# Supplementary material

**Table S1:** Characteristics of included studies

**Figure S1:** Summary of risk of bias analysis using RoB-2 tool

**Table S1: Characteristics of included studies**

| Study ID | Lead author, affiliation and publication date | | Acronym | Study design | Primary endpoint | Phases (duration) | number of patients randomized | Study finding |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1  NCT02417064 | Maggie Fedgchin Janssen (2019) | | TRANSFORM 1 | Phase 3, Double-blind parallel RCT | Change from baseline to day 28 in MADRS total score | Induction (4 weeks) Follow-up (24 weeks) | ESK 56mg: 117 ESK 84mg: 116 PBO: 113 | ESK 56mg: -19·0 ESK 84mg: -18·8 PBO: -14·8 p=0·088 |
| 2  NCT02418585 | | Vanina Popova  Janssen (2019) | TRANSFORM 2 | Phase 3, Double-blind parallel RCT | Change from baseline to day 28 in MADRS total score | Induction (4 weeks) Follow-up (24 weeks) | ESK: 114 PBO: 109 | ESK: -21·4 PBO: -17 **p=0**·**020** |
| 3  NCT02422186 | | Rachel Ochs-Ross Janssen (2019) | TRANSFORM 3 | Phase 3, Double-blind parallel RCT | Change from baseline to day 28 in MADRS total score | Induction (4 weeks) Follow-up (2 weeks) | ESK: 72 PBO: 66 | ESK: -10·0 PBO: -6·3 p=0·059 |
| 4  NCT02493868 | | Ella J Daly Janssen (2019) | SUSTAIN 1 | Phase 3, Double-blind parallel RCT | Time to relapse in patients who achieved stable remission | Induction (4 weeks) Optimization (12 weeks) Maintenance (variable) Follow-up (2 weeks) | ESK: 152 PBO: 145 | 25th Percentile ESK: 153·0 25th Percentile PBO: 33·3 **p=0**·**003** |
| 5  NCT02497287 | | Ewa Wajs Janssen (2020) | SUSTAIN 2 | Phase 3, **Open-label** clinical trial | Treatment-emergent adverse events | Induction (4 weeks) Optimization/Maintenance (48 weeks) Follow-up (4 weeks) | ESK: 802 | Treatment-emergent adverse events were reported in 723/802 patients |
| 6  NCT03039192 | | Dong-Jing Fu Janssen (2020) | ASPIRE 1 | Phase 3, Double-blind parallel RCT | Change from baseline to 24h post-first dose in MADRS total score | Induction (4 weeks) Follow-up (9 weeks) | ESK: 114 PBO: 112 | ESK: -16·4 PBO: -12·8 **p=0**·**006** |
| 7  NCT03097133 | | Dawn F Ionescu Janssen (2021) | ASPIRE 2 | Phase 3, Double-blind parallel RCT | Change from baseline to 24h post-first dose in MADRS total score | Induction (4 weeks) Follow-up (9 weeks) | ESK: 115 PBO: 115 | ESK: -15·7 PBO: -12·4 **p=0**·**006** |
| 8  NCT02133001 | | Carla M Canuso  Janssen  (2018) | - | Phase 2, Double-blind parallel RCT | Change from baseline to 4h post-first dose in MADRS total score | Induction (4 weeks)  Follow-up (8 weeks) | ESK: 35  PBO: 31 | ESK: -13·4  PBO: -9·1  **p=0**·**015** |
| 9  NCT01998958 | | Ella J Daly Janssen (2017) | SYNAPSE | Phase 2, Double-blind parallel RCT | Change from baseline to day 8 (each period) in MADRS total score | - Induction perdiod 1 (1week) - Induction period 2 (1 week) - Optionnal open-Label (8,5 weeks) - Follow up (8 weeks) | ESK: 34 PBO: 33 | ESK 84mg: period 1: -15·3 PBO: period 1: -4·9 **p<0**·**001** ESK 84mg: period 2: -11·4  PBO: period 2: -4·5 **p=0**·**03** |
| 10  NCT02918318 | | Nagahide Takahashi Janssen (2021) | - | Phase 2b, Double-blind parallel RCT | Change from baseline to day 28 in MADRS total score | - Induction (4weeks) - posttraitement (24 weeks)  - optionnal open-label induction (4 weeks) - Follow-up (4 weeks) | ESK:122 PBO: 80 | ESK 28mg: -15·2 ESK 56mg: -14·5 ESK 84mg: -15·1 PBO: 15·3 not statistically significant |

RCT: Randomized Clinical Trial, MADRS : Montgomery-Åsberg Depression Rating Scale, ESK: esketamine + antidepressant, PBO: Placebo + antidepressant

**Figure S1: Summary of risk of bias analysis using RoB-2 tool**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **D1** | **D2** | **D3** | **D4** | **D5** | **Overall** |
| **1** |  |  |  |  |  |  |
| **2** |  |  |  |  |  |  |
| **3** |  |  |  |  |  |  |
| **4** |  |  |  |  |  |  |
| **6** |  |  |  |  |  |  |
| **7** |  |  |  |  |  |  |
| **8** |  |  |  |  |  |  |
| **9** |  |  |  |  |  |  |
| **10** |  |  |  |  |  |  |

D1: Randomisation process, D2: Deviations from the intended interventions, D3: Missing outcome data, D4: