In Reply to Xue W, Ribalov R, Zhou Z-Y, et al. Re: Ganz ML, Chavan A, Dhanda R, et al. Cost-effectiveness of valbenazine compared with deutetrabenazine for the treatment of tardive dyskinesia. J Med Econ. 2021;24(1):103–113

Dear Editor,

We appreciate the interest from Xue et al. in our cost-effectiveness analysis of valbenazine versus deutetrabenazine for the treatment of tardive dyskinesia (TD)1, and are gratified that the transparency of our model enabled a detailed response. While we acknowledge the inherent limitations of modeling, we stand by our methods, inputs and assumptions.

Xue and colleagues argue that the model “inappropriately weighted the deutetrabenazine doses in terms of both efficacy and medication costs”, yet the proportion of patients in the model treated with deutetrabenazine at daily doses of 24 mg, 36 mg and 48 mg was derived to be consistent with a mean dose of 38.3 mg/day as reported in the ARM-TD flexible dose trial2 that was designed to mimic real-world clinical practice. While the 12 mg dose of deutetrabenazine is part of the titration schedule it was excluded from the model as a final dose due to its lack of efficacy3. Had we included the 12 mg dose in the model, an even higher proportion of patients at the 48 mg dose level would have been required to achieve the mean dose of 38.3 mg/day2, at greater overall cost since the highest cost/mg of deutetrabenazine is associated with the 12 mg dose (i.e. two 6 mg tablets). We would note further that the indirect treatment comparison (ITC) of valbenazine and deutetrabenazine4 using pooled data from the placebo-controlled trials of valbenazine5,6 and deutetrabenazine2,3 showed that change from baseline in Abnormal Involuntary Movement Scale (AIMS) total score favored valbenazine whether or not the ineffective 12 mg deutetrabenazine dose was included.

With their second point that the ITC may be subject to bias due to differences in study design, we quite clearly agree, as we had explicitly identified this limitation to our analysis1. However, in the absence of studies that directly compare two treatments, it is generally accepted that an ITC using a single common comparator (i.e. placebo) is a method that provides the closest correlation to head-to-head trials5,8. Since the inclusion and exclusion criteria for the valbenazine and deutetrabenazine placebo-controlled trials were very similar2,3,5,6, any baseline differences in sex or ethnicity are unlikely to affect outcomes as there is no evidence that either drug is more or less effective in demographic subgroups. Additionally, differences in study design were more likely to benefit deutetrabenazine in that the valbenazine trials were of 6 weeks duration5,6 compared to the deutetrabenazine trials, which were of 12 weeks duration and conducted efficacy analyses on an enriched population of patients with AIMS total score ≥6 at baseline2,3. Moreover, given that the first efficacy assessment in the model was at 8 weeks, there was no penalty (i.e. value “subtraction”) for the variable amount of time required to up-titrate deutetrabenazine to a clinically effective dose.

We further agree with Xue et al.’s third point that the assumption of sustained treatment effect based on short-term trials is a limitation to our analysis and, again, we had identified it as such1. It is our contention, however, that utilizing data from short-term, double-blind, placebo-controlled trials is more appropriate than comparing data from single-arm, open-label trials of longer duration.

We do not agree with the assertion that the model’s results are counterintuitive. Both deterministic and probabilistic sensitivity analyses showed the model to be relatively robust, as did scenario analyses stratified by age and assuming no effect of TD response on antipsychotic treatment discontinuation. Xue and colleagues do, however, make a good point about the time horizon used in the model, and we agree that a lifetime horizon may not be a realistic assumption. An earlier version of our model, presented as a poster9, had used a lifetime horizon, and we erroneously stated in the methods of the published version1 that a lifetime horizon was used when in fact the model employed a 5 year horizon to be more relevant for a US payer audience. Additionally, the lower and upper bounds for time horizon used in the deterministic sensitivity analysis were 2 and 10 years, respectively, rather than ±20%. Although the results using a lifetime or 5 year time horizon are similar, we appreciate the opportunity to correct these errors.

In conclusion, we believe that the methods used in our analysis were appropriate and fair. We hope that the clarifications in this reply will be helpful to your readers.

Transparency

Declaration of funding
Neurocrine Biosciences Inc.

Declaration of financial/other relationships
M.S. and C.Y. have disclosed that they are employees of Neurocrine Biosciences Inc. M.L.G. has disclosed that he is an employee of Evidera, which has received consulting fees from Neurocrine Biosciences Inc.
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