Zuranolone for treating postnatal depression [ID6431]

For projector – contains no confidential information

Technology appraisal committee B [6 August 2025]

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Zuranolone for treating postnatal depression

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling
- ❑ Other considerations
- ❑ Cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on postnatal depression (PND)

PND can be a debilitating condition that leads to severe short- and long-term consequences for affected individuals, their children, partners and their families

Causes

- PND is a depressive episode starting during pregnancy or within first 4 weeks and up to 12 months after childbirth
- Exact PND pathophysiology not fully understood, but thought to be driven by genetic, metabolic, endocrine, environmental, and neurobiological factors → distinct disease from MDD
- Risk factors: age <25 years, living separately to partner, physical or mental health problems

Epidemiology

- One of the most common complications of pregnancy and childbirth
- 10-15% of people in England may have had PND in 2024, with ~20-25% of these being moderate to severe PND

Diagnosis and classification

Severity classification: mild, moderate or severe

- In research: MADRS and HAMD tools commonly used to determine disease severity
- Clinical practice: clinical judgement of symptom number and intensity, and degree of functional disability

Symptoms

- May have multiple symptoms e.g., persistent sadness, depressed mood, suicidal or infanticidal ideation → can cause significant functional impairment e.g., difficulty sleeping, decreased energy, and feelings of shame / guilt
- Suicide is leading cause of death 1st year postnatal → people with PND 3x more likely to have suicidal ideation

Prognosis

- ALSPAC study: people with PND symptoms in 1st year after childbirth, especially those with persistent symptoms, are at increased risk of prolonged depression until at least 11 years after childbirth

Abbreviations: PND, postnatal depression; MDD, major depressive disorder; HAMD-17: 17-item Hamilton Rating Scale for Depression; MADRS: Montgomery–Åsberg Depression Rating Scale ALSPAC, Avon longitudinal study of parents and children

Zuranolone (Zurzuvae, Biogen)

Marketing authorisation	• Proposed indication: treatment of adults with [redacted] PND, following childbirth • Granted ILAP by MHRA; licensed via international recognition procedure (FDA) • MHRA regulatory approval: Not yet granted • Understood that only people who had given birth would be eligible; not partners
Mechanism of action	• Zuranolone is a synthetic neuroactive steroid and a selective positive allosteric modulator of synaptic and extrasynaptic GABAA receptors, designed to selectively retain the pharmacological properties of allopregnanolone on GABAA receptors and to have improved oral bioavailability compared with allopregnanolone.
Administration	• 2x25 mg tablets taken once daily, with fat-containing food in the evening or at bedtime • Single course of treatment, 14 days • Dose may be reduced to 40 mg (two 20 mg capsules) if 50 mg dose not tolerated • In special populations, recommended dose of zuranolone is 30 mg • Expected to be initially prescribed by psychiatrists within perinatal mental health services (secondary care)
Price	• Proposed list price: [redacted] • There is a confidential discount available for zuranolone

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; ILAP, Innovative Licensing and Access Pathway; PND, postnatal depression

Clinical perspectives (1)

*Clinical expert submissions received after slides finalised, please see committee papers for details

Submissions from College of Mental Health Pharmacy, NHSE and 2 clinical experts*

Current treatment option:

- Can need several weeks of daily medication and frequent follow-ups to monitor effectiveness and side effects
- ADTs commonly prescribed but not licensed for PND - relies on clinical judgment
- Traditional ADT target neurotransmitters in brain and so are not specific to PND

Current treatments can take weeks to alleviate symptoms leaving women with debilitating symptoms after birth

Opens door to perinatal mental health conditions being recognised as distinct to those at other stages of women's life

Zuranolone benefits:

- Short, fast-acting treatment course with rapid onset (relief within days)
- Licensed treatment specifically designed for PND (targets hormone changes)
- Streamline treatment decisions with evidence-based PND option

- May improve: adherence, recovery rates, maternal QoL, mother-infant bonding, long-term mother/child outcomes
- May reduce: emotional/psychological burden, reliance on SSRIs, burden of long-term therapy, length of stay within mother & baby units, need for hospital admissions, reliance on off-license prescribing
- May prevent: suicides and long-term consequences of untreated depression e.g., chronic mental health issues

Abbreviations: PND, postnatal depression; SSRIs, selective serotonin reuptake inhibitors; CBT, cognitive-behavioural therapy; ADT, antidepressant therapy; QoL, quality of life

Clinical perspectives (2)

Submissions from College of Mental Health Pharmacy and NHSE

Number of unknowns remain e.g., safety of repeated treatment courses, risks of dependence, impact of sedation on mother and baby

Zuranolone considerations:

Safety in breastfeeding mothers not established

- Extra challenge for mothers wanting to breastfeed – breastfeeding benefit for mother and baby
- Practical impact: need alternative feeding option whilst on zuranolone

Side effects e.g., sedation, dizziness, drowsiness - may impact condition management and QoL

- Challenge for new mothers who need to stay alert for caregiving and infant care
- WHO recommend not co-sleeping due to sedative effects - safety concerns for mother and baby

Zuranolone is more appropriate for people with severe PND. It is less appropriate for people with mild to moderate PND

Prescribing:

Prescribing and initial management within Specialist PMHT in secondary care

- Primary care may support post-treatment monitoring
- Need for specialist oversight to ensure appropriate assessment, diagnosis, risk management, and follow-up, especially given its sedative effects

Due to sedating effects, potentially initially only offer within MBU setting where it could be closely monitored

- May offer more widely within community PMH teams once more data available, and it can be done safely
- Important that zuranolone doesn't result in a sizeable increase in referrals to MBU's for this purpose

Abbreviations: QoL, quality of life; WHO, world health organisation; PMHT, Perinatal Mental Health Team; PND, postnatal depression; MBU, mother and baby unit

Patient perspectives

- Patient expert submission to be given at the committee meeting

Treatment pathway

= Established clinical management

Currently no pharmacological treatments with marketing approval specifically for PND in the UK

NICE guideline CG192: clinical management of postnatal mental health

People with **mild to moderate** depression in the postnatal period

- Facilitated self-help: CBT, BA, problem-solving materials, psychoeducation materials
- ID6431: Zuranolone + ECM*

People with **moderate or severe** depression in the postnatal period

- High-intensity psychological intervention
- Pharmacological treatment: TCA, SSRI, SNRI
- Or combination of both
- ID6431: Zuranolone + ECM*

People with history of severe mental health problems who presents with **mild** depression in the postnatal period

- Pharmacological treatments: TCA. SSRI, SNRI
- ID6431: Zuranolone + ECM*

***Company:** Zuranolone expected to fit into existing clinical pathway as a treatment option to be **used alone or as an adjunct** to therapeutic alternatives used as part of ECM

Examples of pharmacological treatments available within the NHS

- **TCAs:** amitriptyline, clomipramine, dosulepin, imipramine, lofepramine, nortriptyline
- **SSRIs:** fluoxetine, citalopram, escitalopram, paroxetine, sertraline
- **SNRIs:** duloxetine, venlafaxine

What are the most appropriate comparators for the population expected to receive zuranolone? Is PND a risk factor for longer term major depressive disorder (MDD)? Does zuranolone change the risk of subsequent MDD?

Abbreviations: BA: Behavioural Activation; CBT: Cognitive Behavioural Therapy; PND: Postnatal Depression; SNRI: Selective Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic Antidepressant; ECM, established clinical management

Equality considerations raised

People from ethnic minorities, younger people, and those in rural communities may be more likely to have restricted access to PMH services

Women's Health

- Women's health historically under-resourced - services for conditions which primarily affect women are perceived to be of lower priority
- Younger people may have heightened fear of judgment = reluctant to seek help making them vulnerable to PND

Race

- Certain communities encounter additional obstacles in obtaining quality care:
  - People from ethnic minority backgrounds in UK at greater risk of developing PND
  - During perinatal period, people from ethnic minorities had significantly lower access to community mental health services and had higher percentages of involuntary admissions compared to White British people
  - Black people are least likely to initiate treatment and receive follow-up for postnatal mental illness

Treatment quality and access

- Perinatal Care Pathways are complex and diagnosing people with PND can be challenging
- Unequal access to specialist PMH services across England e.g., people impacted by socio-economic inequalities or who live in remote areas may have limited access to full services offered by NHSE
- Access to zuranolone in secondary care only may exacerbate health equality issues for people with a lack of access to PMH secondary care

How could a recommendation for zuranolone impact health inequalities?

