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Drug Review Profiles

November 2023

Introduction

The *Pink Sheet's* unique Drug Review Profiles provide a deep dive into the dynamics behind interesting – and sometimes precedent-setting – new drug approvals, with lessons learned for other sponsors.

Mining hundreds of pages of agency documents and following up with key interviews, our *Pink Sheet* expert journalists illuminate how the regulatory process works in practice. Issues might include how agency reviewers applied regulatory terminology to specific new drug and biologics marketing applications. Other aspects that often come into play include trial design, whether the product met criteria for expedited review mechanisms, questions of emerging science, how reviewers weigh evidence of efficacy, risk management, and manufacturing challenges. Our analyses explore how sponsors worked with regulators to resolve areas of uncertainty and where there might be regulatory flexibility – or not.

The resulting takeaways often are helpful for navigating regulatory review far beyond the specific product area in a Profile. Sponsors can anticipate challenging questions regulators might ask about their own applications and work more productively with regulators. It all adds up to increasing the chance for product approval, with indications and labeling optimized for competitiveness in the market.

Find all of this coverage on our Drug Review Profiles webpage.

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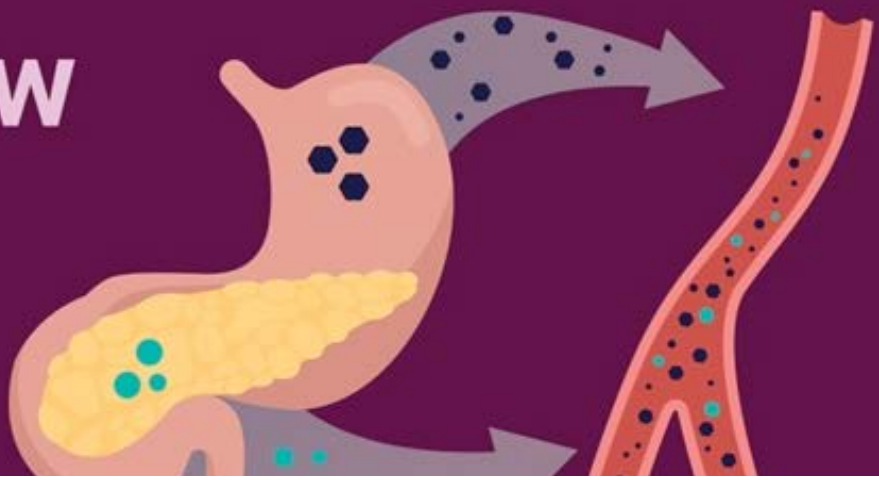


CellTrans' Lantidra: Type 1 Diabetes Cell Therapy Overcame The Odds On Nontraditional Path To Approval

Sue Sutter

12 Sep 2023

Executive Summary

Despite a host of challenges with donislecel's development and BLA, the US FDA approved based on clinical data from only 30 patients, using a clinically meaningful insulin independence endpoint and in a more carefully tailored population. Pink Sheet's Drug Review Profile takes a deep dive into the FDA review of the first approved allogenic pancreas islet cell product.

On its face, the odds for US approval of CellTrans, Inc.'s type 1 diabetes cellular therapy Lantidra (donislecel-jujn) would seem to have been stacked against the sponsor.

The product was a first-in-class, complex biological treatment. The academia-based sponsor was inexperienced in getting therapeutics through the Food and Drug Administration, and the quality of the biologics license application was poor, with missing, inconsistent and uninterpretable data.

In addition, a host of product quality deficiencies had to be addressed after a first-cycle complete response letter.

On the clinical side, FDA reviewers concluded the sponsor's proposed indication for brittle type 1 diabetes was not well defined, and the primary efficacy analyses across two studies based on severe hypoglycemic events and hemoglobin A1c levels was not interpretable due to missing data and the characteristics of the enrolled population.

CellTrans' Lantidra: Type 1 Diabetes Cell Therapy Overcame The Odds On Nontraditional Path To Approval

Despite these challenges, the FDA identified a path to approval for Lantidra based on clinical data from only 30 patients, using an endpoint – insulin independence – that the agency deemed clinically meaningful, and in a more carefully tailored patient population.

The FDA approved Lantidra on 28 June for treatment of adults with type 1 diabetes (T1D) who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. (Also see "US FDA Novel Approvals Total 35 In First Half 2023, Riding Resurgent Biologics Wave" - Pink Sheet, 8 Jul, 2023.)

Although the term "regulatory flexibility" does not appear in either the FDA's summary basis for regulatory action or the clinical review – in contrast to some recent high-profile product approvals in the neuroscience space – internal memos make clear the agency took pains to get Lantidra across the finish line for a rare disease population with unmet need.

This included leveraging some of the agency's own patient preference work and relying upon an "implied" external control when assessing the insulin independence data from the two single-arm trials.

CellTrans CFO Jenny Cook said the company's interactions with the agency during Lantidra's development and review amounted to an education for both parties.

"We're learning about what they need to see, and then we're also kind of educating them on our experience with our patients," she said in an interview with the Pink Sheet.

The agency "really did try to work with us," Cook said. "They knew we were a very small group … and working in an academic medical center and there's limitations around that. At the same time, they needed to meet their regulations, but they could see we were also doing as much as possible, too."

"I think they really tried to be a bit flexible knowing who we were and we want to keep this product affordable for patients," Cook said.

The Lantidra story is one of an unusual product development program, a nontraditional sponsor, and an FDA that was willing to look outside the box. With the burgeoning growth in gene and cell therapy development, and the continuing challenges faced by academic sponsors with limited regulatory expertise, the Lantidra experience could be instructive for future applicants.

Key Takeaways

- FDA reviewers said CellTrans' proposed indication for brittle type 1 diabetes was not well defined, and the primary efficacy analyses across two studies based on severe hypoglycemic events and hemoglobin A1c levels was not interpretable.
- However, the agency concluded that insulin independence experienced by some Lantidra-treated subjects was a clinically meaningful endpoint and compared favorably to the well-established natural history of the disease.
- FDA leveraged its flexibility in getting Lantidra through the approval process with an indication that better defined the target population.

First Allogenic Pancreas Islet Cell Product Under Review

Although insulin remains the primary treatment for patients with T1D, allogenic transplant of cadaveric donor pancreata has been used to restore the production of endogenous insulin for

some patients.

The use of pancreatic islet cells isolated from donor pancreata and implanted in a patient's liver by infusion into the portal vein provides a less invasive approach and allows for the use of donor pancreata that are not suitable for whole organ transplantation.

Lantidra is a cellular therapy product containing purified allogeneic deceased donor pancreas derived islets of Langerhans. It was the first allogenic pancreas islet cell product submitted for FDA review under a marketing application. CellTrans' proposed indication was for the treatment of brittle T1D (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.

The novel nature of the product created complexities from a regulatory perspective, Cook said.

"Some of the regulations they didn't really fit our product, and so I think actually the agency was also struggling a bit with how to comply with their own regulations [and] at the same time fit the needs of a cell product," Cook said. "Some of the regulations actually didn't apply, but we had to address them to kind of check the box."

The investigational new drug application was opened in 2004 by Jose Oberholzer at the University of Illinois Hospital and Health Sciences System (UI Health). Oberholzer subsequently founded CellTrans, which acquired the rights to the IND and the Lantidra development program in 2017 with the purpose of supporting a BLA.

CellTrans initially submitted a BLA in 2017 but withdrew it after the agency identified filing issues. The current BLA was submitted in May 2020.

Independence From Insulin Becomes Efficacy Focus

Lantidra's development was unique in that the clinical trials supporting the BLA were single-site studies conducted by Oberholzer.

Efficacy and safety were evaluated in two non-randomized, single-arm trials (UIH-001 and UIH-002) conducted at UI Health and enrolling a total of 30 participants with T1D and hypoglycemic unawareness.

The clinical development and regulatory review were complicated by changes in the standard of care for T1D since the 001 and 002 studies were initiated in 2004 and 2007, respectively, Cook said. Continuous glucose monitors were not the norm during the early part of the clinical program, and incidents of hypoglycemia had to be documented on paper, she said.

CellTrans' primary efficacy analysis for the two studies used a composite endpoint of HbA1c ≤6.5% and absence of severe hypoglycemic events (SHE) through one year after the subject's last transplant.

However, the FDA said this analysis was not interpretable due to missing data and inclusion of a significant proportion of subjects who, at baseline, had already met or nearly met the primary efficacy endpoint. (Also see "CellTrans' Donislecel: Insulin Independence Data May Offer Path To Market In Type 1 Diabetes" - Pink Sheet, 13 Apr, 2021.)

"There were significant issues with missing baseline data and inclusion of 25/30 (83.3%) subjects without recent baseline SHE and with 6/30 (20%) with a HbA1c at the target HbA1c; this limits the interpretability of the applicant's primary analysis," clinical reviewer Patricia Beaston said in a memo.

"Restoration of endogenous insulin production and insulin independence does not occur spontaneously in T1D; the large treatment effect is attributed to Lantidra." – FDA Summary Basis For Regulatory Action

Nevertheless, the studies showed 21 of 30 treated subjects (70%) did not require exogenous insulin for at least one year after treatment, and 10 subjects (33%) achieved insulin independence for more than five years, with a maximum reported insulin independence of 12.8 years.

Insulin independence was the primary endpoint in UIH-001 and a prespecified secondary endpoint in UIH-002, the clinical review states.

"Restoration of endogenous insulin production and insulin independence does not occur spontaneously in T1D; the large treatment effect is attributed to Lantidra," the summary basis for regulatory action states.

At an April 2021 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee, the majority of panelists said the benefits of independence from insulin outweighed the risks from long-term immunosuppression necessary with Lantidra. However, they said the therapy should be limited only to a very small group of patients, such as those who are eligible for pancreas transplant but cannot tolerate a big operation, and those for whom closed-loop insulin pump systems and continuous glucose monitors were not well tolerated or effective. (Also see "CellTrans' Donislecel Gets US FDA Panel Nod For Small Group Of Type 1 Diabetics" - Pink Sheet, 15 Apr, 2021.)

Patient Experience Data

The FDA performed extensive analyses of the ability of study subjects to achieve insulin independence and the durability of that insulin-free period across the two studies. It also leveraged some of its own patient preference information work in this area.

The FDA Science of Patient Input, Office of Biostatistics and Epidemiology (OBE) group collaborated with the University of California-San Francisco on a project for patient preferences in islet cell therapy. The group presented a poster at the FDA Science Forum in 2021.

"The authors' conclusion was that their study 'suggests that hard-to-control T1DM patients may be willing to accept a certain level of risk (e.g., 5% risk of serious complications) to achieve a certain extent of benefit (the possibility of having five years of insulin independence),'" the clinical review states. The main safety issues associated with Lantidra treatment are risks of the cell product, the transplantation procedure, and concomitant immunosuppression.

The clinical review also notes that while CellTrans did not provide a patient experience report for the subjects enrolled in UIH-001 or UIH-002, it did include testimonials offered at the advisory committee meeting by patients who participated in the studies.

'Implied' External Control

The agency ultimately concluded that CellTrans provided substantial evidence of effectiveness and safety based on the two single-arm studies and supportive evidence.

"Specifically, we consider the integrated data from UIH-001 and UIH-002 compared to the well-established natural history of T1D to compose a single adequate and well-controlled investigation," the summary basis for approval states. "Based on the objective endpoint, insulin independence, and large treatment effect, an external control is adequate to provide substantial evidence of effectiveness."

The agency's use of the term external control is notable in that no specific dataset or nonconcurrent patient cohort was formally offered as an external control for comparison purposes with the two single-arm studies. Rather, the FDA considered the well-understood natural history of T1D as an external control in and of itself.

The agency's use of the term external control is notable in that no specific dataset or nonconcurrent patient cohort was formally offered as an external control for comparison purposes with the two single-arm studies. Rather, the FDA considered the well-understood natural history of T1D as an external control in and of itself, with Beaston's clinical review referencing a "performance goal threshold based on natural history (the implied control)."

The clinical review cites the FDA's 2009 guidance on considerations for pancreatic allogeneic pancreatic islet cell products. The document states that a single-arm, open-label trial with historical controls may be able to provide substantial evidence of efficacy and safety in subjects with metabolically unstable T1D.

"In part, this is because the major observed benefits (insulin independence, spontaneous loss of hypoglycemia with attainment of good metabolic control) do not appear in the natural course of the disease," the guidance states.

"To our knowledge, reversal to insulin independence without therapeutic intervention in patients with established T1DM (i.e., after the so called 'honeymoon period') has not been reported outside of errors in diagnosing monogenetic diabetes, or onset of insulinoma," Beaston said in her clinical review. "Therefore, the occurrence of insulin independence can provide an objective measure of the efficacy of donislecel transplant."

The agency also cited as supportive evidence data from four subjects transplanted with donislecel in a Phase III protocol conducted by the Clinical Islet Transplantation consortium. The results from these four subjects are "consistent with those observed for the 30 subjects in UIH studies. Thus, this clinical data and biologic plausibility of beta cell replacement serves as confirmatory evidence," the summary basis for regulatory action states.

The clinical review reiterates a point made in the FDA's advisory committee briefing document about the agency's willingness in this case to rely upon a post hoc efficacy analysis.

"It is very important to note that FDA does not endorse a change in primary efficacy endpoint for an integrated analysis of efficacy after trials are conducted and analyzed, with rare exceptions in the past," the review states. "However, in this circumstance, the review team understood that durable insulin independence without evidence of hypoglycemia is a stronger demonstration of clinical benefit compared to adequate glycemic control without serious hypoglycemia, is a more conservative endpoint and, in addition, has been proposed in the 2009 FDA guidance as an alternative primary efficacy endpoint."

Revised Indication

The FDA took issue with CellTrans' original indication for the treatment of brittle T1D (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy, asserting it did not identify a specific patient population.

Brittle T1D is a concept and not well defined, the clinical review states, noting the term "symptoms are not well controlled" also was not defined.

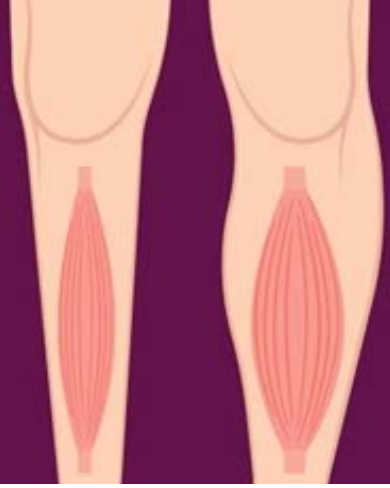
"In general, these patients would be unable to achieve glycemic goals because of severe metabolic events, severe hypoglycemic events (SHE) and/or diabetic ketoacidosis (DKA), despite treatment/supervision by clinicians with expertise in the treatment of type 1 diabetes and access to the appropriate insulins and devices based on the patient's requirements," Beaston said. "It is important to recognize that the insulin products, available devices, and standard of care have changed significantly since the onset of the islet cell investigational programs."

The FDA revised the indication to focus on adults with T1D who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

"While it may be tempting to specify a specific target of HbA1c in the indication, this approach would not be reasonable as the target can be different based on the patient's age, duration of diabetes, and presence of complications (neuropathy, nephropathy, retinopathy)," the clinical review states.

"The use of 'current repeated episodes' identifies a patient population who is at risk for SHE at the time islet cell transplantation would be delivered, rather than those patients who may have had one or more SHE episodes more than one year prior to initial transplantation," Beaston said. "For a favorable benefit-risk determination, patients should have an ongoing risk of SHE to balance against the significant risks of the procedure and required immunosuppression."

Drug Review Profile: Elevidys



Elevidys' Age-Restricted Indication Not Negotiable, CBER's Peter Marks Told Sarepta

Sue Sutter
07 Aug 2023

Executive Summary

FDA team held several internal meetings on the gene therapy after the 12 May advisory committee, culminating in a teleconference with Sarepta in which the CBER director outlined his accelerated approval decision and reiterated recommendations to modify the ongoing EMBARK trial to better ensure confirmation of benefit. *Pink Sheet's* Drug Review Profile dives into the story behind the Elevidys review.

FDA Center for Biologics Evaluation and Research Director Peter Marks' conclusion that Sarepta Therapeutics, Inc.'s gene therapy Elevidys (delandistrogene moxeparvovec-rokl) should receive accelerated approval for an age-restricted indication amounted to a take-it-or-leave-it offer for the sponsor, not subject to negotiation.

In sharing his decision with Sarepta, Marks also made clear agency concerns that the ongoing EMBARK confirmatory trial was designed in such a way that it may not be able to confirm clinical benefit in the 4-5 year-old age group of Duchenne muscular dystrophy patients covered by the accelerated approval indication and, consequently, adjustments should be made to the statistical analysis plan.

FDA review documents reflect the extensive internal deliberations on Elevidys that followed a 12 May advisory committee meeting, in which a slim majority of panelists favored accelerated approval for the treatment of ambulatory DMD patients.

Marks announced his plans to grant accelerated approval limited to ambulatory patients ages 4-5 years old after meeting with review staff and hearing their recommendations for a

Elevidys' Age-Restricted Indication Not Negotiable, CBER's Peter Marks Told Sarepta

complete response letter.

Marks' own deputy, Celia Witten, also favored a complete response in her role as acting director of the Office of Therapeutic Products. In a memo, she said she agreed with the review team's conclusion that available data do not support use of Elevidys micro-dystrophin expression as a surrogate endpoint reasonably likely to predict clinical benefit for accelerated approval for the treatment of ambulatory patients, or for a certain subpopulation of ambulatory patients.

Elevidys, an AAV-directed gene therapy formerly known as SRP-9001, received accelerated approval on 22 June for treatment of ambulatory pediatric patients ages 4-5 years with a confirmed mutation in the DMD gene. Marks co-signed the approval letter with Melissa Mendoza, director of CBER's Office of Compliance and Biologics Quality.

In granting accelerated approval, Marks reasoned that despite the lack of benefit in the overall population of individuals ages 4-7 years enrolled in Study 102, the data in the subgroup of individuals ages 4-5 years was compelling. The results of Elevidys micro-dystrophin protein expression and the results of the North Star Ambulatory Assessment (NSAA) in this age group support an association between the two, "such that Elevidys micro-dystrophin protein expression is reasonably likely to predict clinical outcome in individuals ages 4 through 5 years eligible for this treatment," Marks said in his decisional memo. (Also see "Sarepta's DMD Gene Therapy Helped Across Accelerated Approval Finish Line By CBER's Peter Marks" - Pink Sheet, 22 Jun, 2023.)

However, this was not a conclusion easily reached, review documents show.

Key Takeaways

- After the 12 May advisory committee meeting, FDA's clinical, clinical pharmacology and biostatistics review teams continued to recommend a complete response letter for Elevidys.
- CBER Director Peter Marks made the decision to move forward with accelerated approval for an age-restricted indication, telling Sarepta the FDA's position "is not up for negotiation."
- Marks urged Sarepta to considering modifying the ongoing EMBARK trial to be powered for demonstrating efficacy in the 4-5 year-old age group.

FDA To Sarepta: We Have Concerns About The Surrogate

In at least four meetings with Sarepta from December 2018 to April 2022, agency staff expressed concerns about the company's proposal to rely on SRP-9001 micro-dystrophin as a surrogate endpoint to support accelerated approval. Reviewers cited a lack of correlation between expression of micro-dystrophin at week 12 and a clinically meaningful benefit. (Also see "Elevidys Clinical Development: Confidence In Surrogate Endpoint A Longstanding Concern For FDA Reviewers" - Pink Sheet, 9 Aug, 2023.)

In a meeting with Marks in November 2022, the application's clinical reviewer recommended the agency refuse to file the biologics license application due to concerns about a lack of demonstrated efficacy and inadequacy of the submitted clinical studies. Marks overruled this recommendation, and the application was filed and granted priority review, setting a user fee goal date of 29 May 2023. (Also see "CBER Director Marks' Intervention On Sarepta Gene Therapy Filing Decision Appears To Backfire" - Pink Sheet, 15 Apr, 2023.)

Elevidys' Age-Restricted Indication Not Negotiable, CBER's Peter Marks Told Sarepta

The FDA told Sarepta in a 24 January mid-cycle communication that no advisory committee meeting was expected. However, by the 13 March late-cycle meeting, planning for an advisory committee review was underway, and the agency told Sarepta the meeting tentatively was scheduled for late July based on panel member availability.

This timeline subsequently was accelerated by more than two months. The adcomm occurred on 12 May, just more than two weeks before the user fee goal date.

In a statement to the Pink Sheet, the agency said that recognizing the tremendous interest in SRP-9001, a determination was made late in the review process that input from the Cellular, Tissue and Gene Therapies Advisory Committee would be critical to the agency's evaluation.

"Therefore, the FDA worked expeditiously to schedule an advisory committee meeting to facilitate an open and transparent discussion related to the evaluation of the safety and effectiveness of the product in a timely manner."

The adcomm originally was scheduled for late July, but that timeline was accelerated by more than two months.

At the adcomm, Marks responded to a panelist question about the agency's reversal of course on convening a meeting. "A management decision was made that this would benefit from public discussion as an important gene therapy for an indication under development," he said.

FDA reviewers laid out their concerns about the ability to rely upon SRP-9001 micro-dystrophin as a surrogate endpoint reasonably likely to predict clinical benefit. They noted the only randomized data available to date – from Study 102, Part 1 – did not meet statistical significance on the NSAA primary clinical endpoint in the study population of DMD patients 4-7 years old. Positive results in the 4-5 year-old age group were not prespecified and could only be considered hypothesis-generating, reviewers said. (Also see "Let's Go To The Video: Recordings Of DMD Patients After Elevidys Treatment 'Compelling' But Not Substantial Evidence" - Pink Sheet, 10 Aug, 2023.)

FDA staff also raised concerns about a lack of analytical comparability between the initial and to-be-commercialized manufacturing processes for the gene therapy, and the potential impact of accelerated approval on the ongoing EMBARK confirmatory trial (Study 301). In addition, they noted that due to cross-reactivity between different AAV serotypes, patients who receive SRP-9001 but do not benefit would not be able to receive another AAV-directed gene therapy in the future.

The committee voted 8-6 in favor of accelerated approval, with those in the majority citing the advanced state and imminent completion of the fully enrolled EMBARK study, as well as the opinions of DMD researchers and clinicians who supported approval. (Also see "Slim Adcomm Majority Boosts Sarepta's Gene Therapy In Duchenne Muscular Dystrophy" - Pink Sheet, 12 May, 2023.)

Four Internal Meetings …

After the adcomm, FDA review staff held four internal meetings on the application, according to the publicly available meeting summaries. At a 15 May meeting, the clinical, clinical pharmacology and biostatistics teams stated that the adcomm discussion did not support that Sarepta's micro-dystrophin is reasonably likely to predict clinical benefit to be used as a surrogate endpoint for accelerated approval. These review teams continued to recommend a complete response based on the available data.

Witten, the CBER deputy director who was serving as acting director of OTP, said she

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wanted to discuss the review team's decision with Marks before commenting on a path forward.

Marks took part in a 16 May meeting with the review team. The clinical, clinical pharmacology and biostatistics review teams "all expressed the reasons that their position remained unchanged and that they believe the application should move forward as a complete response based on the data provided," a meeting summary states.

Marks said he wanted to consider the review team's position and justification before commenting on a path forward. He requested the review team examine the comments in the public docket, including videos and a caregiver perspective study conducted Canary Advisors, before making a final conclusion. (Also see "Sarepta's External Controls Analysis Weakened By Elevidys Placebo Data Comparison" - Pink Sheet, 8 Aug, 2023.)

In an 18 May meeting with the review team, Marks "expressed that he has given this application a fair amount of thought and that there are some major issues on data the applicant presented, issues on how the applicant responded to the questions, issues with the external controls and issues on the explanation of the results of their 6-7 year-old population," the summary states.

"Dr. Marks concludes gene therapy may have an effect on the 4-5 years of age population based on totality of information and that the biomarker of micro-dystrophin expression may be able to predict clinical benefit. Therefore, he would like to move forward with an accelerated approval (AA) for that age range based on available data and exercising regulatory flexibility. However, there is not any evidence that the biomarker of micro-dystrophin expression may be able to predict clinical benefit in the 6-7 year-old age range," the summary states.

Limiting the indication in a narrow patient population will minimize potential disruption to the EMBARK trial, FDA's Peter Marks said.

Furthermore, limiting the indication in a narrow patient population will minimize potential disruption to the EMBARK trial, Marks said. EMBARK, a randomized, placebo-controlled study, is fully enrolled at 125 patients ages 4-7 years. The primary analysis requires 52-week data from Part 1 of the study, and all US patients are due to complete their 52-week visits in September. All patients who were originally randomized to placebo can crossover to SRP-9001 after one year.

At the adcomm, Sarepta said that accelerated approval would not impact completion of EMBARK because all 125 patients will have had their 52-week, primary endpoint visit by the end of September 2023, and it likely will take about four months from the time of accelerated approval for DMD patients in the US to get commercial access. (Also see "Gene Therapy: Four-Month Lag In Commercial Access Protects EMBARK Study, Sarepta Says" - Pink Sheet, 13 May, 2023.)

The primary endpoint in EMBARK is change from baseline in NSAA total score at week 52 in the full study population.

"If the outcome from the ongoing confirmatory trial is negative, FDA would have to withdraw the AA. If it is positive, depending on the final data analyses, the label may be expanded to include additional age group(s)," the meeting summary states.

"Dr. Marks reiterated that the review team should write their memos as they feel appropriate. The review team will need to move forward to revise the proposed label."

Elevidys' Age-Restricted Indication Not Negotiable, CBER's Peter Marks Told Sarepta

Marks met with the review team again on 19 May to discuss an updated regulatory timeline, and a new action due date of 22 June was agreed upon.

… Followed By A Call With Sarepta

The CBER director, along with review team representatives, held a teleconference with Sarepta on 22 May to discuss the plans for an age-restricted accelerated approval and the new target action date.

According to the teleconference summary, Marks conveyed the challenges in the BLA data, including: remaining questions about how SRP-9001 micro-dystrophin compares to full length and other truncated dystrophins; challenges with the use of external controls; and the discrepancy between the findings seen in Study 102 Part 1 in the 4-5 year-old and 6-7 year-old groups.

The FDA needed to miss the PDUFA goal date to engage in adequate labeling negotiations, Marks told Sarepta. "Moving forward, the labeling negotiations will focus on consideration of the efficacy data from the 4- and 5-years old subset of Study 102 and the overall safety data set," the summary states.

"FDA is already aware that you may not agree with this parsing of the study data, but please work with the agency on this, as the larger population of ambulatory patients is not under consideration for labeling at this time pending the results of Study 301," Marks told Sarepta.

"Although it is obvious that older patients potentially have more urgent therapeutic need, there are plausible explanations why micro-dystrophin expression might not predict clinical benefit in these individuals, particularly in the setting of the negative results from Study 102 Part 1," the summary states. "FDA must also look at the potential issues with treating older children with a therapy that has not clearly demonstrated the likelihood of efficacy, and that also may preclude treatment in the near future with any one of a number of the several other gene therapies in development."

Concerns About EMBARK's Ability To Confirm Benefit

The meeting summary states that in "the context of the lack of clinical evidence of benefit in the 6 and 7 year-old children, as the team has discussed with the applicant previously, FDA again urged the applicant to consider modifying the ongoing Study 301 trial to be powered for demonstrating efficacy in the 4 to 5 year-old subset, or to be prepared to have to conduct an additional study if Study 301 fails its primary endpoint yet indicates likely efficacy in 4 and 5 year-old subgroup."

"Though FDA hopes that this will not be the case, FDA owes it to the patients to work through the potential contingency situations," the summary states.

"FDA again urged the applicant to consider modifying the ongoing Study 301 trial to be powered for demonstrating efficacy in the 4 to 5 year-old subset, or to be prepared to have to conduct an additional study if Study 301 fails its primary endpoint yet indicates likely efficacy in 4 and 5 year-old subgroup." – 22 May meeting summary

Marks told Sarepta that the FDA has considered all the issues, discussed them carefully and has briefed senior agency leadership, including Principal Deputy Commissioner Janet Woodcock.

As director of the Center for Drug Evaluation and Research, Woodcock over-ruled review staff and granted accelerated approval to Sarepta's Duchenne muscular dystrophy treatment

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Exondys 51 (eteplirsen) in 2016, making it the first of four exon-skipping drugs approved on the basis of increase in dystrophin as reasonably likely to predict clinical benefit. Confirmatory trials have not yet been completed for any of the four drugs.

At the 22 May meeting, Sarepta representatives shared their concern about limiting the indication to only 4-5 year-old patients, including whether efficacy of SRP-9001 needs to be demonstrated in all age groups.

"FDA reiterated that the agency does not know whether SRP-9001 is likely beneficial to the 6-7 years old subgroup based on available data. FDA hopes Study 301 will provide [a] more clear answer. Study 301 is only powered for the overall population of 4 to 7 years old patients and the primary endpoint will be tested solely on the overall population."

"If the study fails in the overall population but wins in the younger age subgroup of 4 to 5 years old, and if the applicant does not specify an inferential subgroup analysis, the applicant won't be able to proceed with testing the subgroup effect following a failed test of the overall population," the meeting summary states. "FDA continues recommending the applicant prespecify the inferential age subgroup analysis based on findings of Study 102 Part 1. This means that the subgroup analysis needs to be prespecified with adequate power and proper alpha control."

"Ultimately, whether data from Study 301 would support an indication broader than the 4-5 years old ambulatory patients with DMD will be a review issue," the meeting summary states. "It is premature to comment in the absence of data."

The meeting summary concludes by stating: "Dr. Marks made it clear that FDA's position is not up for negotiation. If the applicant does not agree with FDA's position, please let FDA know within the next day. The applicant agreed to follow up with any concerns within the next day."

Sarepta Confident In EMBARK Design

When asked whether Sarepta had followed the FDA's statistical analysis design recommendations for Study 301, the company told the Pink Sheet: "EMBARK is powered to show benefit across the population in the trial (ages 4-7) and the study was already fully enrolled at the time of the suggestion. Assuming EMBARK meets its objective, we intend to pursue a non-age-restricted label for all Duchenne patients."

"Duchenne is a heterogenous disease, and functional measures are better indicators of disease status than age," the company said. "Elevidys works the same way in a 4 year-old that it does in a 6 year-old and what we have seen in clinical trials to date is that patients treated with Elevidys, regardless of age, are doing better than natural history would predict."

During an investor call on the day of Elevidys' approval, Sarepta was asked what happens if EMBARK is not a clear win or there are different results in the two different age subgroups, and whether the statistical plan was prespecified to allow for analysis of the data in a manner that maximizes the probability that the study will fulfill its objectives in the eyes of the FDA.

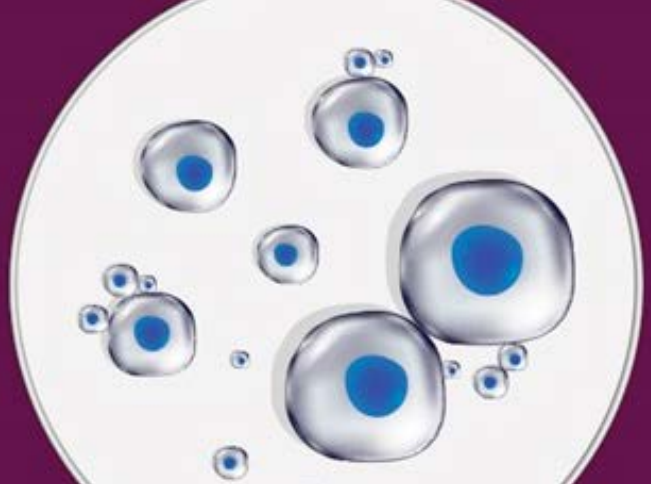
"We have managed our statistics in a way, I think, that maximizes the potential for success, and that is by powering the study to see a statistically significant and clinically meaningful effect across the entire patient population," CEO Douglas Ingram said. "If we started dividing that up in smaller segments, you might lose power."

During Sarepta's Q2 earnings call on 2 August, Chief Scientific Officer and R&D Head Louise Rodino-Klapac said the company's simulation

modeling suggests that statistical significance in EMBARK would be reached even if the observed treatment effect in the overall intent-to-treat population was as low as 1.3 points on the NSAA total score.

Ingram said the company has not had discussions with the FDA about the clinical meaningfulness of a particular number in terms of NSAA treatment effect in EMBARK. However, "this is a disease that is degenerative over time. If we can see a statistically significant benefit in a mere 52 weeks, we have clearly changed the trajectory of this disease in a very positive way."

