Commentary: Carl-Johan Dalsgaard

A surprise finding in the clinic

Every once in a while a discovery in the clinic exceeds researchers' expectations. This is what happened in early February when our company, Vicore Pharma Holding AB, received early data from a Phase 2 study of our candidate product, C21, for idiopathic pulmonary fibrosis (IPF). The data showed the drug's potential to restore lung function rather than merely reduce the rate of decline in the disease, the expected outcome from standard-of-care drugs. Yes, this is interim data, from a trial with no placebo looking at a novel drug aimed at an untested target. But clinicians involved with the trial are excited.

C21 is a small molecule agonist of the angiotensin type 2 receptor (AT2R). In the lung, AT2R is almost exclusively found on type 2 alveolar epithelial cells (AEC2), progenitor cells that restore alveolar cell lining and produce surfactant, a key component of alveolar function. C21 is believed to work by stimulating AEC2 cells, likely leading to enhanced lung epithelial repair and maintenance. Recently obtained autoradiography imaging data in human lung tissue had confirmed that C21 binds AT2R with high specificity and at clinically relevant concentrations. A range of evidence from clinical studies, human tissue studies and animal models also demonstrated that C21 agonism of AT2R instigates multiple physiological changes.

However this had to be further demonstrated in the clinic. Our Phase 2 study called AIR used automated respirometry to measure forced vital capacity (FVC), a standard measure of lung volume which is used in all IPF trials. In essence, FVC is the maximum amount of air that can be exhaled from the lungs after taking the deepest breath possible. In IPF patients, FVC declines on average at a rate of around 250 ml per year; standard-of-care drugs slow that decline by around 50%. Our study was powered to detect a better performance than standard of care, a more gradual decline. If C21 matched the reduction in decline seen with standard-of-care, we considered that its safety profile would make it a commercially competitive option in IPF.

In that context, the interim analysis from AIR was highly encouraging. It indicated that C21 not only slowed FVC decline, but actually improved lung function in these IPF patients. At the time of the interim analysis, 25 patients had been recruited to AIR with nine patients receiving oral C21 for 24 weeks and seven completing the full 36-week treatment period.

From well-documented and extensive patient history data, if C21 had no effect we would expect an average decline in FVC in patients at 24 weeks of 120 ml, and a decline of 180 ml at 36 weeks. Instead, in the nine patients who were treated with 100 mg C21 for 24 weeks, the average change was not a decline but an increase in FVC from baseline of 251 ml. In the seven patients who were treated for 36 weeks, mean FVC increased by 750 ml (p=0.016). To date in the AIR study, C21 has been well tolerated with no serious drug-related adverse events, and no gastrointestinal signals.

Previous larger-scale studies of the anti-fibrotic drugs pirfenidone and nintedanib had not shown improvements in FVC. However, improvements in FVC have been seen at an individual patient level in some of these studies. In a Boehringer Ingelheim-sponsored study called IMPULSIS that was part of the approval submission for nintedanib in IPF, around 9% of the placebo-treated patients (n=423) had stable or increased FVC.

It is possible that all of the first nine patients in our study were going to improve without treatment. However, this seem very unlikely, and the accelerating increase in FVC seen between 24 and 26 weeks of treatment in our study points to an effect that is not a statistical outlier; in addition, the observed effect occurs at a magnitude that goes beyond levels seen in previous studies.

We are confident that the effect we have seen in AIR is real, partly because of the unlikelihood of a statistical anomaly. The company plans to progress C21 rapidly to a second study – AIR 2. Meanwhile, patients already recruited to AIR will complete the original study, providing an opportunity for substantiation of the early results. The second study, AIR 2, will be a randomised-controlled trial that has the potential to accelerate our ability to bring C21 to IPF patients.

The C21 molecule is known to academic and applied researchers who have used it as a probe for AT2R in research and preclinical models. As an AT2R agonist, it activates the 'regenerative arm' of the renin-angiotensin system (RAS). This is the counterpart of the 'rescue arm' of RAS which involves two well-established drug targets – angiotensin-converting enzyme (ACE) and angiotensin type 1 receptor (AT1R) – that are important in the treatment of high blood pressure, for example.

Our understanding of the mechanism of action of C21 in IPF is still evolving however. It appears that agonism of AT2R, most likely on the AEC2 lung stem cells where the receptor is highly expressed, is capable of invoking regenerative processes, not only at the cellular level, but also vasodilation as well as anti-fibrotic activity. In patients with systemic sclerosis, C21 counteracts cold-induced vasoconstriction. In precision-cut human lung tissue from IPF lung-transplant patients, C21 inhibits TGF-beta1 which is both an injury biomarker as well as pro-fibrotic factor. Supplementing the human and human tissue studies, both the anti-fibrotic and vasodilatory effects of C21 have also been demonstrated in several animal models. The observation of improvements in FVC in IPF patients who completed 24-or 36-week treatments with C21 adds to the existing evidence base.

This commentary was written by Carl-Johan Dalsgaard, chief executive officer of Vicore Pharma Holding AB.