NICE National Institute for Health and Care Excellence

Slides for projector– redacted

Esketamine for treatment resistant depression [ID1414]

ACM2 – Chair's presentation

Chair: Gary McVeigh

NICE technical team: Adam Brooke, Christian Griffiths, Jasdeep Hayre

Company: Janssen

5th August 2020

Key issues

Treatment pathway

- What population would use esketamine in current NHS practice?
- What are the appropriate comparator treatments?

Clinical evidence

- What does the evidence from TRANSFORM-2 show?
- What does the evidence from SUSTAIN-1 show?

Model structure

- What is the long-term expected outcome of people with major depressive episodes?
- Is the model structure appropriate?

Stopping treatment

- Would patients stop treatment for reasons other than efficacy?

Health related quality of life

- Are the quality of life measurements used in the model appropriate?

Carer quality of life

- Should carer quality of life be included in the model?

Medical costs

- Are medical costs incorporated into the model appropriately?

Appraisal history

ACD recommendation:
Esketamine with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) is **not recommended**, within its marketing authorisation, for treating treatment-resistant depression that has not responded to at least 2 different antidepressants in the current moderate to severe depressive episode in adults.

Summary committee conclusions – clinical evidence

Topic	Conclusion	ACD
Current clinical practice	Includes different types of treatments for TRD (atypical oral antidepressants, augmentation therapy and ECT), there are differing clinical opinions on the definition of the condition	3.3
Comparator evidence	No evidence was provided comparing esketamine with all the relevant comparators listed in the scope, such as combination or augmentation treatments and ECT	3.4
Psychological therapy	CBT with oral antidepressants and adjunctive therapy is a relevant part of the treatment pathway, but no evidence was presented when combined with esketamine or its comparators	3.5
Blinding	Blinding is difficult, given the dissociative symptoms experienced by people after they had esketamine	3.6
Generalisability to NHS clinical practice	Evidence has limited generalisability because the trials excluded people with moderate to severe alcohol abuse, psychiatric comorbidities, and suicidal ideation in the last 6 months or suicidal behaviour in the last 12 months	3.7
Placebo adjustment	Inappropriate to adjust for placebo because of the risk of bias and the trial design accounts for the placebo effect	3.8
Safety	Because esketamine is a schedule 2 drug, administration and monitoring must be considered to prevent abuse and misuse	3.9

Summary committee conclusions – economic modelling

Topic	Conclusion	ACD
Time horizon	A longer time horizon better captures the natural history of the condition, 20-year time horizon is preferred to 5-year	3.10
Model structure	The model was limited because it did not account for the chronic nature of the condition, underestimates the effectiveness of subsequent treatments, and is unable to include repeat treatments	3.11
Stopping treatment	Assuming an indefinite improvement in quality of life after stopping esketamine treatment is implausible. The least biased estimate would not include discontinuation of esketamine for reasons other than lack of efficacy	3.12
Mortality	Exclusion of people with acute suicide risk in the trials and lack of data means it is not appropriate to model reduced mortality	3.13
Carer disutility	Did not accept a carer disutility as part of the base case but considered it as a scenario	3.14
Resource use	A range of ICERs considered using 1:1 to 1:6 ratio of nurses to patients during the monitoring phase of administration	3.16
Cost of adoption in clinical practice	Esketamine would require significant investment in costs and time to adopt and implement in NHS, not included in the model	3.17

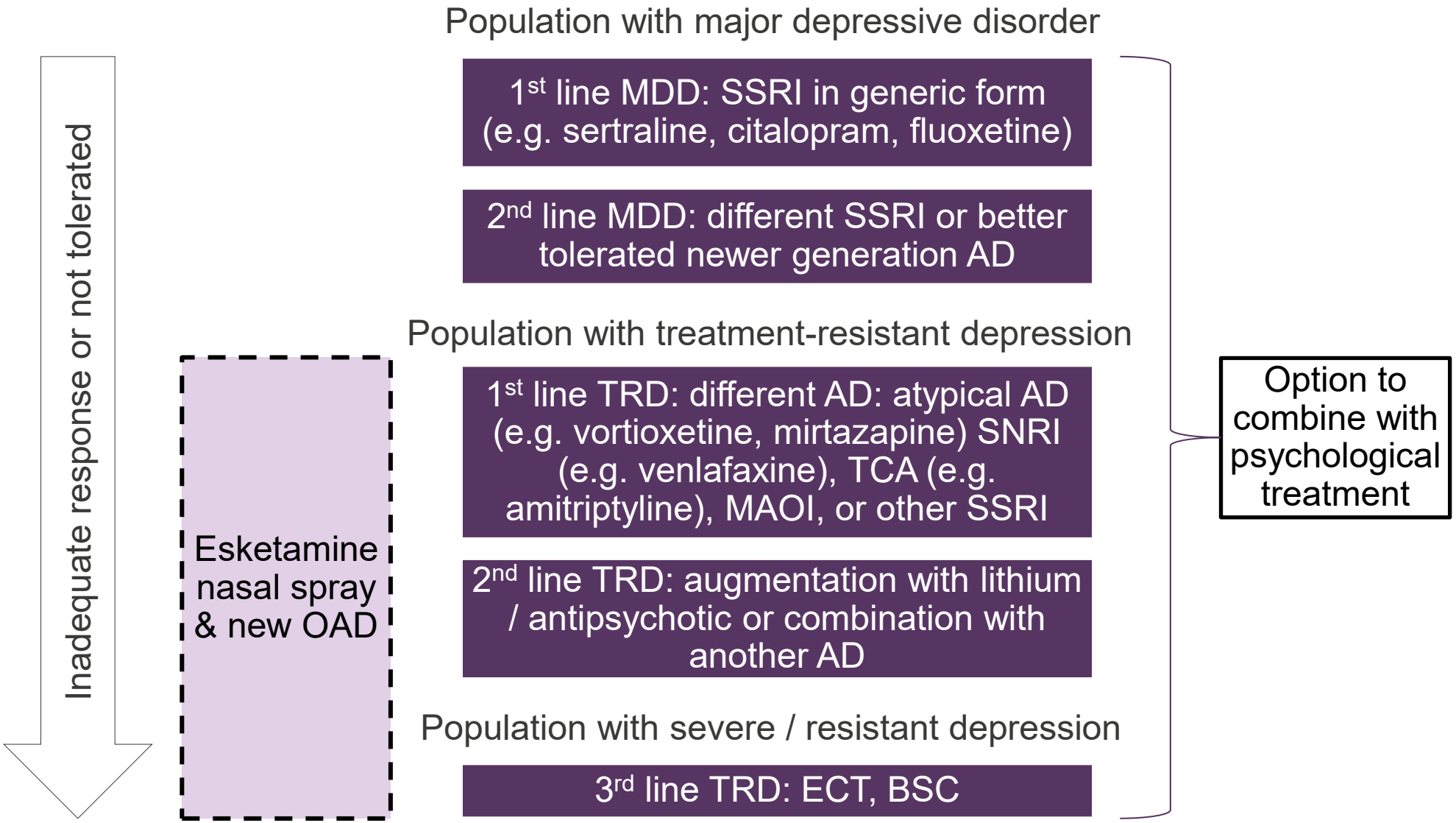
ACD consultation

Contributing consultation comments

- Company (Janssen)
  - Provide consultation comment responses and a revised base case
  - Provide new scenarios for treatment discontinuation, utility decrement after stopping
  - Proposed patient access scheme (Part 2 only)
- Professional Groups
  - Royal College of Psychiatrists (RCP)
  - British Association for Psychopharmacology (BAP)
  - Joint response from multiple psychotherapy-based organisations
- Patient Groups
  - SANE UK
- Clinical expert (CE)
- Web comments
  - Joint response from 12 researchers/clinicians (including 8 psychiatrists)
  - 12 other web commenters

Treatment Pathway

(from NICE guideline CG90)



Abbreviations: AD, antidepressant; ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitor; OAD, oral antidepressant; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; BSC, best supportive care

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Treatment population

1,150,123
Total number of adults diagnosed and receiving pharmacological treatment

133,100
Total number who do not respond to 2 treatments

- Total number covered by the marketing authorisation

12,688
Referred to secondary care

- 9.6% of cases are referred to secondary care services (generally those deemed to be at risk of suicide, CS)
- SmPC: The decision to prescribe esketamine should be determined by a psychiatrist.

472 – 1,679
Year 1-5 company uptake estimates

- Company considers uptake will be limited due to the current mental healthcare commissioning and funding environment
- Uptake curve is based on risperidone uptake in secondary care, which was the first atypical long acting injectable in schizophrenia

Treatment pathway and treatment burden

ACD committee conclusions:

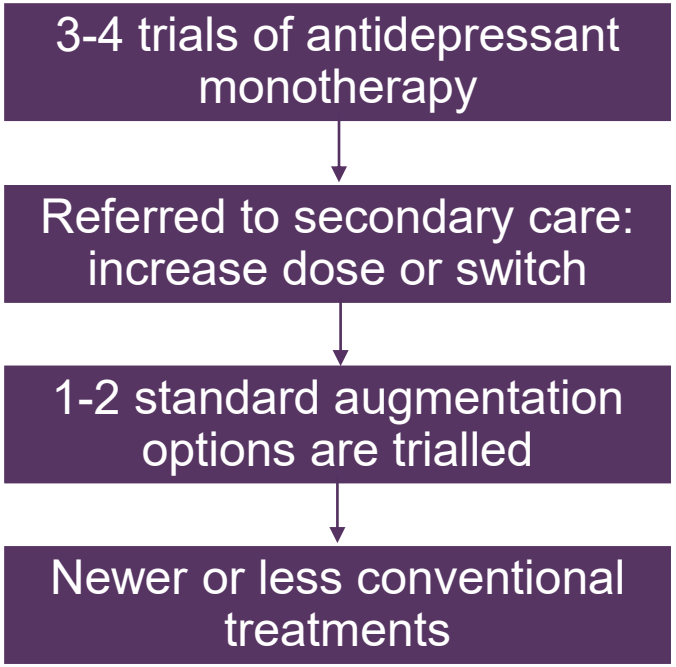
- *CE: 'ECT should also be a comparator because the processes involved in administering esketamine are similar to those for ECT'*

Janssen:

- This is not a relevant rationale for the definition of a comparator
- the processes for administering ESK-NS and ECT are not similar, given the requirements for anaesthetics and a full day admission for ECT

Consultation comments:

- CE: Patients do not follow a treatment pathway reflecting NICE CG90, see alternative pathway.
- CE: High level of treatment burden, patients would need:
  - attend a hospital site twice a week and then weekly for a period of time
  - Potentially need carer support because of the inability to drive after taking esketamine
  - Illness characterised by anergia, amotivation and feelings of hopelessness
- This would affect when esketamine is used and patients would need to be agreeable to undertaking this.
- The smallest extra hassle around prescribing a treatment leads to low rates of prescribing.



Comparator treatments

***ACD committee conclusions**:*

- *'the company did not provide evidence comparing esketamine with all the relevant comparators listed in the scope, such as combination or augmentation treatments and ECT'*

Janssen:

- data comparing ESK-NS to all relevant comparators was reported in both the company submission and the ERG report.

Consultation comments:

- BAP: The evidence for adjunctive therapies such as lithium, or oral antipsychotics is not as strong as that reported in the recent trials of esketamine
- BAP: many people will not wish to have ECT, for reasons such as stigma, as well as medical or psychiatric co-morbidity. Clinically, people offered ECT for TRD are presenting more acutely unwell, have co-morbid psychosis (for which esketamine is contraindicated), and have more medical morbidity, e.g. have stopped eating or drinking.
- CE: There is next to no data comparing pharmacological augmentation strategies in treatment resistant depression
- It is difficult to choose pharmacological comparator(s) due to number of comparators, combinations and doses.

Psychological therapies

ACD committee conclusions:

- *'CBT alongside oral antidepressant therapy and adjunctive therapy is a relevant part of the treatment pathway'*
- *'not seen any evidence on its effect when combined with esketamine or its comparators'*

Janssen:

- Consideration of the combined effect of psychological and pharmacological treatment is inconsistent with previous NICE decision making and this should not be considered further.
- It is possible to receive psychological therapy whilst also receiving ESK-NS treatment

Consultation comments:

- BAP: Only two trials of psychotherapy in people with TRD. 'It is puzzling as to why use of psychotherapy should have any bearing here-especially given that this criterion was never placed on the evidence base for adjunctive therapies such as lithium or antipsychotic medication'.
- Some consistency in approach or a clearer explanation to the different approaches is needed.
- CE: Raising the issue of a lack of inclusion of psychotherapy in the studies of esketamine appears to be setting a hurdle that not a single currently recommended pharmacological treatment has surpassed

Clinical evidence used in the model

	TRANSFORM-2	SUSTAIN-1
Study design	Randomised, double-blind, parallel-group, active-controlled, phase 3	Randomised, double blinded withdrawal design
Population	Adults 18-64 years	Adults 18-64 years with stable remission or stable response after treatment with ESK
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
Primary outcomes	Response (MADRS) Remission (MADRS) Adverse effects HRQoL (EQ-5D)	Relapse (MADRS) Adverse effects HRQoL

Studies used as supporting evidence in company submission

TRANSFORM-1	TRANSFORM-3*	SUSTAIN-2	SUSTAIN-3
Used fixed dose not in line with licence	Used 28mg – below minimum effective dose	Non-comparative & minimal efficacy data	Ongoing study & minimal efficacy data

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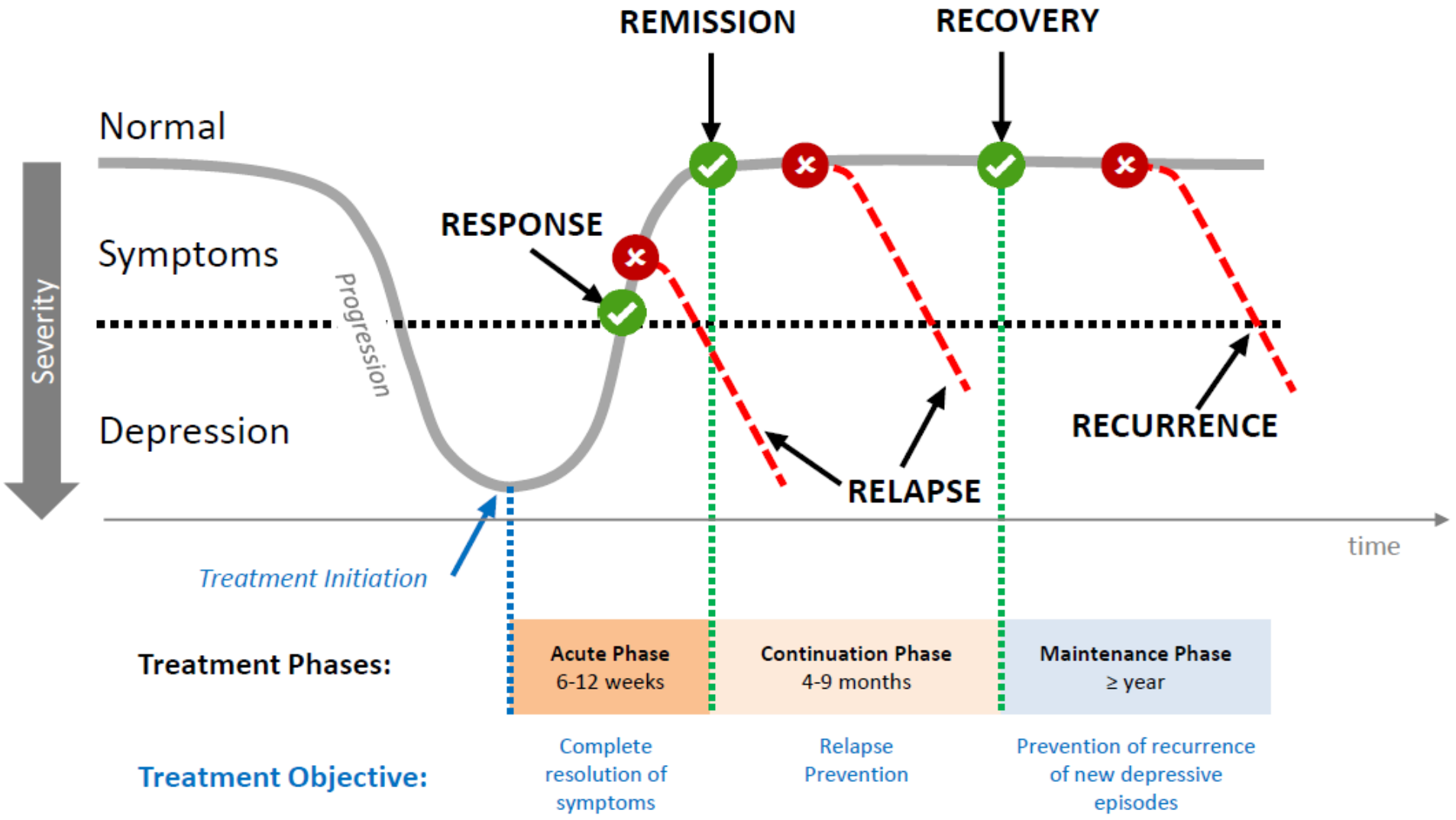
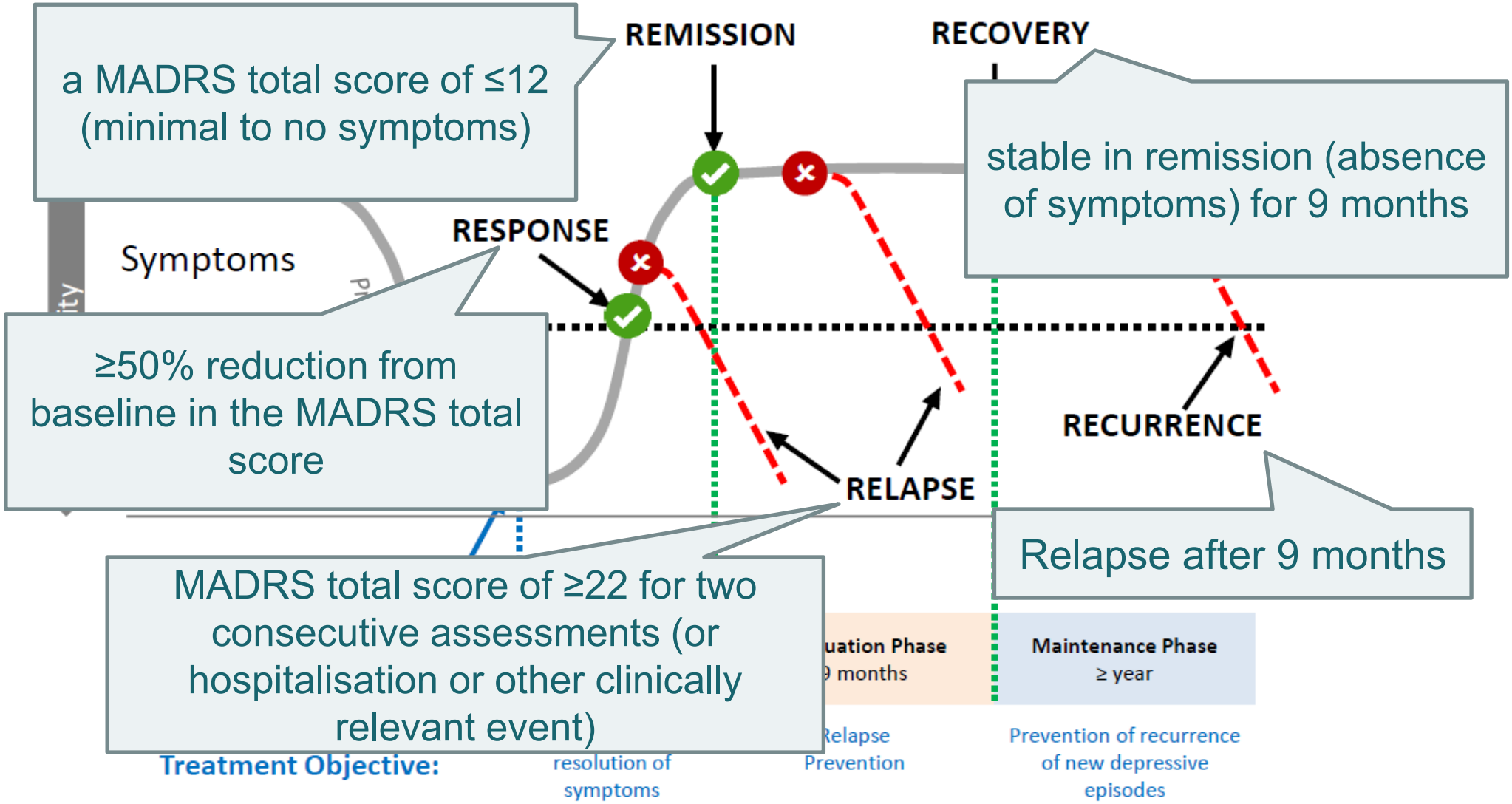
*acute phase data for adults ≥65 were incorporated in the economic model from this study

