NICE National Institute for Health and Care Excellence

Slides for projector

Esketamine for treatment resistant depression [ID1414]

ACM3 – Chair's presentation

Chair: Gary McVeigh

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

Company: Janssen

11th February 2021

Key issues

Treatment population

- Which population would be expected to take esketamine in clinical practice?
- What is the clinical evidence for the 3+ prior treatment population?

Model output and long-term outcomes

- What are the long-term outcomes for patients with TRD?
- What is the expected efficacy of subsequent treatments?

Non-drug costs – healthcare resource use

- What is the most appropriate source of non-drug costs?

Costs of implementation

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

Appraisal history

ACD2 recommendation:
Esketamine nasal spray 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
Treatment pathway and positioning	Esketamine is likely to be used later in the treatment pathway because it has a high treatment burden – consulted on the positioning of esketamine after augmentation therapy	3.4
Comparator evidence	Indirect comparisons with augmentation are highly uncertain because of heterogeneity of study design – comparison with trial results (oral antidepressant with placebo) is acceptable	3.5
MADRS inconsistency	Uncertainty caused by using different MADRS scores for relapse and defining the MDE health state	3.8
TRANSFORM-2 trial duration	Caution in interpreting trial data from a 4-week duration, particularly as response/remission are binary and small absolute differences between arms	3.9
SUSTAIN-1 withdrawal study design	Withdrawal study design introduces bias in favour of esketamine because it selects patients with a stable response or stable remission – only ESK-NS arm used in modelling	3.11
Generalisability of the results	Acute suicidality, psychiatric comorbidities, alcohol abuse and ECT use in the current episode excluded from the trial	3.14
Safety	Esketamine has potential risks associated with its use – risk management in the SPC is appropriate	3.16

Summary committee conclusions – economic modelling

Topic	Conclusion	ACD
Disease course	Economic model does not reflect the course of the disease and or the episodic nature of the condition	3.17
Subsequent treatments	ERG proportional reduction in response at each line is more appropriate than the company's approach with low response and remission rates	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	3.19
Carer disutility	Lack of direct evidence of carer benefit with esketamine and potential for increased carer burden mean a range of values was considered appropriate	3.24
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 (hospitalisations and crisis resolution teams) – it is most appropriate to equalise costs between arms to avoid these problems	3.28
Cost and timeframe of implementation in the NHS	Some costs of adoption were not considered in the model and it could take longer than normal to implement in NHS clinical practise	3.30 + 3.31

ACD2 consultation

Consultation comments

- Company (Janssen)
  - Provide consultation comment responses and a revised base case
  - Provide a new scenario for 3+ prior treatments population
  - Updated patient access scheme
  - Outline ongoing data collection
- Professional Groups
  - Royal College of Psychiatrists (RCPsy)
  - British Association for Psychopharmacology (BAP)
- Web comments
  - Multiple joint responses from psychiatrists and psychologists
  - Patient and clinician responses

