Fibroscan), which may improve NASH diagnosis over the next 5-10 years and become highly preferable to risky and variable liver biopsies. We expect higher patient-diagnosis rates among higher-risk patients, but only model patient-diagnosis rates at ~25% for low risk patients, for whom '4728A treatment may be applicable. Given patient compliance levels with once-daily oral medications, we assume a 80% compliance rate. We assume a potential approval in 2021, but note that trial timing is dependent on BI and trial recruitment timeliness. PXS will receive double digit royalties on sales.

Figure 12

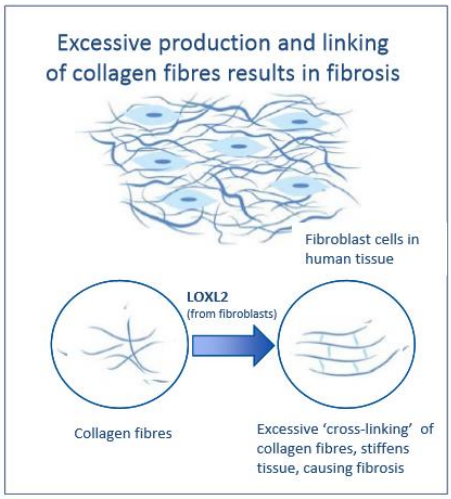
PXS4782A Market Model (NASH)	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US population ('000s)	371,532	375,247	379,000	382,790	386,618	390,484	394,389	398,333	402,316	406,339
US adult population ('000s)	286,080	288,940	291,830	294,748	297,696	300,673	303,679	306,716	309,783	312,881
NASH prevalence in adults ('000s)	22,886	23,115	23,346	23,580	23,816	24,054	24,294	24,537	24,783	25,030
Low Risk Patients ('000s)	18,309	18,492	18,677	18,864	19,053	19,243	19,435	19,630	19,826	20,024
% patients diagnosed	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Low risk diagnosed NASH patients ('000s)	4,577	4,623	4,669	4,716	4,763	4,811	4,859	4,907	4,957	5,006
% penetration	1%	1%	2%	2%	3%	3%	4%	5%	5%	5%
Low patients on '4782A('000s)	23	23	70	94	119	144	194	245	248	250
Price ($)	6,000	6,120	6,242	6,367	6,495	6,624	6,757	6,892	7,030	7,171
Compliance rate	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
SSAO Revenue from NASH patients ($MM)	**$ 102.99**	**$ 106.10**	**$ 327.91**	**$ 450.42**	**$ 580.02**	**$ 717.05**	**$ 984.94**	**$ 1,268.35**	**$ 1,306.66**	**$ 1,346.12**
EU Population	530,760	536,068	541,428	546,843	552,311	557,834	563,413	569,047	574,737	580,484
Adult population	408,685	412,772	416,900	421,069	425,280	429,532	433,828	438,166	442,548	446,973
NASH prevalence in adults	32,695	33,022	33,352	33,686	34,022	34,363	34,706	35,053	35,404	35,758
Low Risk NASH patients	26,156	26,417	26,682	26,948	27,218	27,490	27,765	28,043	28,323	28,606
% patients diagnosed	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Low risk diagnosed NASH patients	6,539	6,604	6,670	6,737	6,804	6,873	6,941	7,011	7,081	7,152
% penetration	1%	1%	2%	2%	3%	3%	3%	3%	3%	3%
High Risk patients on '4782A	33	66	100	135	170	206	208	210	212	215
Price ($)	4,000	4,040	4,080	4,121	4,162	4,204	4,246	4,289	4,331	4,375
Compliance rate	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
EU SSAO Revenue from NASH patients ($M	**$ 98.08**	**$ 200.11**	**$ 306.20**	**$ 416.47**	**$ 531.06**	**$ 650.08**	**$ 663.14**	**$ 676.47**	**$ 690.07**	**$ 703.94**
Total SSAO Revenue	**$ 201.07**	**$ 306.21**	**$ 634.11**	**$ 866.89**	**$ 1,111.08**	**$ 1,367.13**	**$ 1,648.08**	**$ 1,944.83**	**$ 1,996.73**	**$ 2,050.06**

Source: Taylor Collison estimates

LOXL2 Candidate in NASH

Lysl oxidases are involved in collagen and elastin cross-linking. There are 5 members of the LOX family, and lysyl oxidase like 2 (LOXL2) is a well validated target that is upregulated in fibrotic diseases. Inhibiting LOXL2, therefore, could help resolve fibrosis. Early stage data is indicative of potential effect in improving liver function and reducing fibrosis and dampen CCL4-induced gene expression (a frequently used mouse model of fibrosis) of major drivers in fibrosis.

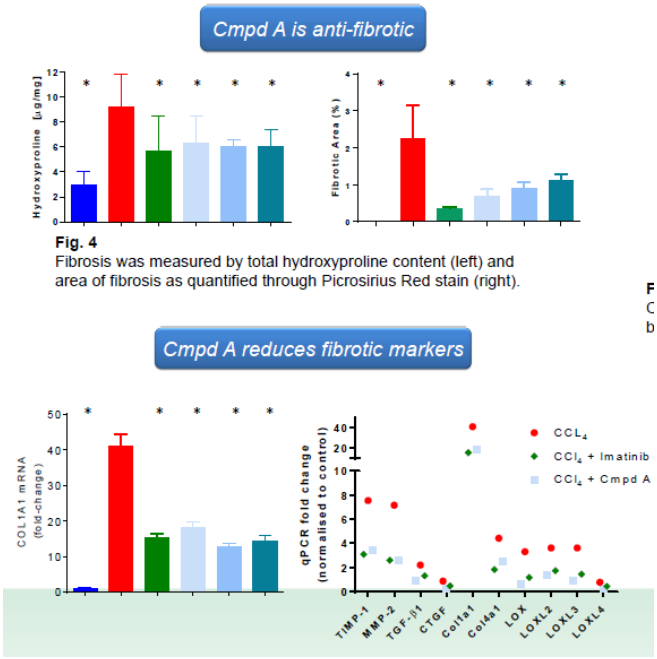
Figure 13



Source: Pharmaxis

The data below show the anti-fibrotic nature of a LOXL2 inhibitor in a NASH animal model. However, we caution against placing too much emphasis on animal models for NASH, given there tends to be poor correlation between animal data and human expression profiles. Mouse models tend to poorly reflect human inflammatory diseases. However, animal models currently remain the gold standard in fibrosis research, although new, sophisticated transgenic approaches will be able to provide more specialized data around fibrosis initiation, progression, and resolution, once they are fully developed.

Figure 14



Source: PXS

LOXL2 Market Model in NASH

We note that the LOXL2 program is early stage, and would not incorporate potential sales from this program into a potential valuation. As previously mentioned, we expect NASH diagnosis rates to improve in the next 5-10 years, and think that even though only about 20% of patients would be classified as "high risk", we estimate an 80% diagnosis rate by the time a potential LOXL2 candidate reaches the market. We price the LOXL2 higher than the SSAO inhibitor, given the pharmaco-economic benefit associated with treating later-stage patients. We model peak US and EU penetration at 15% and 10%, respectively, with room for upside given the potential for the candidate to be used as a combination therapy. Overall, global sales for the drug candidate could reach $5.7B by 2030, according to our assumptions.

Figure 15

LOXL2 NASH Market Model								
		2024	2025	2026	2027	2028	2029	2030
US population ('000s)	1%	382,790	386,618	390,484	394,389	398,333	402,316	406,339
US adult population ('000s)	77%	294,748	297,696	300,673	303,679	306,716	309,783	312,881
NASH prevalence in adults ('000s)	8%	23,580	23,816	24,054	24,294	24,537	24,783	25,030
High risk patients ('000s)	20%	4,716	4,763	4,811	4,859	4,907	4,957	5,006
% patients diagnosed		*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*
High risk diagnosed NASH patients ('000s)		3,773	3,811	3,849	3,887	3,926	3,965	4,005
% penetration		1%	2%	3%	5%	10%	15%	15%
High Risk patients on LOXL2		38	76	115	194	393	595	601
Price	1%	7,070	7,141	7,212	7,284	7,357	7,431	7,505
Compliance rate		75%	75%	75%	75%	75%	75%	75%
LOXL2 Revenue from NASH patients ($MM)		**$ 200.05**	**$ 408.15**	**$ 624.52**	**$ 1,061.79**	**$ 2,166.27**	**$ 3,314.72**	**$ 3,381.35**

		2024	2025	2026	2027	2028	2029	2030
EU population ('000s)	1%	546,843	552,311	557,834	563,413	569,047	574,737	580,484
EU Adult population ('000s)	77%	421,069	425,280	429,532	433,828	438,166	442,548	446,973
NASH prevalence in adults ('000s)	8%	33,686	34,022	34,363	34,706	35,053	35,404	35,758
High risk patients ('000s)	50%	6,737	6,804	6,873	6,941	7,011	7,081	7,152
% patients diagnosed		*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*
High risk diagnosed NASH patients ('000s)		5,390	5,444	5,498	5,553	5,609	5,665	5,721
% penetration		1%	1%	3%	5%	7%	10%	10%
High Risk patients on drug		27	54	165	278	393	566	572
Price	1%	5,050	5,101	5,152	5,203	5,255	5,308	5,361
Compliance rate		75%	75%	75%	75%	75%	75%	75%
LOXL2 Revenue from NASH patients ($MM)		**$ 102.07**	**$ 208.24**	**$ 637.27**	**$ 1,083.46**	**$ 1,547.34**	**$ 2,254.91**	**$ 2,300.23**
Total LOXL2 Revenues in NASH ($MM)		**$ 302.12**	**$ 616.38**	**$ 1,261.79**	**$ 2,145.26**	**$ 3,713.61**	**$ 5,569.63**	**$ 5,681.58**

Source: Taylor Collison estimates

NASH Compounds in Development

Overview of ICPT's Oclavia (Obethicholic Acid, or OCA)

Intercept's OCA is an oral synthetic bile analog and FXR agonist. FXR signalling may play a role in down-regulating abnormal bile production, hepatic inflammation, and hepatic fibrotic activity. OCA received breakthrough designation from FDA based on efficacy and safety data from the FLINT and Phase 2 NAFLD trial. Safety in the Phase 2 trial was controversial. The Phase 3 regenerate trial was started in September 2015 and data from an interim analysis is expected in 1H17.

Phase 3 Regenerate Trial

The Phase 3 REGENERATE trial by ICPT is a good example of what precedent FDA will set in terms of what is an approvable NASH treatment. 1400 patients are expected to be enrolled in the pivotal cohort, and data from 2,500 patients will be included for final enrolment. Patients will be randomized 1:1:1 to 10mg OCA, 25mg OCA, or placebo for 72 weeks. Entry criteria are biopsy confirmed NASH, and fibrosis at stage 2 or stage 3. The co-primary endpoints of the Phase 3 are fibrosis improvement with no worsening of NASH, and NASH resolution with no worsening of fibrosis. Secondary endpoints include the improvement of fibrosis and NASH as a composite endpoint. An interim look at 18 months supports subpart H approval (Subpart H approval pathway allows for accelerated approval based on a surrogate endpoint). The full outcomes endpoint includes progression to cirrhosis, mortality, transplant, HCC, and other events.

Additional Ongoing trials

The ongoing Phase 2 CONTROL trial evaluates the combination of OCA and statins for the monitoring of lipids. The trial evaluates the impact of low doses of statin therapy to modulate LDL in combination with OCA treatment. The trial was initiated in December 2015, and enrolled 80 patients for 16 weeks, with a 2-year open label extension study. The primary endpoint is change from baseline in LDL metabolism. Concentration and particle size/concentration will be measured.

ICPT will initiate an additional 3 Phase 2 trials, and also plans to conduct a Phase 3 trial in patients with cirrhotic NASH.

The Phase 2b FLINT study, which was halted early based on efficacy data on a planned interim analysis, evaluated the improvement in NAS score in 283 patients. Patients were randomized to 25 mg OCA or placebo for 72 weeks. Secondary endpoints included NASH fibrosis, fibrosis score, hepatocellular ballooning, hepatic fat fraction, insulin resistance, GGT, bile acid levels, HR-QoL, glucose, cholesterol and triglycerides, CK-18.

164 randomized patients were evaluated for the interim analysis. Treated patients showed a statistically significant improvement in the primary histological endpoint (p=0.0024). (two-point decrease in NAS with no worsening of fibrosis compared to PBO.) 46% of OCA treated patients vs 21% of the placebo treated patients met the primary endpoint (p>0.001; n=219).

Secondary endpoints also showed improvement. All individual NAS components showed stat sig improvement. 22%of OCA patients vs 13% of placebo patients had NASH resolution. 35% of treated vs 19% placebo showed improvement in fibrosis. We think the improvement in fibrosis is one of the more telling features of efficacy.

Treated patients showed meaningful reductions in ALT, AST, and GGT. A stat sig but modest decrease in bilirubin and increase in ALP were observed, but both remained in normal levels. There enzymes are general measures of liver health, and all returned to pre-treatment values after treatment halted at 24 months.

OCA was generally well tolerated. Data suggests no change in the Framingham CV risk score. The rate of statin initiation was ~50% higher in the treated group than in the placebo group, and, of note, both arms had low (~36%) baseline statin use rate. Changes in serum lipid levels generally returned to baseline after halting treatment at week 24. After 72 weeks, total cholesterol in treated patients increased by 6 points while cholesterol of placebo patients decreased 7 points. LDL cholesterol increased 9 points in treated patients vs a 8 point reduction in placebo patients.

Figure 16

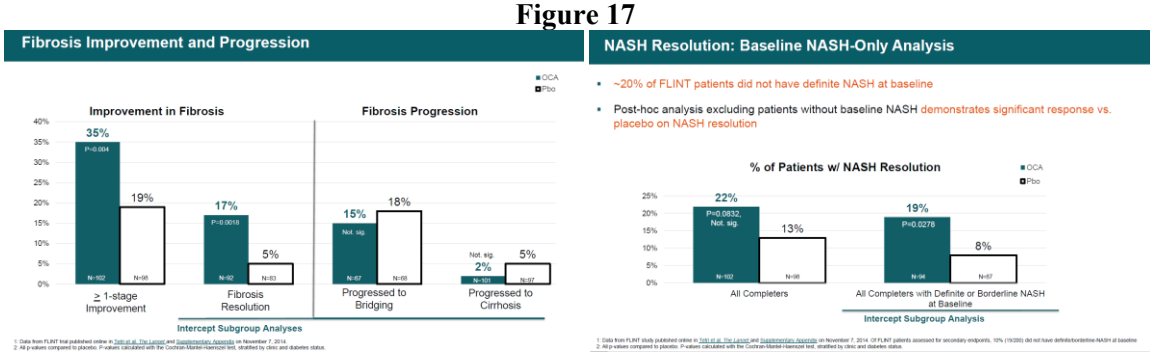
Lipid Parameter (mg/dL, mean values)

	Total Cholesterol		HDL Cholesterol		LDL Cholesterol		Triglycerides	
Time Period	OCA	Pbo	OCA	Pbo	OCA	Pbo	OCA	Pbo
Baseline (n=283)	190	187	42	44	112	111	196	178
Change from baseline to 72 weeks (n=257)	*+6**	*-7**	*-1**	*+1**	*+9**	*-8**	*-20*	*-7*
Change from baseline to 96 weeks (n=240)	*-12*	*-8*	*+1*	*+1*	*-12*	*-12*	*-3*	*0*

Source: ICPT press release

In the Phase 2, OCA was generally well tolerated, although the rate of statin initiation in the OCA arm was 29% for the OCA treated patients, vs 20% in the placebo treated patients. In the Phase 2 FLINT trial, changes in serum lipid levels generally returned to baseline after the 24 week post-treatment period. However, after 72 weeks, total cholesterol in OCA-treated patients increased six points while the placebo patients experienced a 7 point reduction in total cholesterol score. LDL in OCA-treated patients increased 9 points, vs an 8 point reduction in placebo patients.

Figure 17



Source: ICPT Investor Presentation

Additional Phase 2 Studies Show Promising Results

In October 2013, ICPT announced OCA met primary endpoint in a Phase 2 study evaluating insulin sensitization in type 2 diabetic patients with NAFLD. The study was small and relatively short (6 weeks), but it did show improved insulin sensitivity in patients with NAFLD. 6 week study, patients randomized to placebo, 25mg, 50mg OCA. The primary endpoint was to determine insulin sensitivity using insulin clamp. Secondary endpoints included: Serum c4, serum Bas, markers of liver fibrosis, caspase-cleaved keratin-18.

In the 25mg cohort, mean change in GIR showed a stat sig improvement (28 +/- 40.2%; p=0.019). In the high-dose group, mean change in GIR showed a trend to improvement (20.1+/-32.6%; p=0.06). Overall, evaluating the 25 and 50mg cohorts together, there was a stat sig improvement (24.5%; p=0.011). The drug was well tolerated, with diarrhea and constipation as the most commonly reported AEs.

Patients treated with OCA also showed improvements in the secondary endpoints, including in glutamyltransferase, alkaline phosphatase, and trends to improvement in cholesterol levels.
FGF19 increased in both groups, and treated patients experienced reductions in C4

However, a ~20% (and stat sig) increase in LDL levels was observed in patients from both dose groups. While the LDL decreased once patients began to lose weight, this is a concerning characteristic of OCA.

72 week data from the Sumimoto-run Phase 2 trial of OCA in Japanese NASH was generally positive. While topline data barely missed stat sig for the primary endpoint (p=0.053), the study did show dose-dependent responses, with the high 40mg dose reaching stat sig. A pre-specified completer analysis on patients who received biopsies at both baseline and 72 weeks showed that 51% of patients in the 40mg cohort met the primary endpoint, vs 22% in placebo (p=0.0061).

Overview of Genfit's Elafibronor

GFIT's elafibronor (GFT-505) is an oral PPAR alpha and delta agonist. '505 has preferential activity on PPAR-a and concomitant activity on PPAR-d. It effects peripheral and hepatic insulin sensitivity and is associated with improvements in markers of liver dysfunction, insulin sensitivity, and glucose homeostasis. PPAR-a is expressed highly in liver hepatocytes and plays a significant role in regulation of fatty acid transport and b-oxidation and modulating gluconeogenisis and inflammatory responses. PPAR-d also plays a significant role in managing hepatic glucose use and lipoprotein metabolism. It has anti-inflammatory activity in the liver.

The Ph2 GOLDEN data missed statistical significance in the prospective analysis, but a post hoc analysis evaluating patients with NAS>4 showed that the 120mg high dose reached statistical significance. 22.4% of treated pts vs 12.7% of placebo patients showed treatment response (resolution on steatosis, inflammation or ballooning). This indicates a potential clinical benefit for patients with more advanced disease.

GFIT will start a PBO controlled Ph3 trial evaluating 120mg elafibronor in patients with NAS>4. The design uses a primary endpoint of NASH resolution at 18 months (n=900). This should support a subpart H approval, although full approval will be driven by the 1800 patient data on clinical liver outcomes.

Overview of Gilead's Simtuzumab

GILD's simtuzumab is a humanized monoclonal antibody against lysl oxidase like 2. It is currently in a Phase 2b trial for NASH. Simtuzumab is delivered every 2 weeks by intravenous (IV) infusion. Thus, although '4728A and simtuzumab share the same mechanism of action, the oral dosing of '4728A is much more convenient for patients. LOXL2 is crucial for collagen cross linking of fibrillar collagen I, which is critical in the development of fibrosis in the liver as well as other tissues. Targeting loxl2 could stabilize or even clear fibrotic tissue in the liver, bile duct, or lungs.

On their 3Q16 call, GILD announced that the company would halt development on simtuzumab after Phase 2 data showed that Simtuzumab had minimal efficacy in NASH. The phase 2 trial studied patients taking GS-4997 (selonsterib), an investigational inhibitor of apoptosis signal-regulating kinase 1, with or without simtuzumab, and simtuzumab alone. 72 patients with NASH and moderate to severe fibrosis (F2-F3) were enrolled. Top line efficacy analysis showed that simtuzumab alone was associated with a 20% improvement in fibrosis stage, and 20% progressed to cirrhosis. The GS-4997 18mg +/- simtuzumab showed that 43% of patients exhibited fibrosis improvement, and 3% progressed to cirrhosis. In the '4997+/- simtuzumab arm, 30% of patients experienced fibrosis improvement while 7% progressed to cirrhosis.

The result can be interpreted two ways, in relation to how it affects PXS's LOXL2. Either the target, LOXL2, has a minimal effect on fibrosis, or simtuzumab did not have enough of an impact on the LOXL2 pathway. The first has a negative implication for PXS, because it implies that the small molecule inhibitor of LOXL2 will also have a negligible effect on fibrosis. The second, however, could work in PXS's favor, because the previously more progressed compound associated with the same pathway (albeit with a different mechanism of action), is no longer in the market to compete with PXS's LOXL2.

Preclinical data show that Arresto's LOXL2 antibody elicits a dose dependent decrease in enzymatic activity, but it fails to show complete inhibition. 6A shows the partial inhibitory effects of the compound. The PXS compound, however, shows complete LOXL2 inhibition. While we caution against cross-trial comparisons, especially in mouse models, we note that the testing was completed under a similar set of parameters. We remain optimistic for the PXS LOXL2 inhibitor's efficacy given its more robust inhibition vs simtuzumab.

