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EP Vantage exclusive – Boehringer battles delay to put Spiriva combo together

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Boehringer Ingelheim has used the European Respiratory Society meeting in Barcelona to showcase key aspects of its plan to defend the blockbuster Spiriva, but has also revealed that the olodaterol half of a Spiriva combination is mired in a US regulatory delay.

Fortunately for Boehringer the setback is not related to safety or efficacy of the long-acting beta 2 agonist, which was blessed by an advisory panel vote back in January. But there is no time to lose if the private German firm is to make waves in a changing market that could soon see a US generic threat to GlaxoSmithKline's Advair.

Being a private business Boehringer is under no obligation to make market announcements, and as such has never disclosed the US FDA's action date for olodaterol. However, it was clear that things were not proceeding smoothly given the lack of a regulatory decision nine months after a 15-1 vote in favour of the chronic obstructive pulmonary disease (COPD) project (*Boehringer breathes more easily after Striverdi adcom vote, January 30, 2013*).

The company has now told *EP Vantage* that the US agency had responded to the filing with a request for more information. "Safety and efficacy data ... were not brought into question by the FDA response. I can't speculate further on the FDA timeline," a spokesman said.

Manufacturing

The FDA's questions relate to Boehringer's broader manufacturing violations, which had come to light in an FDA warning letter in May. This had cited contaminations in an unnamed API and finished product, and discrepancies in a finished Spiriva Handihaler batch.

Until now the issue with olodaterol appeared to have been its lack of a strong advantage over other products. Indeed, at the ERS meeting Boehringer presented findings from four phase III olodaterol trials in over 3,000 COPD patients, showing statistically significant improvements in lung function versus standard care, and efficacy comparable to formoterol – not exactly the cutting edge of COPD therapy.

However, superiority rarely bothers the FDA as long as a product can demonstrate a sufficient risk-benefit profile; rates of adverse events were comparable between olodaterol, standard care and formoterol.

Either way, olodaterol's main role is not as a standalone drug but as part of a combination with Spiriva. The combo is a key part of Boehringer's plan to protect its COPD franchise beyond the 2018 patent expiry of Spiriva.

Handihaler vs Respimat

Another important piece of this puzzle is the planned use of the Respimat inhaler with the combo. Standalone Spiriva is delivered through either the Handihaler or Respimat device, but only the former is approved in the US.

A retrospective analysis had linked Respimat to an increased risk of early death. As such, US approval of standalone olodaterol – which also uses Respimat – would provide a strong vote of confidence in the device.

Another front in this battle is Boehringer's attempt to get Spiriva itself approved in the US in the Respimat inhaler. To this end at the ERS the company unveiled results from Tiospir, a three-year, 17,000-patient trial comparing once-daily delivery of Spiriva via the two devices.

"We are also waiting for FDA approval for Spiriva Respimat and certainly expect that ahead of [approval of the] combination, and I'm sure the announcement of the Tiospir results will help this process," the spokesman said, again without disclosing timelines. It is possible that the manufacturing snafu is holding matters up here too.

In Tiospir, Spiriva Respimat and Handihaler showed similar median times to COPD exacerbation – 756 and 719 days respectively – and an equal impact on all-cause mortality. This must be seen as highly encouraging given the earlier fears, although Boehringer says US approval of Spiriva Respimat is not a vital pre-requisite for that of the olodaterol combo.

Shifting landscape

This manoeuvring comes as the respiratory landscape shows signs of shifting at last, with US generic versions of Glaxo's Advair blockbuster coming a step closer after the publication of draft FDA guidance yesterday (*GSK moat breached as FDA issues generic Advair guidance, September 10, 2013*). A separate leg of Glaxo's own lifecycle strategy, Anoro Ellipta, faces a US panel vote today.

The next key data point for Boehringer will be two pivotal studies of the Spiriva/olodaterol combination itself in 5,163 COPD patients, due to be completed later this year. "We will publish results of these in due course at future medical meetings," the Boehringer spokesman said.

But first the company must rule out any risk of a protracted delay by fixing the manufacturing violations. Olodaterol might not

have a huge solo role to play, but it must find its way onto the US market soon.

Boehringer's Spiriva lifecycle management strategy			
Study	**Design**	**Trial ID**	**Results**
1222.11	625 COPD pts, olodaterol Respimat vs placebo	NCT00782210	Data at ERS 2013
1222.12	644 COPD pts, olodaterol Respimat vs placebo	NCT00782509	Data at ERS 2013
1222.13	906 COPD pts, olodaterol Respimat vs formoterol	NCT00793624	Data at ERS 2013
1222.14	937 COPD pts, olodaterol Respimat vs formoterol	NCT00796653	Data at ERS 2013
Tiospir	17,210 COPD pts, Spiriva Handihaler vs Respimat	NCT01126437	Data at ERS 2013
Mezzotina	1,071 asthma pts, Spiriva Respimat vs salmeterol	NCT01172808	Data at ERS 2013
Mezzotina	1,032 asthma pts, Spiriva Respimat vs salmeterol	NCT01172821	Data at ERS 2013
Tonado-1	2,624 COPD pts, Spiriva + olodaterol Respimat combo vs standalone ingredients	NCT01431274	Completion Sep 2013
Tonado-2	2,539 COPD pts, Spiriva + olodaterol Respimat combo vs standalone ingredients	NCT01431287	Completion Nov 2013

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