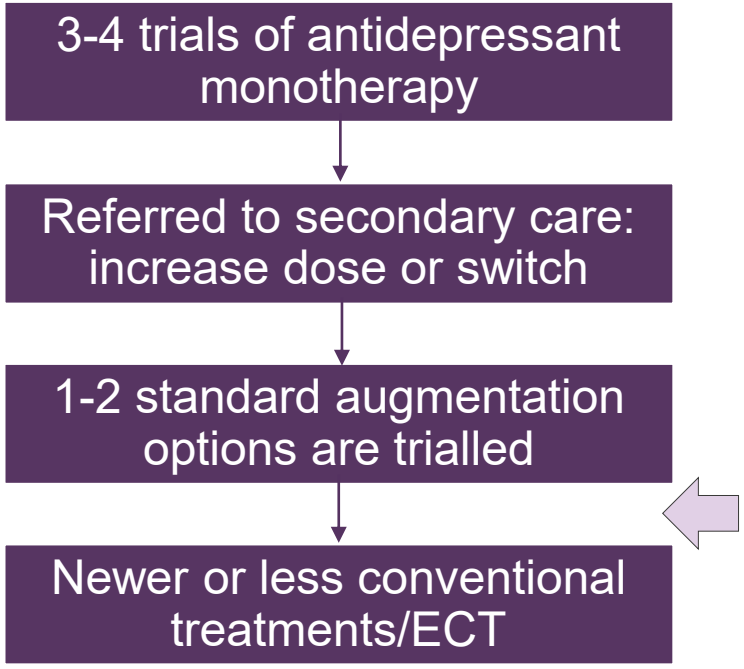
Expected patient population

ACD2 committee conclusions:

- *Because of treatment burden and safety concerns… esketamine [would be] used later in the treatment pathway…after 1 or 2 augmentation therapies have been trialled*

Janssen:

- Maintain full TRD population (defined as 2+ prior treatments) in revised base case
- Provide a scenario analysis with 3+ prior treatments



Consultation comments:

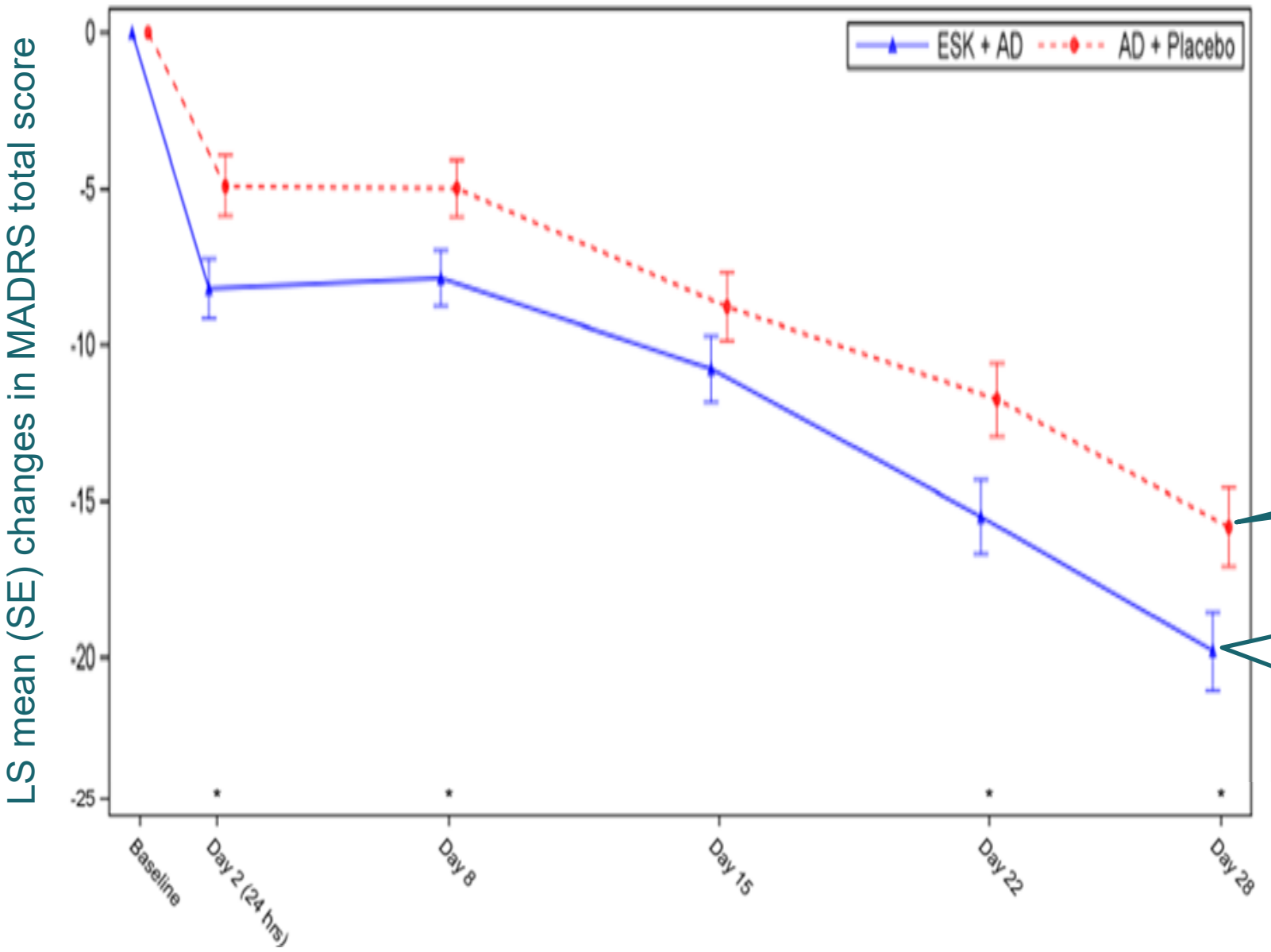
- RCPsy: confirm this is the expected initial placement of esketamine nasal spray but because of expense, novelty and association with a drug of abuse as well as treatment burden – with potential to be used earlier in the treatment pathway when costs come down and there is further support for patients.
- Consultee: it takes a substantial amount of time (measured in years rather than months) for a patient to trial (at a therapeutic dose) the currently available different types of oral anti-depressants before ECT might be considered

