Investor Briefing

Melbourne; 22\textsuperscript{nd} September
Sydney; 24\textsuperscript{th} September

Gary Phillips CEO
Forward looking statement

This document contains forward-looking statements, including statements concerning Pharmaxis’ future financial position, plans, and the potential of its products and product candidates, which are based on information and assumptions available to Pharmaxis as of the date of this document. Actual results, performance or achievements could be significantly different from those expressed in, or implied by, these forward-looking statements. These forward-looking statements are not guarantees or predictions of future results, levels of performance, and involve known and unknown risks, uncertainties and other factors, many of which are beyond our control, and which may cause actual results to differ materially from those expressed in the statements contained in this document. Except as required by law we undertake no obligation to update these forward-looking statements as a result of new information, future events or otherwise.
Pharmaxis today
new business focus already creating value

Drug developer
- Leading position in amine oxidase chemistry and mechanism based inhibitors
- Proven capability in delivering quality programs to achieve phase 2 ready compounds
- Exciting pipeline of drug candidates for valuable targets

BD expertise
- Experienced management team and board
- Extensive Pharma industry network
- Proven capability of executing global transactions with major partners

Drug manufacturer
- Supplies Bronchitol to global markets via experienced commercial partners
- Financial risks shared
- Financial upside from accessing new markets – US, Russia
- Possibility to further rationalise manufacturing infrastructure

Financial strength
- $54m cash balance at June 2015
- Significant value milestones from existing partner deals within reach
## Pharmaxis product portfolio

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Status</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOXL2 inhibitor</strong></td>
<td>NASH, Liver &amp; kidney fibrosis</td>
<td>Lead optimisation</td>
<td>-</td>
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<tr>
<td><strong>LOXL2 inhibitor</strong></td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Lead optimisation</td>
<td>Synairgen</td>
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<tr>
<td>LOX/LOXL2 inhibitor</td>
<td>Fibrosis, cancer</td>
<td>Exploratory</td>
<td></td>
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<tr>
<td>LOX inhibitor</td>
<td>Cancer, scarring</td>
<td>Exploratory</td>
<td></td>
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<tr>
<td><strong>SSAO inhibitor</strong></td>
<td>NASH</td>
<td>Phase 1</td>
<td>Boehringer</td>
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<tr>
<td>SSAO/MAOB inhibitor</td>
<td>Neuro inflammation; Alzheimer's, MS, etc.</td>
<td>Lead candidate selected</td>
<td>-</td>
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<tr>
<td>SSAO/MPO inhibitor</td>
<td>Respiratory inflammation; Asthma, COPD</td>
<td>Lead optimisation</td>
<td>-</td>
</tr>
<tr>
<td>Orbital</td>
<td>Dry powder inhalation device</td>
<td>Phase 1</td>
<td>-</td>
</tr>
<tr>
<td>ASM8</td>
<td>Asthma</td>
<td>Phase 2</td>
<td>-</td>
</tr>
<tr>
<td>Bronchitol US</td>
<td>Cystic Fibrosis</td>
<td>Phase 3 study underway</td>
<td>Chiesi</td>
</tr>
<tr>
<td>Bronchitol EU</td>
<td>Cystic Fibrosis</td>
<td>Marketed</td>
<td>Chiesi</td>
</tr>
<tr>
<td>Bronchitol rest of world</td>
<td>Cystic Fibrosis</td>
<td>Marketed: Australia, CEE Approval pending; Brazil, Russia</td>
<td>Various</td>
</tr>
<tr>
<td>Aridol</td>
<td>Asthma diagnosis</td>
<td>Marketed: Australia, EU, Korea</td>
<td>Various</td>
</tr>
</tbody>
</table>
**Pharmaxis drug discovery strategy**

**Building a biotech powerhouse in fibrosis and inflammation**

### Strategy

**Drug discovery:**
- Build a regional biotech powerhouse in fibrosis and inflammation
  - Multiple drugs from in house amine oxidase chemistry platform
  - Develop to phase 1 or 2

**Partnering:**
- Create value via
  - Licence out to Big Pharma with attractive 1st in class drugs post phase 1 or 2
  - Collaborate to de-risk and accelerate PXS programs
  - Collaborate on in-licensing programs

### Achievements to date

**Drug discovery:**
- First in class NASH drug taken to phase 1
- Three further candidates in lead optimisation phase

**Partnering:**
- In house BD expertise lands valuable deal with Boehringer Ingelheim - A$39m upfront, total > A$750m
- Collaboration with Synairgen Research plc for early stage fibrosis program to widen spread of indications, enhance time to value inflection and spread risk
Valuing the Pharmaxis pipeline
Building a biotech powerhouse in fibrosis and inflammation

Opportunities

- Milestone payments from Boehringer as PXS4728A progresses in NASH
  - next: start of phase 2 ~end 2016

- Synairgen LOXL2 collaboration in pulmonary fibrosis to phase 1 or 2 and subsequent partnering
  - next: commencement of formal preclinical program ~ beginning 2016

- Pharmaxis LOXL2 program for NASH and other fibrotic diseases at lead optimisation stage
  - next: commencement of formal preclinical program ~beginning 2016

Speakers

- Professor Jacob George,
  *University of Sydney, Westmead Hospital*
  - NAS epidemiology, diagnosis and morbidity
  - New treatments
  - Rationale for SSAO and LOXL2.

- Wolfgang Jarolimek,
  *Head of Drug Discovery, Pharmaxis*
  - The Pharmaxis drug discovery process
  - SSAO inhibitor – new data
  - Status of Pharmaxis’ LOXL2 programs.

- Simon Buckingham,
  *Non-Executive Director, Pharmaxis*
  - Insights on transacting with big pharma
  - Biotech anti-fibrotic deal values
  - Inside the Boehringer Ingelheim deal
Clinical perspective
Unmet needs in fatty liver disease (NASH)

Jacob George

STORR LIVER CENTRE

Westmead Millennium Institute for Medical Research

THE UNIVERSITY OF SYDNEY
Why do we treat liver diseases

Progression of fibrosis

- Normal
- Inflamed
- Fibrotic
- Cirrhotic

May be reversible process with treatment of underlying disease

Extensive fibrosis and formation of repetitive nodules
Cirrhosis is not good
What is NAFLD?
NAFLD

- A spectrum of disorders characterized by predominantly steatosis (liver fat)
- In practice
  - Can worsen any liver disease (including alcohol)
The spectrum of NAFLD

- Simple steatosis
  - 5-10% CVD, CKD, T2DM

- NASH
  - 30-38% Fibrosis
  - 5-20% over 20 years Cirrhosis
    - 3-5%/year HCC

References:
Adams, LA. J Hepatol 2005
Ekstedt M, Hepatology 2006
Fassio, E Hepatology 2004
Harrison, SA Gastroenterol 2003
Why does NASH occur?

Global prevalence of Overweight/obesity

- 3.4 m deaths; 3.9% of years of life lost, 3.8% of DALYs; 1769 reports
- Global prevalence 1980-2013: 29% in men to 37%; Women 30% to 38%; 47% increase in children
- >50% in women from Kuwait, Kiribati, Micronesia, Libya, Qatar, Tonga, Samoa

Lancet 2014; 384: 766–81
The problem of obesity: US Data from CDC
Rate of obese adults by US State (BMI ≥30)
GLOBAL EPIDEMIOLOGY OF NAFLD/NASH

- **France:** NAFLD: 60%  NASH: 33%  
  De Ledinghen, J Hepatol 2006
- **Spain:** NAFLD: 44%  
  Caballeria, Eur J Gastro 2012
- **Brazil:** NAFLD: 42%  NASH: 27%  
  27% severe fibrosis/cirrhosis  
  Cotrim HP, Ann Hepatol 2012
- **India:** NAFLD 32%  
- **Japan:** NAFLD 29%  
  Jimba S Diabet Med 2005

- **Texas:** 46% NAFLD  12% NASH  
  3% severe fibrosis/cirrhosis  
  Williams Gastroenterology 2011
Survival: Study of Health in Pomerania (N= 4160)

Haring, Hepatology 2009
Life expectancy in NAFLD

Overall survival of subjects in the study with NASH or bland steatosis. 
n=256; median follow up 24 years

Soderberg et al. Hepatology 2010
NASH Cirrhosis: Poor outcomes

N=247; F3/4
F/U: 85 months (7 years)
19.4% liver related complications (2.8% pa)
13.4% deaths/OLT
A Clinically Silent Disease

• **Symptoms:**
  – None 20 - 77%
  – Right upper quadrant pain 25 - 48%
  – Fatigue 50 - 75% (Obstructive sleep apnea in 40%)

• **Signs:**
  – Overweight/Obese 85 - 95%
  – Acanthosis nigricans 10 -15%
  – Hepatomegaly 25 - 50%

• **Laboratory:**
  – ALT, AST - modest elevation
  – “Normal enzymes” (up to 80% of NAFLD)

• **Radiological:**
  - **Ultrasound:** echogenic parenchyma; beam attenuation
Diagnosis

Liver ultrasound
Liver tests
Fibroscan
Liver biopsy
Principals of treatment

• Reduce liver fat aka IR aka obesity
  – Lifestyle intervention
  – Bariatric surgery
• Reduce liver inflammation
• Reduce liver fibrosis
Current treatment

Steatohepatitis resolution

Two points improvement in NAS

* *Mantel-Haenszel $\chi^2$ test for trend

So the problem is:

• **Big!!!!!!**
  
• Obesity associated NCD exceeds infectious disease as commonest global cause of death
• Can only be managed (not prevented), unless we can change
  – Behaviour –Diet, exercise, PA
Potential treatments

• PPARg agonists (anti-diabetic agents)
• Incretins, Glut2-I
• Vitamin E
• FXR agonists
  – Intercept, Gilead
• PPAR alpha-delta antagonists
  – Genefit
# Treatment trials for NASH

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>MoA</th>
<th>RoA</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raptor</td>
<td>RP103</td>
<td>Antioxidant - cysteine depleting agent</td>
<td>Oral</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Zydus-Cadila</td>
<td>Saroglitazar</td>
<td>PPAR agonist $(\alpha, \gamma)$</td>
<td>Oral</td>
<td>Phase 3</td>
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<tr>
<td>Novo Nordisk</td>
<td>Liraglutide</td>
<td>GLP-1</td>
<td>SubQ</td>
<td>Phase 2</td>
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<tr>
<td>Takeda</td>
<td>Pioglitazone</td>
<td>PPAR agonist</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Islet Sciences</td>
<td>Remogliflozin etabonate</td>
<td>SGLT-2 inhibitor</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Aptalis Pharma</td>
<td>Ursodeoxycholic acid</td>
<td>Bile acid</td>
<td>Undefined</td>
<td>Phase 2</td>
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<tr>
<td>Gilead</td>
<td>Simtuzumab</td>
<td>LOXL2 antibody</td>
<td>IV and SubQ</td>
<td>Phase 2</td>
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<tr>
<td>Conatus</td>
<td>Emricasan</td>
<td>Caspase protease inhibitor</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Galmed</td>
<td>Aramchol</td>
<td>Synthetic fatty acid/bile acid conj</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Tobira</td>
<td>Cenicriviroc</td>
<td>Dual CCR2/CC5 antagonist</td>
<td>Oral</td>
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<tr>
<td>Genfit</td>
<td>GFT 505</td>
<td>PPAR alpha/delta agonist</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Intercept</td>
<td>OCA</td>
<td>FXR agonist</td>
<td>Oral</td>
<td>Phase 2</td>
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<td>Phenex</td>
<td>PX 104</td>
<td>FXR agonist (non bile acid)</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Mochida</td>
<td>Icosapent ethyl ester</td>
<td>Caspase protease inhibitor</td>
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<td>Immuron</td>
<td>IMM 124E</td>
<td>Immunomodulators</td>
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<td>KT&amp;G Life Sciences</td>
<td>MB 12066</td>
<td>Sirtuin stimulants</td>
<td>Oral</td>
<td>Phase 2</td>
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</tbody>
</table>

Adis R&D Insight, Thomson Reuters Cortellis
### Treatment Trials for NASH

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<tr>
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<th>Phase</th>
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<tr>
<td>PharmaKing</td>
<td>Oltipraz</td>
<td>Fatty acid inhibitor</td>
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<td>Novartis</td>
<td>Pradigastat</td>
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<td>Therapix</td>
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<td>CD3 antigen</td>
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<td>Antipodean</td>
<td>Mitoquinone</td>
<td>Antioxidant</td>
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<tr>
<td>KT&amp;G Life Sciences</td>
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<td>Naia</td>
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<td>Undefined</td>
<td>Phase 2</td>
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<td>Kadmon</td>
<td>KD 025</td>
<td>ROCK2 inhibitor</td>
<td>Oral</td>
<td>Phase 1</td>
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<td>Phenex</td>
<td>PX 102</td>
<td>FXR agonist</td>
<td>Oral</td>
<td>Phase 1</td>
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<tr>
<td>Shire</td>
<td>SHP 626</td>
<td>ASBT inhibitor</td>
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<td>Phase 1</td>
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<td>Durect</td>
<td>DUR-928</td>
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<td>Oral</td>
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<td>Daewoong</td>
<td>DWP-10292</td>
<td>Undefined small molecule</td>
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<td>Gilead</td>
<td>GS-4997</td>
<td>ASK1 inhibitor</td>
<td>Oral</td>
<td>Phase 1</td>
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<td>TaiwanJ</td>
<td>JKB-121</td>
<td>TLR-4 antagonist</td>
<td>Oral</td>
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<td>Madrigal</td>
<td>MGL-3196</td>
<td>THR beta agonist</td>
<td>Oral</td>
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<td>Virobay</td>
<td>VBY-376</td>
<td>Cathepsin B inhibitor</td>
<td>Oral</td>
<td>Phase 1</td>
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<td>La Jolla</td>
<td>LGPC-1010</td>
<td>Galectin-3</td>
<td>Oral</td>
<td>Preclinical</td>
</tr>
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</table>
Incretin-based therapies (Liraglutide)

The LEAN Study:

- Multicentre, 26 Liraglutide, 26 placebo
- Double-blinded, randomised, placebo-controlled phase II trial.
- Primary endpoint: Resolution of definite NASH and no worsening F

Overweight patients with NASH with or without diabetes

SC injections of 1.8mg liraglutide

Liraglutide-placebo

48 Weeks

Armstrong MJ, EASL 2015
Liraglutide and NASH

As expected with liraglutide, improvements were also seen in BMI and fasting glucose levels.

No treatment related side effects
FXR effects on lipid metabolism

- FXR
- hSHP
- SREBP-1c
- TG/FA synthesis
- Plasma TG/FFA

- FXR
- hPPARδ
- apoc-II
- apoc-III
- ANGPTL3
- LPL activity
- TG clearance

- FXR
- VLDLR
- hSyndecan-1

- FXR
- SR-BI
- HDL clearance

- FXR
- SR-BI
- Plasma HDL-C

Changes in histological features of the liver after 72 weeks of Obeticholic acid treatment

- Fibrosis: P=0.004
- Hepatocellular ballooning: P=0.03
- Steatosis: P=0.001
- Lobular inflammation: P=0.006

Systemic FXR agonists have issues!

- FLINT Study:
  - Increased LDL, decreased HDL
  - Increased hepatic insulin resistance
  - Pruritus
- The first two problems are likely due to FXR activation in liver
- Pruritus due to Obeticholic Acid being a bile acid
GFT505, New dual PPARα/δ–non PPARγ compound

- GFT 1007 main active circulating metabolite
- **PPAR α activity** (15 nmol vs 30µmol fenofibrate); **PPAR δ activity** (75 nmol vs 1 nmol GW501516)
- Extensive enterohepatic cycling and liver targeted
- No induction of PPAR α or δ genes in muscle
- No PPAR γ activity (no adiponectin induction)
GFT505, Metabolic effects in abdominally obese and prediabetic patients

Cariou, Diabetes Care 2011
Cariou, Diabetes Care 2013
Targeting inflammation

• Vascular adhesion protein-1 (VAP-1)
  – Semicarbazide-sensitive amine oxidase (SSAO)
  – Promotes white cells entering injured tissues
  – Promotes inflammation
  – Promotes oxidative stress
Targeting inflammation

Weston et al JCI 2014
Targeting fibrosis
Lysyl Oxidase-Like 2: LOXL2

SIMTUZUMAB

- Humanized monoclonal antibody that binds LOXL2
- Half life of ~10-20 days when dosed iv
- SC dose is well tolerated
- Safe and well tolerated in > 300 subjects some for >1 year of exposure
- To date has been dosed safely in 57 patients with liver fibrosis

Courtesy J Bornstein, Gilead
Reduction of Fibrosis and Myofibroblasts

♦ AB0023 administered concurrently with CCL4, Balb/C mice
♦ Significant reduction of bridging fibrosis with AB0023 (F1 rather than F3)
♦ Reduction of myofibroblasts, LOXL2 in porto-portal bridges