Drug Review Profile: Omisirge



Expanding Cells, Expanding Access: Gamida Cell's Omisirge Debuts New Donor Source For Stem Cell Transplant

Bridget Silverman

18 May 2023

Executive Summary

Pink Sheet's Drug Review Profile follows the FDA's navigation of the first expanded umbilical cord blood graft with the first indication grounded in neutrophil recovery and infection incidence data.

Gamida Cell Ltd.'s Omisirge (omidubicel-onlv) will be the first substantially modified cord blood-based stem cell graft source for allogeneic hematopoietic progenitor cell transplantation following FDA approval, using the Israeli company's stem cell expansion and enhancement technology to improve clinical outcomes with umbilical cord blood grafts – and in doing so, address a significant health inequity.

The FDA approved Omisirge on 17 April 2023 for adult and pediatric patients 12 years and older with blood cancers who are planned for umbilical cord blood transplantation following myeloablative conditioning. The cell therapy is specifically indicated to "reduce the time to neutrophil recovery and the incidence of infection."

Cord blood is "a relatively immunologically naïve source of cells," chief medical officer Ronit Simantov explained in an interview with the Pink Sheet. Umbilical cord blood units therefore require "much less stringent matching criteria than the other donor sources that come from adults."

The less stringent matching criteria make cord blood the only option for patients who need

hematopoietic stem cell transplant but cannot find a match. However, "the main problem with cord blood is that there are too few cells," she observed.

"It's a very small volume of blood and very few cells in there. That's appropriate for perhaps the tiniest patients, for babies and children. But for adults, it's long been known to be associated with higher mortality after transplant and a higher number of infections and a long, long time to neutrophil engraftment."

Omisirge has the promise to in essence increase the cord blood supply.

"There are at least 1,200 patients each year in the US who are eligible for transplant but cannot find an appropriate donor," chief operating officer Michele Korfin told the Pink Sheet.

"Unfortunately, if you are non-Caucasian, it's very difficult to find a match in the public database. So, for example, if you are a white patient, there's a 79% chance that you will find a match in the database. If you are a black or African American patient, that's 29%."

Umbilical cord blood transplantation is feasible for 96% of Caucasians of European descent, 81% of Black patients, and 82-91% of other minorities, Gamida Cell reported in its annual SEC filing on 27 March 2023.

Thanks to the less stringent matching criteria, Gamida Cell's Phase III trial of Omisirge had "over 40% of patients who are racially and ethnically diverse," Korfin added. "Our data indicates most hematology/oncology studies are more like 5% to 7%."

Simantov noted that the diverse enrollment "happened organically."

Clinical trial diversity has been receiving increasing scrutiny from the FDA. (Also see "US FDA Calls For Clinical Trial Diversity Plan 'As Soon As Practicable' In Product Development" - Pink Sheet, 18 Apr, 2022.)

Indication Changed During Review

The FDA's summary review of the Omisirge BLA shows that Gamida Cell originally sought an indication for "treatment of patients with hematologic malignancies in need of a hematopoietic stem cell transplant," a more general claim than the approved indication statement.

The typical FDA-approved HPC-cord blood product indication is for "hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system."

The agency, however, focused on the specific outcomes measured in the Phase III trial. "The prespecified primary endpoint was a composite of efficacy (time to neutrophil recovery) and safety (donor chimerism) assessed with different windows of follow-up (42- and 100-days following transplantation)," chair of the CBER Omisirge review committee, Division of Cell Therapy 1's Elizabeth Lessey-Morillon, noted in the summary basis for regulatory action.

"This combination of parameters did not clearly describe clinical benefit for the intended population," she stated.

The trial, which compared Omisirge with standard cord blood in 125 hematologic cancer patients, did show a statistically significant effect on time to neutrophil engraftment: 87% of Omisirge patients and 83% of the UCB arm achieved neutrophil recovery, but the Omisirge patients had a median time to recovery of 12 days compared with 22 days for UCBT.

"Although the trial was considered positive, the design of the trial did not support the proposed indication since it was not designed to demonstrate an effect on an endpoint relevant to the treatment of hematologic malignancies (e.g., complete remission or overall survival)," Lessey-Morillon explained. "This presented a challenge in determining an appropriate indication statement supported by the data."

The agency looked at the therapeutic landscape to determine appropriate outcomes and language. "A significant disadvantage of UCBT compared with transplantation from other donor sources is delayed hematopoietic recovery, including neutrophil recovery, and increased serious and life-threatening infections," Lessey-Morillon observed.

"There are currently no marketed products that are designed to be used as HSCT graft sources that are indicated to reduce the time to neutrophil recovery or reduce the incidence of bacterial and fungal infections in patients with hematologic malignancies planned for UCBT following myeloablative conditioning."

Furthermore, "infection in the setting of severe neutropenia is one of the most common causes of non-relapse mortality (NRM) in the early post-transplantation period," she said. "FDA considers a reduction in infection to be direct evidence of clinical benefit for interventions affecting myelopoiesis."

Secondary Endpoint Is 'Evidence of Direct Clinical Benefit'

The Phase III included a secondary endpoint of Grade 2/3 bacterial or Grade 3 fungal infections through day 100 following transplantation. Infections occurred in 39% of Omisirge patients and 60% of patients in the UCB arm. The decreased incidence of infection provides "evidence of direct clinical benefit," Lessey-Morillon said.

"The study, as designed, demonstrates a clinically meaningful benefit with Omisirge and addresses an unmet need for a graft option that addresses the limitations of standard UCBT by reducing the time to neutrophil recovery and the incidence of infection in subjects with hematologic malignancies who are planned for UCBT following myeloablative conditioning," the CBER reviewer summarized. "Therefore, the applicant's proposed indication statement was revised to reflect this assessment."

"We are pleased that this indication reflects the patient population and key outcomes of our Phase III clinical trial," Jenkins told the teleconference. "These are critical advantages that may improve the outcomes of patients undergoing stem cell transplantation."

Creative Paths To Supportive Evidence

The FDA review also took a flexible approach to the supportive efficacy data. A single-arm 36-patient Phase I/II study did not include incidence of infection through day 100 post-transplant as a protocol-specified analysis, but did collect infection data through day 180. Gamida Cell provided a data file with grading by the same criteria in the BLA, and a post hoc analysis found a 19% incidence of grade 2/3 bacterial or grade 3 fungal infections through day 100.

The post hoc 100-day infection data "were considered supportive of the incidence of infection seen in the omidubicel arm" of the Phase III trial, Lessey-Morillon said.

Clinical pharmacology data was also crucial to the intellectual structure of the FDA decision.

"Immune cell reconstitution (IR) after a HSCT is a dynamic process which includes the recovery of the lymphoid cell subsets and maturation of T-cells in the thymus including the induction and generation of a diverse, de-novo lymphocyte repertoire," she observed. IR analysis thus "provides supportive clinical evidence for Omisirge effectiveness."

"Transplantation with Omisirge resulted in rapid and broad immune reconstitution of dendritic cells, monocytes, Natural Killer (NK), CD4+ T cells and CD8+ T cells as early as one-week post-transplantation, and B cells 28 days post transplantation and all lineages throughout the one-year follow-up period," Omisirge labeling reports.

"Robust positive linear correlations between

the CD34(+) cell content in the Omisirge CF, and the reconstitution of T-cells and NK cells were identified. Additionally, dose-response analyses demonstrated a strong correlation between the total CD34+ cell counts and dose/kg for Omisirge with the kinetics of neutrophil recovery."

Lessey-Morillon called assessment of graft function "essential to ensure there was no detriment introduced by manipulation of the graft source." Primary graft failure occurred in 2% of Omisirge and 11% of UBCU patients in Phase III, and the proportion of patients achieving >90% donor chimerism was similar to UCBU or higher at all timepoints. "No detriment to graft function was observed with Omisirge in comparison to UCBT."

Omisirge's similarities to UCBT are notable in the safety labeling approved by the FDA. "The risks of Omisirge relate to its mechanism of action as an UCBT product," Lessey-Morillon observed. "These include infusion reaction, GvHD, graft failure, and malignancies of donor origin and can be managed by routine pharmacovigilance."

The Manufacturing Challenge

The label reports that 8% of patients randomized to Omisirge could not receive the therapy due to manufacturing failure. "Each Omisirge unit is specific to each patient," labeling emphasizes. "In case of manufacturing failure, a second manufacturing attempt may be considered."