TRANSFORM-2 outcomes for 3+ prior treatments

- Company provides subgroup analyses split by number of prior treatments in the current MDE
- ERG: only a very small difference between arms for those who had not responded to 2 prior treatments, most overall benefit comes from benefit in the 3+ prior treatment subgroup. Most of the increase treatment effect for the 3+ subgroup was due to a decrease in the per arm values for OAD

	ESK-NS + OAD		OAD + PBO-NS		Difference in LS Mean CFB
	N	LS Mean CFB [95%CI],	N	LS Mean CFB [95%CI],	Estimate, p-value
All patients	101	**-19.8** [-22.3, -17.3],	100	**-15.8** [-18.3,-13.3],	**-4.0**, 0.0199
Non-response to 2 prior treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response at least 3 prior treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TRANSFORM-2 – full 2+ prior treatment population



52% response
31% remission

69% response
53% remission

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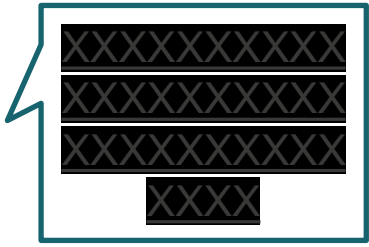
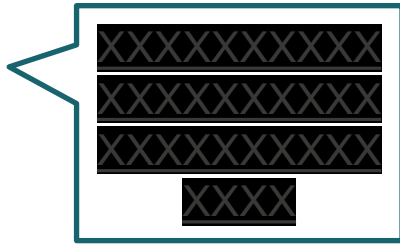
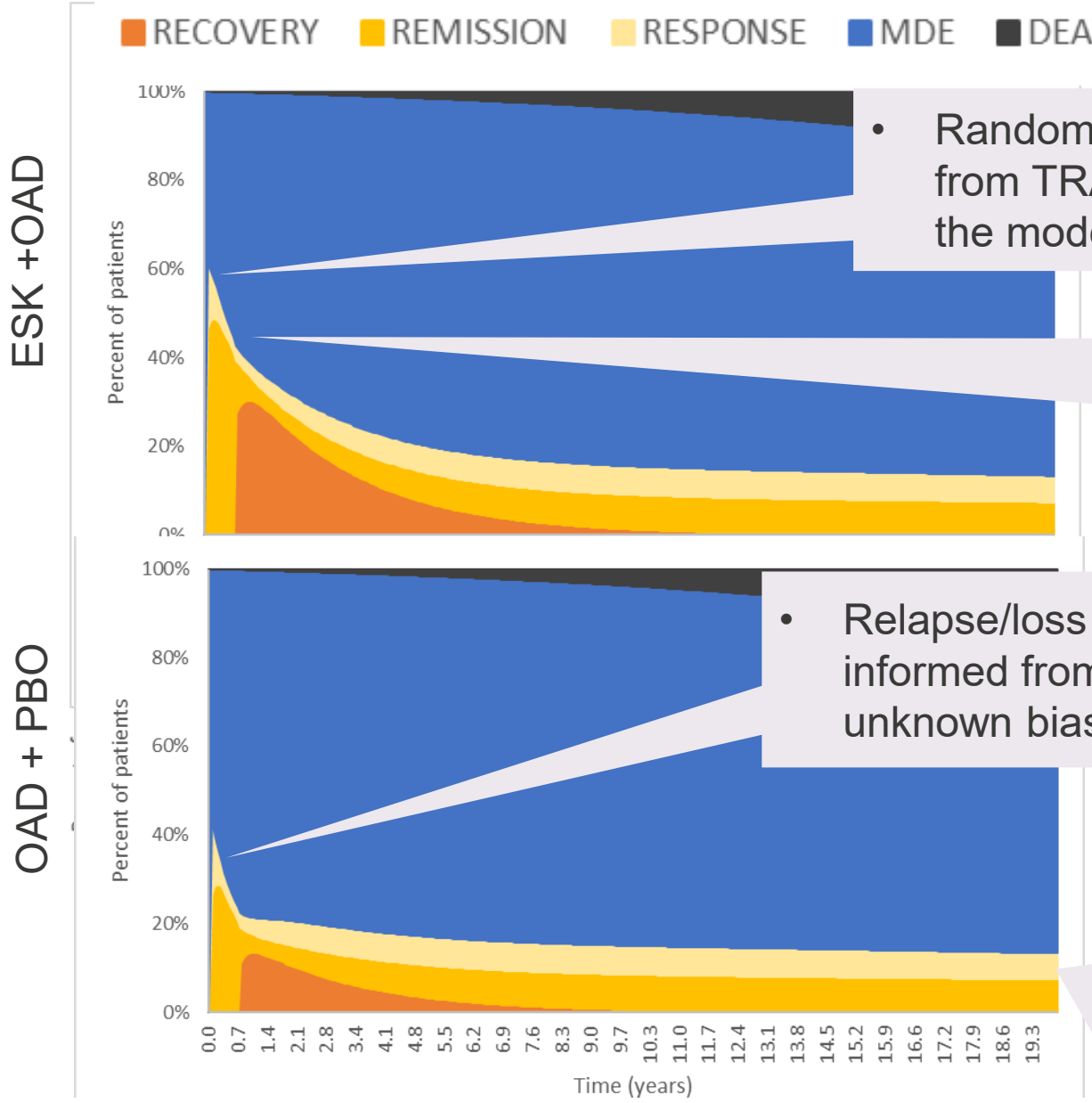
TRANSFORM-2 - 3+ lines of prior treatment subgroup

[redacted]





ACD2 Model structure issues recap



- Randomised comparative data is 4-week data from TRANSFORM-2 which is a key driver on the modelled differences between arms
- Relapse/loss of response data after 4 weeks informed from SUSTAIN-1 for esketamine arm – selection bias may underestimate relapse rate
- Relapse/loss of response data after 4 weeks informed from STAR-D data for control arm – unknown bias in different population and trial design
- Both arms have low long-term chance of remission and no long term recovery caused by modelled BSC state and low subsequent treatment efficacy – committee considered this implausible

Long-term outcomes – company approach

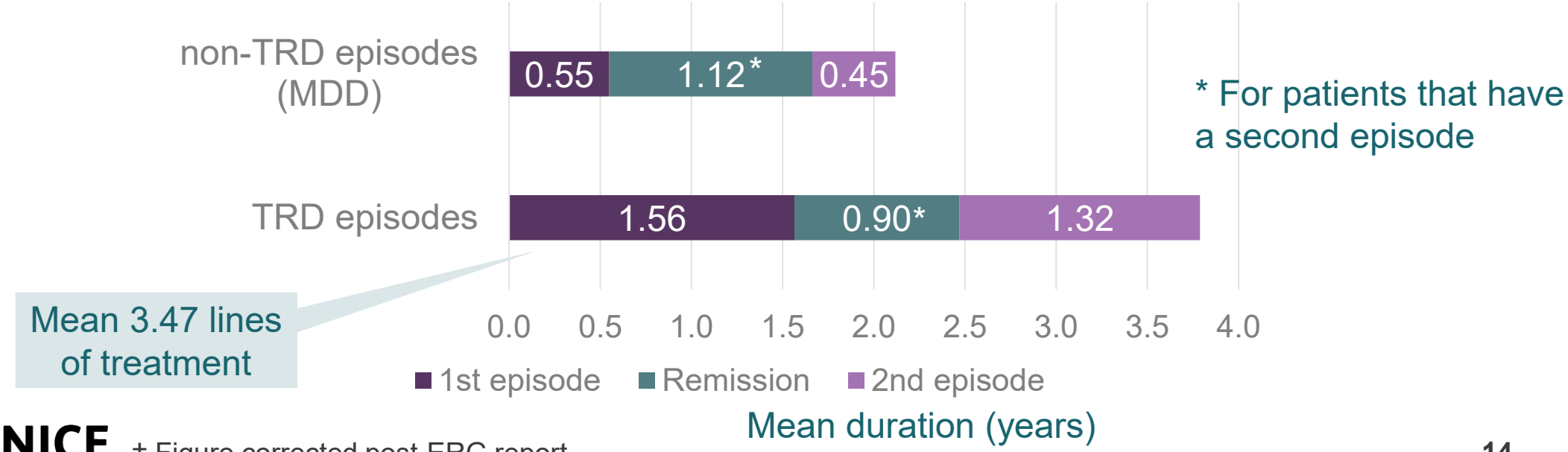
Janssen:

- Performed a targeted literature review of studies with longer-term outcomes
- Consider the results support long-term recovery/remission rates in the model

Study	Outcome time point	Remission	Response	Study design
STAR*D	1 year	5%	Not reported	Large prospective observational; population simulates USA practice
Dunner et al, 2006	2 years	8%	11%	Prospective observational; population substantial Tx resistance
Fonagy et al, 2015	3.5 years	24% (complete and partial)	Not reported	RCT versus long-term psychotherapy; Population mean 3.8 year MDE
Aaronson et al, 2017	5 years	26% cumulative	41% cumulative	Longitudinal TRD registry for VNS; population mean 7.3 prior treatments
Kumar et al, 2019	5 years	Not reported	40% cumulative	Expanded registry data from Aaronson; population mean 8 prior treatments
Fekadu et al, 2011	3 years	36% (time spent)	39% subthreshold (time spent)	Prospective cohort; reported as time spent in each state; UK inpatient population (mean 18.9 years living with depression, 3 year index episode)
Vergunst et al, 2013	1-7 years	40% (time spent)	21% residual symptoms (time spent)	Longitudinal follow up of Fekadu study

Long-term outcomes – ERG approach

- Wu et al (2019) characterises episode-level of treatment journey with MDD and TRD
- Retrospective cohort study from insurance databases in USA – patients with MDD diagnosis and prescribed OAD
- n=48,440 1st episodes [of which 3,317 TRD], n=1739 2nd episodes [of which 93 TRD]
- ERG considers it cannot be assumed that everyone with a first episode of TRD will have a second and that the second episode will be TRD – even if every patient continued to have alternating TRD/non-TRD episodes through a lifetime horizon, this would equate to 47%‡ of life spent in the MDE health state compared to 76% in the company model
- Limitations include episode duration determined by OAD use and USA-based study



‡ Figure corrected post-ERG report

Subsequent treatments

ERG:

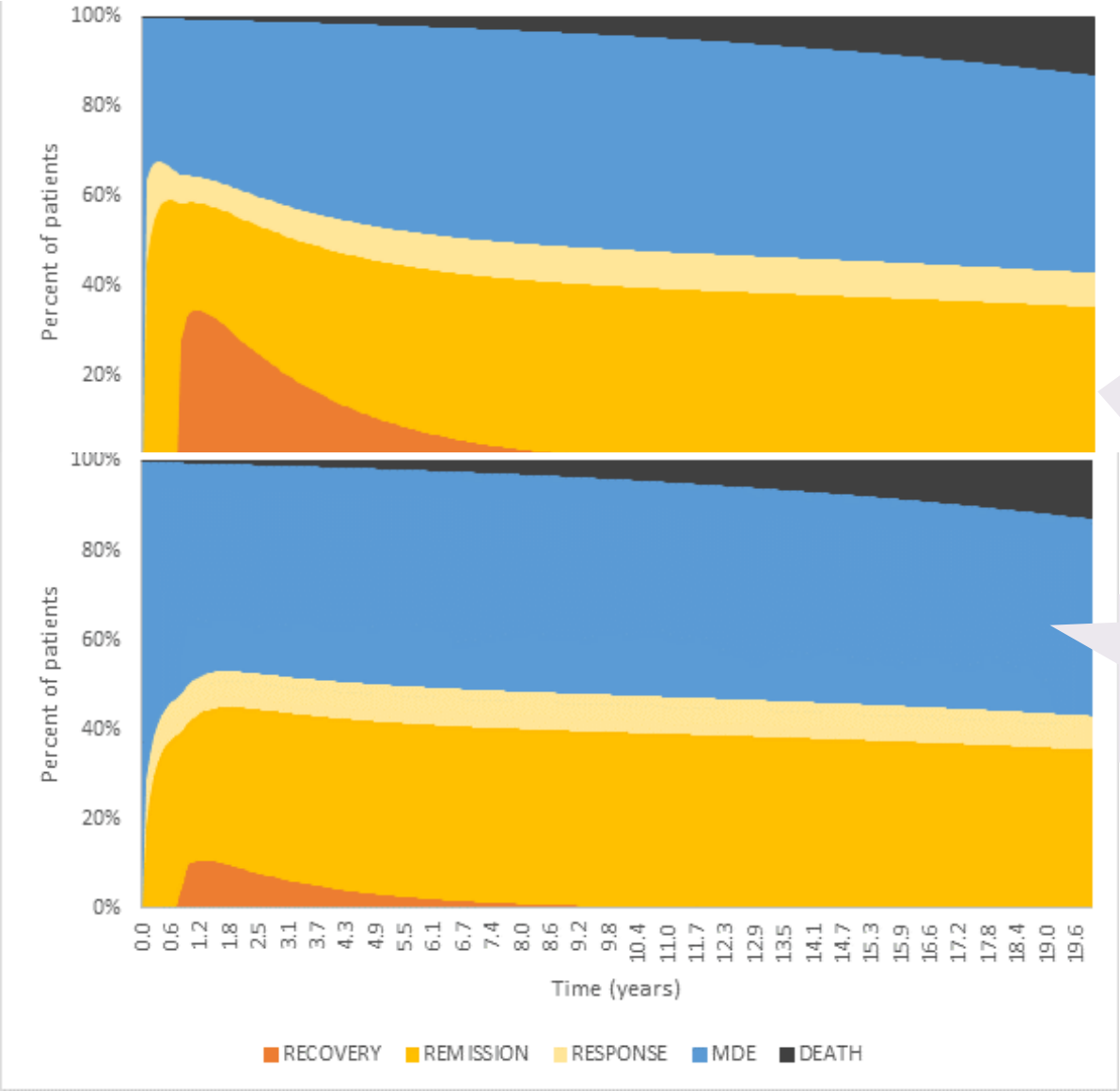
- In the company revised base case there are implausible assumptions about relapse caused by a fault present by applying a factored adjustment (calculated for remission/response) to the chance of relapse and loss of response
- 99% of responders relapse within each 4-week cycle
- ERG propose an additional scenario using a cap (as in original CS) to avoid this implausible scenario – these rates are still higher than the original CS

