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Stakes 'couldn't be higher' – PTC CEO on prospect of Translarna losing EU conditional authorisation

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INTERVIEW

by Thomas Meek

LONDON, 7 Nov (APM) - The stakes "couldn't be higher" regarding the future of PTC Therapeutics' Translarna as a treatment for boys with Duchenne muscular dystrophy (DMD) in the EU, according to the company's chief executive.

Matthew Klein told APM of his concerns with the recent recommendation from the European Medicines Agency (EMA)'s CHMP not to renew the conditional marketing of the drug to treat patients aged two years and older with DMD who are able to walk and who have a nonsense mutation in the dystrophin gene.

The recommendation, which is still to be finalised, comes nearly 10 years after the drug was first approved in the EU in 2014, during which time it has been the only drug approved in the region specifically to treat DMD, a rare muscle wasting condition that mainly affects young males.

"You have got boys who have no other therapy specifically targeting their genetic disease that have been approved, who have a disease that over time they will lose the ability to walk, lose the ability to breathe and will die," Klein said in a recent phone interview.

"Now you have a therapy. It may not be a cure, but it has certainly been

demonstrated to slow the course of disease," he said, adding that the drug has also been shown to be safe and well tolerated.

PTC, which is based in New Jersey, has requested a re-examination of the CHMP's opinion, with Klein telling APM he expects the procedure to run through to late January 2024, after which another opinion will be published.

And PTC is hopeful it can convince the CHMP of the benefits of Translarna (ataluren) in this process, said Klein.

"We have a responsibility to ensure that we clearly demonstrate and clearly articulate these benefits, and clearly address the concerns that have been raised by the CHMP. And we're going to do that. I think the stakes couldn't be higher. This is a fatal disease."

REAL-WORLD DATA

The re-examination process will see PTC make the case for Translarna based on real-world data (RWD) collected via the STRIDE registry, which includes 300 boys with an average treatment duration of over 5.5 years.

Klein said RWD is important to understand the benefits over time of a drug like Translarna, which is intended to increase production of dystrophin, a protein that is lacking in people with DMD. This compares with standard of care steroids, which have a more immediate response in targeting symptoms.

"There's no possible way you can start appreciating the clinical benefits of a therapy [like Translarna] until the biological benefits become manifest," said Klein.

He noted that data from STRIDE has shown that Translarna delays the time to loss of ambulation by 3.5 years.

The CHMP used data from this registry to help inform its latest recommendation, looking in particular at the outcomes of patients treated with Translarna versus natural history data. The CHMP noted the positive results with Translarna in terms of delaying the loss of ambulation, however, the committee "could not draw conclusions from these data due to methodological issues and uncertainty linked to the indirect comparison", said the EMA.

This issue is something that PTC is working on as part of the re-examination process, said Klein, remarking that the company is intending to "more explicitly demonstrate" all of the steps that were taken to show the attribution of treatment effect to Translarna.

This covers several areas, including the design of the registry to ensure that data collection and monitoring are rigorous and appropriate; the processes for patient matching in the natural history cohort; and the use of sensitivity analyses to

ensure all potential sources of bias have been minimised.

"We can't turn a registry into a placebo-controlled trial, but what we can do is demonstrate all known sources of potential bias that could confound the results of that comparison have been addressed and mitigated," said Klein.

He added that this work will be "very helpful in reassuring the CHMP that the benefit recorded is attributable to Translarna".

"And when you talk about a multi-year delay in time to loss of ambulation, that is a lot. That is of unequivocal meaningfulness to patients with DMD," he said.

CONFIRMATORY STUDY

Klein also commented on the results of a confirmatory Phase III story, known as study 041, which also helped inform the CHMP's latest recommendation. This study was requested by the CHMP to verify the benefits of the drug seen in the initial Phase II study used to support conditional approval in 2014.

Study 041 was a double-blind, placebo-controlled trial carried out in 360 patients aged seven years or older with nonsense mutation DMD, with the CHMP looking in particular at the drug's effectiveness in a subgroup of patients with a progressive decline in their ability to walk, as they were expected to benefit more from Translarna treatment than the broader patient population.

However, the CHMP said that in this subgroup of patients, the study "did not show a statistically significant difference between Translarna and placebo" in terms of the distance patients could walk in six minutes after 18 months of treatment and that results in the broader patient population failed to confirm the effect seen in the earlier Phase II study.

Klein took issue with the CHMP's focus on the subgroup, saying that in the overall population, there was "nominal statistical significance across all key endpoints".

"That is unquestionably demonstrative of treatment benefit," he said, adding that it is an "open question" on whether the CHMP will view the data differently in the re-examination process.

OTHER DMD DRUGS

Since the CHMP made its recommendation regarding the conditional authorisation, it has recommended EU approval of Santhera Pharmaceuticals' Agamree (vamorolone) for the treatment of patients aged four years and older with DMD (APMHE 83058). The drug is a dissociative corticosteroid that selectively binds to the glucocorticoid receptor, triggering anti-inflammatory effects.

Klein said it was important not to think of the drug as a direct substitute for Translarna, as its benefits are felt on top of steroid treatment.

"I think it would be not quite accurate for patients, physicians or regulators to think, 'oh, we have vamorolone, we don't need Translarna'. No, the Translarna benefit is on top of standard of care corticosteroids."

UK PROSPECTS

APM also questioned Klein on whether a negative EMA decision could influence a regulatory decision in the UK, where the drug is also approved and reimbursed on the National Health Service (NHS).

"I'm sure the [UK drugs regulator] MHRA is confident that they can do its own assessments," he said, adding that there a number of physicians in the UK who are supportive of the drug and prescribe it to patients. It has also been backed by England's health technology assessment (HTA) body NICE (APMHE 79939).

"There has been scientific rigour applied to the assessment of Translarna and that's been favourable in the UK. Obviously we will continue to work as needed with MHRA to ensure access to the drug for boys in the UK, regardless of the outcome in the EU."

TRANSLARNA U.S.

PTC still has ambitions for Translarna in the U.S. as well despite facing several previous rejections from the Food and Drug Administration (FDA).

Klein said the company plans to meet with the FDA soon to discuss a path to resubmission.

"We believe very strongly that we have a data package incredibly supportive of that benefit, so we look forward to having those discussions," he said.

RESTRUCTURING

Amid the challenges around Translarna, PTC is also undergoing restructuring, announcing at the end of September plans to cut its workforce by about 25% and divert its resources into "differentiated, high potential" R&D programmes and its global commercial infrastructure.

Klein said the changes do not change the mission of the company regarding the development of drugs for rare diseases and are instead about focusing the direction of PTC.

"The restructuring is more of a right-sizing of the organisation given our all the opportunities we have going forward and ensuring that we're in a stronger

financial position as possible to realise all that potential."

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