Abbreviations: PND, postnatal depression; PMH, perinatal mental health

Key issues

Issue	ICER impact
Population	Small
Clinical trial generalisability: ECM definition and trial population	Unknown
Treatment effect duration	Large
Concomitant antidepressant therapy use	Unknown
Utilities	Large
Uncaptured costs and benefits	Unknown

Abbreviations: ICER, incremental cost-effectiveness ratio; ECM, established clinical management

Zuranolone for treating postnatal depression

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Key clinical trials: design and outcomes

	SKYLARK (n=200) – key trial	ROBIN (n=153)
Design	Phase 3, randomised, double-blind, placebo-controlled, outpatient trial	
Population	• Women aged 18-45 years with MDE that began during 3rd trimester or ≤4 weeks postnatal • PND diagnosis (baseline HAMD-17 total score ≥26, classified as severe PND) • Ceased lactation or agreed to not breastfeed infant from Day 1 until 7 days after last dose	
	≤12 months postnatal	≤6 months postnatal
Intervention	Zuranolone (**50mg - licensed dose**)	Zuranolone (30mg – not licensed dose)
Comparator(s)	Placebo	
Duration	14-day treatment course, follow-up through day 45 (4-week follow-up)	
Primary outcome	Change From Baseline in 17-item HAM-D Total Score at Day 15	
Key secondary outcomes	Depressive symptoms, depression severity, anxiety, sleep quality, AE, HRQoL (SF-36; ROBIN trial only)	
Concomitant treatments	• ADT if people on stable dose for ≥30 days prior • Psychotherapy	Psychotropic medication if on stable dose for ≥30 days prior
Locations	78 sites in US, Spain and UK (n=5)	33 sites in US. No UK.
Used in model?	Yes (EPDS and AE data)	Yes (HRQoL data)
Pre-specified subgroup	Race, age, origin country, ADT use at treatment start, baseline BMI, onset of PND, PND family history	
	Baseline HAMD-17 total score category, depression with elevated anxiety by Baseline HAM-A total score	-
Post-hoc subgroup	Severity of PND, MDD history	-

Abbreviations: HAM-D/A, Hamilton Rating Scale for Depression/Anxiety; MDE/D, major depressive episode/disorder; AE, adverse events; SF-36, Short Form Health Survey; HRQoL, Health-related quality of life; PND, postnatal depression; EPDS, Edinburgh Postnatal Depression Scale; AE, adverse events

SKYLARK clinical trial results

Zuranolone significantly improves depressive symptoms by day 15 compared with placebo

LSM change from baseline in HAMD-17 score (primary outcome)

Study visit	Zuranolone N=98		Placebo N=97		LSM difference			p-value
	Mean	SE	Mean	SE	Mean	95% CI lower	95% CI upper	
Baseline	28.6	2.49	28.8	2.34	-	-	-	-
Day 3*	-9.5	0.70	-6.1	0.71	-3.4	-5.4	-1.4	0.001
Day 15*	**-15.6**	**0.82**	**-11.6**	**0.82**	**-4.0**	**-6.3**	**-1.7**	**0.001**
Day 28*	-16.3	0.88	-13.4	0.88	-2.9	-5.4	-0.5	0.020
Day 45*	-17.9	0.90	-14.4	0.90	-3.5	-6.0	-1.0	0.007

*Primary and key secondary endpoints adjusted for multiplicity. Other endpoints interpreted with nominal p-values

LSM change from baseline in EPDS total score (data informing effectiveness in model)

Study visit	Zuranolone N=98		Placebo N=97		LSM difference			Nominal p-value
	Mean	SE	Mean	SE	Mean	95% CI lower	95% CI upper	
Day 3	-3.8	0.49	-2.3	0.49	-1.5	-2.9	-0.1	0.032
Day 15	-10.3	0.66	-8.4	0.66	-2.0	-3.8	-0.1	0.038
Day 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 45	-12.2	0.76	-9.8	0.76	-2.4	-4.5	-0.3	0.028

What is a clinically meaningful change in HAMD-17 and EPDS scores?

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Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; LSM, least square mean; CI, confidence interval; HAMD-17: 17-item Hamilton Rating Scale for Depression; HRQoL, health-related quality of life

Post-hoc subgroup results: PND severity
Decision problem
Trial severity classification

Key Issue: Population (1)

Zuranolone's clinical evidence is for a population narrower than the scope population

Background

- **NICE scope and company decision problem:** adults with postnatal depression
- **EAG:** Trials do not align with decision problem → clinical evidence most applicable to people with severe PND
  - ➢ Clinical trial eligibility: people with HAMD-17 score ≥26 at baseline (classified as severe population)

Company

- SKYLARK trial included:
  - people with severe PND (when classified by HAMD-17 score – trial eligibility)
  - people with moderate and severe PND (when classified by MADRS score – post-hoc subgroup)
    - ➢ MADRS focuses more on psychological symptoms, less on somatic or anxiety-related symptoms
- Clinical evidence provides efficacy of zuranolone in people with moderate to severe PND
  - Post-hoc subgroup analysis showed no difference in treatment effect sizes between severity level
- Trials did not recruit mild PND patients - difficult to show effect in mildly ill people
  - Aware of data limitations but unique mechanism of action of zuranolone supports its efficacy in all PND patients, especially considering high disease burden and lack of therapies licensed specifically for PND
- Expected to be initially prescribed by perinatal psychiatrists in community perinatal mental health services and so most likely be used for the treatment of people with moderate to severe PND

Abbreviations: PND, postnatal depression; HAMD-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale

Key Issue: Population (2)

Efficacy of zuranolone in people with mild or moderate PND cannot be determined

EAG comments

Clinical advisors:

- Zuranolone likely used in secondary care NHS perinatal services → often people with severe PND, complex PND or those with co-occurring psychiatric conditions
- No evidence supporting same efficacy in all people with PND because of its unique mechanism of action
- Severity scales/tools not commonly used in UK clinical practice, use clinical judgement of symptom severity

Model

- Model inputs from mostly severe population – impact unknown if model were based on mild/moderate PND
  - No severity subgroup analysis provided by company due to small numbers and lack of long-term data
  - EAG did scenario analyses by baseline EPDS scores (moderate or severe) - small ICER impact
    - ➢ Does not include interaction between severity and treatment effect
- **Base case:** restrict to **severe PND population subgroup** to match expected NHS use and trial population

Other considerations

- College of Mental Health Pharmacy: zuranolone is more appropriate for people with severe PND and less appropriate for people with mild to moderate PND
- CG192: specialist referral is recommended for severe or treatment-resistant cases

Who is most likely to be treated with zuranolone in NHS practice? How is moderate and severe PND defined in clinical practice? Would an optimised recommendation based on severity of PND be appropriate?

Abbreviations: PND, postnatal depression; EPDS, Edinburgh Postnatal Depression Scale; ICER, incremental cost-effectiveness ratio

Key Issue: Clinical trial generalisability (1)

Treatment pathway - ECM
Decision problem

Background

EAG: concerned about generalisability of SKYLARK trial results to NHS PND clinical practice

1. Population: trials excluded people with psychosis or had attempted/at risk of suicide with current PND episode
2. ECM definition: trials only included ADTs (15% baseline) and psychological therapies (N/A) - most decision problem ECM treatments excluded. People not permitted to change treatment during the trial

- Other likely trial generalisability issues: some exclusion criteria and visual monitoring of study drug adherence

Company

Population

- UK-specific information on demographics and other baseline characteristics of PND patients is limited
- Expect PND population to be similar to SKYLARK - most people 25-45 years and had 1st PND episode (>80%)

ECM definition

- SKYLARK concomitant treatments reflect expected clinical practice: ~85% had zuranolone as monotherapy
  - Zuranolone expected to be used with or without ECM, regardless of history of prior ADT use
  - PND population often untreated at time of symptom onset, for many PND is 1st mental health problem
- Zuranolone likely prescribed in secondary care - expect it will initiate shift towards faster referral to specialists
  - Secondary care referral not only related to response or lack of response to ADTs
    - Includes people with moderate-severe PND, complex PND with other psychiatric comorbidities, or non-responders / inadequate response to ADTs or other treatments

Abbreviations: ECM, established clinical management; ADT, antidepressant treatments; PND, postnatal depression; BSC, best supportive care; N/A, not available

Key Issue: Clinical trial generalisability (2)

ECM used in SKYLARK trial does not match ECM used in NHS clinical practice

EAG comments

Trial population

- Clinical advisors: people with psychosis or attempted suicide would be referred to and treated by perinatal mental health services - applicability to NHS population uncertain, but common exclusions in trials

ECM

- Concerned about comparability of ADT use (15%) and psychotherapies compared with UK population
  - Most people (>90%) considered for zuranolone (secondary care) in UK likely already taking ADTs for PND
  - Many would be considered non-responders to ADTs prescribed before secondary care referral (non-response not in trial inclusion criterion)
- SKYLARK compares zuranolone against placebo – no mention of ECM in both arms
  - Clinical advisors: most patients likely to continue existing therapies whilst taking zuranolone
    - New treatments not permitted during trial → may affect outcomes, particularly placebo arm
- SKYLARK prohibited some scope treatments - particularly concerning for placebo + ECM arm
  - May have led to worse outcomes in placebo arm because higher proportion may have needed augmentation during trial since they were not taking zuranolone (not allowed until end of trial)
- For trial results to reflect NHS practice, need to be no interaction between zuranolone effect and ECM
  - Unclear ICER impact - some indication of reduced effect with baseline ADT use (ICER may increase)

Are the SKYLARK trial results applicable to the NHS ECM and the target PND population?
Is concomitant treatment with ADT likely to be a treatment effect modifier?

Abbreviations: ADT, antidepressant treatments; PND, postnatal depression; ECM, established clinical management; ICER, incremental cost-effectiveness ratio

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Company model structure

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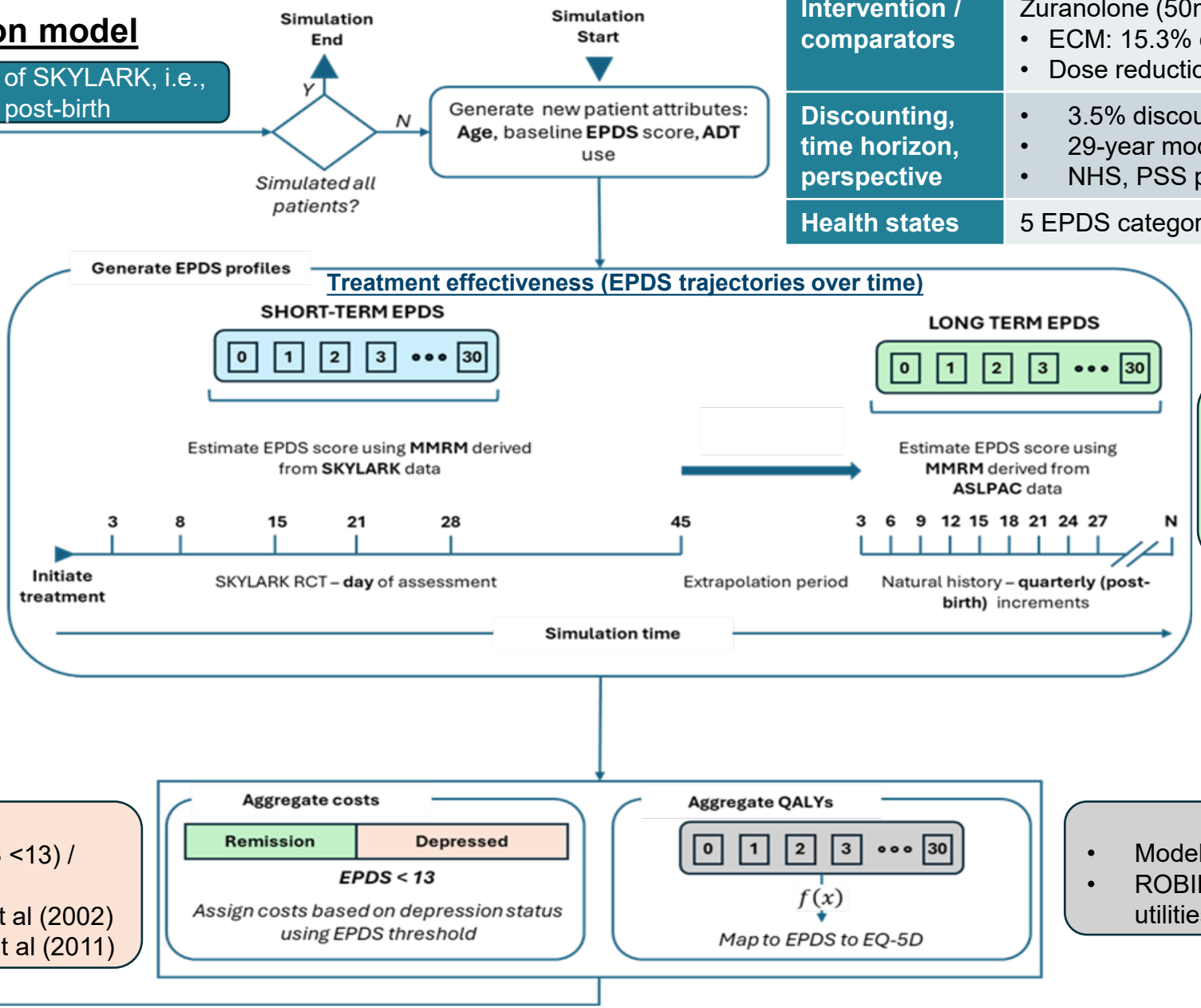
Population	Adults with PND (see population issue)
Intervention / comparators	Zuranolone (50mg) + ECM compared with ECM • ECM: 15.3% concomitant ADT (see issue) • Dose reductions ■ 40mg) based on SKYLARK
Discounting, time horizon, perspective	• 3.5% discount rate (costs and health outcomes) • 29-year model time horizon, • NHS, PSS perspective. See uncaptured benefits
Health states	5 EPDS categories: 0, 1-6, 7-13, 14-18, 19-30

Patient-level simulation model

Model starts at randomisation of SKYLARK, i.e., on average 5 months post-birth



Short-term EPDS
- Up to 3-months post-treatment start
- Based on 45-day follow-up data from SKYLARK

Long term EPDS
Up to 29 years post-birth (see treatment effect duration issue)
- Zuranolone+ECM: ALSPAC data
- ECM: apply treatment effect to zuranolone+ECM arm

Costs
Modelled by remission (EPDS <13) / non-remission (EPDS ≥ 13)
- First 18 months: Petrou et al (2002)
- After 18 months: Byford et al (2011)

Health outcomes
- Modelled by EPDS health states
- ROBIN SF-36 data mapped to SF-6D utilities (see utilities issue)

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Abbreviations: ALSPAC: Avon Longitudinal Study of Parents and Children; ECM: Established Clinical Management; EPDS: Edinburgh Postnatal Depression Scale; m: months; MMRM: Mixed Model for Repeated Measures; yrs: years

Key Issue: Treatment effect duration (1)

Background

- **Company base case**: assume difference in EPDS between treatment arms at 3 months post-treatment initiation is maintained for 29 years
- **EAG**: maintained treatment effect assumption implausible, especially since zuranolone given for 14 days and there is no data on treatment efficacy beyond 45 days – immature evidence informing long-term assumptions

Company

- ALSPAC - long-term natural history data, including [redacted] UK women treated for PND with ECM with EPDS ≥13
  - Only includes treatment with ECM – zuranolone treatment is only 14 days and the short-term impact will predict long-term outcomes, so long-term trends are assumed to be the same in both arms

Long-term EPDS trajectory

- *Zuranolone + ECM*: ALSPAC data used to predict long-term EPDS trajectory
- *ECM*: apply short-term fixed treatment effect to zuranolone + ECM EPDS predictions

Treatment waning scenarios (requested at clarification)

1. EPDS decreased to 12.99 ("remission") over 24 months in both arms for people who have not achieved remission after defined period e.g., 2-, 5- or 10-years (EPDS scores converge between arms)
   - Improved plausibility – assume NHS would intervene to help people achieve long-term remission

Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; ECM, established clinical management; ALSPAC, Avon Longitudinal Study of Parents and Children; PND, postnatal depression

Key Issue: Treatment effect duration (2)

Company and EAG treatment effect waning scenarios

[redacted]

[redacted]

Key Issue: Treatment effect duration (3)

EAG comments

- Zuranolone treatment benefit will eventually diminish to no difference from EPDS trajectory for person on ECM
- Concerns about substantial missing data and relevance of ALSPAC data (1991-1992, ECM may be different)

Reparameterisation of long-term EPDS - prefer long-term model to be used for ECM

- ALSPAC cohort not treated with zuranolone, so consider results from ALSPAC cohort to be most appropriate for ECM arm, rather than the zuranolone + ECM arm
- *ECM*: ALSPAC data used to predict long-term EPDS trajectory (without zuranolone)
- *Zuranolone + ECM*: apply zuranolone treatment effect to ECM arm EPDS score

Treatment effect waning scenarios

- Without waning, benefits of reduced EPDS for zuranolone continue throughout 29-year follow-up, but with waning, curves converge after a period to follow trajectories from long-term ALSPAC model

1. Waning starts 3 months post-treatment initiation and lines converge after a further a) 6 months, b) 1 year, c) 2 years, d) 5 years, e) 10 years
2. Waning starts 1-year post-treatment initiation and lasts for a) 6 months, **b) 1 year (EAG base case)**
    - Treatment benefit may continue beyond PND period (1 year after birth), but would not continue for implausibly long time → treatment effect extrapolation is highly uncertain

Should there be a waning of zuranolone treatment effect over time? If yes, when should waning start (3 months or 1-year post-treatment initiation) and how long should it last (6 months,1, 2, 5 or 10 years)?

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Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; EPDS, EPDS, Edinburgh Postnatal Depression Scale; ECM, established clinical management; PND, postnatal depression

Subgroup analysis: baseline ADT use

Key Issue: Modelled concomitant ADT use

Background

- **Company**: ECM = 15.3% concomitant ADT modelled in both arms, based on SKYLARK trial
- **EAG:** most people (>90%) would be on ADTs before zuranolone → proportion likely higher than modelled

Company

- No subgroup scenario analysis of only people receiving ADT due to small numbers having ADTs in trials
- Scenario: 100% baseline ADT use in short-term prediction model for EPDS scores – ICER slightly increased (no interactions between zuranolone and baseline ADT use included due to insufficient data)

EAG comments

- SKYLARK found treatment benefit only in people without baseline ADT use → acknowledge not powered
- Appreciate sample size from SKYLARK is too small to estimate a subgroup effect for ADT use
  - Reflects concerns with generalisability of results from SKYLARK trial (see trial generalisability issue)
- Additional scenario analyses: 50%, 80%, 90% baseline ADT use (**EAG base case uses 90% scenario**)
  - Only capture impact of ADT on EPDS, and not on interaction between ADT use and treatment effect
- Data to resolve issue: subgroup analyses for EPDS scores at 1.5 months follow-up by baseline ADT use
  - Results from SKYLARK and ROBIN could be pooled in a meta-analysis for baseline ADT use subgroup to increase power – not provided, so EAG unable to explore impact of this

What proportion of people should be taking ADTs at baseline in the model – 15%, 90%, other?

Abbreviations: SSRI, serotonin selective reuptake inhibitors; ADTs, antidepressant therapy; EPDS, Edinburgh Postnatal Depression Scale; PND, postnatal depression; ICER, incremental cost-effectiveness ratio

Key Issue: Utilities (1)

Modelled utilities

Background

- **Company**: ROBIN SF-36 data used to derive SF-6D utilities for 5 EPDS categories (0, 1-6, 7-13, 14-18, 19-30)
  - Utility estimates applied for entire time horizon (29 year), based on 45-day follow-up data
- **EAG**: Prefer to model separate utilities during PND (1-year post-treatment initiation) and post-PND period
  - NICE reference case recommends using utilities estimated from the EQ-5D tool

Company

- ROBIN trial population well matched to SKYLARK – good dataset to derive utilities
  - Unable to adjust by treatment group, baseline utility and EPDS score, or provide ADT subgroup results
- Scenario analysis: utilities mapped from PHQ-9 to EQ-5D, using Mukuria's 2025 mapping model
  - Only mapped ROBIN trial data to be consistent with source of base case SF-6D utility data
  - EPDS categorised into 10 levels: 0, 1-3, 4-6, 7-9, 10-12, 13-15, 16-18, 19-21, 22-24, 25-30
    - Based on review of utility scores distribution so no fewer than 10 observation inform each category
- EQ-5D and SF-6D both capture impact of mental health, but SF-36 better suited to capture depressive symptoms and is superior to EQ-5D-3L in terms of validity and responsiveness
- SF-36 better placed and more sensitive to inform utilities than PHQ-9 → captured broader aspects of QoL
  - Impact of depressive symptoms extend well beyond abnormalities in mood and neurovegetative symptoms e.g., psychological well-being and social, role, and physical functioning

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Abbreviations: PND, postnatal depression; QoL, quality of life; PHQ-9, Patient Health Questionnaire 9; SF-36, 36-item Short Form Health Survey; ADT, antidepression therapy

Return to key issues

Key Issue: Utilities (2)

EAG comments

PND period (up to 1-year post-treatment initiation, i.e. until 17 months post-birth)

Considerable difference in SF-6D utility scores between EPDS categories:

- No evidence to support face-validity of estimates or rationale for people in category EPDS=0 to be clinically different from those in category EPDS 1-6 (should apply same utility value to EPDS 0-6 if SF-36 used)
  - From EPDS groups 0 to 1-6 (where still no diagnosable mental health condition): 0.935 to 0.795
  - From EPSD 1-6 to 7-13 (very mild disease): 0.795 to 0.659
- EPDS = 0 trial utility: 0.935 → aligns with population norm for EQ-5D (0.93) but not SF-6D (0.803)

Utilities estimated by pooling estimates from both arms of ROBIN for same EPDS category

- Assumes zuranolone does not affect QoL of people within EPDS category - no evidence to suggest this
- No adjustment for baseline imbalances, potential confounders, or missing data
- ROBIN has relatively small sample size - some utilities likely estimated from very few people

EAG base case: EQ-5D utilities mapped from PHQ-9 (ROBIN) for duration of PND period (10 EPDS categories)

- EQ-5D has specific depression/anxiety domain, PHQ-9 validated to measure depression symptoms
- SF-36 captures aspects of QoL beyond HRQoL, but not designed to estimate utilities for model
  - Not NICE preferred tool, produces different utilities to EQ-5D, reduces QALY comparability across conditions
- Would have been beneficial to obtain mapping scores from both trials where available
- Categorisation of 10 EPDS groups is arbitrary and not based on clinical evidence / validated in literature

Abbreviations: HRQoL, health-related quality of life; PND, postnatal depression; PHQ-9, patient health questionnaire; EPDS, Edinburgh Postnatal Depression Scale; QALY, quality-adjusted life years

Key Issue: Utilities (3)

EAG comments

Utility estimates beyond PND period (17 months post-birth)

- Agree 45-day trial results can inform QoL changes in PND period, but unlikely to be sustained for 29 years
  - Clinical advice: PND lasts for 1 year after birth. After PND would be treated as MDD (similar symptoms)
- Appropriate to use utilities from an MDD population to inform modelled utilities beyond PND period
  - **Base case**: MDD utilities applied 1 year after treatment initiation to align with treatment effect waning
  - Scenario: MDD utilities applied immediately after PND period (1 year after birth)
- No long-term PND utilities identified, but literature MDD utilities could inform QoL gains after PND period
  - MDD data source: TA367 to inform utilities in “remission”(0.85) and “non-remission” (0.67) health states
  - Rationale: EQ-5D utilities, committee preferred values, aligns with modelling of cost by remission health-state (also typical for MDD utilities), clinical experts advise that PND 1-year post-birth is similar to MDD
    - ➢ Not clear linear link between clinicians' definition of “remission”, and 13-point EPDS cut off in model
  - Limitations: MDD appraisal not PND, EQ-5D utilities from industry trial and French study (MDD UK tariffs)

Which utilities should be used to model PND: SF-6D or EQ-5D mapped from PHQ-9? Should long-term utilities be modelled differently, such as using MDD utility estimates?