Courtesy J Bornstein, Gilead

Summary

• NAFLD/NASH are common
• Major cause of liver disease burden
• Significant cause of liver cancer
• Currently an unmet therapeutic need
• **Target:** fat, inflammation, fibrosis
• Major area for therapeutic drug discovery
Drug Discovery @ Pharmaxis

Melbourne; 22nd September
Sydney; 24th September

Wolfgang Jarolimek, PhD
Head Drug Discovery
Drug Discovery and Development

Target validation

HTS screening

Drug Discovery

Pre-clinical

Clinical trials

FDA review

Clinic

The standard process

http://www.ncats.nih.gov/
Drug Discovery and Development

strategy to improve chances of success

Pharmaxis strategy:

Validated targets
- Compelling pre-clinical evidence
- Clear role in human disease

Tractable chemical starting points
- Small molecules with good properties
- Clinically proven mechanisms

High success in translation to human trials
- Predictive pharmacokinetics
- Plasma biomarker

Accelerated clinical development
- All relevant expertise at Pharmaxis
- Phase 1 run in Australia

Drug Discovery Pre-clinical Clinical trials FDA Clinic review
6.5 years 6 years 1.5 years
http://www.ncats.nih.gov/
Compound progression

@ Pharmaxis and Contract Research Organisations (CRO)

@ CRO and Pharmaxis

Synthesis of compounds

Enzymatic assays

Cellular assays

In vitro and in vivo Pharmacokinetic assays

Disease model

Scale up

Toxicity

Phase 1
**Compound progression**

**Lead optimisation**
1-3 years

1. **Synthesis of compounds**
2. **Enzymatic assays**
3. **Cellular assays**
4. **In vitro and in vivo Pharmacokinetic assays**
5. **Disease model**
6. **Scale up**
7. **Toxicity**
8. **Phase 1**

**Pre-clinical development**
1.5-2 years

**Phase 1**
8 months
Phase 1 Clinical trial: PXS-4728A
(Boehringer partnered drug)

Single ascending dose and multiple ascending dose placebo-controlled double-blind phase 1 study of PXS-4728A administered orally in healthy adult males (PXS-4728A-101)

Primary objective:

To evaluate the safety and tolerability of single ascending or repeated oral doses of PXS-4728A.
  - Recording of adverse events throughout the study.
  - Change from baseline in:
    • Electrocardiogram (ECG) readings
    • Clinical monitoring of blood pressure (BP)
    • Heart rate (HR)
    • Laboratory assessments
**Secondary objectives:**

To evaluate plasma pharmacokinetic parameters after single and repeat oral dosing of PXS-4728A:
- $\text{AUC}_{(0-t)}$ and $\text{AUC}_{(0-inf)}$
- $C_{\text{max}}$ – maximum concentration
- $T_{\text{max}}$ – time to maximum observed plasma drug concentration
- $t_{1/2}$ – Terminal half-life
- Accumulation ratio (For Part B only)

Assessment of plasma pharmacodynamic parameters after single and repeat dosing of PXS-4728A:
- SSAO activity in plasma using enzymatic assay
- SSAO concentration in plasma using ELISA method
Phase 1 Clinical trial: PXS-4728A
Single ascending dose trial

- Fast uptake <1hr to peak
- Linear dose-dependent increase in plasma concentration
- Fast elimination $t_{1/2} < 2$ hrs

- Fast inhibition
- Dose-dependent decrease in enzymatic activity
- Long-lasting inhibition >1day
Phase 1 Clinical trial: PXS-4728A

Outcomes (Single and repeated dose trials):

PXS-4728A successfully completed the Phase 1 study

- Well tolerated, no safety signals in single or repeated dosing
- High oral bioavailability from simple formulation
- Pharmacokinetic properties show expected brief exposure
- Enzyme activity is inhibited > 24 hrs by a single daily dose <10mg
- SSAO/VAP-1 (AOC3 gene): a biomarker for diseases and efficacy of PXS-4728A

PXS-4728A fulfilled all pre-clinical expectations

Boehringer Ingelheim proceeds with the clinical development

Joint presentation at international congress in 2016
LOXL2 and/or LOX and fibrosis

Allosteric inhibition of lysyl oxidase–like-2 impedes the development of a pathologic microenvironment

Publication from Arresto which formed the scientific basis of its acquisition by Gilead in 2010

LOXL2 inhibition decreases hepatic fibrosis

LOX inhibition decreases hepatic fibrosis

Excellent target validation for lysyl oxidase inhibitors
Rat liver fibrosis model

Liver function

Concentration of liver enzyme (ALT) in the plasma is a biomarker for liver disease progression.

