Evaluate Vantage

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Ionis joins the inhaled cystic fibrosis therapy race

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Ionis's inhaled antisense candidate shows promising signs, with Arrowhead and Translate Bio also in the running.

Vertex might be the dominant force in cystic fibrosis, but there is still a small subset of patients in whom the company's drugs are not effective. Companies developing inhaled RNA-targeting projects, including Ionis, Arrowhead and Translate Bio, are hoping to reach the patients that Vertex cannot.

Potentially promising phase I data on Ionis's IONIS-ENAC-2.5Rx, reported yesterday, suggest this project as one to watch, though full results, due later this month, will be needed to gauge the asset's chances properly. Meanwhile, phase I/II trials of Arrowhead and Translate's candidates are set to read out next year.

CF is caused by mutations in the CFTR gene, which in turn leads to a defective and/or missing CFTR protein, which is vital for chloride transport. The result is the poor flow of salt and water into and out of cells in organs including the lung, and a build-up of a thick, sticky mucus.

Vertex has made strides with its CFTR modulators, but even its most advanced drug, the triplet Trikafta, can only treat 90% of the population.

Selected inhaled RNA-targeting projects for cystic fibrosis			
Project	**Company**	**Description**	**Note**
Phase I/II			
ARO-ENaC	Arrowhead	Inhaled ENaC RNAi therapeutic	Ph1/2 trial to complete Aug 2021 (NCT04375514)
MRT5005	Translate Bio	Inhaled CFTR mRNA therapeutic	Ph1/2 MAD data expected 2021 (NCT03375047)
Phase I			
IONIS-ENAC-2.5Rx	Ionis	Inhaled ENaC antisense oligonucleotide	Top-line ph1 data reported (NCT03647228); ph2 trial in COPD not yet recruiting (NCT04441788)
Preclinical			
Cystic Fibrosis Research Program	Translate Bio	"Next-gen" inhaled CFTR mRNA therapeutic	
LUNAR-CF	Arcturus	Inhaled CFTR mRNA therapeutic	IND due 2021
Moderna-Vertex Cystic Fibrosis Research Project	Vertex	Inhaled CFTR mRNA therapeutic	Research collaboration broadened Sep 2020
Source: EvaluatePharma, clinicaltrials.gov.			

The hope now is that new therapies could be effective in the remaining 10% of CF patients, who have a so-called nonsense mutation that essentially leads to no functional CFTR protein being produced.

Some of the projects, including those being developed by Arrowhead and Ionis, could also act synergistically with CFTR modulators.

Both assets are designed to reduce activity of the epithelial sodium channel (Enac) in the lung, as CTFR dysfunction also causes increased Enac activity, which is thought to contribute to airway dehydration. Ionis is using an antisense oligonucleotide, while Arrowhead is employing RNA interference.

Notably, Vertex already tried to inhibit Enac with small molecules licensed from Parion Sciences. But after the lead project, VX-371, fell short in clinical trials, Vertex returned rights to the smaller group at the beginning of this year.

According to Arrowhead, the development of inhaled small molecule Enac inhibitors was limited by on-target renal toxicity and short duration of action in the lung.

In August, that company started a phase I/II study of its candidate, ARO-ENaC, in up to 24 healthy volunteers and up to 30 CF patients. The primary endpoint is safety, but the trial will also evaluate various exploratory efficacy endpoints in CF patients including changes in lung clearance index and forced expiratory volume.

Ionis advances

Ionis is slightly further ahead, having reported some phase I data yesterday with IONIS-ENAC-2.5Rx. However, there is not much to go on: all the company has said is that in healthy volunteers given 75mg there was a mean 56% reduction in Enac mRNA expression – and that this was statistically significant, with $p<0.05$.

The company also noted that, in mouse models, Enac mRNA reductions of 40% or more led to improvement in CF lung disease.

But it is data in humans that matter, and investors will be watching for full presentation of the results, due at the North American Cystic Fibrosis Conference, taking place virtually on October 21-23.

Stifel analysts raised several key questions, including whether any toxicity issues arose and whether the reduction in Enac expression, measured via bronchial cell brushings, was representative of what is happening across the lung.

Both projects could also have utility in other lung diseases like COPD; indeed, Ionis is already planning a phase II trial here.

Translating mRNA

Translate Bio, meanwhile, also hopes that its lead project, MRT5005, could be used in all CF patients, regardless of their mutation. But it is taking a different approach: the asset is designed to deliver mRNA encoding a fully functional CTFR protein to the lungs.

The group reported interim results from the single-ascending dose portion of its phase I/II trial in CF patients last year; data from the multiple-ascending dose portion had been due in 2020, but the trial was stopped earlier this year owing to the Covid-19 pandemic. Enrolment and dosing resumed last month, but Translate has not yet provided updated timelines for data.

For now, Translate is the lead mRNA player in CF, but there are a couple of other projects in preclinical development. Notably, Vertex and Moderna extended their research collaboration in CF in September. Given Vertex's success in the larger CF market, it might be too soon to count the company out completely.