Figure 18

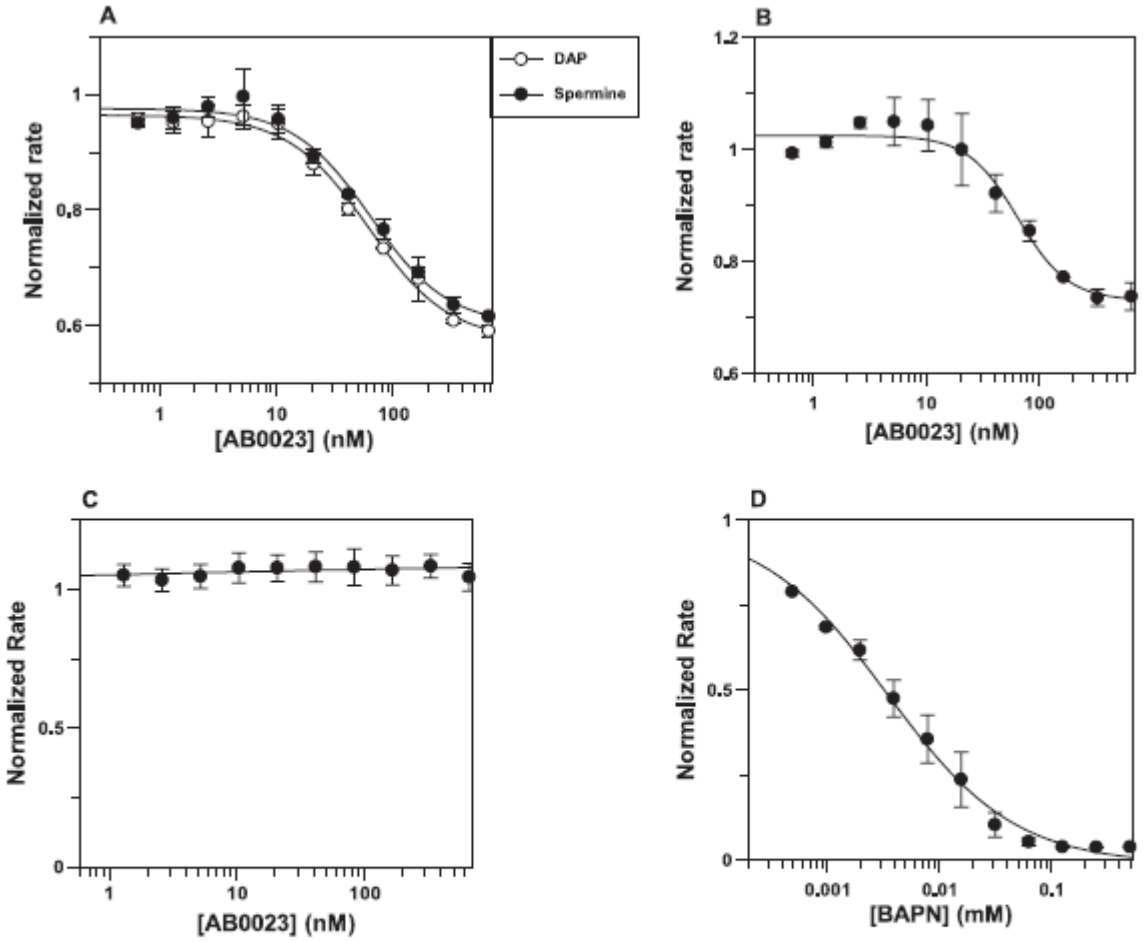


FIGURE 6. Inhibition of LOXL2 by AB0023 in a reaction where DAP ($IC_{50}' = 62 \pm 5.8$ nM) and spermine ($IC_{50}' = 55 \pm 11$ nM) (*A*) or collagen I ($IC_{50}' = 60.9 \pm 3.9$ nM) (*B*) are used as substrate. LOXL2 concentration was at 25 nM when DAP and spermine are used. For collagen I reactions, LOXL2 was at 100 nM. *C*, the effect of AB0023 on the enzymatic activity of active hLOXL3 as a function of AB0023 concentration. The final reaction mixture contained 20 nM hLOXL3, 15 mM DAP, and the indicated concentration of AB0023. *D*, inhibition of hLOXL3 by BAPN where the substrate is DAP. Final conditions are as described in C. The observed IC_{50} for BAPN against hLOXL3 was 3.4 μM $\pm$ 1.9 μM. Data for all figures were normalized to the enzymatic rate in the absence of AB0023 or inhibitor.

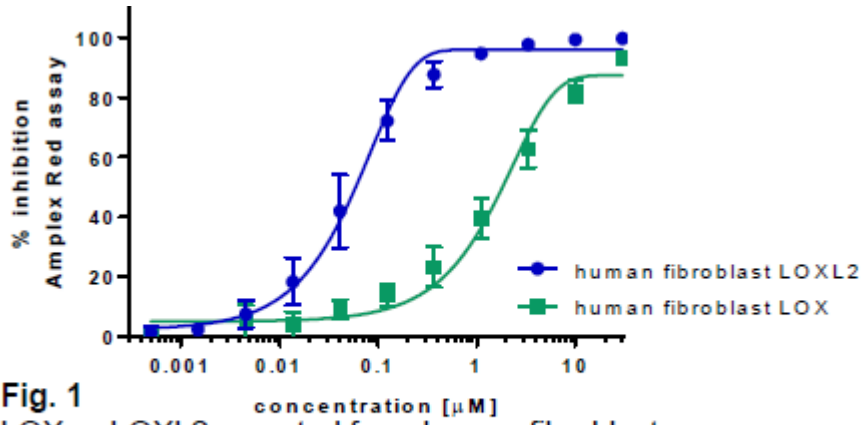


Fig. 1
LOX or LOXL2 secreted from human fibroblasts was pre-incubated with inhibitor for 30 min and activity was measured in physiological buffer solution.

Source: http://www.jbc.org/content/285/27/20964, PXS

Allergan's Cenicriviroc

Allergan acquired Tobira's Cenicriviroc in September 2016 in a deal worth $1.65B. Cenicriviroc is a small molecule dual inhibitor of Chemokine Receptor 2 and Chemokine Receptor 5 (CCR5). CCR5 is a co-receptor involved in the infection of immune cells with HIV-1, and CCR2 may have immuno-inflammatory benefits in HIV-1 infected individuals at increased risk for liver, cardiovascular, and kidney diseases. While the data in these trials were messy, we think AGN made the acquisition because cenicriviroc's marked anti-fibrotic activity, rather than NASH-specific efficacy.

Phase 2 Studies

The CENTAUR trial evaluated 289 patients with liver fibrosis. Once daily for 2 years, placebo daily for 1 year, and dosed daily for 1 year, or placebo daily for 2 years. Trial included patients with high fibrosis scores, and included F1 high risk patients. Biopsies were taken at baseline, 12, 24 months. The primary endpoint was improvement in NAS score with no concurrent worsening of fibrosis stage at year 1. Improvement was defined as minimum 2 point improvement in NAS with at least 1 point improvement in more than 1 category. The secondary endpoint is resolution of NASH, with no concurrent worsening of fibrosis stage at year 1.

The trial failed to meet its primary endpoint, although data showed a stat sig improvement in fibrosis of at least 1 stage with no worsening of NASH at 1 year of treatment. 2 year data will likely be presented in November 2016, and could potentially show more significant improvement over placebo, since it should be easier to see fibrosis benefit at 2 years.

The Phase 2a ORION trial was the proof of concept trial, evaluating the potential benefit of cenicriviroc on insulin sensitivity and lipotoxicity. The trial evaluated 50 adult obese patients with prediabetes or type 2 diabetes mellitus and suspected NAFLD. The primary endpoint was change in insulin sensitivity measured by peripheral and adipose tissue at 24 weeks.

Interim 12 week data showed that cenicriviroc was associated with a reduction in fasting glucose, improvements in HbA1c, and serum free fatty acid levels. The overall consistency between these endpoints is positive, highlighting the anti-inflammatory properties of CVC.

GLP-1 Analogues

Victoza Novo Nordisk's GLP-1 (glucagon-like peptide-1 receptor) agonist which is currently approved to treat type 2 diabetes. It works by binding to the GLP-1 hormone, which stimulates the secretion of insulin. Given the correlation between the prevalence of obesity, type 2 diabetes, and NASH, as well as the common metabolic symptoms including high body fat and insulin resistance, weight loss and insulin sensitivity may be viable therapeutic targets.

The GLP-1 agonist increases insulin secretion, delays gastric emptying, and suppresses prandial glucagon secretion. It causes a decrease in appetite, which then facilitates weight loss, lowers triglyceride levels, making it potentially effective in NASH patients with Type 2 diabetes. We see Victoza as a potential combination therapy in this subset of NASH patients.

The Phase 2 LEAN trial evaluated 52 patients for resolution of NASH and no worsening of fibrosis for 48 weeks. The results showed that 39% (n=9 of 22) of patients receiving liraglitude achieved NASH resolution, but only 9% (n=2 of 23), p=0.019. Data also showed that 9% of patients treated with liraglitude had worsening of fibrosis, vs 36% in the placebo cohort (p=0.026). Secondary endpoints including weight loss, BMI, and fasting glucose all showed stat sig improvements for treated patients. Reductions in ALT and HbA1c trended to improvement with treated patients, but the results were not statistically significant.

SSAO Inhibitor PXS4728A in COPD

COPD Background

COPD, or chronic obstructive pulmonary disease, is a chronic, slowly progressive, and partially reversible airflow obstruction, primarily caused by smoking. There are around 25M COPD patients in both the US and the EU combined. Chronic pulmonary obstruction and then oxygen deprivation (hypoxia), promotes vasoconstriction in the pulmonary arterial bed. Pulmonary vasoconstriction adds pressure to the right side of the heart, causing the heart to have reduced coping ability to stressors, which can lead to progressive cardiac dilation, heart failure, and death. Generally, however, the cardiovascular complications are only known to occur later in the disease-stage. Two related diseases include chronic bronchitis and emphysema. Symptoms of COPD include shortness of breath, cough, phlegm, and lowered activity potential. Current therapies relieve symptoms and reduce pulmonary exacerbations and hospitalization rates but do not reverse the underlying scarring of the lung tissue and airways.
There is little evidence correlating SSAO and COPD, but in smokers, serum SSAO activity is closely correlated with the number of pack years. Of note, nicotine is almost exclusively metabolized by SSAO, and formaldehyde (which is found in cigarettes) is a well-recognized genotoxin and crosslinking agent.

We think COPD may be a viable second indication for the ‘4728A compound as a part of the BI partnership. As a reminder, PXS will receive A$15-20M upon initiation of Phase 2. We will provide a more in-depth analysis on the COPD market, and specifically, the role and potential sales of ‘4728A in the COPD market once more proof-of-concept data has been established, and once ‘4728A enters clinical trials.

‘4728A and COPD

‘4728A has been tested in a mouse model of CS-induced experimental COPD. The model is a good model for human COPD and subjects include symptoms such as chronic airway inflammation, fibrosis, and impaired lung function. Nonetheless, we would have liked to see a model of ‘4728A in COPD not-related to smoking, to ensure the treatment played a role in the underlying disease pathology. Daily oral treatment of ‘4728A completely inhibited systemic SSAO activity induced by acute and chronic CS exposure. Daily oral treatment inhibited airway inflammation and suppressed inflammatory cell influx and fibrosis into the airways, thereby improving lung function.

Daily treatment with ‘4728A inhibited constitutive SSAO activity compared to vehicle-treated CS-exposed mice. SSAO activity in inguinal fat was also completely inhibited with ‘4728A treatment. Thus, ‘4728A has shown promising early indicators of efficacy in vivo in the lung and peripheral tissue. Oral delivery of ‘4728A reduces inflammatory cell influx into the airways following acute CS exposure.

The effects of SSAO inhibition were also apparent when daily oral treatment with ‘4728A reduced the total number of leukocytes into the airways. Although relatively fewer doses were tested, the lower dose (12 mg kg ^-1) caused a reduction in the number of macrophages and lymphocytes, while the higher dose (20 mg kg ^-1) was associated with a significant suppression of neutrophil numbers. With both groups, daily oral treatment was associated with a reduction in the total number of leukocytes in the airways. Daily oral treatment also reduced the levels of the TNF—a protein in a dose-dependent manner. The higher dose reduced levels back to baseline levels in normal air-exposed mice. CXCL levels were also significantly reduced when treated with either dose. The suppression of inflammatory cells associated with treatment in both the acute and chronic models, however, was not necessarily correlated with the suppression of TNF or CXCL. Thus, more study into the reduction of neutrophil and leukocyte numbers in relation to the other inflammatory factors requires further investigation.

Treatment also reduced SSAO activity and inflammatory parameters during acute CS-exposure. Therapeutic delivery reduced disease features in a chronic COPD model. In the chronic model, mice were treated with the higher dose of ‘4728A as well as Rolipram, a PDE-4 inhibitor, from 6 weeks of CS-exposure). Rolipram is used as a positive control, or a pharmacological comparator potential control for the inhibition of COPD. Daily oral treatment with 4728A completely inhibited SSAO activity by induced CS-exposure. Rolipram also reduced SSAO activity to levels found in normal air-exposed controls, likely attributed to the indirect effect of Rolipram on inflammation suppression. Inhibition, however, is quite different to reduction in activity (which Rolipram), and we like the direct link between SSAO inhibition of specific inflammation-causing targets in the COPD disease pathology.

Overall, the data indicates that the inhibition of SSAO can suppress the inflammatory process and therefore reduce acute CS-induced inflammatory cell influx into the airways. Treatment had little effect on emphysema, which we see as a negative, and would like to see more data around functional markers associated with '4728A.

LOXL2 PLATFORM IN ADDITIONAL INDICATIONS

Pharmaxis' LOXL2 mechanism may also have implications in diseases other than NASH. Potential additional indications for the drug candidate include COPD, cancer, and IPF.

Potential for LOXL2 in Cancer:

Metastasis is the process by which tumors replicate and grow. It is a very complex and dynamic process, and accounts for 90% of cancer-related deaths. Fibrotic signals enhance tumor progression and metastasis. Thus, potentially silencing the effect of LOXL2 may create an environment that hinders/slows the growth of a tumor, which could make it an interesting addition to cancer therapies.

LOX post-translationally modifies collagens and elastin in the extracellular matrix (ECM). This allows for efficient crosslinking of fibers, which, in turn, facilitates the stabilization of collagen fibrils, fibers, and elastin. One of the substrates LOX binds to is collagen I. Collagen I is important for tumor stability. LOX-mediated crosslinking of collagen I at primary tumor sites is implicated in cell invasion and malignant progression. In healthy adults, fibroblasts synthesize only small amounts of collagen, but in a fibrotic state, fibroblasts produce collagen and fibronectin. When secreted at high levels, Collagen I is associated with severe morbidity and mortality. It is also crucial for the primary tumor and metastatic microenvironment.

Gilead's Simtuzumab Failed in a Phase 2 Oncology Study

Gilead investigated Simtuzumab in patients with previously treated pancreatic cancer. A Phase 2 study enrolled 236 patients into gemcitabine+200mg simtuzumab, 700mg simtuzumab, and placebo arms. Patients treated with simtuzumab+gemcitabine did not show a significant improvement in the primary endpoint of progression-free survival (3.5 months vs 3.7 months vs 3.7 months).

A Phase 2 of simtuzumab in combination with FOLFIRI for second line KRAS mutant colorectal cancer and in combination with Jakafi in myelofibrosis also showed no sign of clinical efficacy.

LOXL2 in Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis (IPF) overview

IPF (Idiopathic Pulmonary Fibrosis) is a chronic, lower respiratory-tract disorder which is usually seen in adults and starts at around the age of 40. Patients have an underlying defect in which there is proliferation of supportive cells in the lung and a concomitant increase in fibroblasts and collagen. The pulmonary architecture suffers from distortion, lung elasticity decreases, and, in turn, lung function is compromised. The disease initially manifests with patients developing shortness of breath and coughing, and eventually they progress to heart failure and death.

The age-adjusted/sex-adjusted incidence of IPF is 8.8-17.4 cases per 100,000 person-years, although there is limited population data around the disease. Around 200K patients in the US and EU have IPF.

We plan on providing a more in-depth analysis of the IPF market, and specifically, how a LOXL2 therapy like Pharmaxis' could be incorporated into a treatment paradigm pending target identification and more early-stage data.

Collaboration with Synairgen

Pharmaxis collaborates with Synairgen for the development of a LOXL2 drug candidate for IPF. Synairgen is funding preclinical toxicology work, as well as Phase 1. The collaboration also gives Pharmaxis access to Synairgen's BioBank human tissue models technology platform, and could expedite the time to Phase 1 data. We think the relationship with Synairgen is ok for Pharmaxis, given it helps share the risk of the program.

LOXL2 Experience in IPF

Gilead halted a Phase 2 trial of simtuzumab in idiopathic pulmonary fibrosis (IPF). An unblended safety and efficacy analysis by the study's data monitoring committee (DMC) recommended the study be terminated early because of a lack of efficacy. 500 patients were enrolled, and were treated with 125mg simtuzumab for up to 254 weeks. The primary endpoint was progression free survival, with a predefined subgroup analysis for patients with "high" serum LOXL2 levels at baseline.

BRONCHITOL: INHALED MANNITOL FOR CYSTIC FIBROSIS

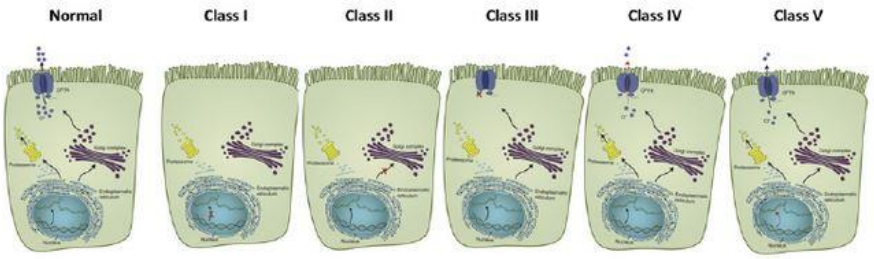
Cystic Fibrosis Overview

Cystic Fibrosis (CF) is a debilitating genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CTFR). Approximately 70,000 people worldwide are affected. CF prevalence is growing at a rate of about 1%/year, given the increased life expectancy following the recent introduction of disease modifying therapies. The disease is most common in Caucasians, and most prevalent in areas populated by those of European and Australian descent. It is a chronic, progressive disease, and life expectancy of patient is about 41 years in spite of the availability of several new therapies. There remains an unmet need for more effective disease modifying treatments which can improve the quality of life and increase the lifespan of CF patients.

CF is a chronic progressive disease and predominantly affects the lungs and digestive system. The disease is incurable. Symptoms vary between patients, and can be variable in severity over time in a specific patient. Lung disease is the main cause of disease progression and morbidity. Because the CFFR protein can't function properly, there is an abnormal transport of chloride ions across cell membranes. This result in patients having thick and sticky mucous in their lungs, resulting in clogged bronchioles and frequent lung infections. *Psuedomonas aeruginosa* is the most common chronic pulmonary infection in patients with CF. It is associated with airway inflammation, a higher frequency of chronic exacerbations, more rapid pulmonary function decline, and overall higher morality. Patients require long term maintenance therapy with inhaled antibiotics once PA lung infection occurs to reduce acute pulmonary exacerbations and preserve lung function. Patients can also show respiratory symptoms such as persistent cough, thick sputum and mucus, wheezing, breathlessness, and decreased ability to exercise. Most CF patients die from respiratory failure.

The CTFR gene encodes a multi-domain membrane protein of the ATP binding cassette transporter C class superfamily. Individual with 2 copies of a defective CFTR gene are affected by the disease. Patients with one normal copy and one defective copies are carriers, but are not normally affected. There are 5 classes of mutations in the CFTR that can cause CF: absence of functional CFTR due to defective protein translation (Class I) absence of functional CFTR due to protein folding (CLASS II), defective channel regulation (Class 3), defective CFTR channel (class 4), and reduced CFTR function and synthesis (Class 5). Classes 1-3 are the most severe, and cause about 85% of cases of CF. Classes 4 and 5 are more mild.

Figure 19



	Normal	Class I	Class II	Class III	Class IV	Class V
Biochemical phenotype		No CFTR synthesis	CFTR trafficking defect	Dysregulation of CFTR (diminished ATP binding and hydrolysis)	Defective chloride conductance or channel gating	Reduced *CFTR* transcription and synthesis
Types of mutations (examples)		Nonsense G542X, W1282X Frameshift 394delTT Splicing 711+1G>T, 1717-1G>A	Missense G85E, S549R, L1065P, N1303K Amino acid deletion ΔF508	Missense S492F, V520F, G551D, R553G, R560S, R560T	Missense R117C, L227R, R347P, A455E, D1152H	Splicing 1811+1.6kb A>G, 2789+5G>A, 3849+10kbC>T, IVS8-5T
Potential therapy (examples)		Gentamicin Ataluren (PTC 124) Gene transfer	Butyrates Curcumin Gentamicin Gene Transfer	Gentamicin Gene transfer	Milrinone Gene transfer	Ataluren (PTC 124) Gene transfer

Source: http://uchealth.com/pulmonary-insights/miracle-drugs-for-cystic-fibrosis/

Current Treatments

The goal of any CF therapy is to improve airway clearance by enhancing mucociliary clearance. FEV1 improvements regarded as clinically meaningful, and reductions in pulmonary exacerbations are considered equally important. New therapies aim to limit the additional burden of treatment, which is important in improving treatment compliance.

Most of the CF patients carry a high disease burden, and pulmonary function continues to decline. Patients receiving nebulised therapy spend about 2 hours per day on treatment. Nebulised therapy also requires a complex and time-consuming setup and cleaning process. About one-third of patients typically follow the recommended cleaning procedures, putting most patients at risk of infection from bacterial contamination of the nebulizer. By age 25, most patients are on at least 6 concurrent therapies. Exacerbations of lung disease are typically induced by chronic bacterial infection which are provoked by the onset of new viral infection. Drugs like tobramycin and aztreonam are approved for large proportions of CF patients on the basis of FEV1, hospitalizations, and patient reported outcomes.