- Improvements in liver function are a surrogate for human liver trials
- Imatinib (Gleevec) is a gold standard in animal models
- Pharmaxis LOXL2 inhibitors perform as well but are given once a day at a lower dose
Collaboration with Synairgen

• True research collaboration with experts in respiratory diseases and fibrosis.
• Synairgen will lead and finance pre-clinical development of one LOXL2 inhibitor for IPF.
• Joint Research Committee will oversee research and development for IPF.
• Pharmaxis maintains options to develop LOX/LOXL2 inhibitors for other fibrotic diseases or cancer.

### Pre-clinical candidate profile

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td><strong>Potency</strong></td>
<td>• <em>In vitro</em> pIC50 against human recombinant LOXL2</td>
</tr>
<tr>
<td></td>
<td>• Mechanism-based inhibitor criteria fulfilled (irreversible, substrate competition, time dependency)</td>
</tr>
<tr>
<td></td>
<td>• No difference against native human native protein and mouse and/or rat LOXL2</td>
</tr>
<tr>
<td><strong>Selectivity</strong></td>
<td>• Selectivity for LOXL2 over LOX</td>
</tr>
<tr>
<td></td>
<td>• Selectivity versus other amine oxidases</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>• Eurofins / CEREP panel screen:</td>
</tr>
<tr>
<td><strong>DMPK / ADME</strong></td>
<td>• CYP inhibition (human)</td>
</tr>
<tr>
<td></td>
<td>• Hepatocyte stability (dog, rat and human)</td>
</tr>
<tr>
<td></td>
<td>• Plasma stability (dog, rat and human)</td>
</tr>
<tr>
<td></td>
<td>• Plasma protein binding (dog, rat and human)</td>
</tr>
<tr>
<td></td>
<td>• Oral bioavailability rat and dog</td>
</tr>
<tr>
<td></td>
<td>• t1/2 in plasma after oral and intravenous dosing</td>
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<tr>
<td><strong>Pharmacology</strong></td>
<td>• Efficacy in the Bleomycin-induced lung injury</td>
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<td></td>
<td>• Efficacy in ex vivo tissue model using IPF cells demonstrating inhibition of crosslink formation</td>
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<tr>
<td><strong>Toxicology</strong></td>
<td>• Functional hERG</td>
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<tr>
<td></td>
<td>• Negative AMES test</td>
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<tr>
<td></td>
<td>• HepG2 cell Health assay</td>
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<tr>
<td></td>
<td>• Phospholipidosis in HepG2</td>
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</tbody>
</table>

• True research collaboration with experts in respiratory diseases and fibrosis.
• Synairgen will lead and finance pre-clinical development of one LOXL2 inhibitor for IPF.
• Joint Research Committee will oversee research and development for IPF.
• Pharmaxis maintains options to develop LOX/LOXL2 inhibitors for other fibrotic diseases or cancer.
Fibrosis is due to accumulation of collagen. Hydroxyproline is a surrogate measurement for collagen.

- Total collagen as measured by hydroxyproline was significantly reduced by Pharmaxis LOXL2 inhibitors.
- PXS-B is distributed to the liver and not present in other tissues.

**Graph:**
- X-axis: treatment groups: control, sham, Imatinib 25 mg/kg twice a day, prophylactic PXS-C 3 mg/kg, PXS-B 3 mg/kg.
- Y-axis: worsening hydroxyproline in [µg/mg] for Week 4-6.
Rat liver fibrosis model

**Total collagen**

Fibrosis is due to accumulation. Hydroxyproline is a surrogate measurement for collagen.

