Cystic fibrosis spotlight turns to Galapagos

Jonathan Gardner

Nivalis Therapeutics’ failure to show that cavosonstat could improve lung function in a phase II cystic fibrosis (CF) trial sets the table for its rival Galapagos, which will see key phase II readout of its CF lead by the end of 2016.

The AbbVie-partnered GLPG1837 is seeking to take on Vertex’s Kalydeco, and in addition Galapagos has an arsenal of CF-modulating agents that aim to mimic Vertex’s combination strategy. The upstarts would trail Vertex by several years in launching a monotherapy, but with ambitious plans to get combinations into the clinic next year the race is getting tighter.

Headed to the dustbin

Nivalis’s approach was unique in the CF pipeline and, ultimately, looks like it has little promise. As an add-on to Vertex’s combination product Orkambi, cavosonstat sought to stabilise CF transmembrane conductance regulator (CFTR) that was misfiring because of a F508 deletion mutation. Shares in the Colorado-based firm fell 54% in early trading today, taking the company’s market capitalisation to cash levels.

By comparison, the Vertex and Galapagos approaches aim to improve the cellular chloride channel functioning of CFTR to prevent the buildup of sticky mucus that clogs the lungs and digestive tracts, leading to tissue damage. This type of therapy is called a potentiator, represented by Vertex’s Kalydeco and GLPG1837.

<table>
<thead>
<tr>
<th>Company</th>
<th>Galapagos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>GLPG1837</td>
</tr>
<tr>
<td>Market cap</td>
<td>$2.9bn</td>
</tr>
<tr>
<td>Event type</td>
<td>Phase II data</td>
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<tr>
<td>Date</td>
<td>December 2016</td>
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Both have a second string to their CF bows – CFTR correctors, represented by the lumacaftor component of Vertex’s Orkambi and Galapagos’s GLPG2222. These treatments are aimed at the F508 deletion, where the potentiators tend to work as monotherapies in the population with the less common G551D mutation.

Getting positive phase II data from its lead project would raise hopes that the Galapagos CF pipeline can be competitive with Vertex.

Stronger dose needed

The Saphira1 phase II trial of GLPG1837 has completed its four-week ascending-dose protocol in 26 G551 deletion patients, and is due to read out by the end of December, Galapagos’s science chief said in the group’s third-quarter results call. It is an open-label study with safety as a primary endpoint, but researchers will also gather biomarker data in the form of sweat chloride concentrations, along with lung function tests.

Galapagos has already released data from another phase II trial, Saphira2, in patients with the S1251N mutation, which the group said was typical in its home Benelux region. This trial included some patients who had been treated with Orkambi, after a washout, and others who had never been treated.

This dosing trial found that pretreated patients only stabilised lung function, while treatment-naive patients saw lung function improvements. Researchers also measured reductions in sweat chloride concentrations. The company described some of the findings as disappointing, but noted that higher doses had been used in Saphira1.

In any case, GLPG1837 is one of three potentiators Galapagos has in its pipeline, with GLPG2451 in a phase I trial in healthy subjects as a monotherapy and combined with the corrector GLPG222. The company says the
The ultimate treatment goal is a triple therapy of one potentiator and two correctors.

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Pharmacological Class</th>
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<tbody>
<tr>
<td>Translarna</td>
<td>PTC Therapeutics</td>
<td>Transcription modulator</td>
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<tr>
<td>VX-661 + ivacaftor</td>
<td>Vertex Pharmaceuticals</td>
<td>CFTR corrector/potentiator</td>
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<tr>
<td>GS-5745</td>
<td>Gilead Sciences</td>
<td>MMP-9 MAb inhibitor</td>
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<tr>
<td>GLPG1837</td>
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<td>Gilead Sciences</td>
<td>Epithelial sodium channel blocker</td>
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<td>VX-371</td>
<td>Vertex Pharmaceuticals</td>
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<tr>
<td>Cavosonstat*</td>
<td>Nivalis Therapeutics</td>
<td>CFTR modulator</td>
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<tr>
<td>Second corrector &amp; VX-661 + ivacaftor</td>
<td>Vertex Pharmaceuticals</td>
<td>CFTR corrector/potentiator</td>
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<tr>
<td>ABBV-974</td>
<td>Galapagos</td>
<td>CFTR potentiator</td>
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<td>VX-440</td>
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These CF assets are part of an AbbVie alliance first struck in 2013 and expanded in 2016 with the goal of establishing the triple combination. If, as planned, the partners start testing a triple in humans toward the middle or end of 2017, they will be a scant one to two years behind Vertex.

Given that AbbVie assumes control of the Galapagos CF pipeline on entry to phase III and will be able to put its big pharma R&D might behind it, the triple combination space seems ready to get more competitive. But first, the sector will be looking for success in the relatively modest single-agent Saphira1 dosing trial.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial ID</th>
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<tbody>
<tr>
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