IQWiG Reports – Commission No. A21-24

Esketamine (treatment-resistant major depressive disorder) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Esketamin (therapieresistente Major Depression) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 May 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
EMA	European Medicines Agency
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
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SNRI	serotonin-noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TRD	treatment-resistant depression

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug esketamine. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 4 March 2021.

Research question

The aim of this report is to assess the added benefit of esketamine in combination with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-noradrenaline reuptake inhibitor (SNRI) in comparison with the appropriate comparator therapy (ACT) in adult patients with treatment-resistant major depressive disorder who have failed to respond to at least 2 different antidepressant therapies in the current moderate to severe depressive episode.

The research question for the benefit assessment is presented in Table 2.

Table 2: Research question of the benefit assessment for esketamine in combination with an SSRI or SNRI

Indication	**ACT**[a, b, c, d]
Adults with treatment-resistant major depressive disorder who have failed to respond to at least 2 different antidepressant therapies in the current moderate to severe depressive episode	▪ Augmentation with lithium or ▪ Augmentation with extended-release quetiapine or ▪ Combination with a 2nd antidepressant[e] or ▪ Switch from antidepressant monotherapy to a different substance class The respective drug approval status must be taken into account.
a. Presented is the ACT specified by the G-BA. b. The treatment concept for major depression also includes psychotherapy. Therefore, psychotherapy in accordance with the psychotherapy guideline should be offered in both treatment arms of any study. c. Electroconvulsive therapy (ECT) is of therapeutic value in the treatment of treatment-resistant depression, but only after the above-cited options have failed. Therefore, it is unsuitable as an ACT in the present therapeutic indication. d. It is assumed that the maximum approved dosage of the antidepressant monotherapy (to the extent tolerated) has been attempted. e. The drugs mianserin or mirtazapine are available for combination therapy with a 2nd antidepressant. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-noradrenaline reuptake inhibitor	

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) were used for

the derivation of added benefit. For the present research question, the required minimum study duration is 6 weeks for acute treatment and 24 months for maintenance therapy.

Results

The check of completeness did not reveal any relevant studies for assessing any added benefit of esketamine in combination with an SSRI or SNRI in comparison with the ACT. This concurs with the company's assessment.

Although the company found the two directly comparative RCTs ESKETINTRD3002 (hereinafter referred to as TRANSFORM-2) and ESKETINTRD3005 (hereinafter referred to as TRANSFORM-3) and presented their results in the dossier, it did not use them for deriving any added benefit of esketamine. This is appropriate. For the present therapeutic indication of treatment-resistant major depressive disorder, the 4-week randomized treatment phase used by both studies is too short for deriving conclusions on any added benefit of esketamine in combination with an SSRI or SNRI in comparison with the ACT. Furthermore, both studies investigate acute therapy only. No data are available on maintenance therapy. Aside from the study duration being too short, lack of implementation of the ACT renders the TRANSFORM-2 and TRANSFORM-3 studies unsuitable for deriving any added benefit of esketamine in comparison with the ACT. Both studies compared esketamine with placebo, each in combination with a newly initiated antidepressant (SNRI or SSRI). Given the option cited by the G-BA, adequate implementation of the ACT would require prior treatment with antidepressant monotherapy (ACT option: switch from antidepressant monotherapy to a different substance class). This requirement was not met by either study.

For long-term treatment with esketamine in combination with an SSRI or SNRI, the company found the 1-arm study ESKETINTRD3004 (hereinafter referred to as SUSTAIN-2) and presented a comparison of individual arms from different studies. Specifically, the company compared the results of the SUSTAIN-2 study to the data of a prospective European cohort study in patients with treatment-resistant depression (hereinafter referred to as TRD cohort). Reasoning that the infeasibility of performing analyses on safety outcomes would place limits on any comparison of individual arms from different studies, the company once again elected to disregard said data when it came to deriving any benefit. This reasoning is plausible.

Hence, no suitable data are available to assess any added benefit of esketamine in combination with an SSRI or an SNRI in comparison with the ACT in adult patients with treatment-resistant major depressive disorder who have failed to respond to at least 2 different antidepressant therapies in the current moderate to severe depressive episode. Consequently, there is no hint of any added benefit of esketamine in combination with an SSRI or SNRI in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of esketamine in combination with an SSRI or SNRI.