	Revised ERG method, as implemented by company	Original CS	ERG cap
Loss of response			
TRD Line 2	23.1%	22.8%	22.8%
TRD Line 3	23.7%	22.8%	
TRD Line 4	24.5%	22.8%	
BSC/ Non-Specific Treatment Mix	25.2%	10.4%	
Relapse			
TRD Line 2	17.1%	12.8%	12.8%
TRD Line 3	32.3%	12.8%	
TRD Line 4	61.0%	12.8%	
BSC/ Non-Specific Treatment Mix	99.0%	4.2%	

ERG scenario with capped response (full population)

ESK +OAD

OAD + PBO



- Key driver of differences between arms becomes the recovery rate which is largely set by initial response at 4-weeks from TRANSFORM-2 and relapse from SUSTAIN-1 for esketamine only

- Approximately 48% of lifetime spent in the MDE health state

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Non-drug costs - overview

ACD2 committee conclusions:

- *Considerable uncertainty whether esketamine would reduce events such as hospitalisation*
- *Appropriate to equalise healthcare resource use across arms due to the importance of the MDE health state*

- ERG proposes an alternative costing study – used in CG90 and TA367

	28-day cost of remission state	28-day cost of non-remission/ MDE
Company TRD characterisation study	£164	£980
Byford et al study for severe patients	£63	£87

ERG:

- It could be argued TRD is more costly than severe, but it does seem questionable that the difference would be so large, 9% of costs in the MDE/non-remission state, 11-fold difference

Non-drug costs – company TRD costing study

- Retrospective chart review study design
- 30 psychiatrists and 9 GPs were asked to provide HRU data from medical records of the last 10 TRD patients seen before a given index date

28-day non-drug costs by health state	Recovery state	Remission state	MDE state
Primary care visits	£3	£7	£11
Specialist psychiatric visits	£30	£31	£53
Crisis resolution home teams	£18	£18	£326
Occupational therapy	£0	£30	£72
Days with any hospitalisation	£12	£42	£380
All other costs including psychotherapy, ECT	£21	£36	£138
Total costs	**£84**	**£164**	**£980**

Non-drug costs – ERG proposed alternative from Byford et al

- Longitudinal study using data from General Practice Research database (450 primary care GP practices in the UK) – 88,935 individuals in the database had depression
- Treatment resistance is not explicitly studied, but the design compared those who remitted within 1 year (stopped antidepressant treatment) to those who had at least 2 treatments and did not remit within 1 year
- ERG also suggested using the severe subgroup only which is defined by read/OXMIS codes as categorised in Martinez et al. (2005) study (e.g., “Recurrent major depressive episodes, severe, no psychosis/psychosis”, “chronic agitated depression”, “endogenous depression”)

28-day health resource use for severe subgroup (inflated using NHS inflation index)	Remitters	Non-remitters
GP visits	£31	£44
Psychological therapies	£0.01	£0.03
Secondary care contacts	£6	£8
Hospitalisations	£16	£14
Accident and emergency	£1	£1
Other medications	£10	£22
Total costs	**£63**	**£87**

Implementation costs

ACD2 committee conclusions:

- *Significant investment needed to use esketamine in the NHS - these costs could be difficult to quantify.*

Janssen:

- Conducted a survey of 16 mental health trusts of key costs identified in ACD:
  - **Conversion of ECT suites**: majority of MHTs are planning on utilising existing clinics or ECT suites. One is already renewing infrastructure to include TMS
  - **Costs of medical equipment**: MHTs see no additional cost of introducing an ESK-NS service unless expanded to community setting
  - **Controlled nature of the drug**: provide a scenario with costs of cabinets added to the ICER calculation (£1.62 per patient)

Consultation comments:

- RCPsy: only physical infrastructure likely to be required in an ECT suite is a Controlled Drug cabinet. In other settings it may also be necessary to purchase suitable comfortable chairs.
- RCPsy: Transporting drugs are part of routine hospital transport systems, disposal uses existing transport arrangements and is low cost

Additional unresolved issues

Issue	Notes	Consequence
Psychological therapies	Not considered in the analysis	Costs and benefits not captured - uncertain effect on results
Inconsistent transitions with MADRS	Relapse threshold was a MADRS score of 22 for SUSTAIN-1, 28 minimum enrolment, MDE utility measured at baseline ~37	Some utility transitions may be inflated – relapse rate may be overestimated in SUSTAIN-1
Generalisability	Exclusion criteria were suicidal ideation in the last 6 months, psychiatric comorbidities, addiction issues	Uncertain generalisability to NHS clinical practice, particularly for a more severe/treatment resistant population (3+ lines)
Potential effect of withdrawal	Potential for confounding measurement of the MADRS scale from withdrawal effects of esketamine	Uncertain effect of potential confounding
Safety	FDA has a safety signal for suicidal ideation (persists when compared with venlafaxine)	Precautions for use and ongoing data collection by the regulatory agencies

Additional unresolved issues

Issue	Notes	Consequence
Time horizon	Original time horizon was 5 years, this was extended to 20 years to capture all changes in the model.	Long-term outcomes are highly uncertain and a key driver of the cost-effectiveness estimate
Stopping rule	Committee agreed some people may stop treatment early if they show long term remission, but some may continue on treatment in the long-term	Potential longer-term use and greater costs for a more severe/treatment resistant population
Costs of esketamine	Dose and dosing schedule are greater for people who respond but do not remit to esketamine	Potential for greater costs for a more severe/treatment resistant population
Carer disutility	Lack of evidence for a direct benefit on carers, committee agreed a carer disutility would be appropriate	A range of ICERs are considered to represent this uncertainty

Ongoing data collection

The company to **collect additional evidence** that addresses uncertainties raised by the Committee and **will commit to a NICE re-review by 2024**.

- **ECHO study -** post launch RWE study - a pan-European study including 100+ UK patients if recommended by NICE. This study will consider the effectiveness and safety of ESK-NS in UK RWE practice and run until 2024.
- **TRD3008 (SUSTAIN-3)** - Phase 3 study which will provide long term safety data. Planned study dates: June 2016-Dec 2022.
- **TRD3013 (ESCAPE-TRD)** - Phase 3b study will provide comparative clinical data versus OAD plus augmentation with quetiapine XR therapy – primary outcome is percentage of participants with remission at 8 weeks. Planned study dates: Aug 2020-Nov 2022.

Updated cost-effectiveness modelling

Company revised base case & scenarios

Company scenario – full TRD population	ICER range (with and without carer disutility)
1. Company revised base case: ○ Company costing study as source of HRU ○ No cap on subsequent treatment relapse ○ Include costs of storage cabinets	[redacted]
Company scenarios – 3+ prior treatment population	
2. Company revised base case using only data from patients with 3+ prior lines of treatment from TRANSFORM 2 and 3	[redacted]
3. Scenario 2 with sensitivity analysis ○ Additional scenario with alternative MDE state utility value ○ 95% CI lower bound of company costing study	[redacted]

ERG revised scenarios

ERG scenarios – full TRD population	ICER range (with and without carer disutility)
1. Company revised base case with subsequent treatment relapse/ loss of response cap	[redacted]
2. Scenario 1 with alternative HRU costs from Byford costing study	[redacted]
ERG scenarios – 3+ prior treatment population	
3. Company optimised scenario with subsequent treatment relapse/loss of response cap	[redacted]
4. Scenario 3 with equal HRU costs between arms (as in ACD2)	[redacted]
5. Scenario 3 with alternative HRU costs from Byford costing study	[redacted]