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LETTER

Comment on "Aripiprazole Plasma Concentrations Delivered from Two 2-Month Long-Acting Injectable Formulations: An Indirect Comparison" [Letter]

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Dear editor

As long-acting injectable antipsychotic administration intervals widen, pharmacokinetic (PK) profiles help facilitate an understanding of drug exposures achieved. Aripiprazole lauroxil (AL [Aristada; Alkermes, Inc., Waltham, MA]) 1064 mg, approved by the US Food and Drug Administration (FDA) in 2017, was the first every-2-month aripiprazole formulation available. A second, aripiprazole 2-month ready-to-use (Ari 2MRTU 960 [Abilify Asimtufii; Otsuka America Pharmaceutical, Inc., Rockville, MD]), was FDA-approved in 2023. The indirect multidose PK comparisons reported by Harlin et al in *Neuropsychiatric Disease and Treatment* prompted this letter addressing methodological and data interpretation concerns.

Harlin et al compared plasma aripiprazole concentrations indirectly using Ari 2MRTU 960 and AL 1064 mg every-2-month regimens from separate Phase 1 trials (NCT04030143; NCT02320032).[1] However, the aripiprazole concentrations for AL 1064 mg are not accurate, as they did not include an AL initiation regimen. According to US FDA–approved prescribing information, AL treatment should be initiated using 1 of 2 methods: in 1 day using a single 675-mg AL NanoCrystal Dispersion (AL_{NCD}) injection (Aristada Initio [Alkermes, Inc.]) and one 30-mg dose of oral aripiprazole or administration of 21 consecutive days of oral aripiprazole supplementation in conjunction with the first AL dose.[2] Harlin et al argue that starting AL without either of these regimens would alter AL 1064 mg PK only during the first dosing interval. However, the greatest source of clinical concern rests in failure to achieve therapeutic levels during the first dosing interval, when the patient could be nonadherent with prolonged oral bridging coverage. For example, PK data indicate that the median plasma aripiprazole level during the first month of aripiprazole monohydrate 400-mg intramuscular 1-month therapy is equivalent to only 10 mg/d of oral aripiprazole without oral supplementation.[3] Not surprisingly, PK modelling data of AL 1064 mg initiated with the 1-day regimen produced substantially higher plasma aripiprazole concentrations 8 weeks after the first AL injection compared with AL 1064 mg initiated alone.[4]

In lieu of Ari 2MRTU 960 clinical efficacy data, Harlin et al make a tacit connection between plasma aripiprazole levels following Ari 2MRTU 960 and AL 1064 mg every-2-month administration and therapeutic efficacy using ≥95 ng/mL as a "relevant benchmark".[1] They suggest that higher plasma aripiprazole concentrations observed for Ari 2MRTU 960 versus AL 1064 mg every-2-months are more likely to "ensure efficacious aripiprazole plasma concentrations are sustained throughout the dosing interval".[1] However, Harlin et al also acknowledge that minimum therapeutic aripiprazole levels have been debated,[1] and we agree that the ≥95 ng/mL value is based on a flawed analysis of aripiprazole once monthly that did not include any AL data.[5] Given the distinct PK profiles associated with AL, the exposure-response analysis for aripiprazole would have potentially resulted in a different cutoff level had AL-related exposure and efficacy data been considered.

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Most importantly, however, there is no need to use aripiprazole plasma concentration data to predict efficacy with AL 1064 every-2-months. The Phase 3b ALPINE (NCT03345979) clinical trial data clearly demonstrated efficacy and tolerability over 25 weeks in the treatment of acutely ill patients with schizophrenia when initiated using AL_{NCD}.[6]

Disclosure

Jonathan M. Meyer reports having received advising fees in the past 24 months from Alkermes, Axsome, BioXcel, Cerevel, ITCI, Karuna, Neurocrine, Otsuka America, Inc., Relmada, Sunovion, and Teva and having received speaking fees in the past 24 months from Alkermes, Axsome, ITCI, Neurocrine, Noven, and Sunovion.

Bhaskar Rege is an employee of Alkermes, Inc., and may own stock/options in the company.

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