Caladrius refuses to give up on Tregs for diabetes

After a trial failure last week, Caladrius Biosciences has not abandoned hope for its T regulatory cell therapy in type 1 diabetes, but funding might become a problem.

Using regulatory T cells to halt the progression of type 1 diabetes had always looked like a long shot. But Caladrius Biosciences tells Vantage that last week’s phase II failure of its Treg candidate CLBS03 might not spell the end for the project.

“The conclusion that people might jump to is that Tregs don’t work as a therapeutic in T1DM – but I think it’s a little premature,” the company’s chief executive, Dave Mazzo, says. Caladrius plans to mine the data from the failed phase II trial to see if there are any particular subgroups in which the Treg approach might work.

CLBS03 is an autologous therapy that involves harvesting patients’ Tregs, expanding them and infusing them back into the patient. The theory is that the enhanced Tregs damp down the immune system and stop the destruction of beta cells in the pancreas, the cause of type 1 diabetes.

So, rather than offering a cure, CLBS03 is designed to preserve patients’ remaining beta cells to reduce or halt the progression of disease.

Too little too late?

Even if this approach works – still a big if – a potential problem in type 1 diabetes is that by the time of diagnosis and treatment patients might not have enough viable beta cells for the pancreas to function properly.

Caladrius had hoped to address this by including only early-stage subjects in its phase Ila Sanford Project T-Rex study, partnered with Sanford Health. 113 adolescents were enrolled within 100 days of their diabetes diagnosis.

However, this did not help the trial meet its primary endpoint, preservation of C-peptide levels at one year versus placebo. And longer-term data, due next year, will probably not change the picture, Mr Mazzo admits. “Candidly, it’s hard to expect anything different between what we saw at the group level at one year versus two years.”

But he maintains that the trial flop is not a disaster for Caladrius. “We never really expected that we could go from this directly into a pivotal trial or pronounce that we’d cured diabetes.”
He claims that there is still a lot to learn from the study, which he describes as the first “truly rigorously controlled trial using Tregs in an autoimmune disease”.

The optimistic view is that there are some patients within this early-stage group who might have enough intact beta cells to benefit from Treg therapy, with Mr Mazzo noting that type 1 diabetes is “an extraordinarily heterogeneous disease”.

Factors the company will be delving into include patients’ baseline insulin production, diet, compliance with insulin therapy, and their stage of puberty, which can affect hormone regulation.

More money needed

Mr Mazzo reckons that Caladrius should have a better idea of the next steps by the end of the year. If there are any glimmers of hope he does not expect to be able to go straight into phase III, but instead to carry out “one or more phase IIb trials to corroborate any hypotheses generated by the data”.

One thing the company will probably not be able to do is increase the dose, as 20 million Tregs per kg, the highest dose in the trial, was the limit set by the FDA in this trial. In general there are concerns that Tregs, by suppressing the immune system, could leave the door open for infections or even cancer.

And the question of how any new trials might be funded is another matter. Caladrius had around $43m in cash at the end of 2018, enough to last around 18 months at the current burn rate, Mr Mazzo says.

A bigger priority for the company during this time will be a US phase III trial of its CD34 cell candidate CLBS14 in refractory angina, set to start later this year. Mr Mazzo expects this to take around two and a half years to complete, meaning that Caladrius is already looking at a funding shortfall.

The chief exec accepts that sifting through the diabetes data will be a big and expensive task, adding that the company is talking to Sanford about who will pay for the various aspects of the T-Rex postmortem.

Caladrius appears to be the only company to have a clinical-stage Treg-based project for type 1 diabetes. Sangamo, which acquired the CAR-Treg specialist Txcell last year, has expressed an interest in the disease, as well as in other autoimmune disorders, but its first CAR-Treg clinical trial, slated to start this year, will look at the prevention of organ transplant rejection.

Caladrius’s stumble demonstrates how difficult it is to develop therapies for type 1 diabetes, beyond insulin. The company has not given up yet, but its Tregs now look like an even longer shot.