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Kinaset takes a sledgehammer to an asthma conundrum

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The nascent company hopes to prove that its inhaled pan-Jak is best in class.

With $40m in venture funding in hand, Kinaset has one mission: proving that its inhaled pan-Jak inhibitor KN-002 works in both eosinophilic and non-eosinophilic severe asthma.

The newly formed company boasts a management team with years of experience in inhaled medicines, and will need to put this to good use: Kinaset lags behind the leaders in this space. Still, the group's chief executive, Robert Clarke, believes that KN-002 could end up being best in class and avoid the side-effects that have hampered systemic Jaks.

It seems a bit early to be making these assertions: KN-002, which Kinaset recently licensed from Vectura, is still at the preclinical stage. But a phase I study of the project, previously known as VR588, is set to start early in the second quarter of next year, so it will soon be put to the test.

Kinaset hopes to address an unmet need: there are several biologicals for severe eosinophilic asthma, but options for the non-eosinophilic subtype, which accounts for around half of severe asthma cases, are limited.

This might not be the case for long, though. In November Amgen and Astrazeneca reported a pivotal trial win for the TSLP inhibitor tezepelumab in eosinophilic and non-eosinophilic asthma; however, more recently the project failed in an oral corticosteroid-sparing study (*Source flop raises tezepelumab questions, December 22, 2020*).

However, Kinaset's Mr Clarke notes that tezepelumab is still an injected antibody, with all the inconvenience that this entails. "If we have a similar dataset, we think patients and prescribers would lean towards our inhaled approach."

Sledgehammer vs scalpel

As for the more selective inhaled Jaks, such as Astrazeneca's AZD0449 and Roche's RG6151, Mr Clarke reckons these might not have the oomph required for non-eosinophilic asthma. "We think the pan-Jak activity is a sledgehammer approach as opposed to a scalpel."

He believes that the more selective inhaled Jaks will end up being reserved for eosinophilic disease, where they would compete with biologicals. Even if this turns out to be the case, this is a market ripe for disruption: a recent Cowen note estimated that only 13% of eligible asthma patients took antibodies.

Mr Clarke acknowledges the side effects that have hampered broader-acting Jaks, but tells *Evaluate Vantage* that delivering KN-002 directly to the lung should have an advantage here, as keeping the drug out of the systemic circulation could reduce adverse events.

If he is right, Kinaset's main competitor will be Theravance, which has an inhaled pan-Jak inhibitor in mid-stage trials. However, this project, called TD-8236, recently stumbled in a phase II lung allergen challenge study in mild allergic asthma patients.

The company tried to put a brave face on the failure, noting during its third-quarter earnings call that this was not the population it would ultimately seek to treat with TD-8236. Theravance is awaiting the final data from part C of its phase I trial in its intended population, moderate to severe patients on background inhaled steroid therapy, and will then evaluate its next steps.

One question is why Theravance chose to carry out a challenge trial in the first place, particularly when other groups have also run into difficulties here – notably Glaxosmithkline, whose IL-5 inhibitor Nucala flunked its allergen challenge study. It should be some consolation to Theravance that Nucala since got approved and is now moving towards blockbuster status.

Mr Clarke is adamant that Kinaset never intends to carry out an allergen challenge study of KN-002 – partly because of the previous failures, but also because such a trial would only include patients with the eosinophilic subtype.

So Kinaset hopes to avoid the tripwire that Theravance just walked into. But Mr Clarke reckons that KN-002 could have an edge over TD-8236 in terms of efficacy, too: he claims that, based on preclinical data to be presented in 2021, KN-002 could be around 1,000-fold more potent than its pan-Jak rival.

A spokesperson for Theravance told *Vantage* that the company had not seen any potency data on KN-002 so could not comment on this. She added: "The most important determinant of therapeutic effect with Jak inhibition is not potency but therapeutic index", or the balancing of benefits against side effects.

Phase I plans

Kinaset now needs to put substance behind its words. The group's phase I trial will enrol around 120 patients and have three parts, starting with healthy volunteers, then mild asthmatics, and finally moderate to severe asthma patients.

As for the split between eosinophilic and non-eosinophilic patients, Kinaset plans to take all comers, Mr Clarke says, then classify them as either subtype.

As well as looking at safety, the study will evaluate fractional exhaled nitric oxide (FeNO) levels, with Kinaset hoping to see reductions of around 8-20%. The trial will also look at various inflammatory biomarkers.

If that goes well, the next step would be to go directly into a phase II study evaluating FEV_1 responses. But the ultimate aim for Kinaset would be showing a decline in the number and/or severity of asthma exacerbations.

All of Kinaset's eggs are currently in the KN-002 basket, but Mr Clarke is certain that the group has the right asset, saying the project stood out in Vectura's pipeline. And Kinaset should know: the company's other two co-founders, Roger Heerman and Frazer Morgan, were both previously Vectura stalwarts.

Still, the path towards drug development has tripped up even experienced execs, and Kinaset still has a long way to go.