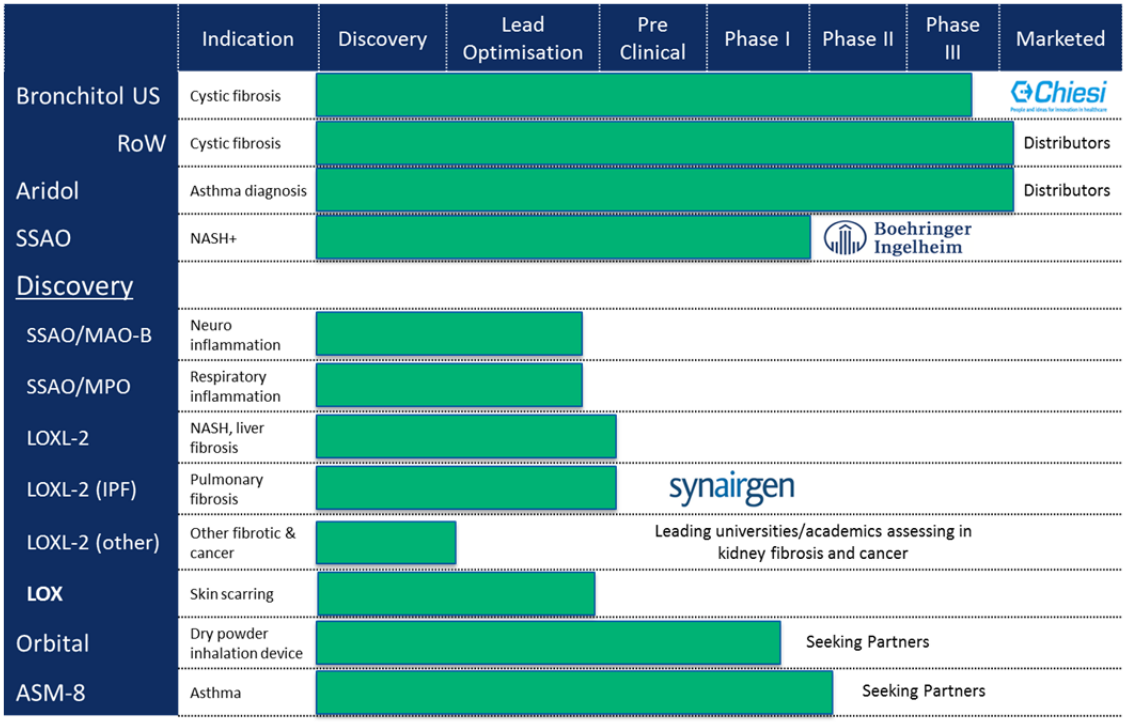
# Pharmaxis Development Pipeline for Fibrosis and NASH

The Pharmaxis pipeline is focused on areas of high unmet clinical need in the treatment of inflammation and fibrosis. The pipeline includes the development of semicarbazide-sensitive amine oxidase (SSAO) inhibitor for NASH and other inflammatory diseases (PXS-4728A) as well as Lysyl Oxidase (LOX) inhibitors for use in fibrotic diseases including NASH, pulmonary fibrosis, scarring and some cancers. The company's drug discovery chemistry platform has been well validated, with one representative asset (PXS-4728A) acquired by Boehringer Ingelheim in 2015 after phase I trials.

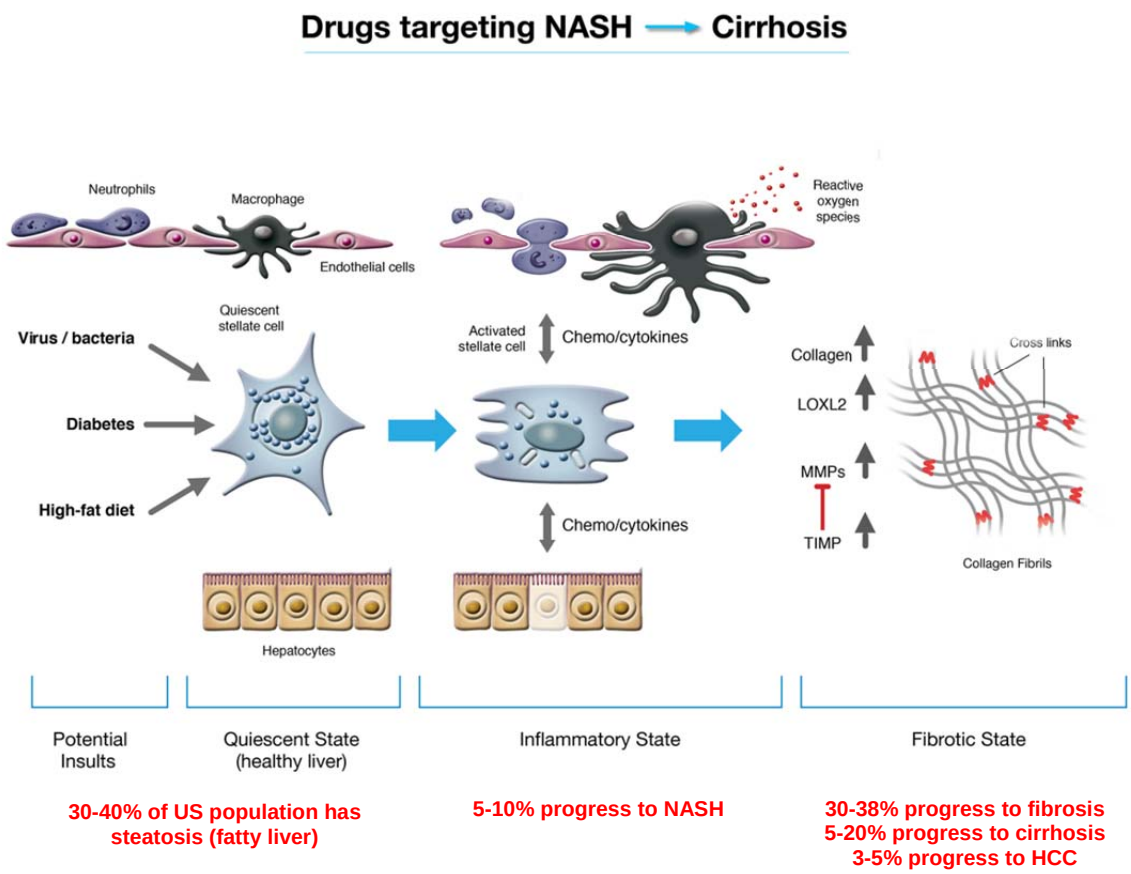



## NASH

Nonalcoholic steatohepatitis (NASH) is a pandemic, metabolic disease which has both inflammatory and fibrotic components; key mechanisms that can be effectively targeted using the Pharmaxis proprietary amine oxidase platform.

For a helpful overview of NASH refer to the U.S. National Institute of Health information at https://www.niddk.nih.gov/health-information/health-topics/liver-disease/nonalcoholic-steatohepatitis/Pages/facts.aspx

NASH is a polyfactorial condition in which diabetes and Western diet are major contributors to disease progression. NASH develops from fatty liver disease due to ongoing inflammation, which in turn may progress through fibrosis, to cirrhosis and end in hepatocellular cancer (HCC) or transplantation. As there are no treatments with an approved indication for NASH, it is currently treated today by lifestyle modification. Given the prevalence of fatty liver disease in markets such as the US and Europe (reported at 30 – 40%) there is an expectation that NASH will become a major chronic disease with correspondingly high levels of morbidity and mortality. The efforts to find effective treatments have been intensifying as the size of the potential market has become clear.




## Approaches to the treatment of NASH

The chronic nature of NASH means that long-term management is required. Moreover, due to the polyfactorial nature of NASH, the expectation is that combination treatments will be crucial to adequately reduce and control the metabolic burden, inflammation and fibrosis associated with disease progression. Consequently it is likely that combination therapies acting in a synergistic fashion will ultimately dominate treatment.