Abbreviations: PND, postnatal depression; MDD, major depressive disorder; QoL, quality of life; PHQ, patient health questionnaire

Zuranolone for treating postnatal depression

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling
- ✓ **Other considerations**
- ❑ Cost effectiveness
- ❑ Summary

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Key Issue: Uncaptured costs and benefits

Not all benefits of zuranolone and impacts of PND are captured within the model

Additional impacts on people with PND

- Beyond adverse psychological effects, PND symptoms can also negatively impact physical and overall functioning of people that are not captured in the model

Impact on baby and support network (partner, family members)

- Does not capture impact on child, partner or family outcomes, or additional PND events after more children
  - PND can negatively affect the partner's own mental health and QoL – at increased risk of depression
- Improvement in mothers' symptoms positively impacts health, wellbeing and resource use needs of baby and support network
- Improves parent-infant bonding - crucial for child's early emotional developmental and long-term outcomes

People who are breastfeeding

- Support for people to continue breastfeeding after treatment or stop breastfeeding was not captured in model

Side effects

- People may be at risk of other rare but serious side effects such as decreased consciousness (risks to baby include if co-sleeping should occur) and potential for abuse or dependence - not captured in trial

Are there any uncaptured benefits or impacts of zuranolone not captured within the model?

Abbreviations: PND, postnatal depression; QoL, quality of life

Return to key issues

Zuranolone for treating postnatal depression

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling
- ❑ Other considerations
- ✓ **Cost effectiveness**
- ❑ Summary

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Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case	ICER impact
Population	Mixed severity PND population (whole SKYLARK population)	People with severe PND (baseline EPDS scores >19)	Small
Long term model (EPDS trajectory)	• Zuranolone + ECM: ALSPAC data predicts long-term EPDS • ECM: short-term fixed treatment effect applied to zuranolone + ECM EPDS predictions	• ECM: ALSPAC data predicts long-term EPDS • Zuranolone + ECM: apply zuranolone treatment effect to ECM arm EPDS predictions	Small
Treatment effect waning	No waning – short-term treatment effect lasts 29 years	Treatment effect starts waning 1-year post-treatment initiation and lasts 1 year	Large
Concomitant ECM treatment	15.3% ADT use	90% ADT use	Small
Utilities	PND period: SF-6D utilities Post-PND period: SF-6D utilities	PND period: mapped EQ-5D utilities Post-PND period: MDD TA367 utilities	Large
Mortality	No difference between depressed and non-depressed people	SMR of 2 for people with EPDS ≥ 13 (“non-remission”)	Small

Abbreviations: PND, post natal depression; MDD, major depressive disorder; ADT, anti-depressant therapy; MMRM, Mixed Model for Repeated Measures; EPDS, Edinburgh Postnatal Depression Scale; SMR, standardised mortality ratio; ECM, established clinical management; ALSPAC, Avon Longitudinal Study of Parents and Children

Base case results

Company incremental base case results (based on 1000 patients)

Technology	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (£/QALY)
Deterministic					
ECM alone	[redacted]	[redacted]	-	-	-
Zuranolone with ECM	[redacted]	[redacted]	[redacted]	[redacted]	£12,704
Probabilistic					
ECM alone	[redacted]	[redacted]	-	-	-
Zuranolone with ECM	[redacted]	[redacted]	[redacted]	[redacted]	£12,706

EAG incremental base case results (based on 1000 patients)

Technology	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (£/QALY)
Deterministic					
ECM alone	[redacted]	[redacted]	-	-	-
Zuranolone with ECM	[redacted]	[redacted]	[redacted]	[redacted]	£194,554
Probabilistic					
ECM alone	[redacted]	[redacted]	-	-	-
Zuranolone with ECM	[redacted]	[redacted]	[redacted]	[redacted]	£188,102

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

EAG preferred assumptions

	Scenarios included in EAG base case
1	Re-parameterisation of long-term MMRM model (ALSPAC data for ECM arm; EAG Scenario 1)
2	Treatment effect waning starts 1-year post-treatment initiation, for 1 year (EAG Scenario 2g)
3	90% on ADT at baseline (EAG Scenario 3c)
4	Mortality: SMR of 2 for patients with EPDS ≥ 13 (Company Scenario S1)
5	PND severity: patients with EPDS > 19 at baseline (EAG Scenario 4a)
6	Utilities: PND period - EQ-5D, MDD period (17 months post-birth) - different utilities (EAG Scenario 5b)

EAG Assumptions	ECM		Zuranolone with ECM		Inc costs	Inc QALYs	ICER (£/QALY)
	Total costs	Total QALYs	Total costs	Total QALYs			
Company base case (0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,704
0+1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,725
0+1+2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£156,898
0+1+2+3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£169,289
0+1+2+3+4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£169,289
0+1+2+3+4+5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£157,848
0+1+2+3+4+5+6 EAG BASE CASE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£194,554

Abbreviations: ADT, antidepressant therapy; PND, postnatal depression; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; MMRM, Mixed Model for Repeated Measures; EPDS, Edinburgh Postnatal Depression Scale; MDD, major depressive disorder; ECM, established clinical management

Company deterministic scenario analysis

#	Scenario	Inc. costs	Inc. QALYs	ICER (£/QALY)
Company base case		[redacted]	[redacted]	£12,704
S1	**Mortality:** Excess mortality for patients with PND	[redacted]	[redacted]	£12,415
S2	**ADT use at baseline**: 0% (alternative short-term model)	[redacted]	[redacted]	£12,736
S3	**Baseline ADT use**: 100% with ADT as a covariate in MMRM	[redacted]	[redacted]	£13,400
S4	**Utility**: EPDS utility values mapped from ROBIN PHQ-9 to EQ-5D	[redacted]	[redacted]	£14,600
Treatment effect waning				
S5	**EPDS after 10 years:** EPDS decreased to 12.99 over 24 months for people not achieved remission after 10 years	[redacted]	[redacted]	£15,227
S6	**EPDS after 5 years:** EPDS decreased to 12.99 over 24 months for people not achieved remission after 5 years	[redacted]	[redacted]	£16,526
S7	**EPDS after 2 years:** EPDS decreased to 12.99 over 24 months for people not achieved remission after 2 years	[redacted]	[redacted]	£17,568

Abbreviations: ADT, antidepressant therapy; PND, postnatal depression; HRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; MMRM, Mixed Model for Repeated Measures; EPDS, Edinburgh Postnatal Depression Scale; PHQ-9, Patient Health Questionnaire 9