Table 3: Esketamine in combination with an SSRI or SNRI – probability and extent of added benefit

Indication	ACT[a, b, c, d]	Probability and extent of added benefit
Adults with treatment-resistant major depressive disorder who have failed to respond to at least 2 different antidepressant therapies in the current moderate to severe depressive episode	▪ Augmentation with lithium or ▪ Augmentation with extended-release quetiapine or ▪ Combination with a 2nd antidepressant[e] or ▪ Switch from antidepressant monotherapy to a different substance class The respective drug approval status must be taken into account.	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The treatment concept for major depression also includes psychotherapy. Therefore, psychotherapy in accordance with the psychotherapy guideline should be offered in both treatment arms of any study.
c. Electroconvulsive therapy (ECT) is of therapeutic value in the treatment of treatment-resistant depression, but only after the above-cited options have failed. Therefore, it is unsuitable as an ACT in the present therapeutic indication.
d. It is assumed that the maximum approved dosage of the antidepressant monotherapy (to the extent tolerated) has been attempted.
e. The drugs mianserin or mirtazapine are available for combination therapy with a 2nd antidepressant.

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

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report is to assess the added benefit of esketamine in combination with an SSRI or SNRI in comparison with the ACT in adult patients with treatment-resistant major depressive disorder who have failed to respond to at least 2 different antidepressant therapies in the current moderate to severe depressive episode.

The research question for the benefit assessment is presented in Table 4.

Table 4: Research question of the benefit assessment of esketamine in combination with an SSRI or SNRI

Indication	**ACT**[a, b, c, d]
Adults with treatment-resistant major depressive disorder who have failed to respond to at least 2 different antidepressant therapies in the current moderate to severe depressive episode	▪ Augmentation with lithium or ▪ Augmentation with extended-release quetiapine or ▪ Combination with a 2nd antidepressant[e] or ▪ Switch from antidepressant monotherapy to a different substance class The respective drug approval status must be taken into account.
a. Presented is the ACT specified by the G-BA. b. The treatment concept for major depression also includes psychotherapy. Therefore, both treatment arms of any study should offer psychotherapeutic treatment in accordance with the psychotherapy guideline [3]. c. Electroconvulsive therapy (ECT) is of therapeutic value in the treatment of treatment-resistant depression, but only after the above-cited options have failed. Therefore, it is unsuitable as an ACT in the present therapeutic indication. d. It is assumed that the maximum approved dosage of the antidepressant monotherapy (to the extent tolerated) has been attempted. e. The drugs mianserin or mirtazapine are available for combination therapy with a 2nd antidepressant. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-noradrenaline reuptake inhibitor	

The company followed the G-BA's specification by listing all potential ACT options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs were used for the derivation of added benefit. In this context, it must be noted that the treatment concept for an episode of therapy-resistant major depressive disorder comprises both acute therapy and maintenance therapy (remission maintenance or relapse prevention) [4]. The required minimum study duration for the present research question is 6 weeks for acute treatment and 24 months for maintenance therapy [4,5]. This deviates from the company's inclusion criteria, which specified a minimum study duration of 4 weeks. The resulting consequences for the present benefit assessment of esketamine are discussed in Section 2.3.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on esketamine (as of 4 January 2021)
- Bibliographic literature search on esketamine (most recent search on 6 January 2021)
- Search in trial registries / study results databases on esketamine (most recent search on 4 January 2021)
- Search on the G-BA website on esketamine (most recent search on 22 January 2021)
- Bibliographic literature search on the ACT (most recent search on 6 January 2021)
- Search in trial registries or results databases on the ACT (most recent search on 4 January 2021)
- Search on the G-BA website for the ACT (most recent search on 22 January 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on esketamine (most recent search on 18 March 2021)

The check of completeness did not reveal any relevant studies for assessing any added benefit of esketamine in combination with an SSRI or SNRI in comparison with the ACT. This concurs with the company's assessment.

Using the cited steps of its information retrieval, the company found, for short-term treatment, the two directly comparative RCTs ESKETINTRD3002 (hereinafter referred to as TRANSFORM-2) [6] and ESKETINTRD3005 (hereinafter referred to as TRANSFORM-3) [7]. While the company presented the results of these studies in the dossier, it did not use them to derive any added benefit of esketamine. The company explained this, in particular, with 28 days being too short a duration for the randomized treatment phase. Further, the company cited insufficient documentation of correct implementation of the ACT "switch from antidepressant monotherapy to another substance class".

For long-term treatment with esketamine in combination with an SSRI or SNRI, the company identified the 1-arm study ESKETINTRD3004 [8] (hereinafter referred to as SUSTAIN-2), and on this basis, it presented a comparison of individual arms from different studies. For this purpose, the company compared the results of the SUSTAIN-2 study to the data of a prospective European cohort study in patients with treatment-resistant depression [9] (hereinafter referred to as TRD cohort). Reasoning that the infeasibility of performing analyses on safety outcomes would place limits on any comparison of individual arms from different studies, the company once again elected to disregard said data when it came to deriving any benefit.

This reasoning is plausible. The reason is explained in more detail below.

Evidence provided by the company

RCTs TRANSFORM-2 and TRANSFORM-3

TRANSFORM-2 and TRANSFORM-3 are randomized, double-blind, placebo-controlled approval studies for esketamine. Both studies investigate acute, flexible-dose treatment with esketamine in comparison with placebo, each in combination with a newly initiated oral antidepressant of the SSRI or SNRI substance class.

The design of both studies comprises a 4-week screening phase and a 4-week double-blind, randomized treatment phase (induction phase). Following the treatment phase, patients had the opportunity to participate in an open-label extension study (ESKETINTRD3003 [SUSTAIN-1] for patients from the TRANSFORM-2 study or SUSTAIN-2 for patients from the TRANSFORM-3 study), provided they met the relevant inclusion criteria. Patients who did not participate in the extension study were followed up for another 24 weeks (TRANSFORM-2) or 2 weeks (TRANSFORM-3) (follow-up phase). The primary outcome was depressive symptoms, operationalized as change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total scores.

The studies included adults 18 to 64 years of age (TRANSFORM-2) or only older patients ≥ 65 years (TRANSFORM-3) with major depressive disorder diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders [DSM-V]) and an Inventory of Depressive Symptoms-Clinician rated, 30-item total score (IDS-C_{30}) of ≥ 34 (TRANSFORM-2) or ≥ 31 (TRANSFORM-3), which corresponds to moderate to severe depression. At the start of the screening phase, patients had to additionally have exhibited failure to respond (defined as ≤ 25% improvement in the MADRS total score) to at least 1 prior treatment with an oral antidepressant in the current depressive episode. In addition, patients had to have been on another oral antidepressant treatment, taking at least the minimum therapeutically effective dose, for at least 2 weeks. Patients had to continue this antidepressant therapy until the end of the 4-week screening phase (prospective treatment phase). Dose adjustments beyond the minimum therapeutically effective dose were allowed. Patients whose depression failed to respond to antidepressant therapy (defined as ≤ 25% improvement in the MADRS total score from Week 1 to Week 4) by the end of the prospective treatment phase were, at the start of the randomized treatment phase (induction phase), randomly allocated in a 1:1 ratio either to treatment with esketamine or to the placebo arm, each in combination with a newly initiated antidepressant (SNRI or SSRI). The use of esketamine was largely in compliance with the specifications of the Summary of Product Characteristics (SPC) [10].

Insufficient duration of the studies presented by the company

The treatment concept for an episode of therapy-resistant major depressive disorder comprises both acute therapy and maintenance therapy (maintenance of remission or relapse prevention) [4]. In acute therapy, the treatment phase extends over a period of 6 to 12 weeks, with the goal

of reducing symptoms and achieving remission, if possible. This period comprises both an uptitration phase, in which a minimum therapeutic dose (at least the standard dosage) is determined, and a 4-week treatment (up to 6 weeks in older patients) using the minimum therapeutically effective dose. Due to the delay in the onset of effect, this period should be completed before deciding whether or not there was a response. To reduce the risk of recurrence after acute therapy, it is recommended (after remission in the acute phase) to follow up with psychopharmacological maintenance therapy for 4 to 9 months at the dose that achieved remission [4]. The weighing of benefit and harm for the benefit assessment of esketamine in combination with an SSRI or SNRI versus the ACT in the therapeutic indication requires studies with a minimum randomized treatment duration of 6 weeks for acute therapy and 6 months for maintenance therapy. This is in line with the recommendations of the European Medicines Agency (EMA) guideline for the clinical investigation of medicinal products for the treatment of depressive disorders [5].

Given that their length of only 4 weeks was too short for randomized treatment and even included the uptitration of the newly initiated antidepressants as well as of esketamine in the intervention arm, the RCTs presented by the company, TRANSFORM-2 and TRANSFORM-3, are therefore overall unsuitable for the benefit assessment in the therapeutic indication of treatment-resistant major depressive disorder. Furthermore, both studies investigate acute therapy only. No data are available on maintenance therapy. This concurs with the company's assessment.

ACT not implemented in the studies

In addition to the insufficient study duration, lack of implementation of the ACT renders the TRANSFORM-2 and TRANSFORM-3 studies unsuitable for deriving any added benefit of esketamine in comparison with the ACT. Both studies compared esketamine with placebo, each in combination with a newly initiated antidepressant (SNRI or SSRI). In accordance with the option cited by the G-BA, prior antidepressant therapy would thus be a prerequisite for adequate implementation of the ACT (ACT option: switched from antidepressant monotherapy to a different substance class). During both studies' prospective treatment phases, patients were to continue the antidepressant medication they had taken for at least 2 weeks at a minimum therapeutically effective dose or higher. This included all medications for the treatment of depression which were taken at the time of screening, including any supportive or adjuvant therapies, such as lithium augmentation. The option listed by the G-BA "switch from antidepressant monotherapy to a different substance class of the ACT" does not comprise combination therapies with 2 antidepressants or augmentation of antidepressant monotherapy. No analyses are available as to how many of the included patients were previously treated exclusively with antidepressant monotherapy as required for the ACT.

This view concurs with that of the company, which stated in the dossier that correct implementation of the ACT "switch from antidepressant monotherapy to a different substance class" was insufficiently documented for therapies undertaken prior to the prospective treatment

phase and that it was therefore impossible to determine whether patients with the ACT were adequately pretreated.

Summary

In summary, due to the insufficient study duration and lack of implementation of the ACT, the TRANSFORM-2 and TRANSFORM-3 studies are unsuitable for answering the research question of the present benefit assessment of esketamine. Therefore, they were not included for deriving any added benefit.

Comparison of individual arms from different studies – SUSTAIN-2 and TRD cohort

For long-term treatment with esketamine in combination with an SSRI or SNRI, the company's dossier presented a comparison of individual arms from different studies. For this purpose, it compared the results of the 1-arm study SUSTAIN-2 on esketamine in combination with an SSRI or SNRI versus the data of a prospective European TRD cohort on the ACT.

For the TRD cohort study, the company's dossier states that adverse events were registered by way of pharmacovigilance reporting rather than being documented in the study itself.

This explains why no data on side effects are available for the comparison of individual arms from different studies. Investigating the comparability of benefit of esketamine in combination with an SSRI or SNRI versus that of the ACT requires effectiveness data as well as data on adverse events.

The comparison of individual arms from different studies, as presented in the company's dossier, is hence unsuitable for drawing any conclusions on any added benefit of esketamine in combination with an SSRI or SNRI in comparison with the ACT. This concurs with the company's assessment.

Ongoing ESCAPE-TRD study

The company reported that it designed the study 54135419TRD3013 (hereinafter referred to as ESCAPE-TRD) [11] in response to the limitations inherent in the directly comparative evidence.

This ongoing RCT ESCAPE-TRD investigates the comparison of esketamine versus extended-release quetiapine, each in combination with an SSRI or SNRI in patients with treatment-resistant major depressive disorder. The study will run for 36 weeks. It started on 21 August 2020, and the expected study end date is 15 December 2022. In line with the company's search, the study has been excluded from the present benefit assessment because the study is still in the recruitment stage and no results are available yet.

2.4 Results on added benefit

No suitable data are available to assess any added benefit of esketamine in combination with an SSRI or an SNRI in comparison with the ACT in adult patients with treatment-resistant

major depressive disorder who have failed to respond to at least 2 different antidepressant therapies in the current moderate to severe depressive episode. Consequently, there is no hint of any added benefit of esketamine in combination with an SSRI or SNRI in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of esketamine in combination with an SSRI or SNRI in comparison with the ACT.

Table 5: Esketamine in combination with an SSRI or SNRI – probability and extent of added benefit

Indication	**ACT**[a, b, c, d]	**Probability and extent of added benefit**
Adults with treatment-resistant major depressive disorder who have failed to respond to at least 2 different antidepressant therapies in the current moderate to severe depressive episode	▪ Augmentation with lithium or ▪ Augmentation with extended-release quetiapine or ▪ Combination with a 2nd antidepressant[e] or ▪ Switch from antidepressant monotherapy to a different substance class The respective drug approval status must be taken into account.	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The treatment concept for major depression also includes psychotherapy. Therefore, both treatment arms of any study should offer psychotherapeutic treatment in accordance with the psychotherapy guideline [3].
c. Electroconvulsive therapy (ECT) is of therapeutic value in the treatment of treatment-resistant depression, but only after the above-cited options have failed. Therefore, it is unsuitable as an ACT in the present therapeutic indication.
d. It is assumed that the maximum approved dosage of the antidepressant monotherapy (to the extent tolerated) has been attempted.
e. The drugs mianserin or mirtazapine are available for combination therapy with a 2nd antidepressant.

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

No added benefit of esketamine has been proven for this research question because no relevant data are available on esketamine in combination with an SSRI or SNRI in comparison with the ACT regarding the treatment of adults with treatment-resistant major depressive disorder who have failed to respond to at least 2 different therapies in the current moderate to severe depressive episode. This concurs with the company's assessment.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Richtlinie des Gemeinsamen Bundesausschusses über die Durchführung der Psychotherapie (Psychotherapie-Richtlinie) [online]. 2020 [Accessed: 26.04.2021]. URL: https://www.g-ba.de/downloads/62-492-2400/PT-RL_2020-11-20_iK-2021-02-18.pdf.

4. Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde, Bundesärztekammer, Kassenärztliche Bundesvereinigung et al. S3-Leitlinie/Nationale VersorgungsLeitlinie. Unipolare Depression. Langfassung [online]. 2015 [Accessed: 22.03.2019]. URL: http://www.awmf.org/uploads/tx_szleitlinien/nvl-005l_S3_Unipolare_Depression_2017-05.pdf.

5. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of depression [online]. 2013 [Accessed: 14.04.2020]. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-depression_en.pdf.

6. Popova V, Daly EJ, Trivedi M et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. Am J Psychiatry 2019; 176(6): 428-438. https://dx.doi.org/10.1176/appi.ajp.2019.19020172.

7. Ochs-Ross R, Daly EJ, Zhang Y et al. Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression-TRANSFORM-3. Am J Geriatr Psychiatry 2020; 28(2): 121-141. https://dx.doi.org/10.1016/j.jagp.2019.10.008.

8. Wajs E, Aluisio L, Holder R et al. Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). J Clin Psychiatry 2020; 81(3). https://dx.doi.org/10.4088/JCP.19m12891.

9. Heerlein K, Young AH, Otte C et al. Real-world evidence from a European cohort study of patients with treatment resistant depression: Baseline patient characteristics. J Affect Disord 2021; 283: 115-122. https://dx.doi.org/10.1016/j.jad.2020.11.124.

10. Janssen. Spravato 28 mg Nasenspray, Lösung [online]. 2021 [Accessed: 08.03.2021]. URL: https://www.fachinfo.de.

11. Janssen-Cilag International. A Long-term Comparison of Esketamine Nasal Spray Versus Quetiapine Extended Release, Both in Combination With a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor, in Participants With Treatment Resistant Major Depressive Disorder (ESCAPE-TRD) [online]. 2021. URL: https://ClinicalTrials.gov/show/NCT04338321.

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