Drugs in development for NASH can be grouped by the mechanism in which they affect the various aspects of liver disease.

### 1. Metabolic modifiers

It is recognised that a major risk factor for NAFLD is systemic insulin resistance associated with obesity and metabolic syndrome. In these circumstances insulin cannot effectively control blood glucose and fatty acids levels, resulting in the accumulation of fat in the liver.

Metabolic modifiers work to improve insulin sensitivity, restore normal glucose metabolism and reduce the amount of lipids in the bloodstream. Numerous companies are currently engaged in the development of metabolic modifiers for the treatment of NASH, including Intercept (Obeticholic acid) and Genfit (Elafibranor). The advantage of metabolic modifiers is that they interfere with the genesis of fatty liver, however, they may not be very efficacious in clearing existing fibrosis and reducing inflammation in the context of continued elevated consumption of lipids and glucose.

**2. Anti-inflammatory drugs**

Hepatic steatosis or fatty liver is very common, and the progression to NASH and more severe forms of fibrosis is facilitated by chronic inflammation in the liver. Contributing factors to chronic inflammation are the influx of immune cells into the liver and on-going oxidative stress which ultimately results in progression of fibrosis.

The goal of anti-inflammatory drugs for NASH is to prevent further damage and halt progression of the disease by either reducing the effects of inflammatory mediators (e.g. using CCR2/5 inhibitors) or by reducing the influx of immune cells (e.g. using SSAO inhibitors). Anti-inflammatory drugs are likely to be most effective during the transition from mild-moderate to moderate-severe NASH, when inflammation plays a critical role.

**3. Anti-fibrotic drugs**

The reduction of fibrosis or the stop of progressing fibrosis is the most important therapy as the degree of fibrosis but not fat content defines disease severity. However, there are only a few anti-fibrotic drugs in development, mainly because of the inherent difficulties associated with targeting this mechanism in a disease specific manner that does not impact on essential healthy fibrotic processes. The exception is probably the reduction in collagen cross-linking (the hallmark of fibrosis) that is achieved by lysyl oxidase inhibitors. While the LOXL2 antibody Simtuzumab likely failed as a consequence of poor efficacy, two companies are progressing potent small molecule inhibitors into and through the clinic. Inhibition of LOXL2 seems to be a promising treatment due to a favourable safety efficacy profile. It is anticipated that such an approach will be most clinically relevant in the context of advanced NASH and marked fibrosis.

## Clinical trials in NASH

Over 30 companies have disclosed clinical stage NASH programs, using agents operating via a range of mechanisms of action. Also of note is the fact that several drugs, including those used for Type 2 diabetes and autoimmune disease, are being repurposed for NASH. Detailed below are the most advanced programs:

**Selected NASH products in development**

| Class | Company | Drug | Mode of action | Highest phase |
|---|---|---|---|---|
| **Metabolic modifier** | Intercept | Obeticholic acid | FXR agonist | Phase III |
| | Genfit | Elafibranor | PPAR α/δ agonist | Phase III |
| | Galmed | Aramchol | Synthetic fatty acid bile conjugate | Phase II/III |
| | Allergan | Evogliptin | DPP-4 inhibitor | repurposed T2D drug |
| | Gilead | GS-9674 | FXR agonist | Phase II |
| | Gilead | GS-0976 | ACC inhibitor | Phase II |
| | Bristol-Myers Squibb | BMS-986036 | FGF21 agonist | Phase II |

| Class | Company | Drug | Mode of action | Highest phase |
|---|---|---|---|---|
| **Metabolic modifier** | Shire | Volixibat | ASBT inhibitor | Phase II |
| | Arisaph Pharmaceuticals | ARI3037MO | Niacin analogue | Phase II |
| | Islet Sciences | Remogliflozin | SGLT2 inhibitor | repurposed T2D drug |
| | Novo Nordisk | Liraglitude | GLP1R agonist | repurposed T2D drug |
| **Anti-inflammatory** | 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 |
| **Anti-fibrotic** | 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 |