Gamida Cell's commercial manufacturing will take place at the company's Kiryat Gat, Israel facility, where the company has been manufacturing clinical batches "for the last year," Korfin said. "We had a very positive inspection with FDA at the end of last year … with no observations."

The Gamida Cell execs also lauded the FDA's "really deep knowledge and professionalism." The Center for Biologics Evaluation and Research staff "are definitely super busy, but they were super engaged," Simantov said.

Omidubicel has held a breakthrough therapy designation since 2016, giving Gamida Cell greater access to the agency during development.

A New Kind Of Transplantation BLA

Gamida Cell's process also brings the cells into the realm of traditional biologics regulation, instead of the lower data requirements established by 2009 FDA guidance on minimally manipulated allogeneic cord and peripheral blood cells intended for hematopoietic reconstitution.

A period of enforcement discretion for minimally manipulated blood cells ended in October 2011, and since then eight umbilical cord blood transplant products have been approved under BLAs, starting with the New York Blood Center's Hemacord (hematopoietic progenitor cells-cord blood) in November 2011.

Omisirge "is the first cell therapy to both enhance and expand stem cells, one of the greatest scientific challenges in cell therapy," Gamida Cell CEO Abigail Jenkins declared during an 18 April teleconference. She called Omisirge "the most significant innovation in transplantation in more than a decade."

Process To Product

"No other products or no other graft sources go through this expansion and enhancement technology," Simantov emphasized to the Pink Sheet.

One of the "key technical challenges" for cell therapy development is "the expansion of therapeutically functional cells," Gamida Cell's 10K filing explained. While the number of donor cells can be increased in cell culture, "the functionality of those cells often diverges from the therapeutic functionality of the original

donor cells."

Gamida Cell uses its nicotinamide (NAM) technology to expand the number of progenitor cells in cord blood while maintaining functional therapeutic characteristics through a "proprietary combination of NAM, intended to maintain silencing of cell differentiation and preservation of gene expression, and particular cytokines which promote cell growth."

"NAM technology overcomes the induction of accelerated proliferation, differentiation, cellular stress and signaling pathways that are typically activated when [hematopoietic progenitor cells] are removed from their natural environment," Omisirge labeling states. "Ex-vivo culturing of cord blood derived HPCs in the presence of NAM leads to preservation of their stemness, homing to the bone marrow (BM) and retained engraftment capacity as demonstrated by rapid neutrophil engraftment and multi lineage immune reconstitution as observed in the clinical trials."

Gamida Cell's proprietary manufacturing process runs "approximately 30 days from the time we start manufacturing," Korfin said. That timeframe "actually has received very positive feedback because an unrelated donor, which the majority of patients are using, could take on average two to three months to align a donor."

"We've spent a couple of decades, honing our skills at expanding and enhancing cells," she commented. "We were able to get the actual harvest down to 21 or 22 days."

Omidubicel consists of two fractions of cord blood separated based on expression of the cell surface marker CD133; the components are administered in sequence with a process that takes six pages of labeling to describe. CD133-positive stem or progenitor cells are isolated and cultured with NAM. The CD133-negative cells represent other mature, differentiated cell types, including immune system essentials such as T cells. "These mature cells cannot engraft but can provide immunological support until T cells derived from the stem cell graft recover," the company said. Both the cultured and non-cultured fractions are derived from the same patient-specific cord blood unit.

Once And Future Collaborations

Gamida Cell emphasized the outside actors that have contributed to omidubicel during the conference call. Korfin pointed to a "very strong partnership" with National Marrow Donor Program/Be The Match "to support transplant center access to Omisirge." The new cell therapy will be a donor source option within MatchSource, Be The Match's widely used search platform, she said.

Be the Match registry offers "the most ethnically diverse listing of potential donors and umbilical cord blood units in the world," the company said, including more than 22m potential donors and 300,000 umbilical cord blood units.

"As the Phase III study concluded, and we saw the positive primary and secondary endpoints, we worked with Be The Match to establish a commercial partnership upon potential FDA approval," Korfin said. "Our strong partnership with Be The Match allows us to have Omisirge now listed as an option" on MatchSource "once a transplant center's onboarded."

Gamida Cell plans to onboard 10-15 transplant centers this year. (Also see "Gamida Cell Bounces Back With Omisirge US Approval" - Scrip, 18 Apr, 2023.)

A Slower Launch Than Planned

Gamida Cell also collaborated Be the Match BioTherapies on the production of omidubicel, including the ordering and supply of cord blood units as starting material.

The approval for omidubicel came two weeks before the BLA's 1 May 2023 user fee goal date, but Gamida Cell is ready to launch – albeit in a

conservative fashion reflecting the company's financial straits. On 27 March, just weeks before the Omisirge approval, the company announced the discontinuation of its preclinical pipeline and headcount reductions.

"The company intends to allocate the vast majority of its resources to executing a launch of omidubicel … although with a more limited investment and slower ramp than previously planned in order to manage its financial resources," Gamida Cell said.

The company is seeking a partner to provide more marketing support for Omisirge. Gamida Cell also recently retained Moelis & Company LLC to "assist in the exploration of partnerships or broader strategic alternatives that would provide additional resources to support the launch of Omisirge and associated commercial activities."

The approval for omidubicel came two weeks before the BLA's 1 May 2023 user fee goal date, but Gamida Cell is ready to launch – albeit in a conservative fashion reflecting the company's financial straits. On 27 March, just weeks before the Omisirge approval, the company announced the discontinuation of its preclinical pipeline and headcount reductions. "The company intends to allocate the vast majority of its resources to executing a launch of omidubicel … although with a more limited investment and slower ramp than previously planned in order to manage its financial resources," Gamida Cell said.

Gamida Cell does not appear to have direct competition coming any time soon. Two other expanded umbilical cord stem cell therapies have received FDA's Regenerative Medicines Advanced Therapy (RMAT) designation:

- Magenta Therapeutics, Inc.'s MGTA-456, which used a low molecular weight aryl hydrocarbon receptor antagonist to expand the cells, and
- ExCellThera Inc.'s ECT-001, which uses the small molecule UM171.

MGTA-456 was discontinued in 2020; ECT-001 completed enrollment in Phase II studies in high-risk leukemia and myelodysplasia patients in November 2022 and is planning extensions.

Drug Review Profile: Leqembi

Leqembi Phase II Missed Clinical Endpoint But Still Provided Support For Amyloid Surrogate

Sue Sutter
06 Mar 2023

Executive Summary

***Pink Sheet's* Drug Review Profile digs into the FDA memos on Eisai/Biogen's lecanemab; Phase II clinical efficacy results were reviewed for whether they supported the likelihood of amyloid plaque reduction to predict clinical benefit, rather than whether they directly provided substantial evidence of effectiveness.**

The failure of Eisai Co., Ltd. and Biogen, Inc.'s Phase II Leqembi (lecanemab-irmb) trial on its primary clinical endpoint did not undermine the view that the drug's ability to lower amyloid plaque is reasonably likely to predict clinical benefit in Alzheimer's disease, a US Food and Drug Administration clinical reviewer said.

In addition, although the imbalance in ApoE ε4 carriers in the lecanemab 10 mg/kg biweekly arm complicated interpretation of the Phase II study results, it did not render them uninterpretable, said Kevin Krudys, the efficacy reviewer on the lecanemab application.

Rather, the clinical endpoint results suggest lecanemab is "very likely to be effective and more likely than not to be effective by at least 25%," Krudys said. In addition, data from the recently completed Phase III trial should provide a clearer picture of the drug's effects in both ApoE ε4 carriers and non-carriers, he said. The FDA granted accelerated approval to lecanemab on 6 January. Krudys' conclusions about the Phase II data are detailed in the drug's clinical review.

Krudys also was a reviewer on Biogen and Eisai's application for Aduhelm (aducanumab-avwa), the first amyloid-lowering antibody to

reach market for treatment of Alzheimer's. Aduhelm received accelerated approval in June 2021.

Krudys supported regular approval of aducanumab, concluding the one successful Phase III trial was robust and exceptionally persuasive, with a treatment effect demonstrated on a clinically meaningful endpoint. (Also see "Aduhelm's 'Complex' Circumstances Drove Extensive In-House Advice Process Before Accelerated Approval, Cavazzoni Says" - Pink Sheet, 22 Jun, 2021.)

