

Therapeutic Focus - Late-stage LAMAs breathing down Spiriva's neck



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Novartis has grabbed much attention at the European Respiratory Society conference over the last few days with its long-acting muscarinic antagonist, NVA237, but the once-daily COPD therapy is not the only new product eyeing a slice of Spiriva's \$4bn market.

Data on two other LAMA contenders were presented at the meeting, Eklira from partners Almirall and Forest Laboratories, and GlaxoSmithKline's umeclidinium. While Eklira is the most advanced of the R&D pack, consensus forecasts suggest NVA237, now branded Seebri Breezhaler, is considered the staunchest competitor for Boehringer Ingelheim's Spiriva (see table below). However, ahead of phase III data on Glaxo's product, the experienced respiratory giant's efforts should certainly not be dismissed.

On the horizon

Launched in 2002, Boehringer's Spiriva has enjoyed many years as the only once-daily LAMA on the market for COPD, with solid efficacy in improving lung function and reducing exacerbations. But these days of dominance are numbered, with a number of rivals close to completing development programmes with agents they believe are more potent, more tolerable and delivered in improved devices.

At the same time, combining a LAMA with a long acting beta 2 adrenoreceptor agonist (LABA) is increasingly being viewed as potent therapeutic option for COPD patients ([ERS - Novartis' indacaterol laying groundwork for combination success](#), September 16, 2009). So Spiriva is likely to face competition on more than one front in the years to come.

Selected muscarinic antagonists on the market and in development					
	Product	Generic Name	Pharmacological Class	Company	Origin
Marketed	Spiriva	tiotropium bromide monohydrate	LAMA	Boehringer Ingelheim	Boehr Ingelh
Filed	Seebri Breezhaler (NVA237)	glycopyrrolate	LAMA	Novartis	A.H. R
	Eklira	aclidinium bromide	LAMA	Forest Laboratories/Almirall/Kyorin Holdings	Almira
Phase III	QVA149	glycopyrrolate; indacaterol maleate	LAMA & LABA	Novartis	A.H. R
	GSK573719/vilanterol	umeclidinium; vilanterol trifenate	LAMA & LABA	GlaxoSmithKline	Thera
	GSK573719	umeclidinium	LAMA	GlaxoSmithKline	Glaxo!
	Spiriva/olodaterol	tiotropium; olodaterol	LAMA & LABA	Boehringer Ingelheim	Yama
Phase II	GSK961081	-	MABA (single molecule)	GlaxoSmithKline	Thera
	AB + Formoterol	aclidinium bromide; formoterol fumarate	LAMA & LABA	Almirall/Forest Laboratories	Almira
	PT001	glycopyrrolate	LAMA	Pearl Therapeutics	A.H. R
	PT003	formoterol fumarate; glycopyrrolate	LAMA & LABA	Pearl Therapeutics	A.H. Robins
	EP-101	glycopyrrolate	LAMA	Elevation Pharmaceuticals	Elevat Pharm
	AZD8683	-	LAMA	AstraZeneca	AstraZ

Big player

A huge player in the respiratory market with Advair, a combination of a LABA and corticosteroid, Glaxo has been working on a new suite of respiratory products with partner Theravance for several years.

They are running seven phase III studies testing their novel LABA and LAMA contenders, vilanterol and umeclidinium, also known as GSK573719. Recruiting over 5,000 patients with COPD, the programme is testing the drugs in combination and as monotherapy, against placebo and Spiriva.

Pivotal data is not due to emerge until next year, but phase II data on '719 as monotherapy was presented at the ERS meeting this week. The improvement in lung function compared favourably with Spiriva, analysts at JP Morgan noted, adding that the data suggests the product could be competitive as a LAMA monotherapy.

Future holds

Also presented was phase IIa data from the companies' first-in-class MABA – an inhaled, single molecule bifunctional bronchodilator with both muscarinic antagonist and beta2 receptor agonist activity. The agent

significantly improved bronchodilation over a free combination of Spiriva and Serevent - an off patent LABA - and showed a non-significant faster onset of action with an encouraging safety profile.

Phase IIb data is due next year; analysts reckon the drug holds potential as part of a triple therapy, combined with an inhaled corticosteroid.

Glaxo will also start to unveil a raft of pivotal data on Advair follow-on Relovair next year. Alongside results from the LAMA/LABA programme this information will indicate what the future holds for the British pharma giant in the respiratory space.

Potent option

At this stage it is not clear whether Glaxo plans to launch umeclidinium as a monotherapy; as with Novartis much of the attention rests on the combination of the LAMA with a LABA. These dual therapies are further behind in development and as such consensus forecasts for the moment are heavily risk adjusted, although analysts and the companies believe these products hold the real commercial potential.

As the dominant incumbent in the LAMA space it is surprising Boehringer has let competitors get so far ahead with a combination product. According to Bernstein analysts, the company's efforts in this area were stymied by a set back in developing a suitable inhaler device. However, the company announced earlier this month that a phase III programme called TOviTO has started, investigating Spiriva plus the LABA olodaterol, using its Respimat Soft Mist inhaler.

The first two trials will compare the combination to its component parts, over 52 weeks and in 5,000 patients. Olodaterol has yet to be filed with regulators and the company plans to publish phase III data in the near future.

Also ran?

Also with a late-stage novel LAMA is Almirall and Forest with aclidinium, a drug that has taken much time and research effort to establish as a viable contender and has failed in past phase III studies, which was blamed on trial design ([*Almirall resuscitates ailing COPD drug, October 15, 2008*](#)).

Branded Eklira, the twice-daily LAMA has already filed for approval in both the EU and US and at ERS detailed data from a third pivotal trial were presented, confirming a potent but uninspiring profile, analysts believe.

As well as its less convenient dosing schedule, data so far suggests the drug is less effective than NVA237, and an "also-ran" future appears to beckon. A combination product is in phase II, pairing aclidinium with off-patent LABA formoterol, and pivotal trials are expected to start next year.

Should the Almirall/Forest products reach the market some analysts believe the partners will compete on price, adding another new dimension to a market currently enjoyed by one, dominant incumbent.

First real test?

Spiriva certainly represents a formidable incumbent to the new LAMAs in development, but it has drawbacks.

Approximately 20% of patients complain of dry mouth - in trials of NVA237 and Eklira this tolerability issue has been cut to around 3%. Meanwhile many patients dislike the inhaler device, and the new entrants all believe they have either smaller or less cumbersome devices to offer.

As such there is certainly scope for new entrants to take share. Should Eklira's regulatory progress be swift it will be the first to really test Boehringer's hold on the market. This prospect could help Almirall sign a weighty marketing partner in Europe, the search for which is ongoing.

But it seems likely the marketing might of Novartis and a little later Glaxo will present the first real test of Spiriva's appeal.