Evaluate Vantage

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Vertex’s second try at a rare lung disorder

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A small molecule for alpha-1 antitrypsin deficiency faces a key clinical test, and its chances of success aren’t good.

VX-814, Vertex’s first foray into the rare respiratory disease alpha-1 antitrypsin deficiency, ended with clinical failure and the loss of $14bn of market cap. Now a vital mid-stage clinical study of VX-864, a separate asset for the same condition, is set to read out by mid-year.

Unfortunately, there is little to suggest that the fate of VX-864 might be different from that of VX-814. Both projects are small molecules with the same mechanism of action, correcting the misfolding of alpha 1-antitrypsin (AAT); beyond stating that VX-864 is structurally distinct, Vertex has shown no human data showing an improved profile.

And when VX-814 failed Leerink analysts wrote off Vertex’s entire AATD programme, citing management’s inability to clarify why VX-864 might have better activity and less liver toxicity (*Clinical setback lays bare Vertex’s weakness, October 15, 2020*).

It was liver toxicity, and an apparent lack of a therapeutic window in a 50-patient phase II trial, that brought about VX-814’s demise, and analysts’ caution is reflected by the fact that VX-864 hardly features in sellside models, with no consensus shown by *Evaluate Pharma*.

Activity?

Still, more bullish Evercore analysts suggest that liver enzyme elevation might have signalled VX-814’s on-target activity.

AATD patients who are genetically homozygous (termed PiZZ) have severe disease; they are unable to transport AAT from the liver to the lungs, causing lung and liver disease. Correction of AAT misfolding takes place in the liver, and Vertex uses the same principle with its hugely successful cystic fibrosis drugs, so perhaps VX-864’s mechanism should not be written off.

Vertex’s blinded phase II study has recruited 40 PiZZ subjects, and compares VX-864 versus placebo. The primary endpoints are simple: change in plasma functional AAT levels after 28 days, and safety. This is virtually identical to the failed trial of VX-814.

The goal is to show proof of concept, which presumably means that functional AAT must get at least to 11µM, the level achievable with IV enzyme augmentation. In the VX-814 trial four of 50 subjects had functional AAT levels over eight times the upper limit of normal, but overall levels could not reach the 11µM target, with liver

enzyme elevations to boot.

Mouse data

Evercore points to mouse data suggesting that VX-864 has better activity than VX-814, specifically citing sixfold versus 4.8-fold increases in AAT levels respectively. Of course nothing like this has been seen in humans.

As for the market, the analysts reckon AATD is analogous to cystic fibrosis, with current $1.5bn sales of enzyme augmentation suggesting a $5bn opportunity for a corrective therapy. It might also be that many cases are undiagnosed, but reluctance to assign future revenues to VX-864 shows how cautious the sellside still is.

And, even if VX-864 succeeds in phase II, Vertex will face competition from RNAi and other projects, at least one of which has already impressed clinically. The group really has it all to do.

Selected AATD projects in development				
Project	**Company**	**Description**	**Status**	**Delivery**
ARO-AAT	Arrowhead	RNAi therapeutic	Ph2/3	SC
VX-864	Vertex	Alpha-1 proteinase inhibitor	Ph2	Oral
MPH-966 (alvelestat)	Mereo (ex Astrazeneca)	Neutrophil elastase inhibitor	Ph2	Oral
DCR-A1AT	Dicerna/Alnylam	RNAi therapeutic	Ph1/2	SC
ALN-AAT02	Alnylam/Dicerna	RNAi therapeutic	Ph1/2	SC
Serpina1 gene therapy	Intellia	Crispr Cas9 gene therapy	Preclinical	IV
VX-814	Vertex	Alpha-1 proteinase inhibitor	Failed ph2	Oral
Source: Evaluate Pharma, clinicaltrials.gov.				