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LETTER

Long-acting formulations delivering aripiprazole: beyond single-value characterizations of steady-state pharmacokinetics

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Dear editor

The recent publication by Salzman et al[1] compared pharmacokinetic (PK) data from population PK (popPK) models for two long-acting antipsychotic formulations: aripiprazole once-monthly 400 mg (AOM 400) and aripiprazole lauroxil (AL). We would like to address a few major concerns. The AL popPK model has been well described in a peer-reviewed publication.[2] However, Salzman et al omitted publishing information regarding the development and validation of the AOM popPK model, including any critical discussion of the covariates, other key characteristics, assumptions and limitations of the AOM model. Thus, a reader cannot objectively assess the simulated values for AOM reported in the publication.

In addition, the authors compared simulations from these two popPK models and focused only on selected PK parameters: the steady-state exposures ($C_{avg,ss}$ and $C_{min,ss}$). With the statement, "At least half of the observed aripiprazole $C_{min,ss}$ for AL 441 mg were below the median $C_{min,ss}$ for oral aripiprazole 10 mg daily," the authors seem to imply that the median minimum plasma concentration of 94 ng/mL, which results from the lowest effective dose of oral aripiprazole (10 mg daily), is a necessary threshold for efficacy, rather than a summary PK value. By definition of the term "median", half of the minimum plasma concentration values for the 10 mg oral aripiprazole dose would also fall below 94 ng/mL. More importantly, the efficacy of AL 441 mg every 4 weeks, with its associated PK profile, was established in a Phase III study.[3] Focusing on a single median steady-state exposure value ignores the intricacies of the entire PK profile and does not contribute to an understanding of overall clinical effectiveness.

The entire aripiprazole concentration–time curve following the administration of AL provides a complete and more meaningful view of the AL PK profile. The prodrug formulation of AL enables sustained release of aripiprazole with consistent drug levels maintained over the dosing interval.[2] The PK profile of AOM 400 mg, however, is different, with peak–trough fluctuations as shown in Figure 1.[4] The half-life of AL doses ranges from 53.9 days to 57.2 days, while the half-life of AOM 400 is 46.5 days.[5,6] Thus, the PK profiles of 882 mg every 4 weeks and AOM 400 mg are not equivalent. These contrasting PK profiles have clinical implications including different dosing intervals and missed dose recommendations for AOM and AL.[5,6]

In summary, the efficacy of AL 441 mg and 882 mg dosed every 4 weeks has been demonstrated, with the 882 mg dose offering higher exposures than 441 mg. All AL doses exhibit stable exposures over the 4–6-week dosing intervals and offer clinicians

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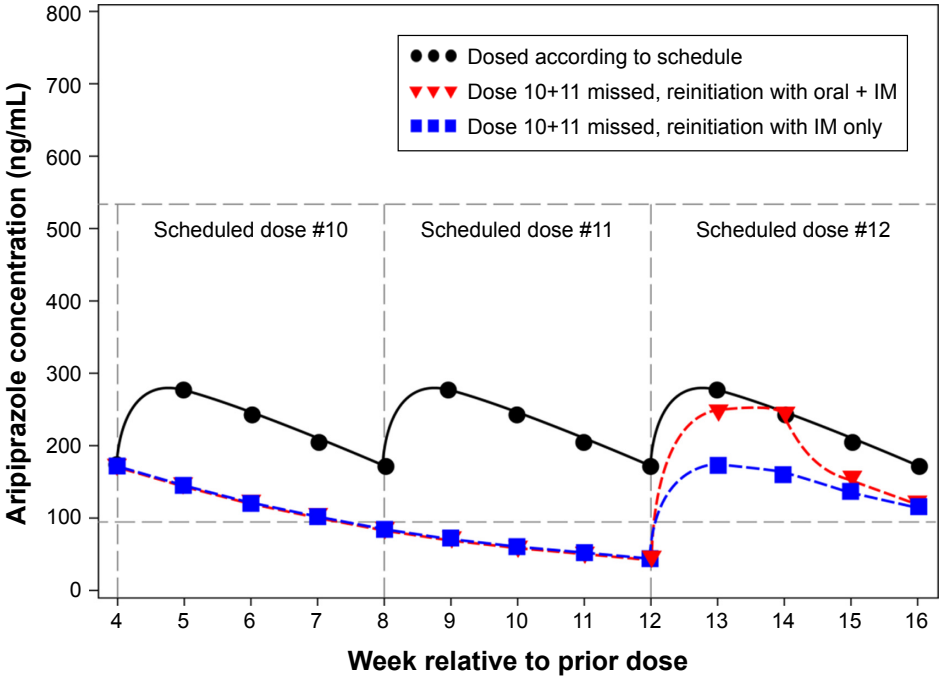

Figure 1 Simulated median aripiprazole concentrations for AOM 400 mg at steady state (black circles) and missed doses with reinitiation (red triangles and blue squares).
Notes: Dashed lines represent the upper and lower boundary of therapeutic window for aripiprazole determined in AOM PK studies. Reproduced from Center for Drug Evaluation and Research. *Application Number: 202971Orig1s000. Clinical Pharmacology and Biopharmaceutics Review(s)*. Silver Spring, MD: US Food and Drug Administration; 2013.[4]
Abbreviations: AOM, aripiprazole once-monthly; IM, intramuscular; PK, pharmacokinetic.

multiple exposure options to match patients' individual treatment needs.

Disclosure

All of the authors are current or former employees of Alkermes, Inc. and MLH is an employee of Nuventra Pharma Sciences. The authors report no other conflicts of interest in this communication.

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