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Sumathi Nambiar, MD, MPH
Director, Division of Anti-Infective Products
U.S. Food & Drug Administration
10903 New Hampshire Avenue, Bldg. W022, Rm. 6236
Silver Spring, MD 20993

Re: Advisory Committee Meeting and Division Review of Aradigm's "Linhaliq" Application

Dear Dr. Nambiar,

In response to the Antimicrobial Drugs Advisory Committee ("AMDAC") meeting, NTM Info & Research ("NTMir") urges the U.S. Food & Drug Administration ("FDA") to act in accordance with AMDAC's majority opinion regarding Linhaliq for the treatment of *Pseudomonas aeruginosa* in moderate to severe bronchiectasis exacerbations. AMDAC's comments during discussion and the majority opinion did not reflect the outcome of the vote.

Background

A 2017 research paper determined that in 2013, there were between 340,000 and 520,000 patients in the United States being treated for bronchiectasis.[1] Several scholarly articles have also reported that anywhere from 20% to 58% of bronchiectasis patients have *P. aeruginosa* infection, which is linked to advancement of the disease and deterioration of lung function in a vicious cycle of harm to the patient.

When the ORBIT studies were designed eight years ago, the applicant indicated to the FDA that they were using the primary endpoint of "frequency of exacerbation" for their studies in Europe because the European Medicines Agency ("EMA") required it, believing as the applicant did, that it was the better endpoint. At that time, the FDA decided that regardless, it would prefer a study with "time to first exacerbation" as the primary endpoint. In the intervening years, the FDA, the advisory committee, leading researchers in the field, and companies working to develop treatments for bronchiectasis, have all acknowledged that frequency is in fact the more relevant endpoint.

Aradigm's Study Data Are Sufficient to Demonstrate Safety, Efficacy, and Meeting a Significant Unmet Need for Patients

Ciprofloxacin has been used for many years to manage infections in bronchiectasis patients, and its safety profile and side effects are well known. However, Linhaliq takes advantage of liposomal technology to render a more effective delivery system for ciprofloxacin with demonstrably better efficacy and safety.

Aradigm's data demonstrated that having resistant bacteria is not correlated with increased exacerbations, and clinicians who spoke during the Open Public Hearing confirmed this. In addition, increased blood serum levels are what lead to increased burden of side effects, including nephrotoxicity. Linhaliq competently addresses this issue by directly delivering the drug to the infection site and maintaining much higher concentrations of the drug at the infection site than would be found with oral or IV therapy, with a 42% reduction in both IV and oral drug exposure. This also aligns with Commissioner Gottlieb's mandate of improving stewardship of vital drugs.[2]

Bronchiectasis patients particularly face a whole host of medical challenges which may necessitate other medications. Because of this, Linhaliq can in fact represent an improved treatment option because it reduces their exposure to other medications.

AMDAC expressed concerns regarding the discrepancy between the ORBIT-3 and ORBIT-4 results. When one looks at the data for off-protocol antibiotic use, it seems that this would have had some impact on the study outcomes. In some ways, this renders Aradigm's studies a more real-world representation. While we would all like to see pristine data from clinical trials, this is not a realistic representation of patients or their experiences, and it is nearly impossible to achieve in a clinical trial setting.

In particular, with patients who have bronchiectasis, pseudomonas, or NTM infections, these patient populations are heterogeneous even among similar infectious strains. Unlike some other diseases where each patient follows a completely predictable pathway through the illness, our patients almost always present with some individual variations. Seeking perfection and homogeneity in such a population will only lead to disappointment and failure and may not be a helpful approach to clinical trial design or analysis in these patient populations.

Several committee members alluded to this in the post-vote discussion when addressing the natural heterogeneity of the bronchiectasis patient population:

Michelle Harkins: "This is a difficult patient population that is very heterogeneous."

Demetre Daskalakis: "I think that, though, it would be hard to figure a way to create a study where you focus on those higher, higher-risk populations."

Paula Carvalho: "…it's a heterogeneous disease, and I think as just about every member has mentioned, ORBIT-3 was a little bit demographically different than ORBIT-4, and the pooled data actually went in the right direction."

Jonathan Honegger: "It does appear to be safe overall, in a very sick population."

Listening to the Voice of the Patient

In a recent survey of 287 bronchiectasis patients conducted jointly by NTMir and the COPD Foundation, with data gathered over a 48-hour period, patients were asked to rank six issues in

order of importance. 51% said that lung function was their highest priority. Since lung function is closely related to the amount of damage to the lungs, and this is directly impacted by the number of exacerbations a patient has, it is apparent that Linhaliq addresses this patient concern.

In the same survey, the second-highest ranked concern for patients was "number of exacerbations per year," followed closely by "overall amount of antibiotics I use each year (oral and IV)". Since Linhaliq reduces frequency of exacerbations and is an inhaled treatment which, as Aradigm's own data demonstrates, reduces the burden of oral and IV antimicrobials, it is apparent that Linhaliq also addresses these patient concerns.