Figure 20

Cystic Fibrosis Therapies in Development			
Mechanism	**Drug**	**Company**	**Phase**
Restore CFTR Function	Kalydeco	Vertex	Marketed
	Orkambi	Vertex	Marketed
	Ataluren	PTC	Phase 3
	VX-661+Ivacaftor	Vertex	Phase 3
	CTP-656	Concert Pharma	Phase 1 complete
	FDL-169	Flatley Discovery Lab	Phase 1/2
	N91115	Nivalis	Phase 2
	QBW251	NVS	Phase 2 terminated
	Riociguat	Bayer	Phase 2
	QR-010	ProQR Therapeutics	Phase 1
	PTI-428	Proteostasis	Phase 1
Mucociliary Clearence	Pulmozyme	Genentech	Marketed
	Hypertonic saline	Generic	Marketed
	Inhaled Mannitol	Pharmaxis	Phase 3
	OligoG	Algi pharma	Phase 2
	VX-371	Vertex	Phase 2
Anti-Inflammatory	Ibuprofen	Generic	Preclin
	CTX-4430	Celtaxys	Phase 2
	GS-5745	Gilead	Phase 2
	JBT-101	Corbus Pharma	Phase 2
	POL6014	Polyphor	Phase 1
Anti-Infective	Azithromycin	Generic	Marketed
	Cayston	Gilead	Marketed
	Inhaled tobramycin	Generic	Marketed
	Tobramycin inhaled powder	Novartis	Marketed
	Inhaled levofloxacin	Raptor	Phase 2 completed
	Inhaled liposomal amikacin	Insmed (Roche)	Phase 3 completed
	Fosfomycin/Tobramycin Inhaled Solution	CURx Pharma	Phase 3
	AeroVanc	Savara	Phase 2
	Gallium	Generic	Phase 2
	Inhaled nitric oxide	Novoteris	Phase 2

Source: Clinicaltrials.gov, Taylor Collison

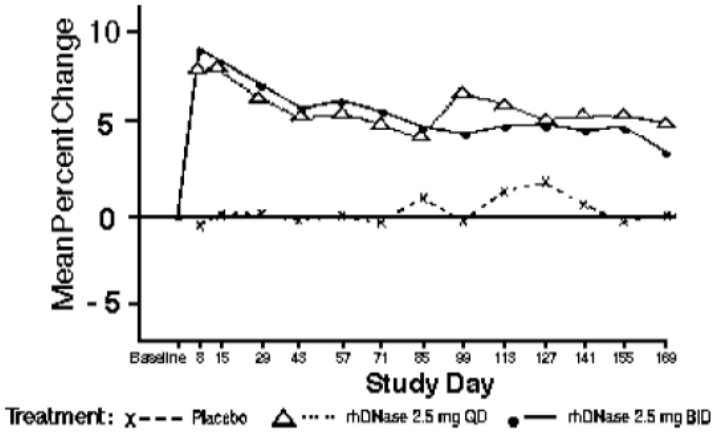
The first drug approved for CF was rhDNAse (Pulmozyme). Aerosolized antibiotic tobramycin was the next approved therapy, which is used for patients who develop infections. Physicians use rhDNase, hypertonic saline (which is generally regarded as safe, although has mixed reviews around efficacy of reduced pulmonary exacerbations and improved lung function), chronic macrolides (for infection), and aerosol antibiotics to treat CF patients.

Pulmozyme, or recombinant deoxyribonuclease I (rhDNase), is an enzyme which selectively cleaves DNA. It hydrozes DNA in the sputum of CF patients, who retain viscous purulent secretions in the airways. The secretions have high concentrations of extracellular DNA released by degenerating leukocytes. When these accumulate, they can cause infection. Thus, reducing sputum viscoelasticity, which helps improve pulmonary function and reduces exacerbations of infection. It is a sterile, clear, colourless, highly purified solution which is delivered in a nebulizer bowl.

Pulmozyme was shown to reduce the relative risk of 27% and 29% in the 2.5mg once and twice daily dose groups in patients with FVC<40%, respectively. Within 8 days from the start of treatment, mean FEV1 increased 7.9% and 9.0% in the once and twice daily treatment groups. The overall mean FEV1 during long term therapy increased 5.8% and 5.6%.

Figure 21

Figure 1. Mean Percent Change from Baseline FEV_1 in Patients with FVC ≥40% of Predicted



Source: https://www.gene.com/download/pdf/pulmozyme_prescribing.pdf

In CF patients with FVC<40% of predicted, Pulmozyme-treated patients showed a 9.4% increase in FEV1 vs 2.1% placebo (p<0.001), and 12.4% improvement in FVC vs 7.3% placebo, p<0.01. In this trial, pulmozyme did not significantly reduce the risk of developing a respiratory tract infection requiring perenteral antibiotics.

Inhaled antibiotics approved for CF are tobramycin, colistimethate sodium, aztreonam, and levofloxacin are approved for the treatment of chronic pseudomonas aeruginosa lung infection in adult patients with CF. Studies show that patients receiving tobramycin showed a 2.5% benefit in FEV1 vs placebo (p=0.0366)

Vertex's Kalydeco was the first drug to address the underlying cause of CF disease. The CTFR potentiator is designed to restore the flow of ions through an activated CTFR by increasing the channel's open probability. It has been developed for use in class III patients, and was first approved in the C551D mutation patients, but has since been approved to treat other class III mutations. Vertex's Orkambi was approved in F508del homozygotes in July 2015.

In a Phase 3 trial, Kalydeco showed a mean absolute improvement in lung function from baseline compared to placebo of 10.6%. Treated patients were 55% less likely to experience pulmonary exacerbation, and treated patients gained 7 lbs more than placebo patients, indicating an improvement in health. Overall, Kalydeco is safe and well-tolerated, with adverse events of headache, upper respiratory tract infections, nasal congestion, rash, dizziness, and bacteria in sputum, although no AEs caused treatment discontinuation.

Vertex's Orkambi is a combination of a potentiator (ivacaftor) and corrector (lumacaftor) for cystic fibrosis patients with the F508del mutation. The two Phase 3 trials, TRAFFIC and TRANSPORT, each enrolled about 550 CF patients age 12 or over homozygous for the F508del mutation. All treatment arms reached their primary endpoint, producing a mean improvement in FEV1 in the range of 2.6% to 4% over placebo. Treated patients experienced mean relative improvements of 4.5% to 6.7% over 24 weeks.

Bronchitol Overview

DPM (dry powder manitol) is being investigated for the management of CF in patients age 6 or older to improve pulmonary function, and is currently marketed in the EU and Australia for Adults with CF. Mannitol is a naturally occurring sugar alcohol, an osmotic agent which was optimized as a 3-micron-sphere dry powder which can be delivered via a disposable inhaler for the treatment of CF. Inhaling mannitol changes the viscoelastic properties of airway phlegm, increases the hydration of airway surface liquid, and contributes to the increased clearance of the retained secretions through mucociliary activity and productive cough action.

Bronchitol, however, also induces bronchospasm, which is an undesired effect for patients with CF. An increase in osmolarity in the airways can result in the release of bronchoconstriction mediators from inflammatory cells in the

airways. As a known bronchial irritant, increased cough as a result of its inhalation may also facilitate increased mucus clearance.

Clinical Trial Overview

Study 202, a Phase 2 trial, provided dose ranging data for Bronchitol in 48 patients. 44 patients completed the study (they did not demonstrate airway hyperresponsiveness). The cross-over design (2 week treatment period followed by a 1 week washout period) was problematic because all patients began treatments sequences with 2 weeks at the highest dose (400mg) twice daily, and were then randomized to the other 2-week dosing treatments. We think the value generated from this Phase 2 study was limited.

The primary EP was change in FEV1 and FVC from baseline. Improvements in % change in FEV1 from baseline were -1.6%, 3.6%, 3.9%, and 8.7% for the 40, 120, 240, and 400 mg twice daily doses, respectively. Results for FVC were similar.

Study 204 was a Phase 2 crossover-designed study conducted in paediatric patients age 6-17. 92 patients were randomized into 400mg bronchitol or placebo twice daily for eight weeks ontop of standard of care. After 8 weeks on treatment, another 8 week treatment period on the alternate treatment. During the bronchitol treatment period, the primary endpoint was met, showing absolute improvement in FEV1 of (3.42%; p=0.004; ppFEV1 4.95%, p=0.005), and the secondary endpoint was change in FEF 25-75 (5.75%, p=0.005). Exacerbations and lung infection were reduced by 25%.

Studies 301 and 302, the two Phase 3 studies, were randomized, double blind, placebo controlled, parallel group trials designed to assess the efficacy and safety of 26 weeks of treatment with DPM 400 mg twice daily in patients ages 6 years and older. The double-blind phase was followed by an open-label phase of up to 52 weeks and 26 weeks duration for trials 301 and 302, respectively.

Inclusion criteria required patients to have an FEV1 between 30-90% predicted for trial 301 and between 40-90% predicted for trial 302. Patients were excluded if they had lung transplants or listed for lung transplant, or a history of significant hemoptysis (> 60 mL within 3 months of enrolment). Patients were allowed to continue their chronic medication regimens, but were not allowed to continue treatment with hypertonic saline, a commonly used but not FDA-approved mucolytic/expectorant, was excluded.

Patients were initially screened for airway hyper-responsiveness by receiving a MTT under medical supervision. Eligible patients were randomized 3:2 to receive either DPM 400 mg (contents of ten 40 mg capsules) or control (50 mg inhaled mannitol as ten 5 mg capsules. A true placebo couldn't be used to control for the sweet taste associated with mannitol, so a 50mg dose was chosen given the lack of response at 40mg in the Phase 2).

Prior to dosing patients were to self-administer a short-acting bronchodilator in order to minimize acute bronchoconstriction. Because patients with CF typically use several inhaled therapies, the following standardized order of treatment was recommended: 1. Short acting bronchodilator 2. Study drug 3. Chest physiotherapy 4. rhDNase (if used) 5. inhaled antibiotics (if used) 6. inhaled corticosteroids (if used) Evaluations were made at screening to assess for eligibility and, once randomized, at baseline, week 6, week 14, and week 26. For the open-label extension periods, additional evaluations were made at weeks 38, 52, 64, and 78 in study 301 and at weeks 38 and 52 only for study 302.

The primary efficacy endpoint was absolute change from baseline (mL) in FEV1 at week 26. Baseline FEV1 was obtained at week 0 (visit 1). Other efficacy endpoints included: Additional respiratory assessments (FVC, FEF25-75), pulmonary exacerbations (PE) based on adverse events entered into the eCRF, protocol defined pulmonary exacerbation (PDPE) defined as occurring when patients were treated with IV antibiotics and experienced at least four of the following 12 signs or symptoms: change in sputum production (volume, color, consistency), dyspnea, new or increased hemoptysis, malaise, fatigue or lethargy, fever (> 38°C), anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, FVC or FEV1 decreased by ≥ 10% from previous recorded value, radiographic signs indicative of pulmonary infection, increased cough, changes in physical examination of the chest), quality of life using Cystic Fibrosis Questionnaire-R (CFQ-R) (completed at weeks 0, 14, and 26, rescue antibiotic use (recorded in the study diary), and days in hospital due to pulmonary exacerbation.

Study personnel in study 302 received better training, which may have led to fewer dropouts (a decrease from around 30% to around 15% in study DPM-CF-302). Another key difference between the two studies was the percentage of patients under 18. The proportion of under-18 patients was around 50% in study 302 vs 36% in study 301.

Results

Study 301: 340 patients were enrolled, and the study was designed with the assumption that about two thirds of patients were using rhDNAse, with a 20% withdrawal rate. There was no plan for imputation of missing data. The overall treatment effect was 54.17ml ($p<0.001$). The difference between rhDNase+DPM patients was statistically significant (108ml), but not statistically significant in patients not dosed with rhDNase (69ml). The mean change in absolute FEV1 was higher in the non-rhDNAse patients vs the rhDNase+DPM patients.

A post-hoc analysis of responders was conducted (patients having an improvement of FEV1>100ml, or >5% relative to baseline, or >5% relative change in % predicted). Among patients who completed the study and received 400mg BD treatment, 41.4% (or 27% of the ITT population) had >5% increase in FEV1%PP.

Study 302: Failed to meet its primary endpoint of FEV1 vs control at 26 weeks ($p=0.059$). While the % improvement was similar to that in study 302 which did meet stat sig, we note differences in patient baseline characteristics between the trials. Patients treated with DPM had an 8.2% (107ml) improvement in FEV1 vs baseline ($p<0.001$), and similar to the 6.3% improvement in study 301. Improvements were seen as early as 6 weeks, and were sustained at weeks 14 and 26. Secondary endpoints showed improvement in FVC ($p=0.022$), and FEV1%PP ($p=0.024$).

A **pooled analysis** of the results from both Phase 3 studies included data from 643 patients across 11 countries. Over the 26 weeks of treatment, DPM treated patients experienced an average of 7.3% improvement in FEV1 ($p<0.001$), and a significant improvement compared to patients in the control group ($p<0.001$). A subgroup analysis of DPM+rhDNase patients showed a 5.3% improvement from baseline ($p<0.001$), and an improvement over control ($p=0.02$). DPM Patients not on rhDNase showed a 9.44% improvement over baseline ($p<0.001$), also superior to control ($p=0.009$). Overall, the rate of exacerbations from Bronchitol patients vs control was 25% (NS), and the number of patients experiencing an exacerbation was 29% lower for those taking Bronchitol. The pooled analysis showed the highest (and most stat sig) effect size in % predicted FEV1 for adults treated with Bronchitol. Adolescent data and child data did not meet stat sig. However, we caution against relying on the pooled analysis data given the child-adolescent subgroup analysis was not pre-specified, the protocols were different between both trials (staff at sites in study 302 received more training), and the weighting of under-18s was much higher in the '301 study.

Figure 22

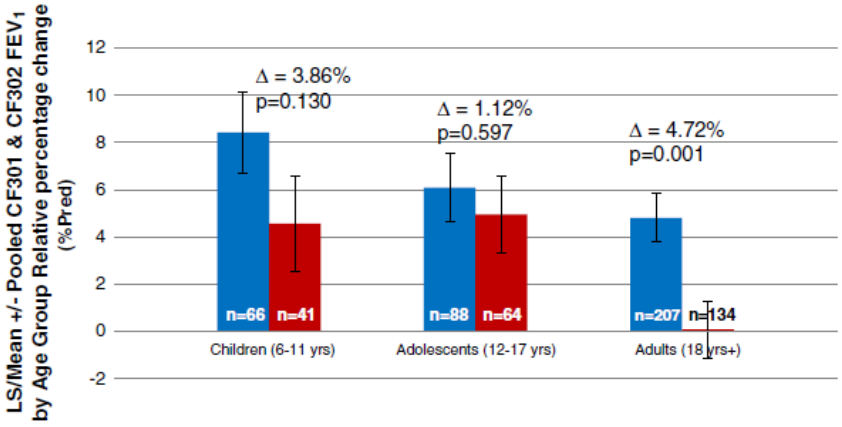


Fig. 3. % Change from baseline in % FEV_1 predicted by age — ITT population.

Source: D. Bilton et al. / Journal of Cystic Fibrosis 12 (2013) 367–376

Analyzed:	DPM-CF-301a (N=272)			DPM-CF-302 (N=297)			Pooled DPM-CF-301 and DPM-CF-302 (N=569)		
Mean absolute change from baseline in FEV_1 (mL)*									
	LS Mean Estimate	95% CI	p-value	LS Mean Estimate	95% CI	p-value	LS Mean Estimate	95% CI	p-value
Difference over 26 weeks	94.45	(46.21, 142.70)	<.001	54.14	(-1.97, 110.26)	0.059	73.42	(36.19, 110.65)	<.001
Mannitol	121.35	(89.18, 153.51)	<.001	106.53	(62.43, 150.62)	<.001	114.05	(87.24, 140.86)	<.001
Control	26.9	(-10.15, 63.94)	0.154	52.38	(2.09, 102.68)	0.041	40.63	(9.90, 71.36)	0.01
Absolute change in FEV_1 percent predicted of normal									
Difference over 26 weeks	2.40	(0.94, 3.85)	0.001	1.87	(-0.02, 3.75)	0.052	2.12	(0.91, 3.33)	<.001
Mannitol	2.85	(1.88, 3.83)	<.001	3.13	(1.65, 4.62)	<.001	2.99	(2.12, 3.86)	<.001
Control	0.46	(-0.66, 1.57)	0.420	1.27	(-0.43, 2.96)	0.142	0.87	(-0.13, 1.87)	0.088

Model: DPM-CF-302 MMRM (with treatment group by visit interaction)

Source: FDA Documents

Ongoing Study 303 for FDA Approval Fully Enrolled as of July 2016, and data are expected in 2Q17. The Phase 3 trial is a 26 week, randomized, double-blind, parallel group investigation of Bronchitol in CF patients over 18. The primary endpoint is the mean change in FEV1 from baseline to week 26. Secondary endpoints are mean change from baseline FVC, time to first pulmonary exacerbation, number of days in hospital due to pulmonary exacerbations, incidence of pulmonary exacerbations, number of days on antibiotics due to pulmonary exacerbations, ease of expectoration, and CFQ-R respiratory domain scale.

Partnership with Chiesi

As a reminder, Pharmaxis is partnered with Chiesi, and Chiesi will fund up to US$22M of the cost of the trial (the total cost is estimated at ~US$26M), US$10M for the launch of Bronchitol in the US, and another US$15M in milestone payments, as well as high-teens % share on in-market sales. Chiesi is also responsible for completing the Bronchitol NDA with the FDA. We think the partnership represents a good way for PXS to retain some upside if Bronchitol receives approval from the FDA while minimizing capital risk.

Regulatory Considerations

FDA Regulatory Interactions

- **2004:** IND opened, received orphan drug status
- **2005**: Bronchitol receives fast track designation from FDA
- **2006**: End of Phase 2 meeting. Determined that Phase 3 study duration depends on primary outcomes, need for 1 year safety data, FEV1 variable is reasonable, but small changes in FEV1 alone is not enough to support approval. More co-primary, or at least secondary, outcomes are required.
- **2006:** SPA request for study 301. Issues included study duration, endpoints, pooling of control subject data, definition of CF exacerbation, and statistical analyses regarding imputation of missing data. No agreement was reached with the Agency.
- **2007:** SPA request for study 302 and type A meeting. Key topics of discussion included study duration to support lung function claim (FEV1) and exacerbation claims, definition of CF exacerbation, acceptability of the proposed control, and inclusion of children 6 years and older with CF. FDA noted that a 6 month treatment duration would not be sufficient to support an exacerbation endpoint. Pharmaxis would also need to justify using the adult dose (400mg twice daily) in a pediatric patient population.
- **2010:** Pre-NDA meeting. PXS suggested post hoc changes to statistical analysis.
- **January 2013:** FDA Advisory Committee rejects Bronchitol

EMA Regulatory Interactions

In October 2011, the CHMP (Committee for Medicinam Products for Human Use) recommended the marketing authorization for Bronchitol as an add-on therapy to standard of care in CF patients. Earlier, in June 2011, the CHMP adopted a negative opinion for Bronchitol in adult patients in with CF, but Pharmaxis subsequently requested a re-examination. The EMA was also concerned with the statistical analyses used to account for the

missing data, and cautioned against using the pooled data analysis given the significant differences between studies 301 and 302.

The CHMP later determined that the modest improvement in FEV1 could be used in addition to the best standard of care. While the committee remained concerned about the hemoptysis risk, they determined the risk was manageable, and that some patients may still benefit from Bronchitol, given the lack of available therapies. The new analysis determined that the benefit of Bronchitol in addition to standard therapy outweighed the risk in adult patients. Bronchitol's treatment effect is small, with a 2-3% absolute change in FEV1 predicted.

Pharmaxis also provided an analysis of Bronchitol in the adolescent/pediatric patient population, in an attempt to gain approval for Bronchitol in a younger patient population. The ITT analysis included 105 patients consisting of 48 pediatrics from 6 to 11 years (31 treated) and 57 adolescents from 12 to 17 years (32 treated). There was a higher dropout rate in adolescent (31.5%) vs pediatric (25%) patients, and there was no age-based stratification procedure. EMA determined that few conclusions can be drawn from this analysis and that no significant difference was shown on FEV1 between the treatment groups.

Market Model for Bronchitol

Our "base case" assumptions around Bronchitol follow NICE (National Institute for Healthcare Excellence, which provides national guidance and advice for healthcare in the UK) guidance for use of Bronchitol not amenable to rhDNAse, and not amenable to hypertonic saline. We also assume mannitol use in patients with P. Aeruginosa infection. Based on the trial drop-outs, we assume only 80% of patients will tolerate the treatment, and, we further assume an 80% treatment compliance rate. Bronchitol is pricing around ~$10K per year in the EU, and we assume a slight premium for US pricing (in the ~$15K/patient/year range). While PXS expects approval for Bronchitol in pediatric patients, we do not model for pediatric approval given the risk/benefit profile associated with the hemoptysis side effects. The base case model (which we caution, is tracking lower than actual Bronchitol sales) shows Bronchitol incrementally detracting from the PXS valuation.