The graph shows hydroxyproline levels over weeks 4-6 for different treatments:
- Control
- Sham
- Imatinib 25 mg/kg, twice a day, prophylactic
- PXS-C 3mg/kg
- PXS-B 3mg/kg

**Key Points**
- **PXS-C All-rounder**
  - Reduces various types of fibrosis
- **PXS-B Targeted Inhibitor**
  - Reduces liver/kidney fibrosis
  - Different pharmacology (LOX family)
  - Different distribution
LOXL2 program
Achievements

- Small molecule selective LOXL2 inhibitors for the treatment of fibrosis.
- Efficacy in pre-clinical models and drug-like properties.
- Collaboration with Synairgen on the development of LOXL2 inhibitors for the treatment of IPF.
- Pharmaxis’ focus on other fibrotic indications and cancer.
- The first molecules are entering full pre-clinical development and Phase 1 ready in 1H 2017.
Business Development Perspectives

Melbourne; 22\textsuperscript{nd} September
Sydney; 24\textsuperscript{th} September

Simon Buckingham
Non executive director
Overview

- Perspectives on deal-making in Big Pharma
- The Pharmaxis experience
- Fibrosis deals 2010-2015
- The Pharmaxis/ Boehringer Ingelheim deal
Drug Development = Challenge!

Source: Pharmaceutical Research and Manufacturers of America
Drivers for change in pharma industry

1. Globalization

2. Increasing R&D costs

3. Threat of revenue loss/patent expiry

4. Tougher political and regulatory environment

5. Demanding financial markets

Intensified Competition Industry Consolidation
Key factors

- Increased R&D cost to bring one drug to market - $2.6B (Tufts 2014)
- Research “stagnation” in large bureaucracies
- Drug approval recovering, but increased challenges – risk averse agencies, higher bar for approval, black-box warnings, post-marketing commitments and market withdrawals
- Revenue loss through patent expiry – US$44B in 2015
FDA approval rates

Exhibit 4

NMEs + NBEs approved

Other companies

Historic big pharma*

*ABBV, AMGN, AZN, BAY, BMY, GSK, JNJ, LLY, MRK, NVS, PFE, ROC, SNY
Consequences

- Greater portion of R&D funding on licensing – now over 20%
- Fear of failure = More irons in fire
- Pay for success
- Increased number of collaborations/ alliances – now well over 100 Pharma/ Biotech per year
- External products account for >2/3 of Big Pharma sales – discovery deals, licensing, M&A
Deal competition

- More companies chasing fewer good targets
- Licensees more active in driving the process
- Fewer bargains
  - existing deal benchmarks known to both sides
- More creative, accommodating, collaborative deals
- Rise of option deals
Law of supply & demand
Deals are expensive!

- **Upfronts**
- **Total milestones**
- **Royalty rates**
  - “Double Digit”
  - “Single Digit”
Nasdaq Biotech Index
2 year performance

Genfit Pharma (phase 2) mkt cap: €958m

Intercept Pharma (PBC: approval; NASH phase 2) mkt cap: US$4.6B
The process

Screen > Evaluate > Get > Manage

Identification
- Proactive/reactive
- Establish visibility
- Contact sources
- Proactive PR
- Scouting at public and private labs
- Network
- Funnel and screen opportunities

Scientific evaluation, prioritization
- Strategic fit
- Science
- Clinical
- Manufacturing
- Marketing
- IP position
- Competition
- Economic
- Due diligence

Corporate BD
- Transaction preparation
- Term negotiations, ‘Pricing’
- Due diligence including exit strategy(ies)
- Contract negotiation

Value creation
- Alliance planning and organization
- Alliance kick-off
- Implementation, governance
Company and product filter

Strategic Fit
Science / Innovation / Unmet Need / Cultural Fit

Detailed Assessment
IP / Manufacturing / Business Case / Structure of Deal / Timing / Portfolio Fit

Due Diligence
Terms

DEAL
The Pharmaxis experience

- Novel compound, high unmet need, large patient pool – gets attention!

- Proof of concept and scientific/clinical advocacy crucial

- Understand partner needs/dynamics – beware “Not Invented Here” mentality!

- Negotiations only after extensive due diligence

- Personal relationships and need for an internal advocate/champion

- Getting senior management over the line!
## Fibrosis deals 2010-2013

<table>
<thead>
<tr>
<th>Pharma</th>
<th>Biotech</th>
<th>Indication/Asset</th>
<th>Phase</th>
<th>Deal Terms</th>
</tr>
</thead>
</table>
| Gilead | Arresto | IPF, NASH, Cancer | Phase 1 | - Paid $225M to acquire co.  
- Including monoclonal antibody manufacturing and research sites |
|        |         | LOXL2 antibody   |       |            |
|        |         | Anti TGF beta antibody |       |            |
| Biogen | Stromedix | Fibrosis | Phase 2 ready | - Paid $75M upfront to acquire co.  
- Up to $487M total in development and sales milestones; No royalties  
- Multiple indications |
| Idec   |         |                 |       |            |
|        |         | Anti TGF beta antibody |       |            |
| BMS    | Amira  | IPF/ Fibrosis   | Phase 2 ready | - Paid $325M to acquire the two assets  
- Up to $150M in additional milestones |
|        |         | LPA1 antagonist - small molecule  
(Also preclinical asset for neuropathic pain and cancer) |       |            |
# Fibrosis deals 2014

