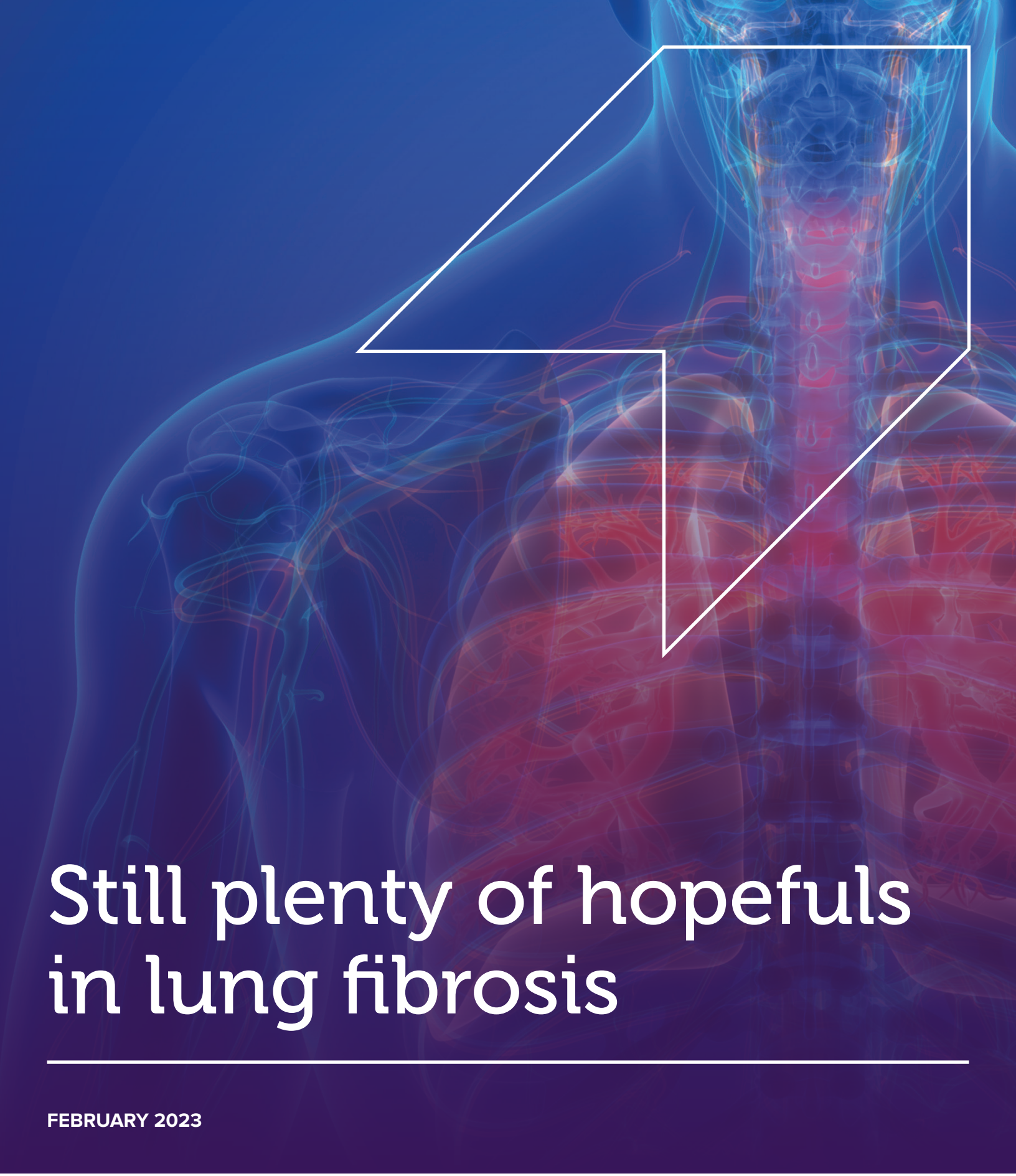

# Still plenty of hopefuls in lung fibrosis

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ARTICLE

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# Still plenty of hopefuls in lung fibrosis

Roche's zinpentraxin alfa is out of the running, but Bristol, Blade, Pliant and others have contenders in the mid-stage idiopathic pulmonary fibrosis pipeline.

Idiopathic pulmonary fibrosis has proved to be a tough disease to crack, as Roche reminded investors this month. That group's intravenous project zinpentraxin alfa is no more – but a look at the pipeline shows that many other groups are still taking a shot at the disorder.

Since the last time *Evaluate Vantage* carried out this analysis, Boehringer Ingelheim has taken BI 1015550 into phase 3, while Bristol Myers Squibb has hinted at positive phase 2 results with BMS-986278. And a number of hopefuls have entered mid-stage testing, including Puretech, Blade Therapeutics and, most recently, Arrowhead.

Arrowhead started a phase 1/2 study in early February with ARO-MMP7, an inhaled RNA interference project designed to reduce the expression of matrix metalloproteinase 7, which is thought to play a role in the pathogenesis of IPF.

This could be a disease-modifying approach; however, the development of inhaled RNAi candidates has not gone smoothly in the past.

## IMPROVING ON ESBRIET?

Puretech is treading a more tried-and-tested path. That company's LYT-100 is a deuterated form of pirfenidone, the active ingredient in Roche's approved IPF drug Esbriet. Puretech hopes that LYT-100 will be better tolerated than Esbriet, which is linked with gastrointestinal side effects; last year, the group reported phase 1 data showing fewer such adverse events with LYT-100 versus Esbriet.

Results from a phase 2 dose-ranging trial of LYT-100 are due by the end of this year.

Still, neither Esbriet nor the other approved IPF therapy, Boehringer Ingelheim's Ofev, are considered disease modifying, so presumably LYT-100 would, at best, only slow the progression of IPF. Boehringer itself acknowledges that new therapies are needed to stop the disease in its tracks. To this end the group is developing BI 1015550, a phosphodiesterase 4B inhibitor; this mechanism is thought to hit both inflammation and fibrosis seen in IPF.

In phase 2 Boehringer tested BI 1015550 alone and on top of Ofev or Esbriet. In patients not on antifibrotics the study found an increase in forced vital capacity (FVC) of 5.7ml with BI 1015550 versus a decrease of 81.7ml with placebo. In patients receiving antifibrotics the corresponding figures were +2.7ml and -59.2ml.

SVB analysts termed this increase "modest", but the data were enough for Boehringer to push into phase 3. One thing to keep an eye on will be adverse events: 13 BI 1015550-treated patients dropped out of the phase 2 trial, versus none on placebo, with

diarrhoea a common culprit. There was also a death due to suspected vasculitis and IPF exacerbation; PDE4 inhibitors have been linked to vasculitis.

## BRISTOL'S BET

Another candidate heading for phase 3 is Bristol Myers Squibb's LPA1 inhibitor BMS-986278. The group said during its fourth-quarter earnings that it had seen positive phase 2 results with the project, and detailed data are expected this half.

Horizon, soon to be part of Amgen if all goes to plan, also has an LPA1 inhibitor, previously in development by Sanofi.

Pliant, meanwhile, is being more cautious, with a phase 2b planned for bexotegrast despite the excitement recently generated by its phase 2a data.

And Algernon has put phase 2b IPF plans on hold, preferring instead to focus on chronic cough with its asset, ifenprodil, for now. Phase 2a data on that project were mixed – the study hit its FVC co-primary endpoint, but not the one measuring cough.

More data on these assets are some way off. A more immediate test will come for Fibrogen, with the first pivotal results on pamrevlumab due mid-year.

The middle of 2023 will also see phase 2 results with Galecto's GB0139, an inhaled galectin-3 inhibitor. However, the project's path has not been smooth: after an imbalance in serious adverse events the company had to discontinue a high-dose (10mg) arm and the combination of GB0139 plus Esbriet or Ofev. Dosing of 3mg GB0139 as monotherapy continued.

Adverse events have been a problem for another class, the autotaxin inhibitors. Development of Galapagos and Gilead's ziritaxestat was stopped on a toxicity signal, while Boehringer handed back rights to Bridge Biotherapeutics' BBT-877 amid toxicity concerns, although development continues.

However, Blade reckons it might have found the answer with its non-competitive autotaxin inhibitor, cudetaxestat. The group says the project could be more potent than competitive inhibitors like ziritaxestat.