EAG deterministic scenario analysis

#	Scenario	Inc costs (£)	Inc QALYs	ICER (£/QALY)
Company base-case		[redacted]	[redacted]	£12,704
1	Re-parameterisation of long-term model (ALSPAC data for ECM arm)	[redacted]	[redacted]	£12,725
Treatment effect waning				
2a	starts 3 months post-treatment initiation, for 6 months	[redacted]	[redacted]	£434,254
2b	starts 3 months post-treatment initiation, for 1 year	[redacted]	[redacted]	£303,851
2c	starts 3 months post-treatment initiation, for 2 years	[redacted]	[redacted]	£188,542
2d	starts 3 months post-treatment initiation, for 5 years	[redacted]	[redacted]	£89,131
2e	starts 3 months post-treatment initiation, for 10 years	[redacted]	[redacted]	£49,103
2f	starts 6 months post-treatment initiation, for 6 months	[redacted]	[redacted]	£299,728
2g	starts 1-year post-treatment initiation, for 1 year	[redacted]	[redacted]	£156,898
Baseline ADT use				
3a	50% on ADT at baseline	[redacted]	[redacted]	£12,839
3b	80% on ADT at baseline	[redacted]	[redacted]	£13,337
3c	90% on ADT at baseline	[redacted]	[redacted]	£13,205
PND severity				
4a	People with EPDS > 19 at baseline (severe PND)	[redacted]	[redacted]	£12,839
4b	People with EPDS ≤ 19 at baseline (moderate PND)	[redacted]	[redacted]	£12,289
Utilities				
5a	Utility estimate of 0.795 for EPDS = 0	[redacted]	[redacted]	£14,754
5b	PND period: EQ-5D, MDD period (17 months post-birth): different utilities	[redacted]	[redacted]	£22,939
5c	PND period: EQ-5D, MDD period (12 months post-birth): different utilities	[redacted]	[redacted]	£23,246
EAG base-case		[redacted]	[redacted]	£194,554
6	No restriction to severe population	[redacted]	[redacted]	£209,838

Abbreviations: ADT, antidepressant therapy; PND, postnatal depression; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EPDS, Edinburgh Postnatal Depression Scale; MDD, major depressive disorder; ECM, established clinical management

Zuranolone for treating postnatal depression

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling
- ❑ Other considerations
- ❑ Cost effectiveness
- ✓ **Summary**

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Key issues

Issue	ICER impact	Slide
Population	Small	14
Clinical trial generalisability: ECM definition and trial population	Unknown	16
Treatment effect duration	Large	20
Modelled concomitant ADT use	Unknown	23
Utilities	Large	24
Uncaptured costs and benefits	Unknown	28

Abbreviations: ICER, incremental cost-effectiveness ratio; ECM, established clinical management; ADT, antidepressant therapy

Decision making framework (1)

What are committee's preferred assumptions?	Option
Population	Who is most likely to be treated with zuranolone in NHS practice? Would an optimised recommendation based on PND severity be appropriate? Which population should be modelled? • Whole SKYLARK trial data or severe PND subgroup population
Clinical trial generalisability	Are the SKYLARK trial results applicable to NHS ECM and the target PND population? Is concomitant treatment with ADT likely to be a treatment effect modifier?
Treatment effect duration	Should there be a waning of zuranolone treatment effect over time? If yes, • When should waning begin (3 months or 1-year post-treatment initiation)? • How long should it last (6 months,1, 2, 5 or 10 years)?
Concomitant ADT use	What proportion of people should be taking ADTs at baseline in the model – 15%, 90%, other?
Utility values	Which should be used to model PND: SF-6D or EQ-5D mapped from PHQ-9? Should the same utilities be used throughout the time horizon or different utilities used after the PND period e.g., MDD utilities?
Uncaptured costs and benefits	Are there any uncaptured benefits or impacts of zuranolone not captured within the model? If so, how should these to be accounted for?

Abbreviations: PND, postnatal depression; ECM, established clinical management; ADT, antidepressant therapy; MDD, major depressive disorder

Decision making framework (2)

What are committee's preferred assumptions?	Options
What is the committee's preferred ICER threshold?	
Should QALYs be weighted for severity and if so which weighting?	Company and EAG agree that the criteria for a severity weight are not met
What is the committee's preferred ICER? (if this is a range, please state whether the committee want the lower, upper, or midpoint of range to be below threshold)	Company base case / EAG base case / scenario analysis presented / other
Is the ICER below preferred ICER threshold?	Yes/no
If yes, recommend for routine commissioning? (considering uncertainty, inequalities, innovation etc that might impact decision if close to threshold)	Yes/no
If no, could key uncertainties be sufficiently resolved during period of managed access	No managed access proposal submitted.

Zuranolone for treating postnatal depression

Supplementary appendix

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Decision problem

	Final scope issued by NICE	Company	EAG comment
Population	Adults with PND	N/A	Clinical evidence narrower than specified in NICE scope and is most applicable to patients with severe PND – see issue 1
Intervention	Zuranolone with ECM	N/A	• Agrees ECM is appropriate intervention for appraisal. • Trial baseline ADT use (15%) considerably less than expected for eligible UK severe PND population- see issue 2. • "Baseline ADT" use subgroup might be more representative of zuranolone + ECM in expected NHS practice
Comparator	ECM without zuranolone which may include: • Psychological therapies • ADTs: TCAs (SSRIs, SNRIs, atypical ADTs) • High-intensity psychological intervention + ADT • Augmentation + additional ADT, antipsychotics, or electroconvulsive therapy • Best supportive care	N/A	• People not allowed to start any new interventions during trial, which differs from ECM in clinical practice - may adversely affect outcomes on placebo with ECM arm more than zuranolone plus ECM arm (see issue 2)
Outcomes	Depressive symptoms, depression severity, cognitive function, anxiety, sleep quality, hospitalisation, mortality, child health-related outcomes, AE, HRQoL	N/A	• Only EPDS and safety outcomes from SKYLARK and SF-6D utilities from ROBIN are used in model. • Hospitalisation and child health related outcomes are not included in the trials or economic model.
Subgroups	If the evidence allows, the following subgroups maybe considered: • Previous history of depression • Severity of PND	PND severity • Sample too small to run subgroup for previous history of depression	• Severity subgroup based on using scale - has different cut-off scores for moderate vs severe disease compared with HAM-D (all classified as severe from HAM-D) • No subgroup analyses conducted for cost-effectiveness due to small samples - not possible to fully assess cost-effectiveness for mild/moderate PND patients, those with baseline ADT use, or those with history of depression

Abbreviations: PND, postnatal depression; ECM, established clinical management; ADT, antidepressant therapy; TCA, tricyclic ADT; AE, adverse event; HRQoL, health-related quality of life; EPDS, Edinburgh postal depression scale; HAM-D, Hamilton depression rating scale; MADRS, Montgomery–Åsberg Depression Rating Scale

NICE appraisals for depression

TA	Issues
Vortioxetine for treating major depressive episodes (TA367) - 2015	
Efficacy	Clinical expert: mean change from baseline in total MADRS score not a useful outcome measure for judging if clinically important difference was observed. • Reduction in 1 item of MADRS by 2 or more be considered clinically meaningful.
Mortality	Did not assume that treating depression lowered risk of suicide
Utilities	Appropriate to use REVIVE EQ-5D utility values for all phases of model, rather than using 2 separate evidence sources for utility values – data represented best evidence available and was more internally consistent
	Baseline / relapse: **0.54**, No remission **0.67**; Remission: **0.85**
Esketamine nasal spray for treatment-resistant depression (TA854) - 2022	
Treatment effect	Key driver of difference between arms was initial response
Mortality	Committee considered it plausible that esketamine could affect mortality. Because of issues with generalisability, excluding people with suicidal ideation and lack of data, committee concluded could not accept a reduced suicide, or mortality, risk
Utilities	EQ-5D-3L values (mapped from EQ-5D-5L). Baseline utility: **0.417** (mean MADRS score 37)

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; TA, technology appraisal

Overview of clinical evidence

Clinical trials

NICE scope category	Key outcomes	Trial source	Outcome	Treatment comparison	Modelled?
Depressive symptoms	HAMD-17	SKYLARK & ROBIN	Primary	Direct	No
Severity of depression	HAMD-17	SKYLARK & ROBIN	Primary	Direct	No
	EPDS	SKYLARK	Secondary	Direct	Yes
		ROBIN	Secondary	Direct	No
	MADRS	SKYLARK & ROBIN	Secondary	Direct	No
	PHQ-9	SKYLARK	Secondary	Direct	No
	CGI-S	SKYLARK	Secondary	Direct	No
	CGI-I	SKYLARK & ROBIN	Secondary	Direct	No
Cognitive function	HAMD-17 (subitem - retardation)	SKYLARK	Secondary	Direct	No
	MADRS (subitem – concentration difficulties)	SKYLARK & ROBIN	Secondary	Direct	No
Anxiety	HAM-A	SKYLARK & ROBIN	Secondary	Direct	No
Sleep quality	HAM-D subitem	SKYLARK & ROBIN	Secondary	Direct	No
	MADRS subitem	SKYLARK & ROBIN	Secondary	Direct	No
	EPDS subitem	ROBIN	Secondary	Direct	No
Mortality	Death (AEs)	SKYLARK	Secondary	Direct	No
Adverse effects	TEAEs, SAE and death	SKYLARK	Secondary	Direct	Yes
		ROBIN	Secondary	Direct	No
HRQoL	SF-36	ROBIN	Secondary	Direct	Yes
Not reported: child health-related outcomes, hospitalisation					