For lecanemab, he supported accelerated approval based on the precedent set by the use of a surrogate for aducanumab, as well as the Phase II and published Phase III data on clinical efficacy.

The lecanemab review documents highlight the extent to which aducanumab's accelerated approval has proven to be a watershed moment in the therapeutic space.

In an October 2018 meeting, the review division raised extensive concerns about the efficacy data in the lecanemab Phase II trial, concluding that the results could not support either regular or accelerated approval. However, almost three years later – and three months after the aducanumab nod – the agency met with Eisai to discuss the contents of a BLA for accelerated approval based on those same Phase II data. (See sidebar for clinical development timeline.)

Unusual and Complex Trial Design

Lecanemab's Phase II trial (Study 201) involved an unusual and complex design and analysis.

In the placebo-controlled period, patients were randomized to one of five lecanemab dosing regimens, including the 10 mg/kg biweekly regimen that ultimately was approved. The study employed Bayesian response adaptive randomization, which allows for interim analyses during the study to update allocation based on clinical endpoint results.

During the study, the Data Safety Monitoring Board recommended that the 10 mg/kg biweekly dose no longer be administered to homozygous ApoE ε4 carriers due to emerging data indicating a higher risk of amyloid-related imaging abnormalities (ARIA) in these patients. This modification was implemented in Protocol Amendment 4.

Following discussion with European health authorities, it was decided that all ApoE ε4 carriers (homozygous and heterozygous) should no longer be administered lecanemab 10 mg/kg biweekly.

Under Protocol Amendment 5, all ApoE ε4 carriers who had been receiving lecanemab 10 mg/kg biweekly for six months or less were discontinued from study drug, and newly enrolled ApoE ε4 carriers were randomized to placebo or another lecanemab dose. Patients who were randomized to the 10 mg/kg biweekly dosing regimen and had been on treatment for more than six months were allowed to continue at that dose.

The primary clinical endpoint was change from baseline in a cognitive composite measure, the Alzheimer's Disease Composite Score (ADCOMS) at week 53. The primary analysis was based on Bayesian statistics.

Amyloid Plaque Reduction

Change from baseline in brain amyloid plaque, as measured by 18F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR), was assessed in a subset of patients at weeks 53 and 79. Although this was a secondary endpoint, these data served as the endpoint supporting accelerated approval.

Compared with placebo, the lecanemab 10 mg/kg biweekly arm demonstrated a statistically significant reduction in brain amyloid plaque at week 79 (mean difference of -0.31 SUVR or -73.5 Centiloids; $p<0.001$).

"Amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of Alzheimer's disease. Although the role of amyloid and its relationship to other pathophysiological features of Alzheimer's disease, such as tau and neurodegeneration, is

complicated, the presence of amyloid plaques is a primary and essential finding in Alzheimer's disease, including early in the disease," Krudys said.

"It is reasonable to conclude that treatment that is targeted at reducing amyloid plaque, and that successfully accomplishes that reduction, has the potential to convey clinical benefit," he said.

'Very Likely To Be Effective'

Given the request for accelerated approval based on amyloid plaque reduction, the clinical efficacy endpoint results from Study 201 "are reviewed in the context of whether they support the likelihood of the surrogate to predict clinical benefit, rather than whether they directly provide substantial evidence of effectiveness of clinical benefit for full approval," Krudys said.

Krudys noted that interpretation of the clinical endpoints in the 10 mg/kg biweekly arm was complicated by the "stark imbalance" in the proportion of ApoE ε4 carriers in this dosing group compared to the other arms, the result of protocol amendments that led to discontinuation of study drug in 25 patients on this dose.

"The fact that the primary result was not successful according to the prespecified threshold should not be incorrectly interpreted as evidence of ineffectiveness of lecanemab. On face, this result suggests that lecanemab is very likely to be effective and more likely than not to be effective by at least 25%." – FDA's Kevin Krudys

The primary Bayesian analysis of ADCOMS at week 53 indicated that the lecanemab 10 mg/kg biweekly had a 64% probability of being superior to placebo by 25%, which did not meet the prespecified criterion for success of 80% probability. (Also see "Eisai's Lecanemab: US FDA Showed Flexibility On Clinical Endpoint Results, Safety Database Size" - Pink Sheet, 11 Jan, 2023.)

The probability of lecanemab 10 mg/kg biweekly being superior to placebo by any amount at week 53 was 98%.

"The fact that the primary result was not successful according to the prespecified threshold should not be incorrectly interpreted as evidence of ineffectiveness of lecanemab," Krudys said. "On face, this result suggests that lecanemab is very likely to be effective and more likely than not to be effective by at least 25%."

Looking at secondary and exploratory clinical efficacy endpoints, the 10 mg/kg biweekly lecanemab dose demonstrated favorable numerical results on the Clinical Dementia Rating Sum of Boxes (CDR-SB) and nominal statistical significance for ADCOMS and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 14) at week 79.

'Important Context' For Clinical Endpoint Results

The memo notes that in 2018, the review division communicated concerns about the clinical efficacy data at an end-of-Phase II meeting. These concerns included the proportion of patients with missing efficacy data, use of ADCOMS as the primary endpoint, statistical issues with multiplicity, and the imbalance in ApoE ε4 carriers between the 10 mg/kg biweekly arm and placebo group.

"These concerns remain valid when considering Study 201 in isolation," Krudys said. "This application, however, is being considered for accelerated approval based on whether the surrogate endpoint of reduction in brain amyloid plaque is reasonably likely to predict a clinical benefit to patients. Since 2018, accumulating data on the association between amyloid plaque reduction and treatment effects on

clinical endpoints provide important context for the favorable clinical endpoint observations in Study 201."

Krudys specifically addressed concerns about the imbalance in ApoE ε4 carriers in the placebo and 10 mg/kg biweekly lecanemab arms.

"One might reasonably hypothesize that the apparent treatment effect observed in the lecanemab 10 mg/kg biweekly arm is driven by the preponderance of ApoE ε4 non-carriers, who presumably have slower disease progression. And, in fact, ApoE ε4 non-carriers were observed to have slower progression than ApoE ε4 carriers for ADCOMS in the placebo arm of Study 201," Krudys said.

However, other observations and results caution against drawing such a conclusion, he said.

"First, it should be noted that slower progression in ApoE ε4 non-carriers is not a universal finding across clinical trials. Second, the progression in ADAS-Cog 14 was greater in ApoE ε4 non-carriers than carriers in the placebo arm … yet this endpoint demonstrated the largest overall treatment effect with the smallest nominal p-value," he said. "Third, analyses using only patients randomized before the change in randomization scheme result in consistent findings."

Furthermore, the 10 mg/kg biweekly dose data were combined with the 10 mg/kg monthly dose data to create a group with comparable proportions of ApoE ε4 non-carriers and carriers to the placebo arm. "In this combined group, the trends were consistent with the overall results."

"Notwithstanding these lines of reasoning, the decision to cease randomization of ApoE ε4 carriers to the 10 mg/kg biweekly regimen introduced uncertainty which can only be fully addressed with a larger dataset," the review states.

The agency's interpretation of the safety data on amyloid-related imaging abnormalities also was complicated by the ApoE ε4 carrier imbalance.

Amyloid Reduction 'Incompatible' With Chance

Krudys concluded that lecanemab's effect on brain amyloid plaque in Study 201 meets the statutory standard for substantial evidence of effectiveness to support accelerated approval, and the magnitude of the reduction is consistent with the observed reduction that supported aducanumab's accelerated approval.

"Although the reduction of brain amyloid plaque was observed in only a subset of patients in a single study, the results are highly persuasive. As observed in the placebo arm of Study 201, amyloid plaque does not spontaneously disappear in patients with Alzheimer's disease. The reduction observed in the lecanemab 10 mg/kg biweekly arm is thus incompatible with variability or chance. Also, the results demonstrated a clear dose- and concentration-response relationship over the dosing regimens included in the study."

"The effects on amyloid are persuasive and consistent across doses and subgroups, supporting the ability of Study 201 to be considered a single adequate and well-controlled trial that is capable of providing substantial evidence of effectiveness."

The clinical endpoint results from Study 201 provide context for the amyloid reduction observed in the study and inform the reasonable likelihood that this effect on the surrogate will predict clinical benefit.