<table>
<thead>
<tr>
<th>Pharma</th>
<th>Biotech</th>
<th>Indication/Asset</th>
<th>Phase</th>
<th>Deal Terms</th>
</tr>
</thead>
</table>
| BMS    | Galecto | IPF                                  | Phase 1 | • Option to license  
• Total payments up to **$444M**  
• Includes option fee and exercise fee  
• Clinical/ regulatory milestones |
|        |         | TD139 - novel inhaled galectin-3 inhibitor |       |                                                                             |
| Shire  | Fibrotech| Diabetic nephropathy/fibrosis         | Phase 1b | • Company acquired for **$75M**  
• Total payments up to **$482M**  
• No royalties/ commercial milestones |
|        |         | FT011                                 |       |                                                                             |
| Shire  | Lumena  | Cholestatic liver disease - LUM001    | Phase 2 | • Company acquisition for **$260M**  
• 2 late stage assets |
|        |         | NASH - LUM002                         |       |                                                                             |
# Fibrosis deals 2015

<table>
<thead>
<tr>
<th>Pharma</th>
<th>Biotech</th>
<th>Indication/Asset</th>
<th>Phase</th>
<th>Deal Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>Promedior</td>
<td><strong>IPF and Myelofibrosis</strong>&lt;br&gt;PRM151 - recombinant human pentraxin-2 protein</td>
<td>Phase 2 (in progress)</td>
<td>• Total payments up to <strong>$1.25B</strong>&lt;br&gt;• Upfront cash for right to acquire co&lt;br&gt;• Exercise fee&lt;br&gt;• Clinical/ reg milestones</td>
</tr>
<tr>
<td>Gilead</td>
<td>Phenex</td>
<td><strong>NASH</strong>&lt;br&gt;Farnesoid X receptor - small molecule</td>
<td>Phase 2 (in progress)</td>
<td>• Total deal value <strong>$470M</strong>&lt;br&gt;• Asset acquisition&lt;br&gt;• Undisclosed upfront payment, development and commercial milestones. No royalties</td>
</tr>
<tr>
<td>AZ</td>
<td>Regulus</td>
<td><strong>NASH</strong>&lt;br&gt;MicoRNA (undisclosed)</td>
<td>Preclin</td>
<td>• <strong>$125M per compound</strong> includes development and commercial milestones&lt;br&gt;• $2.5M for option to license RG-125&lt;br&gt;• $3M paid before for rights to option 3 compounds in discovery alliance.</td>
</tr>
</tbody>
</table>
Boehringer Ingelheim
Acquisition of PXS4728A

Acquisition (May 2015).
• €27.5m (~A$39m)

Commencement of phase 2 and 3
• up to total €55m (~A$80m)

Filing, regulatory & pricing approvals
• up to total €140m (~A$200m)

Second indication
• additional total milestone payments (€195m)

Earn-out payments on annual net sales
• tiered % starting in high single digits; milestones

- **Competitive deal**
  - Demonstrates PXS ability to negotiate valuable global deals
  - Total potential payments to approval for 2 indications: €418.5m (~A$600M),
  - Plus potential sales milestones, and potential earn-out at high single digit % of sales

- **Excellent partner**
  - Boehringer leaders in metabolic disease
  - Industry leading development times
  - Boehringer responsible for all development, and commercialisation activities

- **External validation of PXS drug discovery**
Summary

- Boehringer Ingelheim deal:
  - Great terms, but excellent Phase 1 asset
  - A$39M upfront
  - Total potential > A$600M
- Clear internal strategy to build fibrosis/inflammation powerhouse
- Drug discovery team delivering – Phase 2 ready product; array of novel/innovative leads
- Proven business development ability:
  - Extensive international network
  - License to Big Pharma (BI)
  - Novel research collaboration (Synairgen)