Esketamine for treatment resistant depression [ID1414]

Technology appraisal committee D [5 October 2022]

Chair: Megan John

ERG: Kleijnen Systematic Reviews

Technical team: Elizabeth Bell and Jasdeep Hayre

Company: Janssen

Appraisal committee meeting: 5th Appraisal committee meeting (post appeal)

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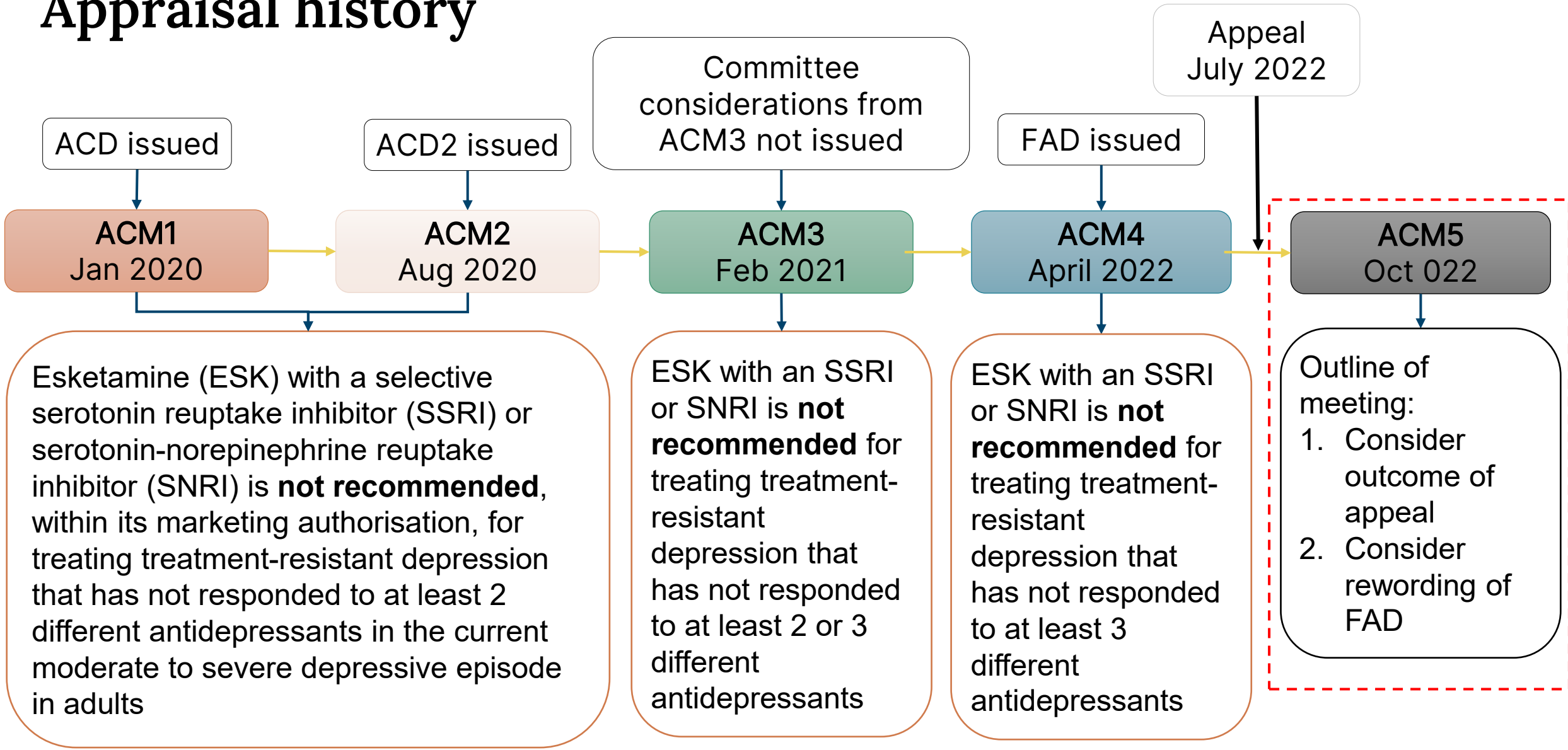
Appraisal history



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ACD, Appraisal consultation document; ACM, Appraisal committee meeting; FAD, Final appraisal document; SNRI, Serotonin-norepinephrine reuptake inhibitor; SRRI, Selective serotonin reuptake inhibitor