EAG has concerns that model effectiveness based on EPDS, rather than primary outcome, HAMD-17

- EPDS not developed to measure depression severity in research settings and is secondary outcome (may not be powered enough to estimate effectiveness based on data from EPDS)
- HAMD-17 would have been preferred - validated scale for measuring depression. Provides most reliable/robust efficacy evidence

Abbreviations: HAM-D, Hamilton Rating Scale for Depression; HRQoL, heath-related quality-of-life; AE, adverse events; EPDS, Edinburgh postnatal depression score

Clinical trials results: primary outcome

Zuranolone significantly improves depressive symptoms by day 15 compared with placebo

SKYLARK - LSM change from baseline in HAMD-17 score

Study visit	Zuranolone (50mg) N=98		Placebo N=97		LSM difference			p-value
	Mean	SE	Mean	SE	Mean	95% CI lower	95% CI upper	
Baseline	28.6	2.49	28.8	2.34	-	-	-	-
Day 3*	-9.5	0.70	-6.1	0.71	-3.4	-5.4	-1.4	0.001
Day 15*	**-15.6**	**0.82**	**-11.6**	**0.82**	**-4.0**	**-6.3**	**-1.7**	**0.001**
Day 28*	-16.3	0.88	-13.4	0.88	-2.9	-5.4	-0.5	0.020
Day 45*	-17.9	0.90	-14.4	0.90	-3.5	-6.0	-1.0	0.007

*Primary and key secondary endpoints adjusted for multiplicity. Other endpoints interpreted with nominal p-values

ROBIN - LSM change from baseline in HAMD-17 score

Study visit	Zuranolone (30 mg) N=98		Placebo N=97		LSM difference			p-value
	Mean	SE	Mean	SE	Mean	95% CI lower	95% CI upper	
Baseline	-12.5	0.93	-9.8	0.95	-2.7	-5.1	-0.3	0.025
Day 3*	-16.3	1.00	-12.9	1.03	-3.4	-6.0	-0.8	0.011
Day 15*	**-17.6**	**1.09**	**-14.4**	**1.11**	**-3.1**	**-6.0**	**-0.3**	**0.032**
Day 28*	-12.5	0.93	-9.8	0.95	-2.7	-5.1	-0.3	0.025
Day 45*	-16.3	1.00	-12.9	1.03	-3.4	-6.0	-0.8	0.011

*Primary and key secondary endpoints adjusted for multiplicity. Other endpoints interpreted with nominal p-values

Abbreviations: LSM, least square mean; CI, confidence interval; HAMD-17: 17-item Hamilton Rating Scale for Depression; HRQoL, health-related quality of life; SE, standard error; MDD, major depressive disorder

ROBIN: HRQoL results

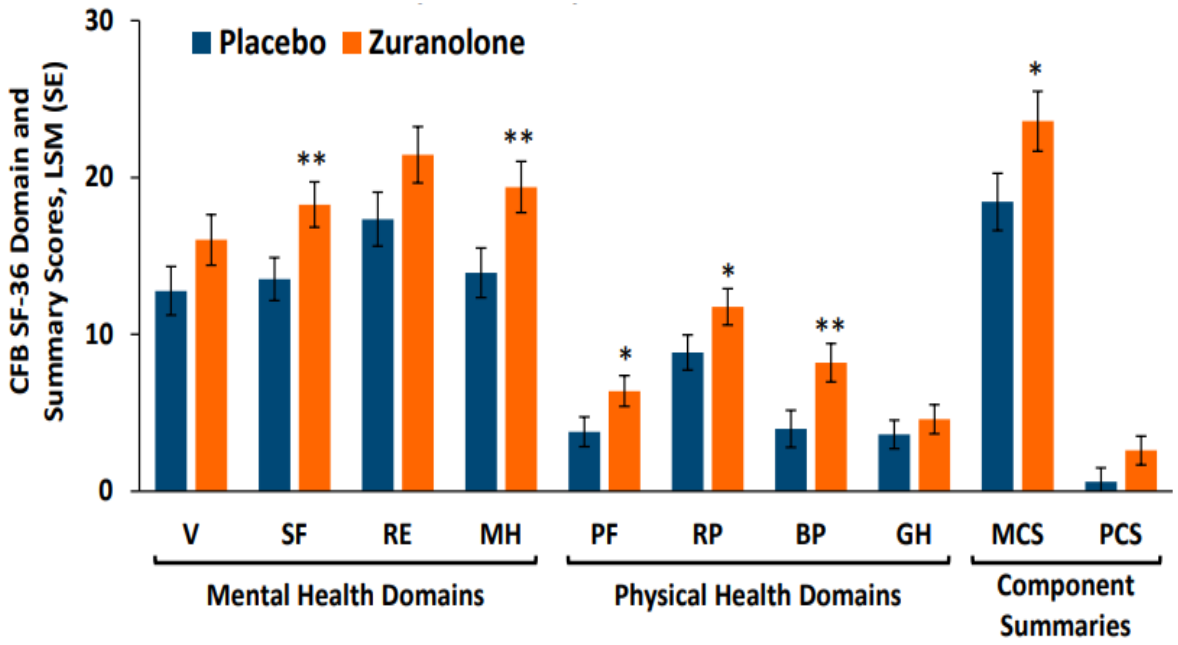
Clinical trial results

Short Form Health Survey (SF-36) (used in company model)

Day 15: numerically greater improvements from baseline with zuranolone than placebo - not statistically significant

Day 45: zuranolone showed significant improvements compared with placebo across 5 SF-36 domains*/**

- Change from baseline in other SF-36 domains was numerically greater with zuranolone vs. placebo



SF-36 domains	Least square mean (SE, 95% CI)		P value
	Zuranolone	Placebo	
Social functioning	[redacted]	[redacted]	[redacted]
Mental health	[redacted]	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]	[redacted]
Role physical	[redacted]	[redacted]	[redacted]
Bodily pain	[redacted]	[redacted]	[redacted]
Mental component summary score	[redacted]	[redacted]	[redacted]

Patient Health Questionnaire (PHQ-9) (not used in company model, used in EAG base case mapped to EQ-5D):

Day 45: least square mean change (SE) was [redacted] for placebo and [redacted] for zuranolone 30mg

- Treatment difference: [redacted]
- Improvement was numerically greater at all timepoints from day 3 to day 45 for zuranolone versus placebo

Abbreviations: BP: Bodily Pain; CFB: Change from Baseline; GH: General Health; MCS: Mental component Score; MH: Mental Health; PCS: Physical Component Score; PF: Physical Functioning; RE: Role Emotional; RP: Role Physical; SE: Standard Error; SF: Social Functioning; SF-36: 36-item Short Form Health Survey; V: Vitality

Clinical trial results: pre-specified subgroups

Neither study powered to detect efficacy differences in subgroups

- SKYLARK: zuranolone favoured in all subgroups, except for ADT use at baseline – but majority of participants did not use ADTs at baseline (did not used ADTs: placebo: 84.7%; zuranolone: 84.7%)
- ROBIN: zuranolone favoured in all subgroups including ADT use at baseline, with statistically significant results in 7/14 subgroups

Abbreviations: ADT, antidepressant treatment; HAMD-D, Hamilton Rating Scale for Depression; PPD, post partum depression; HAM-A, Hamilton Rating Scale for Anxiety

Clinical trial results: post hoc analyses

By PND severity (based on MADRS severity)

- Literature-established MADRS thresholds identified moderate and severe baseline depression severity subgroups
- [redacted]

