Medicinrådet

Baggrund for Medicinrådets anbefaling af esketamin til behandling af behandlingsresistent depression hos voksne

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om Baggrunden for Medicinrådets anbefaling

Baggrund for Medicinrådets anbefaling er en sammenfatning af lægemidlets værdi for patienterne, omkostninger for samfundet og en gengivelse af de vurderinger, der er grundlag for Medicinrådets anbefaling.

Anbefalingen er Medicinrådets vurdering af, om omkostningerne vedrørende brug af lægemidlet er rimelige, når man sammenligner dem med lægemidlets værdi for patienterne. I nogle tilfælde spiller sygdommens alvorlighed en særlig rolle i vurderingen.

Anbefalingen er et klinisk og økonomisk baseret råd til regionerne til brug for deres beslutning om at anvende et givet lægemiddel. Anbefalingen er ikke bindende for regionerne.

Læs eventuelt mere i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Godkendt af Medicinrådet 26. august 2020
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Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
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Indhold

1 Anbefaling vedrørende esketamin til behandling af behandlingsresistent depression hos voksne

Medicinrådet anbefaler ikke esketamin i kombination med SSRI eller SNRI til voksne med moderat til svær depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva under den igangværende moderate til svære depressionsepisode.

Vi anbefaler ikke esketamin, fordi:

- lægemidlet ikke kan kategoriseres efter Medicinrådets Metoder. Det betyder, at data ikke er gode nok til, at vi kan udtale os sikkert om lægemidlet. Samtidig vurderer vi, at det potentielt kan være mindre sikkert end de lægemidler, man bruger i dag.

- lægemidlet ikke er dokumenteret bedre end den behandling, man bruger i dag.

- prisen på esketamin er høj. Når man tager usikkerhed omkring effekt og sikkerhed i betragtning, vil en ibrugtagning af esketamin udløse for høje omkostninger for sundhedsvæsenet.

2 Værdi for patienterne

Medicinrådet vurderer, at den samlede værdi af esketamin i kombination med SSRI eller SNRI sammenlignet med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode, **ikke kan kategoriseres** efter Medicinrådets metoder. Rådet vurderer dog, at esketamin i kombination med SSRI eller SNRI samlet set ikke har bedre effekt eller sikkerhedsprofil end komparator.

Vurderingen er baseret på evidens af meget lav kvalitet.

Høringen har ikke givet anledning til ændringer.

Læs mere i Medicinrådets vurdering af klinisk værdi og den bagvedliggende protokol (bilag 4 og bilag 6).

3 Omkostninger for sundhedsvæsenet

Medicinrådet vurderer, at meromkostningerne pr. patient i officielle priser er ca. 70.000 kr. sammenlignet med standardbehandlingen over en periode på 5 år, og at de årlige budgetkonsekvenser er ca. 112 mio. kr. efter 5 år. Lægemiddelvirksomheden har dog givet en fortrolig rabat, og derfor er de reelle meromkostninger og budgetkonsekvenser lavere.

Læs mere i den sundhedsøkonomiske afrapportering (bilag 1).

4 Alvorlighed

Medicinrådet har ikke anvendt alvorlighedsprincippet i beslutningsgrundlaget for anbefalingen af esketamin til behandlingsresistent depression hos voksne.

5 Anbefalingen betyder

Anbefalingen betyder, at Medicinrådet råder regionerne til ikke at bruge esketamin i kombination med SSRI eller SNRI til voksne med moderat til svær depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva under den igangværende moderate til svære depressionsepisode.

Regionerne er ikke forpligtet til at følge Medicinrådets anbefaling.

6 Sagsbehandlingstid

Medicinrådet har brugt 21 uger og 3 dage på sit arbejde med esketamin til behandlingsresistent depression hos voksne.

7 Kontaktinformation til Medicinrådet

Medicinrådets sekretariat
Dampfærgevej 27-29, 3. th.
2100 København Ø
+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

8 Versionslog

Version	Dato	Ændring
1.0	26. august 2020	Godkendt af Medicinrådet.

9 Bilag

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Medicinrådet

Sundhedsøkonomisk afrapportering

Esketamin

Behandlingsresistent depression hos voksne

Version 1.0

Indholdsfortegnelse

Dokumentets formål

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for esketamin til behandlingsresistent depression til voksne, samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under afsnittene "*Sekretariatets vurdering*". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.

Afsnit 2.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

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Opsummering

Baggrund

Esketamin i kombination med serotoninoptagshæmmer eller nordadrenalingenoptagshæmmer er indiceret til behandlingsresistent depression til voksne patienter. Omkring 10.100 patienter kandiderer årligt til behandling af den ansøgte indikation i Danmark. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af Janssen.

Analyse

Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med esketamin + orale antidepressiva (OA) over en tidshorisont på 5 år for behandlingsresistent depression sammenlignet med placebo + OA.

Inkrementelle omkostninger og budgetkonsekvenser

I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger pr. patient for esketamin + OA over en tidshorisont på 5 år ca. [redacted] DKK sammenlignet med placebo + OA. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger pr. patient 70.000 DKK sammenlignet med placebo.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af esketamin + OA som standardbehandling for behandlingsresistent depression vil være ca. [redacted] DKK i år 1 stigende til ca. [redacted] DKK i år 5 sammenlignet med placebo + OA. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 28 mio. DKK i år 1, og ca. 112 mio. DKK i år 5 sammenlignet med placebo + OA.

Konklusion

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for esketamin i analysen. Respons, dosisjustering og frekvens har stor betydning på analysens resultat.

Dokumentoplysninger	
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Arbejdsgruppe	Louise Greve Dal, Camilla Nybo Holmberg

Liste over forkortelser

AE	Uønsket hændelse
AIP	Apotekernes indkøbspris
HDRS	*Hamilton depression rating scale*
HR	*Hazard ratio*
ICD-10	*Classification of diseases-10*
MADRS	*Montgomery-Asberg Depression Rating Scale*
MDD	*Major depressive disorder*
MDE	*Major depressive episode*
RR	Relativ risiko
SNRI	Serotonin-/noradrenalingenoptagshæmmer
SSRI	Serotoningenoptagshæmmer
TCA	Tricykliske antidepressiva

1. Baggrund for den sundhedsøkonomiske analyse

Janssen (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af esketamin og har den 30. marts 2020 indsendt en ansøgning til Medicinrådet om anbefaling af esketamin som standardbehandling på danske hospitaler til moderat og svær behandlingsresistent depression. Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den sundhedsøkonomiske analyse, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er sekretariatets vurdering af den fremsendte sundhedsøkonomiske analyse (herefter omtalt som analysen).

1.1 Patientpopulation

Depression inddeles i mild, moderat og svær depression. Patienter med svær depression har en overhyppighed af selvmord, og tilbagefald er hyppige og forekommer med stigende frekvens afhængigt af, hvor mange depressioner man tidligere har haft [1]. Nogle får kronisk depression, hvor de depressive symptomer fortsætter igennem flere år [2]. Depression ses ofte sammen med andre psykiske lidelser som f.eks. angst og personlighedsforstyrrelser og kan optræde parallelt til alvorlige fysiske lidelser som f.eks. diabetes, kræft og hjertesygdom [2]. Herudover er misbrugsproblemer også almindeligt hos patienter med svær depression [2].

Den nuværende medicinske behandling virker bl.a. ved at regulere signalstofferne serotonin og noradrenalin i hjernen. Nogle patienter responderer ikke på den nuværende medicinske behandling og beskrives som havende behandlingsresistent depression. Definitionen af denne population er varierende. Ifølge Sundhedsstyrelsen omfatter behandlingsresistent depression voksne patienter over 18 år (både ambulante og indlagte) med moderat til svær depression, diagnosticeret efter ICD-10 (WHO's diagnoseliste) kriterier, der ikke har responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger) eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling eller er vurderet behandlingsresistent på *Rating Scale for Treatment-Resistant Depression* (f.eks. Maudsley) [3]. Behandlingen af behandlingsresistent depression er ikke defineret i den gældende behandlingsvejledning for medicinsk behandling af unipolær depression udarbejdet af Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) i 2015. En national klinisk retningslinje vedrørende vanskelig behandlelig depression er under udarbejdelse af en arbejdsgruppe under Sundhedsstyrelsen. I henhold til RADS' vejledning bør behandlingen af patienter med moderat til svær depression tilgås som følgende:

Den indledende behandling af ikkehospitaliserede patienter skal bestå af SSRI som førstelinjebehandling, der gives over 1-3 måneder. En fuld effekt af antidepressiva kan først ventes efter 4-6 uger. Opnår patienten en tilfredsstillende effekt ved behandlingen, fortsættes i en vedligeholdelsesfase i ca. 6-12 måneder eller længere, afhængigt af kliniske forhold. Hvis der ikke er tegn på bedring efter ca. 2-4 uger på optimal dosis (i praksis ofte

længere), skiftes der til andenlinjebehandling, som består af enten SSRI, SNRI, hæmmere af adrenerge receptorer (NaSSA) eller tricykliske antidepressiva (TCA). Er der fortsat ikke tegn på bedring, henvises der til psykiater eller indlæggelse på psykiatrisk afdeling. Blandt indlagte/hospitaliserede patienter med svær depression skal overvejes start med SNRI eller TCA.

I Danmark anslås prævalensen af moderat til svær depression blandt voksne at være ca. 3 %, svarende til ca. 111.000 voksne individer [4,5]. Det skønnes, at kun 65,3 % af disse, svarende til ca. 72.400 voksne individer, bliver diagnosticeret og kan komme i behandling [5]. Ca. 14 %, svarende til ca. 10.100 voksne individer, har ikke en tilfredsstillende effekt af behandlingen [5,6] og er mulige kandidater til behandling med esketamin + OA.

1.1.1 Komparator

Medicinrådet har defineret placebo + OA som komparator til esketamin + OA for patienter med behandlingsresistent depression, se Tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
Patienter over 18 år med behandlingsresistent depression (patienter der ikke har responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger) eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling eller er vurderet behandlingsresistent på rating scale for treatment-resistent depression.	Placebo + OA

1.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af esketamin + OA som standardbehandling på danske hospitaler af den nævnte indikation.

Medicinrådet har vurderet den kliniske merværdi af esketamin + OA og specificeret følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvad er værdien af esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode?

2. Vurdering af den sundhedsøkonomiske analyse

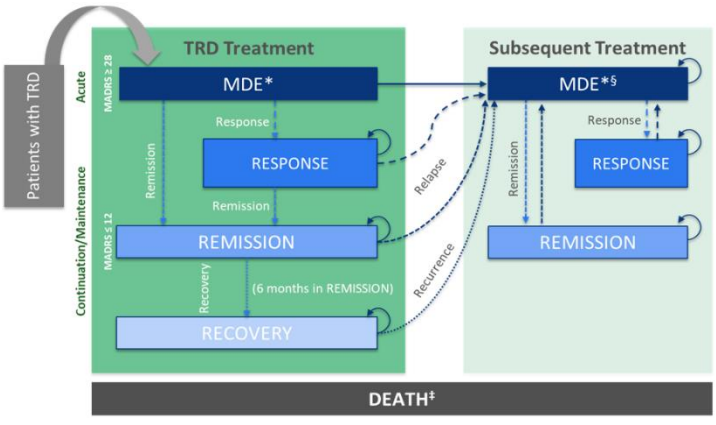
Ansøger har indsendt en sundhedsøkonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for esketamin + OA sammenlignet med placebo + OA for voksne patienter med moderat til svær behandlingsresistent depression. I det nedenstående vil den sundhedsøkonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

2.1 Antagelser og forudsætninger for model

Sammenligningen af esketamin + OA og placebo + OA er lavet på baggrund af en direkte sammenligning, hvor esketamin gives som add-on terapi til antidepressiv, i to randomiserede kliniske fase III-studier[1,2] (TRANSFORM-2 og SUSTAIN-1). Studierne måler, om patienterne opnår respons på behandling, oplever remission, relaps, recovery (rask) eller recurrence (tilbagefald). TRANSFORM-2 indeholder data på den første fase af forsøget (akutfasen), mens SUSTAIN-1 har data på resterende faser i forsøget (optimeringsfasen og vedligeholdelsesfasen).

2.1.1 Modelbeskrivelse

Ansøger har indleveret en Markov-model, der estimerer omkostninger baseret på det sygdomsstadie (helbredstilstand), som patienten befinder sig i. Hvert stadie har bestemte risici forbundet med respons, remission, relaps, recovery og recurrence, se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem sygdomsstadier. Omkostningerne estimeres ud fra en cyklus, der i modellen er 4 uger. Hvor lang tid, patienterne befinder sig i hvert sygdomsstadie, er estimeret ud fra sandsynligheder i de to studier.



*Massiv depressiv episode

Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen.

Respons defineres i modellen som ≥ 50 % forbedring fra baseline i Montgomery-Asberg Depression Rating Scale (MADRS)-scoren (eksklusive patienter der opnår remission). Remission er defineret som en MADRS-score ≤ 12. Recovery defineres som en patient, som har været i remission i 36 uger.

I modellen er en patient i gennemsnit 46 år baseret på TRANSFORM-2-studiet. Patienterne starter i stadiet "*Major depressive disorder*" (MDE), hvor patienten vil modtage behandling med esketamin + OA eller placebo + OA. Ansøger anvender TRANSFORM-2 til akutfasen, som varer 4 uger. Herfra kan patienten forblive i behandling, få respons, remission eller dø. Efter de første 4 uger i akutfasen har patienten enten respons eller remission baseret på data fra TRANSFORM-2. 30 % af patienterne i esketamingruppen i studiet fik ikke respons. Patienter, der ikke får respons eller remission, vil stoppe i behandling med esketamin og derimod kun modtage OA og bevæge sig videre i modellen som placebogruppen.

SUSTAIN-1 anvendes til effekten af esketamin efter akutfasen og benyttes til at vurdere optimeringsfasen og vedligeholdelsesfasen samt hvor mange patienter, der opnår respons og remission og dermed ender i stadiet recovery, hvor patienter vil få OA. 70 % af patienterne stopper behandling med esketamin ved recovery-stadiet (36 uger). Ansøger har på baggrund af beskrivelsen af behandling med esketamin (behandling i mindst 6 måneder) antaget, at 99 % er stoppet med behandling efter 2 år.

SUSTAIN-1 viser en forskel i stabil remission mellem behandling med esketamin og placebo på hhv. 57,6 % og 45,3 %. Ansøger mener, at både respons og remission for placebogruppen er påvirket af de ekstra besøg for placebogruppen, som forsøget har krævet, og justerer derfor respons og stabil remission for placebogruppen, se Tabel 2. Justeringen er beregnet ud fra effekt af besøg ved en meta-analyse af OA[3–7], hvor hvert besøg estimeres at give en forbedring på 0,804 point i MADRS-scoren.

Tabel 2: Andel i respons og remission med justering for effekt for placebo, baseret på antal besøg

	Ikke justeret	6 besøg	7 besøg*
Remission	31 %	18 %	18 %
Repsons	52 %	34 %	31 %

*Ansøger anvender denne i hovedanalysen.

Ansøger anvender desuden STAR*D-studiet[8] til placeboarmen for sandsynligheden fra respons til remission samt tab af respons i vedligeholdelsesfasen, da patienter i placebogruppen i SUSTAIN-1 kan have modtaget esketamin. Der antages samme sandsynlighed for tilbagefald for patienter i behandling med esketamin og placebo efter 36 ugers behandling.

Ansøger anvender følgende sandsynligheder for at bevæge sig mellem de forskellige sygdomsstadier for esketamin og placebo, se Tabel 3.

Tabel 3: Sandsynligheder for bevægelsen af patienterne mellem de forskellige sygdomsstadier.

Behandling	MDE til remission	MDE til respons	Respons til remission	Relaps	Tab af respons	Tilbage-fald
Esketamin + OA	0.525	0.168	0.199	0.056	0.042	0.029
Placebo + OA	0.180	0.130	0.032	0.092	0.224	0.029

For patienter, der befinder sig i sygdomsstadiet "MDE", er en højere dødelighed anvendt på grund af risiko for selvmord. Ansøger anvender en kilde[9] til den højere dødelighed, der har estimeret en rate på 0,47 ud af 100 patienter pr. år. I responsstadiet er en halvering af selvmordsrisikoen anvendt.

I modellen antages, at 70 % er stoppet behandling efter 36 uger, baseret på SUSTAIN-1 og at 99 % af patienterne har stoppet behandling ved år 2.

Se Figur 2 og Figur 3 for fordelingen af patienter i sygdomsstadierne over 5 år mellem esketamin + OA og placebo + OA.

Figur 2: Andel af patienter i de forskellige sygdomsstadier for esketamin.

Figur 3: Andel af patienter i de forskellige sygdomsstadier for placebo.

Sekretariatets vurdering

Sekretariatet har i vurderingsrapporten vurderet effekten af esketamin + OA ud fra studierne TRANSFORM-1, TRANSFORM-2, TRANSFORM-3 og SUSTAIN-1. I den kliniske del vurderes akutfasen ud fra alle tre TRANSFORM-studier, hvilket afviger fra den sundhedsøkonomiske model. Ansøger har argumenteret for, at TRANSFORM-1 ikke vil afspejle klinisk praksis, og at TRANSFORM-3 er baseret på ældre (> 65 år) patienter, og som derfor udgør en mindre andel af patienter end den patientgruppe (18 til 64 år), som TRANSFORM-2-studiet undersøger. Derfor har ansøger i den sundhedsøkonomiske model valgt at tage udgangspunkt i TRANSFORM-2 til akutfasen. Dette valg kan dog have betydning for resultaterne, da esketamins indikation er til patienter over 18 år, og ligeledes inkluderer ældre patienter > 65 år. Alle tre studier er påvirket af studiedesignet, og de poolede resultater fra alle tre studier ville ændre på andelen, der får respons og ændre på resultatet til fordel for placebo. Sekretariatet anvender derfor de poolede resultater fra TRANSFORM-1, TRANSFORM-2 og TRANSFORM-3 til akutfasen i hovedanalysen.

Ansøger har på baggrund af input fra klinikere antaget, at effekten for placeboarmen bør nedjusteres, da de forventer, at effekten i SUSTAIN-1-studiet er for høj grundet ekstra besøg for patienter i denne gruppe. Fagudvalget vurderer, at dette ikke er korrekt at gøre, og at effekten af placebo ikke bør justeres. Dette ændres i sekretariatets hovedanalyse. Sekretariatet ændrer derfor sandsynlighederne for esketamin + OA fra MDE til remission og respons, og alle sandsynligheder for de forskellige stadier i placebogruppen, undtaget tilbagefald. Se Tabel 4.

Tabel 4: Sandsynligheder for bevægelsen af patienterne mellem de forskellige sygdomsstadier estimeret af sekretariatet.

Behandling	MDE til remission	MDE til respons	Respons til remission	Relaps	Tab af respons	Tilbagefald
Esketamin	0.210	0.066	0.199	0.056	0.042	0.029

Placebo	0.140	0.060	0.124	0.123	0.149	0.029

Danske retningslinjer har angivet, at behandling med OA bør fortsættes mindst 6 måneder eller længere, og op til 2 år for at undgå tilbagefald. Der er stor usikkerhed om, hvor lang tid behandling med esketamin bør fortsættes. Fagudvalget har udtrykt, at den egentlige behandlingslængde ikke kan angives ud fra foreliggende datagrundlag, men at den formentlig er længere tid end 9 måneder. Modellen tager desuden ikke højde for gentagne behandlinger med esketamin, men at patienter senere hen vil kunne få en ny episode efter en bestemt tid i stadiet "remission". Fagudvalget vurderer, at hvis esketamin + OA har haft effekt på en patient, og patienten får en ny episode, ville esketamin kunne gives igen. Fagudvalget vurderer dog, at patienten i sin levetid sammenlagt højst vil modtage esketamin i 1-2 år. Sekretariatet udarbejder derfor følsomhedsanalyser, der viser betydningen af "stop af behandling" og ændrer dermed andelen, der fortsætter behandling efter 36 uger (9 måneder) samt andelen, der stadig er i behandling efter 2 år.

Sekretariatet mener ikke, at ansøgers valg om kun at inkludere TRANSFORM-2-studiet er i overensstemmelse med det kliniske, da indikationen også gælder til patienter > 65 år, og at effekten fra denne gruppe dermed er ekskluderet, hvilket kan favorisere esketamin-gruppen. Sekretariatet anvender poolede data fra TRANSFORM-1, -2 og -3 i hovedanalysen, men udarbejder en følsomhedsanalyse med data fra TRANSFORM-2 alene. Baggrunden for at foretage en følsomhedsanalyse på data fra TRANSFORM-2, er, at studiet bedst repræsenterer den dosis og administration af lægemidlet, der forventes anvendt i klinisk praksis af fagudvalget.

Sekretariatet ændrer effekten for placebo i modellen, således at denne ikke er nedjusteret. Der vises desuden følsomhedsanalyser for, hvis en større andel af patienterne fortsætter i behandling efter 36 uger og 2 år.

2.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv. Analysen har en tidshorisont på 5 år. Omkostninger efter første år er diskonteret med 4 %.

Sekretariatets vurdering

Fagudvalget har vurderet, at en tidshorisont på 5 år er rimelig, selvom det er en kronisk sygdom, men at forskelle i omkostninger mellem behandlingerne vil være afspejlet i denne tidshorisont.

Sekretariatet accepterer ansøgers valg.

2.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af behandling med esketamin + OA sammenlignet med placebo + OA. De

inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger og patientomkostninger.

Ansøgers estimering af lægemiddelomkostninger bygger altid på AIP, hvilket i sekretariatets hovedanalyse udskiftes med SAIP.

2.2.1 Lægemiddelomkostninger

Den anbefalede dosis af esketamin er 56 mg eller 84 mg hver uge eller hver anden uge. Ansøger anvender den gennemsnitlige dosis og frekvens fra TRANSFORM-2 (i akutfasen) og SUSTAIN-1 (i optimeringsfasen og vedligeholdelsesfasen). Se Tabel 5 for gennemsnitlige antal sessioner (frekvens) og antal enheder (dosis).