Key: FXR, farnesoid X receptor; PPAR, peroxisome proliferator-activated receptor; ACC, acetyl-CoA carboxylase; FGF21, fibroblast growth factor 21; ASBT, apical sodium bile acid co-transporter; CCR2, chemokine receptor agonist 2; MAPK5, mitogen-activated protein kinase 5; LTD4, leukotriene D4; SSAO, semicarbazide sensitive amine oxidase; LOXL2, lysyl oxidase-like 2; Hsp47, heat shock protein 47; SGLT2, sodium-glucose co-transporter 2; GLP1R, glucagon-like peptide-1 receptor, DPP-4, dipeptidyl peptidase 4.

The Intercept trials provide a good example of a clinical development program.

| Trial | Phase | Duration on drug | Patient numbers | Start | Finish |
|---|---|---|---|---|---|
| FLINT | Phase II | 72 weeks | 283 | Mar 2011 | Jan 2014 |
| REGENERATE | Phase III | 72 weeks + safety | 1,400 - 2,000 | Sept 2015 | Oct 2021 |

The only endpoint currently approved by the FDA is liver biopsy but with the validation of biomarkers and imaging technologies in current trials, this may change over coming years. The FDA has co-sponsored multiple workshops (Liver Forum) to develop guidance on NASH treatments.

## Overview of Selected Key Players

**Intercept: Obeticholic Acid (metabolic)**

Intercept's Obeticholic Acid (OBA) is an oral synthetic bile acid analogue and farnesoid X receptor (FXR, a nuclear hormone receptor) agonist. FXR signaling may play a role in downregulating abnormal bile production, hepatic inflammation and hepatic fibrotic activity and is therefore anticipated to prevent the progression of NASH. Based on positive efficacy data from the FLINT Phase II trial (statistically significant decreases in liver steatosis, inflammation and fibrosis) OCA received "breakthrough therapy designation" from the FDA. Notably, an increase in LDL and reduction in HDL cholesterol were also observed with OCA which does not exist in other FXR agonists. A post-hoc analysis of data suggests that this can be partially controlled by statin use. The REGENERATE Phase III trial is ongoing (with co-administration of statins), with interim analysis expected in 1H17.

**Genfit: Elafibranor (metabolic)**

Genfit's Elafibranor is a dual peroxisome proliferator-activated receptor (PPAR) α/δ agonist. The Phase IIb GOLDEN trial failed to achieve a statistically significant improvement in NASH symptoms (as measured by liver fat reduction and fibrosis stabilisation) when compared with placebo. When analysis was performed excluding patients with early stage disease, Genfit deemed the trial to be a success. Details of the design of the Phase III trial RESOLVE IT were released in November 2015, with interim results expected in 2017.

**Allergan: Cenicriviroc (inflammatory), Evogliptin (repurposed), AKN-083 (metabolic)**

In September 2016 Allergan acquired Cenicriviroc (CVC) and Evogliptin from Tobira Therapeutics. CVC blocks two chemokine receptors, CCR2 and CCR5, involved in the inflammatory and fibrogenic pathways in NASH. In the Phase IIb CENTAUR study, CVC failed to meet the primary endpoint but demonstrated an improvement in fibrosis of at least one stage without worsening of NASH, one of two key secondary endpoints. Evogliptin, an oral DPP-4 (dipeptidyl peptidase-4) inhibitor, is currently being evaluated (with and without CVC) in a Phase I trial. Within the same month, Allergan also announced that it had acquired AKN-083, a preclinical FXR agonist, from Akarna Therapeutics.

**Gilead: Selonsertib (GS-4997) (inflammatory), Simtuzumab, GS-0976 (fibrotic)**

Gilead has several products in development aimed at targeting NASH, the most advanced of which being Selonsertib (GS-4997) a mitogen-activated protein kinase (MAPK5) inhibitor with potential anti-inflammatory, anti-neoplastic and anti-fibrotic activities. Selonsertib recently completed a Phase II trial in patients with moderate to severe fibrosis, meeting both the primary and secondary endpoints. GS-4997 will now be progressed to a Phase III trial. In November 2016 Gilead announced that no further development of Simtuzumab, a humanised monocolonal antibody directed against the enzyme lysyl oxidase-like 2 (LOXL2), will be undertaken. At the same time it announced that GS-0976, the allosteric acetyl-CoA carboxylase (ACC) inhibitor acquired from Nimbus Therapeutics, has reached another milestone and will be swiftly progressed into two Phase II trials.

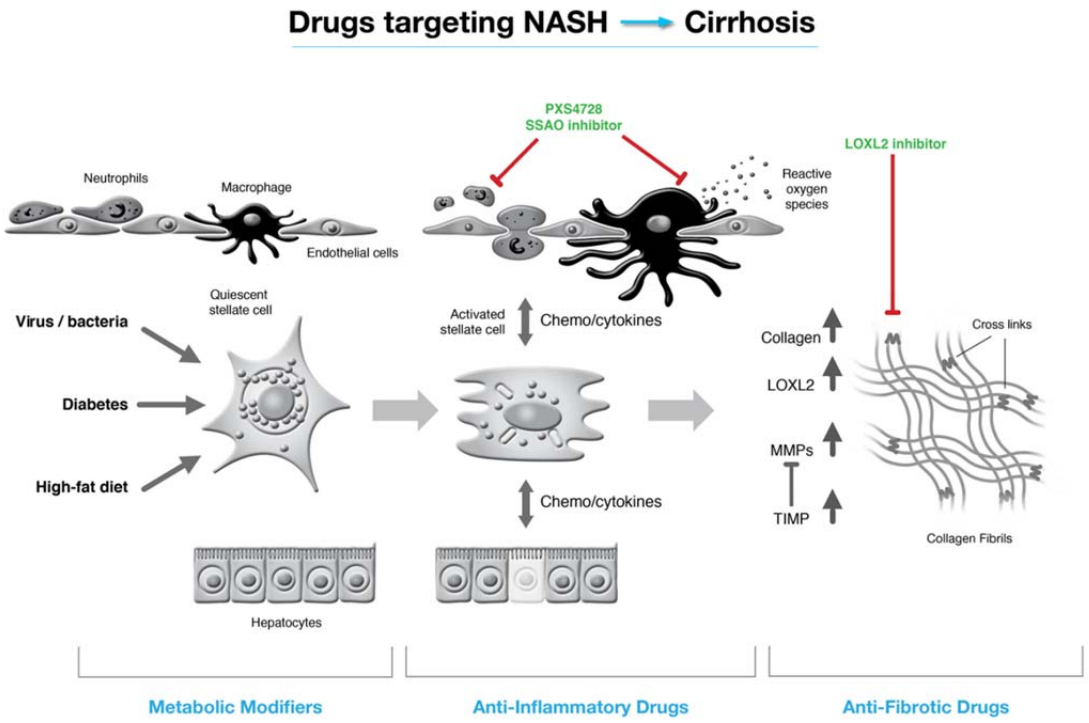
**BMS: ND-L02-s0201 (fibrotic)**

BMS has an ongoing interest in fibrosis and has acquired three companies since 2011 with programs focused on pulmonary fibrosis. In November 2016 BMS announced it had licensed a siRNA program from Nitto Denko against HSP40 with the lead candidate in Phase Ib for NASH.

## Pharmaxis pipeline - a multipronged approach to NASH

Pharmaxis is developing two drug candidates that target different stages of NASH:

- The Pharmaxis drug candidate PXS-4728A, acquired by Boehringer Ingelheim in 2015, is designed to reduce liver inflammation
- The Pharmaxis LOXL2 inhibitor program is developing drug(s) to dampen fibrosis.