	SKYLARK (Moderate=[redacted]; severe=[redacted])		ROBIN (Moderate=[redacted]; severe=[redacted])	
	LSM (95% CI)	P value	LSM (95% CI)	P value
Day 15				
Moderate (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Severe (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Day 45				
Moderate (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Severe (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LSM, least square mean; HAMD-17: 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; CI, confidence interval; PND, postnatal depression

Key issue: population

Clinical trial severity classification

EAG: SKYLARK's mean baseline MADRS scores suggest that "moderate" subgroup only includes upper range of moderate = not representative of a "moderate" subgroup in general population

Severity definitions

Score	Mild	Moderate	Severe
HAMD-17	8-16	17-23	≥24
MADRS	7-19	20-34	≥35
EPDS	7-13	14-19	≥20

Trial severity level proportions by measurement tool

Trial	Moderate PND (n)		Severe PND (n)	
	MADRS	HAMD-17	MADRS	HAMD-17
SKYLARK	[redacted]	0% (0)	[redacted]	100% [redacted]
ROBIN	[redacted]	0% (0)	[redacted]	100% [redacted]

Mean baseline severity depression score for post-hoc subgroups (categorised by MADRS)

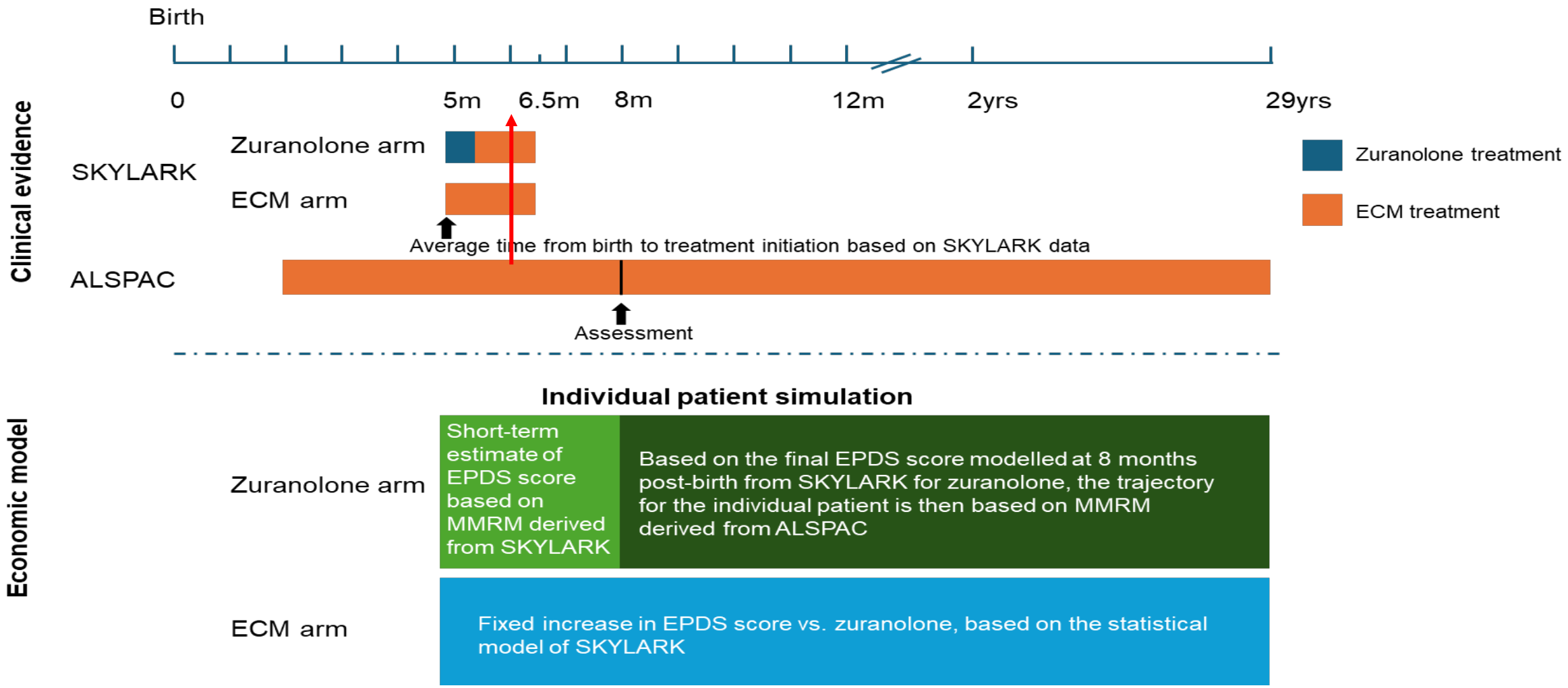
Baseline score (SD)	Zuranolone - Moderate PND			Zuranolone - Severe PND		
	Placebo	Zuranolone	Total	Placebo	Zuranolone	Total
SKYLARK (zuranolone 50 mg)						
HAMD-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MADRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROBIN (zuranolone 30 mg)						
HAMD-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MADRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

Abbreviations: PND, post natal depression; EPDS: Edinburgh Postnatal Depression Scale; HAMD-17: HAMD-17: 17-item Hamilton Rating Scale for Depression; MADRS: Montgomery–Åsberg Depression Rating Scale

Company model structure

Company model: data



Abbreviations: ALSPAC: Avon Longitudinal Study of Parents and Children; ECM: Established Clinical Management; EPDS: Edinburgh Postnatal Depression Scale; m: months; MMRM: Mixed Model for Repeated Measures; yrs: years.

Modelled utilities

Company base case - SF-36 data mapped to SF-6D utilities applied for 29 years

EPDS score	Mean	SE
0	0.935	0.020
1-6	0.795	0.012
7-13	0.659	0.008
14-18	0.573	0.008
19-30	0.520	0.006

EAG base case – MDD-specific utilities for post-PND period: TA367

Health state	Utilities
Remission	0.85
Non-remission	0.67

EAG base case – PND period; ROBIN PHQ-9 mapped to EQ-5D (sample size weighted values across all visits)

EPDS score	Total N	Weighted mean	Weighted SD
0	[redacted]	[redacted]	[redacted]
1-3	[redacted]	[redacted]	[redacted]
4-6	[redacted]	[redacted]	[redacted]
7-9	[redacted]	[redacted]	[redacted]
10-12	[redacted]	[redacted]	[redacted]
13-15	[redacted]	[redacted]	[redacted]
16-18	[redacted]	[redacted]	[redacted]
19-21	[redacted]	[redacted]	[redacted]
22-24	[redacted]	[redacted]	[redacted]
25-30	[redacted]	[redacted]	[redacted]

Abbreviations: SE, standard error; SD, standard deviation: EPDS, Edinburgh Postnatal Depression Score; PHQ, Patient Health Questionnaire; MDD, major depressive disorder; PND, postnatal depression

Mortality

Summary of company and EAG base case assumptions

Company

- Apply general population mortality rates equally to both arms, as there is no evidence that treatment with zuranolone affects mortality
- Scenario analysis: apply SMR to reflect increased suicide/mortality risk for people with an EPDS score of ≥13 ("non-remission") → use SMR of 2 in scenario, which very slightly reduces the ICER
    - SMR from literature review for people with MDD compared to general population, ranged from 1.5 to 2

EAG comments

- Agree there is no evidence of a direct effect of zuranolone on mortality but consider it reasonable that there may be an indirect effect through changes in EPDS score
- Company SMR based on an old study and on people with MDD, rather than PND → unclear whether this would apply to PND patients under current standard of care
- Appropriate to include impact of EPDS on mortality - base case = SMR of 2 for people with EPDS ≥13

Other considerations

- **Vortioxetine for treating major depressive episodes (TA376)** – committee did not assume that treating depression lowered risk of suicide
- **Esketamine nasal spray for treatment-resistant depression (TA854) -** plausible that esketamine could affect mortality but because of issues with generalisability, excluding people with suicidal ideation and lack of data, committee concluded could not accept a reduced suicide, or mortality, risk

Abbreviations: MDD, major depressive disorders; SMR, standardised mortality ratio; EPDS, Edinburgh postnatal depression score; ICER, incremental cost-effectiveness ratio