Figure 23

Base case		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
United States																
# of patients with CF		30,000	30,600	31,212	31,836	32,473	33,122	33,785	34,461	35,150	35,853	36,570	37,301	38,047	38,808	39,584
% CF patients >18	45%	13,500	13,770	14,045	14,326	14,613	14,905	15,203	15,507	15,817	16,134	16,456	16,786	17,121	17,464	17,813
Patients not amenable to pulm	30%	4,050	4,131	4,214	4,298	4,384	4,472	4,561	4,652	4,745	4,840	4,937	5,036	5,136	5,239	5,344
with p. aeruginosa infection	80%	3,240	3,305	3,371	3,438	3,507	3,577	3,649	3,722	3,796	3,872	3,950	4,029	4,109	4,191	4,275
Pts not amenable to hypertonic	44%	1,418	1,446	1,475	1,504	1,534	1,565	1,596	1,628	1,661	1,694	1,728	1,762	1,798	1,834	1,870
Pts amenable to tx	80%	1,134	1,157	1,180	1,203	1,227	1,252	1,277	1,303	1,329	1,355	1,382	1,410	1,438	1,467	1,496
Penetration		0	0	0	0%	2%	4%	6%	8%	10%	12%	14%	16%	18%	20%	20%
Pts on bronchitol		0.0	0.0	0.0	0.0	24.5	50.1	76.6	104.2	132.9	162.6	193.5	225.6	258.9	293.4	299.3
Pts on bronchitol (adherence)	75%	0.0	0.0	0.0	0.0	18.4	37.6	57.5	78.2	99.6	122.0	145.1	169.2	194.2	220.0	224.4
Cost/pt/year	2%	15,000.00	15,300.00	15,606.00	15,918.12	16,236.48	16,561.21	16,892.44	17,230.29	17,574.89	17,926.39	18,284.92	18,650.61	19,023.63	19,404.10	19,792.18
Bronchitol revenues ($M)		**0.0**	**0.0**	**0.0**	**0.0**	**0.3**	**0.6**	**1.0**	**1.3**	**1.8**	**2.2**	**2.7**	**3.2**	**3.7**	**4.3**	**4.4**
18% Distro+royalties						**0.05**	**0.11**	**0.17**	**0.24**	**0.32**	**0.39**	**0.48**	**0.57**	**0.66**	**0.77**	**0.80**
Europe																
# of patients with CF		35,000	35,700	36,414	37,142	37,885	38,643	39,416	40,204	41,008	41,828	42,665	43,518	44,388	45,276	46,182
% CF patients >18	45%	15,750	16,065	16,386	16,714	17,048	17,389	17,737	18,092	18,454	18,823	19,199	19,583	19,975	20,374	20,782
pts not amenable to rhDNAse	30%	4,725	4,820	4,916	5,014	5,114	5,217	5,321	5,428	5,536	5,647	5,760	5,875	5,992	6,112	6,235
with p. aeruginosa infection	80%	3,780	3,856	3,933	4,011	4,092	4,173	4,257	4,342	4,429	4,517	4,608	4,700	4,794	4,890	4,988
Pts not amenable to hypertonic	44%	1,654	1,687	1,721	1,755	1,790	1,826	1,862	1,900	1,938	1,976	2,016	2,056	2,097	2,139	2,182
Pts amenable to tx	80%	1,323	1,349	1,376	1,404	1,432	1,461	1,490	1,520	1,550	1,581	1,613	1,645	1,678	1,711	1,746
Penetration		0%	2%	4%	6%	8%	10%	12%	14%	16%	18%	20%	20%	20%	20%	20%
Pts on bronchitol		-	33.7	68.8	105.3	143.2	182.6	223.5	265.9	310.0	355.7	403.2	411.2	419.5	427.9	436.4
Pts on Bronchitol (adherence)	75%	-	25.3	51.6	79.0	107.4	136.9	167.6	199.5	232.5	266.8	302.4	308.4	314.6	320.9	327.3
Cost/pt/year	1%	10,000.0	10,100.0	10,201.0	10,303.0	10,000.0	10,100.0	10,201.0	10,303.0	10,406.0	10,510.1	10,615.2	10,721.4	10,828.6	10,936.9	11,046.2
Bronchitol revenues Incl Distro	0.5	**-**	**0.3**	**0.3**	**0.4**	**0.5**	**0.7**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.7**	**1.7**	**1.8**	**1.8**
Bronchitol revenues ($M)		**-**	**0.3**	**0.3**	**0.4**	**0.6**	**0.8**	**1.0**	**1.3**	**1.5**	**1.8**	**2.1**	**2.2**	**2.4**	**2.5**	**2.6**

Source: Taylor Collison estimates

Figure 24

Total Revs		-	0.26	0.26	0.41	0.59	0.80	1.03	1.27	1.53	1.80	2.08	2.22	2.37	2.52	2.61
Less CoGS	15%	-	0.04	0.04	0.06	0.09	0.12	0.15	0.19	0.23	0.27	0.31	0.33	0.36	0.38	0.39
Gross profit		0	0.22	0.22	0.35	0.50	0.68	0.88	1.08	1.30	1.53	1.77	1.89	2.01	2.14	2.22
- sales costs (15%)	85%	0	0.18	0.19	0.29	0.43	0.58	0.74	0.92	1.10	1.30	1.50	1.60	1.71	1.82	1.88
Bronchitol R&D Cost		2	2.00	2.00	-	-	-	-	-	-	-	-	-	-	-	-
Profit after R&D		-2	(1.82)	(1.81)	0.29	0.43	0.58	0.74	0.92	1.10	1.30	1.50	1.60	1.71	1.82	1.88
Tax Rate		0%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Product profits after tax		-2	(1.82)	(1.81)	0.29	0.43	0.58	0.74	0.92	1.10	1.30	1.50	1.60	1.71	1.82	1.88

NPV Calculations	
Discount Rate	15.00%
NPV ($)	($1.07)
NoSH (M)	317.33
NPV per Share ($)	($0.00)

Source: Taylor Collison estimates

Our "bear case" model assumes no US approval, estimates that 70% of patients would be amenable to treatment (based on the 30% dropout rate in the first Phase 3 trial), and takes a very conservative penetration rate. While Bronchitol sales currently track well ahead of our "bear case" model, we think penetration rates and pricing power could drop if FDA does not approve Bronchitol based on study 303.

Figure 25

Bear Case		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
United States																
# of patients with CF		30,000	30,600	31,212	31,836	32,473	33,122	33,785	34,461	35,150	35,853	36,570	37,301	38,047	38,808	39,584
% CF patients >18	45%	13,500	13,770	14,045	14,326	14,613	14,905	15,203	15,507	15,817	16,134	16,456	16,786	17,121	17,464	17,813
Patients not amenable to pulm	30%	4,050	4,131	4,214	4,298	4,384	4,472	4,561	4,652	4,745	4,840	4,937	5,036	5,136	5,239	5,344
with p. aeruginosa infection	80%	3,240	3,305	3,371	3,438	3,507	3,577	3,649	3,722	3,796	3,872	3,950	4,029	4,109	4,191	4,275
Pts not amenable to hypertonic	10%	324	330	337	344	351	358	365	372	380	387	395	403	411	419	428
Pts amenable to tx	70%	227	231	236	241	245	250	255	261	266	271	276	282	288	293	299
Penetration		0	0	0	0	1%	2%	3%	4%	5%	5%	5%	5%	5%	5%	5%
Pts on bronchitol		0.0	0.0	0.0	0.0	2.5	5.0	7.7	10.4	13.3	13.6	13.8	14.1	14.4	14.7	15.0
Pts on Bronchitol (adherence)	60%	0.0	0.0	0.0	0.0	1.5	3.0	4.6	6.3	8.0	8.1	8.3	8.5	8.6	8.8	9.0
Cost/pt/year	2%	15,000.00	15,300.00	15,606.00	15,918.12	16,236.48	16,561.21	16,892.44	17,230.29	17,574.89	17,926.39	18,284.92	18,650.61	19,023.63	19,404.10	19,792.18
Bronchitol revenues ($M)		**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.1**	**0.1**	**0.1**	**0.1**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**
18% royalty+distro		**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.01**	**0.01**	**0.02**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**
Europe																
# of patients with CF		35,000	35,700	36,414	37,142	37,885	38,643	39,416	40,204	41,008	41,828	42,665	43,518	44,388	45,276	46,182
% CF patients >18	45%	15,750	16,065	16,386	16,714	17,048	17,389	17,737	18,092	18,454	18,823	19,199	19,583	19,975	20,374	20,782
pts not amenable to rhDNAse	30%	4,725	4,820	4,916	5,014	5,114	5,217	5,321	5,428	5,536	5,647	5,760	5,875	5,992	6,112	6,235
with p. aeruginosa infection	80%	3,780	3,856	3,933	4,011	4,092	4,173	4,257	4,342	4,429	4,517	4,608	4,700	4,794	4,890	4,988
Pts not amenable to hypertonic	10%	378	386	393	401	409	417	426	434	443	452	461	470	479	489	499
Pts amenable to tx	70%	265	270	275	281	286	292	298	304	310	316	323	329	336	342	349
Penetration		0	0	1%	2%	3%	4%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Pts on bronchitol		-	-	2.8	5.6	8.6	11.7	14.9	15.2	15.5	15.8	16.1	16.4	16.8	17.1	17.5
Pts on Bronchitol (adherence)	60%	-	-	1.7	3.4	5.2	7.0	8.9	9.1	9.3	9.5	9.7	9.9	10.1	10.3	10.5
Cost/pt/year	1%	10,000.0	10,100.0	10,201.0	10,303.0	10,000.0	10,100.0	10,201.0	10,303.0	10,406.0	10,510.1	10,615.2	10,721.4	10,828.6	10,936.9	11,046.2
Bronchitol revenues incl distrib	0.5	-	-	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**
Total Bronchitol Revenues ($M)		-	-	**0.0**	**0.0**	**0.0**	**0.0**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**

Source: Taylor Collison estimates

The "bear case" DCF assumes a much lower spend on R&D as well as marketing/commercialization efforts, so the NPV per share is almost as value-hindering as the valuation from the base case. Thus, the Bronchitol valuation is skewed significantly to the negative, likely making it a value-destroyer for the company.

Figure 26

Total Revs		-	-	0.02	0.03	0.03	0.04	0.06	0.07	0.07	0.08	0.08	0.08	0.08	0.09	0.09
Less CoGS	15%	-	-	0.00	0.01	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Gross profit		-	-	0.01	0.03	0.03	0.04	0.05	0.06	0.06	0.06	0.07	0.07	0.07	0.07	0.08
Sales costs			1.00	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Profit after sales		-	(1.00)	(0.99)	(1.47)	(1.97)	(2.46)	(2.95)	(3.44)	(3.94)	(3.94)	(3.93)	(3.93)	(3.93)	(3.93)	(3.92)
Bronchitol R&D Cost		3.00	3.00	3.00	-	-	-	-	-	-	-	-	-	-	-	-
Profit after R&D		(3.00)	(4.00)	(3.99)	(1.47)	(1.97)	(2.46)	(2.95)	(3.44)	(3.94)	(3.94)	(3.93)	(3.93)	(3.93)	(3.93)	(3.92)
Tax Rate		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Product profits after tax		(3.00)	(4.00)	(3.99)	(1.47)	(1.97)	(2.46)	(2.95)	(3.44)	(3.94)	(3.94)	(3.93)	(3.93)	(3.93)	(3.93)	(3.92)

NPV Calculations	
Discount Rate	15.00%
NPV ($)	($18.72)
NoSH (M)	317.33
NPV per Share ($)	($0.06)

Source: Taylor Collison estimates

Our "bull case" model assumes much higher sales potential, and in the model, we do not factor in the NICE guidelines. The only discounts we apply to Bronchitol in the bull case model are the presence of P. Aeruginosa infection, and we assume 80% of patients are eligible for therapy. We also assume a 90% adherence rate, which we think is very generous, and potentially unrealistic. We maintain a lower US market penetration rate, given an unfavourable track record with FDA, and questionable pharmaco-economic benefit associated with treatment.