This mirrors the many statements heard during the Open Public Hearing and aligns well with Commissioner Gottlieb's stated goal of increased patient-centric outcomes.

The purpose of the review and approval process is not to "coerce reluctant sponsors into constructing exhaustive studies – studies that extract every single kernel of potentially relevant clinical information."[3] The purpose of this process is to guide new and innovative medical treatments to market. By employing rigorous science in a flexible manner, it is possible to fulfill this purpose while soundly meeting the agency's obligation to protect consumers.

In fact, when discussing specific labeling during post-vote discussion, committee member Jonathan Honegger stated, "I don't feel that additional studies are necessary."

The Advisory Committee's Comments Do Not Reflect the Outcome of the Vote

Though AMDAC voted 12-3 against approving Linhaliq, with one abstention, the numbers themselves do not tell the story. Because AMDAC's deliberations were restricted to the question posed regarding the primary endpoint of "time to first exacerbation" – an endpoint which even the FDA now acknowledges is not the more appropriate endpoint for a study of this nature – the committee members were unable to vote in accordance with their true feelings on whether Linhaliq should be approved. The FDA, committee members, and applicant all acknowledged that the secondary endpoint of "frequency of exacerbation" is the more relevant endpoint.

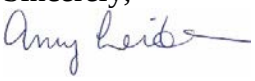
If you examine the post-vote discussion, it becomes clear that at least nine committee members felt that the ORBIT studies demonstrated Linhaliq's worth for at least one segment of the bronchiectasis patient population, largely based on Aradigm's data for the secondary, better endpoint of frequency of exacerbation, and many committee members only voted no because of the specific question asked of AMDAC at the time of voting. (See: Appendix A: Post-Vote Comments of AMDAC Members.)

Conclusion

A decision that is in accordance with the majority opinions expressed by AMDAC is appropriate for Linhaliq. The studies have demonstrated safety and efficacy in an identified subset of bronchiectasis patients who would clearly benefit from the drug, a group of people who face staggering unmet medical needs for an overwhelmingly burdensome illness.

There is no doubt that the longer we go without improved treatments, the more patients will get sicker and die. This is a certainty. We have seen it happen to too many patients already. Continually delaying progress in a quest for exacting certainty where none exists, permits process to trump science. This would represent a failure on the part of the FDA to fulfill its obligation to protect and promote public health and runs counter to the patient-centered outcomes which are the most sensible because in the end, it is the patients who either benefit from progress, or suffer from the lack of it.

Sincerely,



Amy Leitman, JD
Director, Policy & Advocacy
NTM Info & Research

CC: Scott Gottlieb, MD
Janet Woodcock, MD
Edward Cox, MD, MPH
John Farley, MD, MPH
Badrul Chowdhury, MD, PhD
Lydia Gilbert McClain, MD
Philip Leitman, President, NTM Info & Research

Endnotes

[1] Weycker, Derek, et al. "Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013." Chronic Respiratory Disease Vol. 14(4) (2017). 377-384.

[2] Gottlieb, Scott. "Reflections on a Landmark Year for Medical Product Innovation and Public Health Advances and Looking Ahead to Policy in 2018." FDA Voice, U.S. Food & Drug Administration, January 9, 2018, blogs.fda.gov/fdavoice/index.php/2018/01/reflections-on-a-landmark-year-for-medical-product-innovation-and-public-health-advances-and-looking-ahead-to-policy-in-2018/.

[3] Gottlieb, Scott. "Changing the FDA's Culture." *National Affairs* Volume 12, Summer (2012). 108-121.

APPENDIX A: Post-Vote Comments of AMDAC Members

Michelle Harkins (voted YES): "I think looking at number or frequency of exacerbations is really key…"

Demetre Daskalakis: "…that was a very specific question that we were asked. I think that the data is a lot more convincing for, ah, for preventing recurrence, especially in specific populations." "I think if this question were framed differently, and we were looking at that endpoint, my vote would be different."

Jonathan Honegger (voted YES): "…there was a positive trend in all the more clinically relevant secondary endpoints…"

Michael Green: "As I said, I wanted to vote in support of approval, but I recognize that this vote would not strictly be in response to the FDA's specific question on the evidence of impact in time-to-event."

Barbara Gripshover: "…it does look like the drug might have a good effect in the right population. So, which to me does seem to me people who had more frequent exacerbations for sure."

Randy Hawkins (ABSTAINED): "If I strictly answered the question, my vote would be no. I, like others, felt that frequency of exacerbations was the more important endpoint. And I think that was met."

Jasan Zimmerman: "I really wanted to say "yes", but "no" to the question as it was posed."

Paula Carvalho (voted YES): "I had difficulty with the way the question was posed, because I had difficulty with the word "substantial," and I had difficulty with the primary endpoint. Nevertheless, I think that this would be worth a shot to go forward."

Jonathan Green: "The question that was asked was quite specific, and I did not feel that that was met." "I think that there is a role for this. I would like the patients to have it available, on label, so we're looking at paid for."