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Interview – Sterna still has to convince on antisense's chronic promise

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The approval of Biogen and Ionis's spinal muscular atrophy therapy Spinraza in 2016 validated the promise of antisense technology. But, owing to its high cost, antisense is generally perceived as being reserved for rare or life-threatening diseases.

Sterna is taking a different approach, developing an antisense project for chronic disorders such as asthma and atopic dermatitis, and believes that it can compete in these crowded sectors by making its molecules cheaper than rival monoclonal antibodies. But there are other reasons to be cautious about the private German company: its agent aims to hit a novel target that could have safety issues, and with data only available in a small number of patients potential collaborators might want to wait before pulling the trigger.

That target is Gata-3, which Sterna's chief executive, Christian Pangratz, describes as the "master transcription factor" in inflammatory diseases driven by T helper 2 (TH2) cells. He tells *EP Vantage* that hitting Gata-3 could improve efficacy over antibodies that act on a single cytokine late in the inflammatory process, for example IL-5 – the target of Glaxosmithkline's Nucala.

But there is the risk that knocking out something as important as Gata-3 might cause problems, which Mr Pangratz acknowledges. "If you entirely silenced Gata-3 the whole TH2 immune pathway would be silenced, so any antigens would have an open door and could cause serious diseases."

He believes that Sterna has got around this issue by only reducing Gata-3 levels by 75-80%. "I think we've found the secret sauce by knocking out enough of Gata-3 to have a therapeutically relevant effect, but not knocking out Gata-3 entirely and therefore causing other diseases."

The company's claims will need to be proven in larger trials – so far Sterna's three clinical-stage formulations, which all hit Gata-3, have only been tested in phase II studies in a small number of patients.

This is where partners come in, and Mr Pangratz admits that Sterna will need help to progress all its next-generation antisense molecules, which it calls DNAzymes, into phase IIb.

Clinical trials of Sterna's anti-Gata-3 asset

Formulation	Indication(s)	Trial details
SB010 (inhaled)	Asthma, COPD	38-pt phase II asthma trial, NCT01743768; 20-pt phase IIa COPD trial, DRKS00006087
SB011 (dermal)	Atopic dermatitis	25-pt phase II trial, NCT02079688
SB012 (enema)	Ulcerative colitis	20-pt phase II Secure trial, NCT02129439

Source: company website, Clinicaltrials.gov.

The company could take one or two projects forward itself, but would need to raise more cash. The chief exec says that on this front nothing is off the table, including an initial public offering. A lack of funds might explain why progress has been slow so far – SB010 completed a phase II study in its lead indication, asthma, back in 2014.

Active comparators?

As for the design of the next set of trials, Mr Pangratz says the group is considering including active comparator arms – a risky strategy that could make Sterna's candidates either irrelevant or real contenders, but which is probably the only way the company might gain an edge in these markets.

He seems ready to take the gamble: “Do we want to make a splash or a big splash? If we really want to take the market by storm it would make sense to include an active comparator.”

The company will have to hope that potential partners will have been tempted by data published last week from a phase IIa trial in COPD, which found a significant decrease in sputum eosinophil count with SB010 versus placebo.

If Sterna can find either the cash or collaborators it needs, and get its candidates to market, it believes that it will have an edge on price. In asthma the company would be aiming to treat severe disease where its rivals would include MAbs like Nucala, Roche’s Xolair and, perhaps, Sanofi and Regeneron’s Dupixent.

“We would be significantly cheaper than MAbs,” Mr Pangratz says. “DNAzymes have comparable functionality to biologics, but from a manufacturing perspective they’re like small molecules because they use a fully synthetic manufacturing process, which automatically makes them much cheaper.”

Still, Sterna has a long way to go before its dream of antisense therapies for chronic diseases can become a reality. So far the company’s venture investors have been “highly supportive”, according to Mr Pangratz. “Would they mind seeing a return on their investment? Absolutely not. Are they pressing to get out? Absolutely not.”

If safety concerns keep potential partners on the sidelines and Sterna’s progress continues to be slow, though, the patience of its backers might begin to wear thin.

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