Clinical win gives Verona a kiss of life

Jacob Plieth

For Verona’s long-suffering shareholders today brought an unexpected clinical success with ensifentrine.

The UK’s Verona Pharma, for years shunned by investors, today made a valiant attempt at a recovery. A chronic obstructive pulmonary disease study of its lead project, ensifentrine, succeeded in boosting the effects of Boehringer Ingelheim’s Spiriva, initially sending Verona stock surging 60%, albeit from a low base.

Thus one half of the company’s strategy might be in place: the plan is to position ensifentrine as an add-on to Spiriva as well as on top of the dual therapy Stiolto. However, an earlier study of the latter combo failed, and what Verona still lacks is a licensing deal to validate ensifentrine.

This has proved elusive. One problem is that many companies see the respiratory space as commoditised and too risky to spend the huge amounts needed to run the necessary large-scale pivotal studies.

Another is possible doubts about intellectual property. Ensifentrine has been around for so long that its original composition patent expires this year. Any licensing partner would have to take a bullish view of US and EU patents that protect the PDE3/4 inhibitor’s nebulised formulation, and claim exclusivity until 2035.

Success

For now, however, at least Verona has one important clinical win under its belt. In a study of 416 COPD subjects each nebulised ensifentrine dose combined with Spiriva beat a control arm of Spiriva alone in terms of the primary endpoint, improvement in FEV₁ at four weeks.

Importantly, there was a clear numerical dose-response relationship, with the Spiriva-adjusted FEV₁ benefit from baseline increasing with each rising ensifentrine dose; the dose range was 0.375-3mg, and each of the four doses met statistical significance at p≤0.05, Verona stated, with Spiriva control performing as expected.

The data build on an earlier study in 30 patients, where ensifentrine 1.5mg and 6mg plus Spiriva beat a Spiriva control in terms of day-3 FEV₁.

The elephant in the room, however, is that Spiriva itself is being displaced by Boehringer’s more efficacious combo, Stiolto, which comprises Spiriva’s active ingredient combined with the LABA olodaterol. And, given on top of Stiolto, nebulised ensifentrine has failed to beat Stiolto alone.
That disappointment a year ago exacerbated a share price decline, and even after today’s increase Verona’s market cap stands at under $150m. The UK company had raised $78m in 2017 US secondary Nasdaq listing, and its stock still stands well below that.

### Selected nebulised ensifentrine studies in COPD

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Result</th>
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<tbody>
<tr>
<td>NCT03443414</td>
<td>Versus placebo (no LABA use allowed)</td>
<td>0.75mg, 1.5mg, 3mg &amp; 6mg doses all hit 4-week FEV&lt;sub&gt;1&lt;/sub&gt; endpoint</td>
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<tr>
<td>NCT03028142</td>
<td>On top of Spiriva, vs Spiriva</td>
<td>1.5mg &amp; 6mg doses hit day-3 FEV&lt;sub&gt;1&lt;/sub&gt; endpoint; 6mg hit avg FEV&lt;sub&gt;1&lt;/sub&gt; co-primary</td>
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<tr>
<td>NCT03937479</td>
<td>On top of Spiriva, vs Spiriva</td>
<td>0.375mg, 0.75mg, 1.5mg &amp; 3mg doses hit 4-week FEV&lt;sub&gt;1&lt;/sub&gt; primary, with dose response</td>
</tr>
<tr>
<td>NCT03673670</td>
<td>On top of Stiolto, vs Stiolto</td>
<td>1.5mg &amp; 6mg doses failed day-3 FEV&lt;sub&gt;1&lt;/sub&gt; endpoint; numerical benefit claimed for 1.5mg</td>
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How much clinical mileage there is in adding a new drug on top of Spiriva remains an important unanswered question. Despite that failed Stiolto combo study, speaking to Vantage today Verona’s chief executive, Jan-Anders Karlsson, insisted that ensifentrine was active on top of Spiriva and a LABA.

He added that Spiriva remained the most commonly used starting drug for COPD. The company hopes that the data will reinvigorate partnering interest, and clearly it will be up to potential licensees to gauge the size of the opportunity.

Interestingly, the pivotal programme is somewhat agnostic as to the background therapy. Mr Karlsson said two identical phase III studies were envisaged, in which 70% of subjects would be on no background COPD therapy; the remainder would be on a bronchodilator that may or may not be Spiriva, and only later would a pivotal triple combo trial be considered.

The cost of the two pivotal trials would be $100-125m, Verona told an analyst call, something that looks unsustainable while the group remains capitalised at little over $100m. A decision on this and the market opportunity rests with partners.