Figure 27

Bull Case																
United States																
# of patients with CF		30,000	30,600	31,212	31,836	32,473	33,122	33,785	34,461	35,150	35,853	36,570	37,301	38,047	38,808	39,584
% CF patients >18	45%	13,500	13,770	14,045	14,326	14,613	14,905	15,203	15,507	15,817	16,134	16,456	16,786	17,121	17,464	17,813
with p. aeruginosa infection	80%	10,800	11,016	11,236	11,461	11,690	11,924	12,163	12,406	12,654	12,907	13,165	13,428	13,697	13,971	14,250
Pts amenable to tx	80%	8,640	8,813	8,989	9,169	9,352	9,539	9,730	9,925	10,123	10,326	10,532	10,743	10,958	11,177	11,400
Penetration		0	0	0	0	5%	10%	15%	20%	25%	30%	30%	30%	30%	30%	30%
Pts on bronchitol		0.0	0.0	0.0	0.0	467.6	953.9	1459.5	1984.9	2530.8	3097.7	3159.6	3222.8	3287.3	3353.0	3420.1
Pts on Bronchitol (adherence)	90%	0.0	0.0	0.0	0.0	420.8	858.5	1313.6	1786.4	2277.7	2787.9	2843.7	2900.5	2958.6	3017.7	3078.1
Cost/pt/year	2%	15,530.75	15,841.37	16,158.19	16,481.36	20,000.00	20,400.00	20,808.00	21,224.16	21,648.64	22,081.62	22,523.25	22,973.71	23,433.19	23,901.85	24,379.89
Bronchitol revenues ($M)		**0.0**	**0.0**	**0.0**	**0.0**	**8.4**	**17.5**	**27.3**	**37.9**	**49.3**	**61.6**	**64.0**	**66.6**	**69.3**	**72.1**	**75.0**
18% distro, royalties		0	0	0	0	1.52	3.15	4.92	6.82	8.88	11.08	11.53	11.99	12.48	12.98	13.51
Europe																
# of patients with CF		35,000	35,700	36,414	37,142	37,885	38,643	39,416	40,204	41,008	41,828	42,665	43,518	44,388	45,276	46,182
% CF patients >18	45%	15,750	16,065	16,386	16,714	17,048	17,389	17,737	18,092	18,454	18,823	19,199	19,583	19,975	20,374	20,782
with p. aeruginosa infection	80%	12,600	12,852	13,109	13,371	13,639	13,911	14,190	14,473	14,763	15,058	15,359	15,667	15,980	16,299	16,625
Pts amenable to tx	80%	10,080	10,282	10,487	10,697	10,911	11,129	11,352	11,579	11,810	12,047	12,287	12,533	12,784	13,040	13,300
Penetration		0	0	0	0.05	10%	15%	20%	25%	30%	30%	30%	30%	30%	30%	30%
Pts on bronchitol		-	-	-	534.8	1,091.1	1,669.4	2,270.3	2,894.7	3,543.1	3,614.0	3,686.2	3,760.0	3,835.2	3,911.9	3,990.1
Pts on bronchitol (adherence)	90%	-	-	-	481.4	982.0	1,502.4	2,043.3	2,605.2	3,188.8	3,252.6	3,317.6	3,384.0	3,451.6	3,520.7	3,591.1
Cost/pt/year	1%	13,505.0	13,640.1	13,776.5	13,914.2	10,000.0	10,100.0	10,201.0	10,303.0	10,406.0	10,510.1	10,615.2	10,721.4	10,828.6	10,936.9	11,046.2
Bronchitol revenues incl distrit	0.5	-	-	-	**3.3**	**4.9**	**7.6**	**10.4**	**13.4**	**16.6**	**17.1**	**17.6**	**18.1**	**18.7**	**19.3**	**19.8**
Bronchitol revenues ($M)		-	-	-	**3.3**	**13.3**	**25.1**	**37.8**	**51.3**	**65.9**	**78.7**	**81.7**	**84.8**	**88.0**	**91.4**	**94.9**

Source: Taylor Collison estimates

The (generous) bull case model does have some accretive value to the share price, but again, we note the high unlikelihood of PXS achieving such high revenues for Bronchitol.

Figure 28

Total Revs		-	-	-	3.35	13.33	25.10	37.75	51.34	65.90	78.65	81.66	84.78	88.02	91.38	94.88
Less CoGS	15%	-	-	-	0.50	2.00	3.77	5.66	7.70	9.89	11.80	12.25	12.72	13.20	13.71	14.23
Gross profit		-	-	-	2.85	11.33	21.34	32.09	43.64	56.02	66.86	69.41	72.06	74.81	77.67	80.65
- sales costs (15%)	85%	-	-	-	0.43	1.70	3.20	4.81	6.55	8.40	10.03	10.41	10.81	11.22	11.65	12.10
Bronchitol R&D Cost		2.00	2.00	2.00	-	-	-	-	-	-	-	-	-	-	-	-
Profit after R&D		(2.00)	(2.00)	(2.00)	0.43	1.70	3.20	4.81	6.55	8.40	10.03	10.41	10.81	11.22	11.65	12.10
Tax Rate		-	-	-	0.10	0.10	0.10	0.10	0.15	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Product profits after tax		(2.00)	(2.00)	(2.00)	0.38	1.53	2.88	4.33	5.56	5.88	7.02	7.29	7.57	7.86	8.16	8.47

NPV Calculations	
Discount Rate	12.00%
NPV ($)	$15.41
NoSH (M)	317.33
NPV per Share ($)	$0.05

Source: Taylor Collison estimates

RISKS TO INVESTMENT

There are multiple risks inherent with any investment, especially in the biotechnology sector. Aside from systemic risk, there is clinical, regulatory, and commercial risk. PXS may also require significant amounts of capital if it wished to develop its own clinical programs, and the capital-raising environment is always changing. There is a risk that the necessary capital to complete development may not be readily available.

While the partnership between PXS and BI has the attributes of a company-making transaction, milestone payments due to PXS, which support the company's current valuation, are dependent on BI's timelines and decision-making process. A large, multi-national pharmaceutical could halt development of the program for any given reason, especially given the upfront payment has very little impact on BI's balance sheet. The '4728A program has been successful in a Phase 1 trial. This, however, does not guarantee success in future trials as well as successes and potential partnerships in additional indications. A potential delay in milestone payments, or even a potential decision to halt the program, would be detrimental to PXS's financial health.

PXS has not yet identified a lead LOXL2 compound, and while management has provided an indication on timing (end of 2016), this may be delayed. Set-backs in preclinical toxicology work or a Phase 1 could delay data availability on the asset, which could impact timing on potential partnerships. We think such a partnership is crucial for the future growth of PXS.

MANAGEMENT

Figure 29

Name	Position	Joined PXS	Experience
Gary Phillips	CEO, Managing Director	2003	Country and regional management roles at NVS (Hungary, Asia Pacific, Australia). >30 years operational management experience in Pharma/healthcare industry Appointed COO in 2003, CEO in 2013
David McGarvey	CFO	2002	>30 years building and funding Australian-based companies CFO of Filtration and Separations Division, US Filter; Memetec Limited
Brett Charlton	Medical Director	1998	>15 years experience in clinical trial design, management Founding medical Director of National Health Sciences Centre Co-Founder of PXS
Wolfgang Jarolimek	Head of Drug Discovery	2010	>15 years experience in pharma drug discovery Director of Assay Development and Compound Profiling at GSK
Kristin Morgan	Alliance Management	2008	19 years pharma industry in medical affairs, commercial sales
Malcolm McComas	Independent Chairman	2003	Former IB at Grant Samuel, County Natwest, and Morgan Grenfell
Will Delaat	NED	2008	Former MD Merck Australia, Former chairman Medicines Australia
Simon Buckingham	NED	2012	Former President Global Corporate and BD at Actelion

Disclaimer

The following Warning, Disclaimer and Disclosure relate to all material presented in this document and should be read before making any investment decision.

Warning (General Advice Only): Past performance is not a reliable indicator of future performance. This report is a private communication to clients and intending clients and is not intended for public circulation or publication or for the use of any third party, without the approval of Taylor Collison Limited ABN 53 008 172 450 ("Taylor Collison"), an Australian Financial Services Licensee and Participant of the ASX Group. TC Corporate Pty Ltd ABN 31 075 963 352 ("TC Corporate") is a wholly owned subsidiary of Taylor Collison Limited. While the report is based on information from sources that Taylor Collison considers reliable, its accuracy and completeness cannot be guaranteed. This report does not take into account specific investment needs or other considerations, which may be pertinent to individual investors, and for this reason clients should contact Taylor Collison to discuss their individual needs before acting on this report. Those acting upon such information and recommendations without contacting one of our advisors do so entirely at their own risk.

This report may contain "forward-looking statements". The words "expect", "should", "could", "may", "predict", "plan" and other similar expressions are intended to identify forward-looking statements. Indications of and guidance on, future earnings and financial position and performance are also forward looking statements. Forward-looking statements, opinions and estimates provided in this report are based on assumptions and contingencies which are subject to change without notice, as are statements about market and industry trends, which are based on interpretations of current market conditions.

Any opinions, conclusions, forecasts or recommendations are reasonably held at the time of compilation but are subject to change without notice and Taylor Collison assumes no obligation to update this document after it has been issued. Except for any liability which by law cannot be excluded, Taylor Collison, its directors, employees and agents disclaim all liability (whether in negligence or otherwise) for any error, inaccuracy in, or omission from the information contained in this document or any loss or damage suffered by the recipient or any other person directly or indirectly through relying upon the information.

Disclosure: Analyst remuneration is not linked to the rating outcome. Taylor Collison may solicit business from any company mentioned in this report. For the securities discussed in this report, Taylor Collison may make a market and may sell or buy on a principal basis. Taylor Collison, or any individuals preparing this report, may at any time have a position in any securities or options of any of the issuers in this report and holdings may change during the life of this document.

The preparation of this report was funded by ASX in accordance with the ASX Equity Research Scheme. This report was prepared by Taylor Collison and not by ASX. ASX does not provide financial product advice. The views expressed in this report do not necessarily reflect the views of ASX. No responsibility or liability is accepted by ASX in relation to this report.

Analyst Interests: The Analyst(s) may hold the product(s) referred to in this document, but Taylor Collison Limited considers such holdings not to be sufficiently material to compromise the rating or advice. Analyst(s)' holdings may change during the life of this document.

Analyst Certification: The Analyst(s) certify that the views expressed in this document accurately reflect their personal, professional opinion about the financial product(s) to which this document refers.

Date Prepared: November 2016
Analyst: Elyse Shapiro
Release Authorised by: Campbell Taylor

Taylor Collison Limited
Sharebrokers and Investment Advisers
A.B.N. 53 008 172 450 AFSL No. 247083

Participant of the Australian Stock Exchange Group
www.taylorcollison.com.au

ESTABLISHED 1928

Level 16, 211 Victoria Square
Adelaide, South Australia, 5000
G.P.O. Box 2046, Adelaide, South Australia, 5001
Telephone: 08 8217 3900 Facsimile: 08 8231 3506
Email: broker@taylorcollison.com.au

Level 10, 167 Macquarie Street
Sydney, New South Wales, 2000
G.P.O. Box 4261, Sydney, New South Wales, 2001
Telephone: 02 9232 1688 Facsimile: 02 9232 1677
Email: sydney1@taylorcollison.com.au