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Crinetics May Have Drug Profile To Take Leading Position In Acromegaly

by Joseph Haas

Reporting a second positive Phase III trial for oral paltusotine, Crinetics plans an NDA later this year to position its drug against competing injectable somatostatin analogs.

Crinetics Pharmaceuticals, Inc. reported positive topline Phase III data for paltusotine in acromegaly on 19 March, with market analysts saying the data along with a previous positive Phase III study last September could position the oral, selective somatostatin receptor type 2 (SST2) agonist to replace existing somatostatin receptor ligand (SRL) therapies as the standard of care.

In the 111-patient PATHFINDR-2 trial, paltusotine met the primary endpoint measuring the proportion of patients who achieved insulin-like growth factor 1 (IGF-1) levels at or below the upper limit of normal (ULN) after 24 weeks. In treatment-naïve patients or patients who washed out of SRL therapy before receiving paltusotine, 56% (30/54) of treatment-arm patients hit the endpoint compared with 5% (3/57) in the placebo arm ($p<0.0001$).

The trial also succeeded on all of its secondary endpoints, including change from baseline in IGF-1 level, proportion of patients who achieved an IGF-1 level ⩽1.3 times ULN at 24 weeks, and change

Key Takeaways

- Paltusotine demonstrated an ability to normalize IGF-1 levels at 24 weeks in patients with acromegaly.
- With two successful Phase III studies in acromegaly, Crinetics now is working on an NDA it plans to file during the second half of 2024, while also studying paltusotine in carcinoid syndrome.
- If approved, paltusotine would compete with injectable somatostatin analogs

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from baseline in the patient-reported Acromegaly Symptoms Diary (ASD) score. On a same-day call, Crinetics execs noted that they developed the ASD measure in consultation with the US Food and Drug Administration.

whose effects sometimes wear off more quickly than expected.

Last September, the San Diego firm reported that paltusotine hit the same primary endpoint of IGF-1 level normalization in the Phase III PATHFINDR-1 study, which tested the drug in patients switching over from standard-of-care agents such as ocreotide (*Novartis AG*'s Sandostatin and generics) and lancreotide (*Ipsen SA*'s Somatuline and generics). (Also see "*Crinetics' Paltusotine Future Appears Bright With First Phase III Acromegaly Readout*" - Scrip, 11 Sep, 2023.)

CEO Scott Struthers said Crinetics is now working to file a new drug application during the second half of 2024 that the company hopes will yield a broad indication covering both treatment-experienced and -naïve acromegaly patients.

"We designed this program to satisfy the recent guidance from the FDA about developing drugs for treatment and the maintenance of treatment of acromegaly," he told the call. "PATHFINDR-2 and PATHFINDR-1, respectively, were designed to meet those guidelines so that we should be able to argue for a broad use in all acromegaly patients."

Crinetics is also developing paltusotine in another endocrinologic disorder, carcinoid syndrome, with Phase II data expected during the second quarter of 2024. On 28 February, the company revealed that it grossed $350m from a private investment in public equity (PIPE) financing that should fund its operations into 2028. (Also see "*Finance Watch: Denali, Avidity And Others Chase Big Money Via Private Placements*" - Scrip, 1 Mar, 2024.)

Paltusotine Might Hold Multiple Advantages Over SOC

Patients are inadequately served by the somatostatin analogs currently available to treat acromegaly, the exec asserted. An oral therapy could offer a convenience advantage to patients as the standard-of-care injectables are painful and often need to be administered by a health care professional, sometimes more often than the standard monthly dosing, Struthers said.

"Many of the injections wear off too soon and then the patients experience breakthrough symptoms," he said. "Instead of one monthly injection, many patients have to take more frequent injections, sometimes every two or three weeks. Imagine managing all this in addition to dealing with your disease and the rest of everyday life. ... Our vision for paltusotine is to help people focus on living their life, not managing their treatment."

Multiple analysts called the PATHFINDR-2 efficacy data better than expected. Leerink Partners

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analyst Joseph Schwartz called the readout “better than our best-case scenario” in a 19 March note. “Based on the positive update, we believe that Crinetics could get a broad label to treat acromegaly patients,” he added.

Evercore ISI analyst Gavin Clark-Gardner said he had expected an overall response rate for normalization of IGF-1 levels no higher than the low 40% range, maybe somewhere in the 30% range, in a 19 March note. “Not only is the data objectively strong, but it’s also consistent with PATHFINDR-1,” he said. “We have little/no doubt these are approvable datasets.”

Combining the earning potential of the acromegaly and carcinoid syndrome indications, Clark-Gardner projects that paltusotine could exceed $1bn in global peak sales, with US peak earnings of $300m in acromegaly and $500m in carcinoid syndrome. The analyst predicts a gradual launch of the product, reaching market in 2025, nearing $400m in 2028 and topping out at $1.064bn in 2032.

JMP Securities analyst Jonathan Wolleben said injectable SRLs normalize IGF-1 levels in acromegaly patients with varying effectiveness, ranging from about 24% to 54% of patients. “We think [that comparison] bodes well for broad adoption” of paltusotine, he added in a same-day note. He said the drug would offer the convenience of an oral therapy, best-in-class efficacy and a clean safety profile.

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