Roche has form in making IPF acquisitions, picking up Esbriet's originator Intermune in 2014 for $8.3bn, and zinpentraxin alfa's maker Promedior for $390m up front five years later. If it does want to strike another deal in IPF, there are plenty of targets to choose from.

## The mid-to-late stage IPF pipeline

| Project | Company | Mechanism | Route of admin | Trial details |
|---|---|---|---|---|
| **Phase 3** | | | | |
| RG6354 (zinpentraxin alfa; PRM-151) | Roche | Recombinant human serum amyloid P | IV | Starscape stopped for futility Q4 2022 |
| Pamrevlumab | Fibrogen | Anti-CTGF antibody | IV | Zephyrus-1 data due mid-2023; Zephyrus-2 data due mid-2024 |
| BI 1015550 | Boehringer Ingelheim | Phosphodiesterase 4B inhibitor | Oral | NCT05321069 ends Nov 2024 |
| Tyvaso | United Therapeutics/ Mannkind | Prostacyclin mimetic | Inhaled | Teton & Teton 2 end Jun 2025 |
| **Phase 2** | | | | |
| Bexotegrast (PLN-74809) | Pliant Therapeutics | αvß6 and αvß1 integrin inhibitor | Oral | Positive data from ph2a Integris-IPF; ph2b to start mid-2023 |
| Ifenprodil (NP-120) | Algernon Pharmaceuticals | NMDA2B antagonist | Oral | Ph2a met 1 of 2 co-primary endpoints; ph2b planned (chronic cough initially) |
| ND-L02-s0201 (BMS-986263)* | Nitto Denko | HSP47 RNAi | IV | Juniper completed Aug 2022 |
| BMS-986278 | Bristol Myers Squibb | LPA1 antagonist | Oral | NCT04308681 completed Aug 2022; ph3 planned |
| Jaktinib | Suzhou Zelgen Biopharmaceuticals | Jak 1-3 inhibitor | Oral | NCT04312594 (China only) recruiting |
| Setanaxib (GKT831) | Calliditas (via Genkyotex) | NOX1 & 4 inhibitor | Oral | NCT03865927** ends Apr 2023 |
| GB0139 (TD139) | Galecto Biotech | Galectin-3 inhibitor | Inhaled | Galactic-1 ends May 2023 |
| Taladegib (ENV-101) | Endeavor Biomedicines | PTCH1 inhibitor | Oral | NCT04968574 ends Aug 2023 |
| Garadacimab (CSL312) | CSL | Anti-factor XIIa MAb | IV/SC | NCT05130970 ends Nov 2023 |
| Saracatinib | Astrazeneca | Src kinase inhibitor | Oral | Ph1/2 Stop-IPF** ends Dec 2023 |
| Cudetaxestat | Blade Therapeutics | Autotaxin inhibitor | Oral | Respirare ends Dec 2023 |
| Deupirfenidone (LYT-100) | Puretech | Deuterated form of pirfenidone (Esbriet) | Oral | Elevate ends Dec 2023 |
| RXC007 | Redx Pharma | Rock2 inhibitor | Oral | NCT05570058 ends Dec 2023; on US partial clinical hold |
| VP01 (C21) | Vicore Pharma | AT2 agonist | Oral | Air ends Dec 2023 |
| HZN-825 (fipaxalparant) | Horizon (via Sanofi) | LPA1 antagonist | Oral | NCT05032066 ends Jun 2024 |
| AK3280 | Ark Biosciences | Unknown | Oral | NCT05424887 (China only) ends Jul 2024 |
| ARO-MMP7 | Arrowhead | MMP7 RNAi | Inhaled | Ph1/2 ends Aug 2024 |
| BBT-877 | Bridge Biotherapeutics | Autotaxin inhibitor | Oral | NCT05483907 ends Nov 2024 |
| LTP001 | Novartis | Smurf1 inhibitor | Oral | NCT05497284 ends Jan 2025 |
| Ifetroban | Cumberland Pharmaceuticals | Thromboxane receptor antagonist | Oral | NCT05571059 ends May 2025 |

Note: list not exhaustive; *Bristol Myers Squibb has licensed project in liver diseases, and has option in IPF; **investigator-sponsored trial.

Source: Evaluate Pharma & clinicaltrials.gov.

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