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Esketamine (major depressive disorder, psychiatric emergency) –

Addendum to Commission A21-25[1]

Addendum

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
BHS	Beck Hopelessness Scale
CGI-SR-I	Clinical Global Impression of Imminent Suicide Risk
CGI-SS-R	Clinical Global Impression of Severity of Suicidality Revised Version
ECT	electroconvulsive therapy
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
QLDS	Quality of Life in Depression Scale
SIBAT	Suicide Ideation and Behavior Assessment Tool
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 6 July 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-25 (Esketamine – Benefit assessment according to § 35a Social Code Book V) [1].

The pharmaceutical company (hereinafter the "company") presented the randomized controlled phase III studies SUI3001 and SUI3002 and, as supplementary evidence, the phase II study SUI3001 and SUI2001 for the benefit assessment of esketamine as acute short-term treatment in adult patients with a moderate to severe episode of major depressive disorder so as to achieve a rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency For the present therapeutic indication, the G-BA specified the appropriate comparator therapy (ACT) to be treatment upon the physician's discretion, taking into account crisis intervention / psychotherapy, pharmacological acute therapy (of anxiety, insomnia, psychotic symptoms, restlessness), initiation of adequate antidepressant medication or optimization of the existing medication, and electroconvulsive therapy (ECT). The studies identified above were disregarded in the benefit assessment because they failed to appropriately implement the nonpharmacological treatment options of the ACT specified by the G-BA (exclusion of the treatment option of ECT, unclear implementation of psychotherapeutic measures as in crisis intervention) [1].

After the oral hearing [2], the G-BA commissioned IQWiG with assessing the SUI3001 and SUI3002 studies.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is sent to the G-BA. The G-BA decides on the added benefit.

2 Presentation of the studies SUI3001 and SUI3002

This addendum presents the studies SUI3001 [3-6] and SUI3002 [7-10] and assesses their results.

2.1 Study characteristics

A detailed characterization of the SUI3001 and SUI3002 studies is available in dossier assessment A21-25 [1].

Characterization of the study populations

Table 1 shows the patient characteristics of the SUI3001 SUI3002 studies.

Table 1: Characterization of the study populations – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Study	SUI3001 and SUI3002		SUI3001		SUI3002	
Characteristic Category	Esketamine + antidepressant therapy	Placebo + antidepressant therapy	Esketamine + antidepressant therapy	Placebo + antidepressant therapy	Esketamine + antidepressant therapy	Placebo + antidepressant therapy
	N[a] = 229	N[a] = 227	N[a] = 114	N[a] = 112	N[a] = 115	N[a] = 115
Age [years], mean (SD)	41 (13)	40 (13)	41 (13)	38 (13)	40 (13)	41 (13)
Sex [m/f][b], %	41/59	38/62	42/58	35/65	39/61	41/59
Ancestry, n (%)						
White	171 (75)	163 (72)	78 (68)	74 (66)	93 (81)	89 (77)
Asian	29 (13)	30 (13)	28 (25)	28 (25)	1 (< 1)	2 (2)
Black or African American	12 (5)	15 (7)	5 (4)	7 (6)	7 (6)	8 (7)
Other[c]	11 (5)	11 (5)	3 (3)	3 (3)	8 (7)	8 (7)
Missing	6 (3)[d]	8 (4)[d]	0 (0)	0 (0)	6 (5)	8 (7)
Antidepressant therapy at randomization, n (%)						
Antidepressant monotherapy	106 (46)	109 (48)	61 (54)	65 (58)	45 (39)	44 (38)
Antidepressant therapy + augmentation therapy	123 (54)	118 (52)	53 (46)	47 (42)	70 (61)	71 (62)
Antidepressant therapy as actually administered, n (%)						
Antidepressant monotherapy	96 (42)	87 (38)	53 (46)	51 (46)	43 (37)	36 (31)
Antidepressant therapy + augmentation therapy	123 (54)	118 (52)	56 (49)	50 (45)	67 (58)	68 (59)
Antidepressant monotherapy and antidepressant therapy + augmentation therapy	8 (3)	19 (8)	4 (4)	10 (9)	4 (3)	9 (8)
Missing[d]	2 (< 1)	3 (1)	1 (< 1)	1 (< 1)	1 (< 1)	2 (2)
Duration of current depressive episode [months]						
Mean (SD)	42.3 (65.0)[e]	41.8 (68.4)[e]	39.3 (58.6)[f]	33.8 (54.4)[f]	45.4 (71.1)[f]	49.9 (79.4)[f]
Median [min; max]	16.4 [1; 356][e]	15.2 [2; 445][e]	16.0 [1; 356][f];	13.3 [2; 339][f];	16.5 [2; 341][f];	21.2 [2; 445][f];
MADRS total score, mean (SD)	40.3 (5.6)	40.4 (6.0)	41.2 (5.9)	41.0 (6.3)	39.5 (5.2)	39.9 (5.8)

Table 1: Characterization of the study populations – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Study Characteristic Category	SUI3001 and SUI3002		SUI3001		SUI3002	
	Esketamine + antidepressant therapy	Placebo + antidepressant therapy	Esketamine + antidepressant therapy	Placebo + antidepressant therapy	Esketamine + antidepressant therapy	Placebo + antidepressant therapy
	N[a] = 229	N[a] = 227	N[a] = 114	N[a] = 112	N[a] = 115	N[a] = 115
MADRS item 10 (suicidal thoughts)[g], n (%)						
0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	1 (< 1)	2 (< 1)	0 (0)	1 (< 1)	1 (< 1)	1 (< 1)
3	16 (7)	14 (6)	4 (4)	8 (7)	12 (10)	6 (5)
4	61 (27)	52 (23)	31 (27)	27 (24)	30 (26)	25 (22)
5	103 (45)	99 (44)	50 (44)	43 (38)	53 (46)	56 (49)
6	45 (20)	58 (26)	27 (24)	33 (29)	18 (16)	25 (22)
Missing[d]	3 (1)	2 (< 1)	2 (2)	0 (0)	1 (< 1)	2 (2)
Severity of suicidality (SIBAT: CGI-SS-R), n (%)						
Normal, not at all suicidal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Questionably suicidal	6 (3)	6 (3)	5 (4)	3 (3)	1 (< 1)	3 (3)
Mildly suicidal	16 (7)	17 (7)	6 (5)	11 (10)	10 (9)	6 (5)
Moderately suicidal	64 (28)	61 (27)	29 (25)	28 (25)	35 (30)	33 (29)
Markedly suicidal	87 (38)	84 (37)	39 (34)	42 (38)	48 (42)	42 (37)
Severely suicidal	46 (20)	55 (24)	29 (25)	27 (24)	17 (15)	28 (24)
Among the most extremely suicidal participants	7 (3)	2 (< 1)	4 (4)	1 (< 1)	3 (3)	1 (< 1)
Missing[d]	3 (1)	2 (< 1)	2 (2)	0 (0)	1 (< 1)	2 (2)
Prior suicide attempt as per SIBAT, n (%)						
Yes	145 (63)	140 (62)	67 (59)	68 (61)	78 (68)	72 (63)
No	81 (35)	85 (37)	45 (39)	44 (39)	36 (31)	41 (36)
Missing[d]	3 (1)	2 (< 1)	2 (2)	0 (0)	1 (< 1)	2 (2)

Table 1: Characterization of the study populations – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Study	SUI3001 and SUI3002		SUI3001		SUI3002	
Characteristic Category	Esketamine + antidepressant therapy	Placebo + antidepressant therapy	Esketamine + antidepressant therapy	Placebo + antidepressant therapy	Esketamine + antidepressant therapy	Placebo + antidepressant therapy
	N[a] = 229	N[a] = 227	N[a] = 114	N[a] = 112	N[a] = 115	N[a] = 115
MINI number of depressive episodes over the life course, n (%)						
1	55 (24)	49 (22)	23 (20)	22 (20)	32 (28)	27 (23)
2-5	131 (57)	142 (63)	72 (63)	74 (66)	59 (51)	68 (59)
6–10	31 (14)	22 (10)	13 (11)	12 (11)	18 (16)	10 (9)
> 10	12 (5)	14 (6)	6 (5)	4 (4)	6 (5)	10 (9)
Treatment discontinuation, n (%)	37 (16)[d]	40 (18)[d]	12 (11)	19 (17)	25 (22)	21 (18)
Study discontinuation, n (%)	64 (28)[d]	62 (27)[d]	30 (26)[h]	32 (29)[h]	34 (30)[h]	30 (26)[h]

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant. Percentages are based on the number of randomized patients and were calculated by IQWiG where necessary.
b. Discrepancy between data provided in Module 4 B and Module 5. Module 5 states that the majority of each study population was female rather than male, as indicated in Module 4 B. The allocation of patient numbers to each sex was corrected accordingly.
c. IQWiG calculation; pooled from the categories “multiple”, “others”, “Hawaiian or Pacific Islander”, and “Alaska Native or Native American” (SUI3002 only).
d. IQWiG calculations.
e. Based on 200 patients in the intervention arm and 212 in the control arm.
f. Based on 100 patients in the intervention arm and 106 in the control arm.
g. Categorization as per the severity of symptoms: 0 (Enjoys life or takes it as it comes) to 6 (Explicit plans for suicide when there is an opportunity. Active preparation for suicide.)
h. IQWiG calculation from data on patients who completed the entire study duration.

CGI-SS-R: Clinical Global Impression of Severity of Suicidality Revised Version; f: female; m: male; MADRS: Montgomery-Åsberg Depression Rating Scale; max: maximum; min: Minimum; MINI: Mini International Psychiatric Interview; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; SIBAT: Suicide Ideation and Behavior Assessment Tool

Presented are the data on the individual study populations as well as the data on the pooled study population (also see the section below on pooled analyses). Overall, the demographic and clinical characteristics of patients in the SUI3001 and SUI3002 studies were largely similar between treatment arms.

Across the individual studies and study arms, patients were on average 40 years old, and more than half of them were female. At the time of randomization, 47% of patients (56% in SUI3001 and 39% in SUI3002) were to receive antidepressant monotherapy and 53% (44% in SUI3001 and 61% in SUI3002) antidepressant therapy plus augmentation therapy. In departure from the planned procedure, some patients received a different therapy form, but in both studies, these percentages were balanced between the two treatment arms. On average, the current depressive episode was severe (Montgomery-Åsberg Depression Rating Scale [MADRS] total score of approx. 40 points) and had already lasted for a period of about 42 months. According to clinical judgement, more than half of patients were markedly or severely suicidal, as measured with the Clinical Global Impression of Severity of Suicidality Revised Version (CGI-SS-R) of the Suicide Ideation and Behavior Assessment Tool (SIBAT). A total of 60% of the SUI3001 population and 65% of the SUI3002 population already had a history of a prior suicide attempt. The percentage of patients who discontinued therapy was 14% in SUI3001 and 20% in SUI3002. The percentage of patients who discontinued the study was 27% in SUI3001 and 28% in SUI3002.

Summary assessment of the studies' certainty of results

With regard to SUI3001 and SUI3002 participants having received adequate prior therapy, the transferability of study results to the German healthcare context is questionable. In SUI3001 and SUI3002 combined, only 4 patients had received psychotherapy in the 30 days before the study start, despite the fact that, on average, patients had been persistently presenting with a severe depressive episode for a long time (approx. 42 months) [11-13]. The S3 Guideline on Unipolar Depression recommends psychotherapy in these cases [14]. All told, therefore, the certainty of results is deemed limited already by a questionable transferability to the German healthcare context, and a further evaluation of biasing aspects was foregone.

Pooled analyses

The company reportedly pooled the individual patient data of the SUI3001 and SUI3002 studies, but it failed to disclose the method it employed for this purpose. Therefore, it is unclear whether the analyses are summaries from metaanalyses or summaries in which the study factor was disregarded. In addition, the company did not discuss any heterogeneity between the results of the two studies. Therefore, both aspects were investigated on the basis of the aggregated data (IQWiG metaanalyses with fixed effect [inverse variance] or Q-test).

Statistically significant heterogeneity between the results of the two studies was found only in an analysis of suicidality measured with Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) of SIBAT at Day 90. In the present situation, however, this sole exception does not call into question the metaanalytical summary using a fixed-effect model. Since furthermore,

the results of IQWiG metaanalyses show no relevant differences to the results of the pooled data, the results presented in the company's dossier are presented herein.

2.2 Study results

2.2.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for the SUI3001 and SUI3002 studies:

- Mortality
  - All-cause mortality
- Morbidity
  - General depressive symptoms, measured using MADRS as well as the Beck Hopelessness Scale (BHS) and the Quality of Life in Depression Scale (QLDS)
  - Specific depressive symptoms: Suicidality, measured with SIBAT
  - Health status, measured with the visual analogue scale (VAS) of the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D)
- Health-related quality of life
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Specific AEs, if any

Table 2 shows the SUI3001 and SUI3002 outcomes for which data were available.

Table 2: Matrix of outcomes – RCT, direct comparison of esketamine + antidepressant therapy vs. placebo + antidepressant therapy

Study	Outcomes							
	All-cause mortality	General depressive symptoms (MADRS, BHS, QLDS)	Specific depressive symptoms: Suicidality (SIBAT[a])	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs[b]
SUI3001	Yes	Yes	Yes[c]	Yes	No	Yes	Yes	Yes
SUI3002	Yes	Yes	Yes[c]	Yes	No	Yes	Yes	Yes

a. SIBAT consists of 8 modules, 5 of them patient reported (Modules 1 through 5) and 3 clinician rated (Modules 6 through 8). After completion of Modules 1 to 5, with Module 1 (general information on the patient) being surveyed only at the start of treatment, a semistructured interview (Module 6) follows. On the basis of the information from the first 6 modules, the clinician evaluates suicidality (Module 7) and defines a suicide management plan (Module 8). Analyses are planned only for Modules 2, 3, 5, and 7.
b. The following events are considered (MedDRA coding): "Nervous system disorders (SOC, AEs)", "Psychiatric disorders (SOC, AEs)", "Gastrointestinal disorders (SOC, AEs)", "Eye disorders (SOC, AEs)".
c. No usable data are available on Module 5, items 1 and 2.

AE: adverse event; BHS: Beck Hopelessness Scale; EQ-5D: EuroQoL 5 Dimensions; MADRS: Montgomery-Åsberg Depression Rating Scale; MedDRA: Medical Dictionary for Regulatory Activities; QLDS: Quality of Life Depression Scale; RCT: randomized controlled trial; SAE: serious adverse event; SIBAT: Suicide Ideation and Behavior Assessment Tool; SOC: system organ class; VAS: visual analogue scale

2.2.2 Results

Table 3 to Table 8 summarize the results of the comparison of esketamine + antidepressant therapy versus placebo + antidepressant therapy as acute short-term treatment in adult patients with a moderate to severe episode of major depressive disorder so as to achieve a rapid reduction in depressive symptoms which have been clinically judged to constitute a psychiatric emergency. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

For all outcomes, the 2 analysis periods (1) to the end of the treatment phase with esketamine or placebo (Day 25) and (2) across the study to the end of follow-up observation (Day 90) were examined jointly.

Any conclusions regarding statistically significant differences between treatment groups are based on the company's pooled analysis (see Section 2.1 on pooled analyses).

Results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix A for the pooled study population up to Day 90. These results are consistent with the results up to Day 25 [15]. Kaplan-Meier curves on event-time analyses are found in Appendix B. Forest plots on IQWiG metaanalyses are found in Appendix C.

Table 3: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category **Outcome** **Study**	**Esketamine + antidepressant therapy**		**Placebo + antidepressant therapy**		**Esketamine + antidepressant therapy vs. placebo + antidepressant therapy**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Mortality (up to Day 90)					
All-cause mortality					
SUI3001	113	1 (0.9)	112	0 (0)	NC
SUI3002	114	0 (0)	113	0 (0)	NC
Total[b]	227	1 (0.4)	225	0 (0)	NC
Morbidity					
General depressive symptoms (at Day 25)					
Remission (MADRS)[c]					
SUI3001	114	46 (40.4)	112	38 (33.9)	1.21 [0.85; 1.71]; 0.295
SUI3002	115	49 (42.6)	115	31 (27.0)	1.56 [1.05; 2.30]; 0.027
Total[b]	229	95 (41.5)	227	69 (30.4)	1.36 [1.05; 1.77]; 0.020
Response (MADRS)[d]					
SUI3001	114	68 (59.6)	112	51 (45.5)	1.35 [1.05; 1.74]; 0.020
SUI3002	115	67 (58.3)	115	54 (47.0)	1.23 [0.94; 1.61]; 0.124
Total[b]	229	135 (59.0)	227	105 (46.3)	1.29 [1.07; 1.55]; 0.007
Health status (EQ-5D VAS[e], at Day 25)					
SUI3001	114	68 (59.6)	112	49 (43.8)	1.35 [1.03; 1.79]; 0.032
SUI3002	115	67 (58.3)	115	61 (53.0)	1.17 [0.91; 1.49]; 0.217
Total[b]	229	135 (59.0)	227	110 (48.5)	1.25 [1.04; 1.50]; 0.017

Table 3: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category **Outcome** **Study**	**Esketamine + antidepressant therapy**		**Placebo + antidepressant therapy**		**Esketamine + antidepressant therapy vs. placebo + antidepressant therapy**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Health-related quality of life	Outcome not surveyed				
Side effects (up to Day 90)					
AEs (supplementary information)					
SUI3001	113	105 (92.9)	112	87 (77.7)	–
SUI3002	114	108 (94.7)	113	95 (84.1)	–
Total[b]	227	213 (93.8)	225	182 (80.9)	–
SAEs					
SUI3001	113	17 (15.0)	112	15 (13.4)	1.12 [0.59; 2.14]; 0.723
SUI3002	114	13 (11.4)	113	17 (15.0)	0.76 [0.39; 1.49]; 0.420
Total[b]	227	30 (13.2)	225	32 (14.2)	0.93 [0.59; 1.48]; 0.756
Discontinuation due to AEs					
SUI3001	113	5 (4.4)	112	5 (4.5)	0.99 [0.30; 3.33]; 0.989
SUI3002	114	9 (7.9)	113	3 (2.7)	2.97 [0.83; 10.70]; 0.095
Total[b]	227	14 (6.2)	225	8 (3.6)	1.73 [0.74; 4.05]; 0.204
Nervous system disorders (SOC, AEs)					
SUI3001	113	79 (69.9)	112	51 (45.5)	1.54 [1.21; 1.94]; < 0.001
SUI3002	114	87 (76.3)	113	57 (50.4)	1.51 [1.23; 1.87]; < 0.001
Total[b]	227	166 (73.1)	225	108 (48.0)	1.52 [1.30; 1.78]; < 0.001
Psychiatric disorders (SOC, AEs)					
SUI3001	113	64 (56.6)	112	40 (35.7)	1.59 [1.18; 2.13]; 0.002
SUI3002	114	82 (71.9)	113	53 (46.9)	1.53 [1.22; 1.92]; < 0.001
Total[b]	227	146 (64.3)	225	93 (41.3)	1.56 [1.30; 1.87]; < 0.001

Table 3: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category **Outcome** **Study**	**Esketamine + antidepressant therapy**		**Placebo + antidepressant therapy**		**Esketamine + antidepressant therapy vs. placebo + antidepressant therapy**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Gastrointestinal disorders (SOC, AEs)					
SUI3001	113	45 (39.8)	112	34 (30.4)	1.31 [0.91; 1.88]; 0.140
SUI3002	114	65 (57.0)	113	42 (37.2)	1.53 [1.15; 2.05]; 0.004
Total[b]	227	110 (48.5)	225	76 (33.8)	1.43 [1.14; 1.80]; 0.002
Eye disorders (SOC, AEs)					
SUI3001	113	14 (12.4)	112	6 (5.4)	2.31 [0.92; 5.80]; 0.074
SUI3002	114	22 (19.3)	113	9 (8.0)	2.42 [1.17; 5.03]; 0.018
Total[b]	227	36 (15.9)	225	15 (6.7)	2.38 [1.34; 4.22]; 0.003

a. Cochran-Mantel-Haenszel method; morbidity outcomes stratified by centre and antidepressant therapy at randomization (antidepressant monotherapy / antidepressant therapy plus augmentation); side effects outcomes unstratified.
b. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.
c. Percentage of patients with remission, defined as MADRS total score ≤ 12; scale range 0 to 60 points; clinician-rated.
d. Percentage of patients with response, defined as improvement in MADRS total score by ≥ 50% over baseline; scale range 0 to 60 points; clinician-rated.
e. Percentage of patients with improvement, defined as a score increase by ≥ 15 points over baseline; scale range: 0 to 100 points

AE: adverse event; CI: confidence interval; EQ-5D: EuroQoL 5 Dimensions; IPD: individual patient data; MADRS: Montgomery-Åsberg Depression Rating Scale; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculated; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

Table 4: Results (morbidity, time to event) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy

Outcome category Outcome Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Morbidity					
General depressive symptoms (up to Day 90)					
Remission (MADRS)[b]					
SUI3001	114	17.1 [11.9; 21.9] 90 (78.9)	112	25.0 [17.1; 39.0] 72 (64.3)	1.48 [1.08; 2.02]; 0.014
SUI3002	115	14.9 [10.0; 21.0] 84 (73.0)	115	18.0 [11.0; 23.1] 86 (74.8)	1.23 [0.91; 1.66]; 0.181
Total[c]	229	14.9 [11.9; 18.0] 174 (76.0)	227	21.9 [14.9; 25.0] 158 (69.6)	1.34 [1.08; 1.67]; 0.007
Response (MADRS)[d]					
SUI3001	114	4.9 [2.1; 7.9] 100 (87.7)	112	7.9 [4.9; 14.0] 92 (82.1)	1.26 [0.95; 1.67]; 0.113
SUI3002	115	4.9 [2.1; 7.9] 97 (84.3)	115	7.9 [4.9; 11.0] 99 (86.1)	1.23 [0.93; 1.62]; 0.156
Total[c]	229	4.9 [2.1; 7.9] 197 (86.0)	227	7.9 [7.0; 10.0] 191 (84.1)	1.24 [1.02; 1.52]; 0.032
Health status (EQ-5D VAS[e], up to Day 90)					
SUI3001	114	10.0 [10.0; 11.9] 79 (69.3)	112	24.1 [11.9; 27.1] 76 (67.9)	1.22 [0.89; 1.67]; 0.218
SUI3002	115	11.0 [10.0; 11.9] 87 (75.7)	115	11.9 [11.0; 24.1] 78 (67.8)	1.32 [0.97; 1.79]; 0.078
Total[c]	229	11.0 [10.0; 11.9] 166 (72.5)	227	13.1 [11.9; 24.1] 154 (67.8)	1.26 [1.01; 1.57]; 0.036

a. Cox proportional hazards model; remission and response nonstratified; health status stratified by centre and antidepressant therapy at randomization (antidepressant monotherapy /antidepressant therapy plus augmentation).
b. Time to remission, defined as MADRS total score ≤ 12; scale range 0 to 60 points; clinician-rated.
c. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.
d. Time to response, defined as improvement of MADRS total score by ≥ 50% over baseline; scale range 0 to 60 points; clinician-rated.
e. Time to improvement, defined as a score increase by ≥ 15 points from baseline; scale range: 0 to 100 points

CI: confidence interval; EQ-5D: EuroQoL 5 Dimensions; HR: hazard ratio; IPD: individual patient data; MADRS: Montgomery-Åsberg Depression Rating Scale; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; VAS: visual analogue scale

Table 5: Results (morbidity, continuous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category Outcome Time point Study	Esketamine + antidepressant therapy			Placebo + antidepressant therapy			Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
	N[a]	Values at baseline mean (SD)	Change up to analysis time point Mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change up to analysis time point Mean[b] (SE)	MD [95% CI]; p-value[b] SMD
Morbidity							
General depressive symptoms							
BHS[c]							
At Day 25							
SUI3001	105	15.2 (4.3)	-7.1 (0.6)	98	15.9 (4.6)	-6.0 (0.6)	-1.07 [-2.75; 0.61]; 0.211
SUI3002	91	15.5 (4.2)	-7.5 (0.7)	96	15.6 (4.0)	-6.6 (0.7)	-0.86 [-2.64; 0.91]; 0.338
Total[d]	196	15.4 (4.2)	-7.4 (0.5)	194	15.8 (4.3)	-6.3 (0.5)	-1.01 [-2.23; 0.21]; 0.103
At Day 90							
SUI3001	84	15.2 (4.3)	-7.5 (0.7)	79	15.9 (4.6)	-7.1 (0.7)	-0.36 [-2.27; 1.56]; 0.712
SUI3002	78	15.5 (4.2)	-8.6 (0.7)	86	15.6 (4.0)	-7.7 (0.7)	-0.83 [-2.69; 1.03]; 0.381
Total[d]	162	15.4 (4.2)	-8.1 (0.5)	165	15.8 (4.3)	-7.5 (0.5)	-0.65 [-1.98; 0.67]; 0.330
QLDS[e]							
At Day 25							
SUI3001	104	27.3 (6.3)	-14.1 (1.1)	97	27.1 (6.5)	-11.3 (1.1)	-2.83 [-5.72; 0.06]; 0.055
SUI3002	92	26.7 (6.2)	-14.8 (1.1)	95	26.9 (5.0)	-11.4 (1.1)	-3.47 [-6.52; -0.41]; 0.026
Total[d]	196	27.0 (6.3)	-14.5 (0.8)	192	27.0 (5.8)	-11.4 (0.8)	-3.12 [-5.21; -1.02]; 0.004 Hedges' g: -0.29 [-0.49; -0.09]
At Day 90							
SUI3001	84	27.3 (6.3)	-15.0 (1.2)	79	27.1 (6.5)	-14.3 (1.3)	-0.73 [-4.18; 2.73]; 0.679
SUI3002	78	26.7 (6.2)	-16.2 (1.2)	86	26.9 (5.0)	-15.0 (1.2)	-1.19 [-4.48; 2.09]; 0.475
Total[d]	162	27.0 (6.3)	-15.6 (0.9)	165	27.0 (5.8)	-14.6 (0.9)	-0.96 [-3.33; 1.41]; 0.425

Table 5: Results (morbidity, continuous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category Outcome Time point Study	Esketamine + antidepressant therapy			Placebo + antidepressant therapy			Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
	N[a]	Values at baseline mean (SD)	Change up to analysis time point Mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change up to analysis time point Mean[b] (SE)	MD [95% CI]; p-value[b] SMD

a. Number of patients included in the analysis for calculating the effect estimation; baseline values may be based on different patient numbers.
b. Mean and SE (mean change by Day 25 and Day 90 per treatment arm) as well as mean difference, 95% CI, and p-value (between-group comparison): MMRM; variables used include, among others, baseline at study start and the stratification factors of centre and antidepressant therapy at randomization (antidepressant monotherapy / antidepressant therapy plus augmentation).
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention; scale range of 0 to 20 points.
d. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.
e. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention; scale range of 0 to 34 points.

BHS: Beck Hopelessness Scale; CI: confidence interval; EQ-5D: EuroQoL 5 Dimensions; IPD: individual patient data; MADRS: Montgomery-Åsberg Depression Rating Scale; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; QLDS: Quality of Life in Depression Scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

Table 6: Results (morbidity: suicidality, continuous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category Outcome Time point Study	Esketamine + antidepressant therapy			Placebo + antidepressant therapy			Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
	N[a]	Values at baseline mean (SD)	Change by analysis time point Mean (SD)	N[a]	Values at baseline mean (SD)	Change by analysis time point Mean (SD)	MD [95% CI]; p-value[b]
Morbidity							
Specific depressive symptoms: Suicidality (SIBAT)[c]							
Self-assessment of risk/protective factors (Module 2[d])							
At Day 25							
SUI3001	102	64.5 (9.8)	-25.1 (17.6)	94	66.8 (11.1)	-24.7 (18.6)	-0.40 [-5.50; 4.70]; 0.877
SUI3002	90	65.2 (9.4)	-29.2 (20.1)	94	62.7 (11.2)	-24.1 (19.5)	-5.10 [-10.86; 0.66]; 0.082
Total							-2.47 [-6.27; 1.33]; 0.203[e]
At Day 90							
SUI3001	87	64.2 (10.3)	-24.8 (20.6)	85	66.9 (11.3)	-25.4 (21.1)	0.60 [-5.67; 6.87]; 0.850
SUI3002	83	65.3 (9.5)	-31.7 (19.2)	88	62.6 (11.1)	-26.9 (19.7)	-4.80 [-10.68; 1.08]; 0.109
Total							-2.28 [-6.53; 1.98]; 0.294[e]
Self-assessment of suicidal thoughts (Module 3)[f]							
At Day 25							
SUI3001	96	149.4 (31.2)	-69.1 (47.2)	93	149.1 (35.3)	-59.2 (46.2)	-9.90 [-23.31; 3.51]; 0.147
SUI3002	84	142.0 (28.4)	-69.4 (43.5)	88	141.8 (30.7)	-65.3 (44.7)	-4.10 [-17.38; 9.18]; 0.543
Total							-6.97 [-16.34; 2.40]; 0.145[e]
At Day 90							
SUI3001	82	148.7 (32.0)	-68.1 (56.2)	79	148.7 (36.0)	-68.5 (49.7)	0.40 [-16.15; 16.95]; 0.962
SUI3002	80	140.6 (27.6)	-77.8 (46.4)	86	140.8 (30.9)	-73.0 (49.5)	-4.80 [-19.53; 9.93]; 0.521
Total							-2.50 [-13.40; 8.40]; 0.653[e]

Table 6: Results (morbidity: suicidality, continuous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category **Outcome** **Time point** **Study**	**Esketamine + antidepressant therapy**			**Placebo + antidepressant therapy**			**Esketamine + antidepressant therapy vs. placebo + antidepressant therapy**
	N[a]	**Values at study start Median [min; max]**	**Changes by analysis time Median [min; max]**	**N[a]**	**Values at study start Median [min; max]**	**Changes by analysis time Median [min; max]**	**MD [95% CI]; p value**
Self-assessment of desire to die (Module 5, Item 1)[g]							
At Day 25							
SUI3001	96	3.0 [0; 4]	-2.0 [-4; 1]	93	3.0 [0; 4]	-2.0 [-4; 1]	ND
SUI3002	84	3.0 [0; 4]	-2.0 [-4; 2]	88	3.0 [0; 4]	-2.0 [-4; 2]	ND
Total					ND		
At Day 90							
SUI3001	82	3.0 [0; 4]	-2.0 [-4; 2]	79	3.0 [0; 4]	-2.0 [-4; 1]	ND
SUI3002	80	3.0 [0; 4]	-3.0 [-4; 1]	86	3.0 [0; 4]	-2.0 [-4; 2]	ND
Total					ND		
Self-assessment of suicide intent (Module 5, Item 2)[g]							
At Day 25							
SUI3001	96	3.0 [0; 4]	-2.0 [-4; 1]	93	3.0 [0; 4]	-2.0 [-4; 1]	ND
SUI3002	84	3.0 [0; 4]	-2.0 [-4; 2]	88	3.0 [0; 4]	-2.0 [-4; 2]	ND
Total					ND		
At Day 90							
SUI3001	82	3.0 [0; 4]	-2.0 [-4; 1]	79	3.0 [0; 4]	-2.0 [-4; 1]	ND
SUI3002	80	3.0 [0; 4]	-2.0 [-4; 0]	86	3.0 [0; 4]	-2.0 [-4; 2]	ND
Total					ND		

Table 6: Results (morbidity: suicidality, continuous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category Outcome Time point Study	Esketamine + antidepressant therapy			Placebo + antidepressant therapy			Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
	N[a]	Values at study start Median [min; max]	Change by analysis time point Mean[b] (SE)[h]	N[a]	Values at study start Median [min; max]	Change by analysis time point Mean[b] (SE)[h]	MD [95% CI][h]; p-value[i]
Self-assessment of the frequency of suicidal thoughts (Module 5, Item 3)[g]							
At Day 25							
SUI3001	96	3.0 [0; 4]	-1.8 (0.1)	93	3.0 [0; 4]	-1.8 (0.1)	-0.12 [-0.38; 0.15]; 0.380
SUI3002	84	2.0 [0; 4]	-1.8 (0.1)	88	3.0 [0; 4]	-1.8 (0.1)	-0.01 [-0.31; 0.29]; 0.935
Total[j]	180	2.0 [0; 4]	-1.8 (0.1)	181	3.0 [0; 4]	-1.8 (0.1)	-0.07 [-0.27; 0.13]; 0.476
At Day 90							
SUI3001	82	3.0 [0; 4]	-1.7 (0.1)	79	3.0 [0; 4]	-1.8 (0.1)	0.09 [-0.22; 0.40]; 0.552
SUI3002	80	2.0 [0; 4]	-1.9 (0.1)	86	3.0 [0; 4]	-1.7 (0.1)	-0.12 [-0.36; 0.11]; 0.299
Total[j]	162	2.0 [0; 4]	-1.8 (0.1)	165	3.0 [0; 4]	-1.8 (0.1)	-0.02 [-0.22; 0.18]; 0.838
Self-assessment of the likelihood of suicide (Module 5, Item 4)[g]							
At Day 25							
SUI3001	96	2.0 [0; 4]	-1.7 (0.1)	93	2.0 [0; 4]	-1.5 (0.1)	-0.14 [-0.37; 0.09]; 0.218
SUI3002	84	2.0 [0; 4]	-1.4 (0.1)	88	2.0 [0; 4]	-1.3 (0.1)	-0.10 [-0.40; 0.20]; 0.503
Total[j]	180	2.0 [0; 4]	-1.6 (0.1)	181	2.0 [0; 4]	-1.4 (0.1)	-0.13 [-0.31; 0.06]; 0.180
At Day 90							
SUI3001	82	2.0 [0; 4]	-1.6 (0.1)	79	2.0 [0; 4]	-1.6 (0.1)	0.00 [-0.26; 0.27]; 0.974
SUI3002	80	2.0 [0; 4]	-1.6 (0.1)	86	2.0 [0; 4]	-1.5 (0.1)	-0.09 [-0.30; 0.12]; 0.402
Total[j]	162	2.0 [0; 4]	-1.6 (0.1)	165	2.0 [0; 4]	-1.6 (0.1)	-0.05 [-0.22; 0.11]; 0.530

Table 6: Results (morbidity: suicidality, continuous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category **Outcome** **Time point** **Study**	**Esketamine + antidepressant therapy**			**Placebo + antidepressant therapy**			**Esketamine + antidepressant therapy vs. placebo + antidepressant therapy**
	N[a]	**Values at study start Median [min; max]**	**Change by analysis time point Mean[b] (SE)[h]**	**N[a]**	**Values at study start Median [min; max]**	**Change by analysis time point Mean[b] (SE)[h]**	**MD [95% CI][h]; p-value[i]**
Global clinical impression of the frequency of suicidal thinking (Module7, FoST)[k]							
At Day 25							
SUI3001	95	3.0 [1; 5]	-2.4 (0.1)	93	3.0 [1; 5]	-2.4 (0.1)	0.01 [-0.28; 0.30]; 0.961
SUI3002	85	3.0 [1; 5]	-2.6 (0.1)	88	3.0 [1; 5]	-2.4 (0.1)	-0.18 [-0.53; 0.17]; 0.306
Total[j]	180	3.0 [1; 5]	-2.5 (0.1)	181	3.0 [1; 5]	-2.4 (0.1)	-0.09 [-0.31; 0.14]; 0.445
At Day 90							
SUI3001	84	3.0 [1; 5]	-2.5 (0.1)	79	3.0 [1; 5]	-2.5 (0.1)	0.01 [-0.35; 0.37]; 0.961
SUI3002	80	3.0 [1; 5]	-2.7 (0.1)	86	3.0 [1; 5]	-2.4 (0.1)	-0.30 [-0.57; -0.04]; 0.027
Total[j]	164	3.0 [1; 5]	-2.6 (0.1)	165	3.0 [1; 5]	-2.4 (0.1)	-0.15 [-0.38; 0.07]; 0.179
Clinical global impression of imminent suicide risk (Module 7, CGI-SR-I)[l]							
At Day 25							
SUI3001	95	4.0 [0; 6]	-2.7 (0.1)	93	4.0 [0; 6]	-2.6 (0.1)	-0.07 [-0.38; 0.23]; 0.649
SUI3002	85	4.0 [0; 6]	-3.0 (0.1)	88	4.0 [1; 6]	-2.7 (0.1)	-0.36 [-0.68; -0.04]; 0.029
Total[j]	180	4.0 [0; 6]	-2.9 (0.1)	181	4.0 [0; 6]	-2.7 (0.1)	-0.21 [-0.43; 0.01]; 0.067
At Day 90							
SUI3001	84	4.0 [0; 6]	-2.8 (0.1)	79	4.0 [0; 6]	-3.1 (0.1)	0.24 [-0.12; 0.60]; 0.187
SUI3002	80	4.0 [0; 6]	-3.0 (0.1)	86	4.0 [1; 6]	-2.7 (0.1)	-0.24 [-0.54; 0.06]; 0.111
Total[j]	164	4.0 [0; 6]	-2.9 (0.1)	165	4.0 [0; 6]	-2.9 (0.1)	0.00 [-0.23; 0.23]; 0.990

Table 6: Results (morbidity: suicidality, continuous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category **Outcome** **Time point** **Study**	**Esketamine + antidepressant therapy**			**Placebo + antidepressant therapy**			**Esketamine + antidepressant therapy vs. placebo + antidepressant therapy**
	N[a]	**Values at study start Median [min; max]**	**Change by analysis time point Mean (SE)[h]**	**N[a]**	**Values at study start Median [min; max]**	**Change by analysis time point Mean (SE)[h]**	**MD [95% CI][h]; p-value[i]**
Clinical global impression of long-term suicide risk (Module 7, CGI-SR-LT)[l]							
At Day 25							
SUI3001	95	4.0 [1; 6]	-2.1 (0.1)	93	4.0 [1; 6]	-2.1 (0.1)	0.00 [-0.31; 0.31]; 0.993
SUI3002	85	4.0 [1; 6]	-2.1 (0.1)	88	4.0 [1; 6]	-1.9 (0.1)	-0.22 [-0.55; 0.12]; 0.201
Total[j]	180	4.0 [1; 6]	-2.1 (0.1)	181	4.0 [1; 6]	-2.0 (0.1)	-0.10 [-0.33; 0.12]; 0.359
At Day 90							
SUI3001	84	4.0 [1; 6]	-2.3 (0.1)	79	4.0 [1; 6]	-2.4 (0.1)	0.08 [-0.30; 0.46]; 0.670
SUI3002	80	4.0 [1; 6]	-2.4 (0.1)	86	4.0 [1; 6]	-2.1 (0.1)	-0.28 [-0.60; 0.04]; 0.088
Total[j]	164	4.0 [1; 6]	-2.3 (0.1)	165	4.0 [1; 6]	-2.3 (0.1)	-0.09 [-0.33; 0.16]; 0.476

Table 6: Results (morbidity: suicidality, continuous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Outcome category Outcome Time point Study	Esketamine + antidepressant therapy	Placebo + antidepressant therapy	Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
a. Number of patients included in the analysis for calculating the effect estimation; baseline values may be based on different patient numbers. b. MD, CI, and p-value: IQWiG calculation (t-test). c. SIBAT consists of 8 modules, 5 of them patient reported (Modules 1 through 5) and 3 clinician rated (Modules 6 through 8). Completion of Modules 1 to 5, with Module 1 (general information on the patient) being surveyed only at the start of treatment, is followed by a semistructured interview (Module 6). On the basis of the information from the first 6 modules, the clinician evaluates suicidality (Module 7) and defines a suicide management plan (Module 8). Analyses are planned only for Modules 2, 3, 5, and 7. d. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention; scale range of 0 to 105 points. e. Metaanalysis with fixed effect (inverse variance); IQWiG calculation. f. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention; scale range of 0 to 240 points. g. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention; scale range of 0 to 4 points. h. Mean and SE (mean change by Day 25 or Day 90 per treatment arm) as well as mean difference and 95% CI (between-group comparison): ANCOVA of changes from study start, with the variables of treatment, analysis centre, antidepressant therapy at randomization (antidepressant monotherapy / antidepressant therapy + augmentation therapy), and baseline value. i. p-value: ANCOVA on the ranks of changes from study start, with the variables of treatment, analysis centre, antidepressant therapy at randomization (antidepressant monotherapy / antidepressant therapy + augmentation therapy), and baseline value (not as rank). j. “Pooled analysis” by the company on the basis of IPD; see Section 2.1 on pooled analyses. k. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention; scale range of 0 to 5 points. l. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention; scale range of 0 to 6 points. CGI-SR-I: Clinical Global Impression of Imminent Suicide Risk; CGI-SR-LT: Clinical Global Impression of Long-Term Suicide Risk; CGI-SS-R: Clinical Global Impression of Severity of Suicidality Revised Version; CI: confidence interval; FoST: Frequency of Suicidal Thinking; IPD: individual patient data; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SIBAT: Suicide Ideation and Behavior Assessment Tool; SMD: standardised mean difference			

Table 7: Results (morbidity: suicidality, dichotomous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy

Outcome category **Outcome** **Study**	**Esketamine + antidepressant therapy**		**Placebo + antidepressant therapy**		**Esketamine + antidepressant therapy vs. placebo + antidepressant therapy**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Morbidity (at Day 25)					
Specific depressive symptoms: Suicidality (SIBAT)					
Clinical Global Impression of Severity of Suicidality (Module 7, CGI-SS-R score of 0 or 1)[b]					
SUI3001	114	71 (62.3)	112	57 (50.9)	1.24 [0.99; 1.55]; 0.064
SUI3002	115	69 (60.0)	115	66 (57.4)	1.05 [0.83; 1.32]; 0.670
Total[c]	229	140 (61.1)	227	123 (54.2)	1.14 [0.97; 1.34]; 0.125

a. Cochran-Mantel-Haenszel method; stratified by centre and antidepressant therapy at randomization (antidepressant monotherapy / antidepressant plus augmentation).
b. On a scale of 0 to 6 points.
c. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.

CGI-SS-R: Clinical Global Impression of Severity of Suicidality Revised Version; CI: confidence interval; IPD: individual patient data; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

Table 8: Results (morbidity: suicidality, time to event) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy

Outcome category Outcome Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Morbidity (at Day 90)					
Specific depressive symptoms: Suicidality (SIBAT)					
Clinical Global Impression of Severity of Suicidality (Module 7, CGI-SS-R score of 0 or 1)[b]					
SUI3001	114	4.9 [2.1; 7.9] 100 (87.7)	112	7.9 [4.0; 14.0] 96 (85.7)	1.21 [0.91; 1.60]; 0.183
SUI3002	115	4.0 [2.1; 6.1] 103 (89.6)	115	4.9 [3.0; 7.9] 101 (87.8)	1.22 [0.93; 1.61]; 0.156
Total[c]	229	4.0 [2.1; 7.0] 203 (88.6)	227	7.0 [4.0; 10.0] 197 (86.8)	1.21 [0.99; 1.47]; 0.058

a. Cox proportional hazards model; unstratified.
b. On a scale of 0 to 6 points.
c. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.

CGI-SS-R: Clinical Global Impression of Severity of Suicidality Revised Version; CI: confidence interval; HR: hazard ratio; IPD: individual patient data; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial

Mortality

All-cause mortality

Up to Day 90, 1 person died in the intervention arm, and nobody died in the control arm. For the outcome of all-cause mortality, this results in no apparent advantage or disadvantage for esketamine + antidepressant therapy in comparison with placebo + antidepressant therapy.

Morbidity

General depressive symptoms (MADRS, BHS, and QLDS)

For the outcome of general depressive symptoms, surveyed with MADRS, BHS, and QLDS, the pooled analysis shows statistically significant and relevant differences between treatment groups only in MADRS. Both the responder analysis at Day 25 and the time-to-event analysis at Day 90 show an advantage for esketamine + antidepressant therapy versus placebo + antidepressant therapy for remission and response. While the pooled analysis does show a statistically significant advantage of esketamine + antidepressant therapy versus placebo + antidepressant therapy at Day 25 for QLDS, the confidence interval of the standardized mean difference is not fully outside the irrelevance range of -0.2 to 0.2. The effect can therefore not be inferred to be relevant.

Health status (EQ-5D VAS)

For the outcome of health status, measured by an improvement by ≥ 15 points in the EQ-5D VAS, the pooled analysis shows a statistically significant difference in favour or esketamine + antidepressant therapy versus placebo + antidepressant therapy both in the responder analysis at Day 25 and in the time-to-event analysis at Day 90.

The analyses on improvement by ≥ 7 and ≥ 10 points are presented as supplementary information in Appendix D.

Specific depressive symptoms: Suicidality (SIBAT)

For the outcome "specific depressive symptoms, suicidality", as measured with SIBAT, analyses are available on all relevant modules except items 1 and 2 of Module 5. The pooled analyses show no statistically significant difference between treatment groups at Day 25 or Day 90, neither for patient-reported modules nor for clinician-rated modules. The available descriptive data on items 1 and 2 of Module 5 likewise reveal no advantage or disadvantage of esketamine + antidepressant therapy versus placebo + antidepressant therapy.

Health-related quality of life

The SUI3001 and SUI3002 studies did not survey any outcomes in this category.

Side effects

SAEs, discontinuation due to AEs

For the outcomes of SAEs and discontinuation due to AEs, the pooled analysis shows no statistically significant differences between treatment groups.

Specific AEs

For each of the specific AEs of nervous system disorders, psychiatric disorders, gastrointestinal disorders, and eye disorders (each system organ class [SOC], AEs), the pooled analysis shows a statistically significant difference to the disadvantage of esketamine + antidepressant therapy versus placebo + antidepressant therapy.

2.2.3 Subgroups and other effect modifiers

For this addendum, the following potential effect modifiers were taken into account:

- Sex (female/male)
- Age (18 to 34 years / 35 to 54 years / 55 to 64 years)
- MADRS total score at study start (≤ median / > median)

None of the 3 characteristics showed any statistically significant interactions which were consistent across the studied operationalizations and across multiple related outcomes (e.g. response and remission [MADRS]). In summary, there are no relevant effect modifications or

subgroup effects. The presentation of isolated subgroup results was therefore foregone despite statistically significant interaction regarding the corresponding characteristic.

2.3 Summary

Overall, the results of the SUI3001 and SUI3002 studies show the following for esketamine + antidepressant therapy versus placebo + antidepressant therapy:

- An advantage of esketamine + antidepressant therapy with regard to general depressive symptoms as measured with MADRS (remission and response), but not as measured with BHS and QLDS; congruently, an advantage of esketamine + antidepressant therapy was found with regard to health status (EQ-5D VAS); these advantages became apparent as early as in the initial weeks of treatment
- No advantage or disadvantage of esketamine + antidepressant therapy with regard to suicidality as measured with SIBAT
- A disadvantage of esketamine + antidepressant therapy with regard to multiple specific AEs (nervous system disorders, psychiatric disorders, gastrointestinal disorders, eye disorders); these disadvantages likewise became apparent already in the initial weeks of treatment
- No advantage or disadvantage of esketamine + antidepressant therapy with regard to SAEs and discontinuation due to AEs

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Appendix A Results on side effects

For total rates of AEs and SAEs, the tables below present events for SOCs and preferred terms (PTs) as per Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Total rate of AEs (any severity): events which occurred in at least 10% of patients in 1 study arm
- Total rate of SAEs: events which occurred in at least 5% of patients in 1 study arm
- Additionally, for all events of any severity: events which occurred in at least 10 patients and in at least 1% of patients in 1 study arm

For the outcome of discontinuation due to AEs, all events (SOCs/PTs) which lead to discontinuation are presented.

Table 9: Common AEs[a] – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Esketamine + antidepressant therapy** **N = 227**	**Placebo + antidepressant therapy** **N = 225**
SUI3001 and SUI3002[c]		
Total rate of AEs up to Day 90	213 (93.8)	182 (80.9)
Nervous system disorders	166 (73.1)	108 (48.0)
Dizziness	89 (39.2)	33 (14.7)
Headache	52 (22.9)	55 (24.4)
Somnolence	49 (21.6)	24 (10.7)
Dysgeusia	45 (19.8)	29 (12.9)
Paraesthesia	27 (11.9)	8 (3.6)
Sedation	24 (10.6)	6 (2.7)
Hypaesthesia	20 (8.8)	3 (1.3)
Dizziness, orthostatic	15 (6.6)	4 (1.8)
Tremor	9 (4.0)	10 (4.4)
Psychiatric disorders	146 (64.3)	93 (41.3)
Dissociation	77 (33.9)	13 (5.8)
Anxiety	30 (13.2)	33 (14.7)
Insomnia	27 (11.9)	25 (11.1)
Euphoric mood	17 (7.5)	1 (0.4)
Suicidal thoughts	17 (7.5)	20 (8.9)
Depression	16 (7.0)	15 (6.7)
Depersonalization-derealization disorder	14 (6.2)	0 (0)
Suicide attempt	11 (4.8)	6 (2.7)
Derealization	10 (4.4)	3 (1.3)
Gastrointestinal disorders	110 (48.5)	76 (33.8)
Nausea	64 (28.2)	34 (15.1)
Vomiting	28 (12.3)	13 (5.8)
Constipation	24 (10.6)	17 (7.6)
Paraesthesia, oral	16 (7.0)	3 (1.3)
Hypoaesthesia, oral	12 (5.3)	2 (0.9)
Dry mouth	10 (4.4)	6 (2.7)
Diarrhoea	8 (3.5)	13 (5.8)
Respiratory, thoracic, and mediastinal disorders	52 (22.9)	36 (16.0)
Nasal symptoms	12 (5.3)	13 (5.8)
Oropharyngeal pain	12 (5.3)	4 (1.8)
General disorders and administration site conditions	47 (20.7)	28 (12.4)

Table 9: Common AEs[a] – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Esketamine + antidepressant therapy** **N = 227**	**Placebo + antidepressant therapy** **N = 225**
Investigations	44 (19.4)	25 (11.1)
Elevated blood pressure	27 (11.9)	9 (4.0)
Eye disorders	36 (15.9)	15 (6.7)
Blurry vision	27 (11.9)	11 (4.9)
Infections and infestations	34 (15.0)	30 (13.3)
Diseases of the skin and subcutaneous tissue	28 (12.3)	21 (9.3)
Hyperhidrosis	10 (4.4)	4 (1.8)
Musculoskeletal and connective tissue disorders	27 (11.9)	22 (9.8)
Disorders of the ear and labyrinth	21 (9.3)	7 (3.1)
Vertigo	14 (6.2)	1 (0.4)
Injury, poisoning, and procedural complications	13 (5.7)	13 (5.8)
Metabolic and nutritional disorders	9 (4.0)	14 (6.2)
Reproductive system and breast disorders	4 (1.8)	10 (4.4)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 21.1; SOC and PT terminology adopted unrevised from Module 4 B.
c. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.

AE: adverse event; IPD: individual patient data; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Table 10: Common AEs[a] – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Esketamine + antidepressant therapy N = 227**	**Placebo + antidepressant therapy N = 225**
SUI3001 and SUI3002[c]		
Total rate of SAEs up to Day 90	30 (13.2)	32 (14.2)
Psychiatric disorders	29 (12.8)	22 (9.8)
Suicide attempt	11 (4.8)	6 (2.7)
Suicidal thoughts	6 (2.6)	10 (4.4)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 21.1; SOC and PT terminology adopted unmodified from Module 4 B.
c. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.

IPD: individual patient data; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class

Table 11: Discontinuation due to AEs – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Study	Patients with event n (%)	
SOC[a] PT[a]	Esketamine + antidepressant therapy N = 227	Placebo + antidepressant therapy N = 225
SUI3001 and SUI3002[b]		
Total rate of discontinuation due to AEs up to Day 90	14 (6.2)	8 (3.6)
Psychiatric disorders	7 (3.1)	3 (1.3)
Dissociation	3 (1.3)	0 (0)
Depersonalization-derealization disorder	2 (0.9)	0 (0)
Confusion	1 (0.4)	0 (0)
Hallucination, optical	1 (0.4)	0 (0)
Aggression	0 (0)	1 (0.4)
Depression, suicidal	0 (0)	1 (0.4)
Suicidal thoughts	0 (0)	1 (0.4)
Gastrointestinal disorders	4 (1.8)	0 (0)
Nausea	2 (0.9)	0 (0)
Dyspepsia	1 (0.4)	0 (0)
Paraesthesia, oral	1 (0.4)	0 (0)
Vomiting	1 (0.4)	0 (0)
Nervous system disorders	4 (1.8)	0 (0)
Dizziness	1 (0.4)	0 (0)
Dizziness, orthostatic	1 (0.4)	0 (0)
Headache	1 (0.4)	0 (0)
Hypaesthesia	1 (0.4)	0 (0)
Sedation	1 (0.4)	0 (0)
Somnolence	1 (0.4)	0 (0)
Respiratory, thoracic, and mediastinal disorders	3 (1.3)	1 (0.4)
Nasal symptoms	1 (0.4)	0 (0)
Pharyngeal hypoesthesia	1 (0.4)	0 (0)
Pharyngeal irritation	1 (0.4)	0 (0)
Pneumothorax	0 (0)	1 (0.4)
Investigations	2 (0.9)	1 (0.4)
Elevated blood pressure	2 (0.9)	0 (0)
Elevated diastolic blood pressure	0 (0)	1 (0.4)
Heart disease	0 (0)	3 (1.3)
Arrhythmia	0 (0)	1 (0.4)
Atrioventricular bloc, first degree	0 (0)	1 (0.4)
Pericardial effusion	0 (0)	1 (0.4)
Hepatobiliary disorders	0 (0)	1 (0.4)
Hypertransaminasemia	0 (0)	1 (0.4)

Table 11: Discontinuation due to AEs – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Esketamine + antidepressant therapy** **N = 227**	**Placebo + antidepressant therapy** **N = 225**
a. MedDRA version 21.1; SOC and PT terminology adopted unmodified from M 4 B. b. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses. AE: adverse event; IPD: individual patient data; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class		

Appendix B Graphic representation of the company's pooled time-to-event analyses (Kaplan-Meier curves)

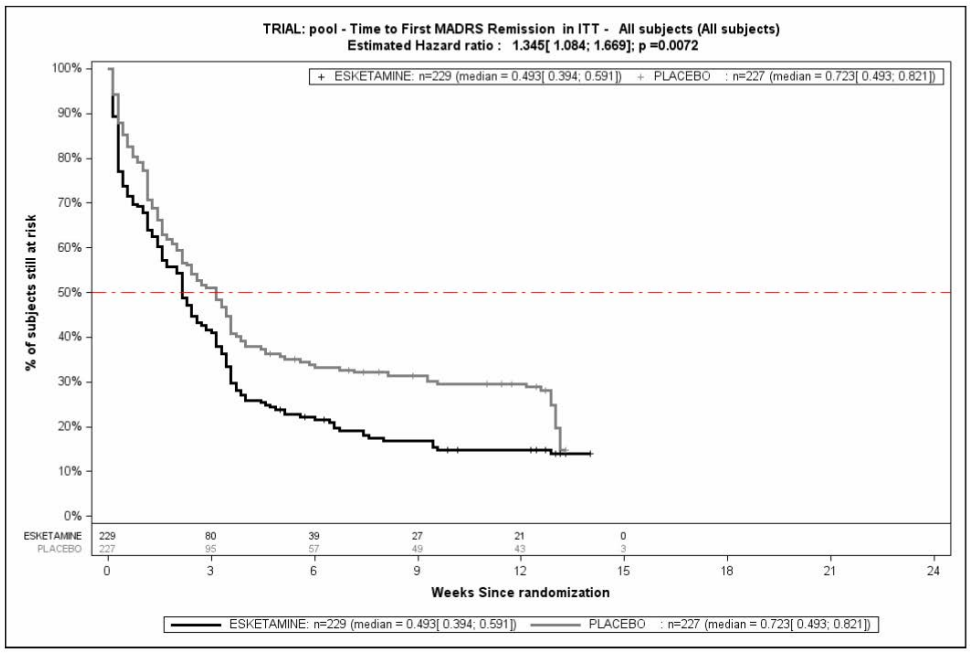


Figure 1: Kaplan-Meier curves on the outcome of general depressive symptoms: remission (MADRS total score ≤ 12) by Day 90; pooled analysis (SUI3001 + SUI3002)

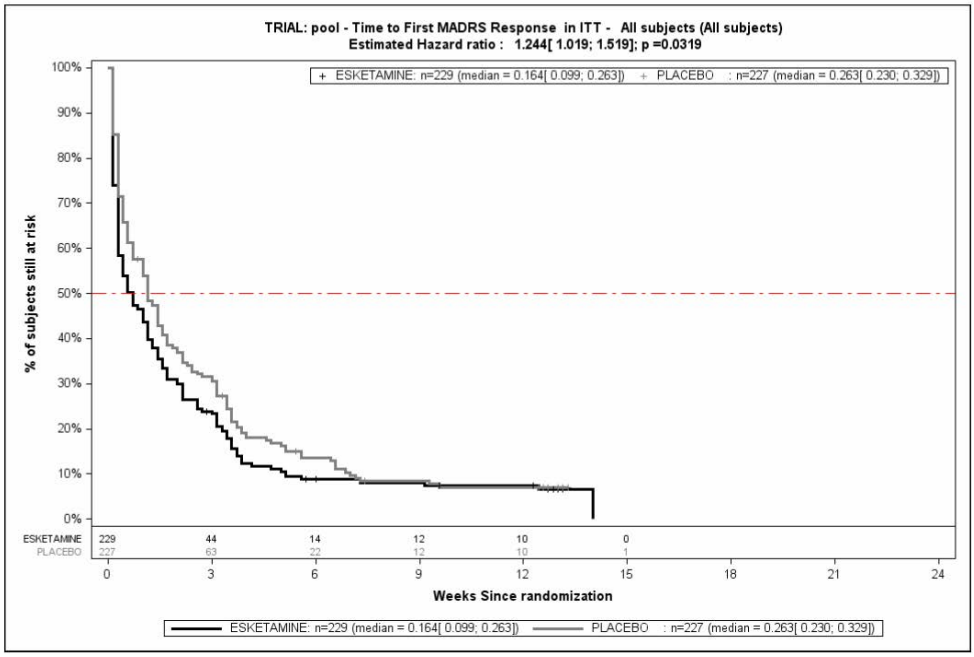


Figure 2: Kaplan-Meier curves on the outcome of general depressive symptoms: response (improvement in MADRS total score by ≥ 50%) by Day 90; pooled analysis (SUI3001 + SUI3002)

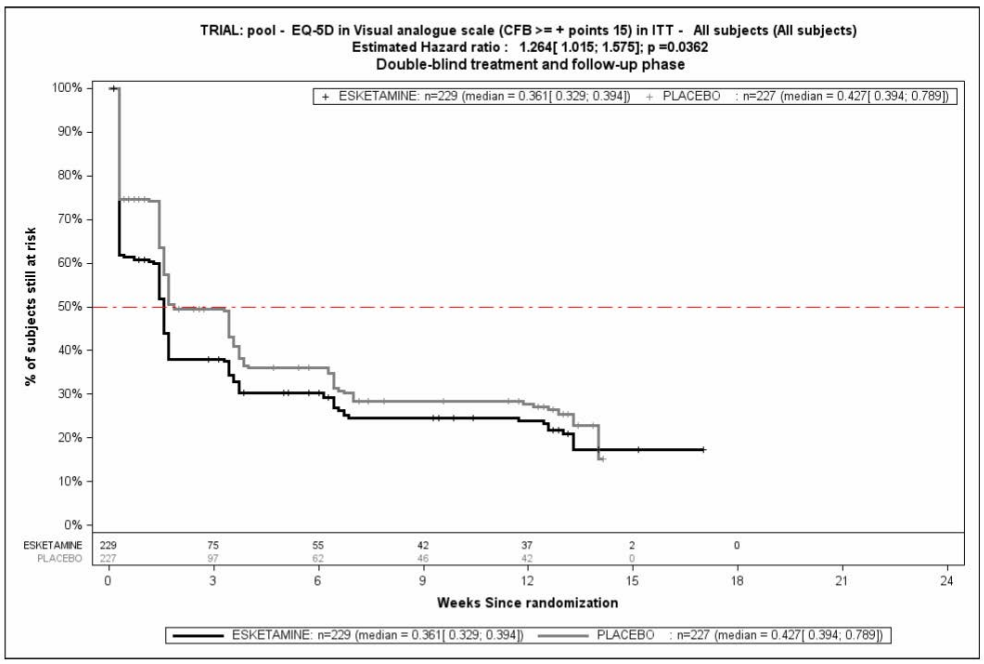


Figure 3: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS, improvement by ≥ 15 points) up to Day 90; pooled analysis (SUI3001 + SUI3002)

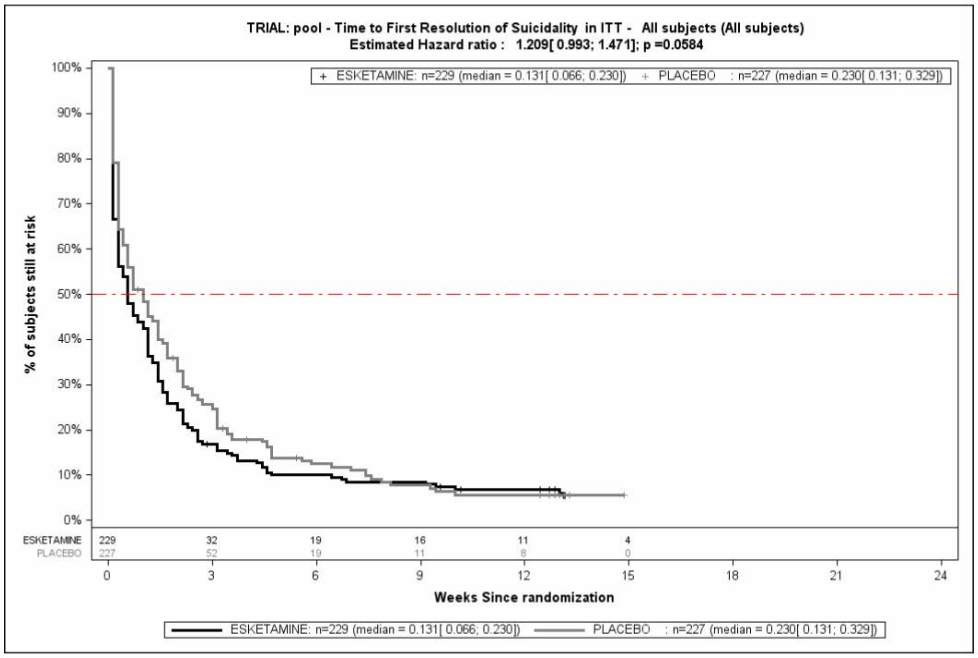
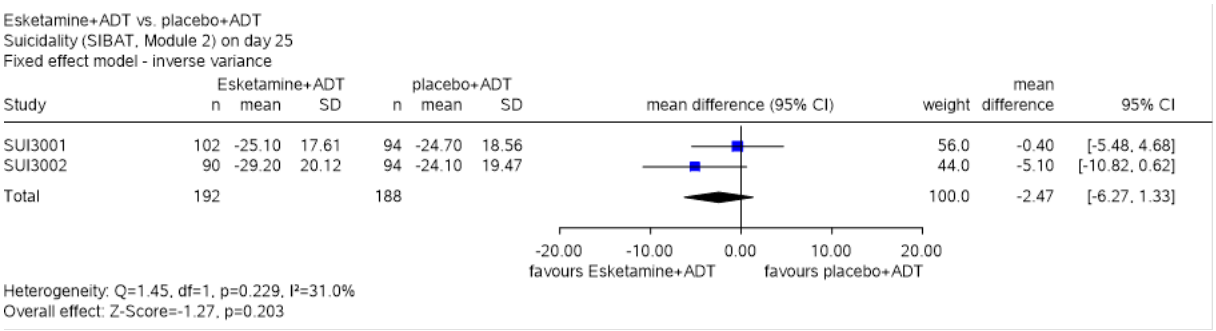


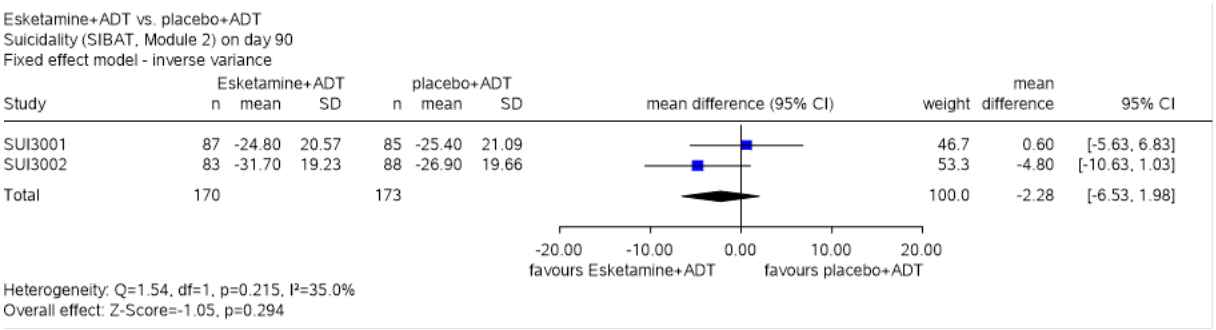
Figure 4: Kaplan-Meier curves on the outcome of specific depressive symptoms: suicidality (SIBAT), Clinical Global Impression of the Severity of Suicidality (Module 7, CGI-SS-R score of 0 to 1) by Day 90; pooled analysis (SUI3001 + SUI3002)

Appendix C Figures for IQWiG metaanalysis



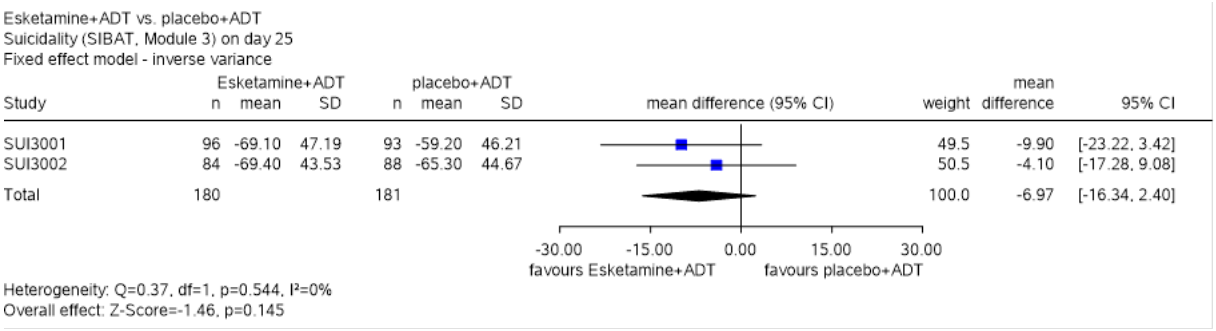
ADT: antidepressant therapy

Figure 5: Metaanalysis (model with fixed effect; inverse variance method) for the outcome of specific depressive symptoms: suicidality (SIBAT, Module 2) at Day 25



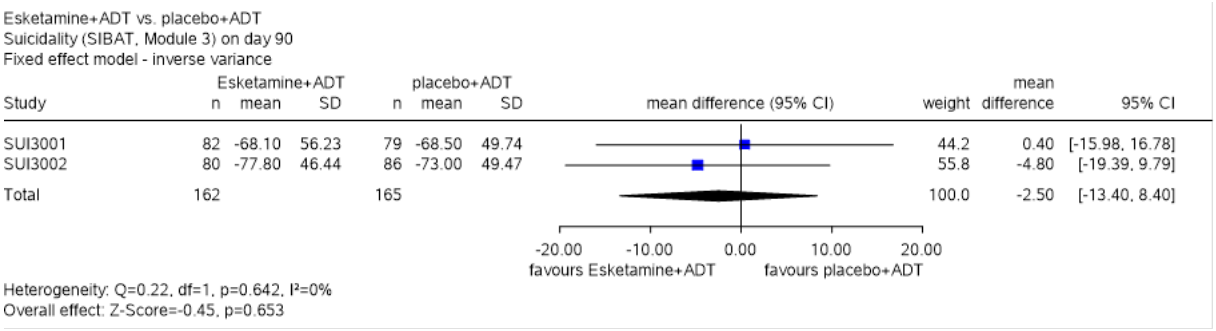
ADT: antidepressant therapy

Figure 6: Metaanalysis (model with fixed effect; inverse variance method) for the outcome of specific depressive symptoms: suicidality (SIBAT, Module 2) at Day 90



ADT: antidepressant therapy

Figure 7: Metaanalysis (model with fixed effect; inverse variance method) for the outcome of specific depressive symptoms: suicidality (SIBAT, Module 3) at Day 25



ADT: antidepressant therapy

Figure 8: Metaanalysis (model with fixed effect; inverse variance method) for the outcome of specific depressive symptoms: suicidality (SIBAT, Module 3) at Day 90

Appendix D Supplementary presentation of results on morbidity

Table 12: Results (morbidity, supplementary presentation, dichotomous) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy

Outcome category Outcome Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Morbidity (at Day 25)					
Health status (EQ-5D VAS)					
Improvement by ≥ 7 points)[b]					
SUI3001	114	82 (71.9)	112	82 (73.2)	0.95 [0.81; 1.12]; 0.556
SUI3002	115	87 (75.7)	115	87 (75.7)	1.06 [0.91; 1.24]; 0.446
Total[c]	229	169 (73.8)	227	169 (74.4)	1.01 [0.90; 1.13]; 0.896
Improvement by ≥ 10 points[b]					
SUI3001	114	78 (68.4)	112	78 (69.6)	0.95 [0.79; 1.13]; 0.540
SUI3002	115	86 (74.8)	115	84 (73.0)	1.08 [0.92; 1.28]; 0.342
Total[c]	229	164 (71.6)	227	162 (71.4)	1.01 [0.90; 1.14]; 0.811

a. Cochran-Mantel-Haenszel method; stratified by centre and antidepressant therapy at randomization (antidepressant monotherapy / antidepressant plus augmentation).
b. Percentage of patients with improvement, defined as a score increase by the respective points over baseline; scale range 0 to 100 points.
c. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.

CI: confidence interval; EQ-5D: EuroQoL 5 Dimensions; IPD: individual patient data; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; VAS: visual analogue scale

Table 13: Results (morbidity, supplementary presentation, time to event) – RCT, direct comparison: esketamine + antidepressant therapy vs. placebo + antidepressant therapy

Outcome category Outcome Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs. placebo + antidepressant therapy
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Morbidity (Day 90)					
Health status (EQ-5D VAS)					
Improvement by ≥ 7 points)[b]					
SUI3001	114	3.0 [2.1; 10.0] 86 (75.4)	112	11.0 [10.0; 11.9] 88 (78.6)	1.04 [0.77; 1.40]; 0.797
SUI3002	115	2.1 [2.1; 10.0] 97 (84.3)	115	10.0 [2.1; 10.0] 91 (79.1)	1.25 [0.94; 1.66]; 0.132
Total[c]	229	2.1 [2.1; 10.0] 183 (79.9)	227	10.0 [10.0; 11.0] 179 (78.9)	1.13 [0.92; 1.39]; 0.238
Improvement by ≥ 10 points[b]					
SUI3001	114	10.0 [2.1; 11.9] 83 (72.8)	112	11.0 [10.0; 11.9] 85 (75.9)	1.02 [0.75; 1.38]; 0.904
SUI3002	115	2.1 [2.1; 10.0] 94 (81.7)	115	10.0 [2.1; 11.0] 90 (78.3)	1.23 [0.92; 1.64]; 0.169
Total[c]	229	10.0 [2.1; 10.0] 177 (77.3)	227	10.0 [10.0; 11.0] 175 (77.1)	1.11 [0.90; 1.37]; 0.334

a. Cox proportional hazards model; unstratified.
b. Time to improvement, defined as a score increase by the respective points over baseline; scale range 0 to 100 points.
c. "Pooled analysis" by the company on the basis of IPD; see Section 2.1 on pooled analyses.

CI: confidence interval; EQ-5D: EuroQoL 5 Dimensions; HR: hazard ratio; IPD: individual patient data; MADRS: Montgomery-Åsberg Depression Rating Scale; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; VAS: visual analogue scale

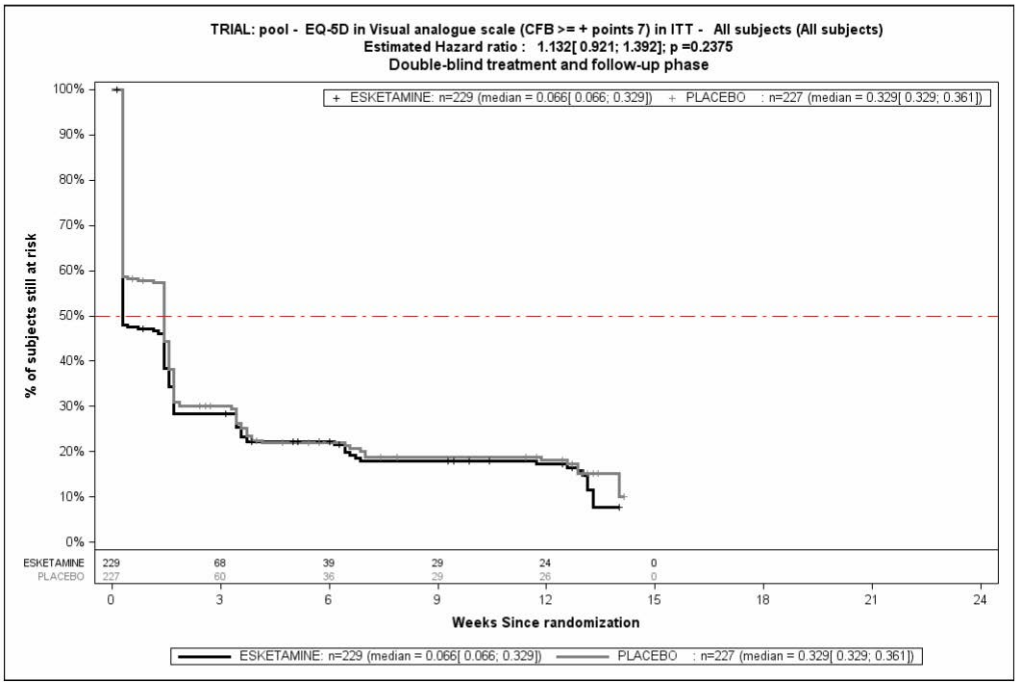


Figure 9: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS, improvement by ≥ 7 points) by Day 90; pooled analysis (SUI3001 + SUI3002)

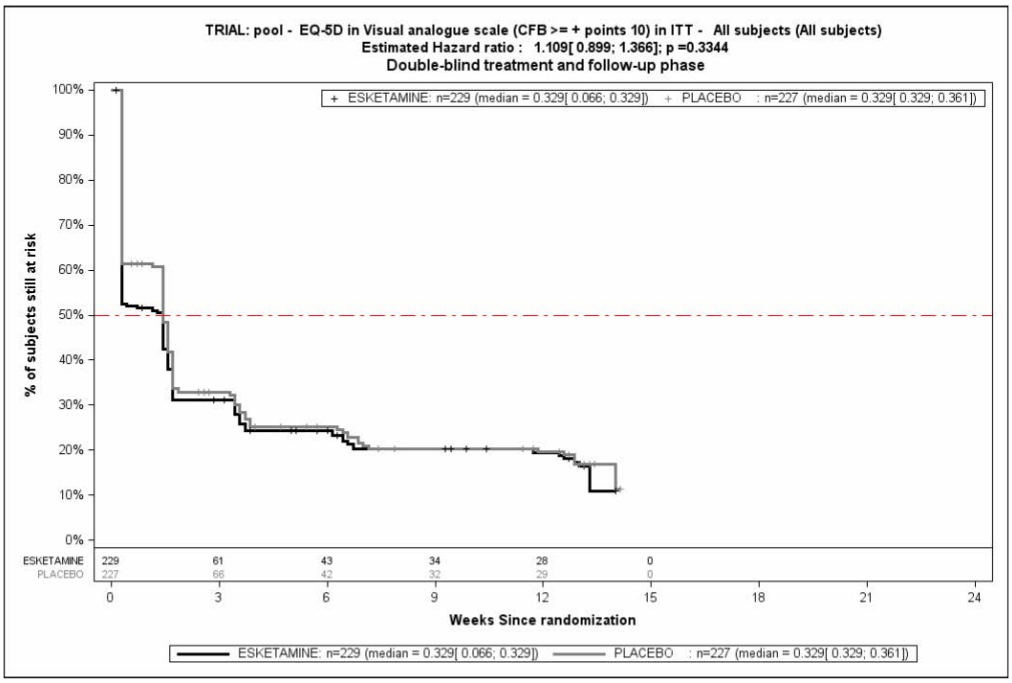


Figure 10: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS, improvement by ≥ 10 points) by Day 90; pooled analysis (SUI3001 + SUI3002)