Such Great Heights

Pediatric growth hormone deficiency treatments could soon be painless.

BY DEREK BAGLEY

Fernando Cassorla, MD, is traveling from Chile to Chicago to present research at **ENDO 2023** that could potentially change the way pediatric hormone treatments are administered. If a pill could replace painful injections, patients and caregivers alike can finally wipe away their tears.

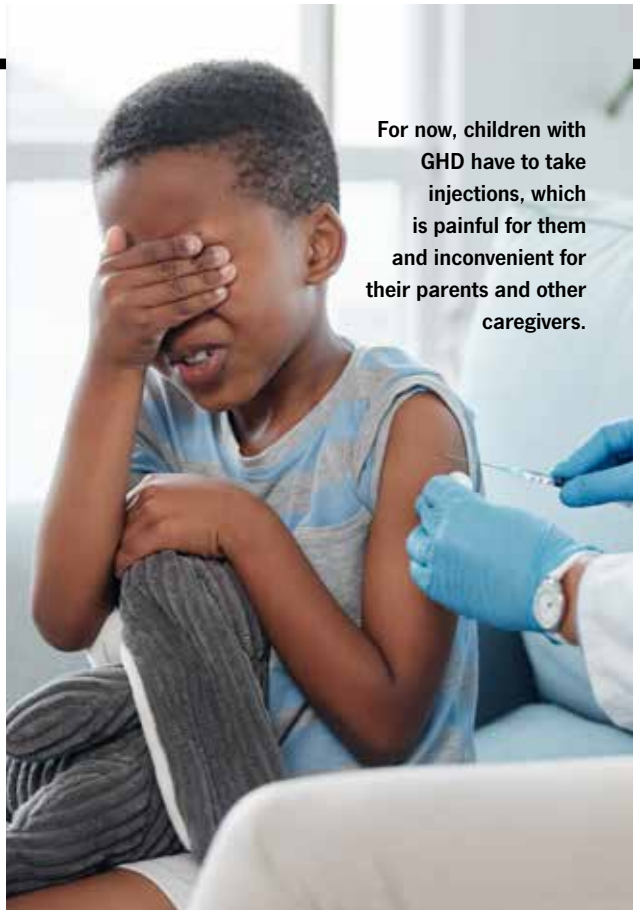
A convenient, well-tolerated treatment for pediatric growth hormone deficiency has until just recently remained elusive for children with this condition and their parents and caregivers who have had to administer daily, painful injections. Several pharmaceutical companies have introduced long-acting growth hormone therapies (LAGH), after the Growth Hormone Research Society recognized the need for these treatments in 2015, citing non-compliance rates as high as 82%.

This past March, Fernando Cassorla, MD, chief of Pediatric Endocrinology at the University of Chile in Santiago, traveled to Buenos Aires, Argentina, to present positive data on an investigational oral treatment for idiopathic pediatric growth hormone deficiency (iPGHD) at the 2023 International Meeting of Pediatric Endocrinology (IMPE). The drug, LUM-201 (ibutamoren) is a growth hormone secretagogue (GHS) that's currently in three Phase 2 trials.

Cassorla reported findings from the OraGrowtH212 trial (funded by Lumos Pharma, Inc.), a single-site open-label trial evaluating the pharmacokinetic (PK) and pharmacodynamic (PD) effects of oral LUM-201 in 22 treatment-naïve PGHD subjects at two dose levels, 1.6 and 3.2 mg/kg/day, on which he is the lead author. The subjects in this trial were first tested with a predictive enrichment marker (PEM), used to identify patients previously diagnosed with iPGHD who are likely to respond to LUM-201.

For this presentation, attendees in Buenos Aires heard the results of analysis of 15 subjects. The updated analysis included data on five additional subjects (three in the 1.6 mg/kg treatment arm, two in the 3.2 mg/kg treatment arm) since interim results of the OraGrowtH212 Trial were announced in November 2022. Results showed that across the dose range of 1.6 to 3.2 mg/kg/day for six months, LUM-201 is well-tolerated and produces dose-dependent and substantial increases in growth hormone under the baseline-corrected plasma concentration versus time curve from 0 to 12 hours (AUC0-12h). Results also showed that increased growth hormone pulse amplitude was associated with improved height velocity compared to baseline, and that effects on annualized height velocity were durable through 12 months.

Cassorla says that the findings made it clear that the amplitude of the GH pulses was higher, rather than the number of pulses,



For now, children with GHD have to take injections, which is painful for them and inconvenient for their parents and other caregivers.

and that the children were growing better than they were before starting the trial. "We were very encouraged by this, because it's indicated that if you select the correct population, then it's very likely, in contrast to what we observed several years ago with the original study, that patient selection here is key," he says. "And if you do that, then it's very likely that these patients will grow quicker."

This month, Cassorla will make the trip to Chicago for **ENDO 2023** to present an update on the OraGrotH212 trial — most notably results from evaluating IGF-1 levels in these patients. Here we'll look at the background of this oral treatment, the promising findings from these ongoing trials, and what this drug could mean for children with growth hormone deficiency.

Cautious Optimism

Cassorla says that before 1985, there was no recombinant available, just the National Pituitary Agency in Baltimore. The National Hormone and Pituitary Program (NHPP), funded by the U.S. Department of Health and Human Services (HHS) would gather pituitaries from corpses, purify them, and allocate a little bit of human growth hormone (hGH) to institutions for study and treatment. Clinicians could give patients growth hormone three times a week, but as there was not enough product, they couldn't treat patients through their full growing period.

> The question is, for these patients with partial to moderate growth hormone deficiency, how do we treat them, how do we define them? This is a group of patients that we think will benefit from this drug. This is a key message, and I think it's a promising area of research. **We'll see whether the preliminary data is confirmed by longer-term data, but up to now, it looks quite promising."**
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> — FERNANDO CASSORLA, MD, CHIEF OF PEDIATRIC ENDOCRINOLOGY, UNIVERSITY OF CHILE, SANTIAGO, CHILE

Then, in 1985, when the HHS discovered that three men treated with pituitary hGH died of Creutzfeld-Jakob disease and suspected the deaths were related to pituitary hGH, they halted the program, and so the era of recombinant growth hormone was born. "At that stage, we ended up having a lot of growth hormone commercially available, were able to treat patients until final height, seven days a week," Cassorla says. "There was a huge shift in the way children with growth hormone deficiency were treated from 1984 to 1985."

Another such shift may be on the horizon. A few years ago, Cassorla was part of a team investigating an oral treatment for pediatric growth hormone deficiency, in a study funded by Merck. The researchers had the idea that growth hormone secretagogue stimulates the ghrelin receptor in the brain, and this receptor stimulates both appetite and the secretion of growth hormone by the pituitary. Cassorla says after several years of study, it became clear that this peptide is produced in the stomach, and it stimulates at the level of the pituitary and at the level of the hypothalamus as secretion of growth hormone. However, Merck eventually abandoned pursuing the drug because of mixed results from patients who had unresponsive pituitaries.

"If you were to stimulate a pituitary that doesn't produce almost anything at all, it was not surprising that when you gave this drug, the patients would not produce growth hormone and would not grow very much," Cassorla says.

So, the researchers decided they would need to be more careful in patient selection, and only include candidates with responsive pituitaries, reasoning that those participants would produce more growth hormone and potentially grow more when this drug is given orally. "When the time came to look at this drug again under the umbrella of a different company, Lumos, patient selection would be key," Cassorla says. "And that's what happened in the second study. OraGrowtH212 has already enrolled and has completed enrollment for 22 patients. All of these are prepubertal children with partial or moderate growth hormone deficiency. That's the key point here, to get the message across."

"Now I may be too optimistic, but I envision another big shift in the way these patients are treated, if we can confirm that this orally administered drug can actually be helpful with patients with moderate growth deficiency, who are the vast majority of patients that we see in our clinics," he continues. "And I might add that living in Chile and living in South America, access to growth hormone because of cost and everything else is not that simple."

ENDO 2023

Update on Pediatric Growth Disorders – Oral Abstract – OR21

June 17, 2023 3:30 PM – 5:00 PM

Location: W-178B

"Dose Responsiveness of LUM-201 as Measured by Acute GH Response and IGF-1 and Annualized Height Velocity (AHV) Measured at 6 Months in the Interim Analysis of the OraGrowtH212 Study in Idiopathic Pediatric Growth Hormone Deficiency (iPGHD)" – **Fernando Cassorla, MD**

Potential for Sustained Success

Again, the results from these trials are promising, but there's still work to be done. Lumos Pharma hopes to complete these studies and announce top line results in the fourth quarter of 2023. Cassorla, who has no financial ties or commercial connection to Lumos, says his focus is on providing children and their families with simpler treatments and hopefully less expensive treatments, if possible. "That's my part of the goal, my part of the job here," he says. "And if we can have a relationship with the industry that is very clear, very transparent, and very honest, we're all in favor of doing it, because ultimately, it will benefit our patients."

For now, Cassorla has secured enough of LUM-201 for all 22 patients until they reach their final height. He says that while Lumos will proceed with regulatory steps to get the drug through the U.S. Food and Drug Administration (FDA), his job is to finish the study with the six-month pulsatility period that needs to be done in the other seven patients.

Of course, there are some concerns, as with any investigational drug. Some patients saw an increase in appetite, so the researchers worried that the children may grow taller but would have excess weight. The increase in appetite proved to be transient, and there were no significant changes in BMI. The researchers also braced for pituitary desensitization, but they did not observe that at all, and Cassorla says that the pituitary pulsatility actually increased. "That suggests that this is sustained, that they continue growing up to a year," he says.

Lines of Investigation

Cassorla says that he's the first one to tell you how cautious he is about all this, since it's a small sample of patients and most of them have not yet reached the 12-month mark, and the patients will continue therapy beyond that mark. He says that patients treated with classic growth hormone usually decrease their growth velocity during the second year compared to the first year. "Ultimately, we will find out whether the growth velocity changes during the second year," he says.

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Cassorla tells *Endocrine News* that what attracts him to this particular drug is that it intends to reproduce physiology, something that growth hormone treatments don't do. He explains that a bolus injection of growth hormone circulates at high levels, but those levels decrease before the next injection. And while growth hormone injections are effective, they come at the expense of using a drug that circulates for quite some time at relatively high levels and it then goes down. "This drug has the potential advantage of attempting to reproduce physiology by stimulating the endogenous pituitary to produce growth hormone," Cassorla says.

And again, Cassorla is careful to say that these are just preliminary results that have only been presented at meetings (like IMPE in March and **ENDO 2023**). "These are lines of investigation that may pan out, they may not pan out," he says. "The question is, for these patients with partial to moderate growth hormone deficiency, how do we treat them, how do we define them? This is a group of patients that we think will benefit from this drug. This is a key message, and I think it's a promising area of research. We'll see whether the preliminary data is confirmed by longer-term data, but up to now, it looks quite promising." EN

– BAGLEY IS THE SENIOR EDITOR OF *ENDOCRINE NEWS*. HE WROTE ABOUT THE THREE-SESSION **ENDO 2023** SYMPOSIUM ON OUR EVER-CHANGING FOOD ENVIRONMENT, "IMPACT OF THE CHANGES IN FOOD ENVIRONMENT IN THE DEVELOPMENT OF OBESITY," IN THE MAY ISSUE.