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CymaBay's Seladelpar Hits Three Endpoints In Phase III PBC Study

by Joseph Haas

Seladelpar may threaten an entrenched second-line therapy, Intercept's Ocaliva, with better efficacy, based on benefits demonstrated in the pivotal RESPONSE trial.

CymaBay Therapeutics, Inc. reported data that analysts called nearly a best-case scenario across three key endpoints for its PPAR delta agonist seladelpar in primary biliary cholangitis (PBC) on 7 September, but a few questions persist about a higher-than-expected placebo response on the Phase III trial's primary endpoint. Still, the broad expectation is that seladelpar likely will be approved for second-line treatment of PBC and prove strong competition in that setting to *Intercept Pharmaceuticals, Inc.*'s Ocaliva (obeticholic acid).

Initially, CymaBay was developing seladelpar as one of several PPAR agonists for non-alcoholic steatohepatitis, but missed its primary endpoint of liver fat reduction from baseline in a Phase II study in 2019. (Also see "*CymaBay Alters NASH Hypothesis After Phase IIb Failure In Hepatic Fat Reduction*" - Scrip, 11 Jun, 2019.) At that point, the Newark, CA-based firm shifted its priority to advancing the drug in PBC, a rare, chronic, inflammatory liver disease whose progression is associated with increased risk of liver-related death. (Also see "*CymaBay Focused On PBC With Seladelpar, Wants Partner For NASH*" - Scrip, 16 Nov, 2020.)

An estimated 130,000 people in the US, mostly women, suffer from PBC. First-line therapy is generic ursodeoxycholic acid (UDCA), while Ocaliva, also a failed NASH candidate, was approved as second-line therapy in 2016. Second-line therapy is used in patients who are non-responsive to or intolerant of UDCA, but Ocaliva, an FXR agonist, has run into headwinds since its PBC approval due to concerns about liver injury and cases of worsened pruritis. (Also see "*Intercept's Ocaliva: 'Dangling' PBC Indication At Risk As Near-Term NASH Approval Looks Unlikely*" - Pink Sheet, 30 May, 2023.)

Also competing to enter the second-line PBC space is *Genfit SA*'s elafibranor, a pan-PPAR

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agonist that also was positioned as a therapy for NASH but failed its Phase III trial in 2020. (Also see "*Genfit's Post-NASH Plans Center On ACLF, Cholestatic Liver Disease*" - Scrip, 12 May, 2021.) Following CymaBay's readout of the Phase III RESPONSE study on 7 September, analysts said seladelpar appears to hold multiple advantages over Ocaliva, while offering at least competitive efficacy compared to elafibranor with a likely tolerability edge in pruritus.

Genfit/Ipsen's PBC Data Leave Door Open For CymaBay

By Joseph Haas

30 Jun 2023

Genfit/Ipsen's elafibranor and CymaBay's seladelpar are vying to supplant Intercept's Ocaliva in second-line primary biliary cholangitis, but elafibranor failed to hit a key differentiation endpoint in pruritus.

Read the full article here

The placebo-controlled study randomized 193 patients 2:1 to seladelpar 10mg daily or placebo. Enrollment criteria required patients to have inadequate response or intolerance to UDCA and a serum alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of normal (ULN) after 12 months of treatment. The study also measured a secondary endpoint in enrollees with pruritus who had a score of at least 4 on the 10-point numerical rating scale (NRS) at baseline, with 0 meaning no itch and 10 meaning worst possible itch.

Top-line data from the study met a trio of key endpoints – the primary endpoint of a composite measure of serum ALP and bilirubin levels 12 months from baseline, normalization of ALP at 12 months and statistical significance on reducing NRS score for pruritus. On the primary endpoint, 61.7% of treated patients met statistical significance compared to 20% in the control group, a higher-than-expected placebo response, but still good for a p-value of <0.0001.

Twenty-five percent of treatment arm patients demonstrated an anti-cholestatic benefit with normalization of ALP levels at 12 months, compared with zero in the placebo arm ($p<0.0001$). In the subset of patients with moderate-to-severe pruritus at baseline, seladelpar-treated patients had a least-square mean reduction of 3.2 points on NRS compared with a 1.7 point mean reduction for placebo recipients ($p<0.005$).

"As we turn our attention to discussions and filings with regulators, we believe seladelpar has the potential to be the first-ever approved treatment for patients with PBC to significantly improve markers of disease activity and symptoms," CymaBay CEO Sujal Shah told a same-day call. "Our goal is to help patients have longer and better lives."

Pruritus Benefit Expected To Provide Differentiation

Analysts asked about the 20% of placebo-arm patients who met the primary endpoint, with

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CymaBay chief scientific officer Charles McWherter saying that might have been due to a high number of control-arm patients having ALP levels closer to the ULN than in the treatment arm. "We've seen that in prior trials," he added.

William Blair analyst Andy Hsieh called McWherter's rationale "a reasonable explanation" of the placebo effect in a 7 September note, adding that seladelpar has demonstrated consistent magnitudes of ALP reduction across a Phase II study and a previous Phase III study, ENHANCE. "We do not believe the higher-than-expected placebo rate will have material impact on physicians' choice of therapy," Hsieh added.

Key opinion leader Gideon Hirschfield, chair of liver disease research at the Toronto Centre for Liver Disease, said he believes the benefit demonstrated in pruritus reduction – a symptom Ocaliva is known to worsen and in which elafibranor has failed to demonstrate statistical significance – will be the key determinant in which therapy doctors choose in second-line PBC if seladelpar is approved. "For patients living with moderate-to-severe pruritis, a really dreadful and underserved symptom, seladelpar improved parameters in a robust, sustained and statistically significant manner," he told the call.

Raymond James analyst Steven Seedhouse pointed out in a same-day note that pruritus leads to discontinuation of Ocaliva therapy "in many patients" because the drug actually worsens PBC's most prominent disease symptom.

Cantor Fitzgerald analyst Kristen Kluska called the pruritus benefit seen in RESPONSE the "biggest differentiator" for seladelpar. "We understand it's a major complaint for patients, thus has been a key focus for physicians for therapies in clinical stage," she said in a 7 September note. She added that the high placebo response on the primary endpoint might be overlooked since seladelpar had a higher response rate for reducing ALP and bilirubin than Ocaliva and elafibranor did in their Phase III studies, 61.7% versus 48% and 51%, respectively.

However, Genfit's Phase III ELATIVE data for elafibranor in PBC reported out in June showed only a 4% placebo response on the primary endpoint, meaning a treatment delta of approximately 47%, compared to about a 42% delta in CymaBay's study. Kluska also cautioned that none of the three companies' Phase III trials were head-to-head studies. "We think investors were looking for a non-placebo-adjusted response of greater than 60%, which was achieved," the analyst said.

Leerink Partners analyst Thomas Smith highlighted the RESPONSE trial's success in normalizing ALP levels after 12 months of treatment, saying that key secondary endpoint is "an important metric of increasing focus that is aligned with emerging treatment goals of biochemical normalization in PBC."

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“Our priority now will shift to regulatory discussions and filings while we also accelerate our medical affairs activities and pre-commercial preparation,” CymaBay’s Shah said. “We believe the RESPONSE results represent a potential breakthrough for patients with PBC, offering the potential to reduce the risk of disease progression, while also improving symptoms and quality of life.”

The CEO added that a long-term, open-label safety study of seladelpar in PBC patients is ongoing as well as the Phase III IDEAL study, which is enrolling patients with ALP levels between 1 and 1.67 times ULN. Raymond James analyst Seedhouse asserted that IDEAL could yield crucial data that might double the addressable population for seladelpar, giving it potential to achieve US sales of $1.2bn by 2030, with global sales possibly reaching $1.5bn that year.

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