**PXS-4728A**

PXS-4728A is an anti-inflammatory drug with anti-fibrotic properties that mediates its effects by potent inhibition of the enzyme SSAO/VAP-1 (semicarbazide-sensitive amine oxidase/vascular adhesion protein-1). SSAO/VAP-1 plays an important role in chronic inflammation and plasma SSAO/VAP-1 levels are positively correlated with disease progression in patients with liver fibrosis and cirrhosis (including NAFLD and NASH) as well as kidney fibrosis, scleroderma, cardiovascular diseases and metabolic disorders.

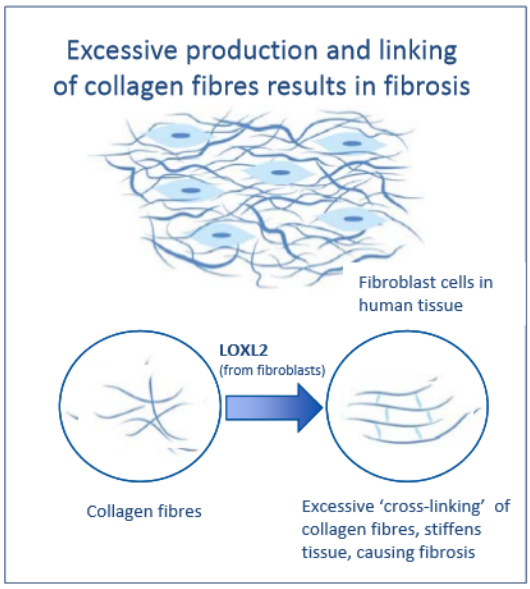
PXS-4728A was acquired by Boehringer Ingelheim (BI) after Phase I for A$39M upfront, with a total ~A$600M in milestone payments to approval plus payments on net sales. The next milestone of ~A$25M is due upon Phase II initiation, expected to occur in 2017.

Phase I data show that PXS-4728A is safe and well tolerated, with good PK properties and long-lasting enzyme inhibition after a single dose.

The mechanism of action of PXS-4728A means that it is targeted towards the inflammatory stages of NASH. It is therefore expected that PXS-4728A will be most effective in non-cirrhotic patients. As NASH progresses, scarring (or fibrosis) of the liver occurs. Consequently, for patients with more advanced disease (either developing or with cirrhosis) the addition of a potent anti-fibrotic agent will be required for adequate disease control and treatment.

**LOXL2 inhibitor**

The process of fibrosis involves the formation of crosslinks between collagen and elastin fibres. Lysyl oxidases (LOX) are a family of amine oxidase enzymes responsible for the formation of such cross-links. There are 5 family members [lysyl oxidase (LOX) and lysyl oxidase 1-4 (LOXL1-4)] with LOXL2 identified as being up-regulated in many fibrotic disease states.




Substantial evidence in support of LOXL2 as an important anti-fibrotic target is provided by numerous preclinical models. In particular, the work of Arresto involving the use of a mouse LOXL2 antibody in models of liver and lung fibrosis clearly demonstrates pronounced anti-fibrotic activity. The humanised variant (Simtuzumab) progressed by Gilead subsequently failed in clinical trials, however this is likely attributable to the low potency and poor efficacy of the antibody combined with limited cell and tissue penetration.

The approach taken by Pharmaxis (and attempted by other companies) has been the development of small molecules inhibitors of LOXL2 capable of achieving higher potency and complete inhibition of the enzyme target. In matched in vitro studies presented in published papers and scientific conferences, simtuzumab has achieved a maximum inhibition of LOXL2 of 40% whilst Pharmaxis inhibitors have demonstrated 100% inhibition at lower doses. These small molecules are suitable for once a day oral dosing and are expected to significantly reduce fibrosis. Indeed, data presented by Pharmaxis have shown that the inhibitors reduce fibrosis in pre-clinical models of both liver and kidney fibrosis.