Appeal summary

Appeals submitted by company and Royal College of Psychiatrists

- 8 points submitted
- 1 upheld
- 3 suggestions for clarification

Committee asked to:	Explain how the uncertainties in the evidence that are inherent to clinical trials in mental health were taken into account in its decision making
Committee may wish to consider rewording FAD to clarify:	• How the uncertainties identified were related to the patient group's protected characteristics and to explain how it had to sought to adjust for these • The nature of research required in section 4 • The focus was on assessing the clinical and cost-effectiveness of ESK, not its efficacy

ESK, Esketamine; FAD, Final appraisal document

Upheld appeal point summary

Uncertainties inherent to clinical trials in mental health but no explanation of how this was taken account in decision making

Appeal panel conclusion

From the FAD, satisfied that the committee had:

- Identified and outlined the clinical uncertainties that are inherent in clinical trials in mental illness
- Identified and outlined the difficulties in designing, recruiting to and interpreting results of trials in this disease area

From the verbal evidence presented, satisfied that the committee had:

- Taken the uncertainties into account in their decision-making and had also considered how uncertainties were resolvable or unresolvable

There was not:

- Sufficient explanation about how the specific inherent difficulties in clinical trials and the uncertainties that result from them, had been taken into account in their reasoning and decision-making, or the extent to which they had or had not been disregarded
- Explanation in its conclusions about which uncertainties were, in its opinion, potentially resolvable and those that were unresolvable, since these might inform future trial design in this important disease area

Upheld appeal point – "inherent clinical uncertainties"

1. Identify *"inherent difficulties in clinical trials and the uncertainties that result from them"*

2. Which uncertainties do the committee think were resolvable and which are not

3. How they had been taken into account in decision making

Partially resolvable?

Resolvable?

FAD	Clinical uncertainties identified by committee	Committee approach
3.3	• Treatment pathway not clearly defined	Uncertainty, but accepted in model
3.14	• The mandated regulatory endpoints of the clinical trials mean the trials are short	Uncertainty in model, but accepted clinically
3.13	• Impact of patients having regular clinical contact for administering of ESK and placebo in the trial and differentiating this from positive effect of drug • Potential unblinding, due to ESK short-term adverse events	Large placebo response in trials, relied on relative effect from RCT Substantial uncertainty but broadly accepted use in the model
3.7	• Exclusion of psychological therapies from trials	Uncertainty, but accepted in model
3.16	• TRANSFORM-2 and SUSTAIN-1 excluded patients with multiple comorbidities	Considered qualitatively by committee

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How should the FAD have better explained the committee considerations?

ESK, Esketamine; FAD, Final appraisal document; RCT, Randomised controlled trial

Committee may wish to consider rewording FAD (1)

- To clarify section 4 of FAD:
  - Appeal panel conclusion: committee should include in section 4:
    - A duplicative statement from section 1, stating need to also undertake research into uncertainties that remain
    - Confirm that remaining recommendations in section 4 are not directed specifically towards Janssen
  - NICE technical team:
    - From “Research is recommended into the long-term course of treatment-resistant depression, the natural history of the disease and health-related quality of life in the long-term.” AND “Research is recommended into characterising the healthcare resource use of people with depression, including exploration of which patients use services like hospitals and crisis resolution home teams.”
    - To “Research is recommended into the long-term course of treatment-resistant depression, including the natural history of the disease, healthcare resource use and health-related quality of life in the long-term.”

How should the FAD be revised to reflect the above?

Committee may wish to consider rewording FAD (2)

- To clarify section 1 of FAD:
  - **Appeal panel conclusion**: the FAD should be re-worded to remove doubt that the committee's focus was on assessing the clinical and cost-effectiveness of ESK, not its efficacy
  - **NICE technical team:**
    - From: "But this is very uncertain, because this evidence only considers a small number of people from the full trial population"
    - To: "The clinical trial evidence is uncertain because it only considers a small number of people from the full trial population"
- To clarify section 3.40 of FAD:
  - **Appeal panel conclusion**: committee should explain how the uncertainties identified were related to the patient group's protected characteristics and to explain how it had to sought to adjust for these

How should the FAD be revised to reflect the above?

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Thank you.