Evaluate Vantage

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Galapagos goes for broke in cystic fibrosis

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With promising data in hand, Galapagos appears to have one part of its cystic fibrosis triplet in place in the shape of the C1 corrector GLPG2222. But with triplet trials yet to start, the company and its partner Abbvie are around two years behind Vertex, which could have the cystic fibrosis space sewn up by then.

This does not seem to have dampened Galapagos's enthusiasm. The group has six compounds in development that could be mixed and matched to form a triplet, and it hopes to start its first three-drug trials by the end of the year (see table below).

Triplets comprise a CFTR potentiator and CFTR correctors from two different drug classes, with the aim of treating 90% of cystic fibrosis patients. While subjects with certain mutations respond well to existing therapies, other groups currently have few options.

Vertex threat

Vertex is already well ahead, and could have a triplet approved as early as 2020. It helps that the company already has two of the components in place: its potentiator, Kalydeco, is marketed, while one corrector, tezacaftor, is awaiting approval.

Tezacaftor in combination with ivacaftor – the active ingredient of Kalydeco – has a PDUFA date of February 28 for patients homozygous for the F508del mutation, or patients with one F508del mutation and one residual function mutation.

For its triple combo, therefore, Vertex only needs to find a second corrector, and it currently has four candidates: VX-440, VX-152, VX-659 and VX-445. The group presented promising phase II data with the first two in July (*Vertex eyes the treble in cystic fibrosis, July 19, 2017*).

At the time, Vertex said it would start phase III trials with one or two of its triplets in the first half of 2018, but declined to give more details of its plans.

It is thought that one regimen will consist of tezacaftor, ivacaftor and one of the new correctors given twice daily, while the other could comprise tezacaftor, VX-561 – deuterated ivacaftor (formerly CTP-656) – and a different second-generation corrector, administered once daily. *EvaluatePharma* sellside consensus predicts that whatever Vertex triplet wins out, it will bring in sales of around $3bn in 2022.

Developing an in-house triplet will be a harder task for Galapagos, which discontinued its potentiator GLPG1837, and whose remaining cystic fibrosis projects are all in phase II or earlier.

Galapagos CF pipeline						
Project	**Mechanism**	**Status**	**Population**	**Dosing**	**Trial ID**	**Data**
GLPG2222	C1 corrector	Phase II	F508del/gating mutation	150mg/300mg 2222 + Kalydeco	NCT03045523 (Albatross)	Reported
			F508del homozygous	Monotherapy, four doses	NCT03119649 (Flamingo)	Primary completion Mar 2018
GLPG2737	C2 corrector	Phase II	F508del homozygous	2737 + Orkambi vs Orkambi alone	2017-002181-42 (Pelican)	Unknown
GLPG2451	Potentiator	Phase I	Healthy subjects	2451 + 2222	NCT03214614; NCT02788721	Completed
GLPG3067	Potentiator	Phase I	Healthy subjects	3067 +/- 2222	NCT03128606	Reported
GLPG2851	C1 corrector	Preclinical	-	-	-	-
GLPG3221	C2 corrector	Preclinical	-	-	-	-
Source: Company website; Clinicaltrials.gov; Leerink note November 3, 2017.						

GLPG2222 is the common component of the company's triplets, and data from the phase II Albatross study, released on Sunday, appear to be enough for Galapagos to proceed with development.

However, some analysts have questioned whether the data live up to those seen with tezacaftor/ivacaftor in phase II in the same population: patients with one F508del mutation and one gating (class III) mutation.

Albatross tested GLPG2222, at 150mg or 300mg per day, on top of Kalydeco, with a primary endpoint of safety. Secondary endpoints included change in sweat chloride concentration and FEV1, a measure of lung function.

The sweat chloride reduction with the 300mg dose was in line with tezacaftor/ivacaftor's phase II result, but the improvement in FEV1 with GLPG2222 fell short.

Across-trial phase II comparison of GLPG2222 and tezacaftor/ivacaftor				
	Albatross results with GLPG2222			**Tezacaftor/ivacaftor phase II**
	Placebo (n=7)	**150mg (n=15)**	**300mg (n=14)**	
Mean change in sweat chloride vs baseline, mmol/l	+5.6	-3.8*	-6.0*	-7.02
Mean change in ppFEV1 vs baseline	-0.8%	-0.6%	+2.2%	+4.6 percentage points*^
**p<0.05; ^not placebo-adjusted. Source: company presentation; Stifel note November 20, 2017.*				

While the usual caveats about across-trial comparisons apply, this appears to bode ill for GLPG2222, and there is another reason for caution: tezacaftor/ivacaftor failed in phase III in this population. Leerink analysts note that these patients are already well controlled on Kalydeco, which could make it difficult to show a benefit with additional therapy.

Still, Galapagos was encouraged by the signs of efficacy and GLPG2222's clean safety profile, and is pushing on. A study of its first in-house triplet, comprising GLPG2222, GLPG2737 and GLPG2451, is expected to start by the end of the year, with data due in mid-2018.

Meanwhile, a second triplet, made up of GLPG2222, GLPG2737 and GLPG3067, could move into trials in healthy volunteers this year, and begin studies in patients in the first half of 2018.

Both triplet trials are expected to be conducted in Europe, which has led some analysts to question Galapagos's US strategy.

And the group’s aggressive approach is also risky, although understandable given Vertex’s headstart. Beginning triplet trials without first carrying out studies of dual combinations means that if any safety signals arise it might be difficult to determine which component is responsible, Stifel anlaysts noted.

A case in point could be GLPG2451. This project has a half-life of around one month, which has led to concerns about toxicity.

Galapagos is taking a big gamble in its quest to catch up with Vertex. Clues might start to emerge next year about whether this will pay off.

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