"Despite limitations introduced by the under-enrollment of ApoE ε4 carriers in the lecanemab 10 mg/kg biweekly arm and the adaptive design of the trial, the estimates of the treatment effect at Week 79 across clinical endpoints are consistent with a modest reduction of clinical decline," Krudys said.

Leqembi Phase II Missed Clinical Endpoint But Still Provided Support For Amyloid Surrogate

"Importantly, a similar degree of reduction (approximately 20% to 40%) in the decline of clinical endpoints has been observed in other studies in which brain amyloid was reduced to a similar extent. This reduction corresponds to a delay in progression of several months over the 18 months of the study. Patients and caregivers have clearly expressed that a delay of several months at this stage of the disease is clinically important."

Looking To Phase III Results For Additional Support

Furthermore, the top-line results from the Phase III trial (Study 301) provide both important context and additional support for the reasonable likelihood that that reduction in brain amyloid plaque with lecanemab will predict clinical benefit, Krudys said.

In the Phase III CLARITY-AD trial, results of which were published in the New England Journal of Medicine in November, lecanemab demonstrated a statistically significant benefit on a clinical primary endpoint – a -0.45 difference versus placebo at 18 months on the CDR-SB, representing a 27% slowing in the rate of decline versus placebo. (Also see "Eisai/ Biogen's Lecanemab Effective Across Endpoints, But Will Safety Limit Use?" - Scrip, 30 Nov, 2022.)

Eisai submitted the Phase III data in a supplemental application seeking regular approval on the same day that lecanemab received accelerated approval. Consequently, the agency had not yet reviewed these data in detail at the time of accelerated approval.

Nevertheless, Krudys said the positive top-line results in Study 301 "appear to be consistent with the results of Study 201 and what is already known about the relationship between brain amyloid plaque reduction and effect on clinical endpoints. The top-line results for the gantenerumab studies, although negative, are entirely consistent with the known relationship between amyloid plaque reduction and clinical endpoints."

Roche announced in November that its anti-amyloid antibody gantenerumab was not statistically significantly better than placebo at slowing the rate of clinical decline in two Phase III trials. Relative reduction in the rate of clinical decline compared to placebo was 8% and 6% in the GRADUATE I and II trials, respectively, based on CDR-SB scores at 116 weeks. Roche also noted that amyloid was cleared from the brains of gantenerumab-treated patients at lower levels than expected. (Also see "Roche's Alzheimer's Drug Fails In Phase III Giving Eisai/ Biogen A Clear Run" - Scrip, 14 Nov, 2022.)

Statisticians Dissent

As was the case with aducanumab, the FDA's statistical team disagreed with the decision to grant accelerated approval.

The statistical review cites many issues with the Bayesian response adaptive randomization design of Study 201, including: multiple interim analyses performed to allow for possibly stopping the trial earlier; failure to control for Type 1 error at the level of 0.05 two-sided, or 0.025 one-sided, due to the Bayesian dose selection; and interim analyses without any multiplicity correction.

The apparent lack of clinical effects in ApoE ε4 non-carriers "seems to not align with the biomarker treatment effect being thought of as reasonably likely to predict a corresponding clinical treatment effect for all patients." – FDA's Tristan Massie

"Due to the failure of the primary endpoint and the large number of secondary endpoints, all secondary endpoints should be considered exploratory," statistical reviewer Tristan Massie said. In addition, the PET substudy was voluntary, "so the balance of baseline

demographics and disease characteristics within the substudy may not be guaranteed and the substudy sample may not be representative of the randomized population."

Massie said there do not appear to be clinical effects in ApoE ε4 non-carriers, even though there were effects on amyloid SUVR in non-carriers comparable to those seen in ApoE ε4 carriers.

"This seems to not align with the biomarker treatment effect being thought of as reasonably likely to predict a corresponding clinical treatment effect for all patients."

Krudys' review suggests Massie's conclusion about lack of clinical effects in ApoE ε4 non-carriers is premature.

Of the eight subgroups defined in the statistical analysis plan, "the statistical review presents one (ApoE ε4 carrier status) to raise uncertainty regarding the impact of amyloid reduction on clinical endpoints because there is no apparent treatment effect on the clinical endpoint in ApoE ε4 non-carriers," Krudys said.

"Subgroup analyses on clinical endpoints are better suited for the larger confirmatory Study 301.

It is worth noting that in the top-line results for that study, ApoE ε4 non-carriers appeared to demonstrate a treatment effect on clinical endpoints," Krudys said, citing the NEJM publication with the Phase III data.

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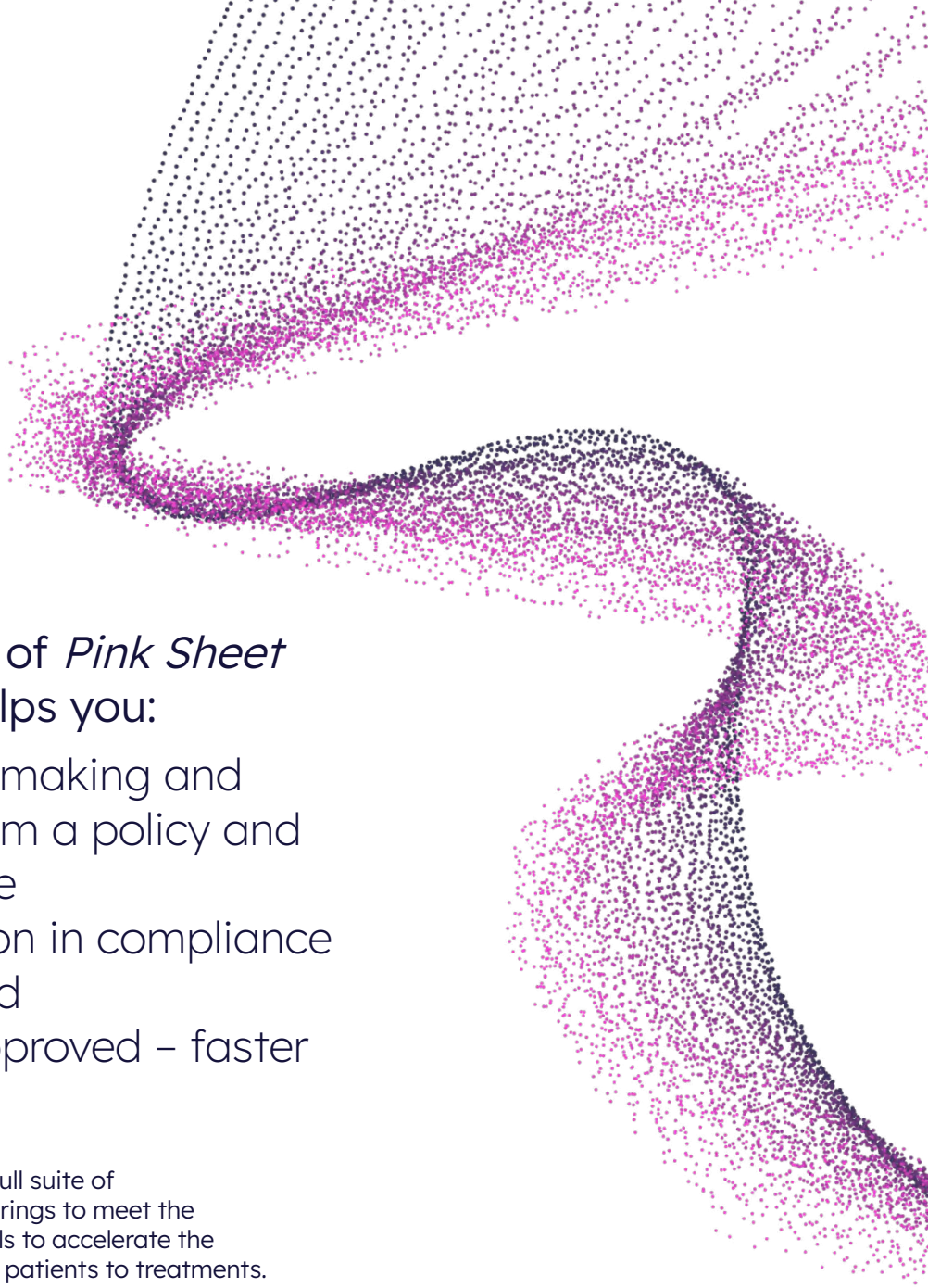

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