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NICE National Institute for Health and Care Excellence

Esketamine for treatment resistant depression [ID1414]

ACM4 – Chair's presentation

Chair: Megan John

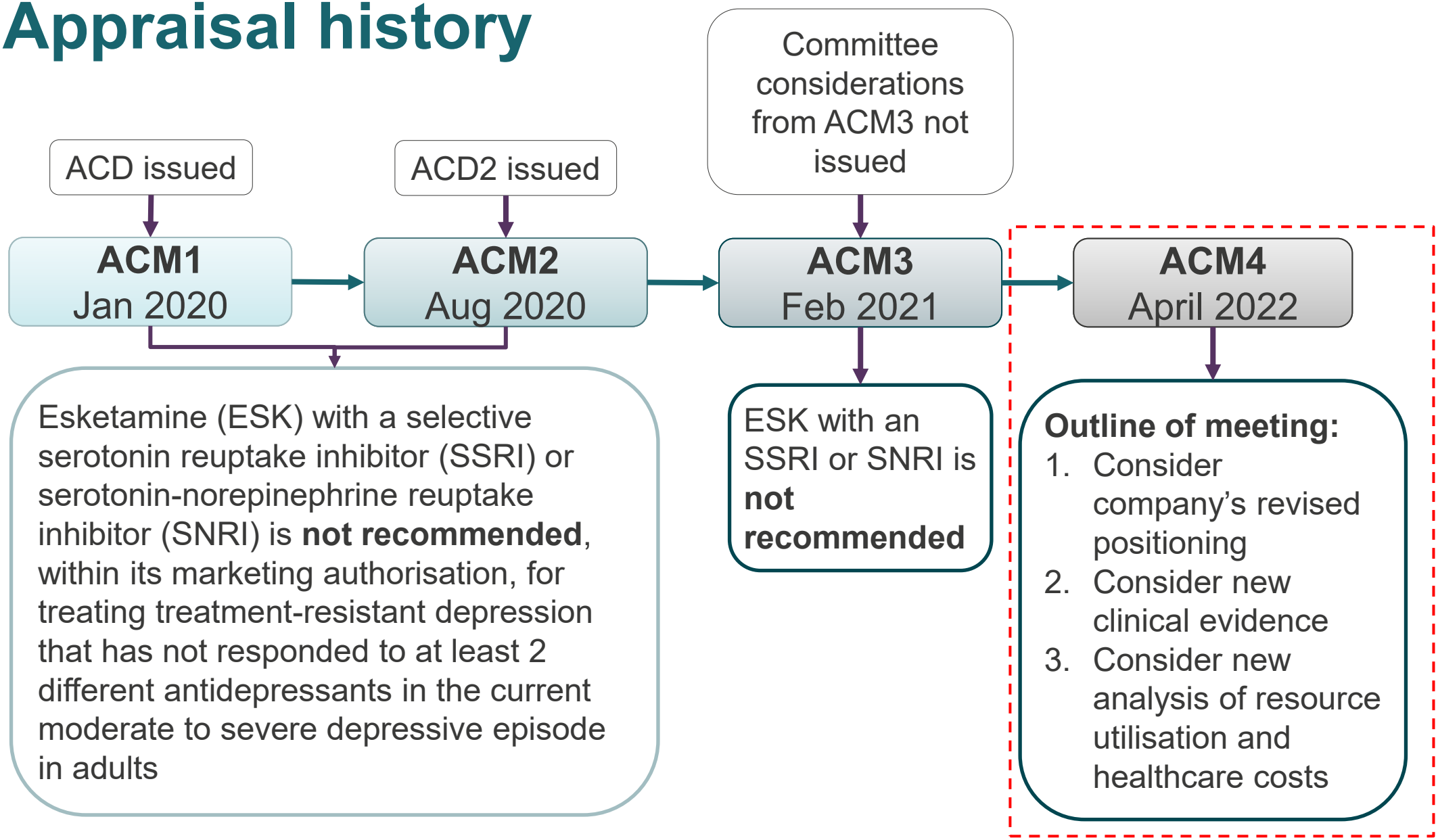
NICE technical team: Elizabeth Bell, Adam Brooke, Linda Landells

ERG: Kleijnen Systematic Reviews

Company: Janssen

7th April 2022

Appraisal history



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

Disease background

Treatment-resistant depression (TRD) is defined as major depressive disorder (MDD) that has not responded to at least 2 different treatments with antidepressants in the current moderate to severe depressive episode.

People with TRD can experience:

- Psychological, physical and social effects
- At least 30% of people with TRD attempt suicide at least once
- There is an additional impact on carers and family

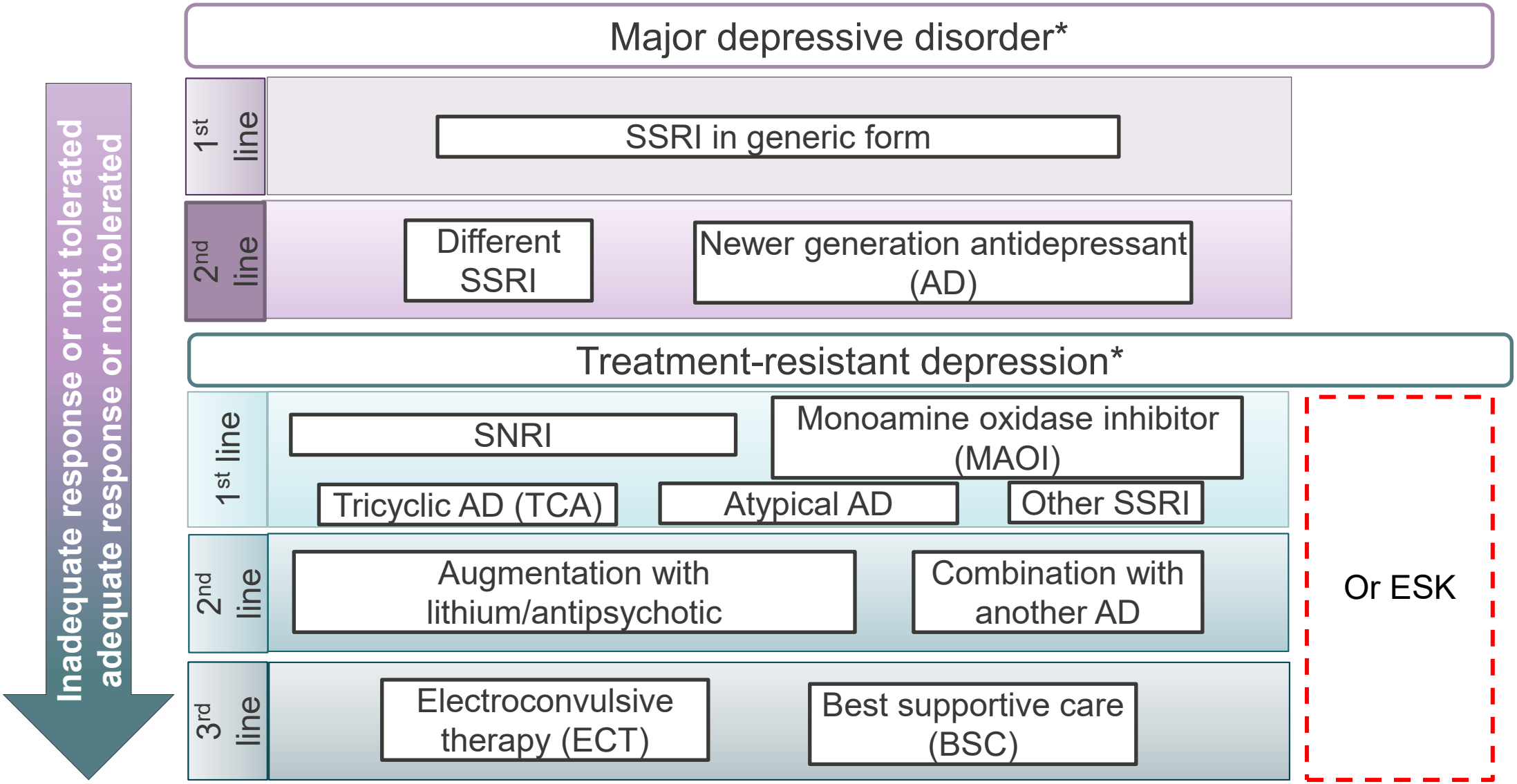
- MDD affects about **2 million** people at any given time in the UK
- TRD affects more than **130,000** people in England.

Patient experts from ACM3:

- *TRD has a burden on all aspects of life. People with TRD often have feelings of hopelessness, fear and despair.*
- *When multiple courses of treatment do not work, feelings of hopelessness get worse.*

ACM: Appraisal committee meeting; MDD: Major depressive disorder; TRD: Treatment-resistant depression

ACM3 treatment pathway



*Option to combine all treatments with psychological therapy

AD: Antidepressant; BSC: Best supportive care; ECT: Electroconvulsive therapy; MAOI: Monoamine oxidase inhibitor; OAD: Oral antidepressant; SNRI: Serotonin–norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant

Esketamine (Spravato, Janssen)

Marketing authorisation	Esketamine, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant MDD, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode
Mechanism of action	Transient NMDA receptor blockade or modulation
Administration	• Single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril) • Self-administered under supervision of healthcare professional
Dose	• Induction phase weeks 1-4: 56mg (<65yr) or 28mg (≥65yr) on day 1, subsequent doses are 56mg or 84mg twice a week. • Maintenance phase weeks 5-8: 56mg or 84mg once weekly, and • From week 9: 56mg or 84mg every 2 weeks or once weekly.
Cost (commercial arrangement available)	• £163 per 28 mg device • 56 mg dose (2 x 28 mg devices, £326) • 84 mg dose (3 x 28 mg devices, £489)

MDD: Major depressive disorder; SNRI: Serotonin–norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor

Summary of new company analyses

Overview of new company analyses	Company reasoning
1. Revised treatment population • 3+ OAD • 3+ OAD after augmentation	Smaller population, aligned to clinical expert input about highest unmet need and most likely to benefit from ESK
2. Safety profile • New evidence on use of ESK from SUSTAIN-2 and SUSTAIN-3	To address safety concerns and data paucity about the long-term effects of ESK
3. Real world evidence • Real world-evidence from French and Spanish cohort	To address safety concerns and data paucity about the long-term effects of ESK
4. Updated treatment cap • Validate time spent in major depressive episode (MDE)	Committee preferred assumptions included a cap on relapse rates, so company included a corrected cap
5. Non-drug costs • Additional analyses from South London and Maudsley NHS Foundation Trust	To address uncertainties regarding non-pharmacological healthcare resource use costs
6. New PAS price	Value proposition
7. Modelling assumptions • Updated modelling assumptions	See slides 13 to 14

MDE: Major depressive episode; OAD: Oral antidepressant; PAS: Patient access scheme; TRD: Treatment-resistant depression

Proposed data collection

Janssen

- Understand that uncertainties are irreducible without post-reimbursement data collection on real-world use.
- Possibility of including a UK cohort within a pan-European post-access real world evidence study, or clinical studies like ECHO, if committee can recommend ESK in 1 of the populations presented.
    - ECHO: a non-interventional cohort study which will collect data from routine clinical practice to understand:
        - Clinical, social and economic outcomes of ESK
        - Treatment dosing, frequency and duration of ESK
        - Impact on safety
        - Clinical, social and economic outcomes up to 6 months following discontinuation from ESK.
- Provides an additional option for people with treatment resistant depression who have a high unmet need.

NICE technical team

- Committee can consider all possible routes for access.
    - ECHO was given an unfavourable opinion by London South East Research ethics committee for unknown reasons.

Clinical evidence (1)

Studies used as evidence in company submission

	TRANSFORM-2	SUSTAIN-1
Study design	Randomised, double-blind, parallel-group, active-controlled, phase 3	Randomised, long-term, follow-up study (withdrawal trial)
Population	Adults with TRD 18 to 64 years, • Subgroup of 73 people with at least 3 prior treatments	Adults 18 to 64 years with stable remission or stable response after treatment with ESK • Subgroup of 41 people with at least 3 prior treatments
Intervention	Flexible dose of ESK plus newly initiated OAD	
Comparator	Placebo nasal spray plus newly initiated OAD	
Study phases	4 week screening phase 4 week double-blind induction phase 24 week post-treatment follow-up	4 week open label induction phase 12 week optimisation phase Double-blind maintenance phase
Outcomes	Non-response to at least 3 prior treatments showed benefit	Non-response to at least 3 prior treatments showed statistically significant improvement

OAD: Oral antidepressant; TRD: Treatment-resistant depression

Clinical evidence (2)

Studies used as supporting evidence in company submission (population with no suicidal ideation)

	TRANSFORM-1	TRANSFORM-3	SUSTAIN-2	SUSTAIN-3
Study design	Randomised, double-blind fixed dosing trial	Randomised, double-blind trial	Long-term safety study	Ongoing study safety study
Population	Adults 18 to 64 years with TRD	Adults ≥65 years with TRD	Adults with TRD	Adults with TRD
Intervention	ESK fixed dose (not in line with licence)	ESK 28 mg or 56 mg or 84 mg (28mg below minimum effective dose)	ESK 28 mg (for ≥ 65 years), 56 mg or 84 mg given twice weekly <65 years	
Comparator	Placebo + OAD			None
Study phases	4 weeks treatment phase 24 weeks follow-up/entry into SUSTAIN-1	4 weeks treatment phase 24 weeks follow-up/entry into SUSTAIN-1	4 week induction phase 48 weeks optimisation/maintenance 4 week follow-up	Continued intermittent ESK dosing of up to 58 months in this study
Outcomes	No statistically significant improvements for ESK		ESK 28 mg (for ≥ 65 years), 56 mg or 84 mg	Not applicable (NA)

NA: Not applicable; OAD: Oral antidepressant; TRD: Treatment-resistant depression

Clinical evidence (3)

Studies including people with suicidal ideation identified from Cochrane review

	NCT02133001	ASPIRE I	ASPIRE II
Study design	Double-blind proof-of-concept study	Phase 3, double-blind study	Double-blind randomised trial
Population	68 people aged 19 to 64 years with MDD, without psychotic features and suicidal ideation	226 adults aged 18 to 64 years with MDD, active suicidal ideation with intent and need for psychiatric hospitalisation	230 adults aged 18 to 64 years with active suicidal ideation with intent
Intervention	84mg of esketamine twice weekly		84mg or 56mg dose
Comparator	Standard of care (SoC) plus placebo	Placebo plus SoC	Placebo
Study phases	4 weeks treatment 8 weeks follow-up	4 weeks treatment 9-week post treatment follow-up	Treatment day 1 to 25 Day 26 to 90 follow-up
Outcomes	No statistically significant decrease in suicide risk	No statistically significant difference in suicide risk between groups	Severity of suicidality improved in both treatment groups at the end of double-blind treatment

MDD: Major depressive disorder; SoC: Standard of care

Key terminology

Term	Definition
Montgomery-Asberg Depression Rating Scale (MADRS)	Severity of depressive symptoms
Response	50% reduction from baseline in the MADRS total score
Remission	MADRS total score of ≤12 (symptom-free or only minimal symptoms)
Recovery	Stable in remission (absence of symptoms) for 9 months
Stable response	≥50% reduction in the MADRS total score from baseline in each of the last two weeks of the optimisation phase without meeting the criteria for stable remission
Stable remission	MADRS total score of ≤12 for at least three of the last four weeks of the optimisation phase. The MADRS total score at Weeks 15 and 16 was required to be ≤12
Relapse	MADRS total score of ≥22 for 2 consecutive assessments separated by 5–15 days and/or hospitalisation for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalisation for suicide prevention
Recurrence	Transition from the recovery health state to the MDE health state

MADRS: Montgomery-Asberg Depression Rating Scale; MDE: Major depressive episode

AMC3 committee considerations

Summary committee considerations – clinical evidence

Topic	Conclusion	ACM3	New analysis
Treatment positioning	ESK is likely to be used later in the treatment pathway because it has a high treatment burden	3.4	✓
Comparator evidence	Indirect comparisons with augmentation are highly uncertain so comparison with trial results is acceptable	3.5	NA
MADRS inconsistency	Uncertainty caused by using different MADRS scores for relapse and defining the MDE health state	3.8	×
3+ line of treatment	Considering the 3+ OAD group is appropriate, but still substantial uncertainty about the true treatment effect	3.9	✓
TRANSFORM-2 trial duration	Caution in interpreting trial data from a 4-week duration	3.10	✓
SUSTAIN-1 withdrawal study design	Withdrawal study design introduces bias in favour of ESK because it selects patients with a stable response or stable remission	3.11	×
Generalisability of the results	Acute suicidality, psychiatric comorbidities, alcohol abuse and ECT use in the current episode excluded from the trial	3.12	✓
Safety	ESK has potential risks associated with its use – risk management in the SPC is appropriate	3.14	✓

ECT: Electroconvulsive therapy; MADRS: Montgomery-Asberg Depression Rating Scale; MDE: Major depressive episode; NA: Not applicable; OAD: Oral antidepressant

Summary committee considerations – economic modelling

Topic	Conclusion	AMC3	New analysis
Disease course	Key driver of difference between arms is the initial response rate so accurate response and remission rates are needed	3.16	✓
Subsequent treatments	ERG proportional reduction in response at each line is more appropriate than the company's approach	3.18	✓
Time horizon	A 20-year time horizon is appropriate – uncertainty about long-term outcomes would not be resolved with a 5-year time horizon	3.20	✓
Carer disutility	Lack of direct evidence of carer benefit with esketamine and potential for increased carer burden mean a range of values should be considered	3.23	✓ (scenario analysis)
Stopping treatment	No evidence to support a stopping rule, stopping treatment would be highly individualised dependent on the patient	3.25	×
Healthcare resource use	Costs in the model are highly event driven and likely to lie between the ERG and company approaches	3.27	✓
Cost of implementation	Some costs of adoption were not considered in the model and significant investment would be needed	3.29	✓

Key issues with additional company analyses

Key issue	Summary	Slide
Treatment population	• Which population would be expected to take ESK in clinical practice? • What is the clinical evidence for the treatment populations? • What are the costs of implementing ESK within routine NHS practice?	18 to 21
Model output and long-term outcomes	• What is the safety profile of ESK? • What are the long-term outcomes for patients with TRD? • What is the expected efficacy of subsequent treatments?	23 to 29
Non-drug costs and healthcare resource use	• What is the most appropriate source of non-drug costs?	31 to 32

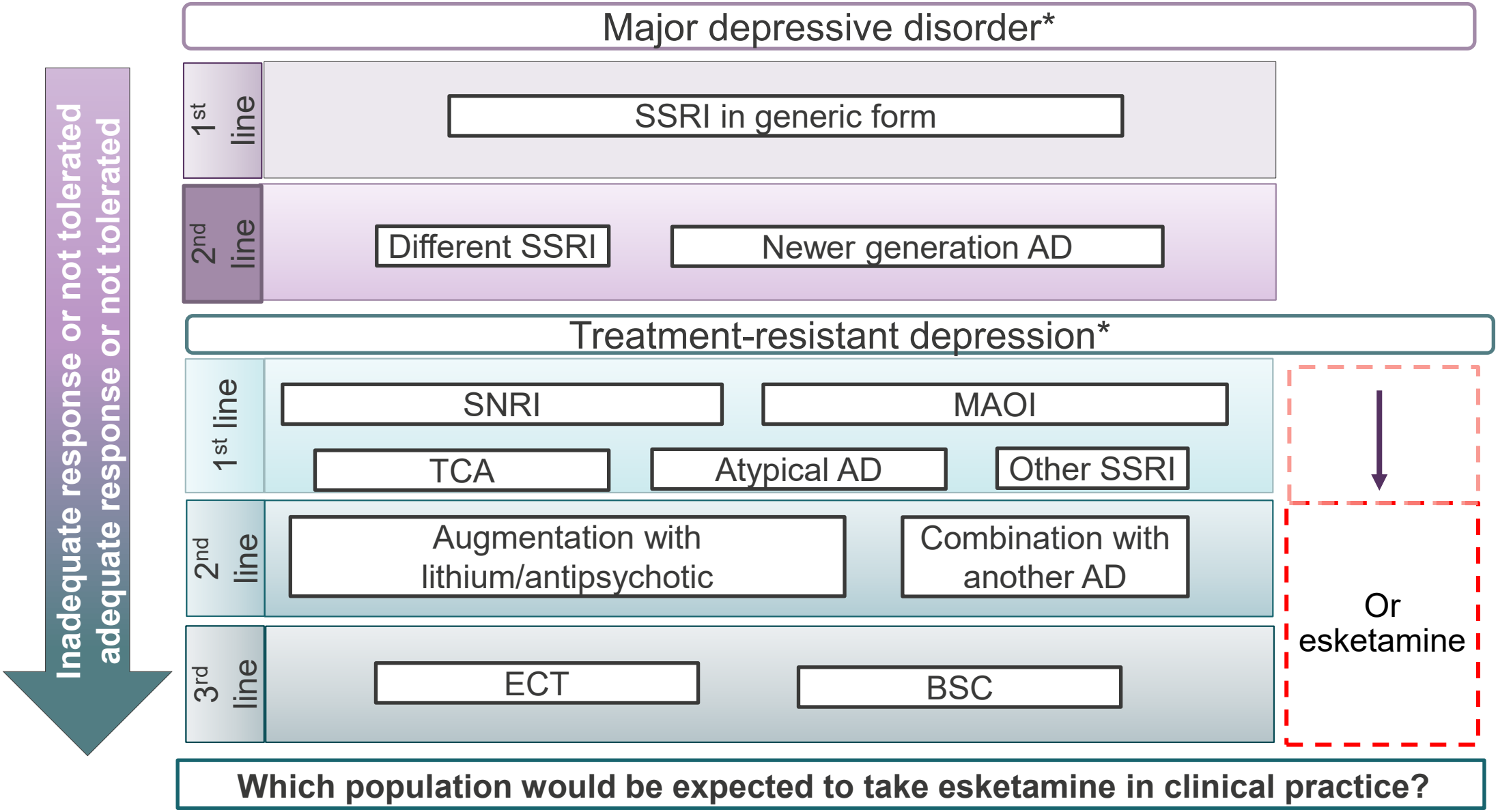
TRD: Treatment-resistant depression

Additional key issues

Issue	Committee considerations ACM3	NICE technical team
Time horizon	• The committee noted uncertainty about long-term outcomes but concluded that a shorter time horizon may not solve this issue.	• In the absence of resolving uncertainty around long-term outcomes, the 20-year time horizon is not explicitly a committee preference and can still be explored in sensitivity analysis.
Stopping rule	• There is no evidence on the effect of stopping ESK for reasons other than lack of efficacy. • It is less appropriate to model stopping treatment for the expected treatment population and the 3 or more treatments subgroup without any data.	• Removing the stopping rule is a large driver of the cost-effectiveness estimates.

Treatment population and implementation

Updated treatment pathway



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Patient population (1)

ACM3 committee considerations:

- *…the committee concluded that it was appropriate to consider **the 3 or more treatments subgroup** in its decision making as well as the full population.*
- *However, it considered there is still substantial uncertainty associated with the true treatment effect and how initial response is used in the economic model.*

Janssen:

- Two revised base cases to align with highest unmet need and burden of illness (as evidenced by Discover dataset):
  - 3+ prior OADs
  - 3+ prior OADs and augmentation.

ERG:

- General trend of increasing resource use and duration of depression, but not that large and notable exceptions.

Source		Total response	Of which are remission	Clinical data source
3+ OAD	PBO-NS+OAD	[redacted]	[redacted]	TRANSFORM-2, -3
	ESK+OAD	[redacted]	[redacted]	
3+ OAD and augmentation	OAD	[redacted]	[redacted]	TRANSFORM-2, -3
	ESK +OAD	[redacted]	[redacted]	Relative treatment effect between SUSTAIN-2, 3+ OAD and 3+ OAD and augmentation, applied to TRANSFORM ESK+PBO arm

NHS England: TRANSFORM-3 was a small study and ESK + OAD did not achieve statistical significance for primary endpoint compared with placebo + OAD.

Patient population (2)

	Janssen	ERG
Conservative approach	• Not adjusted treatment effect downwards for OAD+PBO in 3+ OAD and augmentation, despite drop in efficacy between lines of treatment, seen in TRANSFORM-2 trial, STAR*D and purported by clinical experts.	• Approach probably conservative, but difficult to be sure as unclear of augmentation effect. • Ideally this data would be from TRANSFORM RCTs.

Comparator for ESK	• OAD+PBO main comparator in 3+ OAD and augmentation
	  • Comparators in the scope were highly uncertain and lack evidence
	  • Clinical practice reflects this assumption
	  • Comparison with OAD is conservative.
		• Augmentation is the appropriate comparator for 3+ OAD as it forms basis of population.
		• If appropriate comparator not OAD for 3+ OAD and augmentation then effect of comparator in subgroup likely underestimated.

Supporting evidence	• To overcome the issue of small patient numbers Janssen presented supportive evidence from SUSTAIN-2 induction phase for 3+ OAD group.	• Unclear why company used treatment effect from SUSTAIN-2 instead of estimates of 3+ prior OAD and augmentation group from TRANSFORM studies. • Potential generalisability issues of populations.

	Remission	Response
TRANSFORM-2	[redacted]	[redacted]
SUSTAIN-2	[redacted]	[redacted]

NHS England: optimised populations have higher rates of suicidal ideation/intent and comorbidities.

Is the clinical evidence for the treatment population appropriate?

Implementation

ACM3 committee considerations:

- *The committee concluded that there would need to be **significant investment** to use esketamine in the NHS using the company's implementation proposal, which was not captured in the analysis.*
- *It considered the costs using the company's proposal would **underestimate the true cost of** implementing esketamine clinics in clinical practice.*

	Janssen	ERG

3+ OAD after augmentation	• Estimate *total* population: 14,745 to 15,940 .
	• No assumed costs for implementation (1:1 cost for ratio of nurse)
	  • People in this subgroup will now be managed within secondary care settings
	  • Approach uses existing infrastructure.
	• Fewer treatment options in this group.
		• Unclear how people being prescribed augmentation in secondary care would affect the need for change in infrastructure due to introduction of ESK.

3+ OAD population	• Estimate *total* population: 46,131.
	• Some implementation costs but none included in modelling:
	  • Unclear what these may comprise
	  • Implementation costs would be one-off
	  • Costs will depend on uptake.
		NICE technical team
		• Company have not addressed issues of implementation in 3+ OAD population with potential large patient numbers.

What are the costs of implementing esketamine within routine NHS practice?

OAD: Oral antidepressant

Model output and long-term outcomes

Safety profile (1)

ACM3 committee considerations:

- *The committee considered that uncertainty about long-term safety could be partially resolved by conclusion of the ongoing SUSTAIN-3 trial.*
- *It concluded that the precautions regarding **risk of suicide and close supervision and monitoring in the SPC should be taken into account** when prescribing esketamine, particularly during early treatment and after dose changes.*

Janssen:

- New evidence on the use of ESK from:
  - SUSTAIN-2 and SUSTAIN-3 (phase 3 clinical trails).
- "*…both long-term studies highlight that the safety of esketamine nasal spray was favourable with an acceptable tolerability, and that long-term exposure to esketamine resulted in no additional safety concerns.*"

SUSTAIN-2	SUSTAIN-3
• Design: Long term open-label safety study • Population: People with TRD in 21 countries • Outcomes: Long term safety was favourable, with acceptable tolerability.	• Design: Open-label long-term extension safety study • Population: People with TRD • Outcomes: No additional safety concerns or trends.

TRD: Treatment-resistant depression

Safety profile (2)

SUSTAIN-2 detailed outcomes

- [redacted] had severe adverse events during treatment
  - 75% of events resolved on the day.
- 6.9% had serious adverse events
  - Depression, suicidal ideation, suicide attempt, anxiety and gastroenteritis.

SUSTAIN-3 detailed outcomes

- [redacted] had serious adverse events
  - [redacted]
- [redacted]

ERG

- Non-comparative open label study
- [redacted]
- ERG remains concerned regarding safety data.

- Uncertainty about long-term safety might have been partially resolved by including results of the SUSTAIN-3 trial.
- However, concerns raised, especially regarding “suicides in people who stopped esketamine in a population who had no recent suicidal ideation or behaviour” are not fully resolved.

NHS England:

- It is unknown if problems will occur if dosing frequency is increased with loss of response or with discontinuation of ESK after long-term administration.
- [redacted] of people in SUSTAIN-2 without suicidal ideation at baseline, reported new suicidal ideation during the study.

Treatment efficacy (1)

ACM3 committee considerations:

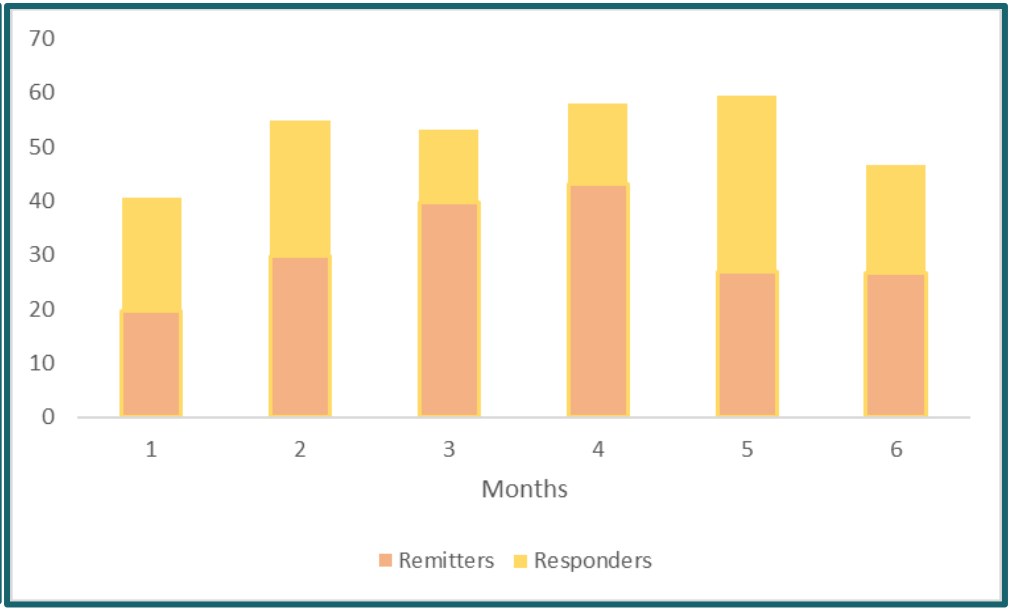
- *The committee also noted that the **population in the trials may not be in line with the population expected to have esketamine in clinical practice**.*
- *The committee concluded that excluding people with recent suicidal ideation with intent or suicidal behaviour limited the generalisability of the trials to the NHS for people with treatment-resistant depression.*

Janssen:

- Real world evidence from a French and Spanish cohort.

ESKALE (French cohort)

- Design: Retrospective, observational study.
- Population:160 adults ≥18 years with TRD (3 dropped out)
  - People with severe or rare disease and high unmet need
  - Average 2.1 suicide attempts during whole life.
- Low number of observations.



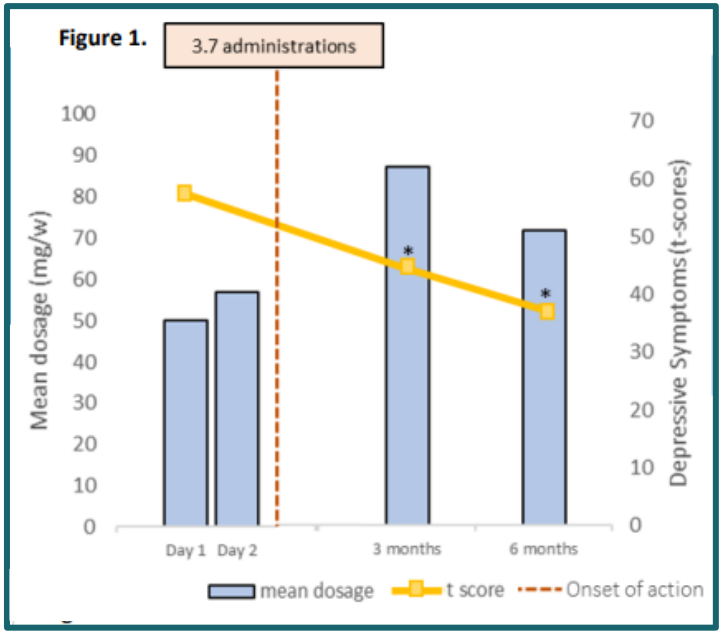
NICE

TRD: Treatment-resistant depression

Treatment efficacy (2)

Spanish ESK compassionate use

- Design: Compassionate use programme (CUP).
- Population: 32 people who had not responded to 2 or more AD trials, 1 augmentation strategy and non-pharmacological therapy.
- Outcomes: ESK was effective in 88% (n=28) people
  - After 6 months:
    - Response rates 56% (n=18)
    - Remission rates 31% (n=10).



ERG:

- *It is unclear how the provided results from both real-world studies can:*
  - *Overcome the concerns regarding the generalizability to NHS patients in England and Wales*
  - *Address the concerns of excluding a "substantial proportion of people with treatment-resistant depression".*

NHS England:

- *"Efficacy must be clearly established for a new and expensive"*
- *A study of ESK + OAD vs placebo + OAD in a Japanese population with TRD showed no statistical or clinically significant difference in change from baseline at day 28.*

Are the long-term outcomes for people with TRD taking esketamine robust?

AD: antidepressant; CUP: Compassionate use programme; OAD: Oral antidepressant; TRD: Treatment-resistant depression

Treatment cap (1)

ACM3 committee considerations:

- *The ERG proposed a scenario that applied a proportional reduction in each line of therapy.*
- *The committee considered that despite the increased efficacy of subsequent treatments, the best supportive care transitions still had the greatest effect on long-term outcomes, which were highly uncertain. This affected the costs because it meant* ***a large amount of time was spent in the MDE health state in the model.***

	Company cap		ERG cap
	3+ OAD	3+OAD after augmentation	
4- weekly rate of loss of response			
TRD Line 3 (4 prior treatments)	23.7%	N/A	23.1%
TRD Line 4		23.7%	
TRD Line 5			
TRD Line 6	N/A		
BSC/ Non-Specific Treatment Mix	23.7%		
Relapse			
TRD Line 3 (4 prior treatments)	31.8%	N/A	16.8%
TRD Line 4		31.8%	
TRD Line 5			
TRD Line 6	N/A		
BSC/ Non-Specific Treatment Mix	31.8%		

MDE: Major depressive episode; OAD: Oral antidepressant; TRD: Treatment-resistant depression

Treatment cap (2)

Janssen:

- Additional new evidence suggests ERG cap to validate time spend in MDE state from Wu et al. underestimates the level of relapse in the model for subsequent treatments.
  - Wu et al. estimated length of first TRD episode was 1.6 years and length of remission was 0.9 years.
- It is generally accepted that relapse rates increase with each additional line of therapy
  - Evidence from:
    - *Clinical expert:* true estimate lies between ERG and Janssen assumptions
    - *DISCOVER:* longitudinal dataset covering over 2.5 million people in London
    - *Study from 3 UK centres:* median duration of 5 years
    - *Real-world evidence from European cohort:* after 6-months 16.7% achieved remission and 73.5% showed no response. 60% of people had not changed treatment
      - *UK cohort:* mean duration of current episode: 6.1 years.

ERG:

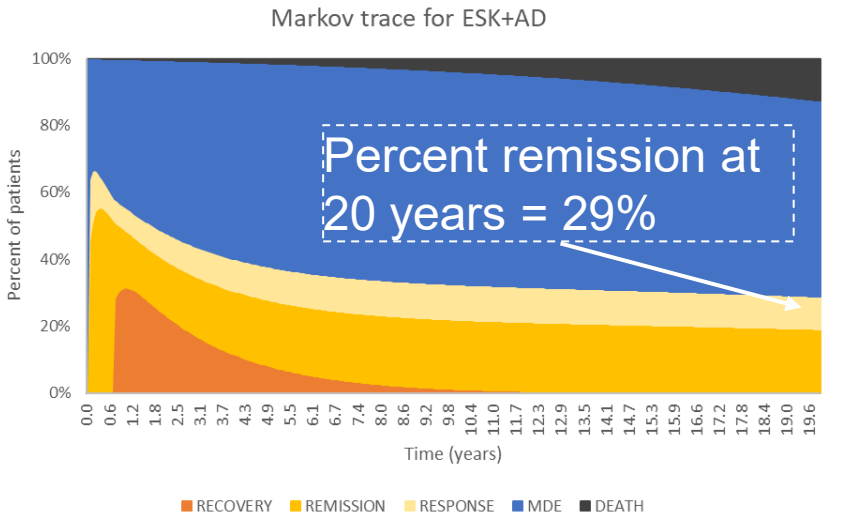
- DISCOVER data suggests longer duration of MDE, potentially Wu et al. estimate was optimistic.
  - But unclear why the results from Wu et al. study cannot be applicable to an episodic model.
- Difference between DISCOVER and Wu et al. is very large:
  - Are the studies measuring the same thing?
  - Is there conflation between definitions of episode?
- Company estimates result in time in MDE health state of 66% of life expectancy (13.8 years)
  - Unlikely for heterogenous to spend whole time in this state with no remission.

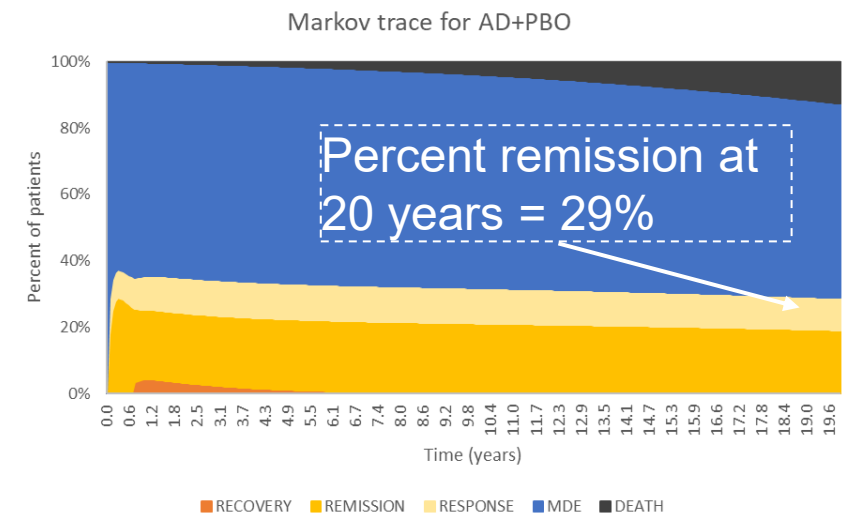
What is the expected efficacy of subsequent treatments?

MDE: Major depressive episode; TRD: Treatment-resistant depression

Treatment cap outputs (3+ OAD population)

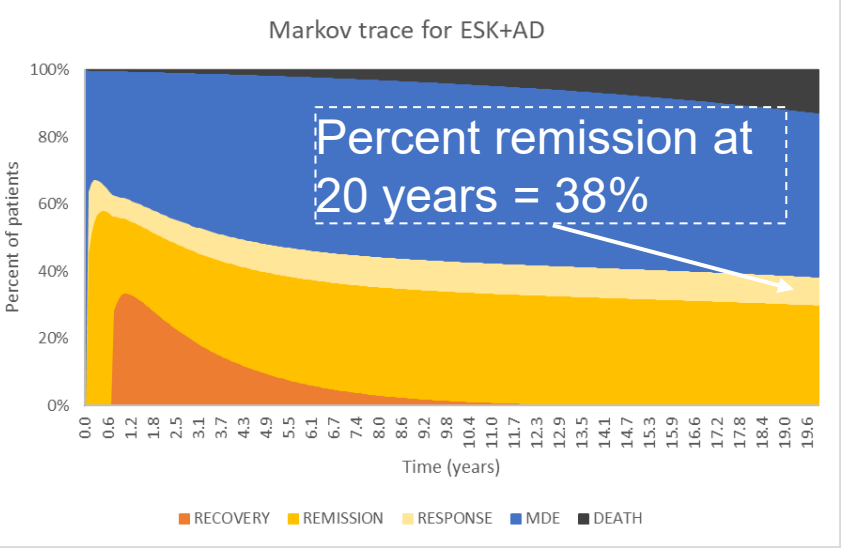
Janssen

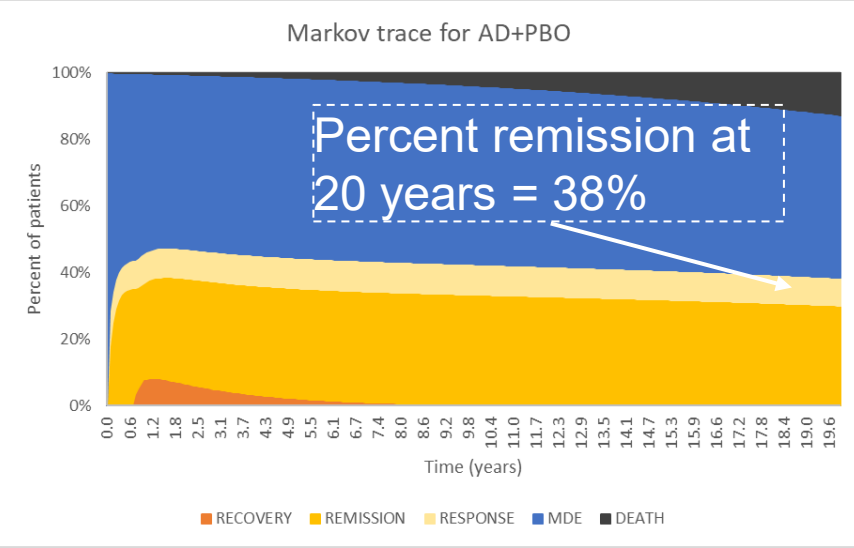




- DISCOVER dataset: average duration of depression episode for people with TRD was [redacted]

ERG





- ERG treatment cap leads to higher remission rates (and higher cost-effectiveness estimates).

NICE technical team:

- Key driver of differences between arms is the recovery rate which is largely set by initial response at 4-weeks from TRANSFORM studies for ESK only.

OAD: Oral antidepressant; TRD: Treatment-resistant depression

Non-drug costs and healthcare resource use

Non-drug costs – overview

ACM3 committee considerations:

- *Company measured resource use using a retrospective chart review. ERG provided an alternative healthcare resource use scenario using Byford et al.*
- *Non-pharmacological healthcare resource costs accounted for almost all of the total costs and were a key driver of cost-effectiveness results.*

Janssen:

- 3+ OAD treatment group: 25% Byford et al and 75% TRD cost study.
  - Byford et al not appropriate for costing as it is a primary care population and not TRD.
- 3+ OAD after augmentation group: TRD cost study.

Health state	Byford et al	TRD cost study
MDE	£90	£1,069
Response	£65	£179
Remission	£65	£179
Recovery	£65	£91

ERG:

- Using a primary care source doesn't mean secondary care costs were not included and that costs for TRD are not all included in secondary care setting.
  - Acknowledge unclear resource implication from broad definitions of depression in database.
- MDE might increase with later lines of treatment, but might only affect duration in MDE rather than cost per unit time in the state.

NHS England: No consideration for costs/resource use for people who may abuse ESK.

Non-drug costs – additional analysis

Janssen:

- Significant NHS healthcare resources that people with TRD utilise is highlighted in the TRD cost study and confirmed in recently conducted retrospective database study
  - TRD population in a secondary care mental health setting using Clinical Record Interactive Search (CRIS) database at South London and Maudsley NHS Foundation Trust
  - TRD defined according to application of 2 algorithms.
- Study is supportive of cost attached to MDE health state in model (£1,069).

Category	2 prior OADs	3 prior OADs	4 prior OADs
Number of people	[redacted]	[redacted]	[redacted]
Cost per 28 days	[redacted]	[redacted]	[redacted]
Inpatient bed nights (mean)	[redacted]	[redacted]	[redacted]
MDE episode [redacted]	[redacted]	[redacted]	[redacted]

ERG:

- TRD might be misidentified by the algorithm.
- Median and interquartile ranges for inpatient bed nights are [redacted] despite this cost being a high proportion
  - Suggests bed days are skewed.
- If treatment resistance is main driver of cost costs may increase with line of therapy but no increase from 3 to 4 prior OADs.
- No information on other characteristics, such as psychosis of suicidal ideation.

CRIS: Clinical Record Interactive Search; MDE: Major depressive episode; OAD: Oral antidepressant; TRD: Treatment-resistant depression

Innovation and equality

Innovation:

- No new innovation issues raised
  - Committee considered ESK is innovative because it has a novel biological mechanism.

Equality/equity:

- New 3+ OAD after augmentation population addressed many of the previously noted implementation and equity concerns discussed by the committee
  - Smaller population
  - Largely managed in specialist secondary care where existing infrastructure is available to provide ESK.
- NHS England note as people in the optimised populations are treated in secondary care, access may be problematic given large catchment areas, covered by mental health facilities

- **Is ESK an innovative treatment for TRD after 3+ lines of therapy and 3+ lines of therapy and augmentation?**
- **Are there any additional benefits of ESK that have not been captured adequately in the economic model?**
- **Are there any equality issues relevant to this appraisal?**

OAD: Oral antidepressant; TRD: Treatment-resistant depression

Cost-effectiveness modelling

Company revised base case

ESK patient access scheme (PAS) price

Company base case – 3+ OAD treatments	ICER range (with and without company carer disutility)
○ 75% TRD costing study & 25% Byford as sources of healthcare resource use (HRU) ○ Company cap applied to subsequent treatments	[redacted]
Company base case – 3+ OAD treatments and augmentation	
○ Short-term efficacy from TRANSFORM-2 adjusted for a population who have 3+ OAD treatments and augmentation sourced from SUSTAIN-2 ○ TRD costing study as source of HRU ○ Company cap applied to subsequent treatments	[redacted]

Detailed results (with carer disutility)

Population	Incremental			
	Drug costs	Admin costs	Health state costs	Utility
3+ OAD	[redacted]	[redacted]	[redacted]	[redacted]
3+ OAD and augmentation	[redacted]	[redacted]	[redacted]	[redacted]

HRU: Healthcare resource use; ICER: Incremental cost-effectiveness ratio; OAD: Oral antidepressant; PAS: Patient access scheme; TRD: Treatment-resistant depression

ERG scenario analyses 1

ESK PAS price

ERG – 3+ OAD treatments	ICER (with ERG carer disutility)
• 100% Byford as source of HRU • ERG cap applied to subsequent treatments	[redacted]
ERG – 3+ OAD treatments and augmentation	**ICER (with ERG carer disutility)**
• Short-term efficacy from TRANSFORM-2 adjusted for a population who have 3+ OAD treatments and augmentation sourced from SUSTAIN-2 • 100% Byford as source of HRU • ERG cap applied to subsequent treatments	[redacted]

Detailed results (with ERG carer disutility)

Population	Incremental			
	Drug costs	Admin costs	Health state costs	Utility
3+ OAD	[redacted]	[redacted]	[redacted]	[redacted]
3+ OAD and augmentation	[redacted]	[redacted]	[redacted]	[redacted]

HRU: Healthcare resource use; ICER: Incremental cost-effectiveness ratio; OAD: Oral antidepressant; PAS: Patient access scheme; TRD: Treatment-resistant depression

ERG sensitivity analyses overview

Uncertainties:

1. **Costs of a treatment course:**
   - ESKALE and Spanish CUP scenarios
2. **Stopping rule:**
   - Scenarios without stopping rule
3. **Administration costs:**
   - No scenarios
4. **Costs of implementation:**
   - Unresolvable, no scenarios

Uncertainties:

1. **Source of medical costs:**
   - Byford and TRD costing study scenarios
2. **Subsequent treatment cap:**
   - Scenario reduces number of people in the MDE health state long-term
3. **Time horizon:**
   - Scenarios exploring where benefit is modelled

$$\text{ICER} = \frac{\text{Costs of using esketamine} - \text{medical costs saved}}{\text{Utility benefit}}$$

Uncertainties:

1. **Subsequent treatment cap:**
   - Increases effectiveness of comparator arm and reduces utility benefit
2. **Time horizon:**
   - Scenarios exploring where benefit is modelled
3. **Response:**
   - No other comparative response/remission data scenarios available

ERG sensitivity analyses – time horizon

3+ OAD population

- Base case

Base case +
- 1 year time horizon
- 2 years time horizon
- 5 years time horizon

$$\text{ICER} = \frac{\text{Costs of using esketamine} - \text{medical costs saved}}{\text{Utility benefit}}$$

Base case +
- 1 year time horizon
- 2 years time horizon
- 5 years time horizon

Scenario	Company base case: [redacted]	ERG: [redacted]
Time horizon	ICER with company carer disutility (ESK PAS price)	ICER with ERG carer disutility (ESK PAS price)
○ 1 year	[redacted]	[redacted]
○ 2 years	[redacted]	[redacted]
○ 5 years	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio; OAD: Oral antidepressant; PAS: Patient access scheme;

ERG sensitivity analyses – stopping rule

3+ OAD population

Base case +
- No stopping rule

- Base case

$$\text{ICER} = \frac{\text{Costs of using esketamine} - \text{medical costs saved}}{\text{Utility benefit}}$$

- Base case

Scenario	Company base case: [redacted]	ERG: [redacted]
Stopping rule	ICER with company carer disutility (ESK PAS price)	ICER with ERG carer disutility (ESK PAS price)
○ No stopping rule	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio; OAD: Oral antidepressant; PAS: Patient access scheme