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12 Oct 2023 | **Analysis**

US WorldMeds' Neuroblastoma Drug: External Controls, Confirmatory Evidence, And A Concern About Precedent

by Sue Sutter

US FDA officials said the high-quality nature of the patient-level data used in the external control arm, and the use of animal models considered to be translatable, justify reliance upon a nontraditional data package for eflornithine (DFMO) in high-risk neuroblastoma, but some adcomm members worry that an approval will open the door too widely for others to follow.

The US Food and Drug Administration appears comfortable with the idea of approving *US WorldMeds, LLC*'s new drug application for eflornithine (DFMO) in high-risk neuroblastoma based upon the results from an externally controlled trial, with animal data as confirmatory evidence.

Such an approval would be groundbreaking. FDA review staff said the agency has not previously relied upon a single, externally controlled trial to support approval in oncology. Furthermore, nonclinical data on mechanism of action and animal models in the proposed indication are being considered in the context of confirmatory evidence, which is unique to this application.

Amid concerns from Oncologic Drugs Advisory Committee members about the precedent-setting nature of such an approval, FDA officials emphasized the unique situation presented with the DFMO application.

This includes an external control arm comprising high-quality, patient-level

Key Takeaways

- US WorldMeds seeks approval of DFMO in neuroblastoma based on a single-arm trial compared with an external control arm,

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data from another trial, as well as preclinical data based on animal models the agency considers to be sufficiently established and translatable – even though this view does not exactly align with a recent draft guidance addressing the use of animal data for confirmatory evidence. (*See sidebar for related story.*)

FDA officials also took pains to tamp down concerns that an exercise of regulatory flexibility for DFMO in neuroblastoma would lead to a "slippery slope," clearing the way for use of this type of data package in other cases less deserving.

"Whatever decisions made in this very unique circumstance with … an externally controlled study with confirmatory evidence would only be appropriate to review in rare circumstances with very high-quality, comparable patient-level data in an external control," Oncology Center of Excellence Deputy Director Paul Kluetz said.

with confirmatory evidence coming from preclinical animal models.

- FDA has not previously relied upon a single externally controlled trial to support approval in oncology, and consideration of animal model data in the context of confirmatory evidence is unusual.

- FDA officials sought to tamp down concerns that approval would encourage other sponsors to rush forward with externally controlled trials, saying the DFMO application is an unusual case involving high-quality, patient-level data and there remains a high bar for considering whether an external control data source is fit for purpose.

Ultimately, the committee voted 14-6 that US WorldMeds provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma. (Also see "*US WorldMeds' Eflornithine Gets US FDA Panel Nod For Pediatric Neuroblastoma*" - Pink Sheet, 4 Oct, 2023.)

US WorldMeds' Data Package

US WorldMeds seeks approval of DFMO to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multi-agent, multi-modality therapy. The new drug application is based on a nontraditional data package, with the primary evidence being results from a single-arm trial (Study 3(b)) that were compared against an external control arm from a different trial (Study ANBL0032) through propensity score matching.

The company's primary analysis resulted in event-free survival and overall survival hazard ratios of 0.48 and 0.32, respectively, favoring the DFMO arm. Generally similar results were observed in multiple sensitivity and supportive analyses conducted to assess the impact of potential differences between the investigational and external control arms. (Also see "*FDA Panel Will*

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Have To Weigh Pediatric Cancer Drug's 'Higher Level' Of Uncertainty Against Rare, Devastating Disease" - Pink Sheet, 2 Oct, 2023.)

The FDA said it initially recommended that a randomized, controlled trial be conducted to evaluate DFMO's efficacy in this setting, but the investigator sponsor subsequently conducted the single-arm Study 3(b), data from which appeared to suggest a substantive improvement over a benchmark historic control.

A February 2023 draft guidance generally discourages use of externally controlled trials in all but a very limited number of situations that are truly ripe for such an approach. (Also see "*External Controls: FDA Guidance Provides Clarity But Does Little To Remove Hurdles*" - Pink Sheet, 6 Feb, 2023.) It would appear that DFMO for pediatric high-risk neuroblastoma fits into this narrow category.

