Evaluate Vantage

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Vertex eyes the treble in cystic fibrosis

Madeleine Armstrong

Vertex could soon be able to treat 90% of cystic fibrosis patients after posting impressive results in a currently untreated population. The data, with three different triple combinations, pile more pressure on rivals like Galapagos and Abbvie, which are jointly developing a triplet of their own.

Several major questions remain: how quickly Vertex can get one of its triplets approved – it currently has four contenders in development – and how much this will cost, with cystic fibrosis doublets already expensive. Then there is the perennial question about whether Vertex will be acquired – although with its market cap now at $42bn investors might wonder if it has been priced out of the market.

Vertex's chief executive, Jeff Leiden, said during a conference call yesterday that it was "far too early" to talk about the cost of a triplet. However, he hinted that this might be high, saying the price would need to reflect the value of the medicine to patients, how much Vertex has spent on research, and how much it will need to invest in the future to fulfil its aim of treating all cystic fibrosis patients.

As for approval plans, Vertex plans to await more data from the ongoing studies, plus results from two new phase II trials, before making a decision on which agent or agents to move into pivotal development.

Vertex's triple combo projects

Next-gen CFTR corrector	Status	Trial ID	Notes
VX-440	Phase II data reported	NCT02951182	-
VX-152	Phase II data reported	NCT02951195	-
VX-659	Phase I data reported	NCT03029455	Phase II to start Aug 2017; data early 2018
VX-445	Phase II study under way	-	Data early 2018

All in combination with tezacaftor and ivacaftor.

Phase III trials of one or two of the triplets should start in the first half of 2018. When asked how long these might take, Mr Leiden was reluctant to give details, but said: "We're talking about designing the most expedited trials ... to get it to patients as quickly as possible."

Leerink analysts now expect a Vertex triplet to be launched in 2020, versus 2021 previously. They assume a US price of $164,000 per year, lower than the $270,000 price tag for Vertex's marketed doublet Orkambi.

Decisions, decisions

The decision on which project(s) to take forward will be based on their risk/benefit profiles, Mr Leiden said. All else being equal, convenience might also come into it: VX-659 and VX-445 are both given once daily, while VX-440 and VX-152 are administered twice a day.

But it is VX-440 and VX-152 that are grabbing the headlines right now. Vertex reported results from two phase II trials of the compounds, both given in combination with Kalydeco and tezacaftor in two patient populations: those homozygous for the F508del mutation in the CFTR gene; and those with one F508del mutation and one minimal function mutation.

The former population is already covered by Vertex's Orkambi, as well as the tezacaftor/ivacaftor doublet, which is being reviewed by the FDA after posting positive pivotal results in March (*Vertex investors toast birth of the son of Orkambi, March 29, 2017*).

But for the latter population, known as F508del/Min, there are no treatment options. Vertex estimates that of the 75,000 cystic fibrosis patients worldwide around 24,000 have the F508del/Min genotype.

The tezacaftor/ivacaftor doublet has also shown promise in another population: those with one F508del mutation and one residual function mutation.

Breathing easy

In the F508del/Min population, all doses of both triplets significantly improved forced expiratory volume in one second (FEV1), a measure of lung function, over baseline. The magnitude of the benefit far exceeded what was expected from these treatments, and these impressive results, which should tighten Vertex's grip on this valuable market, helped drive the company's shares up 23% to a record high of $162 today.

Phase II data in F508del/minimal patients				
	Change in ppFEV1 from baseline			
Project	**100mg**	**200mg**	**600mg**	**Placebo**
VX-440 triplet	-	+10; p<0.0001	+12; p<0.0001	+1.4
VX-152 triplet	+5.6; p=0.0135	+9.7; p=0.0017	-	-0.9

In addition, safety looked good in both trials, with VX-152 avoiding the gastrointestinal issues that were seen in phase I, likely helped by lower doses being used in phase II. The trial also includes a 300mg VX-152 dose arm, with data expected later in 2017.

Meanwhile, data in F508del homozygous patients suggest that a triplet containing either VX-440 or VX-152 could improve lung function over the tezacaftor/ivacaftor doublet.

Vertex also reported promising phase I results with a triplet containing VX-659 in F508del/Min patients. It plans to start a phase II trial in August, with data set to become available in early 2018. At around the same time, a phase II study of the VX-445-containing triple should also be reported.

At this point, Vertex will have some hard decisions to make on which of the four triplets to move into phase III. But, with its dominance in cystic fibrosis set to continue, this is a nice problem to have.

Top five cystic fibrosis products in 2022					
				Global sales ($m)	
Project	**Company**	**Status**	**Mechanism**	**2016**	**2022e**
Orkambi	Vertex	Marketed	CFTR potentiator + CFTR corrector	980	2,293
Tezacaftor + ivacaftor	Vertex	Filed	CFTR potentiator + CFTR corrector	-	1,002
Second corrector + tezacaftor + ivacaftor	Vertex	Phase II	CFTR potentiator + CFTR corrector	-	971
Creon	Abbvie	Marketed	Enzyme replacement therapy	565	829
Kalydeco	Vertex	Marketed	CFTR potentiator	703	798
Source: EvaluatePharma.					

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