Treatment phases and duration



Key definitions



Note: MADRS scale is between 0 and 60, 0 indicating no depressive symptoms

Clinical evidence – TRANSFORM-2

ACD committee conclusions:

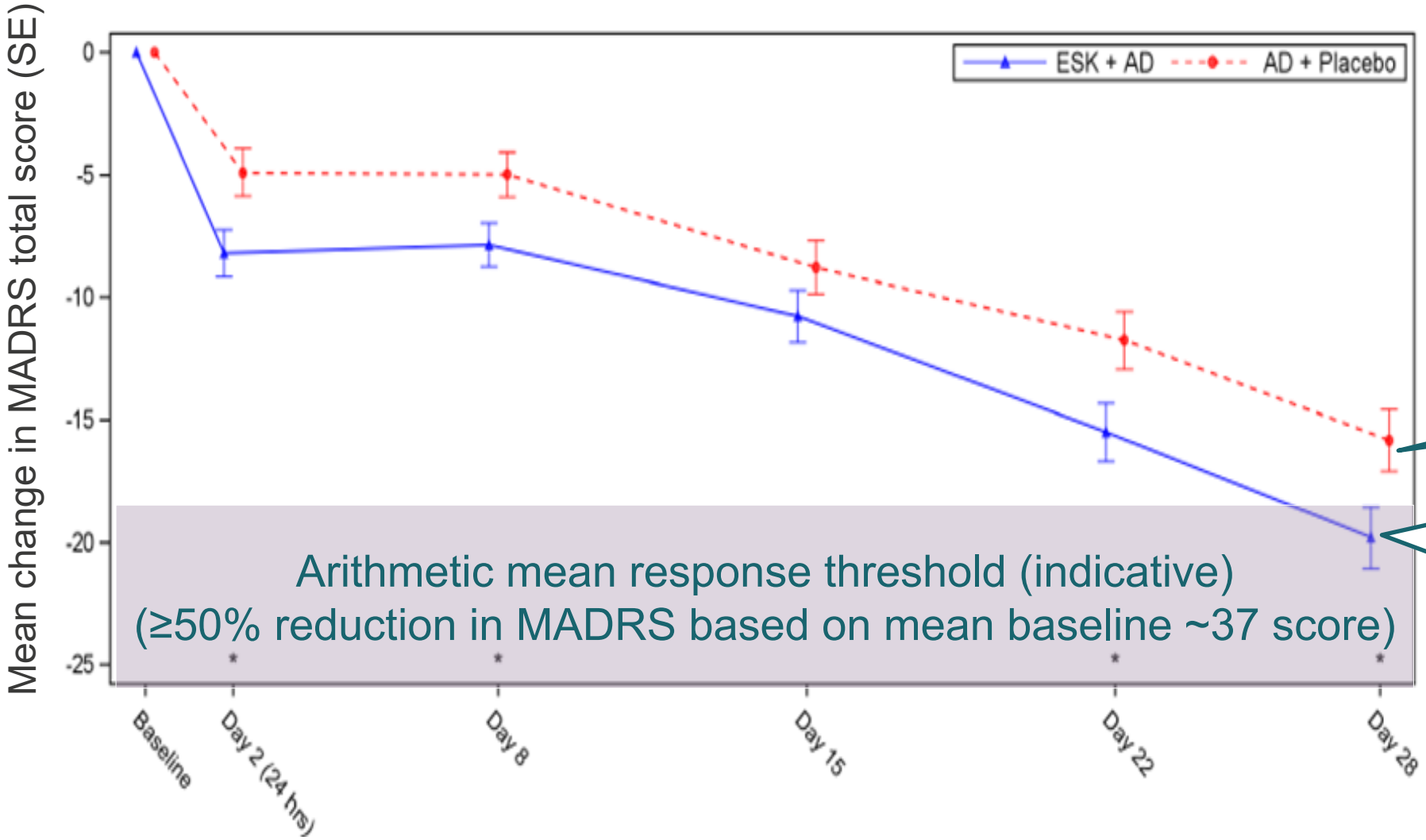
- *'Clinical trials suggest that esketamine with an oral antidepressant may be more effective at relieving the symptoms of depression than placebo and an oral antidepressant'*

Consultation comments:

- 'Dichotomised data tends to inflate the differences between groups especially when the differences between groups are small on the primary data'
- 'Methodological experts are unanimous in advising the use of primary data (the MADRS) rather than dichotomised versions of the data (response or remission rates)'
- Clinical global impression (CGI) scale defines 'minimally improved' as 7-9 and 'much improved' as 16-17 – therefore, the difference is less than minimal change and less than a quarter of the placebo response.
- Differences could be explained by unblinding caused by noticeable psychoactive effects
- Time period of 28 days has little bearing on the treatment for depression
- NB: a difference of 6.5 MADRS points was used for power estimations for all TRANSFORM studies, therefore this carries the risk of being a false positive result

Outcome	ESK + OAD	PBO-NS + OAD	Difference in LS means
Baseline MADRS	37.0 (5.69)	37.3 (5.66)	-
Change in MADRS at 28 days	-21.4 (12.32)	-17.0 (13.88)	-4.0 (1.69, -7.31 to -0.64)

Clinical evidence – TRANSFORM-2



52% response
31% remission

69% response
53% remission

Clinical evidence – SUSTAIN-1

ACD committee conclusions:

- *'The committee understood that …SUSTAIN-1 results showed an improvement in … relapse rates for esketamine plus oral antidepressant compared with placebo plus oral antidepressant.'*

Consultation comments:

- There is potential for confounding of relapse from potential withdrawal effects of esketamine
- Widely recognised withdrawal symptoms when stopping ketamine in recreational use. (characterised by anxiety, dysphoria, shaking, sweating and palpitations, and craving the drug)
- Unclear how withdrawal (as measured by the Physician Withdrawal checklist [PWC]) was differentiated from seemingly identical measures on the MADRS, potential for misclassification of withdrawal events
- 48.7% of relapses occurred in the first four weeks following esketamine cessation, the time most likely for withdrawal effects to occur.
- NB: PWC showed 26-27% increase in patients with anxiety 2 weeks after stopping treatment
- NB: 93% of all relapses were from patients reaching the MADRS threshold for relapse of 22
- Company does not consider a withdrawal effect is possible due to pharmacokinetic profile of ESK-NS

Physician Withdrawal Checklist	MADRS
Dysphoric-mood depression	Apparent/reported sadness
Insomnia	Reduced sleep
Anxiety-nervousness	Inner tension
Lack of appetite	Reduced appetite
Difficulty concentrating/ remembering	Concentration difficulties
Fatigue	Lassitude

Clinical evidence – SUSTAIN-1

ACD committee conclusions:

- *'The committee understood that …SUSTAIN-1 results showed an improvement in … relapse rates for esketamine plus oral antidepressant compared with placebo plus oral antidepressant.'*

Consultation comments:

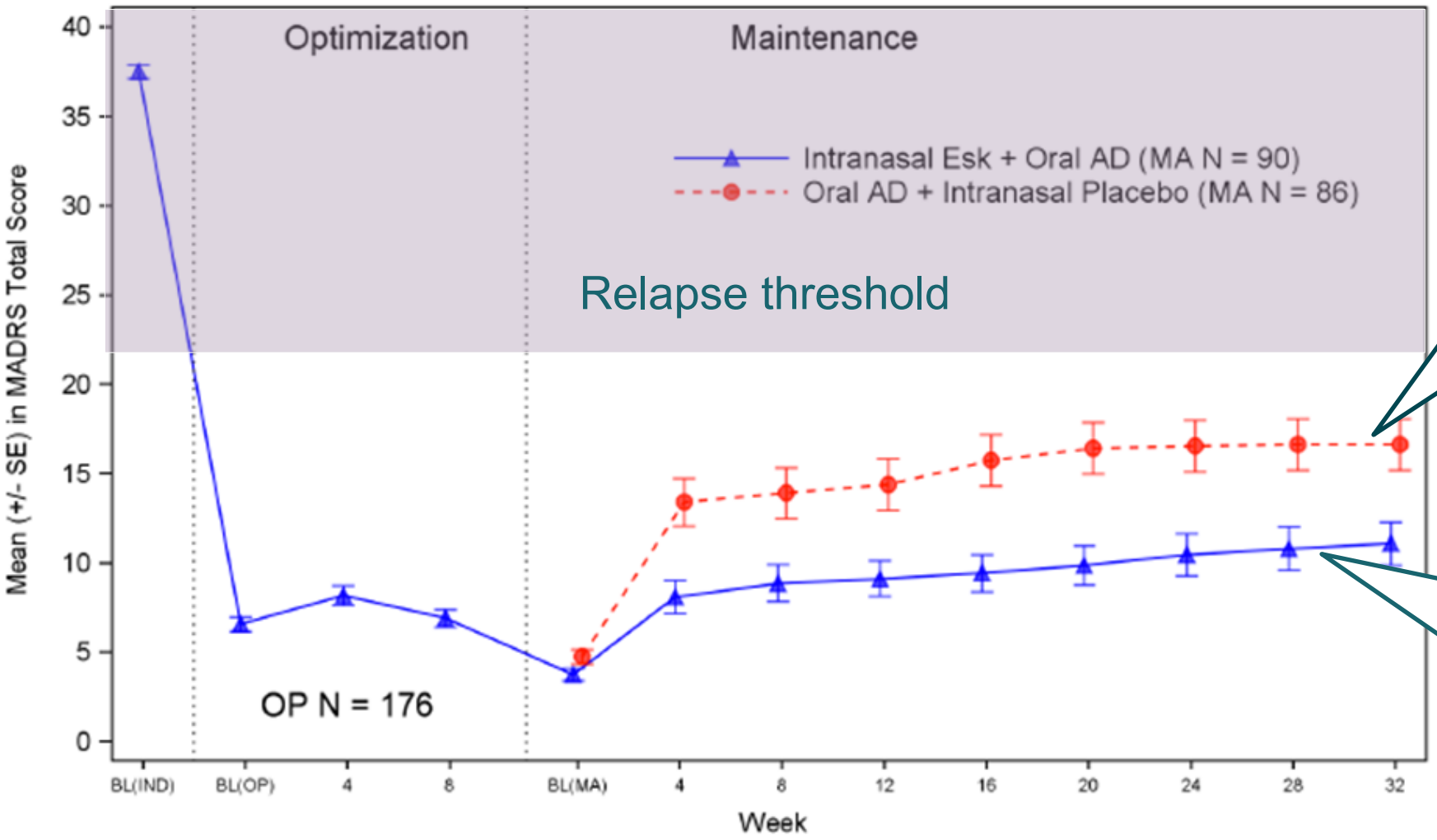
- Potential for functional unblinding: the absence of esketamine's psychoactive effects would be noticed by participants randomised to placebo and consequent negative expectations would tend to increase their chance of relapse.
- Higher dissociation scores while on treatment were correlated with shorter time to relapse, consistent with this hypothesis.
- NB: A proportion of patients were not blinded to treatment during the optimisation phase.
- FDA raised the concern that the positive results of the study were driven by a single site where there was 100% relapse rate in the placebo arm. (16 out of 16 subjects on placebo versus 2 out of 9 on esketamine relapsed)
- NB: EMA is relevant regulator and neither EMA or FDA found issue with the site
- "If this outlier site is excluded there is no significant difference between esketamine and placebo" – company provide response to this at technical engagement
- NB: Only 24.1% of those continuing placebo from TRANSFORM studies relapsed in the maintenance phase

ERG comment:

- No evidence for rate of relapse for those that discontinue treatment

Clinical evidence – SUSTAIN-1

Arithmetic Mean MADRS scores for stable remitters

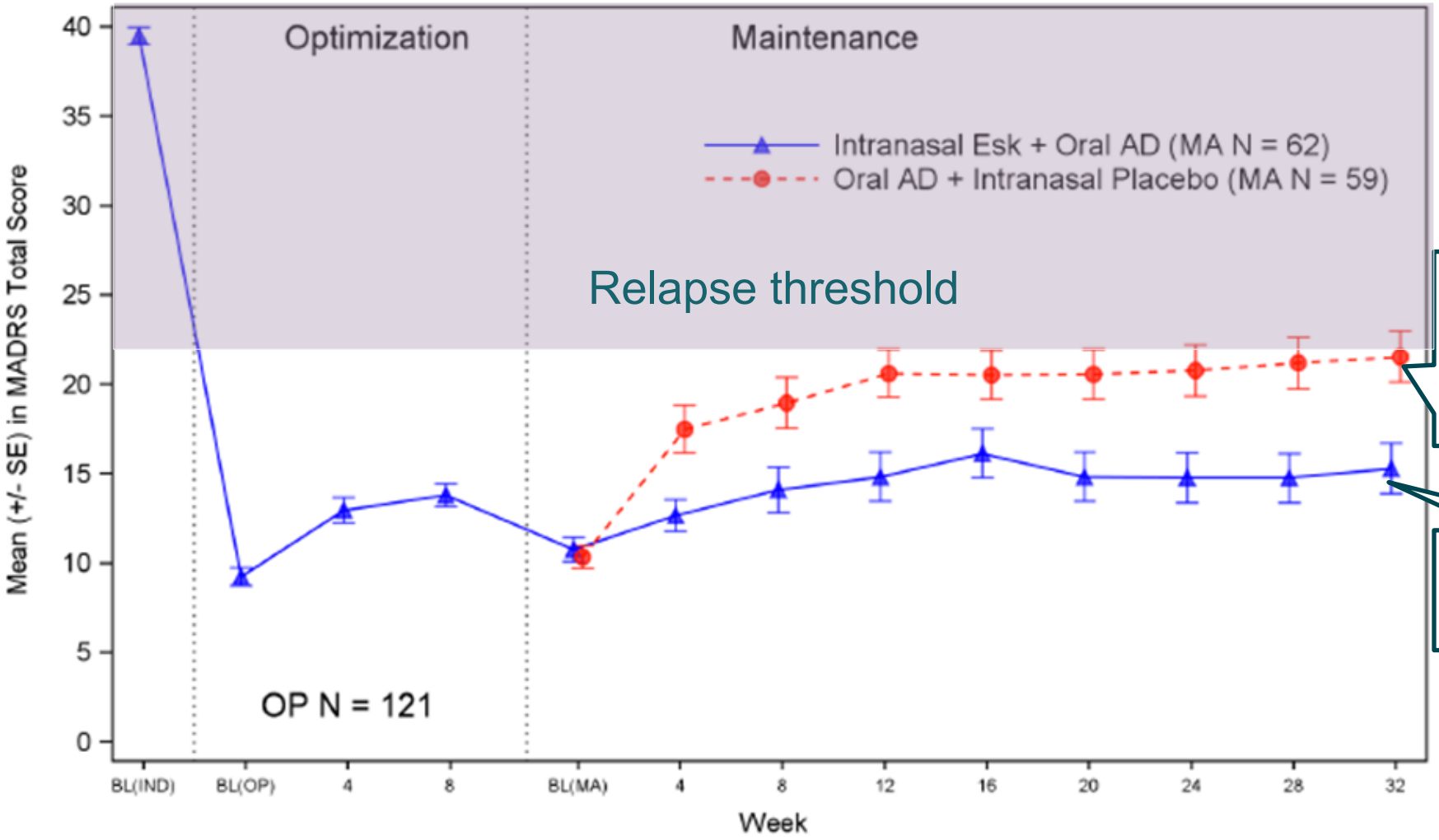


39/86 relapses (45.3%)
Inc. 1 clinically relevant event

24/90 relapses (26.7%)
Inc. 3 hospitalisations and 3 clinically relevant events

Clinical evidence – SUSTAIN-1

Arithmetic Mean MADRS scores for stable responders



34/59 relapses (57.6%)
Inc. 1 clinically relevant event

16/62 relapses (25.8%)

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Clinical evidence – safety

ACD committee conclusions:

- *'no evidence on the effects of withdrawal from esketamine treatment'*
- *'safety must be taken into account when administering and monitoring esketamine to prevent abuse and misuse'*

Consultation comments:

- 3 suicides occurred in participants 4, 12 and 20 days after the last dose of esketamine
- 2 of these patients showed no previous signs of suicidal ideas during the study, either at entry to the study or at the last visit (data was not available for the third patient)
- Potential that this fits with a pattern of a severe withdrawal reaction, consistent with other reports of suicide from ketamine and are significant enough in number to constitute a worrying signal
- increase in depression and suicidality was also observed during esketamine treatment. In one 4-week trial 6 patients in the esketamine group became more depressed, compared to only one on placebo; 4 patients expressed new onset suicidal ideas in the esketamine group, compared to only 1 on placebo
- **NB**: PWC-20 checklist showed a 26-27% increase in anxiety 2 weeks after discontinuation but the full results are not presented

Generalisability

ACD committee conclusions:

- *'the extent of the exclusion criteria (moderate to severe alcohol abuse, psychiatric comorbidities, treatment with ECT, recent suicidal ideation or behaviour) and the lack of participants from England in the trials mean the evidence for esketamine is limited in generalisability to the NHS population .'*

Janssen:

- ESK-NS trials are consistent to other antidepressant trials in depression and TA367

Consultation comments:

- BAP: a number of NICE guidelines in mental illness would be obsolete, including recommendations from the 2009 Depression guideline that are cited by the ERG.
- BAP: evidence from trials of IV ketamine suggest beneficial effects of the compound on suicidal ideation
- CE: It is disappointing that there were not more UK patients included. However, I would be extremely concerned if a situation arose where only drugs tested in UK populations were approved for use in this country
- CE: exclusion criteria are pretty standard across studies of this type, impossible to achieve balance between treatment arms across many different comorbidities of low signal to noise ratios, means that to NOT exclude patients for significant alcohol problems or any psychiatric comorbidity would require unfeasible sample sizes in studies
- CE: It is always a concern when risk of suicide is included as an exclusion criteria.

Model structure and time horizon

***ACD committee conclusions**:*

- *'the modelled effectiveness of subsequent treatments appeared to be underestimated'*
- *'model was limited because it did not account for the chronic nature of the condition, underestimates the effectiveness of subsequent treatments, and is unable to include repeat treatments'*
- *'a longer time horizon better captures the natural history of the condition, and that it preferred the 20-year horizon to the 5-year horizon'*

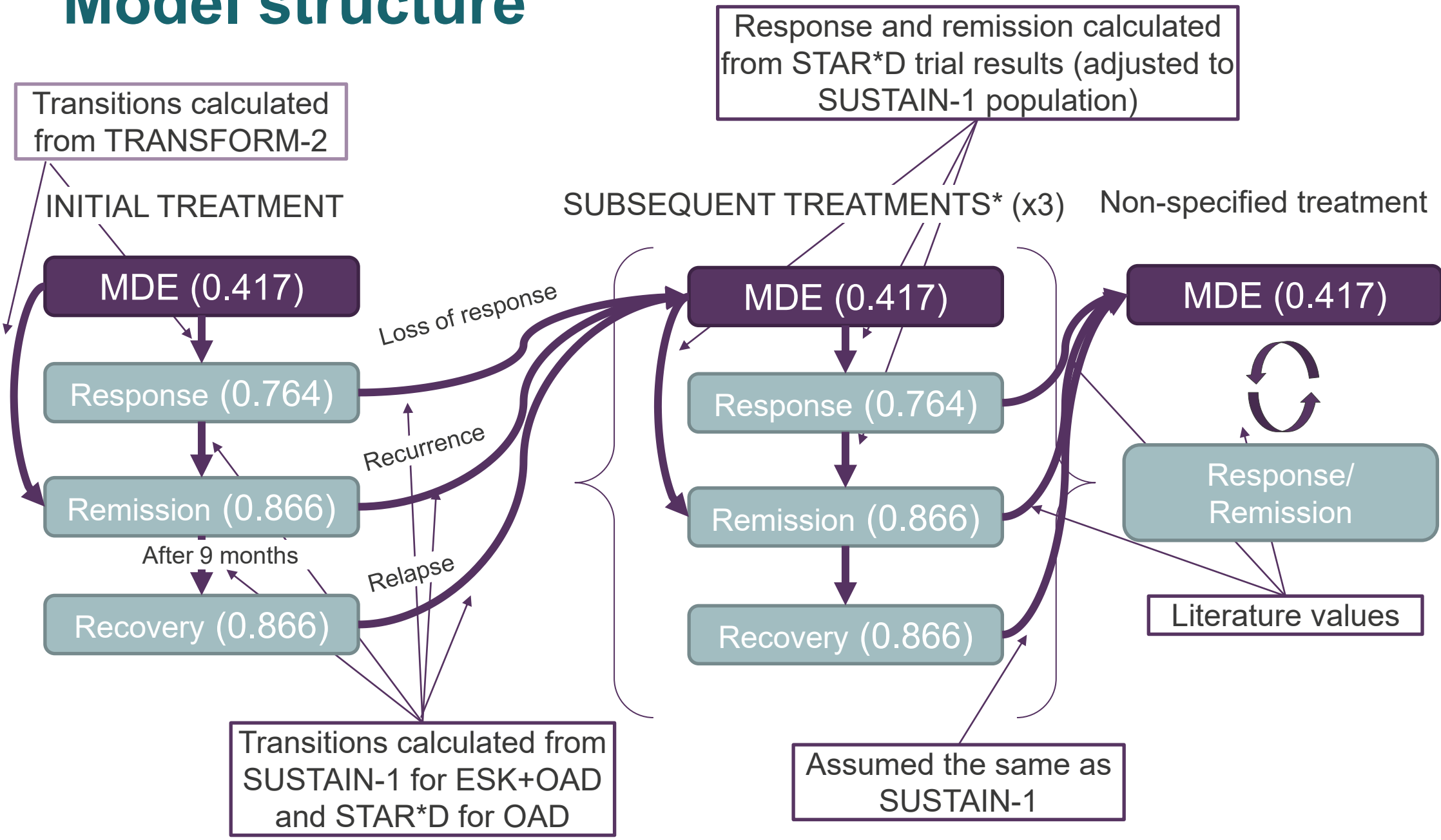
Janssen:

- Provide a 'retreatment model' that allows people that are in stable remission for 9 months with ESK + OAD to retreat with esketamine upon recurrence
- Believe that 'using a longer time horizon and including assumptions to inform retreatment brings additional uncertainty due to the lack of data to inform the analysis'.
- Consider that retreatment has not been considered previously in the other NICE decision making and that Committee are considering retreatment in the context of this appraisal only

Consultation comments:

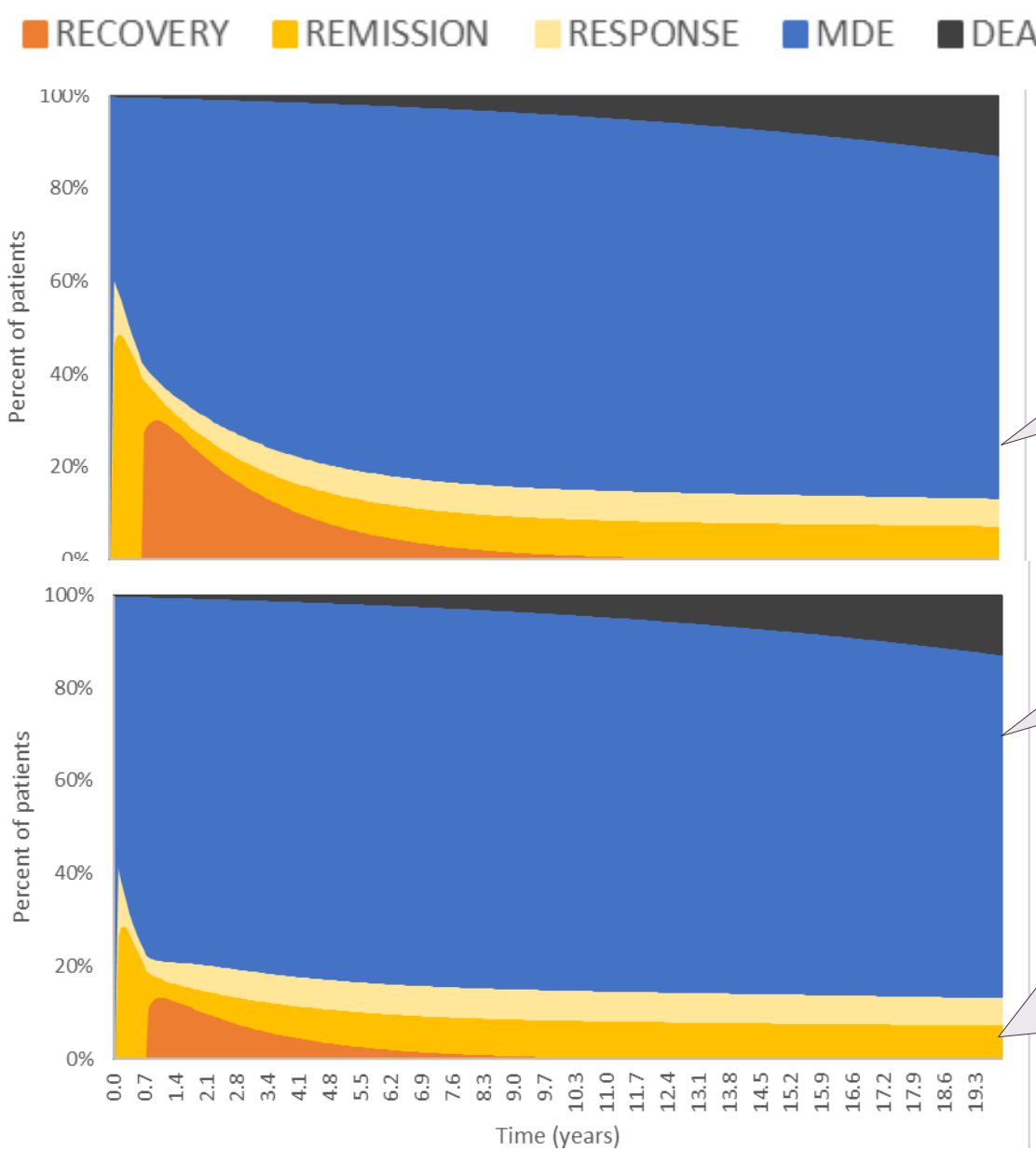
- RCP: depression tends to recur and can run a protracted course, but on the individual level there is much variability in clinical outcomes, and prediction of outcome in a given patient is notoriously inaccurate
- SANE: episodic nature of treatment-resistant depression has not been adequately taken into account by the committee

Model structure



* Subsequent retreatment with esketamine allowed for patients that reach recovery in company retreatment model

Model outputs - Markov trace



- High proportion in MDE state after 20 years
- Total 78% in MDE state within 1 year
- Represents standard care - Forms steady state of remission and relapse in final model health state of 16%

Use of STAR*D data

Relapse, loss of response and recurrence rates– OAD arm

- Company consider “patients randomised to OAD had received (and responded to) prior treatment with ESK-NS + OAD, it was unclear whether the withdrawal of ESK-NS might impact their loss of response or risk of relapse” so use data from STAR*D trial for OAD arm
- ERG propose a scenario that equalises these arms as done in TA367

Data source for OAD arm	Relapse rate 4-weekly	Loss of response 4-weekly	Recurrence 4-weekly
Estimated from KM curves in STAR*D trial data (company base case)	**9.24%**	**22.43%**	**2.88%**
Observed in SUSTAIN-1	**12.3%**	**14.9%**	Assumed same
Equivalent value for ESK-NS (ERG scenario)	**5.57%**	**4.19%**	**2.88%**

Long-term outcomes

ACD committee conclusions:

- *'the modelled effectiveness of subsequent treatments appeared to be underestimated'*
- *'model was limited because it did not account for the chronic nature of the condition, underestimates the effectiveness of subsequent treatments, and is unable to include repeat treatments'*

Janssen:

- The source of subsequent treatment effectiveness were validated as appropriate source with four UK psychiatrists
- ERG scenario (see next slide) including clinically unreasonable and unvalidated assumptions on the efficacy of subsequent treatments should be considered inappropriate

Consultation comments:

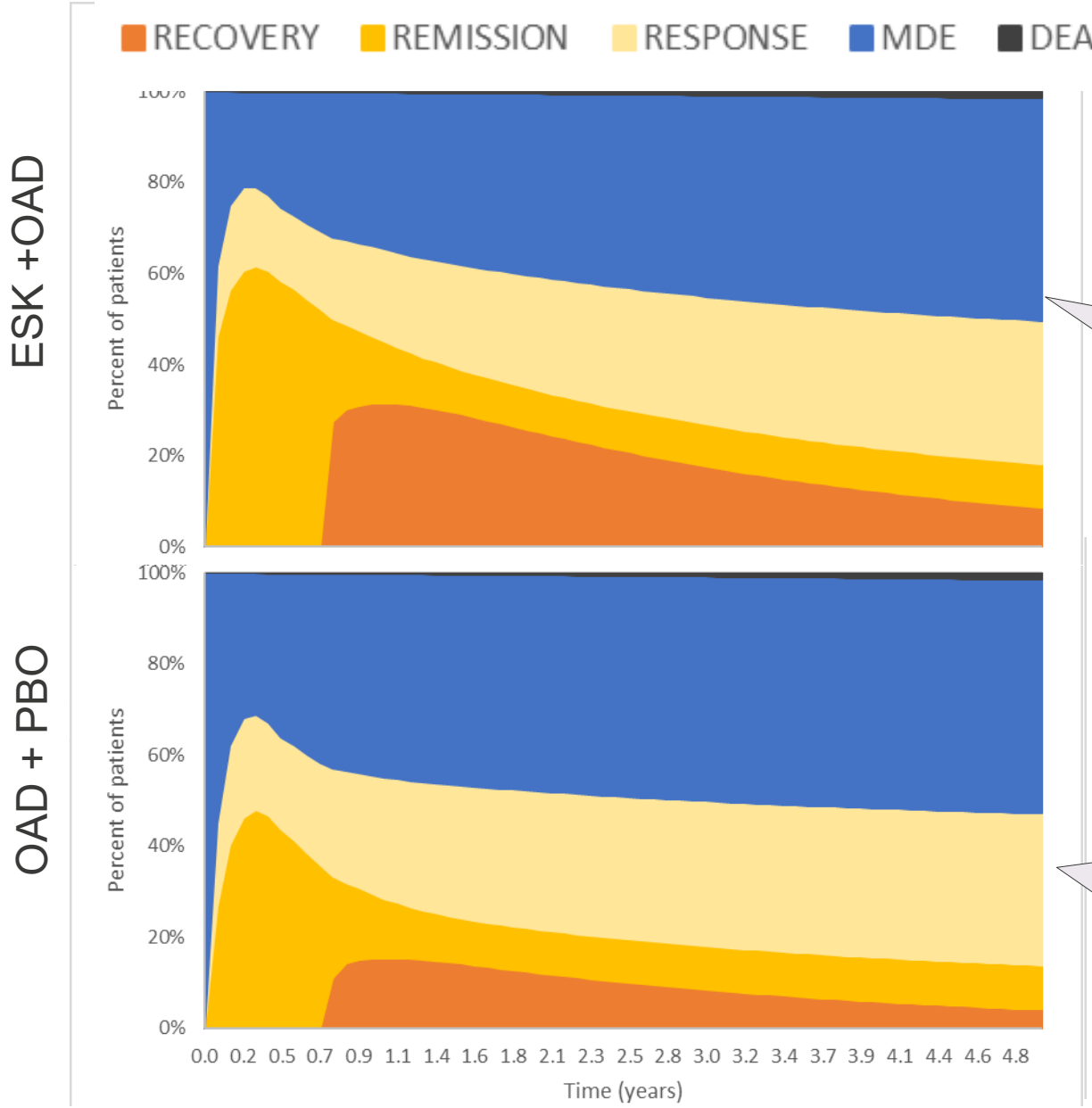
- BAP: Tertiary service indicated that, post-discharge, over a mean of 3 years, 35% of people with TRD had a poor outcome
- RCP: Quote Wooderson et al study that has a remission rate of 50% at 3 years in tertiary services (NB: This model estimates <20% response/remission for current practice)
- BAP: Patients with TRD generally maintained their improvements seen at the end of acute treatment, and even on average improved further
- SANE: depression can be highly episodic, with a good success rate when patients are compliant with treatment. Relapse can happen, but there can be long periods when a patient is 'in remission', and some can recover from depression

Subsequent treatments – ERG scenario

- The ERG considered the effect of subsequent treatments were underestimated and provided a scenario that decreased effectiveness proportionally by each line of therapy based on the ratio as seen in STAR*D between lines 3 and 4 (as recommended in TA367)
- ERG considers that the method of calculating response of subsequent treatments was unclear and may not have been converted to 4-weekly appropriately because of the large difference between observed 3rd/4th line total response rate and weekly estimation – additionally non-response within 1 cycle led to progression to the next treatment
- This scenario also fixes problem of using data from external source and population

Treatment line	4-weekly estimate from STAR*D (company base case)		4-weekly estimate in ERG scenario	
	Remission	Response	Remission	Response
Subsequent treatment 1	3.54%	0.86%	25.2%	17.8%
Subsequent treatment 2	2.75%	0.65%	23.9%	17.3%
Subsequent treatment 3	2.14%	0.49%	22.7%	16.8%
Best supportive care	0.41%	0.83%	21.5%	16.3%

Model outputs - Markov trace of ERG scenario



- Lower proportion (<50%) in MDE state after 5 years than company base case

- Represents standard care - Forms steady state of remission and relapse in final model health state of ~40%

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Mortality

ACD committee conclusions:

- *'because of issues with generalisability and the exclusion of people with an acute suicide risk and the lack of data, it could not accept a reduced suicide risk, and therefore did not accept a reduced mortality risk with esketamine treatment'*

Janssen:

- Do not agree on the Committee's preferred assumptions for removing excess mortality in the MDE health state but include this assumption in the revised base case

Consultation comments:

- BAP: evidence from trials of IV ketamine suggest beneficial effects of the compound on suicidal ideation
- remission appears to reduce all-cause mortality within the NHS, naturalistically
- CE: All cause mortality in patients defined as 'treatment resistant' is 29-35% higher than for non-treatment resistant depressed patients
- Long term follow up of NHS patients with TRD shows clearly that entering remission is associated with reduced all cause mortality during long term follow up

Stopping treatment

ACD committee conclusions:

- *'people would be fully involved in the decisions around continuing treatment, and that decisions about how long treatment lasts and reasons for stopping it vary based on individual circumstances'*
- *'assuming an indefinite improvement in quality of life after stopping esketamine treatment was implausible'*
- *'without data the least biased estimate of cost effectiveness would be to not include discontinuation of esketamine for reasons other than lack of efficacy'*

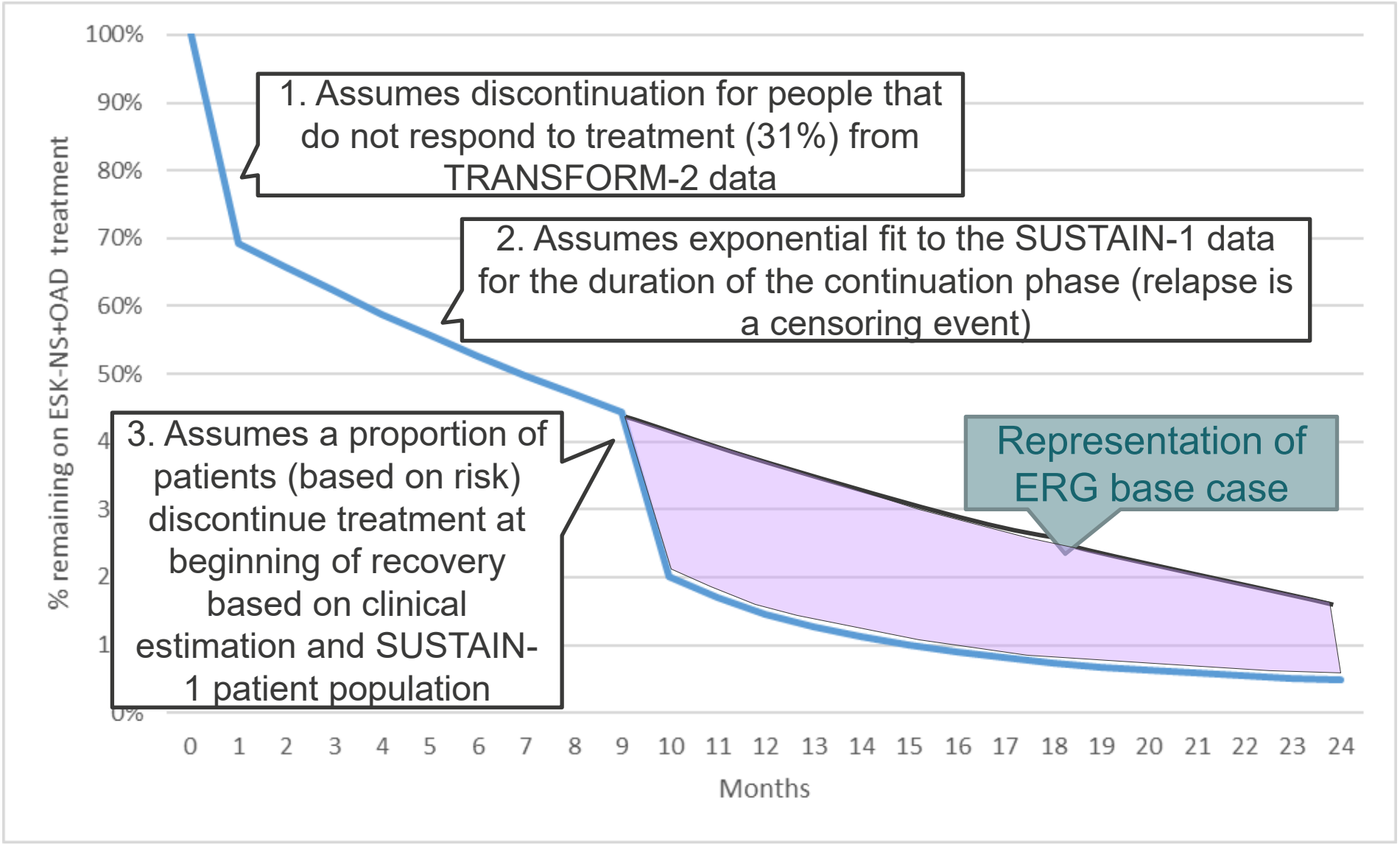
Janssen:

- The company consider the recurrence rate sufficiently accounts for worsening of quality of life after stopping treatment (rather than indefinite improvement)
- Company provide further modelling assumptions and suggested stopping criteria

Consultation comments:

- BAP: The stark reality in clinical practice is that a lot of people do not take psychotropic medication as prescribed. People tend to stop treatment for a variety of reasons other than lack of efficacy. For people with depression these include feeling better, and adverse events
- Improvement in treatment resistant depression is often maintained whilst reducing medication
- CE: whether a patient continues with treatment will only loosely correlate with degree of symptomatic improvement. Some patients do continue taking it long term, but some choose to at least take a pause from treatment, even if they are responding
- After a median of 3 years, 43% of patients reduce medication, 35% the same, 22% increase

Stopping treatment – company base case



Stopping treatment – ERG comments

ERG:

- **Assumption 1**: It is reasonable to assume no discontinuation during the acute phase
- **Assumption 2**: Appears to be reasonable but based on an arbitrary definition of stable and choice of exponential distribution. No evidence presented for rate of relapse in patients that discontinue which may bias this curve.
- **Assumption 3**: Not reasonable and based on assumptions. The % are from market research data which is based entirely on risk categories (number of previous MDD episodes) that may not be generalisable to UK clinical practice.

- Additionally, some patients (represented by the shaded area) continue to receive a treatment benefit without treatment costs (discontinuation with no decrease in QALYs)
- It is unclear whether there might be a diminution in utility and thus a loss of QALYs even if relapse or recurrence do not occur.

Janssen:

- Provide 3 scenarios with different stopping treatment rules and 3 additional scenarios with discount in utility associated with discontinuation of esketamine (from SUSTAIN-1 data)

Treatment stopping criteria

Janssen propose the following treatment stopping criteria:

ESK-NS treatment discontinuation guidance

- **Assess patients after 4 weeks for response to determine the need for continued treatment**
- **The need for continued treatment should be re-examined every 6 months**
- **Treat patients who are in stable remission for a total of 9 months after achieving remission and then consider discontinuing esketamine nasal spray while continuing the oral antidepressant for recurrence prevention**
- **Treat patients who remain in a response health state (not remission) for up to two years based on the higher risk of relapse compared to remitters**
- **Exceptions will occur based on clinical judgement (e.g., some patients may exceptionally require longer treatment as is seen with Electroconvulsive Therapy (ECT)**

New treatment stopping scenarios

Discontinuation scenario	Stable remitters that discontinue at 9 months	Recovered patients that discontinue between 9 months and 2 years	Recovered patients that continue treatment beyond 2 years
Scenario A	50%	-	1%
Scenario B (base case)	52%	32%	16%
Scenario C	0%	70%	30%

- Treatment waning scenarios – represents observed data of utility decrement of people discontinuing treatment after 9 months in SUSTAIN-2 after 4 weeks

Treatment waning effect	Utility decrement from post-hoc analysis of SUSTAIN-2	Double utility decrement from post-hoc analysis of SUSTAIN-2	Triple utility decrement from post-hoc analysis of SUSTAIN-2
Utility decrement	[redacted]	[redacted]	[redacted]

Costs of esketamine

ACD committee conclusions:

- '*The model did not fully account for a scenario in which a greater proportion of people receive the more expensive 84 mg dose, or the proportion who would receive the dose once weekly compared with once every 2 weeks*'
- *'the model may underestimate the cost of a course of esketamine treatment'*

Janssen:

- The average number of sessions per week and devices per session in the acute phase were derived from TRANSFORM-2, while for subsequent time-points they were derived from SUSTAIN-1

- Optimisation phase lasts 12 weeks in the trial but only 4 weeks in the model, it is unclear how these doses have been calculated
- Optimisation dose frequencies were not continued into the maintenance phase
- Decision to increase dose was based on clinical opinion and decision to increase dose frequency was dependent on MADRS score (remission for every other week frequency in the optimisation phase)

Dose at the end of optimisation phase	56mg	84mg
Percentage	36.9%	62.8%

Freq. at:	Weekly	Every other week
Week 4	40.7%	59.3%
Week 8	61.9%	38.1%

NICE

Utility values

Health states	Utility value
MDE	0.417
Response	0.764
Remission	0.866
Recovery	0.866 (assumed)

- Utility values for the health states were derived from the TRANSFORM-2 trial
- EQ-5D-5L data were measured in the trial and mapped to EQ-5D-3L utility values
- MDE state was calculated by baseline results in the TRANSFORM-2 trial (with an average MADRS score of ~37)
- Response and remission utility values were calculated by results at day 28 of TRANSFORM-2

SUSTAIN-1 EQ-5D-5L results	Stable remitters		Stable responders	
	ESK-NS + OAD	OAD + PBO-NS	ESK-NS + OAD	OAD + PBO-NS
Mean score at the start of maintenance	0.925	0.918	0.877	0.875
Mean score at the end of maintenance phase	0.857	0.822	0.855	0.802

- Results for SUSTAIN-1 were not converted to EQ-5D-3L values or used in the analysis

Consultation comments:

- There is evidence that patients with low enough levels of depressive symptoms to meet remission criteria can still experience significant psychosocial dysfunction
- SANE: Only 57% of patients believe the benefits of antidepressants outweigh the side effects

Carer quality of life

ACD committee conclusions:

- *'uncertainty about the appropriateness of including a carer disutility because of the lack of data on the direct effect on carers of people with TRD'*
- *'adjusting for carer disutility was not part of any other NICE TAs in mental health'*
- *'did not accept a carer disutility as part of the base case but considered it as a scenario'*

Janssen:

- there are several previous NICE TAs where carer HRQoL was included. **NB**: not mental health
- Inconsistent with NICE technical team and ERG during Technical Engagement and at all stages prior to Appraisal Committee meeting
- Direct robust evidence was provided previously in the TRD carer HRQoL study which demonstrates impact on carers of patients with TRD

Consultation comments:

- The sustained impact on family and carers, whilst living with and trying to keep patients with TRD safe, is phenomenal and can continue for years

ERG:

- Note that the ERG considers a methodologically better way to estimate disutility associated with a given state is to subtract the utility of that state from the utility associated with full health. Scenarios are provided with this method.

NB: Carer quality of life is applied only in the MDE state

Health-state unit costs and resource use

- Resource use was measured in SUSTAIN-1, but the company used a retrospective chart review of medical records of patients with TRD involving 295 patients in UK clinical practice to model resource use
- Resource use and costs were based on health-state as described in the model
- Costs were calculated using information on use of primary care visits, specialist care visits, crisis resolution home treatment (CRHT), hospitalisations, ECT, psychological treatments (counselling, psychotherapy, CBT, mindfulness, behavioural activation therapy, health coaching)
- These costs were converted into 28-day cost average and used in the economic model
- MDE patients used most resource with £326 of the 28 day average costs attributable to CRHT and £380 of the 28 day average costs attributable to the cost of hospitalisations.

Health states	Value per cycle (95% CI)
MDE	£980 (761.48, 1,198.67)
Response	£164 (102.81, 226.11)
Remission	£164 (102.81, 226.11)
Recovery	£84 (47.97, 119.53)

Treatment	Medical costs in the economic model
ESK + OAD	£143,905 (93% of total costs)
AD + PBO	£150,537 (99% of total costs)

Health-state unit costs and resource use

- Resource use is highly event driven –
  - 33% of the costs in the MDE health state are attributable to crisis resolution home teams as measured in the cost study report
  - 39% of the costs in the MDE health state are attributable to nights hospitalised as measured in the cost study report

Total number of events	ESK+OAD arm in SUSTAIN-1	OAD+PBO arm in SUSTAIN-1	Cost study report Counts per 28-days in the MDE state
Hospitalisations (cost study report gives nights hospitalised)	3	0	1.4 nights in hospital
Clinically relevant events (assumed depressive episodes that require CRHT)	3	2	0.13 crisis resolution home visits

Administration costs

ACD committee conclusions:

- *'more additional training or more experienced nurses may be needed to manage the dissociative effects of esketamine'*
- *'without further evidence, ICERs should be estimated based on nurse to patient ratios across a range from 1:1 to 1:6 during the monitoring phase of administration'*

Janssen:

- Janssen do not believe the 1:1 nurse: patient ratio for the post-administration observation as used as the lower bound by the Committee is appropriate.
- The rare occasions where a 1:1 nurse: patient ratio is expected to occur in clinical practice are included in the average ratio of 1:2 and 1:6 as included in the revised company base case, which is based on extensive clinical input.
- Supervising multiple patients in the post-administration observation is clinically reasonable and based on extensive clinical input

Consultation comments:

- Observations would usually be undertaken by a band 3 MH Health Care Assistant (HCA) under the supervision of a registered MH nurse (RMN)
- 'There will be a need for some staff commitment but this does not seem to us to be a significant investment, particularly if you care to compare this with other new technologies'
- 'It seems inconceivable that 1:1 nursing would be needed. Established clinics I have seen work on far lower ratios'

Costs of implementation

ACD committee conclusions:

- *'adopting esketamine would result in displacement of other mental health treatments because of its cost'*
- *'some infrastructure costs may not be captured in the model'*
- *'esketamine would require significant investment in costs and time to adopt and implement in NHS services'*

Janssen:

- Feedback from NHS at Trust level has clearly said that significant infrastructure investments are not required
- Other mental health treatments will be displaced because of the block contract funding system, not only due to the ESK-NS cost
- Janssen will provide additional educational materials for clinicians and patients. On request further training can be provided. Additional costs of training should therefore not be included in the model.

Consultation comments:

- Consensus that a registry is appropriate NB: costs of these not included in modelling
- Esketamine would need: "a quiet room, a reclining chair and a blood monitoring machine"

Costs of implementation

NHS commissioning expert:

- Feasible that some trusts could turn their ECT suites into esketamine administration and monitoring facilities, but this will not be the case for all/the majority of trusts.
- Trusts should establish/convert/adapt their community mental health facilities to enable the safe administration and monitoring and minimise travel for patients - some patients may have to travel further distances
- Not all current ECT suites could be used this way (currently 54 trusts with at least one ECT suite) but negotiating use is not straight forward for all trusts and not viable for all trusts
- It would be wrong to limit the use/availability to those trusts that have an ECT suite that can be "easily" converted to allow esketamine administration and post dose monitoring
- Adequate "medical" equipment to monitor and deal with the immediate management of any post dose medical complications is required – some ECT suites may make these available
- Regarding controlled nature of the drug:
  - Adequate staffing and governance procedures
  - Storage (controlled drug storage cabinet and governance procedures)
  - Transportation and disposal
  - Registry system would need to be managed in real time through a single source of supply

Other comments from commentators

- Organisations above are highly supportive of the decision based on the lack of evidence of efficacy for esketamine and lack of analysis of long-term outcomes
- Also express methodological concerns for the NICE guideline for the same reasons

- Additional support of the decision from 12 researchers/clinicians who consider esketamine to be a ‘dissociative anaesthetic agent, and known street drug of abuse, being marketed as a treatment for people with complex emotional difficulties, which are often based on social adversities’

Other comments from commentators

- ‘This treatment has a fundamentally different mechanism of action – all other current treatments, both monotherapies and augmentation strategies, relates to monoaminergic neurotransmission. There is great excitement amongst patients and clinicians when a treatment is developed that has a fundamentally different mechanism of action’

- ‘Our patients have a potentially treatable condition, are already subject to a disparity of resources, and I fear that we will merely exacerbate this if we do not evaluate new treatments in a less draconian fashion.’

- ‘We would welcome comparative and robust trials, with proper placebo groups, full randomisation and blinding, and for adequate duration, properly costed but this should not delay any approval of esketamine’

- ‘NICE should be able to use their expertise to recommend the subset of patients to whom this new treatment may be of benefit’

Other comments from commentators

- BAP/CE: IV ketamine should be a comparator because ketamine is the same broad class of drug, it is reasonable to make inferences about effects, in much the same way one would do for beta-blockers-and thus makes the point regarding generalisability and suicidality difficult to comprehend.
- RCP: We also stated ‘should esketamine be licensed for use and approved as a treatment by NICE, the College Centre for Quality Improvement (CCQI) would consider developing a proposal for a network for esketamine services, analogous to the 20 other networks which CCQI operate. This would involve the Academy of Royal Medical Colleges and other stakeholders (including anaesthetists, general practitioners, and general physicians)
- **We would only support the introduction of prescribing on the NHS with these appropriate safeguards for patients in place**

Updated cost-effectiveness modelling

Company revised base case (without PAS discount)

- The company provide a revised base case including some of the committee assumptions:
  - Excluding placebo treatment adjustment effect (ACD section 3.8)
  - Exclusion of additional mortality in the MDE state (ACD section 3.13)
  - Extending the time horizon to 20-years (ACD section 3.10)
- The company did not accept committee assumptions for:
  - Treatment discontinuation as described by data from market research
  - Applying a disutility to represent carer disutility
  - Administration costs based on 1:6 nurse:patients ratio (instead of 1:1- 1:6 range)

Scenario	Incremental costs	Incremental QALYs	ICER
Company base case	£3,444	0.319	£10,790

Scenario analysis on company base (without PAS discount)

Scenario	Incremental costs	Incremental QALYs	ICER (1:6 nurse ratio)
Company base case	£3,444	0.319	£10,790
Retreatment with esketamine for patients in remission for 9 months that relapse	-£856	0.788	-£1,087
Carer utility scenarios			
No carer utility decrement in the MDE state	£3,444	0.249	£13,821
Implemented as described in the ERG report	£3,444	0.279	£12,339
Treatment stopping scenarios			
50% immediately discontinue at 9 months, 1% continue beyond 1 year (scenario A)	£2,807	0.319	£8,794
0% immediately discontinue at 9 months, 30% continue beyond 1 year (scenario C)	£5,596	0.319	£17,529
Health state costs scenarios			
Equalisation of costs between arms	£10,077	0.319	£31,566
Equalisation of hospitalisation and CRHT costs	£8,220	0.319	£25,479

Scenario analysis on company base (without PAS discount)

Scenario	Incremental costs	Incremental QALYs	ICER (1:6 nurse ratio)
Company base case	£3,444	0.319	£10,790
Dose and frequency of dose variation			
84mg dose for all patients	£5,088	0.319	£15,939
Weekly maintenance dosing schedule for all patients	£6,166	0.319	£18,502
Alternative recurrence/loss of response data for OAD arm			
Using SUSTAIN-1 data	£2,716	0.354	£7,665
ERG scenario equalising to ESK-NS arm recurrence data (as in TA367 appraisal)	£6,786	0.161	£42,085
Subsequent treatment effectiveness			
ERG scenario with proportional decrease at each subsequent line (as suggested in TA367)	£5,679	0.222	£25,596

ERG comment

- The ERG amended the company base case to align with committee assumptions by:
  - Increased effect of subsequent treatments (modified STAR*D trial response and remission rates proportional decrease at each line of subsequent therapy)
  - Implementing fixed carer disutility as described in the ERG report
  - Treatment discontinuation as described in ERG report (no discontinuation other than lack of efficacy)
  - Applying nurse:patient ratios including 1:1 as most conservative scenario

ERG scenarios	ICER £/QALY Patient to nurse ratio 6:1	ICER £/QALY Patient to nurse ratio 1:1
Scenario 1: All changes above	£35,883	£40,900
Scenario 2: All changes excluding decrease in response and remission at each line of subsequent therapy	£21,879	£25,827
Scenario 3: All changes excluding treatment discontinuation scenario	£24,196	£28,207
Scenario 4: All changes excluding decrease in response and remission at each line of subsequent therapy and ERG treatment discontinuation scenario	£12,682	£15,839

Technical team cumulative scenario

Scenario	Incremental costs	Incremental QALYs	ICER (1:6 nursing)
Company base case + • Scenario C treatment discontinuation (70% of recovered patients decrease with 30% continuing beyond 2 years) • No carer utility decrement • Equalisation of medical costs between arms • Weekly dosing schedule in the maintenance phase	£15,728	0.249	£63,111

Comments about the decision problem

- CE suggests 3 forms of optimisation:
  - esketamine is only recommended for patients with TRD who have failed to respond to at least two conventional augmentation strategies or ECT (TA367 gives precedent for optimising to this population)
  - clear guidelines with regards to ongoing treatment
    - the patient must be showing demonstrable benefit for treatment to continue, with this regularly assessed
    - there should be a recommendation to at least pause treatment if there is a period of sustained remission
  - using a register to collect long term outcome from patients