"The use of an [externally] controlled trial to support a marketing application may be acceptable in the setting of a rare disease with a well-defined natural history and poor prognosis if the expected treatment effect is estimated to be large, particularly in a setting where conduct of an RCT may be infeasible," the FDA's advisory committee briefing document states.

Animal Models: Adcomm Exposes Internal Rift In How FDA Defines 'Translational' For Purposes Of Confirmatory Evidence

By Sue Sutter

12 Oct 2023
FDA review staff consider the animal models used in development of US WorldMeds' eflornithine for neuroblastoma to be translational to humans, even though this does not align with the definition in a September 2023 draft guidance on types of confirmatory evidence.

Read the full article here

"The review team considered the use of an external control in this unique setting to be reasonable given the external control data source (e.g., patient-level data from a large, randomized clinical trial), similarity of the propensity score matched Study 3(b) and ANBL0032 populations, and difficulty in conducting a new randomized controlled trial in light of the published results of DFMO for the proposed indication," the briefing document states.

"FDA review has noted that the ECT appears adequate and well-controlled with a clear statement of objectives, an appropriately constructed design with appropriate patient selection, and reliably conducted clinical assessments to evaluate the effect of the drug."

US WorldMeds' proposed confirmatory evidence was primarily in the form of preclinical *in vivo*

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and animal model data.

Agency review staff pointed to the FDA's December 2019 draft guidance on demonstrating substantial evidence of effectiveness, as well as the September 2023 draft guidance on demonstrating substantial evidence with one adequate and well-controlled clinical investigation and confirmatory evidence. The latter guidance lists seven potential sources of confirmatory evidence, relevant animal models. (Also see "*Real-World Data Or Studies Of Competitor Drugs Can Serve As Confirmatory Evidence For US FDA*" - Pink Sheet, 18 Sep, 2023.)

"This application is unique in that we have not previously relied upon a single externally controlled trial as the primary source of evidence in oncology," FDA clinical reviewer Elizabeth Duke said. "The external control data is of high quality due to its provenance and the relatively large set of individual patient-level trial data. And the results of sensitivity analyses are generally consistent with the applicant's primary analysis."

"However, residual uncertainties remain, given the lack of a randomized design to interpret the effect on a time-to-event endpoint and the uncertainty in the magnitude of the treatment effect."

"Regarding confirmatory evidence to support the single trial, the available nonclinical data are robust and supportive of a cytostatic mechanism of action," Duke said. "However, nonclinical data is rarely used as the primary source of confirmatory evidence. There are some clinical data from small studies and an expanded access program, but there are limitations to their interpretability."

'Uniquely Strong Data Source'

Some adcomm members raised concerns that approving DFMO on the basis of a single-arm trial with an external control comparison would open the door to a rush of other applicants seeking to capitalize on a similar approach.

"I do think there are an awful lot of companies that would like to do an open-label, single-arm study because they believe their evidence to date, such as from Phase II trials, prevents equipoise or feasibility" of conducting a randomized trial, said Caleb Alexander, a pharmacoepidemiologist at Johns Hopkins University.

> *"I'd like to emphasize again that generally there is a high bar for considering an external control data source is fit for purpose." –*

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FDA's Martha Donoghue

Panelists also questioned whether the FDA performed a formal analysis on the feasibility of conducting a randomized controlled trial in this population.

Martha Donoghue, OCE's associate director for pediatric oncology, said the agency did not undertake a formal feasibility analysis.

"Our strong preference is for the conduct of randomized trials to evaluate effectiveness of new products in the maintenance setting for patients with high-risk neuroblastoma," she said. "We know this is possible because it has been done before" in the ANBL0032 trial, which led to the approval of *United Therapeutics Corporation*'s Unituxin (dinutuximab) in the front-line setting for high-risk neuroblastoma.

"However, in this unique case, once we became aware of the results of Study 3(b) we considered it appropriate to review this application" she said. "And the primary reason was due to the uniquely strong data source for an external controlled trial, namely the high-quality, patient-level data from study ANBL0032 and the fact that most of the patients in Study 3(b) had also enrolled in the same trial."

"This particular source of data mitigated many of the factors that can preclude a determination that the data are fit for purpose as an external control," Donoghue said. "In this unique case … we considered the already published results in Study 3(b) which appeared to show a large treatment effect in a population that has a high unmet medical need."

"I'd like to emphasize again that generally there is a high bar for considering an external control data source is fit for purpose, and the use of a randomized design would have been a less risky approach from a drug development perspective and could also potentially generate the necessary data more quickly," Donoghue said.

'Fairly Extraordinary Situation'

Despite FDA officials' assurances, a few panelists continued to express concerns about how an approval here could impact other drug development programs.

"I agree with all the comments in regards to the need for randomization to truly measure the strength of the evidence, but at the same time this is probably, I think, as good as we may get in regards to an externally controlled trial," said Christopher Lieu, director of the gastrointestinal

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medical oncology program at the University of Colorado and ODAC's acting chairman.

> *"I certainly have significant concerns about setting a precedent for utilization of an externally controlled trial. I don't want to get us into a situation where the discussion or decision to do a randomized trial is really influenced by the decision at this panel." – University of Colorado's Christopher Lieu*

"But I certainly have significant concerns about setting a precedent for utilization of an externally controlled trial. I don't want to get us into a situation where the discussion or decision to do a randomized trial is really influenced by the decision at this panel. I think that this is a fairly extraordinary situation," Lieu said.

"It's hard not to think that should the FDA move forward that this isn't precedent-setting, so I think it's sort of naive to think otherwise as much as we may hear assurances to the contrary," Alexander said. He did, however, acknowledge that this is a "fairly unusual setting."

Different Views On The 'Slippery Slope'

In explaining their votes, some adcomm members applauded the FDA's willingness to exercise regulatory flexibility on this application, while others reiterated concern that it would open the floodgates to applications less worthy of such flexibility.

"I think these types of analyses need to be done in the pediatric cohort, and this may be a good precedent," said Shahab Asgharzadeh, director of the Neuroblastoma Basic and Translational Program at Children's Hospital Los Angeles. "There are easily ... circumstances where we could avoid this in certain diseases [where] there are sufficient patients to do a randomized trial quickly, but I felt in this setting the evidence shows that DFMO is effective," he said.

Alexander also voted in the majority on the belief that DFMO has activity and the animal models will translate to humans.

> *"I support this kind of flexible approach for the rare disease*

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population, and I'm pretty confident that it will not inspire an uncontrollable slippery slope of precedent." – ODAC patient representative Gianna McMillan

However, "I'm not clear that the evidence that we've reviewed meets statutory thresholds," Alexander said. "I also think FDA has to be careful what they wish for, and the ways that any favorable decision here may have significant consequences on future drug development and be precedent-setting."

"I'm also not confident that an RCT is infeasible," he continued. "And while on the one hand this may seem like water over the dam, on the other it's actually a contextual factor that I think we heard, based on guidance, should be considered about what constitutes substantial evidence."

Gianna McMillan, the panel's patient representative, also voted in favor of a demonstration of efficacy. "I support this kind of flexible approach for the rare disease population, and I'm pretty confident that it will not inspire an uncontrollable slippery slope of precedent."

However, Neil Vasan, assistant professor in the department of hematology and oncology at Columbia University, voted "no."

"I applaud the FDA and the applicant for their rigorous analyses in their application files. Given the large effect size, I believe a randomized trial could be conducted which would rule out other confounders that were discussed," he said. "I do want to say that I think that the conceptualization, development and analysis of this application will serve as a model for future drug development."

"There are clear areas of disagreement within the panel," adcomm chair Lieu said in summarizing the group's deliberations and vote. "And that is whether this type of data should really ever be used given the concern regarding confounders and biases that are just inherent in these type of external controls."

"Certainly, there's a lot of concern from the group about what the future holds for drug development, and what level of evidence the FDA will require in similar situations in the future," Lieu said. "And I think there's some concerns about a slippery slope, and then others on the panel that are not worried about that type of slippery slope. There's also some disagreement in this group about whether a randomized controlled trial is potentially feasible, and whether it can be done in a timely fashion."