Insights to Fibrosis Drug Discovery & Development

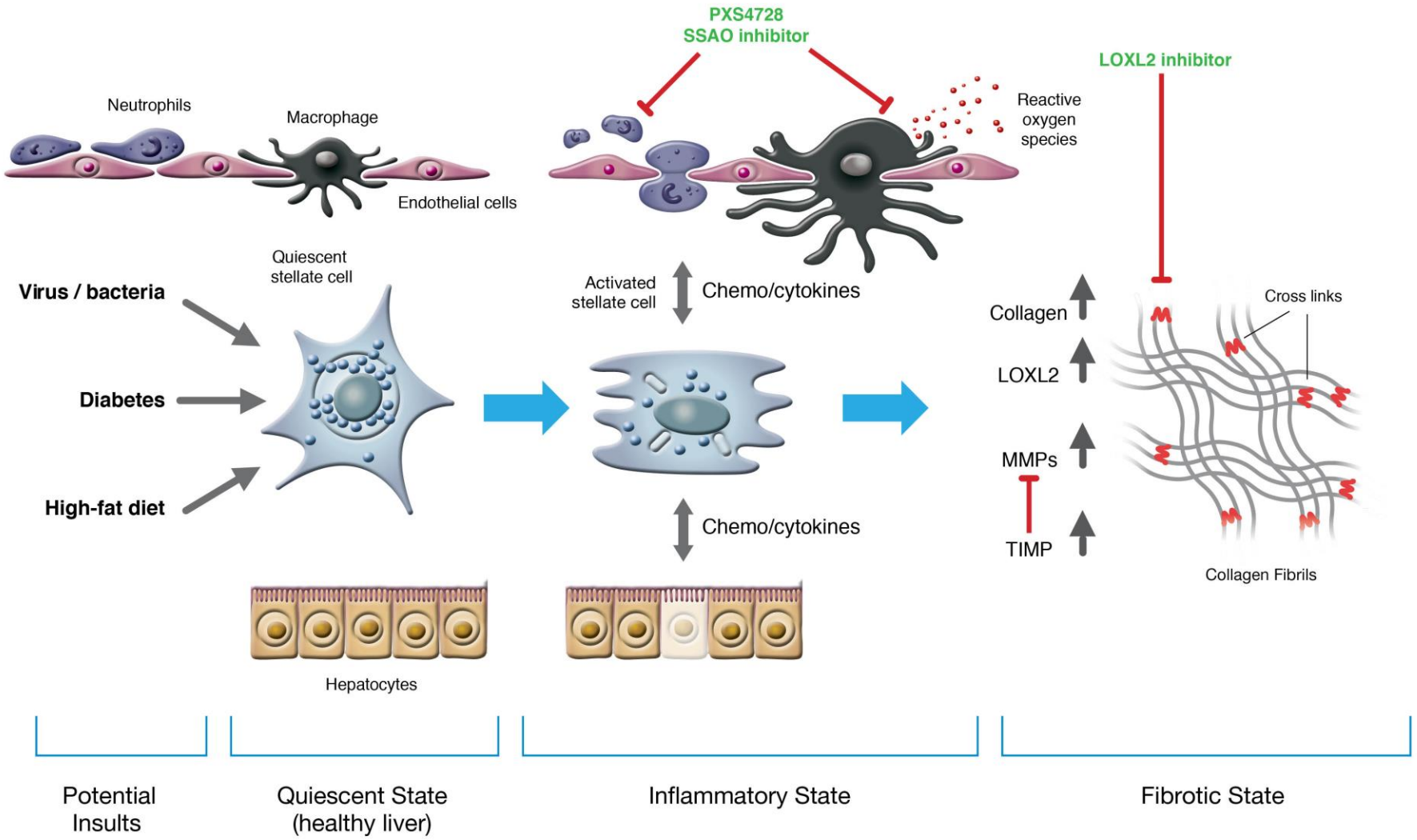
Gary Phillips, Pharmaxis CEO

Bioshares Biotech Summit, July 2017

Presentation Overview

- Mechanism of action - NASH
- SSAO inhibitor (anti inflammatory)
- LOXL2 inhibitor (anti fibrotic)
  - Why target LOXL2?
  - Differentiation against antibody
  - Pre candidate Profile
- What does Big Pharma want?

Drugs targeting NASH → Cirrhosis



pharmaxis

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SSAO for NASH

SSAO inhibitor PXS4728A sold to Boehringer Ingelheim in May 2015

PXS-4728A

- Mechanism based inhibitor of SSAO
  - Small molecule oral drug
  - Important pathway in several inflammatory diseases of the liver, kidney, heart, eye and CNS.
- Development status
  - Pharmaxis discovery – patent filed 2012
  - Effective in pre clinical models of NASH and airway inflammation
  - Phase 1 study reported
    - orally bioavailable
    - long lasting enzyme inhibition after single dose
    - progressive dose response
  - Phase 2 NASH trial scheduled Q3 2017

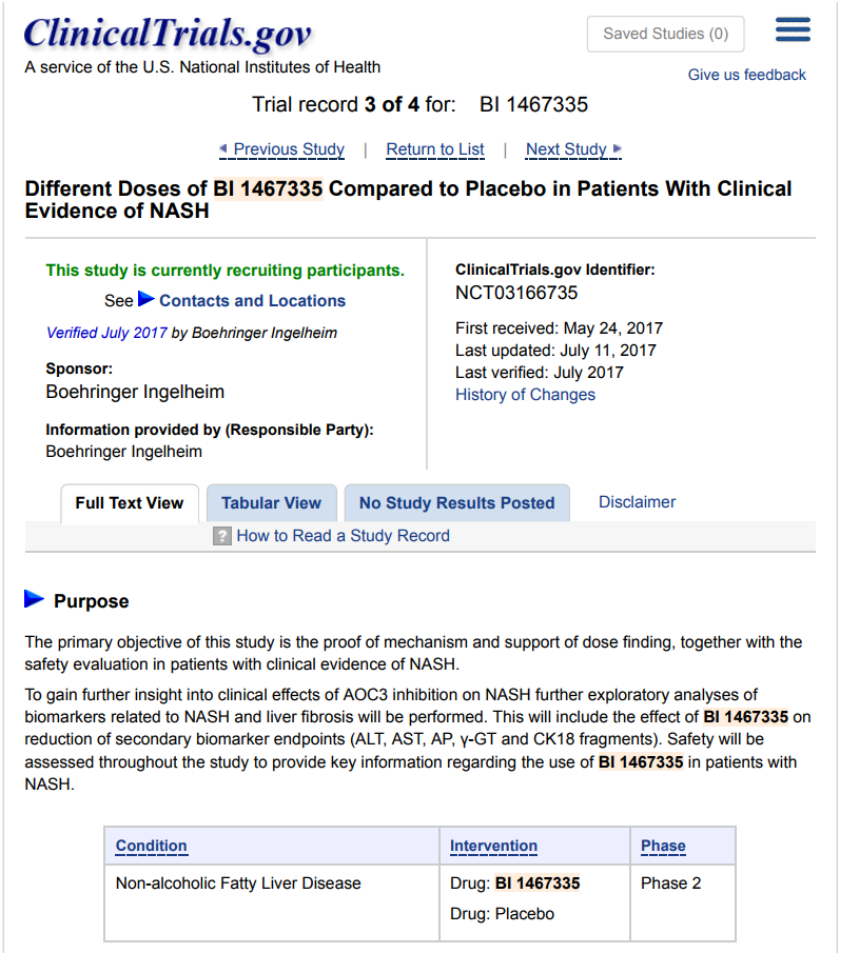
End of Phase 1 deal with Boehringer

- Potential milestones to approval: €418.5m (~A$600m)
  - Upfront (May 2015): €27.5m (~A$39m)
  - 1st Indication (NASH)
    - Commencement of phase 2 €18m (~A$27m) and phase 3: €37m
    - Filing, regulatory & pricing approvals: total €140m(~A$200m)
  - 2nd indication (commercial in confidence)
    - Commencement of phase 2: €10m
    - Total milestone payments to approval: €195m (~A$280m)
- Earn-out payments on annual net sales
  - Tiered percentages increasing from high single digits
  - Plus sales milestones

External validation of PXS drug discovery and ability to negotiate valuable global deals

Boehringer NASH study

Recruitment open



ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Saved Studies (0)

Give us feedback

Trial record **3 of 4** for: BI 1467335

Previous Study | Return to List | Next Study

Different Doses of BI 1467335 Compared to Placebo in Patients With Clinical Evidence of NASH

This study is currently recruiting participants.

See Contacts and Locations

Verified July 2017 by Boehringer Ingelheim

Sponsor:
Boehringer Ingelheim

Information provided by (Responsible Party):
Boehringer Ingelheim

ClinicalTrials.gov Identifier:
NCT03166735

First received: May 24, 2017
Last updated: July 11, 2017
Last verified: July 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer

How to Read a Study Record

Purpose

The primary objective of this study is the proof of mechanism and support of dose finding, together with the safety evaluation in patients with clinical evidence of NASH.

To gain further insight into clinical effects of AOC3 inhibition on NASH further exploratory analyses of biomarkers related to NASH and liver fibrosis will be performed. This will include the effect of **BI 1467335** on reduction of secondary biomarker endpoints (ALT, AST, AP, γ-GT and CK18 fragments). Safety will be assessed throughout the study to provide key information regarding the use of **BI 1467335** in patients with NASH.

Condition	Intervention	Phase
Non-alcoholic Fatty Liver Disease	Drug: **BI 1467335** Drug: Placebo	Phase 2

- 150 patients with moderate to severe steatosis
- 4 doses placebo controlled
- 12 week duration
- proof of mechanism and support of dose finding
- safety evaluation in patients with clinical evidence of NASH
- 1st patient in triggers €18m milestone payment.

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Target Validation of LOXL2 in Fibrosis
Human diseases, antibody and KO mice

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Comparative analysis of lysyl oxidase (like) family members in pulmonary fibrosis

Received: 13 December 2016
Accepted: 14 February 2017

Verena Aumiller[1], Benjamin Strobel[2], Merrit Romeike[1], Michael Schuler[2], Birgit E. Stierstorfer[2] & Sebastian Kreuz[1]

Gut Online First, published on January 10, 2017 as 10.1136/gutjnl-2016-312473
Hepatology

ORIGINAL ARTICLE

Selective targeting of lysyl oxidase-like 2 (LOXL2) suppresses hepatic fibrosis progression and accelerates its reversal

Naoki Ikenaga,[1] Zhen-Wei Peng,[1,2] Kahini A Vaid,[1] Susan B Liu,[1] Shuhei Yoshida,[1] Deanna Y Sverdlov,[1] Amanda Mikels-Vigdal,[3] Victoria Smith,[3] Detlef Schuppan,[1,4] Yury V Popov[1]

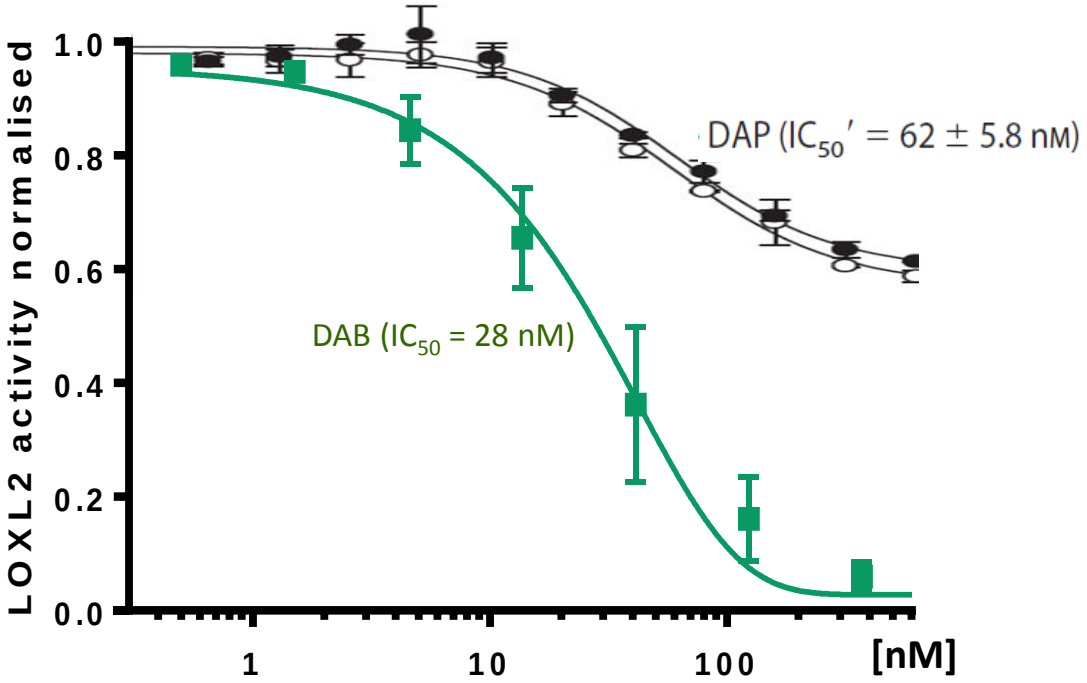
Received 11 Aug 2016 | Accepted 26 Oct 2016 | Published 14 Dec 2016

DOI: 10.1038/ncomms13710 OPEN

Targeting LOXL2 for cardiac interstitial fibrosis and heart failure treatment

Overwhelming link of LOXL2 and fibrotic diseases in humans.
Aim is to **BLOCK** LOXL2 with small molecule.

Simtuzumab versus PXS small molecule



- PXS-3rd series
- Arresto data: THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 285, NO. 27, pp. 20964–20974, July 2, 2010

Poor functional activity of antibody confirmed: http://www.pharmakea.com/images/Keystone2017Final.pdf

PXS molecules are fast-acting, mechanism-based selective inhibitors
- with higher potency and achieving complete inhibition
- good tissue/cell penetration

Enzyme: R&D Systems recombinant human LOXL2
DAB: diaminobutane
DAP: diaminopentane

Pharmacology: Lead-candidate

		Pre-candidate
Inhibition pIC_{50}	r human LOXL2	Available under CDA
	r mouse LOXL2	
	bovine LOX	
	r human LOXL1	
	r human LOXL3	
	r human LOXL4	
Kinetics	Kinact/K_I LOXL2 (h recomb)	
	Kinact/K_I LOX (bovine native)	
	Selectivity LOXL2/LOX (Kinact/K_I)	
Selectivity pIC_{50}	r human AOC3	
	r human MAO-A	
	r human MAO-B	

100x selectivity vs LOX / LOXL1
No activity against other amine oxidase enzymes

In vitro ADME: Lead-candidate

		Pre-candidate
Plasma stability; Remaining @1hr	Human, Rat, Dog	
Plasma protein binding; % bound	Human, Rat, Dog	
Microsomal stability; Remaining @ 1hr	Human, Rat, Dog	
Hepatocyte stability; Remaining @ 1hr	Human, Rat, Dog	
Cyp inhibition (1A2; 2C9; 2C19; 2D6; 3A4)	Human	
Cell Health Assay: highest conc. survival	HepG2	
Pgp substrate		
Permeability (CaCo, MDCK2)		

Available under CDA

Excellent in vitro ADME properties
No development flags

In vivo ADME:
Lead-candidate properties

		Pre-candidate
Oral bioavailability	Dog – Rat	
$T_{1/2}$	Dog – Rat	
Vss	Dog – Rat	
Excretion urine (parent)	Dog	
Dose linearity in oral absorption	Dog	

Available under CDA

Excellent in vivo properties
No development flags

Summary of *in vivo* studies

- Liver fibrosis
  - CCl_4-induced (Pharmalegacy, Shanghai)
    - 6 wk mouse
    - 4 – 9 wks rat
  - Thioacetamide-induced (Pharmalegacy, Shanghai)
  - Stelic NASH model (SMC, Tokyo)
- Kidney fibrosis
  - Diabetic nephropathy (Kolling Institute, Sydney)
- Cardiac fibrosis
  - Carotic aorta occlusion (CL Laboratory, Baltimore)
  - Ischemia/reperfusion (HRI, Sydney)
- Lung fibrosis
  - Bleomycin-induced (Aragen, San Francisco)
  - Ad-TGF-β-induced (McMaster University, Toronto)
- Cancer
  - Oral cancer (Boston University)

- Studies have shown a consistent reduction in the area of fibrosis.
- Efficacious compounds are from different chemical series, using prophylactic and therapeutic doses between 3-30 mg/kg by once a day, oral gavage.

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Drugs in the clinic targeting NASH

Several large Pharma companies seeking to build competitive portfolios

	Metabolic modifiers	Anti-inflammatory	Anti-fibrotic
Intercept	Ph 3		
Genfit	Ph 3		
Galmed	Ph 2/3		
Allergan	Ph 2	Ph 2	
Gilead	Ph 2 x 2	Ph 2	
BMS	Ph 2		Ph 1
Galectin			Ph 2
Novartis	Ph 2		
AstraZeneca		Ph 2	
Shire	Ph 2		
Boehringer Ingelheim		Ph 1	
Other	Ph 2 x 3	Ph 2 x4	

What program elements add value in a partnering deal for an anti fibrotic?

Feature	Value Drivers	Pharmaxis LOXL2 program status
Disease target	Independent validation	Multiple references including Pharma company authored. No clinical PoC.
Pre clinical proof of concept	2 or more different animal models	9 different models across 5 different diseases. Combination studies planned
Drug like qualities	No flags	Clean profile
Dosing regimen	Ease of use	Oral once a day tablet or capsule
Patent	Uncomplicated Composition of matter As long as possible	100% Pharmaxis owned Composition of matter 2016 filing date
Cost of Goods	Low	Small molecule with easy synthesis
# Compounds	1 plus backups	2 lead candidates plus back ups
Toxicity	Wide therapeutic window As long as possible	Work in progress 28 day
Clinical phase	Phase 1 or 2	Planned for phase 1 in 2H 17

Shareholders & trading

ASX code: PXS

Shareholders (26 May 17)

- Shares on issue: 319m
- Employee options: 10m
- Institutional shareholders ~50%:
  - Australia/NZ: Australian Ethical (10%); Allan Gray (8%); Other (1%)
  - US - BVF Partners (19%); Other (2%)
  - UK - Montoya Investments (6%); Other (3%)

Shares traded to 26 June 17

- Three months: 35m
- Six months: 49m
- Twelve months: 84m

Market capitalisation

- A$80m (26 June 17)