# 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 |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1NCT02417064 | Maggie FedgchinJanssen(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: 117ESK 84mg: 116PBO: 113 | ESK 56mg: -19·0ESK 84mg: -18·8PBO: -14·8p=0·088 |
| 2NCT02418585 | 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: 114PBO: 109 | ESK: -21·4PBO: -17**p=0**·**020** |
| 3NCT02422186 | Rachel Ochs-RossJanssen(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: 72PBO: 66 | ESK: -10·0PBO: -6·3p=0·059 |
| 4NCT02493868 | Ella J DalyJanssen(2019) | SUSTAIN 1 | Phase 3, Double-blind parallel RCT | Time to relapse in patients who achievedstable remission | Induction (4 weeks)Optimization (12 weeks)Maintenance (variable)Follow-up (2 weeks) | ESK: 152PBO: 145 | 25th Percentile ESK: 153·025th Percentile PBO: 33·3**p=0**·**003** |
| 5NCT02497287 | Ewa WajsJanssen(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 |
| 6NCT03039192 | Dong-Jing FuJanssen(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: 114PBO: 112 | ESK: -16·4PBO: -12·8**p=0**·**006** |
| 7NCT03097133 | Dawn F IonescuJanssen(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: 115PBO: 115 | ESK: -15·7PBO: -12·4**p=0**·**006** |
| 8NCT02133001 | Carla M CanusoJanssen(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: 35PBO: 31 | ESK: -13·4PBO: -9·1**p=0**·**015** |
| 9NCT01998958 | Ella J DalyJanssen(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: 34PBO: 33 | ESK 84mg: period 1: -15·3PBO: period 1: -4·9**p<0**·**001**ESK 84mg: period 2: -11·4 PBO: period 2: -4·5**p=0**·**03** |
| 10NCT02918318 | Nagahide TakahashiJanssen(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:122PBO: 80 | ESK 28mg: -15·2ESK 56mg: -14·5ESK 84mg: -15·1PBO: 15·3not 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: