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Approval of esketamine for treatment-resistant depression -Author Reply

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We acknowledge Janssen's reply to concerns raised about the regulatory process that brought esketamine for treatment-resistant depression (TRD) on the market. We regret the lack of response from the Food and Drug Administration. We forwarded our concerns to the Committee for Medicinal Products for Human Use of the European Medicine Agency, whose written response elaborated on the same main arguments as Janssen's reply.

Pivotal in both replies is the notion of minimal clinically important difference (MCID, i.e. the smallest change in outcome to qualify as important). Specifically, a MADRS difference of 2 points is denoted as clinically meaningful, even when statistically not significant, an astonishing claim that undercuts the rationale of significance testing altogether. Nevertheless, measuring and establishing a MCID is contentious, with both lower (i.e., 2 MADRS points)[1] and higher threshold (i.e., 7-9 points)[2] proposed. Moreover, any threshold must be selected on a case-by-case basis, weighing the drug's potential for harms and context of use. As esketamine carries well-known risks, this threshold should be nominally higher and, for a chronic condition like TRD, observing improvements at 4 weeks is insufficient. A meaningful MCID should be reported versus existent treatment alternatives (psychotherapy, electroconvulsive treatment).

Moreover, the pre-specified MADRS difference used for sample size calculations in the three initiation trials (TRD3001[3], TRD3002[4], TRD3005[5]) was 6.5, meaning that for differences below this threshold, it was considered acceptable to risk overlooking an effect. A meta-analysis of the pivotal esketamine trials[6] reported a summary estimate versus placebo of 4.08 MADRS points [95% CI 1.99 to 6.18], again below the *a priori* threshold of 6.5 points.

A posteriori debates on appropriate thresholds are impossible to settle. Conversely, we believe regulatory science could benefit from the model of *a priori* registration, such as "registered drug approvals", following the "data-blind" peer-review model of registered reports (https://cos.io/rr/). With adequate success criteria, this model would guarantee transparency in establishing the threshold employed in defining meaningful change.

Authors' contributions

IAC and FN conceived, drafted and revised the manuscript.

Declaration of interest

IAC and FN have no conflicts of interest to disclose.

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