LETTER TO THE EDITOR

Response to Comment on "An Integrated Pharmacokinetic-Pharmacodynamic-Pharmacoeconomic Modeling Method to Evaluate Treatments for Adults with Schizophrenia"

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Dear Editor,

We appreciate the opportunity to respond to the comments submitted to you by Dr. Bhaskar Rege and colleagues [1] regarding our October 2021 article entitled, "An integrated pharmacokinetic–pharmacodynamics–pharmacoeconomic modeling method to evaluate treatments for adults with schizophrenia" [2]. As mentioned in the introduction section of our article, the purpose of this article was to present an application of a novel pharmacokinetic–pharmacodynamics–pharmacoeconomic (PK–PD–PE) framework that would enable pharmacoeconomic comparisons of the aripiprazole lauroxil (AL) and aripiprazole monohydrate (AM) long-acting injectable formulations based on publicly available, where possible peer-reviewed sources given that no comparative clinical evidence currently exists. It is our understanding that Dr. Rege and colleagues [1] question the validity of the PD inputs of our PK–PD–PE model as well as the validity of the pharmacoeconomic conclusions of our

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study. For the reasons explained below, we stand behind the validity of our model and our conclusions in the article.

First, the commentators state that we "cite no clinical evidence for the use of 95 ng/mL or for an association between that threshold and the probability of relapse for AL". We modeled the link between aripiprazole plasma concentrations, which are generated through the respective PK models for AL [3] and AM [4], and relapses using an exposure–response relationship (PD model). As no exposure–response relationships for aripiprazole have been published based on AL clinical trials, we used the only published relationship between aripiprazole plasma concentrations and relapses (Wang et al. [4]), which was based on AM studies. Further, in their argument that "no exposure-response relationship has been observed for oral aripiprazole or for AL", the commentators cite two published meta-analyses of a dose response of antipsychotic drugs [5, 6]. However, failure to establish a dose response does not preclude establishing a relationship between pharmacokinetics-pharmacodynamics, especially as the latter takes into account differences in drug plasma concentrations between individuals receiving the same dose. In addition, as both AM and AL exert their action via the common active aripiprazole, it is plausible to assume the same aripiprazole exposure–response relationship for both formulations. The difference between the long-acting injectable formulations is not in the pharmacodynamics but in the pharmacokinetics of the two formulations (i.e., the different PK profiles), as mentioned by the commentators [1]. We account for those differences between the formulations in the PK part of our PK–PD–PE analysis.

Second, the selection of an exponential survival model with the 95-ng/mL concentration threshold by Wang et al. [4] was informed by observed clinical trial data. The exposure–response analysis initially evaluated aripiprazole minimum plasma concentration (C_{min}) as a continuous variable;

however, the model resulted in a misfit at $C_{min} > 95$ ng/mL (i.e., the model predicted increasing C_{min} was associated with a longer time to relapse at $C_{min} > 95$ ng/mL), whereas the observed data showed a similar time to relapse in this exposure range. As a result, an exponential survival model with the 95-ng/mL concentration threshold was evaluated and the results showed that the model prediction agreed reasonably well with the observed data. Therefore, the model was considered sufficiently robust to predict the probability of relapse in patients with schizophrenia based on aripiprazole C_{min}. Of note, a recently published article [7] supports the conclusions of Wang et al. [4], proposing a minimum aripiprazole therapeutic reference range of 120 ng/mL regardless of the formulation.

Third, the commentators [1] question the use of a dichotomous hazard function for C_{min}. As explained above, the use of this hazard function is validated against observed clinical trial data and considered robust to predict the probability of relapse. In addition, as mentioned in the article, we tested the impact of a continuous hazard function on the model outcomes and found a decrease in the number of relapses and total costs for all regimens, resulting in increased incremental costs per relapse avoided in most comparisons. However, using a continuous hazard function does not change the conclusions of our study.

Last, the commentators raised two points pertaining to dosing regimens used in practice and our analysis. The first relates to our statement regarding the use of AL 441 mg. While we acknowledge that the AL 441 mg dose may be used for all persons taking AL (not just those who cannot tolerate higher doses), it remains true that this dose is used less often in clinical practice (based on IQVIA prescription data) and may be used in those patients who cannot be prescribed higher doses as per the prescribing information, which advises to adjust the AL dose as needed [8]. The second relates to the inclusion of the AL 1064 mg every 6 weeks regimen in our analysis. Early dosing of AL may be considered as per the prescribing information [8], and IQVIA prescription data suggest this regimen is being used in clinical practice in the USA. Again, in the absence of efficacy data regarding this dose, we felt the need to include it in our analysis to provide decision makers with cost-effectiveness information. We reject the statement that conclusions regarding this dose are not meaningful; there is no reason to assume the PK profile of 1064 mg every 6 weeks cannot be estimated using the same population PK model as used for other AL regimens [3].

In summary, in the absence of comparative clinical evidence of AM versus AL, we developed a novel PK–PD–PE model to conduct a pharmacoeconomic evaluation of aripiprazole long-acting injectable regimens in schizophrenia in the USA. As expressly stated in our article, the results of our analysis are subject to uncertainty and rely on assumptions, but we used the best-available peer-reviewed evidence for the PK and PD inputs. Therefore, we remain with our conclusion that a PK–PD–PE modeling framework can be used to help to inform clinical and payer decisions in the absence of clinical trial data in a post-marketing setting.

Thank you again for the opportunity to respond to this letter.

Declarations

References

1. Rege B, et al. Comment on "an integrated pharmacokinetic-pharmacodynamic-pharmacoeconomic modeling method to evaluate treatments for adults with schizophrenia." Pharmacoeconomics. 2022. https://doi.org/10.1007/s40273-022-01200-3.

2. Piena MA, et al. An integrated pharmacokinetic-pharmacodynamic-pharmacoeconomic modeling method to evaluate treatments for adults with schizophrenia. Pharmacoeconomics. 2022;40:121–31. https://doi.org/10.1007/s40273-021-01077-8.

3. Hard ML, et al. Pharmacokinetic profile of a 2-month dose regimen of aripiprazole lauroxil: a phase I study and a population pharmacokinetic model. CNS Drugs. 2017;31:617–24. https://doi.org/10.1007/s40263-017-0447-7.

4. Wang X, et al. Population pharmacokinetic modeling and exposure-response analysis for aripiprazole once monthly in subjects with schizophrenia. Clin Pharmacol Drug Dev. 2022;11:150–64. https://doi.org/10.1002/cpdd.1022.

5. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol. 2004;24:192–208. https://doi.org/10.1097/01.jcp.0000117422.05703.ae.

6. Leucht S, et al. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. Am J Psychiatry. 2020;177:342–53. https://doi.org/10.1176/appi.ajp.2019.19010034.

7. Hart XM, et al. Therapeutic reference range for aripiprazole in schizophrenia revised: a systematic review and metaanalysis. Psychopharmacology. 2022;239:3377–91. https://doi.org/10.1007/s00213-022-06233-2.

8. Alkermes. Aristada: prescribing information. 2021.