Esketamine
(treatment-resistant major depression 1)

Addendum to Project A23-18
(dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
C-SSRS	Columbia Suicide Severity Rating Scale
ECT	electroconvulsive therapy
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
MCS	mental sum score
NRI	non-responder imputation
NVL	Nationale VersorgungsLeitlinie (German National Care Guideline)
PHQ-9	Patient Health Questionnaire
PSC	physical sum score
QLDS	Quality of Life in Depression Scale
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SDS	Sheehan Disability Scale
SDS	Sheehan Disability Scale
SF-36v2	Short Form (36) – version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SNRI	serotonin-noradrenaline reuptake inhibitor
SPC	Summary of Product Characteristics
SSRI	selective serotonin reuptake inhibitor

1 Background

On 25 July 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-18 (Esketamine – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the supplementary assessment of the ESCAPE-TRD study, taking into account the information in the dossier [2] as well as all data submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [3].

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

2 Assessment of the ESCAPE-TRD study

The research question of the benefit assessment was to assess the added benefit of esketamine in combination with a selective serotonin reuptake inhibitor (SSRI) or an serotonin-noradrenaline reuptake inhibitor (SNRI) versus treatment of physician's choice as an appropriate comparator therapy (ACT) in adult patients with treatment-resistant major depression who have not responded to at least 2 different therapies with antidepressants in the current moderate to severe depressive episode.

In the course of the procedure, the ACT was changed [4]. As a result of the change, a change in antidepressant monotherapy is no longer considered part of the ACT. The research question presented in Table 1 results from the change of the ACT specified by the G-BA.

Table 1: Research question of the benefit assessment of esketamine in combination with an SSRI or SNRI

Therapeutic indication	**ACT**[a, b]
Adults with treatment-resistant major depression, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode	Treatment of physician's choice choosing from: ▪ augmentation with lithium[c] or quetiapine retard[c] ▪ a combination with a second antidepressant[c] ▪ electroconvulsive therapy (ECT)
a. Presented is the ACT specified by the G-BA. b. The therapy concept for the treatment of major depression also includes psychotherapeutic procedures. According to the psychotherapy guideline [5], psychotherapeutic treatment should therefore be offered to patients in both treatment arms of a study. c. As an add-on to the last antidepressant monotherapy administered. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor	

In the dossier, the company presented the ESCAPE-TRD study [6-8] comparing esketamine with quetiapine retard, in each case in combination with an SSRI or an SNRI. As, according to the inclusion criteria, the patients in the ESCAPE-TRD study already had to be pretreated with ≥ 2 drug classes, the change of the antidepressant monotherapy in line with the approach of the company is not considered a suitable treatment option for the patients in the study (see also A23-18 [1]). The change in the ACT therefore has no consequences for the assessment of the ESCAPE-TRD study.

Implementation of the ACT in the ESCAPE-TRD study

The ESCAPE-TRD study was disregarded in the benefit assessment since the treatment in the study's comparator arm was deemed an inadequate implementation of treatment of physician's choice (ACT). The written comments [3] and the discussion in the oral hearing [9] resulted in the ESCAPE-TRD study's comparator therapy being deemed to represent a sufficient approximation of the ACT and the study therefore being suitable for the benefit

assessment. However, on the basis of the available information, it remains unclear whether the augmentation with quetiapine retard used in the study's comparator arm represents a complete implementation of the ACT. This is justified below.

As described in dossier assessment A23-18, it cannot be inferred from the presented information whether augmentation with quetiapine retard used for all patients in the ESCAPE-TRD study represents an adequate implementation of the treatment of physician's choice specified by the G-BA. It remained unclear how many patients had already received a combination therapy with a second antidepressant before being included in the study or for how many patients electroconvulsive therapy (ECT) had also been considered a suitable treatment option by the physician prior to randomization. Moreover, it was not clear from the available information whether and to what extent psychotherapy or psychotherapeutic measures were used to support the drug therapy.

Within the framework of its comments [3], the company submitted data on the previous therapies and the suitability of ECT for the patients included in the ESCAPE-TRD study. These data show that 90 patients (26.8%) in the intervention arm and 95 patients (27.9%) in the comparator arm had received at least 1 prior antidepressant combination therapy. In addition, 28 patients (8.3%) in the intervention arm and 33 patients (9.7%) in the comparator arm had at least 1 prior augmentation, including aripiprazole, brexpiprazole, lithium and olanzapine. In its comments, the company also states that at the start of the study, ECT was also specified as a possible treatment option by the physician for 19.4% of the patients (18.8% in the intervention arm and 20.0% in the comparator arm).

The subsequently submitted data show that ≥ 70% of the patients had not yet received a combination with a second antidepressant before inclusion in the study, which is why this treatment option basically represents a suitable treatment option for the majority of the patients included in the study. However, the commenting procedure and the discussion in the oral hearing [9] have shown that in the present therapeutic indication there is uncertainty as to which patients benefit from treatment with a combination with a second antidepressant or an augmentation, or which treatment approach is to be preferred and when. ECT was only indicated as a suitable treatment option for a smaller proportion of patients, and the discussion in the oral hearing also suggested that ECT is regarded as a secondary treatment option in everyday health care. However, due to the lack of comparative data and the strong recommendation in the German National Health Care Guideline Unipolar Depression [10], especially for patients in higher lines of therapy, ECT cannot be completely ruled out as a suitable treatment option.

In its comments, the company also states that a continuation of their ongoing psychotherapy or the initiation of a new one was discussed with 86.9% of the patients in the ESCAPE-TRD. Taking into account the current clinical condition, 355 (52.5%) of the patients were

recommended to undergo psychotherapy before randomization. Of these, 217 patients (61.1%) decided to follow this recommendation. These were evenly distributed across the two treatment arms (109 in the intervention arm [32.4%], 108 in the comparator arm [31.8%]). Moreover, the discussion in the oral hearing revealed that this proportion reflects everyday health care. Thus, it is assumed that sufficient psychotherapeutic support was provided to the patients in the ESCAPE-TRD study.

In summary, it remains unclear whether the comparator treatment used in the ESCAPE-TRD study represents a full implementation of the ACT. The remaining uncertainties described above did not result in an exclusion of the study, however. Instead, it was assumed that conclusions on the added benefit of esketamine in combination with an SSRI or SNRI versus the ACT can be drawn on the basis of the study results. However, the uncertainties described were taken into account in the assessment of the certainty of conclusions of results (see Section 2.2.2).

The results for the ESCAPE-TRD study's total population are described and assessed below. The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

The present addendum is structured as follows: Section 2.1 describes the characteristics of the ESCAPE-TRD study. Sections 2.2 and 2.3 present the results and the derivation of the overall conclusion on the added benefit of esketamine in combination with an SSRI or SNRI in the present research question based on the ESCAPE-TRD study. A summary of the benefit assessment is found in Section 2.4.

2.1 Study characteristics

A detailed characterization of the ESCAPE-TRD study can be found in dossier assessment A23-18 [1] and its Appendix B.

Patient characteristics

The patient characteristics were largely comparable between the treatment arms of the ESCAPE-TRD study. The mean age of the patients was 45 years, with about 95% of the patients being 18 to 64 years old. At 67% in the intervention arm and 65% in the comparator arm, the proportion of female patients was higher than the proportion of male patients. About 61% of patients had 2 and the remaining patients had ≥ 3 prior therapies with no response. At baseline, the patients had a mean Montgomery-Åsberg Depression Rating Scale (MADRS) score of 31, which corresponds to moderate depressive symptoms. Only 17% of the patients had only 1 major depressive episode, whereas almost 70% had already had 2 to 5 such episodes.

Significantly more patients in the comparator arm discontinued the treatment or the study by both week 8 and week 32. In both study arms, the main reason for treatment discontinuation was lack of efficacy, whereas the most common reason for study discontinuation in both study arms was withdrawal of consent.

A detailed characterization of the study population can be found in dossier assessment A23-18 [1] and its Appendix B.

Planned duration of follow-up observation

Table 2 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 2: Planned duration of follow-up observation – randomized controlled trial (RCT), direct comparison: esketamine + SNRI/SSRI vs. quetiapine retard + SNRI/SSRI

Study **outcome category** **outcome**	**Planned follow-up observation**[a]
ESCAPE-TRD	
Mortality	
All-cause mortality[b]	30 days after the last administration of the study medication[c]
Morbidity	
Remission and response (MADRS)	Until the last study visit at week 32[d]
Functional remission (SDS)	Until the last study visit at week 32[e]
General depressive symptoms (PHQ-9)	Until the last study visit at week 32[d]
General depressive symptoms (QLDS)	Until the last study visit at week 32[e]
Suicidality (C-SSRS)	2 weeks (± 2 days) after the last administration of the study medication[e]
Health status (EQ-5D VAS)	Until the last study visit at week 32[e]
Health-related quality of life (SF-36v2)	Until the last study visit at week 32[e]
Side effects	
AEs	2 weeks (± 2 days) after the last administration of the study medication[c]
SAEs	30 days after the last administration of the study medication[c]

a. Patients who discontinued the study were followed up for up to 2 weeks (± 2 days) after the last administration of the study medication.
b. Deaths determined by recording of AEs.
c. For patients who received standard treatment with esketamine or another antidepressant therapy of the company after discontinuation of treatment, the AEs were recorded up to week 32. For patients who received another standard therapy after treatment discontinuation, AEs were not systematically recorded after the last visit 2 weeks after the last administration of the study medication.
d. Patients who discontinued treatment were followed up every 2 weeks (± 3 days) until week 32.
e. Patients who discontinued treatment were followed up every 4 weeks (± 3 days) until week 32.

AE: adverse event; C-SSRS: Columbia Suicide Severity Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; QLDS: Quality of Life in Depression Scale; RCT: randomized controlled trial; SDS: Sheehan Disability Scale; SF-36v2: Short Form (36) – version 2 Health Survey; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; SAE: serious adverse event; VAS: visual analogue scale

In the ESCAPE-TRD study, patients were to switch to standard therapy if they discontinued treatment; all patient- and physician-reported instruments on efficacy, morbidity and health-related quality had to be collected up to week 32 and side effects up to 2 weeks after discontinuation. The outcome of all-cause mortality was surveyed via the collection of serious adverse events (SAEs) and was thus observed until 30 days after the last administration of the study medication.

Data on treatment and observation periods

Table 3 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes.

Table 3: Information on the course of the study – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study **duration of the study phase** **outcome category**	**Esketamine + SSRI/SNRI** **N = 336**	**Quetiapine retard + SSRI/SNRI** **N = 340**
ESCAPE-TRD		
Treatment duration [weeks][a, b]		
Median [min; max]	31 [1; 34]	32 [1; 35]
Mean (SD)	26.8 (9.5)	23.4 (12.2)
Observation duration [weeks] across outcomes[b]		
Median [Q1; Q3]	33 [32; 34]	34 [26; 34]
Mean (SD)	ND	ND
Observation period [weeks][b]		
Overall survival[c]	ND	ND
Morbidity (MADRS)		
Median [Q1; Q3]	32 [32; 32]	32 [22; 32]
Mean (SD)	ND	ND
Morbidity (SDS)[d]		
Median [Q1; Q3]	32 [20; 32]	32 [5; 32]
Mean (SD)	ND	ND
Morbidity (PHQ-9)		
Median [Q1; Q3]	32 [32; 32]	32 [23; 32]
Mean (SD)	ND	ND
Morbidity (QLDS, EQ-5D VAS, C-SSRS)		
Median [Q1; Q3]	32 [32; 32]	32 [21; 32]
Mean (SD)	ND	ND
Health-related quality of life (SF-36v2)		
Median [Q1; Q3]	32 [32; 32]	32 [21; 32]
Mean (SD)	ND	ND
Side effects	ND	ND

a. Data refer to the safety population (334 vs. 336 patients).
b. Data refer to the entire study duration. Data on treatment and observation duration for the induction therapy (up to week 8) are not available.
c. Deaths determined by recording of AEs.
d. Data refer to the observation period without imputation. The SDS questionnaire was considered missing if 1 of the 3 items was not answered. In this case, imputation was performed by the company as a sensitivity analysis by imputing the SDS total score as the sum of the scores from the available responses on 2 areas of life, multiplied by 3 and divided by 2. The median observation duration with imputation [Q1; Q3] was 32 [32; 32] weeks in the intervention arm and 32 [21; 32] weeks in the comparator arm.

Table 3: Information on the course of the study – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study **duration of the study phase** **outcome category**	**Esketamine + SSRI/SNRI** **N = 336**	**Quetiapine retard + SSRI/SNRI** **N = 340**
AE: adverse event; C-SSRS: Columbia Suicide Severity Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; max: maximum; min: minimum; N: number of patients; PHQ-9: Patient Health Questionnaire-9; Q1: first quartile; Q3: third quartile; QLDS: Quality of Life in Depression Scale; RCT: randomized controlled trial; SD: standard deviation; SDS: Sheehan Disability Scale; SF-36v2: Short Form (36) – version 2 Health Survey; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; VAS: visual analogue scale		

Being 31 weeks in the intervention arm and 32 weeks in the control arm, the median treatment durations are comparable.

The median observation duration across outcomes was 33 weeks in the intervention arm and 34 weeks in the control arm. The median observation duration for all outcomes was 32 weeks in both study arms, with more patients having a shorter observation duration in the quetiapine arm than in the esketamine arm due to higher dropout rates. No information on observation durations is available for the outcomes on side effects and the outcome of all-cause mortality, which was recorded via the survey of adverse events (AEs).

Subsequent antidepressant therapies

In the ESCAPE-TRD study, patients were supposed to switch to a standard therapy in case of treatment discontinuation. According to the study design, all patient- and physician-recorded instruments on efficacy, morbidity and health-related quality of life were to be collected up to week 32. Moreover, in the subsequent submission following the oral hearing [9], the company clarifies that, in contrast to what is described in Module 4 A, patients are also included in the analyses after treatment discontinuation and are only replaced by means of non-responder imputation (NRI) in the event of study discontinuation. Consequently, in the present assessment situation, it is necessary to assess to what extent the follow-up therapies used were adequate. Data on standard therapies started after a treatment discontinuation are not available. The study documents only contain information on concomitant medications during the follow-up observation. These include active substances that are approved for the treatment of major depression.

Table 4 shows which antidepressant concomitant medications patients received after discontinuing the study medication during the follow-up observation.

Table 4: Information on concomitant medications during the follow-up observation – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (ESCAPE-TRD)

Study drug	**Patients with subsequent therapy n (%)**	
	esketamine + SSRI/SNRI N = 336	**quetiapine + SSRI/SNRI N = 340**
ESCAPE-TRD		
Number of patients with treatment discontinuation (week 32)	78	137
Number of patients within follow-up observation.	76	133
Total[a]	23 (6.8[b])	34 (10.0[b])
Mirtazapine	2 (0.6[b])	9 (2.6[b])
Bupropion	3 (0.9[b])	4 (1.2[b])
Quetiapine	0 (0[b])	4 (1.2[b])
Quetiapine fumarate	1 (0.3[b])	3 (0.9[b])
Lithium carbonate	2 (0.6[b])	1 (0.3[b])
Agomelatine	2 (0.6[b])	0 (0[b])
Trazodone hydrochloride	0 (0[b])	2 (0.6[b])
Venlaflaxin	0 (0[b])	2 (0.6[b])
Amitriptyline	0 (0[b])	1 (0.3[b])
Amitriptyline hydrochloride	0 (0[b])	1 (0.3[b])
Bupropion hydrochloride	0 (0[b])	1 (0.3[b])
Escitalopram	0 (0[b])	1 (0.3[b])
Esketamine hydrochloride	0 (0[b])	1 (0.3[b])
Fluoxetine	0 (0[b])	1 (0.3[b])
Fluoxetine hydrochloride	0 (0[b])	1 (0.3[b])
Maprotiline hydrochloride	0 (0[b])	1 (0.3[b])
Nortriptyline	1 (0.3[b])	0 (0[b])
Paroxetine	1 (0.3[b])	0 (0[b])
Sertraline	0 (0[b])	1 (0.3[b])
Sulpiride	1 (0.3[b])	0 (0[b])
Tranylcypromine sulphate	1 (0.3[b])	0 (0[b])
Trazodone	1 (0.3[b])	0 (0[b])
Venlaflaxine hydrochloride	0 (0[b])	1 (0.3[b])

a. Includes all concomitant medications (both antidepressant and non-antidepressant therapies).
b. Institute's calculation.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

In the ESCAPE-TRD study, 6.8% of the patients in the intervention arm and 10.0% of the patients in the comparator arm received ≥ 1 concomitant medication during the follow-up

observation. In terms of patients who were in follow-up, this is 30.3% in the esketamine arm and 25.6% in the quetiapine arm. However, non-antidepressant therapies are also included. In addition, the current German National Care Guideline (NVL) does not provide any clear therapy recommendations for the present therapeutic indication (treatment-resistant major depression) in the case of multiple non-responses [10]. However, according to the NVL, non-drug therapies are particularly eligible. Moreover, there are no substantial differences between the subsequent therapies in the intervention and the comparator arm. On the basis of the available information, it cannot be conclusively assessed to what extent adequate standard antidepressant therapy was used after treatment discontinuation. The small proportion of patients with subsequent therapy can potentially be explained by the high proportion of study dropouts and the fact that the study was discontinued before a subsequent therapy was initiated after treatment discontinuation.

Transferability of the study results to the German health care context

In Module 4 A of its dossier, the company states that 228 (67.9%) of the patients in the intervention arm and 225 (66.2%) of the patients in the comparator arm of the ESCAPE-TRD study came from Europe, and 37 (11.0%) and 41 (12.1%) of these came from Germany. There were no indications of biodynamic or kinetic differences between the individual population groups or countries involved and Germany to the extent that they would have a significant impact on the study results. From the company's point of view, the results are generally transferable to the German healthcare context, in consideration of the uncertainty associated with the transferability of clinical data.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.2 Results on added benefit

2.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Remission recorded with the MADRS
  - Functional remission with the Sheehan Disability Scale (SDS)
  - Response recorded with the MADRS
  - Relapse

- Health status recorded using the EQ-5D VAS
- General depressive symptoms recorded using the Patient Health Questionnaire (PHQ-9) and the Quality of Life in Depression Scale (QLDS)
- Suicidality recorded using the Columbia Suicide Severity Rating Scale (C-SSRS)

- Health-related quality of life
  - Surveyed using the Short Form (36) – version 2 Health Survey (SF-36v2)
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Gastrointestinal disorders (System Organ Class [SOC], AEs)
  - Psychiatric disorders (SOC, AEs)
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that by the company, which used further outcomes in the dossier (Module 4 A).

Table 5 shows the outcomes for which data were available in the included study.

Table 5: Matrix of outcomes – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI

Study	Outcomes													
	All-cause mortality[a]	Remission (MADRS)[b]	Functional remission (SDS)[c]	Response (MADRS)[d]	Relapse	General depressive symptoms (PHQ-9, QLDS)	Suicidality (C-SSRS)[e]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Nervous system disorders (SOC, AEs)	Psychiatric disorders (SOC, AEs)	Further specific AEs[f]
ESCAPE-TRD	Yes	Yes	Yes	Yes	No[g]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Deaths determined by recording of AEs.
b. Operationalized as the proportion of patients with remission (defined as MADRS total score ≤ 12 points) and time to definitive remission (MADRS total score ≤ 12).
c. Operationalized as ≤ 2 points in each item and SDS total score ≤ 6 points.
d. Operationalized as an improvement of ≥ 50% in the MADRS total score compared to baseline.
e. Operationalized as a "yes" response at any time during treatment to 1 of the 5 questions on suicidal ideation (categories 1 to 5) in the C-SSRS (suicidal ideation) or as a "yes" response at any time during treatment to 1 of the 5 questions on suicidal behaviour (categories 6 to 10) in the C-SSRS (suicidal behaviour).
f. The following (MedDRA-coded) events were considered: respiratory, thoracic and mediastinal disorders (SOC, AEs), nausea (PT, AEs), and vomiting (PT, AEs).
g. No suitable operationalization available; for justification, see body of text below.

AE: adverse event; C-SSRS: Columbia Suicide Severity Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MedDRA: Medical Dictionary for Regulatory Activities; PHQ-9: Patient Health Questionnaire-9; PT: Preferred Term; QLDS: Quality of Life in Depression Scale; RCT: randomized controlled trial; SAE: serious adverse event; SDS: Sheehan Disability Scale; SF-36v2: Short Form (36) – version 2 Health Survey; SNRI: serotonin-noradrenaline reuptake inhibitor; SOC: System Organ Class; SSRI: selective serotonin reuptake inhibitor; VAS: visual analogue scale

Notes on outcomes

Dates of analysis

The Summary of Product Characteristics (SPC) of esketamine describes a 4-week induction phase, at the end of which the therapeutic benefit is to be assessed in order to decide on the need for further treatment. According to the SPC, the need for further treatment should then be reviewed at regular intervals. In the ESCAPE-TRD study presented, esketamine was used as an 8-week acute treatment followed by 24 weeks of maintenance treatment. In the

intervention arm, a clinical assessment was made by the treating physician after 4 weeks. If there was no therapeutic benefit, the treatment could be discontinued in consultation with the patient. In both study arms of the ESCAPE-TRD study, the investigator regularly assessed whether the treatment should be continued from week 8 onwards. The company presented analyses for all outcomes at week 8 and week 32, both of which were initially used for the benefit assessment. Analyses at the end of the induction phase according to the SPC (week 4) are not available.

Analyses on symptoms and health-related quality of life presented by the company

The company presented responder analyses at week 8 and week 32 for the third party-assessed outcomes of response and remission (each recorded using the MADRS) and responder analyses at week 8 and week 32 for the patient-reported outcomes (recorded using SDS, PHQ-9, QLDS, EQ-5D VAS and SF-36v2), each for improvement and deterioration. In addition, it presented event time analyses operationalized as time to first and time to definitive improvement or deterioration, as well as continuous analyses on changes compared to baseline. In the present therapeutic indication, the treatment goal is an improvement of symptoms and health-related quality of life [10], which is why the analyses of the proportion of patients with improvement are used in each case.

As explained in the IQWiG *General Methods* [11], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified and exactly 15% of the scale range in post-hoc analyses. The company presented predefined responder analyses for each of the patient-reported outcomes of general depressive symptoms (PHQ-9 and QLDS), health status (EQ-5D VAS) and health-related quality of life (SF-36v2) for the improvement by ≥ 15% of the scale range. For the benefit assessment, these analyses were used at week 8 and week 32.

The QLDS is a validated instrument for assessing the symptoms of patients with depression. Deviating from the company's approach, it is therefore assigned to morbidity.

The SDS comprises the 3 items "work and school" (1), "family life and tasks at home" (2) and "social life" (3). Each item is rated on a scale from 0 (no impairment) to 10 (extreme impairment). The total score is 30. The analyses on the proportion of study participants with functional remission (SDS total score ≤ 6 points, with each individual item at least ≤ 2 points) submitted by the company are considered to be meaningful in terms of content and were used for the benefit assessment.

Remission

In the ESCAPE-TRD study, the outcome of remission, recorded using the MADRS, was operationalized as a MADRS total score ≤ 10 points at week 8 or at week 32. In addition, the company pre-specified the operationalization "MADRS total score ≤ 12 points" in a statistical

analysis plan (SAP) prepared for the benefit assessment. For the present benefit assessment, an MADRS total score ≤ 12 points was considered a suitable operationalization for a remission and the responder analysis of the company was used.

In addition to responder analyses at week 8 and week 32, the company also presented analyses on the time to first remission and the time to definitive remission for the outcome of remission. For the present therapeutic indication, the time to definitive remission is basically considered to be patient-relevant, since the patients had already been in their depressive episode for more than 1 year on average, have had several unsuccessful therapies and there is a risk of relapse or recurrence. According to the German National Care Guideline [10], recovery is also assumed when a patient is symptom-free for 6 months after remission.

Patients in the ESCAPE-TRD study were in definitive remission if they remained in remission at ≥ 2 consecutive measurement time points until the end of the study (week 32) at each measurement time point, with only the time point of the second measurement included in the analysis. The median on the time to definitive improvement was 6.5 months in the intervention arm and 7.5 months in the comparator arm. It remains unclear whether a definitive remission or a confirmed remission (i.e. remission in 2 consecutive measurement time points) actually occurred or whether, in particular, the comparator arm includes a relevant proportion of patients who only had a confirmed remission. From the observation times presented by the company, it can be seen that observation in the comparator arm was terminated earlier, so that the comparability between the treatment arms is limited and the durability of the remission in the comparator arm is also questionable. The results on the time to definitive remission therefore present no suitable analysis in the present data situation. However, for the present research question, an event-driven study is basically conceivable for the proof of a definitive remission.

Relapse

For the outcome of relapse, the company presented analyses for the operationalization "relapse-free after remission" and operationalizes the relapse as

- deterioration of depressive symptoms, defined as a MADRS total score ≥ 22,
- stay in a psychiatric hospital due to deterioration of the depression or suicide prevention or due to a suicide attempt or
- suicide attempt, completed suicide, or other clinically relevant event which, in the physician's clinical judgement, indicates a relapse of the depressive disorder, but for which there was no admission to hospital.

This operationalization is not suitable, as it is questionable to what extent patients who were previously in remission (i.e. MADRS ≤ 12) can actually be considered relapse-free with a

maximum MADRS total score of 21. In addition, for the outcome of interest "relapse for patients who previously had remission at any time point", there are no separate analyses for the individual components.

Transience of AEs

In the dossier, in addition to the analysis of AEs and SAEs according to the dossier template, the company also presented an analysis on AEs whose onset and end were documented on the same day (transient) or not on the same day (non-transient) and which occurred in at least 5% of patients. It argues that the AEs typical of esketamine are of short duration and thus less indicative of patient distress than, for example discontinuation due to AEs. This rationale of the company was not followed. On the one hand, in the study centres, esketamine was administered under controlled conditions that allowed systematic observation, while patients in the comparator arm took quetiapine self-reliantly outside the study centre. This means that the duration of AEs under quetiapine was not adequately recorded. On the other hand, a transient AE can also lead to patient distress if this AE occurs regularly or repeatedly when taking the drug. The company's analysis on the transience of the AEs is not considered for the present assessment.

2.2.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI

Study		Outcomes													
	Study level	All-cause mortality[a]	Remission (MADRS)[b]	Functional remission (SDS)[c]	Response (MADRS)[d]	Relapse	General depressive symptoms (PHQ-9, QLDS)	Suicidality (C-SSRS)[e]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Nervous system disorders (SOC, AEs)	Psychiatric disorders (SOC, AEs)	Further specific AEs[f]
ESCAPE-TRD	L	H[g]	H[h, i]	H[h, i]	H[h, i]	-[j]	H[h, i]	H[h, k]	H[h, i]	H[h, i]	H[g]	H[g, h]	H[g, h]	H[g, h]	H[g, h]

a. Deaths determined by recording of AEs.
b. Operationalized as MADRS total score ≤ 12 points and time to definitive remission (MADRS total score ≤ 12).
c. Operationalized as ≤ 2 points in each item and SDS total score ≤ 6 points.
d. Operationalized as an improvement of ≥ 50% in the MADRS total score compared to baseline.
e. Operationalized as a "yes" response at any time during treatment to 1 of the 5 questions on suicidal ideation (categories 1 to 5) in the C-SSRS (suicidal ideation) or as a "yes" response at any time during treatment to 1 of the 5 questions on suicidal behaviour (categories 6 to 10) in the C-SSRS (suicidal behaviour).
f. The following (MedDRA-coded) events were considered: respiratory, thoracic and mediastinal disorders (SOC, AEs), nausea (PT, AEs), and vomiting (PT, AEs).
g. Potentially informative censoring due to different proportions of study discontinuations and reasons for study discontinuation.
h. Lack of blinding in subjective recording of outcomes.
i. High and discrepant proportion of imputed values between treatment arms.
j. No suitable data available; see Table 5.
k. High proportion of patients not included in the analysis (> 10%) or large difference between the treatment groups (> 5 percentage points).

AE: adverse event; C-SSRS: Columbia Suicide Severity Rating Scale; H: high; L: low; MADRS: Montgomery-Åsberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; QLDS: Quality of Life in Depression Scale; RCT: randomized controlled trial; SAE: serious adverse event; SDS: Sheehan Disability Scale; SF-36v2: Short Form (36) – version 2 Health Survey; SNRI: serotonin-noradrenaline reuptake inhibitor; SOC: System Organ Class; SSRI: selective serotonin reuptake inhibitor; VAS: visual analogue scale

The risk of bias of the results for all outcomes was rated as high.

Deviating from the company, the risk of bias for the outcomes of remission and response, each assessed using the MADRS, was assessed as high. The company rated the risk of bias for these

outcomes as low and justified this with the blinded recording of outcomes. However, since in the ESCAPE-TRD study the patients who answered questions about their symptoms during the MADRS survey were not blinded, subjective recording of outcomes can be assumed, which leads to a high risk of bias. In addition, a high and discrepant proportion of imputed values between the treatment arms (7.1% in the intervention arm vs. 15.3% in the comparator arm at week 8 and 19.1% in the intervention arm vs. 31.2% in the comparator arm at week 32) contributed to a high risk of bias.

For the results of the outcomes of functional remission (SDS), general depressive symptoms (PHQ-9, QLDS), health status (EQ-5D VAS) and health-related quality of life (SF-36v2), the risk of bias was rated as high because of the open-label study design in subjective recording of outcomes and a high proportion of imputed values (7.1 % to 9.2 % in the intervention arm vs. 15.3% to 19.1% in the comparator arm at week 8 and about 19% in the intervention arm vs. 32% in the comparator arm at week 32), which, moreover, are discrepant between the arms. The proportion of imputed values was clearly higher for the mental sum score (MCS) of the SF-36v2 than for the other outcomes (19.9% in the intervention arm and 28.2% in the comparator arm at week 8 and 26.2% in the intervention arm and 41.2% in the comparator arm). The company provided no information on imputed values for the physical sum score (PCS) of the SF-36v2. However, it is assumed that these are comparable to the values of the MCS. The company does not provide an explanation for this high proportion of missing values for SF-36v2.

In addition to the open-label study design in subjective recording of outcomes, the high proportion of patients not included in the analysis (> 10%) and the large difference between the treatment groups (> 5 percentage points) lead to a high potential for bias for the results of the outcome “suicidality” (C-SSRS).

For the outcome of all-cause mortality, captured via the recording of AEs, and the side effects outcomes, the risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons. For instance, by week 32, 19% of patients in the intervention arm and 32% in the comparator arm had discontinued the study. In both arms, withdrawal of consent was the most common reason for study discontinuations (13% vs. 20%), which meant that these patients were no longer followed up. For non-severe side effects, the lack of blinding in subjective recording of outcomes also leads to a high risk of bias.

Summary assessment of the certainty of conclusions

For the present benefit assessment, it remains unclear whether the comparator therapy used in the ESCAPE-TRD study represents a full implementation of the ACT (see Chapter 2 under implementation of the ACT).

Based on the results from the ESCAPE-TRD study, at most hints, e.g. of an added benefit, can be determined for all outcomes presented.

2.2.3 Results

Table 7 summarizes the results on the comparison of esketamine in combination with an SNRI or an SSRI versus treatment of physician's choice as an ACT in patients with treatment-resistant major depression who have not responded to at least 2 different therapies with antidepressants in the current moderate to severe depressive episode.

Table 7: Results (mortality, morbidity, side effects) – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study **outcome category** **outcome** **time point**	**Esketamine + SSRI/SNRI**		**Quetiapine retard + SSRI/SNRI**		**Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
ESCAPE-TRD					
Mortality					
All-cause mortality (up to week 32)	334	1 (0.3)	336	1 (0.3)	0.97 [0.07; 14.35]; 0.984
Morbidity					
Remission (MADRS)[b]					
Week 8	336	132 (39.3)	340	81 (23.8)	1.66 [1.31; 2.09]; < 0.001
Week 32	336	204 (60.7)	340	153 (45)	1.35 [1.17; 1.57]; < 0.001
Response (MADRS)[c]					
Week 8	336	180 (53.6)	340	130 (38.2)	1.41 [1.19; 1.66]; < 0.001
Week 32	336	232 (69.1)	340	181 (53.2)	1.30 [1.15; 1.47]; < 0.001
Functional remission (SDS)[d]					
Week 8	314	43 (13.7)	307	37 (12.1)	1.14 [0.75; 1.71]; 0.555[e]
Week 32	315	107 (34.0)	308	73 (23.7)	1.43 [1.11; 1.85]; 0.005[e]
Relapse				No usable data[f]	
General depressive symptoms (proportion of patients with improvement)					
PHQ-9[g]					
Week 8	336	231 (68.8)	340	198 (58.2)	1.18 [1.05; 1.32]; 0.005
Week 32	336	232 (69.1)	340	192 (56.5)	1.23 [1.09; 1.38]; < 0.001
QLDS[h]					
Week 8	336	221 (65.8)	340	170 (50)	1.32 [1.16; 1.50]; < 0.001
Week 32	336	229 (68.2)	340	175 (51.5)	1.33 [1.17; 1.50]; < 0.001
Health status (EQ-5D VAS[i]) (proportion of patients with improvement)					
Week 8	336	183 (54.5)	340	145 (42.7)	1.28 [1.09; 1.50]; 0.002
Week 32	336	195 (58)	340	158 (46.5)	1.25 [1.08; 1.45]; 0.002
Suicidality (C-SSRS)					
Suicidal ideation[j]					
Week 8	311	25 (8)	291	19 (6.5)	1.24 [0.69; 2.21]; 0.472
Week 32	271	9 (3.3)	229	5 (2.2)	1.53 [0.53; 4.46]; 0.432
Suicidal behaviour[k]					
Week 8	311	0 (0)	291	1 (0.3)	ND
Week 32	271	0 (0)	229	1 (0.4)	ND

Table 7: Results (mortality, morbidity, side effects) – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study outcome category outcome time point	Esketamine + SSRI/SNRI N	 patients with event n (%)	Quetiapine retard + SSRI/SNRI N	 patients with event n (%)	Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI RR [95% CI]; p-value[a]
Health-related quality of life					
SF-36v2 (proportion of patients with improvement)					
PCS[l, m]					
Week 8	336	47 (14)	340	40 (11.8)	1.20 [0.80; 1.78]; 0.379
Week 32	336	72 (21.4)	340	52 (15.3)	1.41 [1.02; 1.95]; 0.037
MCS[m, n]					
Week 8	336	180 (53.6)	340	138 (40.6)	1.32 [1.12; 1.55]; < 0.001
Week 32	336	195 (58)	340	150 (44.1)	1.32 [1.14; 1.53]; < 0.001
Side effects (up to week 32)					
AEs (supplementary information)	334	307 (91.9)	336	262 (78.0)	–
SAEs	334	19 (5.7)	336	17 (5.1)	1.11 [0.59; 2.09]; 0.746
Discontinuation due to AEs	334	14 (4.2)	336	37 (11)	0.38 [0.21; 0.69]; 0.002
Nervous system disorders (SOC, AEs)[o]	334	231 (69.2)	336	161 (47.9)	1.44 [1.26; 1.65]; < 0.001
Psychiatric disorders (SOC, AEs)[p]	334	156 (46.7)	336	44 (13.1)	3.58 [2.65; 4.82]; < 0.001
Respiratory, thoracic, and mediastinal disorders (SOC, AEs)[q]	334	54 (16.2)	336	10 (3.0)	5.43 [2.81; 10.48]; < 0.001
Nausea (PT, AEs)	334	98 (29.3)	336	12 (3.6)	8.17 [4.58; 14.58]; < 0.001
Vomiting (PT, AEs)	334	36 (10.8)	336	5 (1.5)	7.14 [2.84; 17.93]; < 0.001

Table 7: Results (mortality, morbidity, side effects) – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study outcome category outcome time point	Esketamine + SSRI/SNRI		Quetiapine retard + SSRI/SNRI		Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
a. Cochran-Mantel-Haenszel method; stratified by age and number of prior therapies to which patients did not respond. b. Defined as MADRS total score ≤ 12. c. Defined as an improvement in the MADRS total score by ≥ 50% compared to baseline (scale range 0 to 60 points). d. Defined as SDS total score ≤ 6, with each individual item scoring at least ≤ 2 points. e. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [12]). f. No usable data; see Section 2.2.1. g. Proportion of patients with improvement, defined as a decrease in score by ≥ 5 points compared to baseline (corresponds to 15% of the scale range: 0 to 27 points). h. Proportion of patients with improvement, defined as a decrease in score by ≥ 6 points compared to baseline (corresponds to 15% of the scale range: 0 to 34 points). i. Proportion of patients with improvement, defined as an increase in score of ≥ 15 points compared to baseline; scale range: 0 to 100 points. j. Operationalized as a "yes" response at any time during treatment to 1 of the 5 questions on suicidal ideation (categories 1 to 5) in the C-SSRS (suicidal ideation). k. Operationalized as a "yes" response at any time during treatment to 1 of the 5 questions on suicidal behaviour (categories 6 to 10) in the C-SSRS (suicidal behaviour). l. Percentage of patients with improvement: increase in PCS score by ≥ 9.4 points compared to baseline (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 7 and a maximum of approx. 70). m. There are only continuous analyses for the subscales of the SF-36v2. n. Proportion of patients with improvement: increase in MCS score by ≥ 9.6 points compared to baseline (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 6 and a maximum of approx. 70). o. Including, among others, the PTs dizziness, headache, dysgeusia and paraesthesia. p. Including, among others, the PTs dissociation and confusional state. q. Including, among others, the PTs sneezing, rhinalgia and throat irritation. AE: adverse event; CI: confidence interval; C-SSRS: Columbia Suicide Severity Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; PCS: Physical Component Summary; PHQ-9: Patient Health Questionnaire-9; PT: Preferred Term; QLDS: Quality of Life in Depression Scale; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SDS: Sheehan Disability Scale; SF-36v2: Short Form (36) – version 2 Health Survey; SNRI: serotonin-noradrenaline reuptake inhibitor; SOC: System Organ Class; SSRI: selective serotonin reuptake inhibitor; VAS: visual analogue scale					

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This results in no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven for this outcome.

Morbidity

Remission

For the outcome of remission (responder analysis on a MADRS total score ≤ 12 points), there are significant differences between the treatment arms both at week 8 and week 32, each in favour of esketamine. For both time points, there is a hint of added benefit of esketamine in comparison with treatment of physician's choice.

Response

For the outcome of response (responder analysis on the improvement in MADRS total score by ≥ 50% compared to baseline), there is a statistically significant difference between the treatment arms in favour of esketamine at week 8. For the time point week 8, there is a hint of added benefit of esketamine in comparison with treatment of physician's choice.

For the outcome of response (responder analysis on the improvement of the MADRS total score by ≥ 50% compared to baseline), there is also a statistically significant difference between the treatment arms in favour of esketamine at week 32; however, there is an effect modification by the characteristic "substance class of the pre-existing antidepressant" (see Section 2.2.4). In patients whose pre-existing antidepressant was an SNRI, there is a hint of an added benefit of esketamine compared to treatment of physician's choice. In patients whose pre-existing antidepressant was an SSRI, there is no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven for these patients.

Functional remission

For the outcome "functional remission" (responder analysis on the SDS total score ≤ 6, each item at least ≤ 2 points), there is no statistically significant difference between the treatment arms at week 8. For the time point "week 8", this results in no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven for this outcome.

For the outcome of functional remission at week 32, however, there is a statistically significant difference between the treatment arms in favour of esketamine. For the time point week 32, there is a hint of added benefit of esketamine in comparison with treatment of physician's choice.

Relapse

No usable operationalization is available for the outcome of relapse (for reasons, see Section 2.2.1). This results in no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven for this outcome.

General depressive symptoms (PHQ-9)

For the outcome of general depressive symptoms (responder analysis on the improvement in the PHQ-9 total score by ≥ 5 points), there are statistically significant differences between the treatment arms both at week 8 and week 32, each in favour of esketamine. For both time points, there is a hint of added benefit of esketamine in comparison with treatment of physician's choice.

General depressive symptoms (QLDS)

For the outcome of general depressive symptoms (responder analysis on the improvement in the QLDS total score by ≥ 6 points), there is a statistically significant difference between the treatment arms in favour of esketamine at week 8; however, there is an effect modification by the characteristic "substance class of the pre-existing antidepressant" (see Section 2.2.4). In patients whose pre-existing antidepressant was an SNRI, there is a hint of an added benefit of esketamine compared to treatment of physician's choice. In patients whose pre-existing antidepressant was an SSRI, there is no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven for these patients.

For the outcome of general depressive symptoms (responder analysis on the improvement in the QLDS total score by ≥ 6 points), there are statistically significant differences between the treatment arms at week 32, each in favour of esketamine. For the time point week 32, there is a hint of added benefit of esketamine in comparison with treatment of physician's choice.

Health status (EQ-5D VAS)

For the outcome of health status (responder analysis on the improvement in the EQ-5D VAS by ≥ 15 points), there are statistically significant differences between the treatment arms both at week 8 and week 32, each in favour of esketamine. For both time points, there is a hint of added benefit of esketamine in comparison with treatment of physician's choice.

Suicidality (C-SSRS)

For the outcomes of suicidal ideation and suicidal behaviour (C-SSRS), there was no statistically significant difference between the treatment arms at either week 8 or week 32. There is no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven for these outcomes.

Health-related quality of life (SF-36v2)

At week 8, no statistically significant difference between the treatment arms was shown for the PCS of the SF-36v2 (responder analysis on the improvement in PCS by ≥ 9.4 points). For the time point "week 8", there is no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven for this outcome.

For the PCS, however, there is a statistically significant difference between the treatment arms in favour of esketamine at week 32. For the time point week 32, there is a hint of added benefit of esketamine in comparison with treatment of physician's choice.

At week 8, a statistically significant difference between the treatment arms in favour of esketamine was shown for the MCS of the SF-36v2 (responder analysis on the improvement in MCS by ≥ 9.6 points). For the time point week 8, there is a hint of added benefit of esketamine in comparison with treatment of physician's choice.

For the MSC of the SF-36v2 (responder analysis on the improvement in the MCS total score by ≥ 9.6 points), there is also a statistically significant difference between the treatment arms in favour of esketamine at week 32; however, there is an effect modification by the characteristic "substance class of the pre-existing antidepressant" (see Section 2.2.4). In patients whose pre-existing antidepressant was an SNRI, there is a hint of an added benefit of esketamine compared to treatment of physician's choice. In patients whose pre-existing antidepressant was an SSRI, there is no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven for these patients.

Side effects (up to week 32)

SAEs

There was no statistically significant difference between the treatment arms for the outcome of SAEs. There is no hint of an added benefit of esketamine in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven for this outcome.

Discontinuation due to AEs

A statistically significant difference in favour of esketamine was shown between the treatment arms for the outcome "discontinuation due to AEs". There is a hint of lesser harm from esketamine in comparison with treatment of physician's choice.

Specific AEs

Psychiatric disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), nausea (PT, AEs), vomiting (PT, AEs)

For psychiatric disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), nausea (PT, AEs) and vomiting (PT, AEs), statistically significant differences to the disadvantage

of esketamine are shown between the treatment arms. For each of these outcomes, there is a hint of greater harm from esketamine in comparison with treatment of physician's choice.

Nervous system disorders (SOC, AEs)

For the outcome of nervous system disorders (SOC, AEs), there is a statistically significant difference between the treatment arms to the disadvantage of esketamine; however, there is an effect modification by the characteristic "disease severity" (see Section 2.2.4). For patients with an MADRS total score ≤ 34, there is a hint of greater harm from esketamine compared to treatment of physician's choice. For patients with an MADRS total score > 34, there is no hint of greater or lesser harm from esketamine compared to treatment of physician's choice; an added benefit is therefore not proven for these patients.

2.2.4 Subgroups and effect modifiers

The following subgroup characteristics were considered for the present benefit assessment:

- Age (< 65 years/≥ 65 years)
- Sex (female/male)
- Disease severity at baseline according to MADRS total score (≤ 34/> 34)
- Substance class of the pre-existing antidepressant (SNRI/SSRI)

The results on the subgroup characteristic age are not used in the present benefit assessment because in the ESCAPE-TRD study the pre-specified subgroup 65 to 74 years with a total of 37 patients (19 in the intervention arm and 18 in the comparator arm) was clearly smaller than the subgroup 18 to 64 years with a total of 639 patients (317 in the intervention arm and 322 in the comparator arm). Moreover, only few events occurred in the subgroup 65 to 74 years. Thus, it cannot be ruled out that observed effects have occurred by chance.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

Table 8 summarizes the subgroup results on the comparison of esketamine in combination with an SNRI or an SSRI with treatment of physician's choice as ACT in patients with treatment-resistant major depression who have not responded to at least 2 different therapies with antidepressants in the current moderate to severe depressive episode.

Table 8: Subgroups (mortality, morbidity, side effects) – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI

Study outcome characteristic subgroup	Esketamine + SSRI/SNRI		Quetiapine retard + SSRI/SNRI		Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI	
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI][a]	p-value[a]
ESCAPE-TRD						
Response (MADRS)[b], week 32						
Substance class of the pre-existing AD						
SNRI	161	121 (75.2)	152	76 (50.0)	1.50 [1.25; 1.80]	< 0.001
SSRI	175	111 (63.4)	188	105 (55.9)	1.14 [0.96; 1.35]	0.142
Total					Interaction[c]:	0.015
General depressive symptoms (QLDS)[d], week 8						
Substance class of the pre-existing AD						
SNRI	161	115 (71.4)	152	73 (48.0)	1.49 [1.23; 1.80]	< 0.001
SSRI	175	106 (60.6)	188	97 (51.6)	1.17 [0.98; 1.41]	0.086
Total					Interaction[c]:	0.048
MCS[e], week 32						
Substance class of the pre-existing AD						
SNRI	161	101 (62.7)	152	61 (40.1)	1.56 [1.25; 1.96]	< 0.001
SSRI	175	94 (53.7)	188	89 (47.3)	1.14 [0.93; 1.39]	0.225
Total					Interaction[c]:	0.033
Nervous system disorders (SOC, AEs)[f], week 32						
Disease severity at baseline according to MADRS total score						
≤ 34	243	172 (70.8)	246	109 (44.3)	1.60 [1.36; 1.88]	< 0.001
> 34	91	59 (64.8)	90	52 (57.8)	1.12 [0.89; 1.42]	0.331
Total					Interaction[c]:	0.024

a. Cochran-Mantel-Haenszel method; stratified by age and number of prior therapies to which patients did not respond.
b. Operationalized as an improvement of ≥ 50% in the MADRS total score compared to baseline.
c. Logistic regression model with interaction term treatment x subgroup characteristic.
d. Proportion of patients with improvement, defined as a decrease in score by ≥ 6 points compared to baseline (corresponds to 15% of the scale range: 0 to 34 points).
e. Proportion of patients with improvement: increase in MCS score by ≥ 9.6 points compared to baseline (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 6 and a maximum of approx. 70).
f. Including, among others, the PTs dizziness, headache, dysgeusia and paraesthesia.

AD: antidepressant; AE: adverse event; CI: confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; QLDS: Quality of Life in Depression Scale; RCT: randomized controlled trial; RR: relative risk; SNRI: serotonin-noradrenaline reuptake inhibitor; SOC: System Organ Class; SSRI: selective serotonin reuptake inhibitor

Morbidity

Response (MADRS), week 32

For the outcome of response (responder analysis on the improvement in the MADRS total score by ≥ 50% compared to baseline) at week 32, there is an effect modification due to the characteristic substance class of the pre-existing antidepressant (SNRI vs. SSRI). For patients whose pre-existing antidepressant was an SNRI, there is a statistically significant difference between treatment arms in favour of esketamine. There is a hint of an added benefit in comparison with treatment of physician's choice.

However, there is no statistically significant difference between the treatment arms for patients whose pre-existing antidepressant was an SSRI. There is no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven.

General depressive symptoms (QLDS), week 8

For the outcome of general depressive symptoms (responder analysis on the improvement in the QLDS total score by ≥ 6 points) at week 8, there is an effect modification by the characteristic substance class of the pre-existing antidepressant (SNRI vs. SSRI). For patients whose pre-existing antidepressant was an SNRI, there is a statistically significant difference between treatment arms in favour of esketamine. There is a hint of an added benefit in comparison with treatment of physician's choice.

However, there is no statistically significant difference between the treatment arms for patients whose pre-existing antidepressant was an SSRI. There is no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life (SF-36v2)

MCS, week 32

For the outcome of MCS of the SF-36v2 (responder analysis on the improvement in MCS by ≥ 9.6 points) at week 32, there is an effect modification by the characteristic substance class of the pre-existing antidepressant (SNRI vs. SSRI). For patients whose pre-existing antidepressant was an SNRI, there is a statistically significant difference between treatment arms in favour of esketamine. There is a hint of an added benefit in comparison with treatment of physician's choice.

However, there is no statistically significant difference between the treatment arms for patients whose pre-existing antidepressant was an SSRI. There is no hint of added benefit of esketamine in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Side effects (up to week 32)

Nervous system disorders (SOC, AEs)

For the outcome "nervous system disorders" (SOC, AEs), there is an effect modification by the characteristic disease severity at baseline according to the MADRS total score (≤ 34 points vs. > 34 points). For patients with an MADRS total score ≤ 34 points at baseline, there is a statistically significant difference between the treatment arms to the disadvantage of esketamine. There is a hint of greater harm from esketamine in comparison with treatment of physician's choice.

However, for patients with an MADRS total score ≥ 34 points at baseline, there was no statistically significant difference between the treatment arms. There is no hint of greater or lesser harm from esketamine in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [11].

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2 (see Table 9).

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Determination of the outcome category for symptom outcomes

Remission and response (each recorded with the MADRS), functional remission (recorded with SDS) and general depressive symptoms (recorded using PHQ-9 and QLDS)

The ESCAPE TRD study included only patients with moderate to severe depression. In addition, ≥ 80% of the included patients had already had ≥ 2 major depressive episodes, and the median duration of the current depressive episode was ≥ 38 weeks in both treatment arms. Overall, it is therefore assumed that the disease of the patients in the ESCAPE-TRD study was associated with severe symptoms. This is also reflected in the baseline values of the various instruments. Therefore, the outcomes of remission, response, functional remission and general depressive symptoms are assigned to the outcome category of serious/severe symptoms/late complications.

Health status (EQ-5D VAS)

No information is available on the assignment of the severity grade for the outcome of health status (recorded using the EQ-5D VAS) that allows a classification as serious/severe. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Determination of the outcome category for the outcomes on side effects

Discontinuation due to AEs

No information is available on the assignment of the severity grade for the outcome of discontinuation due to AEs that allows a classification as serious/severe. Therefore, the outcome "discontinuation due to AEs" was assigned to the category of non-serious/non-severe side effects.

Table 9: Extent of added benefit at outcome level: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality (up to week 32)	0.3% vs. 0.3% RR: 0.97 [0.07; 14.35]; p = 0.984	Lesser/added benefit not proven
Morbidity		
Remission (MADRS), improvement by ≥ 12 points week 8	39.3% vs. 23.8% RR: 1.66 [1.31; 2.09] RR: 0.60 [0.48; 0.76][c] p < 0.001 probability: “hint”	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: “considerable”
Remission (MADRS), improvement by ≥ 12 points week 32	60.7% vs. 45.0% RR: 1.35 [1.17; 1.57] RR: 0.74 [0.64; 0.85][c] p < 0.001 probability: “hint”	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: “considerable”
Response (MADRS), improvement from baseline by ≥ 50% week 8	53.6% vs. 38.2% RR: 1.41 [1.19; 1.66] RR: 0.71 [0.60; 0.84][c] p < 0.001 probability: hint	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: “considerable”
Response (MADRS), improvement from baseline by ≥ 50% week 32		
Substance class of the pre-existing AD		
SNRI	75.2% vs. 50.0% RR: 1.50 [1.25; 1.80] RR: 0.67 [0.56; 0.80][c] p < 0.001 probability: hint	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: “considerable”
SSRI	63.4% vs. 55.9% RR: 1.14 [0.96; 1.35] p = 0.142	Lesser/added benefit not proven
Functional remission (SDS), ≤ 2 points in each item and SDS total score ≤ 6 points week 8	13.7% vs. 12.1% RR: 1.14 [0.75; 1.71]; p = 0.555	Lesser/added benefit not proven

Table 9: Extent of added benefit at outcome level: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Functional remission (SDS), ≤ 2 points in each item and SDS total score ≤ 6 points week 32	34.0% vs. 23.7% RR: 1.43 [1.11; 1.85] RR: 0.70 [0.54; 0.90][c] p = 0.005 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Relapse (MADRS)	No usable data	Lesser/added benefit not proven
General depressive symptoms (PHQ-9), improvement by ≥ 5 points week 8	68.8% vs. 58.2% RR: 1.18 [1.05; 1.32] RR: 0.85 [0.76; 0.95][c] p = 0.005 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
General depressive symptoms (PHQ-9), improvement by ≥ 5 points week 32	69.1% vs. 56.5% RR: 1.23 [1.09; 1.38] RR: 0.81 [0.72; 0.92][c] p < 0.001 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
General depressive symptoms (QLDS), improvement by ≥ 6 points, week 8		
Substance class of the pre-existing AD		
SNRI	71.4% vs. 48.0% RR: 1.49 [1.23; 1.80] RR: 0.67 [0.56; 0.81][c] p < 0.001 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
SSRI	60.6% vs. 51.6% RR: 1.17 [0.98; 1.41] p = 0.086	Lesser/added benefit not proven
General depressive symptoms (QLDS), improvement by ≥ 6 points week 32	68.2% vs. 51.5% RR: 1.33 [1.17; 1.50] RR: 0.75 [0.67; 0.85][c] p < 0.001 probability: hint	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Health status (EQ-5D VAS); improvement ≥ 15 points week 8	54.5% vs. 42.7% RR: 1.28 [1.09; 1.50] RR: 0.78 [0.67; 0.92][c] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser/added benefit not proven[d]

Table 9: Extent of added benefit at outcome level: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Health status (EQ-5D VAS); improvement ≥ 15 points week 32	58.0% vs. 46.5% RR: 1.25 [1.08; 1.45] RR: 0.80 [0.69; 0.93][c] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser/added benefit not proven[d]
Suicidal ideation (C-SSRS) week 8	8.0% vs. 6.5% RR: 1.24 [0.69; 2.21]; p = 0.472	Lesser/added benefit not proven
Suicidal ideation (C-SSRS) week 32	3.3% vs. 2.2% RR: 1.53 [0.53; 4.46]; p = 0.432	Lesser/added benefit not proven
Suicidal behaviour (C-SSRS) week 8	0% vs. 0.3% RR: ND p = ND	Lesser/added benefit not proven
Suicidal behaviour (C-SSRS) week 32	0% vs. 0.4% RR: ND p = ND	Lesser/added benefit not proven
Health-related quality of life		
SF-36v2		
PCS, improvement by ≥ 9.4 points week 8	14.0% vs. 11.8% RR: 1.20 [0.80; 1.78]; p = 0.379	Lesser/added benefit not proven
PCS, improvement by ≥ 9.4 points week 32	21.4% vs. 15.3% RR: 1.41 [1.02; 1.95] RR: 0.71 [0.51; 0.98][c] p = 0.037 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
MCS, improvement by ≥ 9.6 points week 8	53.6% vs. 40.6% RR: 1.32 [1.12; 1.55] RR: 0.76 [0.65; 0.89][c] p < 0.001 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"

Table 9: Extent of added benefit at outcome level: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
MCS, improvement by ≥ 9.6 points, week 32		
Substance class of the pre-existing AD		
SNRI	62.7% vs. 40.1% RR: 1.56 [1.25; 1.96] RR: 0.64 [0.51; 0.80][c] p < 0.001 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
SSRI	53.7% vs. 47.3% RR: 1.14 [0.93; 1.39] p = 0.225	Lesser/added benefit not proven
Side effects (up to week 32)		
SAEs	5.7% vs. 5.1% RR: 1.11 [0.59; 2.09]; p = 0.746	Greater/lesser harm not proven
Discontinuation due to AEs	4.2% vs. 11.0% RR: 0.38 [0.21; 0.69]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm; extent: "considerable"
Nervous system disorders (AE)		
Disease severity at baseline according to MADRS total score		
≤ 34	70.8% vs. 44.3% RR: 1.60 [1.36; 1.88] RR: 0.63 [0.53; 0.74][c] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: considerable
> 34	64.8% vs. 57.8% RR: 1.12 [0.89; 1.42] p = 0.331	Greater/lesser harm not proven
Psychiatric disorders (AE)	46.7% vs. 13.1% RR: 3.58 [2.65; 4.82] RR: 0.28 [0.21; 0.38][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: considerable

Table 9: Extent of added benefit at outcome level: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Respiratory, thoracic, and mediastinal disorders (AE)	16.2% vs. 3.0% RR: 5.43 [2.81; 10.48] RR: 0.18 [0.10; 0.36][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm; extent: considerable
Nausea (AE)	29.3% vs. 3.6% RR: 8.17 [4.58; 14.58] RR: 0.12 [0.07; 0.22][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm; extent: considerable
Vomiting (AE)	10.8% vs. 1.5% RR: 7.14 [2.84; 17.93] RR: 0.14 [0.06; 0.35][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm; extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AD: antidepressant; AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; C-SSRS: Columbia Suicide Severity Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MCS: Mental Component Summary; PCS: Physical Component Summary; PHQ-9: Patient Health Questionnaire-9; QLDS: Quality of Life in Depression Scale; RR: relative risk; SAE: serious adverse event; SDS: Sheehan Disability Scale; SF-36v2: Short Form (36) – version 2 Health Survey; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; VAS: visual analogue scale

2.3.2 Overall conclusion on added benefit

Table 10 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 10: Positive and negative effects from the assessment of esketamine in combination with an SSRI or SNRI compared with treatment of physician's choice

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ remission (MADRS) week 8 and week 32 ▪ response (MADRS) week 8 ▪ response (MADRS) week 32 ▫ substance class of the pre-existing oral AD (SNRI) ▪ general depressive symptoms (QLDS) week 8 ▫ substance class of the pre-existing oral AD (SNRI) ▪ general depressive symptoms (QLDS) week 32 for each, hint of an added benefit – extent: "considerable" ▪ functional remission (SDS) week 32 ▪ general depressive symptoms (PHQ-9) week 8 and week 32 for each, hint of an added benefit – extent: minor	Non-serious/non-severe side effects (up to week 32) ▪ psychiatric disorders, respiratory, thoracic and mediastinal disorders, nausea, vomiting (each AE) ▪ nervous system disorders (AE) ▫ disease severity at baseline according to MADRS total score (≤ 34) for each, hint of greater harm – extent: "considerable"
Health-related quality of life SF-36v2 ▪ PCS week 32: hint of an added benefit – extent: "considerable" ▪ MCS week 8 ▪ MCS week 32 ▫ substance class of the pre-existing oral AD (SNRI) for each, hint of an added benefit – extent: "considerable"	
Non-serious/non-severe side effects (up to week 32) ▪ discontinuation due to AEs: hint of lesser harm - extent: "considerable"	
No suitable data were available for the outcome of relapse.	
AD: antidepressant; AE: adverse event; MADRS: Montgomery-Åsberg Depression Rating Scale; MCS: Mental Component Summary; PCS: Physical Component Summary; SDS: Sheehan Disability Scale; PHQ-9: Patient Health Questionnaire-9; QLDS: Quality of Life in Depression Scale; SF-36v2: Short Form-36 Health Survey Version 2; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor	

Overall, several positive effects in the outcome categories of serious/severe symptoms/late complications, health-related quality of life and non-serious/non-severe side effects are offset by some negative effects in the outcome category of non-serious/non-severe side effects.

At both time points (week 8 and week 32), the outcomes of remission, response, general depressive symptoms (QLDS), and the MCS of the SF-36v2 each show hints of an added benefit, each with the extent: "considerable". For the outcome of general depressive symptoms (QLDS) at week 8 and the outcomes of response (MADRS) and MCS of the SF-36v2 both at week 32, these positive effects are shown exclusively for patients whose substance class of the pre-existing oral antidepressant was an SNRI. Moreover, there is a hint of minor added benefit for the outcome of general depressive symptoms (PHQ-9).

At week 32, the outcome of functional remission and the PCS of the SF-36v2 also each show a hint of an added benefit with the extent: “minor”. In addition, the outcome of discontinuation due to AEs shows a hint of lesser harm with the extent: “considerable”.

This is offset by hints of greater harm with the extent “considerable” in several specific AEs, e.g. in the PTs “dissociation”, “confusional state” (relevant in the SOC “psychiatric disorders”) and nausea. All specific AEs are non-serious/non-severe side effects and moreover, the effects to the disadvantage of esketamine are not reflected in SAEs or discontinuations due to AEs. Overall, the negative effects do therefore not call into question the largely considerable extent in several outcomes of the outcome categories of serious/severe symptoms/late complications and health-related quality of life.

The observed effects at outcome level are largely comparable in terms of direction and extent between week 8 and week 32, so that the added benefit is not derived separately for the use of esketamine as induction and maintenance therapy.

In summary, for adult patients with treatment-resistant major depression who have not responded to at least 2 different antidepressant therapies in the current moderate to severe depressive episode, there is a hint of an added benefit with the extent “considerable” for esketamine in combination with an SSRI or SNRI over treatment of physician’s choice.

As described in Section 2.2.2, the reliability of the study results for the present research question is reduced because it remains unclear whether the comparator therapy used in the ESCAPE-TRD study is a complete implementation of the ACT.

2.4 Summary

The data subsequently submitted by the company during the commenting procedure change the conclusion on the added benefit of esketamine drawn in dossier assessment A23-18 [1]. The following Table 11 shows the result of the benefit assessment of esketamine under consideration of dossier assessment A23-18 and the present addendum.

Table 11: Esketamine in combination with SSRI or SNRI – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Adults with treatment-resistant major depression, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode	Treatment of physician's choice choosing from: ▪ augmentation with lithium[c] or quetiapine retard[c], ▪ a combination with a second antidepressant[c], ▪ ECT	Hint of considerable added benefit[d]

a. Presented is the respective ACT specified by the G-BA.
b. The therapy concept for the treatment of major depression also includes psychotherapeutic procedures. According to the psychotherapy guideline [5], psychotherapeutic treatment should therefore be offered to patients in both treatment arms of a study.
c. As an add-on to the last antidepressant monotherapy administered.
d. The ESCAPE TRD study only included patients aged 18 to 74 years. It remains unclear whether the observed effects can be transferred to patients > 75 years. Data are available for both induction and subsequent maintenance therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

The G-BA decides on the added benefit.

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Appendix A Results on side effects

The tables below present events for Medical Dictionary for Regulatory Activities (MedDRA) SOCs and PTs for the overall rates of AEs and SAEs, each on the basis of the following criteria:

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

For the outcome of discontinuation due to AEs, all events (SOC/PT) that resulted in discontinuation are completely presented.

Table 12: : Common AEs[a] – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**esketamine + SSRI/SNRI** **N = 334**	**quetiapine retard + SSRI/SNRI** **N = 336**
ESCAPE-TRD, week 32		
Overall AE rate	307 (91.9)	262 (78.0)
Nervous system disorders	231 (69.2)	161 (47.9)
Dizziness	156 (46.7)	28 (8.3)
Headache	82 (24.6)	43 (12.8)
Somnolence	50 (15.0)	78 (23.2)
Dysgeusia	40 (12.0)	1 (0.3)
Paraesthesia	37 (11.1)	2 (0.6)
Sedation	22 (6.6)	29 (8.6)
Hypoaesthesia	19 (5.7)	1 (0.3)
Psychiatric disorders	156 (46.7)	44 (13.1)
Dissociation	94 (28.1)	2 (0.6)
Confusional state	20 (6.0)	1 (0.3)
Derealisation	14 (4.2)	1 (0.3)
Insomnia	14 (4.2)	6 (1.8)
Anxiety	14 (4.2)	7 (2.1)
Psychomotor slowdown	10 (3.0)	2 (0.6)
Gastrointestinal disorders	141 (42.2)	68 (20.2)
Nausea	98 (29.3)	12 (3.6)
Vomiting	36 (10.8)	5 (1.5)
Hypoaesthesia, oral	15 (4.5)	0 (0)
Paraesthesia, oral	13 (3.9)	0 (0)
Constipation	4 (1.2)	11 (3.3)
Dry mouth	3 (0.9)	22 (6.5)
Infections and infestations	70 (21.0)	69 (20.5)
COVID-19	24 (7.2)	29 (8.6)
Nasopharyngitis	21 (6.3)	11 (3.3)
Ear and labyrinth disorders	67 (20.1)	5 (1.5)
Vertigo	63 (18.9)	3 (0.9)
General disorders and administration site conditions	66 (19.8)	53 (15.8)
Fatigue	19 (5.7)	34 (10.1)
Asthenia	13 (3.9)	1 (0.3)

Table 12: : Common AEs[a] – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study	**Patients with event n (%)**	
SOC[b] / **PT[b]**	**esketamine + SSRI/SNRI N = 334**	**quetiapine retard + SSRI/SNRI N = 336**
Respiratory, thoracic and mediastinal disorders	54 (16.2)	10 (3.0)
Sneezing	15 (4.5)	0 (0)
Rhinalgia	14 (4.2)	1 (0.3)
Throat irritation	10 (3.0)	0 (0)
Investigations	51 (15.3)	54 (16.1)
Blood pressure increased	28 (8.4)	4 (1.2)
Weight increased	9 (2.7)	42 (12.5)
Musculoskeletal and connective tissue disorders	40 (12.0)	26 (7.7)
Back pain	17 (5.1)	9 (2.7)
Eye disorders	32 (9.6)	5 (1.5)
Vision blurred	21 (6.3)	3 (0.9)
Skin and subcutaneous tissue disorders	18 (5.4)	8 (2.4)
Vascular disorders	12 (3.6)	13 (3.9)
Injury, poisoning and procedural complications	10 (3.0)	9 (2.7)
Metabolism and nutrition disorders	9 (2.7)	21 (6.3)
Increased appetite	1 (0.3)	11 (3.3)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SNRI: serotonin-noradrenaline reuptake inhibitor; SOC: System Organ Class; SSRI: selective serotonin reuptake inhibitor

Table 13: Common SAEs[a] – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI

Study	**Patients with event n (%)**	
SOC[b]	**esketamine + SSRI/SNRI N = 334**	**quetiapine retard + SSRI/SNRI N = 336**
ESCAPE-TRD, week 32		
Overall SAE rate	19 (5.7)	17 (5.1)
Psychiatric disorders	9 (2.7)	11 (3.3)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC notation taken from Module 4.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SNRI: serotonin-noradrenaline reuptake inhibitor; SOC: System Organ Class; SSRI: selective serotonin reuptake inhibitor

Table 14: Discontinuations due to AEs – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**esketamine + SSRI/SNRI** **N = 334**	**quetiapine retard + SSRI/SNRI** **N = 336**
ESCAPE-TRD, week 32		
Overall rate of discontinuations due to AEs	14 (4.2)	37 (11.0)
Nervous system disorders	3 (0.9)	18 (5.4)
Dizziness	2 (0.6)	4 (1.2)
Hypokinesia	1 (0.3)	0 (0)
Generalized tonic-clonic seizure	0 (0)	1 (0.3)
Headache	0 (0)	1 (0.3)
Migraine	0 (0)	1 (0.3)
Restless legs syndrome	0 (0)	1 (0.3)
Sedation	0 (0)	7 (2.1)
Somnolence	0 (0)	5 (1.5)
Psychiatric disorders	4 (1.2)	4 (1.2)
Dissociation	2 (0.6)	0 (0)
Alcoholism	1 (0.3)	0 (0)
Anxiety	1 (0.3)	0 (0)
Suicide attempt	1 (0.3)	1 (0.3)
Apathy	0 (0)	1 (0.3)
Restlessness	0 (0)	1 (0.3)
Suicidal ideation	0 (0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.6)	0 (0)
Oropharyngeal pain	1 (0.3)	0 (0)
Rhinalgia	1 (0.3)	0 (0)
Cardiac disorders	2 (0.6)	0 (0)
Acute coronary syndrome	1 (0.3)	0 (0)
Atrial fibrillation	1 (0.3)	0 (0)
Gastrointestinal disorders	2 (0.6)	2 (0.6)
Vomiting	2 (0.6)	0 (0)
Abdominal pain	0 (0)	1 (0.3)
Diarrhoea	0 (0)	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.3)	0 (0)
Arthralgia	1 (0.3)	0 (0)
Congenital, familial and genetic disorders	1 (0.3)	0 (0)
Brugada syndrome	1 (0.3)	0 (0)

Table 14: Discontinuations due to AEs – RCT, direct comparison: esketamine + SSRI/SNRI vs. quetiapine retard + SSRI/SNRI (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**esketamine + SSRI/SNRI** **N = 334**	**quetiapine retard + SSRI/SNRI** **N = 336**
Investigations	0 (0)	7 (2.1)
Weight increased	0 (0)	6 (1.8)
Hepatic enzyme increased	0 (0)	1 (0.3)
General disorders and administration site conditions	0 (0)	6 (1.8)
Fatigue	0 (0)	4 (1.2)
Hangover	0 (0)	2 (0.6)
Metabolism and nutrition disorders	0 (0)	2 (0.6)
Ravenous hunger	0 (0)	1 (0.3)
Increased appetite	0 (0)	1 (0.3)
Blood and lymphatic system disorders	0 (0)	1 (0.3)
Mediastinal lymphadenopathy	0 (0)	1 (0.3)
Eye disorders	0 (0)	1 (0.3)
Cataract	0 (0)	1 (0.3)
Infections and infestations	0 (0)	1 (0.3)
Infectious mononucleosis	0 (0)	1 (0.3)
Skin and subcutaneous tissue disorders	0 (0)	1 (0.3)
Rash	0 (0)	1 (0.3)

a. MedDRA version 25.0; SOCs and PTs taken from Module 4.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SNRI: serotonin-noradrenaline reuptake inhibitor; SOC: System Organ Class; SSRI: selective serotonin reuptake inhibitor