Tabel 5: Gennemsnitlig dosis og frekvens for esketamin pr. uge

Akutfase		Optimeringsfasen		Vedligeholdelsesfasen		Recovery	
Session	Enhed	Session	Enhed	Session	Enhed	Session	Enhed
1,85	2,53	0,99	2,60	0,71	2,60	0,67	2,56

Ansøger anvender *Real World Evidence* (RWE)-data, som er baseret på en registerundersøgelse offentliggjort i en rapport (TRIDEN: Treatment Resistant Depression in Denmark), til at afgøre, hvilke OA patienterne er i behandling med af, hhv. SSRI- og SNRI-lægemidler. Lægemidlerne anvendes til placebogruppen og som add-on til esketamingruppen. De anvendte SSRI og SNRI er i overensstemmelse med anbefalinger i dansk klinisk praksis. De fire lægemidler, to SSRI-produkter (escitalopram og sertralin) og to SNRI-produkter (duloxetin og venlafaxin) får lige fordeling. Behandling med add-on til placebo og add-on til esketamin består altså af 25 % fordeling af hvert af de fire lægemidler, se Tabel 6.

Tabel 6: Dosis pr. dag for anvendte SSRI- og SNRI-præparater

Lægemiddel	Dosis pr. dag
Duloxetin	120 mg
Escitalopram	20 mg
Sertralin	200 mg
Venlafaxin	375 mg

Alle anvendte lægemiddelpriser er i SAIP, se Tabel 7.

Tabel 7: Anvendte lægemiddelpriser, SAIP (april 2020).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Esketamin	28 mg	1 stk.	[redacted]	Janssen
Duloxetin	60 mg	98 stk.	[redacted]	Medicin-priser.dk
Escitalopram	20 mg	100 stk.	[redacted]	
Sertralin	50 mg	250 stk.	[redacted]	
Venlafaxin	75 mg	100 stk.	[redacted]	

Sekretariatets vurdering

Da esketamin både kan gives som 56 mg og 84 mg, og enten én gang om ugen eller hver anden uge, er der stor usikkerhed om, hvad det gennemsnitlige antal doser og frekvens vil være i dansk klinisk praksis. Da patienter i SUSTAIN-1 er selekterede patienter, kunne dosis og frekvens være højere i dansk klinisk praksis. Sekretariatet udarbejder derfor følsomhedsanalyser, der belyser hhv. lav dosis og høj dosis hhv. én gang om ugen og hver anden uge.

Sekretariatet accepterer ansøgers antagelser for lægemiddelomkostninger til hovedanalysen.

2.2.2 Hospitalsomkostninger

Til at estimere ressourceomkostninger anvender ansøger den førnævnte rapport TRIDEN. Data er fra Landspatientregisteret fra 1996 til 2016 og belyser behandling af patienter med behandlingsresistent depression behandlet med SSRI og SNRI som 1. linjebehandling. Rapporten indeholder en opgørelse af antal kontakter til blandt andet lægebesøg, privat psykiatri, psykolog, hospitalsdage, akutmodtagelse og primære sundhedsspecialister.

Ressourceforbruget opgøres både for patienter, der kan have respons eller være i remission. Ansøger anvender den gennemsnitlige fordeling af forbruget mellem SSRI og SNRI anvendte lægemidler for MDE-stadiet, se Tabel 8. Se Tabel 9 for enhedsomkostninger til ressourcerne og Tabel 10 for samlede omkostninger til MDE-stadiet.

For at finde omkostningerne til stadierne remission og recovery anvender ansøger en anden kilde[10], der opgør forskellen i omkostninger mellem MDE-stadiet og remission. For stadiet respons antager ansøger et gennemsnit af MDE- og remissionsstadiet. Omkostninger for de forskellige sygdomsstadier ses i Tabel 11.

Tabel 8: Gennemsnitlig antal besøg/hospitalsdage pr. år for behandlingsresistent depression for MDE-stadiet

Ressource	SSRI	SNRI
Psykiatriske kontakter		
Akut hospitalsindlæggelse	4,7	5,3
Elektiv hospitalsindlæggelse	1,0	1,1
Akut ambulant besøg	0,2	0,2
Somatiske kontakter		
Akut hospitalsindlæggelse	2,6	2,0
Elektiv hospitalsindlæggelse	0,7	0,6
Akut ambulant besøg	0,4	0,3
Ambulant besøg	3,2	3,0
Lægebesøg	9,2	9,6

Tabel 9: Enhedsomkostninger pr. ressource.

Administration	Enhedsomkostning [DKK]	Kilde
Psykiatrisk ambulant besøg	1.919	DRG-2020
Somatisk ambulant besøg	2.148	19MA98
Akut ambulant psykiatrisk besøg	1.919	DRG-2020
Akut ambulant somatisk besøg	2.148	19MA98
Hospitalsindlæggelse psykiatri	3.835	DRG-2020
Hospitalsindlæggelse somatisk	16.814	19MA02
Hjemmebesøg	2.148	19MA98
Psykiatrisk hjemmebesøg	1.919	DRG-2020
Lægebesøg	143	Medicinrådets værdisætning af enhedsomkostninger

Tabel 10: Estimater på ressourceomkostninger for MDE-stadiet.

Ressource	MDE-omkostninger
Psykiatriske kontakter	
Akut hospitalsindlæggelse	19.175
Elektiv hospitalsindlæggelse	4.027
Akut ambulant besøg	384
Somatiske kontakter	
Akut hospitalsindlæggelse	16.814
Elektiv hospitalsindlæggelse	10.929
Akut ambulant besøg	752
Ambulant besøg	6.659
Lægebesøg	1.348
Total årlige omkostninger	**60.088**
Omkostninger pr. cyklus	**4.606**

De estimerede omkostninger pr. cyklus og pr. sygdomsstadie kan ses i Tabel 11.

Tabel 11: Omkostninger pr. cyklus og pr. sygdomsstadie.

Sundhedsstadie	Omkostninger pr. cyklus
MDE	4.606
Respons	2.628
Remission	650
Recovery	650

Omkostninger forbundet med administration og monitorering differentierer mellem OA og esketamin.

For esketamin antages, at der er 5 minutters pause mellem dosering (2 pauser ved 56 mg dosis og 3 pauser ved 84 mg dosis). Der er undersøgt, at postdosisobservation for esketamin er ca. 90 minutter. Ansøger antager, at der til dette er et ressourceforbrug på en times lægetid og 1,5 time for en sygeplejerske. Se Tabel 12 for administration og monitoreringsomkostninger for esketamin. Derudover antager ansøger, at patienter på esketamin har follow-up hver måned med en omkostning for en halv times lægetid på 390 DKK.

Tabel 12: Administrations omkostninger for esketamin.

Ressourcebrug	Omkostning pr. time [DKK]	Tid brugt pr. ressource [timer]	Antal patienter administreret pr. gang	Omkostning pr. session [DKK]
Læge "reservelæge"	780	1	3	537
Sygeplejerske	554	1,5		

Ansøger anvender TRIDEN til vurdering af follow-up-omkostninger for SSRI- og SNRI-behandling og anvender DRG-taksten for psykiatrisk ambulant besøg på 1.919 DKK per besøg (både ambulant og hjemmebesøg). Dette giver en månedlig follow-up-omkostning på 1.434 DKK.

Sekretariatets vurdering

Estimeringen af ressourceforbruget har store usikkerheder, da estimaterne er basereret på data for både mild, moderat og svær depression. Sekretariatet accepterer ansøgers antagelser, men belyser usikkerheden i omkostninger for ressourceforbrug i en følsomhedsanalyse.

Fagudvalget vurderer, at monitorering af behandling med esketamin minimum kræver et ambulant besøg pr. gang, lægemidlet skal doseres og follow-up. Sekretariatet vurderer ansøgers estimerede follow-up-omkostning til at være den ambulante DRG-takst på 2.148 kr. pr. patient, og at follow-up varer 1 time, således at kun sygeplejersketiden fordeles på flere patienter. Der er desuden stor usikkerhed omkring, hvor mange patienter sygeplejersken kan observere samtidig. Dette belyses ved følsomhedsanalyser, hvor patientantallet varieres fra 1-5 patienter.

Fagudvalget vurderer desuden, at standardbehandling med esketamin vil kræve store strukturelle ændringer på ambulatorierne. Ansøger har ikke inkluderet omkostninger til dette, da ansøger ikke vurderer, at behandlingen forudsætter ændringer i organiseringen af behandlingen. Der findes ikke estimater på sådanne omkostninger.

Sekretariatet accepterer ansøgers antagelser for monitoreringsomkostninger for de forskellige sygdomsstadier og follow-up for behandling med SSRI og SNRI.

Sekretariatet ændrer omkostningen for administration og follow-up for esketamin til 2.148 kr. pr. patientbesøg.

2.2.3 Bivirkningsomkostninger

Ansøger har inkluderet bivirkningsomkostninger for esketamin + OA og placebo + OA i akutfasen, da det antages, at patienterne har vænnet sig til behandling med esketamin i optimeringsfasen og vedligeholdelsesfasen. Bivirkningsfrekvenserne er baseret på TRANSFORM-2-studiet.

Ansøger har vurderet, at kun dissociation kræver behandling, og at denne bivirkning forekommer i forbindelse med administrationstiden. Ansøger har derfor inkluderet en omkostning på 537 DKK baseret på en session for esketamin.

Se bivirkningsfrekvenser i Tabel 13 og totale bivirkningsomkostninger i Tabel 14.

Tabel 13: Rapporterede bivirkningsfrekvenser for akutfasen ved behandling med esketamin og placebo.

AE	Esketamin [%]	Placebo [%]	Enhedsomkostning [DKK]	Kilde
Dissociation	0,122	0,018	537	Læge + sygeplejerske (Administrations- og observationsomkostning for esketamin)

Tabel 14: Totale omkostninger relateret til bivirkninger.

Behandling	Totale omkostninger [DKK]
Esketamin + OA	33
Placebo + OA	5

Sekretariatets vurdering

Der er stor usikkerhed om, hvor omfattende bivirkninger vil være, og hvad det kræver at håndtere dem for de enkelte patienter. Dette er især omfanget af angst, som er svær at vurdere. Fagudvalget har dog vurderet, at bivirkninger er håndterbare, når de opstår i forbindelse med patientens behandling med esketamin på ambulatorierne. Derfor har omkostninger til bivirkninger lille betydning for analysens resultatet.

Sekretariatet accepterer ansøgers tilgang.

2.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrering af lægemidlet og monitoreringsbesøg på hospitalet og i primærsektoren. Dette inkluderer den effektive tid på hospitalet, ventetid og transporttid. Ansøger anvender en timeomkostning på 179 DKK og transportomkostninger på 100 DKK pr. besøg baseret på Medicinrådets værdisætning af enhedsomkostninger. Patienttid for esketamin er estimeret på baggrund af kliniske eksperters estimater og SPC'et[11]. Ansøger antager, at inhalation af esketamin varer 20 minutter, og at ventetiden efterfølgende er 90 minutter. Patienttid for esketamin estimeres pr. session, som varierer efter antagelsen af frekvens, se Tabel 15 for omkostninger pr. session.

Patient- og transport tid for SSRI- og SNRI-behandling er estimeret på baggrund af TRIDEN, se Tabel 16 for antagelser om patienttid og transport.

Tabel 15: Patienttid- og transportomkostninger pr. session.

Antal minutter pr. session [minutter]	Timer pr. session [timer]	Omkostninger pr. session [DKK]
110	1,83	**428**

Tabel 16: Estimering af patienttid og gennemsnitlig omkostning for patienttid og transport pr. ressourceenhed for SSRI- og SNRI-behandling.

Ressource	SSRI	SNRI	Antal timer pr. enhed	Gns. Omkostning [DKK]
Psykiatriske kontakter				
Akut hospitalsindlæggelse	4,7	5,3	24	21.980
Elektiv hospitalsindlæggelse	1,0	1,1	24	4.616
Akut ambulant besøg	0,2	0,2	0,5	1.535
Hjemmebesøg			0,5	148
Somatiske kontakter				
Akut hospitalsindlæggelse	2,6	2,0	24	10.111
Elektiv hospitalsindlæggelse	0,7	0,6	24	2.857
Akut ambulant besøg	0,4	0,3	0,5	66
Ambulant besøg	3,2	3,0	0,5	587
Lægebesøg	9,2	9,6	0,5	1.781
Omkostning pr. år				43.720
Omkostning pr. cyklus				**3.352**

Sekretariatets vurdering

Der er usikkerheder omkring estimeringen af patienttid for behandling af SSRI og SNRI, da antagelserne er baseret på TRIDEN-studiet, der inkluderer patienter med mild, moderat og svær depression. Det har ikke være muligt at finde andre kilder, der estimerer patient-tid for behandlingen. Sekretariatet udfører en følsomhedsanalyse, der belyser en 50 % reducering af patienttiden for SNRI- og SRRI-behandling.

Sekretariatet accepterer ansøgers tilgang.

2.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen. Ansøger har udarbejdet en række følsomhedsanalyser, hvor konsekvenser af at variere forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

- Ændring af tidshorisont til 3 og 7 år
- Risici for relaps for esketamin + OA og placebo + OA ændres
- Risici for remission for esketamin + OA og placebo + OA ændres
- Dosis justeres for esketamin i den akutte fase
- Frekvens for dosis justeres
- Behandlingsstop justeres
- Antal patienter, der kan overvåges af sygeplejerske ved behandling af esketamin varieres

Sekretariatets vurdering

Sekretariatet vurderer, at ansøgers følsomhedsanalyser er relevante og præsenterer disse.

Sekretariatet udarbejder yderligere følgende følsomhedsanalyser:

- Ressourceforbrug +/- 20 %
- Behandlingsstop efter 36 uger ændres fra 70% til hhv. 0 %, 25 %, 50 % og 100 %
- Behandlingsstop efter 2 år ændres fra 99 % til hhv. 0 %, 25 %, 50 % og 75 %
- Behandlingsstop efter 36 uger ændres til 0 % og behandlingsstop efter 2 år ændres til 0 %
- Behandlingsstop efter 36 uger ændres til 25 % og behandlingsstop efter 2 år ændres til 25 %
- Behandlingsstop efter 36 uger ændres til 50 % og behandlingsstop efter 2 år ændres til 50 %
- Patienttid reduceres med 50 %
- Respons og remission i akutfasen for esketamin + OA estimeres ud fra data fra TRANSFORM-2

Sekretariatet vælger at præsentere ansøgers følsomhedsanalyser og udarbejder yderligere følsomhedsanalyser.

2.4 Opsummering af basisantagelser

I Tabel 17 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 17: Basisantagelser for ansøgers og sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Sekretariatet
Komparator	Placebo + OA	Placebo + OA
Modeltype	Markov-model	Markov-model
Tidshorisont	5 år	5 år
Diskonteringsrate	3 %	3 %
Inkluderede omkostninger	Lægemiddelomkostning Hospitalsomkostning Bivirkningsomkostning Patientomkostning	Lægemiddelomkostning Hospitalsomkostning Bivirkningsomkostning Patientomkostning
Risici forbundet med respons og remission for placebo	Baseret på TRANSFORM-2 og flere ældre studier og anvendt justeringsfaktor på estimater	Anvender poolede data fra TRANSFORM-1, -2 og -3 til akutfasen. Anvender ikke justering for placebo effekt
Patientantal*	6.152	10.100
Håndtering af usikkerhed	One-way følsomhedsanalyser	One-way følsomhedsanalyser

*Se afsnit 3. Budgetkonsekvenser

3. Resultater

3.1 Resultatet af sekretariatets hovedanalyse

Sekretariatets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, men med følgende justeringer:

- Sandsynligheder for respons og remission i akutfasen ændres så disse baseres på poolede data fra TRANSFORM-1, -2 og -3
- Ingen justering for effekten af placebo
- Administrationsomkostning for esketamin ændres til 2.148 DKK

Sekretariatets hovedanalyse resulterer i inkrementelle omkostninger pr. patient over en tidshorisont på 5 år for esketamin + OA sammenlignet med placebo + OA på [redacted] DKK.

Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient 70.000 DKK sammenlignet med placebo + OA.

Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 18.

Tabel 18: Resultatet af sekretariatets hovedanalyse, DKK, diskonterede tal.

	Esketamin + OA	Placebo + OA	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	531.446	517.995	13.451
Bivirkningsomkostninger	61	17	43
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.1.1 Resultatet af sekretariatets følsomhedsanalyser

Sekretariatet udfører følgende udvalgte af ansøgers følsomhedsanalyser, se Tabel 19.

Tabel 19: Resultatet af sekretariatets følsomhedsanalyser, DKK.

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Tidshorisont 3 år	[redacted]
Tidshorisont 7 år	[redacted]

Frekvens for dosis justeres	Dosis én gang om ugen	[redacted]
	Dosis hver anden uge	[redacted]
Dosis justeres for esketamin	56 mg	[redacted]
	84 mg	[redacted]
Behandlingsstop efter 36 uger	0 %	[redacted]
	25 %	[redacted]
	50 %	[redacted]
	100 %	[redacted]
Behandlingsstop efter 2 år	0 %	[redacted]
	25 %	[redacted]
	50 %	[redacted]
	75 %	[redacted]
Behandlingsstop efter 36 uger = 0 % behandlingsstop efter 2 = 0 %		[redacted]
Behandlingsstop efter 36 uger = 25 % behandlingsstop efter 2 = 25 %		[redacted]
Behandlingsstop efter 36 uger = 50 % behandlingsstop efter 2 = 50 %		[redacted]
5 patienter behandlet med esketamin overvåges af én sygeplejerske		[redacted]

1 patient behandlet med esketamin overvåges af én sygeplejerske		[redacted]
Administrationsom-kostninger placebo	- 20 %	[redacted]
	+20 %	[redacted]
Patienttid placebo -50 %		[redacted]
Data baseret på TRANSFORM-2		[redacted]

4. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at esketamin + OA vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- Esketamin + OA bliver anbefalet som standardbehandling af Medicinrådet til indikationerne, som denne analyse omhandler
- Esketamin + OA bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimat af patientantal og markedsandel

Ansøger estimerer, at 6.152 patienter kandiderer til behandling af esketamin om året, med stigende incidens.

Ansøger baserer antagelserne på markedsoptag på et andet præparat indenfor samme sygdomsområde og antager et markedsoptag for esketamin på 4 % i år 1, 8 % i år 2, 11 % i år 3, 14 % i år 4 stigende til 16 % i år 5. Hvis esketamin ikke anbefales, antager ansøger et markedsoptag på 0 %.

Tabel 20 viser ansøgers estimat af antal patienter årligt for det kliniske spørgsmål.

Tabel 20: Ansøgers estimat af antal nye patienter pr. år

Anbefales					
	År 1	År 2	År 3	År 4	År 5
Esketamin + OA	246	495	684	875	1.005
Placebo + OA	5.906	5.690	5.534	5.375	5.276
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5
Esketamin + OA	0	0	0	0	0
Placebo + OA	6.152	6.185	6.218	6.250	6.281

Sekretariatets vurdering

Fagudvalget har ud fra indikationen vurderet, at et højere antal patienter på 10.100[12] vil være mulige kandidater til behandling med esketamin + OA. Sekretariatet udarbejder egen budgetkonsekvens analyse, hvor fagudvalget estimat på patientantal anvendes, men ansøgers forventning til markedsoptag anvendes. Se Tabel 21 for sekretariatets antal af nye patienter.

Tabel 21: Sekretariatets estimat af antal nye patienter pr. år

Anbefales					
	År 1	År 2	År 3	År 4	År 5
Esketamin + OA	404	808	1.111	1.414	1.616
Placebo + OA	9.696	9.292	8.989	8.686	8.484
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5
Esketamin + OA	0	0	0	0	0
Placebo + OA	10.100	10.100	10.100	10.100	10.100

Da de strukturelle ændringer for ambulatorierne ved anbefaling af esketamin + OA som mulig standardbehandling er ukendte, og dermed bliver patientoptaget meget usikkert. Derfor udarbejdes en følsomhedsanalyse, der viser hhv. 50 % og 100 % markedsoptag, for at illustrere budgetkonsekvenserne, hvis alle mulige patienter kom i behandling.

Fagudvalget finder, at en mindre andel patienter, som har forsøgt adskillige behandlingsalternativer uden held, kan forsøge behandling med esketamin. Dette estimat er ca. 1000 patienter, og sekretariatet vil udarbejde en følsomhedsanalyse på baggrund af dette estimat og 100% markedsoptag.

Sekretariatet udarbejder egen budgetkonsekvensanalyse

Sekretariatet udarbejder en følsomhedsanalyse med 100 % markedsoptag og en følsomhedsanalyse med den andel på 1000 patienter der har forsøgt adskillige behandlingsalternativer uden held.

4.2 Sekretariatets budgetkonsekvensanalyse

Sekretariatet estimerer, at anvendelse af esketamin + OA sammenlignet med placebo + OA, vil resultere i budgetkonsekvenser på [redacted] DKK i år 1 stigende til [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 22.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 112,5 mio. DKK i år 5 sammenlignet med placebo.

Tabel 22: Sekretariatets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.3 Sekretariatets følsomhedsbudgetkonsekvensanalyser

I Tabel 24 ses sekretariatets følsomhedsanalyse af budgetkonsekvenser på 50 % markeds-optag.

Tabel 23: Sekretariatets følsomhedsanalyse af totale budgetkonsekvenser med 50 % markedsoptag, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

I Tabel 24 ses sekretariatets følsomhedsanalyse af budgetkonsekvenser på 100 % mar-kedsoptag.

Tabel 24: Sekretariatets følsomhedsanalyse af totale budgetkonsekvenser med 100 % markedsop-tag, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

I Tabel 25 ses sekretariatets følsomhedsanalyse af budgetkonsekvenser på den andel af patienter (1000 patienter) som har fejlet på adskillige behandlingsalternativer.

Tabel 25: Sekretariatets følsomhedsanalyse på 1000 patienter med 100% markedsoptag, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Diskussion

Behandling med esketamin + OA er forbundet med høje inkrementelle omkostninger sammenlignet med behandling med placebo + OA. De inkrementelle omkostninger er drevet af lægemiddelomkostningerne for esketamin.

4.4 Usikkerheder

Der er stor usikkerhed forbundet med sandsynlighederne for hhv. remission, respons og tilbagefald (de forskellige stadier i modellen), da disse er baseret på studierne af esketamin (TRANSFORM-1-3 og SUSTAIN-1) eller andre studier for orale antidepressiva. Usikkerhederne skyldes især studiernes opbygning, da TRANSFORM-1-studiet anvender en fikseret dosis, mens TRANSFORM-2 og -3 indeholder fleksibel dosis, men to forskellige populationer (18-65 år og > 65 år). Populationen i SUSTAIN-1 indeholder både patienter fra TRANSFORM-1 og -2 og nye patienter, der går ind i studiet. Kun patienter der har haft respons på esketamin i TRANSFORM-studierne, fortsætter i esketaminarmen i SUSTAIN-1. I SUSTAIN-1 efter uge 16, bliver dem i esketaminarmen randomiseret til at fortsætte i behandling eller gå over til placebo. Andelen af patienter, der får hhv. respons, remission og tilbagefald, har stor betydning på analysens resultat.

På baggrund af studiernes opbygning vil det ligeledes være usikkert, hvordan dosisfordelingen (hhv. lav 56 mg eller 84 mg) vil være, og om patienterne vil modtage dosis én gang om ugen eller hver anden uge. Dosis og frekvens har stor betydning på analysens resultat.

Indikationen for esketamin er, at behandling anbefales i mindst 9 måneder, hvis patienten har et stabilt respons eller opnår remission. Det er uvist, om patienterne vil fortsætte i behandling i længere tid. Det er ligeledes uvist pga. studiernes opbygning, hvor stor en andel, der vil være stoppet med behandlingen efter 36 uger. Behandlingsstop har meget stor betydning for analysens resultat og afspejler i den grad omkostninger forbundet med behandling.

Der er stor usikkerhed omkring ressourceforbrug og omkostninger ved behandling med orale antidepressiva, da disse er baseret på TRIDEN-studiet, der inkluderer patienter med mild, moderat og svær depression, men det var ikke muligt at finde bedre kilder.

Derudover er der uvished om konsekvenserne af den strukturelle ændring i ambulatorierne, som behandling med esketamin vil indebære. Disse omkostninger findes der ikke estimater på. Herudover er patientkapaciteten usikkert, og budgetkonsekvenserne vil formentlig ligge mellem følsomhedsanalysens resultat og et markedsoptag på 100% baseret på hovedanalysen.

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6. Bilag

6.1 Resultatet af ansøgers hovedanalyse

Ansøgers hovedanalyse resulterer i inkrementelle omkostninger pr. patient over en tidshorisont på 5 år for esketamin + OA sammenlignet med placebo + OA på ca. [redacted] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 26.

Tabel 26: Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal.

	Esketamin	Placebo	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	469.821	513.845	-44.023
Bivirkningsomkostninger	60,52	17,19	43,33
Totale omkostninger	[redacted]	[redacted]	[redacted]

6.2 Ansøgers budgetkonsekvensanalyse

Ansøger har estimeret et andet patientantal end fagudvalget.

Med ansøgers antagelser om patientantal og markedsandel, estimerer ansøger at anvendelse af esketamin + OA vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 sammenlignet med placebo + OA.

Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 27.

Tabel 27: Ansøgers analyse af totale budgetkonsekvenser, mio. DKK, ikkediskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	26-08-2020
Leverandør	Janssen
Lægemiddel	Esketamin (Spravato)
EMA-indikation	Behandling af behandlingsresistent depression hos voksne

Forhandlingsresultat

Amgros har opnået følgende pris på esketamin:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Esketamin	28 mg	1	1.660,00	[redacted]	[redacted]
Esketamin	28 mg	2	3.320,00	[redacted]	[redacted]
Esketamin	28 mg	3	4.980,00	[redacted]	[redacted]

Ved salg af 36.000 doser ændres prisen til

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Esketamin	28 mg	1	1.660,00	[redacted]	[redacted]
Esketamin	28 mg	2	3.320,00	[redacted]	[redacted]
Esketamin	28 mg	3	4.980,00	[redacted]	[redacted]

Aftalen løber indtil 31.08.2021.
[redacted]

En patient vil ved maksimal dosis bruge 160 pakninger om året svarende til ca. [redacted] kr. om året udelukkende for esketamin.

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt **ikke** har opnået den bedst mulige pris. Denne vurdering baserer vi på følgende punkter:

- Leverandøren er uenig i den overordnede kliniske vurdering af esketamin.
  [redacted].
- En 1-årig aftale håndterer ikke de potentielle budgetkonsekvenser tilstrækkeligt
  [redacted]
- Esketamin vurderes ikke som et relevant behandlingsvalg til hele gruppen af patienter på ca. 10.000, men kun som et muligt alternativt til en særlig gruppe patienter på ca. 1.000.
  [redacted]

Konklusion

Det er Amgros konklusion, at vi **ikke** har opnået den bedste pris,
[redacted] Amgros vurderer overordnet set, at vi ikke opnår nok sundhed for pengene med nuværende tilbud.

Status på andre lande

NT-rådet i Sverige har den 26.05.2020 givet en begrænset anbefaling på esketamin. Esketamin kan anvendes, når alle andre behandlingsmuligheder er udtømt, og når patienten har prøvet mindst fire andre behandlingsalternativer inden esketamin.[1]
Esketamin blev i januar 2020 ikke anbefalet af NICE, da der er behov for mere evidens for både den kliniske og økonomiske effekt[2], vurderingen er stadig i gang.

[1] https://janusinfo.se/download/18.4f6bed70172c02901d0e9fd2/1593087696372/Esketamin-(Spravato)-200625.pdf
[2] https://www.nice.org.uk/news/article/nasal-spray-medicine-for-treatment-resistant-depression-not-recommended-by-nice

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02. juli 2020

Consultative response to the clinical categorization of Spravato®

Upon the receipt of the Spravato® (esketamine) assessment report, Janssen considers it positive that the Expert Committee finds that Spravato® in combination with SSRI or SNRI can have a beneficial short-term effect in some patients and that in a proportion with immediate effect of treatment, the effect appears to be sustained. In addition it is positive that Spravato® is found as a treatment option that may be addressed in patients where other current therapies have been considered but are not considered relevant.

However, Janssen does not agree with the clinical categorization "cannot be categorized" as well as Janssen does not agree with the Council´s conclusion that the overall efficacy and safetfy profile of Spravato® (esketamine) in combination with SSRI or SNRI is not better than the comparator.
Janssen does not consider that the reasons provided for giving the clinical categorization are valid, i.e. the long-term effect not being sufficiently elucidated and the data underlying the categorization is based on selected patients who do not reflect Danish clinical practice.

Consequently, Janssen suggests that a re-evaluation of the clinical categorization should take place based on this consultative response with main arguments summarized in bullets.

- The Expert Committee states that patients in Danish clinical practice have additional and significant psychiatric comorbidities that are not represented in the study populations. However, most of the listed comorbidities are mentioned in the *Summary of product characteristics* under *Special warnings and precautions for use – Other populations at risk.* Patients with these comorbidities should be carefully assessed before prescribing Spravato® and treatment initiated only if the benefit outweighs the risk.(1) Janssen acknowledges that the patients studied in the phase 3 trials may not be generalizable to all patients treated in real world settings. However, Janssen does not agree that the proportion of patients excluded from the studies represent the main population with TRD for the evaluation of Spravato®.

- SUSTAIN-1 use the recommended study design based on guidelines from several health authorities.(2, 3) This design was discussed and agreed upon with both FDA and CHMP and is therefore considered suitable for long-term comparison of efficacy.

- The Medicines Council evaluates, in other therapeutic areas, the long-term efficacy of treatments based on similar response re-randomization studies as SUSTAIN-1. The randomization of patients who were stable remitters to esketamine and oral AD to continue esktetamine or to switch to placebo nasal spary while continuing the oral AD, is appropriate based on the design. Consequently the data from patients randomized to switch to oral AD + placebo nasal spray in the maintenance phase, should be accepted as a valid comparator for long-term efficacy evaluation.

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SUSTAIN-1

The Expert Committee states, on page 17 of the evaluation, that data from SUSTIAN-1 is reviewed collectively and narratively in section 5.2.1 due to study design (relapse study). Furthermore, it is stated that data for the comparator has not been provided as well as the review of the long-term efficacy reflected in SUSTAIN-1 is assessed with two reservations. The two reservations mentioned are, 1) The selection of patients prior to randomization in SUSTAIN-1 and, 2) The desired efficacy endpoint is sustained remission or response, which is not defined in the same way as relapse. The time from remission / response to relapse is often a period in which the patient gets progressively worse, and this period should not be counted as sustained remission / response.

The abovementioned reservations and conclusion regarding SUSTAIN-1 not being adequate to reflect the long-term efficacy of Spravato® will be addressed in the following section.

Study design – scientific and ethical point of view

As MDD usually is a cyclic disease, longer double-blind trials are necessary to demonstrate that the acute effect is maintained during a major depressive episode (MDE) and can delay recurrence. Typically, this is conducted by a randomized double-blind withdrawal trial where efficacy is expressed as rate of patient worsening (relapsing) and or/time to this event. Such trials generally include a stabilization period followed by randomization to either continued treatment or placebo in accordance with clinical guidelines of medical products in the treatment of depression defined by both EMA and FDA. SUSTAIN-1 was designed according to these international recognized gold standards and is therefore considered suitable for long-term comparison of efficacy. Furthermore, EMA states following:

"Short- and long-term efficacy of esketamine on top of an SSRI or SNRI in TRD patients has been established. Demonstration of maintenance of the antidepressant effect was achieved via a relapse prevention study of adequate duration. Furthermore, supportive efficacy data were observed in an open-label long term mainly safety study. As such, and further to clarifications provided, the clinical program can be considered comprehensive for intranasal esketamine as an adjunctive treatment administered concomitantly with a SSRI or SNRI. Based on the totality of the submitted data, including significant and clinically relevant differences from placebo and clear trends in line with the significant results, the product is considered efficacious.(4)

From a scientific and ethical point of view it is important to note that it is only appropriate to conduct long-term efficacy studies in those patients achieving response or remission, as it would be inappropriate to continue treatment in patients with a lack of response to treatment. As relapses can have severe and negative consequences for patients with TRD it is equally important to minimize the risk of relapse. Thus, all long-term studies including SUSTAIN-1 will ultimately be enriched populations as it would only make sense to provide evidence of long-term efficacy in patients with an initial response or remission.

Further, patients in SUSTAIN-1 was enrolled by either direct-entry or transfer-entry (TRANSFORM-1 and TRANSFORM-2). Direct-entry patients were all initiated on ESK-NS+OAD in a 4-week induction phase, while transfer-entry responders and remitters were enrolled into

the following 12-week optimization phase and continued their current treatment under blinded conditions (ESK-NS+OAD or OAD+PBO). To clarify, determination of stable remission or stable response was made at the end of the 12-week optimization phase, prior to randomization into the maintenance phase. The duration of the optimization phase was agreed with Health Authorities as it was recognized that it was important for patients to be clinically stable before the randomized withdrawal phase.

Thus, patients randomized in the maintenance phase consisted of ESK-NS+OAD-treated patients (n=298) who achieved stable response or remission at the end of the optimization phase. In addition a total of 55 OAD+PBO-treated patients who achieved stable response or remission proceeded to the maintenance phase but were not randomized. Importantly, the comparison of transfer entry OAD+PBO patients (not randomized) with esketamine subjects who were randomized to one of two groups should not be compared as it has no basis in randomization. Note that the transfer entry OAD+PBO patients were able to either achieve stable remission or stable response with oral AD alone and did not require esketamine.

The randomization of stable remitters and responders into continuous treatment with ESK-NS+OAD or discontinuation of ESK-NS during the double-blind randomized withdrawal/ relapse prevention phase provides a controlled scientific setting to compare the direct long-term efficacy of ESK-NS against an active comparator (OAD) in those who had achieved stable remission or response with ESK. Furthermore, in SUSTAIN-1, among those who had achieved stable remission, 29 (45.3%) patients in the antidepressant plus placebo group experienced a relapse event during the maintenance phase.(5) This observation is in line with relapse rates seen in the STAR*D study in level 3 and 4, respectively, where relapse rates in those achieving remission following the 12- to 14- week acute treatment phase were 42.9% and 50% with mean times to relapse of 3.9 and 2.5 months, respectively, even while continuing the treatment to which they had responded.(6) Thus, in patients with TRD, the relapse rates observed after cessation of esketamine and continuation on antidepressant plus placebo resemble those reported during maintenance treatment with an oral antidepressant alone. We therefore believe that the SUSTAIN-1 is a valid trial for comparison of long-term efficacy according to the Medicines Councils clinical question on the topic.

Study design – Usage in The Medicines Council

While the Expert Committee argues that the SUSTAIN-1 study design does not contain an appropriate comparator, Janssen would like to highlight that the Medicines Council evaluates the long-term efficacy of treatments based on similar response re-randomization studies in other therapeutic areas. Examples of this is seen in: the evaluation of ustekinumab for the treatment of moderate to severe ulcerative colitis and the evaluation of tofacitinib for the treatment of moderate to severe ulcerative colitis.
Furthermore, the Expert Committee states that the results from SUSTAIN-1 cannot be directly used to elucidate whether there is a longer-term effect of treatment with esketamine vs. placebo. However, in the Medicines Council´s protocol for assessment of esketamine for treatment of treatment resistant depression in adults - vers. 1.1, it is stated that SUSTAIN-1 can be used for direct comparison for the defined endpoints.

Thus, we believe that dismissing the use of SUSTAIN-1 as an adequate study to reflect the treatment effect of ESK + OAD compared to SSRI or SNRI + OAD is not consistent and contradictory with the normal practice conducted by the Medicines Council.

This is thought to be a significant concern as the dismissing of the data and statistical analyses provided for the long-term efficacy lead to the narrative evaluation of SUSTAIN-1 with no other possible clinical categorization than "cannot be categorized". However, approving SUSTAIN-1 as adequate for the evaluation of long-term efficacy, thus being consistent across therapeutic areas and with the protocol for the assessment for esketamine, would result in reaching moderate added clinical value for the proportion of patients achieving remission at the end of the maintenance period for the stable remitters with an RR of 1.557 (1.163-2.084) whereas the clinical added value for the proportion of stable responders reaching remission would be clinical added value of unknown size with a RR of 1.840 (1.103-3.068).

Data for the comparator

The Expert Committee states, on page 16 of the evaluation, that the results of SUSTAIN-1 cannot be used to evaluate whether there is a long-term effect of treatment with esketamine vs. oral AD plus placebo due to data not being provided for the comparator. We want to highlight that data for the comparator has been provided and that it reflects the desired endpoint of sustained remission or response which e.g. is available in table 19 of the submission. It is correct that data have not been provided if the Expert Committee by "comparator" refers to data not being provided separately for the transfer entry patients that responded to oral AD + placebo at induction (in TRANSFORM 1 or 2) which subsequently were not randomized in the maintenance phase, thus receiving placebo in the optimization and maintenance phase of SUSTAIN-1.

Potential impact of functional unblinding related to dissociation in SUSTAIN-1

We notice that one of the main arguments for stating that the comparator data, provided in the submission, is not useful is stated under the section "Blinding" in the evaluation: "Esketamine has a dissociative effect in some patients, which is experienced by patients after administration of the drug. This is not possible to imitate in patients in the comparator group, so the blinding is not optimal. Potential consequences of this include the nocebo effect, where negative expectations for placebo treatment counteract an effect or produce apparent side effects."

Several measures were taken during the study to ensure blinding was maintained. These measures including having remote, independent, blinding MADRS assessments and using a bittering agent in the placebo nasal spray as esketamine nasal spray has a bitter taste. The independent raters were blinded to the patient's treatment and safety information. Patients were instructed to not share any information regarding safety (eg, adverse experience/effects) with the independent rater during their MADRS interviews. The trained, independent raters used a structured interview guide for each MADRS assessment that included an opening statement that reminded patients that no safety information was to be disclosed during the interview. Interviews were generally conducted on a weekly basis and were to be scheduled prior to an intranasal treatment session.

Typically, if a study is unblinded, the expectation is that the placebo response would be low, as those receiving placebo would know they are receiving placebo. However, to the contrary, the response in the OAD + PBO treatment groups of the Phase 3 efficacy trials in adults was higher than expected. It is noteworthy that dissociative symptoms, as measured by the Clinician Administered Dissociative States Scale (CADSS) total score, were reported in 20-30% of adult subjects in the OAD+PBO treatment groups. A "nocebo" effect is defined as an adverse effect following an 'inert' treatment; the increased CADSS total scores in the OAD + PBO groups reflect a nocebo effect observed in these studies, which provides additional supportive evidence of the adequacy of blinding in the study.

However, to assess whether potential unblinding, especially due to dissociation, could have affected the results, additional assessments of the study data was conducted.
Janssen has carried out a causal mediation analysis, based on counterfactual framework, to assess the potential impact of dissociation on the treatment effect (as part of the FDA submission) on patients that reported a significant change in dissociation and sedation.(7, 8) The patients assessed were patients that showed a significant different in AEs prior to vs after randomisation to the maintenance phase and relapsed quickly, in the first 4 weeks after discontinuing ESK treatment.(7, 8) Specifically, we examined the CADSS plots for 19 patients who relapsed in those first 4 weeks. The majority of of patients did not have dissociative symptoms (CADSS=0) prior to discontinuing esketamine, this is as we might expect since dissociative symptoms tend to reduce in severity over time with repeated dosing and only 26% of patients overall experienced dissociation across the clinical trial program. There were only 3 patients who had CADSS >0 while on esketamine and did not have these symptoms after discontinuing esketamine. We censored for these patients and it did not change the overall efficacy result.

This is outlined in the slides (page 54-59) that Janssen presented during the FDA advisory committee and is publicly available. (8)

The analyses showed that indirect effect was not statistically significant, and the direct effect was significant. For the direct effect; the randomization continuation of esketamine would decrease the number of relapses by 2 persons per day per 1000 persons, independent of dissociative effects. These results indicate that the absence or presence of dissociation did not account for esketamine's treatment effect, thus suggesting that unblinding did not appear to be a factor in the difference between groups. Of note, from the clinical perspective, patients with TRD generally relapse earlier than the general population of patients with MDD, as demonstrated in STAR*D, which showed relapse rates under treatment with oral antidepressants alone that are similar to those in the participants randomised to receive OAD+PBO in SUSTAIN-1.(6)

Given the findings that unblinding did not appear to be a factor in the difference between groups of, Janssen consider dismissing of SUSTAIN-1 based on this consideration is not valid.

Selection of patient prior to randomization in SUSTAIN-1 reflects the label of Spravato®

In the conclusion by the Expert Committee, on page 31 of the evaluation, it is stated that the reason for Spravato® receiving the clinical added value "Cannot be categorized" is that the long-term effect is not sufficiently elucidated and that the data underlying the categorization is based on selected patients who do not reflect Danish clinical practice.

More specifically regarding the selected patients, the Expert Committee finds that patients in Danish clinical practice have additional and significant psychiatric comorbidities that are not represented in the study populations, among other things as a result of the exclusion criteria below:

- ongoing or previous DSM-5 diagnosis for psychotic conditions
- MDD with psychosis
- bipolar disorder and the like
- ongoing obsessive compulsive disorder (OCD)
- intellectual disability (DSM-5 diagnostic codes: 317, 318.0-2, 315.8, 319)
- autism
- borderline personality disorder
- antisocial personality disorder

However, Janssen believe there has been a misinterpretation of the exclusion criteria in the trials and where Spravato® is recommended per label. The Expert Committee list the exclusion criteria above and suggest that patients in Danish clinical practice have additional and significant psychiatric comorbidities that are not represented in the study populations. Consequently, the studies do not reflect the patients in the Danish clinical setting. However, most of the listed comorbidities are mentioned in the label under section *4.4. Special warnings and precautions for use – Other populations at risk*.(1) More specifically it is stated that Spravato® should be used with caution in patients with the following conditions:

- Presence or history of psychosis;
- Presence or history of mania or bipolar disorder;

These patients should be carefully assessed before prescribing Spravato® and treatment initiated only if the benefit outweighs the risk. As such Spravato® should not as standard be used in these patients and only after appropriate evaluation by a clinician.

Janssen acknowledges that the patients studied in this phase 3 registration study may not be generalizable to all patients treated in real world settings, However, we do not agree that those patients excluded from the studies represent the main population with TRD for the evaluation of Spravato®. Consequently, Janssen finds the included population suitable for the evaluation of Spravato®.

Comorbidities observed in clinical pratice

Janssen wants to outline that psychiatric comorbidities in TRD have been assessed in a recent register-based cohort study in Sweden with an entire cohort of 118.774 MDD patients. Study

results show that 73.6% of TRD patients do not have additional psychiatric comorbidities (anxiety disorder, attention deficit hyperactivity disorder, autism spectrum disorder, eating disorder and personality disorder).(9) However, psyciatric comorbidity affects roughly one-fourth (26.4%) of all TRD patients. While comorbid manic episode, bipolar disorder, persistent mood disorder, or other unspecified, or schizophrenia spectrum disorder only occur in 12% of all Danish unipolar depression patients, it has been consistently reported that anxiety disorder is the most common psychiatric comorbidity in MDD and TRD (10-12).

As described, the phase 3 registration program for esketamine in TRD did exclude patients with some specific psychiatric comorbidities, but the studies did include patients with the most common psychiatric comorbidities, ie. those with comorbid anxiety disorder. As addressed in the application, the number of patients with comorbid anixety are similar to those reported in other studies in this patient population e.g. the recent Danish register-based cohort study. (10) Thus, while Janssen acknowledges that the study exclusions of some psychiatric comorbidities limits the generalizability of these findings to all patients in real world practice, we do not agree that it contributes to noticeable differences between the trial populations and the Danish patient population and any additional psychiatric comorbidities are not reflective of the majority of patients with TRD.

Generalisibility and somatic comorbidities

In continuation of the above comments regarding the exclusion of psychiatric comorbidities, the Expert Committee also finds it problematic for the generalizability that ordinary somatic comorbidities appear as exclusion criteria, including among other things, heart problems, and uncontrolled high blood pressure.

However, patients with somatic comorbidities including clinically significant or unstable cardiovascular conditions and uncontrolled hypertension were excluded from the esketamine nasal spray clinical trials from a patient safety perspective.

This safety aspect is further outlined under *special warnings and precautions for use* in the *summary of product characteristics* for esketamine nasal spray to exclude patients to whom esketamine nasal spray treatment could pose a risk.(1) While the Medicines Council may find that a proportion of the TRD population would have somatic comorbidities such as heart problems or uncontrolled hypertension it would be highly unethical and a potential safety concern to treat such patients with esketamine. Only patients in line with the summary of product characteristics should be treated with esketamine nasal spray.

The esketamne phase 3 trials did exclude certain somatic comorbidities from a safety perspective, but in line with several European studies, half or more of the TRD population do not have a somatic comorbidity. (13-15) Thus, we don´t find the somatic exclusion in the phase 3 trials problematic for the assessment of Spravato®.

Definition of treatment resistant depression

On page 12 of the evaluation, the Expert Committee recognizes that the patients in the studies fall under the applied definition of treatment-resistant depression, but emphasizes that the definition is of a more practical nature. Furthermore, the Expert Committee considers that the number of previous treatments is very limited and believes that patients, based on two previous treatment trials with two antidepressants, are unlikely to be considered treatment resistant in a clinical context.

Janssen wants to clarify that within the esketamine programme two failed AD treatment trails are defined as the minimum requirement for the definition of TRD but it is clear from table 3 of the Medicines Councils evaluation that 87,9%, 90,9% and 84,7% of patients in the TRANSFORM-1, 2 and 3 respectively have been treated with 2 or more antidepressant retrospectively and obtained from Massachusetts General Hospital Antidepressant Treatment Response Questionnaire before inclusion in the screening/prospective observational phase. As 1 AD treatment failure was assessed prospectively during the screening/prospective observational phase of the studies it underlines that the majority of patients had at least 3 antidepressant treatment failures before enrollment in the double-blinded randomized phase, in which they received a new oral antidepressant (fourth AD trial). These data are in line with the SUSTAIN-1 population. Based on the evaluation by the Medicines Council it appears that a misinterpretation has occurred regarding the included study population's past number of antidepressant treatments in the current episode.

Serious adverse events - Death

As highlighted by the Medicines Council, 4 deaths were reported in the 6 completed phase 2 and phase 3 TRD studies among 1,708 subjects receiving ESK (611 patient-years of exposure ; 1 during double-blind treatment and 3 during open-label treatment). No deaths were reported in these studies among the 486 subjects who received oral AD + placebo (108 patient-years of exposure). In an ongoing long-term, open-label safety extension study (SUSTAIN-3), 3 deaths were reported in ESK treated subjects (as of December 31, 2018). Although death is always tragic no cases of death were after extensive review by study site investigators deemed related to esketamine treatment (either not related or doubtfully related). Furthermore, only 1 incidence of death were reported during double-blinded treatment, while the remaining occurred during open-label single arm treatment without a comparator group. Based on this a comparison with the placebo group is not possible as highlighted by the Medicines Council. However, while 3 out of 7 cases of death were due to completed suicide (all during open-label treatment), the suicide completion rate (0.49 per 100 patient-years of treatment) was not greater than the completed sucide rate of 0.47 (95% CI: 0.22–1.00) per 100 patient-years reported in a-meta-analysis of 30 TRD studies that included over 15000 patients with TRD.(16) After extensive review by study site investigators, none of the suicides were deemed related to ESK. Additionally, safety data was reviewed every 6 months by an Independent Data Monitoring Committee (IDMC) to ensure the continuing safety of the patients enrolled in the phase 3 trials.

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Fixed effects versus random effect meta-analysis

For the studies TRANSFORM-1, -2, and -3, the Expert Committee, for all the effect measures, chose to use a random effects model in the meta-analyzes instead of a fixed effects model used in our submission. The reason for this is that the Expert Committee considers that the conditions for using a fixed effects model (homogeneity between studies and study populations) are not met due to the studies not representing the same age groups and because the administration of esketamine is different between the studies (dose differences).

However, we believe that the use of the fixed effect meta-analyses presented in the submission is a valid method and should be accepted based on the following argumentation.

Heterogeneity is not present

Forest plots available in section 7.3 of the submission shows that all chi-squared test was non-significant, thus the tests for heterogeneity does not indicate presence of heterogeneity. However, since the the chi-squared test has low power in the (common) situation of a meta-analysis when studies are few in number, an additional test for identifying and measuring heterogeneity was performed using I^2 statistic.

The I^2 statistics method has been developed for quantifying inconsistency across studies that move the focus away from testing whether heterogeneity is present since clinical and methodological diversity always occur in a meta-analysis and therefore statistical heterogeneity is inevitable.(17) Instead the I^2 statistics method assesses its impact on the meta-analysis and describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). (17) Furthermore, one of the advantage of the I^2, as stated in the article by Higgens et al. 2003 is that it does not inherently depend on the number of studies in the meta-analysis. (18) Consequently, arguments regarding the I^2 tests being unstable and have low strength to detect heterogeneity, especially when few studies are included in the assessment, is not a valid argument.

I^2 is a percentage and its values lie between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.(17)
Another guide to interpretation is: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity.(17)

Furthermore, the use of fixed effects method is also supported by a comparison between fixed effect meta-analysis and random effect meta-analysis. The random-effects method and the fixed-effect method will give identical results when there is no heterogeneity among the studies. (19)

As seen in table 1, the random-effects and the fixed-effects method yields exactly the same results for four out of five endpoints in the meta-analyses combing the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies. However, the estimate for remission at induction does differ marginally between the two methods. But as the I^2 of the random effects meta-analysis assessing remission at induction is 31%, the percentage of the

variability in effect estimates that is due to heterogeneity is between 0% to 40% and therefore might not be important. It is found that this potential heterogeneity is not important as all the other outcomes assessed with both random-effects method and the fixed-effect method will give identical results and the chi-sqaured results for remission with both methods are non-significant. Conclusively there is no heterogeneity among the studies.

Table 1. Differences between fixed effect meta-analysis submitted by Janssen and random effect meta-analysis conducted by the Medicines Council.

Efficacy endpoints	Studies	Meta-analysis **fixed effect** inverse variance			Meta-analysis **random effect** inverse variance		
		RR (CI)	Chi-Squared	I^2	RR (CI)	Chi-Squared	I^2
SAE – Induction	TRANSFORM-1,2,3	1.293 (0.375-4.460)	P=0.900	0%	1.293 (0.375-4.460)	P=0.90	0%
Discontinuation - Induction	TRANSFORM-1,2,3	2.598 (0.966-6.985)	P=0.509	0%	2.598 (0.966-6.985)	P=0.50	0%
Remission - Induction	TRANSFORM-1,2,3	1.473 (1.163-1.860)	P=0.235	0%	1.50 (1.100-2.044)	P=0.23	31%
Response - Induction	TRANSFORM-1,2,3	1.379 (1.164-1.634)	P=0.589	0%	1.379 (1.164-1.634)	P=0.58	0%
EQ5D - induction	TRANSFORM-1,2,3	0.054 (0.017-0.092)	P=0.993	0%	0.054 (0.017-0.092)	P=1.00	0%

Furthermore, as the Medicines Council has allowed use of fixed effects meta-analysis in other submissions where difference between fixed effects meta-analyses and random effects meta-analyses has been observed on several endpoint, we argue that the fixed effect meta-analysis should be used for the evaluation of the endpoints in this submission. An example of this is evident from the Medicines Councils assessment of risankizumab for the treatment of moderate to severe plaque psoriasis. The Medicines Council approved the use of fixed effects meta-analyses with several of the meta-analyses in the assessment of risankizumab showing I^2 statistics varying between 10% to 50%, as presented in figure 6.3.5, figure 6.3.6, figure 6.3.12, figure 6.3.13 and figure 6.3.16 of the application for the assessment of clinically added value of risankizumab for moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.(20)

Consequently, the fixed effects meta-analyses used in the assessment of Spravato® should be accepted by the Medicines Council as one efficacy measure reporting a I^2 of 31% using random effects does not gives rise to using random effect instead of a fixed effect meta-analyses when several efficacy measures varying between 10% to 50% does not gives rise to using random effects meta-analyses. Furhermore, the Medicines Council uses fixed-effects meta-analyses regulary when conduction new treatment guidelines, examples for this is available in:

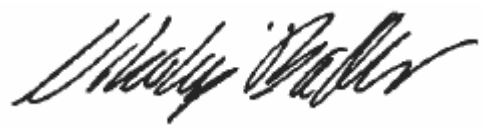
- Background of the Medicines Council's treatment guide for medicines for moderate to severe plaque psoriasis.
- Background to the Medicines Council's treatment guide for treatments for metastatic kidney cancer.
- Background to the Medicines Council's treatment guide for bone marrow cancer drugs (myeloma)

Consequently, the use of fixed effects meta analyses should be allowed as this is also a normal practice done by the Medicines Council.

Regarding heterogeneity in study design this is always a very qualitative assessment which can be about any elements of study design and discussed infinitely. It is true that in the present case, there are some minor differences regarding the different study populations and dosing. However, the concern regarding differences in e.g. dosage between studies which is stated to might give rise to the use of random effects rather than fixed effects meta-analyses is without reason. This has been proved by the quantitative heterogeneity assessment presented above. Furthermore, as there is no gold standard regarding what is a valid pooling of studies or produced guideline documents on this topics as well as no clear recommendations from the Medicines Council, heterogeneity in study results, which is actually quantitatively assessed, is found to be a more accurate estimate for heterogeneity than a qualitative assessment.

Consequently, a re-evaluation of the clinical categorization using fixed effects meta-analysis should be done.

Best regards,
Janssen-Cilag A/S



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Medicinrådet

Medicinrådets vurdering af esketamin til behandling af behandlingsresistent depression hos voksne

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette sammenfatter vi i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Godkendt af Medicinrådet den 22. juni 2020
Dokumentnummer 80454
Versionsnummer 1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf

Indhold

1 Medicinrådets konklusion

Medicinrådet vurderer, at den samlede værdi af esketamin i kombination med SSRI eller SNRI sammenlignet med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode, **ikke kan kategoriseres** efter Medicinrådets metoder. Rådet vurderer dog, at esketamin i kombination med SSRI eller SNRI samlet set ikke har bedre effekt eller sikkerhedsprofil end komparator.

Vurderingen er baseret på evidens af meget lav kvalitet.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

• **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.

• **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.

• **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

• **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

• **Samlet værdi kan ikke kategoriseres:** På grund af usikkerheder omkring effektforhold er det ikke muligt at kategorisere lægemidlets samlede værdi.

Medicinrådet vurderer kvaliteten af de data, der ligger til grund for vurderingen af lægemidlet (evidensens kvalitet) i en af følgende GRADE-kategorier:

• **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.

• **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.

• **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.

• **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2 Begreber og forkortelser

AMPAR:	*α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid Receptor*
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HDRS:	*Hamilton Depression Rating Scale*
HR:	Hazard ratio
HTA:	*Health Technology Assessment*
ICD-10:	*International Classification of Diseases-10*
MADRS:	*Montgomery-Åsberg Depression Rating Scale*
MDD:	*Major Depressive Disorder*
NaSSA:	Hæmmere af adrenerge og serotonerge receptorer
NICE:	*National Institute for Health and Care Excellence*
NMDA:	*N-methyl-D-aspartat*
NNT:	*Numbers Needed to Treat*
OR:	*Odds ratio*
RADS:	Rådet for Anvendelse af Dyr Sygehusmedicin
RR:	Relativ risiko
SMD:	Standardiseret middelforskel
SNRI:	Serotonin-/noradrenalingenoptagelseshæmmer
SSRI:	Selektiv serotoningenoptagshæmmer
TCA:	Tricykliske antidepressiva

3 Introduktion

Formålet med Medicinrådets vurdering af esketamin i kombination med en SSRI eller SNRI til voksne med moderat til svær depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva under den igangværende moderate til svære depressionsepisode er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling. Sådanne patienter benævnes i denne sammenhæng behandlingsresistente.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Janssen-Cilag A/S. Vi modtog ansøgningen den 30. marts 2020.

Det kliniske spørgsmål er:

Hvad er værdien af esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode?

3.1 Behandlingsresistent depression

Moderat til svær unipolar depression, eller *Major Depressive Disorder* (MDD), vil ifølge WHO inden for en tidsramme af 20 år være blandt de to mest belastende sygdomme i verden, hvad angår sygdomsbyrde og økonomiske konsekvenser for samfundet. I Danmark anslås prævalensen af moderat til svær depression blandt voksne at være ca. 3 %, svarende til ca. 111.000 voksne individer [1,2]. Det skønnes, at kun 2/3 af disse, svarende til ca. 72.400 voksne individer, bliver diagnosticeret og vil komme i behandling [2]. Ca. 14 %, svarende til ca. 10.100 voksne individer, har ikke en tilfredsstillende effekt af den medicinske behandling [2,3] og er mulige kandidater til behandling med esketamin.

Depression viser sig på mange måder, men præsenterer sig typisk med symptomer som en følelse af at være trist og træt over længere tid, manglende selvværd, isolationstendens, selvbebrejdelser, nedsat eller øget appetit, tab af livslyst og ledsages ofte af selvmordstanker eller -planer [4]. I alvorlige tilfælde kan der være psykotiske symptomer i form af hallucinationer og vrangforestillinger [4].

Depression inddeles iht. ICD-10 i mild, moderat, og svær depression, sidstnævnte med eller uden psykotiske symptomer. Patienter med depression har en overhyppighed af selvmord, og tilbagefald er hyppige og forekommer med stigende frekvens afhængigt af, hvor mange depressioner man tidligere har haft [5]. Nogle får kronisk depression, hvor de depressive symptomer fortsætter vedvarende igennem mere end 2 år [4]. Depression ses ofte sammen med andre psykiske lidelser som f.eks. angst og personlighedsforstyrrelser og kan optræde parallelt til alvorlige fysiske lidelser som f.eks. diabetes, kræft og hjertesygdom [4]. Herudover er misbrug af alkohol eller andre euforiserende stoffer også almindelige hos patienter med svær depression [4].

Depression kan udløses af længerevarende somatisk sygdom, stress, tab af nærtstående og eksistentielle kriser, men ofte er de udløsende faktorer ukendte. Genetisk prædisposition og personlighedsmæssige disponerende forhold bidrager til at øge risikoen for sygdommen [4]. Den nuværende medicinske behandling virker bl.a. ved at påvirke signalstofferne serotonin og noradrenalin i hjernen. En stigende mængde evidens indikerer desuden, at dysregulering af glutamatsignaleringen i hjernen også kan være involveret i depression [6].

En betydende andel af patienterne responderer ikke på den nuværende medicinske behandling og beskrives som havende behandlingsresistent depression. Definitionen af denne population er varierende i den videnskabelige litteratur, men i denne sammenhæng omfatter behandlingsresistent depression voksne patienter over 18 år med moderat til svær depression, diagnosticeret efter ICD-10 (WHO's diagnoseliste)

kriterier, der ikke har responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger) eller uafbrudt har haft depression i mere end to år uanset behandling eller er vurderet behandlingsresistent på et relevant scoringsredskab (f.eks. *The Maudsley Staging Method for Treatment-Resistant Depression*)[7].

Hvis patienten med depression tidligere har haft maniske eller hypomane episoder, betegnes depressionen som en bipolar depression, der er led i en bipolar lidelse. En andel af patienterne med behandlingsresistent depression vil have en ikkediagnosticeret bipolar depression, hvor de senere i forløbet vil udvikle mani eller hypomani [5,8].

3.2 Esketamin

Esketamin, eller s-ketamin, er ét af to spejlmolekyler af ketamin (s- og r-ketamin). Brugen af s-ketamin fremfor r-ketamin forventes at øge specificiteten og derved mindske bivirkninger ved brug [9]. Esketamin udøver sin effekt i hjernen via antagonisme af N-methyl-D-aspartat (NMDA)-receptoren.

Glutamat frigives normalvis som et signalmolekyle i kontaktfladen mellem nerveceller i hjernen. Esketamin leder til en forbigående forøgelse i frigivelsen af glutamat, som trinvist fører til en forøgelse i neurotrofisk signalering, der er essentiel for nervecellernes funktion og overlevelse [6,10,11]. Dette antages at bidrage til at genoprette funktionen i hjerneområder involveret i reguleringen af affektive og emotionelle tilstande [6,10,11]. Intravenøs esketamin anvendes allerede på sygehuse i Danmark som anæstetikum ved mindre indgreb og indledningsvist ved længerevarende bedøvelse i særlige tilfælde. Esketamin, som ketamin, har dissociative effekter, der typisk efterlader brugeren med en følelse af at forlade kroppen [9]. Andre psykotomimetiske effekter er også beskrevet.

Til behandlingen af behandlingsresistent depression hos voksne er esketamin udviklet som en nasal formulering [2]. Den intranasale administrationsvej tillader en hurtig indsættende effekt, og absorptionen er i modsætning til peroral indgift langt mere stabil, mens det kan tage flere uger at opnå en ønsket effekt af andre traditionelt, anvendte orale antidepressiva [2]. Esketamin har været administreret i kliniske studier som monoterapi og som add-on terapi med antidepressiva [12–14]. Den nuværende anbefalede behandling inkluderer en induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg eller 56 mg (afhængigt af alder, effektivitet og tolerabilitet) nasal esketamin plus nyligt initieret daglig oralt antidepressivum, som ikke har indgået i behandling tidligere, på dag 1 efterfulgt af administration med 28 mg, 56 mg eller 84 mg esketamin plus nyligt initieret daglig oralt antidepressivum ved efterfølgende behandling [2]. De intranasale doser er udvalgt med udgangspunkt i erfaringer fra studier med intravenøs administration. Efter induktionsfasen følger en vedligeholdelsesbehandling med nasal esketamin 56 mg eller 84 mg en gang ugentlig fra uge 5-8 og herefter hver anden uge eller ugentligt samt vedligeholdelse af oralt antidepressivum administreret som under induktionsfasen [2]. Hvornår/om behandlingen kan eller skal stoppes, er endnu uafklaret.

3.3 Nuværende behandling

Diagnosticering af depression kan være vanskelig, og kun omkring halvdelen af alle patienter med depression får stillet en korrekt diagnose, hvis der ikke anvendes flere samtaler [7]. Langt de fleste med depression behandles i almen praksis [4].

Behandlingen af behandlingsresistent depression er ikke defineret i den gældende behandlingsvejledning for medicinsk behandling af unipolar depression udarbejdet af Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) i 2015. En national klinisk retningslinje vedrørende vanskelig behandlelig depression er under udarbejdelse.

Ifølge RADS's vejledning skal den indledende behandling af ikkehospitaliserede patienter bestå af SSRI som førstelinjebehandling, der gives over 1-3 måneder. En fuld effekt af antidepressiva kan først ventes efter 4-6 uger. Opnår patienten en tilfredsstillende effekt ved behandlingen, fortsættes i en vedligeholdelsesfase i ca. 6-12 måneder eller længere, afhængigt af kliniske forhold. Hvis der ikke er tegn på bedring efter ca. 2-4 uger på optimal dosis (i praksis ofte længere), skiftes der til andenlinjebehandling, som består af enten et andet SSRI, SNRI, hæmmere af adrenerge receptorer (NaSSA) eller tricykliske antidepressiva (TCA). Er der fortsat ikke tegn på bedring, henvises der til psykiatrisk regi – enten privatpraktiserende psykiater eller den hospitalsbaserede ambulante psykiatri. Blandt indlagte/hospitaliserede patienter med svær depression skal overvejes start med SNRI eller TCA.

Dansk registerdata viser, at SSRI og SNRI er de hyppigst anvendte tredjelinjebehandlinger i Danmark [3].

Behandlingsvarigheden varierer fra patient til patient. Til patienter, der er refraktære overfor behandling med antidepressiva, overvejes en række alternativer. Disse inkluderer: augmenterende farmakologisk behandling (lithium, thyroideahormon, antipsykotika, stemningsstabiliserende medicin), psykoterapi, elektrokonvulsiv terapi (ECT) og transkraniel magnetstimulation (TMS).

Ketamin har været kendt for sine bedøvende egenskaber siden 1960'erne. I Danmark er ketamin udelukkende godkendt som anæstetikum, men benyttes dog også som et misbrugsstof. Ketamin har igennem knap 20 år været undersøgt i kliniske studier som middel mod svær depression og har vist både god og hurtigindsættende effekt [15,16]. Der er dog tale om en relativt kortvarig effekt (dage til uger) ved den indledende behandling uden en efterfølgende vedligeholdelsesfase [16]. Ketamin anvendes i dag som off-label-behandling af behandlingsresistent depression i flere europæiske lande, men ifølge fagudvalget stort set ikke i Danmark. Undersøgelser viser, at ketamin har en akut indsættende effekt på selvmordstanker [16,17].

Målet med behandling af behandlingsresistent depression er at opnå remission af depressive symptomer, øge livskvaliteten og forhindre selvmord blandt en patientgruppe med øget selvmordstendens.

4 Metode

Medicinrådets protokol for vurdering af esketamin beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan vi vil vurdere lægemidlets værdi for patienterne.

Det kliniske spørgsmål er:

Hvad er værdien af esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode?

Population:

Patienter over 18 år med behandlingsresistent depression. Ved dette forstås her patienter, der ikke har responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger) eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling eller er vurderet behandlingsresistent på rating scale for treatment-resistant depression.

Intervention:

Induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg[1] eller 56 mg esketamin plus nyligt initieret daglig oralt antidepressivum, som ikke har indgået i behandling tidligere, på dag 1 efterfulgt af administration med 28 mg[1], 56 mg eller 84 mg esketamin plus daglig oralt antidepressivum ved efterfølgende behandling.

Vedligeholdelsesbehandling med esketamin 28 mg[1], 56 mg eller 84 mg en gang ugentlig fra uge 5-8 og fra uge 9 hver anden uge eller ugentligt samt vedligeholdelse af oralt antidepressivum administreret under induktionsfasen.

Komparator:

Placebo, intranasalt, i kombination med SSRI eller SNRI, oralt.

Andre forhold, der har betydning for vurderingsrapporten:

Medicinrådet har foretaget ændringer af beregninger og resultatfremstilling som angivet i afsnit *5.2 Databehandling og analyse*. Herudover har fagudvalget forholdt sig til en række overvejelser i afsnit *6 Andre overvejelser*, bl.a. misbrugspotentiale, behandlingsvarighed og overførbarhed til danske patienter. Alle forhold, der har betydning for vurderingen af esketamin.

Aktuelle effektmål, som anført i protokollen, er angivet i tabel 1.

Tabel 1. Effektmålstabel, som anført i protokollen.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Uønskede hændelser	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel der oplever alvorlige uønskede hændelser (SAE'er)	5 %-point
			Andel der ophører behandling	20 %-point
			Narrativ gennemgang af specifikke hændelser, død uanset årsag og selvmordsstudie	-
Remission	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	HDRS-17 eller MADRS. Andel der reducerer score til hhv. ≤ 7 point og ≤ 11 point	15 %-point
Respons	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	HDRS-17 eller MADRS. Andel der reducerer score fra baseline med 50 %	20 %-point
Livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på WHO-5 eller EQ-5D i prioriteret rækkefølge	10 point/0,07 point

Generelt om måletidspunkter:

To måletidspunkter, efter endt behandling (induktionsfasen) og efter endt opfølgning (endt vedligeholdelsesfase eller længst mulig follow-up), gælder jf. protokollen for samtlige effektmål. Måletidspunktet for endt behandling skal være minimum fire uger efter første administration ud fra rationalet om, at antidepressiva (komparator) først har begyndende effekt efter fire uger. Måletidspunktet for endt

[1]Patienter ≥ 65 år.

opfølgning skal være minimum seks måneder efter første administration ud fra rationalet om, at tilbagefald efter at have opnået remission af seks måneders varighed, ikke tæller som relaps, men tæller som en ny depressiv episode. De to måletidspunkter vægtes lige højt og anses af fagudvalget for at være et udtryk for hhv. en umiddelbar effekt af behandling og vedvarende (sustained) effekt af behandling. En umiddelbar effekt målt på remission eller respons kan muligvis have en akut antiselvmordseffekt, mens en vedvarende effekt anses for at være kurativ for indeværende depressive episode.

5 Resultater

5.1 Litteratur

Nedenfor beskriver og vurderer vi den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøgningen baserer sig på de fire artikler, der er angivet i protokollen. Tabel 2 indeholder en oversigt over studier og populationsstørrelser, indsendte analyser og deres anvendelighed i vurderingen. EPAR, produktresumé og NICE-rapport er medtaget som litteratur, der supplerer fuldtekstartikler fra ansøger.

Tabel 2: Data anvendt af ansøger til besvarelse af det kliniske spørgsmål samt Medicinrådets anvendelse i vurderingen af klinisk merværdi.

Datakilde	Klinisk studie	N	Effektmål	Anvendt i vurdering
Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). Fedchin M, Int J Neuropsychopharmacol. 2019	TRANSFORM-1 (TRD3001) NCT02417064	342	Direkte analyse af alle effektmål Uønskede hændelser, remission, respons og livskvalitet	Ja, til vurdering af den hurtigindsættende effekt
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. Popova V, Am J Psychiatry. 2019	TRANSFORM-2 (TRD3002) NCT02418585	223		
Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression—TRANSFORM-3. Ochs-Ross R, Am J Geriatr Psychiatry. 2020	TRANSFORM-3 (TRD3005) NCT02422186	137		
Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. Daly EJ, JAMA Psychiatry. 2019	SUSTAIN-1 (TRD3003) NCT02493868	297	Direkte analyse af alle effektmål Uønskede hændelser, remission, respons og livskvalitet*	Data er beskrevet narrativt og giver indirekte information om en mulig vedvarende effekt, (se afsnit 8)

* Kun data for patienter behandlet med esketamin med stabil respons og remission ved 16 uger grundet studiets design

5.1.1 Gennemgang af studier

TRANSFORM-1 (esketamin + SSRI/SNRI versus placebo + SSRI/SNRI, fast dosis)

TRANSFORM-1 er et dobbeltblindet randomiseret multicenter fase III-studie, der sammenligner to faste doser intranasal esketamin plus oralt antidepressiva med intranasal placebo plus oralt antidepressiva hos voksne i alderen 18-64 år. Studiedesignet inkluderer en 4-ugers screeningsfase, hvorefter egnede studiedeltagere randomiseres til tre arme (1:1:1) hhv. placebo (n = 113), 56 mg esketamin (n = 115) eller 84 mg esketamin (n = 114). Resultaterne opgøres efter 4-ugers induktionsfase. Respondere fra alle arme kan gå videre til SUSTAIN-1-studiet.

Det primære endepunkt for TRANSFORM-1 er ændring i MADRS totalscore målt fra baseline for induktionsfase til uge 4 (dag 28) eller sidste måling i induktionsfasen. Af relevans for denne vurdering findes også data for livskvalitet, behandlingsophør og sikkerhed i form af uønskede hændelser.

TRANSFORM-2 (esketamin + SSRI/SNRI versus placebo + SSRI/SNRI, fleksibel dosis)

TRANSFORM-2 er et dobbeltblindet randomiseret multicenter fase III-studie, der sammenligner en fleksibel dosis (56 mg eller 84 mg) intranasal esketamin plus oralt antidepressiva med intranasal placebo plus oralt antidepressiva hos voksne i alderen 16-64 år. Studiedesignet inkluderer en 4-ugers screeningsfase, hvorefter egnede studiedeltagere randomiseres til to arme (1:1) hhv. placebo (n = 111) eller fleksibel dosis esketamin (56 mg/84 mg) (n = 116). Resultaterne opgøres efter 4-ugers induktionsfase. Respondere fra alle arme kan gå videre til SUSTAIN-1-studiet. Det primære endepunkt er som for TRANSFORM-1. Af relevans for denne vurdering findes også data for livskvalitet, behandlingsophør og sikkerhed i form af uønskede hændelser.

TRANSFORM-3 (ældre over 64 år, esketamin + SSRI/SNRI versus placebo + SSRI/SNRI, fleksibel dosis)

TRANSFORM-3 er et dobbeltblindet randomiseret multicenter fase III-studie, der sammenligner en fleksibel dosis (28 mg, 56 mg, eller 84 mg) intranasal esketamin plus oralt antidepressiva med intranasal placebo plus oralt antidepressiva hos ældre over 64 år. Studiedesignet inkluderer en 4-ugers screeningsfase, hvorefter egnede studiedeltagere randomiseres (1:1) til hhv. placebo (n = 66) eller fleksibel dosis esketamin (28 mg/ 56 mg/84 mg) (n = 72). Resultaterne opgøres efter 4-ugers induktionsfase. Ingen patienter fra TRANSFORM-3 overgår til SUSTAIN-1.

Det primære endepunkt er det samme som i TRANSFORM-1 og -2. De sekundære endepunkter er: 1) Andel, der opnår remission og respons som defineret ved MADRS til tiden 4 uger eller ved sidste måling i induktionsfasen, og 2) Ændring i CGI-S og EQ-5D-5L målt fra baseline for induktionsfase til tiden 4 uger eller sidste måling i induktionsfasen. Af relevans for denne vurdering findes også data for livskvalitet, behandlingsophør og sikkerhed i form af uønskede hændelser.

SUSTAIN-1 (esketamin + SSRI/SNRI versus placebo + SSRI/SNRI)

SUSTAIN-1 studiet er et dobbeltblindet, randomiseret relapsstudie. Studiet sammenligner effekt af fortsat esketaminbehandling med effekt af ophør af esketamin-behandling (overgår til placebo), hos patienter, der har opretholdt respons fra induktion (uge 4) til uge 16 med esketamin-behandling.

SUSTAIN-1 inkluderer både patienter overført fra TRANSFORM-1 og -2 og patienter, som direkte indtræder i studiet. De patienter, som indtræder direkte, gennemgår tilsvarende screenings- og induktionsfase som de patienter, der overføres fra TRANSFORM-studierne. Patienter, som har respons (defineret som ≥ 50 procent reduktion i MADRS samlede score fra baseline), går videre til en optimeringsfase på 12 uger. Ved

fortsat stabilt respons eller stabil remission randomiseres patienter herefter (1:1) til placebo (n = 145) eller fortsat esketamin (n = 152) begge dele i kombination med samme antidepressiva, som blev givet i induktions- og optimeringsfasen. Denne fase er blindet og kaldes vedligeholdelsesfasen. Varigheden af denne fase er individuel og vil afhænge af, hvornår patienten er indtrådt i studiet, og hvornår der opleves et tilbagefald (relaps). Denne fase forløber, indtil et tilstrækkeligt antal studiedeltagere oplever tilbagefald baseret på statistiske styrkeberegninger.

Det primære endepunkt for SUSTAIN-1 er tid til tilbagefald for patienter i stabil remission efter behandling med esketamin i tidligere faser. De sekundære endepunkter er: 1) tid til tilbagefald for patienter med stabilt respons efter behandling med esketamin i tidligere faser, og 2) ændring i baseline fra start vedligehold til slut vedligehold i MADRS, PHQ-9, CGI-S, GAD-7, EQ-5D-5L og SDS.

5.1.2 Studie- og populationskarakteristika

Baselinekarakteristika, betydende afvigelser i studierne og overførbarhed til danske forhold gennemgås i det følgende.

Baselinekarakteristika

Fremgår af tabel 3. Baselinekarakteristika adskiller sig ikke nævneværdigt mellem studierne, hvad angår MADRS-score, køn, antal tidligere behandlinger og antal klasser af antidepressiva behandlet med forud for studiedeltagelse. Med undtagelse af TRANSFORM-3, hvor studiepopulationen udgøres af en ældrepopulation, er der ydermere ingen nævneværdig forskel på den gennemsnitlige alder for studiedeltagere. Forskelle i baselinekarakteristika består af varighed af den indeværende depressive episode (ca. 200 uger i TRANSFORM-1 vs. ca. 115 uger i TRANSFORM-2 og 216 uger i TRANSFORM-3, SUSTAIN-1 132 uger).

Kriterier for inklusion og eksklusion

Kriterierne for inklusion for alle studierne anses af fagudvalget at være selektive, idet patienter med somatiske komorbiditeter og andre psykiatriske komorbiditeter er ekskluderet. Studiepopulationerne afspejler herved ikke majoriteten af patienter i dansk klinisk praksis.

Psykiatriske komorbiditeter

Den endelige ansøgning indeholder en oversigt (tabel 35) over de almindelige psykiatriske komorbiditeter, der er registreret i TRANSFORM-studierne og i SUSTAIN-1-studiet. Oversigten omfatter angstlidelser og posttraumatisk stresssyndrom (PTSD), som blev registreret igennem diagnostiske interviews udført under første screeningsbesøg. Andelen af angstlidelser og PTSD i studierne er i overensstemmelse med, hvad der kan forventes i den danske population. Fagudvalget finder dog, at patienter i dansk klinisk praksis har yderligere og betydelige psykiatriske komorbiditeter, som ikke er repræsenteret i studiepopulationerne, blandt andet som følge af nedenstående eksklusionskriterier:

- igangværende eller tidligere DSM-5 diagnose for psykotiske tilstande
- MDD med psykose
- bipolær sygdom og lignende
- igangværende *obsessive compulsive disorder* (OCD)
- intellektuel disability (DSM-5 diagnostiske koder: 317, 318.0-2, 315.8, 319)
- autisme
- borderline personlighedsforstyrrelse
- antisocial personlighedsforstyrrelse
- histrionisk personlighedsforstyrrelse

- narcissistisk personlighedsforstyrrelse
- positiv urinprøve for udvalgte narkotika, herunder cannabinoider

Fagudvalget vurderer, at flere psykiatriske komorbiditeter typisk medfører en mere behandlingsresistent depression, og at tilstedeværelsen af psykiatriske komorbiditeter er mere reglen end undtagelsen for den aktuelle patientpopulation. Her fremhæver fagudvalget især komorbid angstlidelse.

I forlængelse heraf finder fagudvalget det også problematisk for generaliserbarheden, at almindelige somatiske komorbiditeter optræder som eksklusionskriterier herunder bl.a. hjerteproblemer, ukontrolleret forhøjet blodtryk etc.

Fagudvalget bemærker desuden at tidligere non-response til ECT er eksklusionskriterie. Dette kan være problematisk, fordi mange danske behandlingsrefraktære patienter vil have prøvet ECT tidligere uden effekt.

De stramme inklusions-/eksklusionskriterier kan også ses ved, at blot omkring 30-50 % af de screenede patienter bliver randomiseret.

Fagudvalget vurderer at ved anvendelse af de stramme kriterier for inklusion, afspejler populationen i studiet i mindre grad de patienter, der er i klinisk praksis.

Varighed af depression og tidligere behandlinger

Varighed af indeværende depressive periode kan være kort (6 uger, se baselinekarakteristika) i studierne, jf. inklusionskriterierne. Varigheden er opgjort som middelværdi (mean) med et meget bredt spænd (range), hvorfor det er svært at vurdere, om forskellen mellem studier har klinisk relevans. Opgørelser af varighed som medianværdier havde givet et bedre sammenligningsgrundlag. Fagudvalget vurderer, at danske patienter med behandlingsresistent depression har en sammenhængende depressiv episode på minimum et år, men ofte mere. Generelt finder fagudvalget, at jo længere sygdomsvarighed des sværere er det at behandle depressionen. Fagudvalget anerkender, at patienterne i studierne falder under den anvendte definition på behandlingsresistent depression, men fremhæver at definitionen er af mere praktisk karakter. Fagudvalget vurderer, at antal tidligere behandlinger er meget begrænsede og mener, at det er usandsynligt, at patienter, der alene på baggrund af to tidligere behandlingsforsøg med to antidepressiva, vil blive vurderet behandlingsresistente i en klinisk kontekst. Disse vil mere sandsynligt repræsentere patienter, som ikke har haft mulighed for at blive behandlet effektivt, eller hvor betydende komorbiditet ikke er erkendt. Fagudvalget beskriver, at patienter typisk behandles med forskellige antidepressiva, til der opnås en partiel eller absolut effekt, men bemærker at der i øvrigt ikke er en forudbestemt behandlingsalgoritme for den aktuelle population. Behandlingen bestemmes individuelt og ofte ud fra effekt og tolerabilitet samt patientpræferencer. Dette stemmer overens med den fleksible behandling (dosis og interval), som gives til patienterne i studierne vedr. esketamin. Fagudvalget fremhæver andre relevante behandlinger som psykoterapi og ECT, som også typisk vil kombineres med antidepressiva.

Samtidig behandling med oral antidepressiva

I esketaminstudierne opstartes nye antidepressiva samtidig med opstart af esketamin. Fagudvalget finder, at igangsættelse af to nye behandlinger (uafhængigt af hvilken behandling) simultant, som gjort i esketamin-studierne, er problematisk, idet det bliver uklart, hvorvidt effekterne hos den enkelte patient – gavnlige eller negative – kan tilskrives antidepressiva, esketamin eller en kombination af disse. Fagudvalget bemærker i øvrigt, at en mere rationel fremgangsmåde til behandling af den aktuelle population med esketamin i dansk kontekst ofte ville være at fortsætte en behandling med antidepressiva, som evt. giver et partielt respons hos

patienten og herefter behandle med esketamin i tillæg.

Blinding

Esketamin har hos nogle patienter en dissociativ effekt, som opleves af patienter efter administration af lægemidlet. Dette er ikke muligt at efterligne hos patienter i komparatorgruppen, hvorfor blindingen ikke er optimal. En del patienter og personel har derfor i forbindelse med administration været klar over, om patienterne har fået administreret esketamin eller placebo. Dette forventes især at være tilfældet for placebogruppen i SUSTAIN-1, som tidligere fik esketamin og dermed kender de umiddelbare virkninger af esketamin. Potentielle konsekvenser heraf inkluderer noceboeffekt, hvor negative forventninger til placebobehandling modvirker en effekt eller giver tilsyneladende bivirkninger. Det gælder for esketamingruppen, at patienter kan opleve placeboeffekt ved at kende til at få det aktive stof. Potentielle nocebo- og placeboeffekter og deres indvirkning på effektestimaterne kan ikke afklares yderligere.

Tabel 3. Population og baselinekarakteristika. Oplysninger fra den endelig ansøgning og EPAR.

	TRANSFORM-1 (n = 342)	TRANSFORM-2 (n = 223)	TRANSFORM-3 (n = 137)	SUSTAIN-1 (n = 297)
MADRS-score ved baseline (mean) [range]	37,6 (5,51) [18-53]	37,1 (5,67) [21-52]	35,2 (6,16) [19-51]	37,9 (5,50) [4[i]-53]
Alder, år (mean (SD)	46,3 (11,9)	45,7 (11,89)	70,0 (4,52)	46,1 (11,10)
Kvinder, n (%)	241 (70,5)	138 (61,9)	85 (62,0)	193 (64,8)
Varighed af nuværende depressive episode, uger, mean (SD) [range]	202.9 (290,24) [6-2288]	114.6 (15,.96) [ikke oplyst]	215,8 (341,71) [ikke oplyst]	132.2 (209,18) [9-1248]
Antal tidligere behandlinger med antidepressiva, n (%)*				
1	27 (12,1)	31 (9,1)	21 (15,3)	208 (70,0)
2	123 (55,2)	174 (51,2)	63 (46,0)	
3	46 (20,6)	94 (27,6)	30 (21,9)	87 (29,3)
4	20 (9,0)	34 (10,0)	16 (11,7)	
5	4 (1,8)	6 (1,8)	5 (3,6)	
6, 7, 8 eller 9	≤ 1 % i hver kategori	≤ 1 % i hver kategori	≤ 1 % i hver kategori	
Generelle klasser OAD, indeværende episode, n (%)**				
1	49 (22,0)	75 (21,9)	32 (23,4)	Ikke oplyst
2	134 (60,1)	208 (60,8)	79 (57,7)	Ikke oplyst
Flere end 2	40 (17,9)	59 (17,3)	26 (19,0)	Ikke oplyst

***** Patienter i induktionsfasen havde fejlet på mindst to antidepressiva (1 retrospektiv og 1 vurderet i screeningsfasen). Non-respons var i studiet defineret som ≤ 25 % forbedring målt i mindst 6 uger i løbet af den aktuelle episode frem til screeningstart. **Generelle klasser: Monoaminoxidaseinhibitorer (MAOI'er), tricykliske antidepressiva; serotonin og noradrenalin genoptagelsesinhibitor (SNRI); selektiv serotonin-genoptagelsesinhibitor (SSRI); eller andre. *** Varighed: Behandlingsvarigheden for igangværende antidepressiva ved screening (eller antidepressiva taget frem til en uge inden screening). Ved behandling med flere præparater ved screening blev behandlingsvarigheden af det antidepressiva, der var behandlet med i længst tid, inkluderet i opgørelsen. [i]En enkelt patient havde et dramatisk fald efter screeningperioden og frafaldt efter induktionsfasen.

5.2 Evidensens kvalitet

Fagudvalget har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 1).

Der er nedgraderet for risk of bias grundet mangelfuld blinding. Der er nedgraderet for indirekthed, fordi populationer er kraftigt selekterede.

Evidensens kvalitet ved 4 uger er meget lav.

Evidensens kvalitet ved 6 måneder kan ikke vurderes, hvilket reducerer den samlede evidenskvalitet.

Samlet anses evidensens kvalitet at være meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.3 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier.

Tabel 4. Resultater for det kliniske spørgsmål

Effektmål	Vigtighed	Måleenhed (mindste klinisk relevante forskel)	Tidshorisont	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
				Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Uønskede hændelser	Kritisk	Andel der oplever alvorlige uønskede hændelser (SAE'er) (5 %-point)	4 uger	0,4 %-point [-0,63; 4,29]	Kan ikke kategoriseres	1,40 [0,37;5,29]	Kan ikke kategoriseres	Kan ikke kategoriseres
			6 mdr.	Narrativ gennemgang	Kan ikke kategoriseres	Narrativ gennemgang	Kan ikke kategoriseres	
		Andel der ophører behandling (20 %-point)	4 uger	2,72 %-point [-0,051; 10,183]	Kan ikke kategoriseres	2,60 [0,97;6,99]	Kan ikke kategoriseres	
			6 mdr.	Narrativ gennemgang	Kan ikke kategoriseres	Narrativ gennemgang	Kan ikke kategoriseres	
Remission	Kritisk	Andel der reducerer score til ≤ 11 point på MADRS (15 %-point), NNT = 7	4 uger	7,0 %-point, [1,4;14,56], NNT=14	Ingen dokumenteret merværdi	1,50 [1,10;2,04]	Merværdi af ukendt størrelse	Kan ikke kategoriseres
			6 mdr.	Narrativ gennemgang	Kan ikke kategoriseres	Narrativ gennemgang	Kan ikke kategoriseres	
Respons	Vigtig	Andel der reducerer MADRS score fra baseline med 50 % (20 %-point), NNT = 5	4 uger	7,6 %-point [3,2;12,6], NNT=13	Ingen dokumenteret merværdi	1,38 [1,16;1,63]	Moderat merværdi	Kan ikke kategoriseres
			6 mdr.	Narrativ gennemgang	Kan ikke kategoriseres	Narrativ gennemgang	Kan ikke kategoriseres	
Livskvalitet	Vigtig	Gennemsnitlig ændring fra baseline på EQ-5D (index score) (0,07 point)	4 uger	0,06 point [0,01;0,10]	Ingen dokumenteret merværdi	-	-	Kan ikke kategoriseres
			6 mdr.	-	Kan ikke kategoriseres	-	-	
Samlet kategori for lægemidlets værdi			Kan ikke kategoriseres					
Kvalitet af den samlede evidens			Meget lav					

CI = konfidensinterval, HR = hazard ratio, OR = odds ratio, RR = relativ risiko

5.4 Databehandling og analyse

I dette afsnit beskrives datagrundlag, databehandling og analyse for hvert effektmål.

Protokollen definerer to relevante måletidspunkter (4 uger og 6 måneder) for at belyse hhv. den hurtigindtrædende effekt og den vedvarende effekt af esketamin. Begge måletidspunkter er vurderet lige vigtige og vægtes ens, jf. protokollen.

De kliniske studier, der er medtaget i den endelige ansøgning, inkluderer fire randomiserede kliniske studier, hvoraf tre (TRANSFORM-1, -2 og -3) kombineres i en metaanalyse til at belyse effektforskellen efter 4 uger i en direkte sammenligning mellem esketamin i kombination med antidepressiva og placebo i kombination med antidepressiva. Det fjerde studie (SUSTAIN-1) anvendes til at belyse den vedvarende effekt af esketamin. Data fra SUSTAIN-1 gennemgås samlet og narrativt i afsnit 5.2.1 pga. studiedesign (relapsstudie).

Medicinrådet har foretaget følgende ændringer af beregninger og resultatfremstilling:

Model i metaanalyse
For studierne TRANSFORM-1, -2, og -3 har fagudvalget, for samtlige effektmål, valgt at anvende en *random effects*-model i metaanalyserne i stedet for en *fixed effects*-model, som ansøger har anvendt i den endelige ansøgning. Baggrunden for dette er, at fagudvalget vurderer, at vilkåret for at anvende en fixed effects-model (homogenitet mellem studier og studiepopulationer) ikke er opfyldt: studierne repræsenterer ikke samme aldersgrupper, og administrationen af esketamin er forskellig mellem studierne (dosisforskelle).

Hændelsesrater
Til beregning af de absolutte forskelle for sammenligning mellem esketamin og placebo efter 4 uger (TRANSFORM-1, -2, og -3) har fagudvalget valgt at anvende de hændelsesrater for respons og remission, som er estimeret i protokollen, og som svarer til de rater, man ville forvente med komparator i en dansk kontekst. Ansøger har anvendt hændelsesrater fra studierne (komparatorarmen), men fagudvalget vurderer, at de er usædvanligt høje. Det kan blandt andet skyldes, at populationen er så selekteret, som tidligere nævnt, en større grad af interaktion med sundhedspersonale, opstart af nyt antidepressiva samtidig med esketamin og ny administrationsform.

Vedvarende effekt
Langtidseffekterne af behandling måles jf. protokollen ved 6 måneder. Fagudvalget vurderer, at resultaterne fra SUSTAIN-1 ikke direkte kan anvendes til at belyse, om der er længerevarende effekt af behandling med esketamin vs. placebo. Dette skyldes, at der ikke er indsendt data for komparator. Resultaterne fra SUSTAIN-1 gennemgås dog narrativt i afsnit 8.3, men kan ikke føre til en kategorisering af lægemidlets effekt ved 6 måneder.

Fagudvalget vil i forbindelse med den narrative gennemgang vurdere, hvilke af de tilgængelige resultater der har relevans og vil udelukkende gennemgå disse. Langtidseffekterne vurderes med følgende forbehold:

- Selektionen af patienter forud for randomisering i SUSTAIN-1.
- Det efterspurgte effektmål er vedvarende remission eller respons, hvilket ikke defineres på samme måde som relaps. Tiden fra remission/respons til relaps er ofte en periode, hvor patienten får det tiltagende værre, og denne periode bør ikke medregnes som vedvarende remission/respons.

Uønskede hændelser (kritisk)

Effektmålet *uønskede hændelser* er kritisk for vurderingen af lægemidlets værdi for patienterne, idet de har stor betydning for den enkelte patients livskvalitet. Fagudvalget fremhæver, at der må accepteres et vist

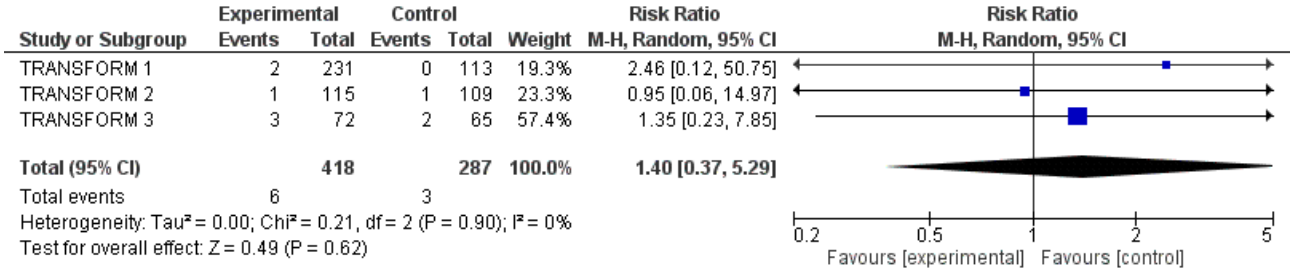
niveau af behandlingsophør, hvis den andel af patienter, som forbliver i behandling, oplever en relevant bedring.

Effektmålet ønskes belyst på 3 måder kvantitativt som 1) andel, der oplever SAE'er (mindste klinisk relevante forskel: 5 %-point) og 2) andel, der ophører behandling (mindste klinisk relevante forskel: 20 %-point) til tiden 4 uger samt 3) en kvalitativ gennemgang af uønskede hændelser og død uanset årsag. Gennemgangen tager udgangspunkt i publicerede studier, produktresumé og EPAR med henblik på at vurdere, om der er forskel mellem grupperne mht. alvorlighed, håndterbarhed og hyppighed af uønskede hændelser og død uanset årsag.

Måletidspunkt 4 uger, alvorlige uønskede hændelser:
Det samlede resultat fra metaanalysen efter 4 ugers behandling viser, at andelen af patienter med alvorlige uønskede hændelser er 1,4 % (6/418) hos patienter, der modtog esketamin sammenlignet med 1,0 % (3/287) hos patienter, der modtog placebo og heraf en beregnet relativ forskel på 1,40 [0,37: 5,29], se figur 5.2a. Baseret på den relative effektforskel som også fremgår af tabel 4, kan esketamin foreløbigt ikke kategoriseres vedr. alvorlige uønskede hændelser.

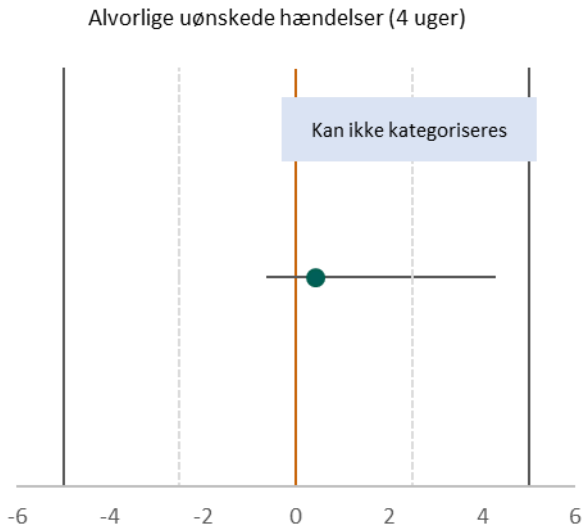
Der er ikke påvist en klinisk relevant forskel mellem esketamin og placebo for effektmålet *uønskede hændelser*. Pga. få hændelser er konfidensintervallet bredt og indeholder værdier, som kan føre til forskellige konklusioner, hvorfor den kan kliniske værdi på den relative skala ikke kan kategoriseres.

Figur 5.2a. Forest plot over relativ risiko (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin. Alvorlige uønskede hændelser.



Med en samlet hændelsesrate i placebogruppen på 1,0 % beregnes den absolutte forskel til 0,4 %-point [-0,63; 4,29] flere SAE's med esketamin. Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0. Derfor kan den foreløbige værdi af esketamin vedr. andel, der oplever alvorlige uønskede hændelser, ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i figur 5.2b nedenfor.



Figur 5.2b. Punktestimat og 95 % konfidensinterval for den absolutte forskel for alvorlige uønskede hændelser ved 4 uger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Fagudvalget vurderer ud fra ovenstående beregninger og de meget små hændelsesrater, at der ikke er betydende klinisk forskel mellem esketamin og placebo for andel af patienter, der oplever en SAE indenfor 4 ugers behandling.

Måletidspunkt 6 måneder, alvorlige uønskede hændelser:
Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin på effektmålet alvorlige uønskede hændelser ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres efter medicinrådets metoder ved 6 måneder.

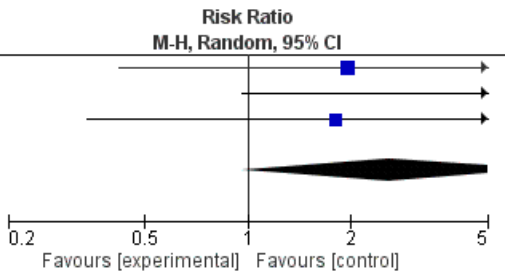
Måletidspunkt 4 uger, behandlingsophør grundet uønskede hændelser:
Det samlede resultat fra metaanalysen efter 4 ugers behandling viser, at andelen af patienter med behandlingsophør er 4,8 % (20/418) hos patienter, der modtog esketamin sammenlignet med 1,7 % (5/287) hos patienter, der modtog placebo og heraf en beregnet relativ forskel på 2,60 [0,97: 6,99], se figur 5.2c.

Baseret på den relative effektforskel som også fremgår af tabel 4, kan esketamin foreløbigt ikke kategoriseres vedr. behandlingsophør. Der er ikke påvist en forskel mellem esketamin og placebo. Pga. få hændelser er konfidensintervallet bredt og indeholder værdier, som kan føre til forskellige konklusioner, hvorfor den kan kliniske værdi på den relative skala ikke kan kategoriseres.

Figur 5.2c. Forest plot over relativ risiko (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin. Behandlingsophør grundet uønskede hændelser

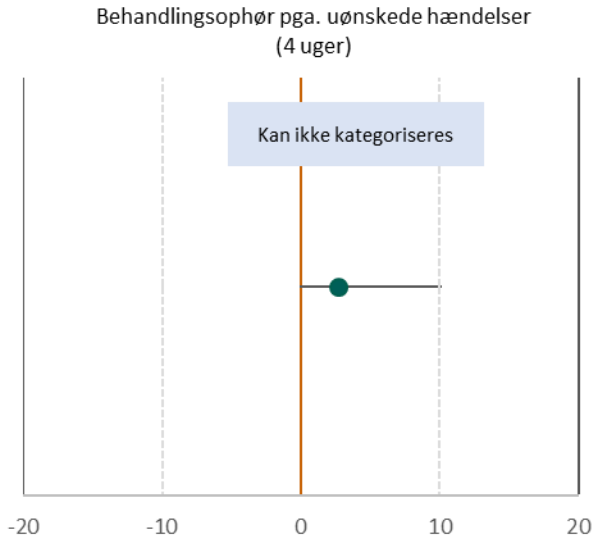
	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
TRANSFORM 1	8	231	2	113	41.6%	1.96 [0.42, 9.06]
TRANSFORM 2	8	115	1	109	23.0%	7.58 [0.96, 59.63]
TRANSFORM 3	4	72	2	65	35.3%	1.81 [0.34, 9.53]
Total (95% CI)		**418**		**287**	**100.0%**	**2.60 [0.97, 6.99]**
Total events	20		5			

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)



Med en samlet hændelsesrate i placebogruppen på 1,7 % beregnes den absolutte forskel til 2,72 %-point [-0,051; 10,183]. Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af esketamin vedr. behandlingsophør ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i figur 5.2d nedenfor.



Figur 5.2d. Punktestimat og 95 % konfidensinterval for den absolutte forskel for behandlingsophør ved 4 uger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Fagudvalget vurderer ud fra ovenstående beregninger, at der indenfor 4 ugers behandling formentlig er flere patienter, som ophører behandling med esketamin i forhold til placebo. Forskellen er dog i en størrelsesorden, der ikke er klinisk relevant.

Måletidspunkt 6 måneder, behandlingsophør grundet uønskede hændelser:
Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres ved 6 måneder.

Kvalitativ gennemgang af uønskede hændelser, behandlingsophør og død uanset årsag, alle måletidspunkter:

Død uanset årsag
Ét dødsfald er rapporteret i esketamingruppen under TRANSFORM-2: en 41-årig mand døde som følge af en færdselsulykke ca. 28 timer efter sidste dosisadministration af esketamin (84 mg, dag 16). Ingen tidligere selvmordstanker eller -forsøg er registreret for patienten, som herudover heller ikke oplevede uønskede hændelser forud for færdselsulykken. Ingen dødsfald er registeret under SUSTAIN-1. Øvrige dødsfald: Ifølge EPAR'en er der på tværs af alle fase II- og III-studier registreret 4 dødsfald ud af 1.708 studiedeltagere (0,2 %) behandlet med esketamin. Udover nævnte dødsfald som følge af en færdselsulykke er der registeret en 60-årig mand med akut respiratorisk svigt og akut hjertesvigt 113 dage inde i studiet, en 55-årig kvinde med selvmord 188 dage inde i studiet og 12 dage efter sidste dosisadministration af esketamin (begge fra det ukontrollerede sikkerhedsstudie SUSTAIN-2/TRD3004), en 41-årig mand med selvmord 45 dage inde i studiet og 20 dage efter sidste dosisadministration af esketamin (fase II, TRD2003). Herudover er der registreret tre dødsfald i et on-going ukontrolleret studie (SUSTAIN-3/TRD3008) inkl. et selvmord, et

polytraume og et myokardieinfarkt. Til sammenligning er ingen dødsfald registreret for placebogruppen, hvori der indgår 486 studiedeltagere. Eftersom observationstiden ikke er den samme, kan opgivelser omkring patienter, der behandles med og uden esketamin, dog ikke sammenlignes én til én.

Alvorligt uønskede hændelser (SAE'er)
Ansøger opgør *severe treatment emergent adverse events* (TEAE's). De hyppigst forekommende i fase III-studierne inkluderer smagsforstyrrelser, svimmelhed (vertigo og dizziness), dissociation, sedering, kvalme, træthed, opkastning og døsighed (somnolens). EPAR'en angiver, at hovedparten af uønskede hændelser er milde til moderate, og de fleste ophører inden for et døgn (88,9 % i esketamingrupperne og 83,3 % i placebogrupperne sammenlagt for TRANSFORM-1 og -2). Bivirkninger (*adverse drug reactions*) til behandling med esketamin knytter sig primært til symptomer relateret til nervesystemet (64,1 %), psykiatriske symptomer (46,1 %) og mave-tarm-symtomer (32,2 %).

SUSTAIN-1 rapporterer følgende for *severe* TEAE'er:

- Induktionsfasen:10,1 % patienter i esketamingruppen (direkte indtrådte patienter)
- Optimeringsfasen: 7,5 % patienter i esketamingruppen (direkte indtrådte + overførte patienter)
- Vedligeholdelsesfasen: 7,9 % patienter i esketamingruppen vs. 4,1 % patienter som randomiseres til placebo (direkte indtrådte + overførte patienter)

Incidensen af severe TEAE'er i SUSTAIN-1 er tilnærmelsesvis lige frekvent i esketamingruppen i de forskellige studiefaser, men næsten halveres ved skift til placebo i vedligeholdelsesfasen.

Behandlingsophør grundet uønskede hændelser
Behandlingsophør som følge af TEAE'er optræder hyppigere i esketamingruppen (4,6 % vs. 1,4 % i TRANSFORM-1 og -2; 5,6 % vs. 3,1 % i TRANSFORM-3). Behandlingsophør som følge af TEAE'er specifikt for SUSTAIN-1 er som følger: Induktionsfasen: 22/437 (5 %) patienter i esketamingruppen (direkte indtrådte patienter); optimeringsfasen: 5/455 (1,1 %) patienter i esketamingruppen (direkte indtrådte + overførte patienter); vedligeholdelsesfasen: 4/152 (2,6 %) patienter i esketamingruppen vs. 3/145 (2,1 %) patienter som randomiseres til placebo (direkte indtrådte patienter + overførte patienter). Behandlingsophør skyldes forværring i depressive symptomer hos alle (7/7 patienter) samt yderligere for patienter, der fortsætter behandling med esketamin; angst og confusional state/forvirring (3/4 patienter). Ifølge sikkerhedsstudiet SUSTAIN-2/TRD3004 er den overordnede rate for behandlingsophør efter op til et års behandling med esketamin lig 9,5 %. De typiske TEAE'er, der ligger til grund for behandlingsopgør, er, på tværs af fase III-studierne og i rækkefølge af hyppighed: angst, depression, forhøjet blodtryk, svimmelhed, suicidal ideation, dissociation og kvalme.

Beskrivelse af udvalgte hændelser

Dissociative symptomer. På tværs af alle fase II- og fase III-studier er dissociative symptomer den hyppigst forekommende uønskede hændelse og optræder hos 12,5-27,6 % ved behandling med esketamin. Dissociative symptomer forekommer ikke i placebogruppen. Herudover observeres jf. EPAR'en dosisafhængige effekter af esketamin på dissociative symptomer.

Det almindelige forløb er en stigning i totalscoren målt med *Clinician Administred Dissociative States* (CADSS, range: 0-92 point), der typisk falder indenfor 1,5 time til baselineniveau. Den maksimale middelværdi på tværs af fase II- og fase III-studier overstiger ikke 10 point på CADSS, og i både TRANSFORM-studierne og SUSTAIN-1 observeres et gradvist fald over gentagen administration af esketamin. Symptomerne er af forbigående og milde til moderate af karakter. Intense dissociative symptomer beskrives hos færre end 4 % på tværs af studier og er ifølge EPAR'en ikke alvorlige. I SUSTAIN-2/TRD3004 udgør dissociative symptomer 1,9 % af alle severe TEAE'er og dermed den hyppigst forekommende severe TEAE.

Angst. Ifølge EPAR'en optræder angst (bredt defineret) i højere grad i esketamingruppen sammenlignet med placebogruppen hos voksne (9,0 % vs. 5,4 % i TRANSFORM-1 og -2, og 12/152 (7,9 %) vs. 5/145 (3,4 %) i vedligeholdelsesfasen af SUSTAIN-1). Det modsatte er tilfældet hos de ældre (esketamin overfor placebo, 4,2 % vs. 7,7 % i TRANFORM-3). Vurderet ud fra det ukontrollerede sikkerhedsstudie SUSTAIN-2/TRD3004 er der umiddelbart ikke en stigning i tilfælde af angst over tid. Studiet rapporterer angst hos 9,0 % i esketamingruppen. Ifølge EPAR'en er angst en bivirkning (*adverse drug reaction*) af esketamin. Svær og ekstreme angsttilfælde, der resulterer i panikanfald eller der leder til ophør af behandling, er under 2 % på tværs af alle studier.

Psykoselignende symptomer. Ingen psykose er observeret på tværs af fase II- og fase III-studierne, og generelt er de psykoselignende symptomer, der er registreret med *Brief Psychiatric rating Scale* (BPRS, range: 0-24 point), væk indenfor 1,5 time efter administration. Andelen af patienter med en totalscore ≥ 3 point på BPRS er væsentlig større i esketamingruppen sammenlignet med placebo i fase III-studierne (op til 28,1 % vs. 1,8 % i TRANSFORM-2/TRD3004), uden at det er tydeligt, hvilken klinisk betydning det har.

Selvmordstanker. Selvmordstanker er målt med C-SSRS *(Columbia-Suicide Severity Rating Scale*). I TRANSFORM-studierne er selvmordstanker ved baseline rapporteret hos 17,1 % til 25,3 % i esketamin-gruppen og 16,9 til 27,0 % i placebogruppen, og optræder derfor kun hos omtrent ¼ af patienterne ved indtræden i studierne. I alle fase III-studier er der ikke er nævneværdig forskel mellem grupperne i forhold til raten af mindst et tilfælde suicidal ideation for patienter, der **ikke** har selvmordstanker ved baseline (nul point i C-SSRS). I SUSTAIN-1 observeres højere C-SSRS score hos nogle patienter uden dog at nå skæregrænsen for selvmordstanker: Induktionsfasen: 42/362 (11,6 %) patienter med højere score (direkte indtrådte patienter); optimeringsfasen: 22/386 (5,7 %) patienter med højere score (direkte indtrådte + overførte patienter); vedligeholdelsesfasen: 3/125 (2,4 %) vs. 6/133 (4,5 %) patienter med højere score i hhv. esketamingruppen og patienter, der randomiseres til placebo (direkte indtrådte + overførte patienter). For patienter på tværs af fase III-studierne, der **ikke** har selvmordstanker ved baseline, men oplever forværring, er der ingen nævneværdig forskel mellem grupperne. For patienter på tværs af fase III-studierne, der **har en positiv score** for selvmordstanker ved baseline, udviser fem patienter (alle i esketamingruppen) selvmordsrelateret adfærd. I alt ti patienter i fase III-studierne er registeret med selvmordsrelateret adfærd (bestemt ved en score på 6-10 point, C-SSRS) - alle med en livslang historik for samme. I sikkerhedsstudiet SUSTAIN-2/TRD3004 rapporteres, at selvmordstanker optræder hos 5,2 % af patienterne. Alvorlige selvmordstanker udgør under 1 % af disse.

Forhøjet blodtryk beskrives i studierne som en forbigående (primært asymptomatisk) stigning i systolisk og diastolisk blodtryk, der forekommer umiddelbart efter administration af esketamin. Den maksimale mean ændring i blodtryk nås typisk indenfor 40 minutter efter administration og falder til udgangspunktet indenfor 1,5 time.

På tværs af fase III-studierne er observeret abnorme stigninger i blodtryk defineret som systolisk blodtryk ≥ 180 mm Hg og/eller diastolisk blodtryk ≥ 110 mm Hg (tilsvarende akut hypertension) hos op til 5 % i esketamingruppen (vs. 0,9 % i placebogruppen) med undtagelse af ældrepopulationen i TRANSFORM-3, hvor 11,1 % i esketamingruppen (vs. 6,2 % i placebogruppen) oplevede forbigående forhøjet blodtryk. På tværs af fase III-studierne er få tilfælde af blodtrykstigninger eller hurtig puls (takykardi) af alvorlig karakter og leder typisk ikke til behandlingsophør.

Mellem 90 %-100 % forhøjet blodtryk optræder på administrationsdagen i alle fase III-studier. Op mod 7 % af disse normaliseres ikke spontant samme dag. Ifølge en subgruppeanalyse optræder kardiovaskulære hændelser hyppigere blandt patienter med kardiovaskulære risikofaktorer. Ingen klinisk signifikante ændringer i EKG i hverken esketamin- eller placebogruppen optræder.

Esketamin er kontraindiceret hos patienter, hvor en stigning i blodtrykket eller intrakranielt tryk udgør en alvorlig risiko. Det gælder bl.a. patienter med aneurismal karsygdom (herunder i intrakranielle kar, kar i thorax eller aorta abdominalis eller perifere arterier), patienter der tidligere har haft hjerneblødning og patienter med nylig (inden for 6 uger) kardiovaskulær hændelse, herunder myokardieinfarkt.

Samlet vurdering af effektmålet uønskede hændelser:

Fagudvalget finder, at esketamin aggregeret ikke kan kategorises vedr. uønskede hændelser. Fagudvalget vurderer, at der ikke er betydende klinisk forskel mellem esketamin og placebo for andel af patienter, der oplever en SAE og andel, der ophører pga. uønskede hændelser indenfor 4 ugers behandling.

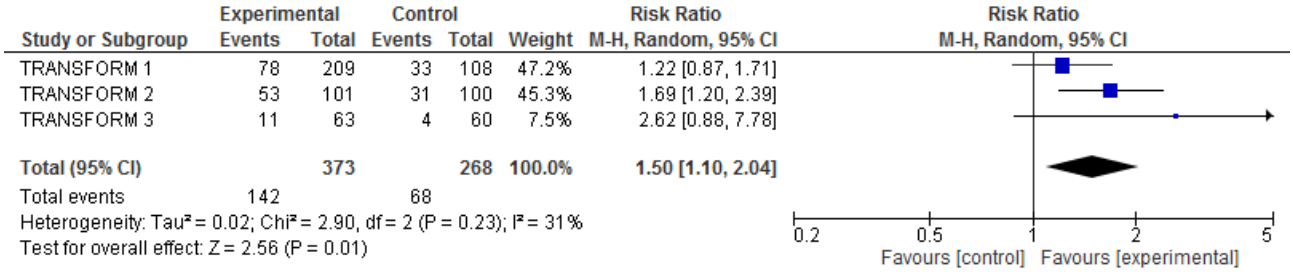
Fagudvalget vurderer, ud fra den narrative gennemgang af data fra studier og EPAR, at der ikke er nævneværdig øget behandlingsophør grundet uønskede hændelser eller øget forekomst af dødsfald efter behandling med esketamin sammenlignet med placebo. Efter dosering med esketamin skal blodtrykket revurderes efter ca. 40 minutter og efterfølgende, som det findes klinisk relevant. På grund af muligheden for sedation, dissociation og forhøjet blodtryk skal patienterne overvåges af en sundhedsperson, indtil patienten anses for at være klinisk stabil og parat til at forlade klinikken [18]. Fagudvalget fremhæver, at dissociative symptomer kan variere betydeligt i deres sværhedsgrad og finder, at graden eller omfanget af de dissociative symptomer er utilstrækkeligt beskrevet for studiepopulationerne. Selvom EPAR'en angiver, at færre end 4 % af de dissociative tilfælde har en intensiv karakter, ville detaljerede symptombilleder have været at foretrække. Fagudvalget udtrykker derfor generelt bekymring for dissociative symptomer, men også for blodtryksstigninger forbundet med anvendelse af esketamin. Især lægges vægt på, at bivirkninger ved længere tids behandling endnu ikke er tilstrækkeligt belyst. Fagudvalget finder det sandsynligt, at esketamin kan vise sig at have lignende uønskede effekter, som det ses fra studier med ketamin, heriblandt misbrugspotentiale, langtidseffekter på kognition og ketaminassocieret uropati [19,20].

Remission (kritisk)

Effektmålet *remission* ønskes opgjort som andel, der reducerer scoren til ≤ 11 point på MADRS (mindste klinisk relevante forskel: 15 %-point). Cut-off for remission i studierne er en MADRAS score ≤ 12. Fagudvalget vurderer, at denne forskel i cut-off ikke vil påvirke effektestimaterne væsentligt.

Måletidspunkt 4 uger, remission:

Resultat fra metaanalysen efter 4 ugers behandling viser, at andelen af patienter, der opnår remission på tværs af de tre studier, er 38 % (142/373) hos patienter, der modtog esketamin, sammenlignet med 25 % (68/268) hos patienter, der modtog placebo og heraf en beregnet relativ forskel på RR 1,50 [1,10; 2,04] til fordel for esketamin (figur 5.2e).



Figur 5.2e. Remission. Forest plot over relativ risiko (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin.

Baseret på den *relative effektforskel* kategoriseres esketamin foreløbigt med merværdi af ukendt størrelse vedr. remission efter 4 ugers behandling.

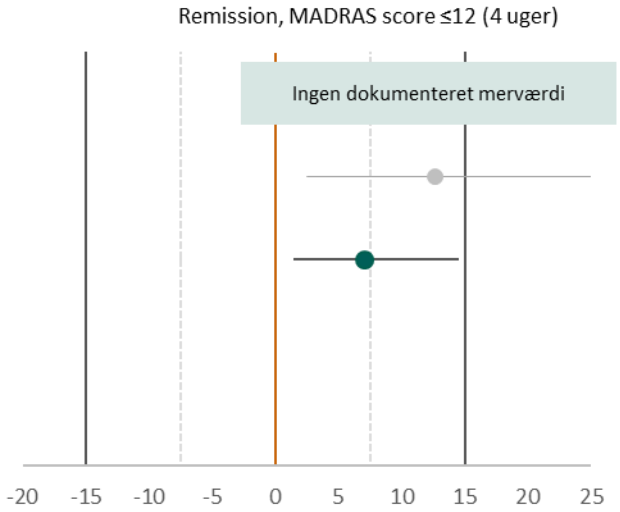
Ansøger har indsendt data for ”observed cases” fremfor ITT-populationen. Det vil sige, at missing data ikke er imputeret, hvilket også er beskrevet i Medicinrådets metodevejledning. Denne fremgangsmåde kan dog i nogle tilfælde føre til en uhensigtsmæssig favorisering af behandlingsarme med mest missing data; i dette tilfælde interventionsarmen. Hvad angår effektmålet *remission* vurderer fagudvalget, at det er relevant med en sensitivitetsanalyse, hvor man antager, at patienter som af forskellige årsager er udgået af studiet, ikke er i fuld remission. I sensitivitetsanalysen er der observeret tilsvarende resultat som i hovedanalysen (RR = 1,44 [1,05; 1,97]).

Remissionsraten for den danske population med behandlingsresistent depression for komparator er i protokollen sat til at være 14 %. Ved beregning via den relative forskel på RR 1,50 [1,10; 2,04] bliver den absolutte effektforskel 7,0 %-point [1,4;14,56] (NNT=14).

Ansøger har anvendt en hændelsesrate baseret på remissionsraterne i TRANSFORM-studierne. Fagudvalget vurderer, at remissionsraterne er bemærkelsesværdig høje. Til sammenligning, hvis man anvender remissionsraten fra studierne på 25,4 %, er den absolutte effektforskel 12,7 %-point [2,5; 26,4] til fordel for esketamin.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effektforskel) end på den mindste klinisk relevante forskel. Samtidig inkluderer konfidensintervallet ikke effektstørrelser med en negativ værdi. Derfor er den foreløbige klinisk relevante værdi af esketamin ingen dokumenteret merværdi vedr. remission ved 4 uger.

Den absolutte forskel er afbildet i figur 5.2f nedenfor.



Figur 5.2f. Punktestimat og 95 % konfidensinterval for den absolutte forskel for remission ved 4 uger. Det grønne estimat angiver effektforskellen baseret på hændelsesraten i protokollen, mens det grå estimat angiver effektforskellen baseret på hændelsesraten fra studierne. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Måletidspunkt 6 måneder, remission:
Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres ved 6 måneder. Data fra SUSTAIN-1 gennemgås narrativt i afsnit 5.2.1.

Samlet vurdering af effektmålet remission:

Fagudvalget vurderer, at esketamin aggregeret **ikke kan kategorises** efter Medicinrådets metoder vedr. remission, da den længerevarende effekt ikke er tilstrækkeligt belyst, samt at populationerne adskiller sig i en grad, der medfører usikkerhed om, hvorvidt de rapporterede estimater kan overføres til danske patienter.

Fagudvalget vurderer, at den absolutte forskel i remissionsraterne ved 4 uger på 7,0 %-point har værdi for patienter med behandlingsresistent depression, selvom effekten er mindre end den mindste klinisk relevante forskel på 15 %-point. Fagudvalget lægger især vægt på, at remission er svært at opnå hos patienter med behandlingsresistent depression, der lever med en alvorlig, livsforringende kronisk sygdom uden mange behandlingsmuligheder.

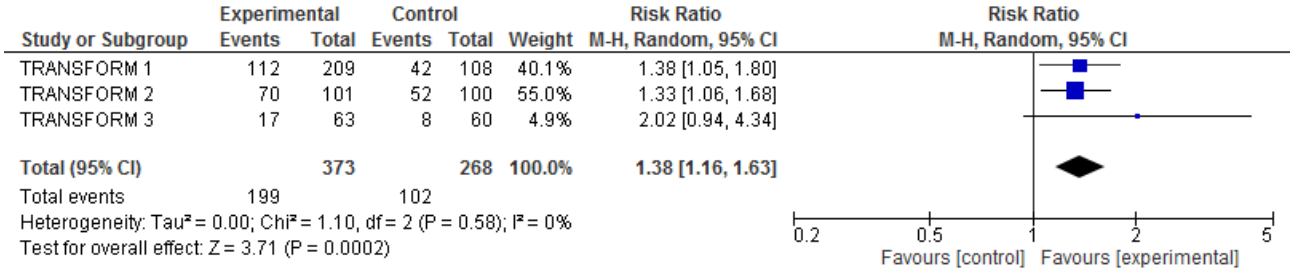
Effektmålet *remission* i SUSTAIN-1 kan ikke vurderes, da disse data ikke er opgjort separat for placeboarmen. Fagudvalget vurderer, at effekten ved 6 måneder ikke kan kategoriseres, da der ikke er tilstrækkeligt datagrundlag.

Se den samlede vurdering af data fra SUSTAIN-1 studiet i afsnit *"Respons"* herunder.

Respons (vigtig)

Måletidspunkt 4 uger, respons:

Resultat fra metaanalysen efter 4 ugers behandling viser, at andelen af patienter, der opnår et respons på tværs af de tre studier, er 53 % (199/373) hos patienter, der modtog esketamin, sammenlignet med 38 % (102/268) hos patienter, der modtog placebo og heraf en beregnet relativ forskel på RR 1,38 [1,16; 1,63] til fordel for esketamin (figur 5.2g).



Figur 5.2g. Respons. Forest plot over relativ risiko (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin.

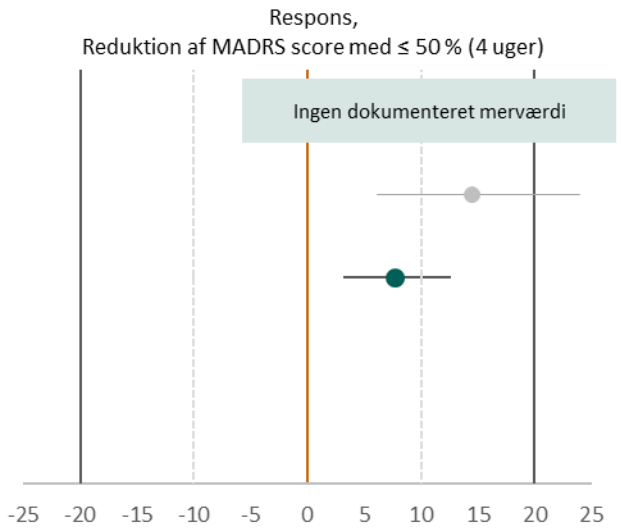
Baseret på den *relative effektforskel* kategoriseres esketamin foreløbigt med moderat merværdi vedr. respons efter 4 ugers behandling.

Ansøger har indsendt data for "observed cases" fremfor ITT-populationen. Det vil sige, at missing data ikke er imputeret, hvilket også er beskrevet i Medicinrådets metodevejledning. Denne fremgangsmåde kan dog i nogle tilfælde føre til en uhensigtsmæssig favorisering af behandlingsarme med mest missing data; i dette tilfælde interventionsarmen. Hvad angår effektmålet *respons*, vurderer fagudvalget, at det er relevant med en sensitivitetsanalyse, hvor man antager, at patienter, som af forskellige årsager er udgået af studiet, ikke er i respons. I sensitivitetsanalysen er der observeret samme resultat som i hovedanalysen (RR = 1,36 [1,14; 1,62]).

Responsraten for den danske population med behandlingsresistent depression for komparator er i protokollen sat til at være 20 %. Ved anvendelse af responsrate på 20 % er den absolutte effekt 7,6 %-point [3,2;12,6].

Ansøger har anvendt en hændelsesrate baseret på responsraterne i studierne. Fagudvalget vurderer, at responsraterne er bemærkelsesværdig høje. Til sammenligning, hvis man anvender responsraten fra studierne på 38,1 %, er den absolutte effektforskel 14,5 %-point [6,1; 24,0] til fordel for esketamin.

Den absolutte forskel er afbildet i figur 5.2h nedenfor.



Figur 5.2h. Punktestimat og 95 % konfidensinterval for den absolutte forskel for respons ved 4 uger. Det grønne estimat angiver effektforskellen baseret på hændelsesraten i protokollen, mens det grå estimat angiver effektforskellen baseret på hændelsesraten fra studierne. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effektforskel) end på den mindste klinisk relevante forskel. Samtidig inkluderer konfidensintervallet ikke effektstørrelser med en negativ værdi. Derfor er den foreløbige værdi af esketamin ingen dokumenteret merværdi vedr. respons ved 4 uger.

Måletidspunkt 6 måneder, respons:
Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres ved 6 måneder. Data fra SUSTAIN-1 gennemgås narrativt i afsnit 5.2.1.

Samlet vurdering af effektmålet respons:

Fagudvalget vurderer, at esketamin aggregeret **ikke kan kategorises** efter Medicinrådets metoder vedr. respons, idet den længerevarende effekt ikke er tilstrækkeligt belyst, samt at populationerne adskiller sig i en grad, der medfører usikkerhed om, hvorvidt de rapporterede estimater kan overføres til danske patienter.

Fagudvalget vurderer, at den absolutte forskel på 7,6 %-point svarende til NNT på 13 i responsraterne ved 4 uger ikke er klinisk relevant. Fagudvalget lægger især vægt på, at behandlingsrespons sjældnere er et udtryk for en blivende effekt hos patienter med behandlingsresistent depression.

Fagudvalget vurderer, at effekten ved 6 måneder ikke kan kategoriseres, da der ikke er tilstrækkeligt datagrundlag.

Fagudvalget vurderer, at data ved 16 uger støtter konklusionen for data ved 4 uger. Data viser, at der hos patienter, der opnår respons med esketamin ved 4 uger, er et vedvarende respons ved uge 16 for ca. 2/3 af

patienterne. Denne andel er tilsvarende til den andel, der har vedvarende respons fra uge 4-16 i placeboarmen. Der ses altså ikke en yderligere mereffekt af esketamin fra uge 4-16 hos patienter, som har oplevet remission eller respons i studiernes induktionsfase (op til uge 4) og heller ikke et øget tilbagefald. Data kan ikke opdeles i stabil remission og stabilt respons, da disse data ikke er opgjort separat for placeboarmen.

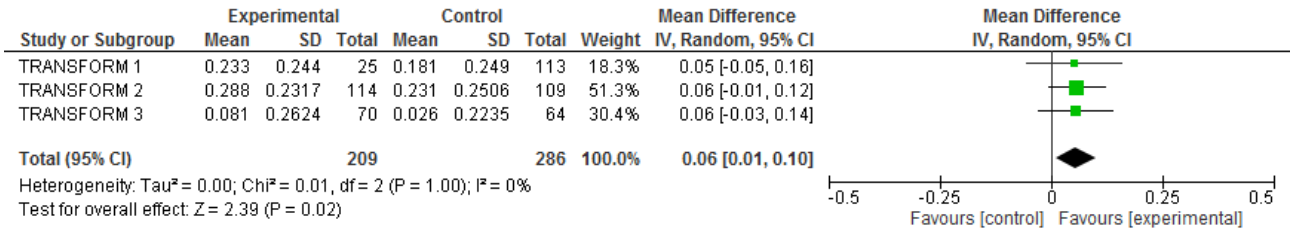
Fagudvalget vurderer, at behandlingen ikke bør seponeres efter 16 uger hos patienter, der har opnået stabilt respons eller stabil remission med esketaminbehandling, idet at der vil være større risiko for at få et tilbagefald. Fagudvalget kan på foreliggende datagrundlag ikke vurdere, hvornår behandling med esketamin kan forsøges seponeret.

Livskvalitet (vigtig)

Måletidspunkt 4 uger, livskvalitet:

Jævnfør protokollen er effektmålet *livskvalitet* opgjort som den gennemsnitlig ændring fra baseline på EQ-5D (mindste klinisk relevante forskel: 0,07 point). Der er leveret data fra de tre TRANSFORM-studier. Hændelsesraten til beregning af den absolutte forskel er hentet fra studierne.

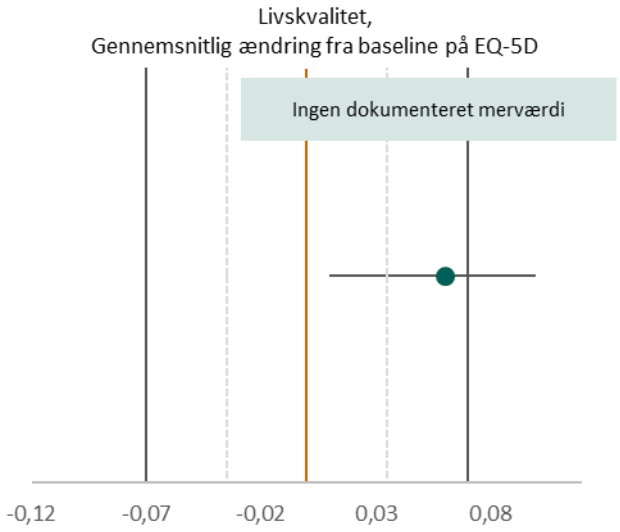
Livskvalitet ved 4 uger:



Figur 5.2i. Livskvalitet. Forest plot over absolutte forskelle (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel (figur 5.2i). Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effektforskel) end på den mindste klinisk relevante forskel. Samtidig inkluderer konfidensintervallet ikke effektstørrelser med en negativ værdi. Derfor er den foreløbige værdi af esketamin ingen dokumenteret merværdi vedr. livskvalitet ved 4 uger.

Den absolutte forskel er afbildet i figur 5.2j nedenfor.



Figur 5.2j. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet (EQ-5D index score) ved 4 uger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Måletidspunkt 6 måneder, livskvalitet:
Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres ved 6 måneder. Livkvalitet i SUSTAIN-1 er målt som ændring fra baseline i vedligeholdelsesfasen til det tidspunkt, hvor den enkelte patient afslutter studiet. Tidsperioden fra baseline til afslutning kan være forskellig fra patient til patient og kan være defineret af tilbagefald, studieafslutning eller ophør af andre årsager. Fagudvalget vurderer derfor (som EMA), at dette livskvalitetsdata ikke bør indgå i vurderingen, da det usikkert, og at der er risiko for introduktion af bias ved at have forskellige måletidspunkter, hvoraf nogle er influeret af sygdomstilbagefald.

Samlet vurdering af effektmålet livskvalitet:

Fagudvalget vurderer, at esketamin aggregeret **ikke kan kategorises** efter Medicinrådets metoder vedr. livskvalitet, idet den længerevarende effekt ikke er tilstrækkeligt belyst. Ved 4 uger har esketamin ingen dokumenteret merværdi vedr. livskvalitet.

Vedvarende effekter til tiden 6 måneder (gennemgang af SUSTAIN-1)

SUSTAIN-1 er et relapsstudie, som måler på tid til relaps ved fortsat behandling med esketamin og det SSRI/SNRI, som er blevet initiereret ved påstart med esketamin eller ophør med behandling (skift til placebo) efter 16 ugers behandling. Der kan fra dette studie ligeledes findes information omkring, hvor stor en andel af patienter, som er i stabil remission eller har stabilt respons efter 16 ugers behandling (4 ugers induktion og 12 ugers optimering).

Stabil remission defineres som MADRS score ≤ 12 i ≥ 3 af de seneste 4 uger. Stabilt respons defineres i studierne som ≥ 50 procent reduktion i MADRS samlede score fra baseline til hver måling i de sidste 2 uger af optimeringsfasen, men uden at opfylde kriterierne for stabil remission. Baseline defineres som dag 1 af induktionsfasen før den første intranasale dosis af esketamin. Relaps i studierne defineres som total MADRS score ≥ 22 ved to konsekutive målinger adskilt med 5-15 dage og/eller hospitalisering for forværring i depressive symptomer eller enhver anden klinisk relevant begivenhed, der indikerer relaps af depressiv sygdom såsom selvmordsforsøg eller fuldbyrdet selvmord eller hospitalisering som følge af selvmordsforebyggelse.

Tidshorisonten for den enkelte patient er tid fra randomisering til det første relaps i vedligeholdelsesfasen (op til 92 uger).

Studiedesign

I SUSTAIN-1 indgår patienter, som overføres fra TRANSFORM-1 og -2, og patienter som træder direkte ind i SUSTAIN-1 studiet. Studiet består af flere faser.

Screeningfase 4 uger og induktionsfase 4 uger: Direkte indtrædende patienter gennemgår først en screeningsfase på 4 uger, som er tilsvarende til screeningsfasen i TRANSFORM-studierne. Patienter, som opfylder alle inklusionskriterier, går herefter videre til en open-label induktionsfase, som består af 4 ugers esketaminbehandling med fleksibel dosering 2 gange om ugen plus antidepressiva (tilsvarende til esketaminbehandling i TRANSFORM-2).

Optimeringsfase 12 uger: Patienter fra TRANSFORM-1, -2 og direkte indtrædende patienter i SUSTAIN-1, som har respons eller er i remission efter 4 ugers induktionsbehandling, går herefter videre til optimeringsfasen. Patienter, som overføres fra TRANSFORM 1-2, beholder deres behandling fra TRANSFORM, og blindingen opretholdes. Alle patienters dosis af esketamin fra induktionsfasen beholdes, men doseringsfrekvensen nedtrappes til 1 gang ugentligt i de første 4 uger, herefter individuelt tilpasset til én gang ugentlig eller hver anden uge. Ved slutningen af denne fase har esketaminbehandlede patienter (både direkte indtrædende og overførte patienter) gennemgået 16 ugers behandling med esketamin og antidepressiva. Tilsvarende har de overførte placebobehandlede patienter fra TRANSFORM gennemgået 16 ugers behandling med placebo og antidepressiva.

Vedligeholdelsesfase: Esketaminbehandlede patienter, som var i stabil remission eller opnåede stabil respons uden remission ved slutningen af optimeringsfasen, blev i denne fase randomiseret til at fortsætte esketaminbehandling eller overgå til placebo. Patienternes dosis og doseringsfrekvens beholdes fra foregående fase og ændres ikke i denne fase. Patienter fra placeboarmene i TRANSFORM-1 og -2, som var i stabil remission eller respons, fortsatte deres behandling. Disse patienter indgik ikke i efterfølgende analyser i SUSTAIN-1-studiet, men indgik i "safety".

I vedligeholdelsesfasen var det primære effektmål *tid til relaps*. Data blev opgjort, når et tilstrækkeligt antal tilbagefald var observeret, baseret på statistiske styrkeberegninger

Kvalitativ gennemgang af resultater fra SUSTAIN-1, der omfatter effektmålene remission og respons

TRANSFORM-1:

- Esketaminbehandlede patienter:
  - 78/233 patienter var i remission efter 4 uger. 112/233 havde respons efter 4 uger (48 %).
  - Efter 16 uger er der 46 stabile remittere (20 %). Efter 16 uger var der 25 stabile respondere (11 %).
  - 112 overføres til SUSTAIN-1 (46 + 25)/112 = 63 % bevarer et respons.

- Placebo:
  - 33/113 var i remission efter 4 uger. 42/113 havde respons efter 4 uger (37 %).
  - Efter 16 uger var der samlet 22/113 i stabil remission eller respons (19 %).
  - 38 overføres til SUSTAIN-1 22/38 = 58 % bevarer et respons.

TRANSFORM 2:

- Esketaminbehandlede patienter:
  - 53/116 patienter var i remission efter 4 uger. 70/116 havde respons efter 4 uger (60 %).

- Efter 16 uger er der 20 stabile remittere (17 %). Efter 16 uger var der 26 stabile respondere (22 %).
- 70 overføres til SUSTAIN-1 (20 + 26)/70 = 66 % bevarer et respons.

- Placebo:
  - 31/111 var i remission efter 4 uger. 52/111 havde respons efter 4 uger (47 %).
  - Efter 16 uger var der samlet 33/111 i stabil remission eller respons (30 %).
  - 48 overføres til SUSTAIN-1 33/48 = 69 % bevarer et respons.

SUSTAIN-1 direkte indtræden:

- Esketaminbehandlede patienter:
  - 273/437 havde respons efter 4 uger.
  - Efter 16 uger er der 110 stabile remittere (25 %). Efter 16 uger var der 73 stabile respondere (17 %).
  - 273 fortsætter i SUSTAIN-1 (110 + 73)/273 = 67 % bevarer et respons.

Optimeringsfase 4-16 uger:

I alle 3 studier (TRANSFORM-1, -2 og SUSTAIN-1 direkte indtræden) var der hhv. 48 %, 60 % og 62 %, der fik et respons på esketamin ved 4 uger. Af patienter som blev behandlet med esketamin og som fik et respons ved 4 uger, var der forsat et respons for 63-67 % af patienterne ved 16 uger.

Der var i TRANSFORM-1 og -2 færre patienter i placeboarmene (37 % og 47 %), der fik respons til tiden 4 uger i forhold til esketaminarmene (48 % og 60 %). Af patienter, som fik placebo, og som fik et respons ved 4 uger, var der fortsat en effekt for hhv. 58 % og 69 % af patienterne i TRANSFORM-1 og -2 ved 16 uger.

Dermed kan man se, at der fortsat er flere patienter, som har respons med esketaminbehandling end ved placebo ved 16 uger, og at der stadig er et respons for 63-67 % af patienterne. Samtidig kan det dog ses, at hvis man har opnået en effekt ved 4 ugers placebobehandling, er der fortsat respons for en tilsvarende andel ved 16 uger (58-69 %). Ved sammenligning af esketamin overfor placebo fra 4 til 16 uger ses altså en vedvarende effekt, som er i omtrentlig samme relative størrelsesorden, som observeres ved 4 uger. Dette tyder på, at der ikke er nogen mereffekt af esketamin overfor placebo fra 4 til 16 uger.

Vedligeholdelsesfase:

I vedligeholdelsesfasen randomiseres patienter i stabil remission eller stabilt respons til at fortsætte esketamin eller overgå til placebo, og der måles på tid til relaps. Både for patienter i stabil remission eller i stabilt respons ses flere tilfælde af relaps hos patienter, som stopper esketaminbehandling (remission HR: 0,49; 95 % CI, 0,29-0,84; respons HR: 0,30; 95 % CI, 0,16-0,55).

Den vedvarende effekt af esketamin kunne ifølge fagudvalget bedst have været belyst, hvis ansøger havde fortsat TRANSFORM-studierne i længere tid og med opfølgning efter endt behandling. Sådanne studier ville også kunne belyse omfanget af alvorlige uønskede hændelser efter længerevarende brug af esketamin, misbrugspotentialet og eventuelle forventelige udfordringer med seponering i relation til en ægte placebogruppe. Fagudvalget mener, at observationelle data for effekter af esketamin uden en placebokontrol kan være særligt skævvridende, da de høje hændelsesrater i kontrolgrupperne fra TRANSFORM-1, -2 og -3 og SUSTAIN-1 indikerer placebo- og noceboeffekter af behandling.

6 Andre overvejelser

6.1 Behandlingslængde

Der er endnu uvished om, hvor lang behandlingsvarigheden med esketamin bliver. Evidensen for terapeutiske fordele skal evalueres ved afslutningen af induktionsfasen (4 uger) for at afgøre behovet for fortsat behandling. Ansøger angiver en forventet behandlingslængde med esketamin på 9 måneder (ca. 36 uger) efter induktionsfasen (4 uger). Ved forbedring af depressive symptomer anbefaler produktresuméet fortsat behandling i minimum 6 måneder.

Behandling med antidepressiva er ofte mangeårig eller livslang, og det er uklart, om behandling med esketamin vil kurere patienterne, så de ikke længere har behov for hverken esketamin eller antidepressiva. En ny depressiv episode defineres som tilbagevendende depression efter 6 måneder med stabil remission. Fagudvalget vurderer, at der er stor risiko for nye episoder hos patienterne, der i givet fald vil skulle behandles på ny.

Fagudvalget kan ikke vurdere, hvornår behandling med esketamin kan forsøges seponeret, eller om der vil være særlige udfordringer i denne forbindelse.

Fagudvalget vurderer, at det er positivt, at man allerede efter 4 uger kan vurdere, om der har været den ønskede effekt af behandling med esketamin. Dette betyder, at omkostningerne til patienter uden effekt af esketamin vil være begrænset til en kort periode, herunder eventuelle hospitals- og patientomkostninger.

6.2 Administration af esketamin og adhærens til behandling

Esketamin skal selvadministreres under supervision af sundhedsfagligt personale, hvilket betyder, at patienter fysisk skal indfinde sig på den klinisk eller afdeling, der er godkendt til at foretage behandlingen. Besøgene vil skulle aflægges lige så frekvent, som esketamin skal administreres (fleksibelt, i starten to gange ugentligt og senere ugentligt eller hver anden uge) og i lige så lang tid, behandling varer (ifølge den endelige ansøgning i snit 40 uger). Patienterne skal monitoreres i mindst en time per besøg. Ansøger har tilkendegivet, at der i de studier, der foreligger, ikke er registreret problemer med adhærens til behandling i de tilfælde, hvor patienterne har haft et behandlingsrespons. Det fremhæves herudover af ansøger, at det kontrollerede behandlingsforløb vil have karakter af monitorering, så der kan gøres de nødvendige tiltag for, at patienterne fortsætter i behandling. Fagudvalget vurderer det sandsynligt, at nogle patienter, der ikke godkendes til behandling med esketamin, vil forsøge at selvmedicinere med ketamin eller opsøge private klinikker i Danmark eller udlandet, hvor der behandles med ketamin.

6.3 Misbrugspotentiale

Ifølge EPAR'en har esketamin samme misbrugspotentiale som ketamin. Behandling af behandlingsresistent depression med esketamin, som estimeret af ansøger, svarer til et kronisk brug af et dissociativt medikament. Fagudvalget fremhæver derfor, at der skal være opmærksomhed omkring, hvilke utilsigtede effekter der potentielt kan forekomme ved kronisk/vedvarende brug inkl. risiko for udvikling af misbrug (af esketamin eller ketamin).

6.4 Tilfælde af mani under behandling og opfølgning

To tilfælde af mani er registreret på tværs af fase II- og fase III-studierne. Begge er forbigående. Der er ikke observeret tilfælde af hypomani. Det er uklart, hvordan patienter med en udiagnostiseret bipolær lidelse vil reagere på esketaminbehandling, lige såvel som det er uklart, om et vedvarene brug af esketamin kan udløse maniske episoder på sigt.

6.5 Fluktuation i remission og respons-score under behandling og opfølgning

Der er ikke leveret tilstrækkelig information til at belyse fluktuationer i remission- og respons-score. Ansøger har angivet data med *last observation carried forward*, som ikke anses at være retvisende for den efterspurgte information.

7 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af esketamin i kombination med SSRI eller SNRI sammenlignet med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode, **ikke kan kategoriseres** efter Medicinrådets metoder. Baggrunden herfor er, at den længerevarende effekt ikke er tilstrækkeligt belyst. Samtidig er det data, som ligger til grund for kategoriseringen baseret på selekterede patienter, som ikke afspejler dansk klinisk praksis. Fagudvalget vurderer, at esketamin i kombination med SSRI eller SNRI kan have en gavnlig kortidseffekt hos nogle patienter. Antallet af patienter, der opnår denne effekt i sammenligning med SSRI eller SNRI alene, er dog relativt beskedent vurderet ud fra datagrundlaget. Hos en andel med umiddelbar effekt af behandlingen ser det ud til, at effekten er vedvarende. Der er dog usikkerhed omkring effekten af at stoppe esketamin efter længere tids behandling. Det er ikke undersøgt, om patienter, som har opnået en forbedring af deres symptomer, kan forvente, at denne effekt er vedvarende efter seponering af esketamin. Fagudvalget udtrykker samtidig bekymring for længerevarende og irreversible bivirkninger, som endnu ikke er tilstrækkeligt belyst samt det misbrugspotentiale, som er forbundet med anvendelse af lægemidlet.

Den samlede kategori for lægemidlet og kvaliteten af den samlede evidens fremgår af tabel 4.

Samlet set vurderer fagudvalget, at esketamin ikke vil være et relevant behandlingsvalg for hele gruppen af patienter med behandlingsresistent depression ud fra den anvendte definition. Den gruppe, som fagudvalget vurderer, esketamin er relevant til, er en særligt sårbar patientgruppe, som ikke er tilstrækkeligt repræsenteret i studierne. Der er dog patienter, som har prøvet adskillige alternativer som TCA, monoaminoxidasehæmmere (Isokarboxazid = Marplan), augmentering med lithium, quetiapin eller psykostimulantia, ECT og hvor det derfor kan være relevant at forsøge med esketamin. Disse patienter har stort behov for alternative behandlingsmuligheder, og fagudvalget vurderer, at det hos disse patienter vil det være relevant at gøre et forsøg med esketamin. Fagudvalget vurderer, at behandlingen forudsætter, at patienten er grundigt udredt forinden bl.a. mht. flg. punkter:

- Er diagnosen korrekt?
- Foreligger der uopdaget misbrug af alkohol eller euforisende stoffer?
- Er relevante somatiske sygdomme, der kan udløse eller vedligeholde depressive symptomer, udelukket?
- Har man udelukket bivirkninger ved andre medikamenter, som patienten modtager?
- Har kompliance været sikret i tilstrækkelig grad ved de hidtidige behandlingsforsøg?
- Har man udelukket farmakokinetiske interaktioner og genetiske polymorfismer?

Herudover bør følgende behandlinger være forsøgt (eller er udelukket):

- kognitiv terapi eller anden relevant form for psykoterapi
- andre strategier (augmentering med litium eller antipsykotika)
- ECT
- isocarboxazid

Ved alvorlige bivirkninger eller manglende respons efter 4 uger bør lægemidlet seponeres.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og fagudvalget har derfor ikke taget stilling til en foreløbig placering af lægemidlet.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende behandlingsresistent depression hos voksne

Formand	**Indstillet af**
Poul Videbech Professor, overlæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
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Simon Hjerrild Overlæge, klinisk lektor, ph.d.	Region Midtjylland
Claus Havregaard Sørensen Overlæge	Region Syddanmark
Dénes Langyel Overlæge	Region Sjælland
Lars Vedel Kessing Professor, overlæge	Region Hovedstaden
Louise Wulff Patient/patientrepræsentant	Danske Patienter
Leni Grundtvig Nielsen Patient/patientrepræsentant	Danske Patienter
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Jonas Meile Speciallæge i almen medicin	Dansk Selskab for Almen Medicin
Klaus Martiny Professor, overlæge	Inviteret af formanden
Martin Balslev Jørgensen Professor, overlæge	Inviteret af formanden

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11 Versionslog

Version	**Dato**	**Ændring**
1.0	22. juni 2020	Godkendt af Medicinrådet.

12 Bilag 1: Evidensens kvalitet

12.1 Cochrane, Risk of Bias

Vurdering af risiko for bias ved Cochranes RoB 2.0 assessment tool.

	Risiko for bias i randomiserings-processen	**Risiko for bias grundet afvigelser fra tilsigtet intervention** **(effekt af tildeling til intervention)**	**Manglende data for effektmål**	**Risiko for bias ved indsamlin-gen af data**	**Risiko for bias ved udvælgelse af resultater der rapporteres**	**Overordnet risiko for bias**
TRANSFORM-1	lav	forbehold	forbehold	forbehold	lav	forbehold
TRANSFORM-2	lav	forbehold	lav	forbehold	lav	forbehold
TRANSFORM-3	lav	forbehold	lav	forbehold	lav	forbehold

12.2 GRADE-profil

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**esketamin**	**komparator**	**Relativ [95 % CI]**	**Absolut 95 % CI]**		
Alvorlige uønskede hændelser (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Alvorlig[c]	Ingen	6/418 (1,4 %)	3/287 (1,0 %)	RR: 1,40 [0,37; 5,29]	0,4 %-point [-0,63; 4,39]	⊕◯◯◯ MEGET LAV	KRITISK
Behandlingsophør grundet uønskede hændelser (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Alvorlig[c]	Ingen	20/418 (4,8 %)	5/287 (1,7 %)	RR: 2,60 [0,97; 6,99]	2,72 %-point [0,05; 10,18]	⊕◯◯◯ MEGET LAV	KRITISK
Remission, MADRAS score ≤12 (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ikke alvorlig	Ingen	142/373 (38 %)	68/268 (25 %)	RR: 1,50 [1,10; 2,04]	7,0 %-point [1,4; 14,6]	⊕⊕◯◯ LAV	KRITISK
Respons, andel der reducerer MADRS score med 50 % eller mere (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ikke alvorlig	Ingen	199/373 (53 %)	102/268 (38 %)	RR: 1,38 [1,16; 1,63]	7,6 %-point [3,2; 12,6]	⊕⊕◯◯ LAV	VIGTIGT
Livskvalitet, gennemsnitlig ændring fra baseline på EQ-5D index score (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Alvorlig[d]	Ingen	209	286		0,06 point [0,01; 0,10]	⊕◯◯◯ MEGET LAV	VIGTIGT

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio

a. Der er nedgraderet for RoB, idet der er fare for afblinding i studiet grundet esketamins dissociative effekter.

b. Der er betydelig indirekthed i forhold til den danske population pga. studiernes in-/eksklusion kriterier

c. Der nedgraderes for evidensens kvalitet ét niveau pga. unøjagtighed, da usikkerheden om det relative effektestimat kan føre til forskellige konklusioner.

d. Der er nedgraderet ét niveau, da kriteriet for optimal information size ikke er opfyldt.

Application for the assessment of clinically added value of Spravato® (esketamine) for treatment resistant depression in adults

Contents

1 Basic information

Table 1 Contact information

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Table 2 Overview of the pharmaceutical (1)

Proprietary name	SPRAVATO®
Generic name	Esketamine
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 DK-3460 Birkerød
ATC code	N06AX27
Pharmacotherapeutic group	Psychoanaleptic, Other antidepressants
Active substance(s)	Esketamine hydrochloride
Pharmaceutical form(s)	28 mg Nasal Spray, solution
Mechanism of action	Esketamine is the S-enantiomer of racemic ketamine. It is a non-selective, non-competitive, antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling which may contribute to the restoration of synaptic function in these brain regions involved with the regulation of mood and emotional behaviour. Restoration of dopaminergic neurotransmission in brain regions involved in the reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response.
Dosage regimen	The dose recommendations for Spravato® are shown in Table A and Table B (adults ≥65 years). It is recommended to maintain the dose the patient receives at the end of the induction phase in the maintenance phase. Dose adjustments should be made based on efficacy and tolerability to the previous dose. During the

<table>
<tr><td></td><td>maintenance phase, Spravato® dosing should be individualised to the lowest frequency to maintain remission/response.

<table>
<tr><th colspan="2">Table A: Recommended dosing for SPRAVATO® in adults <65 years</th></tr>
<tr><th>Induction phase*</th><th>Maintenance phase**</th></tr>
<tr><td><u>Week 1-4:</u>
Starting day 1 dose: 56 mg
Subsequent doses: 56 mg or 84 mg twice a week</td><td><u>Week 5-8:</u>
56 mg or 84 mg once weekly

<u>From week 9:</u>
56 mg or 84 mg every 2 weeks or once weekly</td></tr>
</table>

<table>
<tr><th colspan="2">Table B: Recommended dosing for SPRAVATO® in adults ≥65 years</th></tr>
<tr><th>Induction phase*</th><th>Maintenance phase**</th></tr>
<tr><td><u>Week 1-4:</u>
Starting day 1 dose: 28 mg
Subsequent doses: 28 mg, 56 mg or 84 mg twice a week, all dose changes should be in 28 mg increments</td><td><u>Week 5-8:</u>
28 mg, 56 mg or 84 mg once weekly, all dose changes should be in 28 mg increments

<u>From week 9:</u>
28 mg, 56 mg or 84 mg every 2 weeks or once weekly, all dose changes should be in 28 mg increments</td></tr>
</table>

* Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment
** The need for continued treatment should be reexamined periodically</td></tr>
<tr><td>Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)</td><td>SPRAVATO®, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode</td></tr>
<tr><td>Other approved therapeutic indications</td><td>No</td></tr>
<tr><td>Will dispensing be restricted to hospitals?</td><td>Yes . dispensing code BEGR</td></tr>
<tr><td>Combination therapy and/or co-medication</td><td>SPRAVATO®, in combination with a SSRI or SNRI</td></tr>
<tr><td>Packaging – types, sizes/number of units, and concentrations</td><td><u>SPRAVATO® (esketamine) 28 mg Dose Kit*</u>
1x28 mg Nasal Spray Device, 1 Device, 28 mg esketamine

<u>SPRAVATO® (esketamine) 56 mg Dose Kit*</u>
2x28 mg Nasal Spray Devices, 2 Devices, 56 mg esketamine

<u>SPRAVATO® (esketamine) 84 mg Dose Kit*</u>
3x28 mg Nasal Spray Devices, 3 Devices, 84 mg esketamine

*Each Nasal Spray device contains: esketamine hydrochloride corresponding to 28 mg esketamine; Each device delivers: 2 sprays, 1 spray into each nostril;
Total volume to be delivered (per device): 0.2 mL, equivalent to 28 mg of esketamine</td></tr>
<tr><td>Orphan drug designation</td><td>No</td></tr>
</table>

2 Abbreviations

AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor
ANCOVA	analysis of covariance
BEGR	Må kun udleveres til sygehuse. Udlevering sker efter bestemmelserne i lægemidler i udleveringsgruppe A
BP	Blood Pressure
CGI-S	Clinical Global Impression Severity
CI	Confidence Interval
C-SSRS	Columbia Suicide Severity Rating Scale
DBS	Deep Brain Stimulation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiogram
ECT	Electroconvulsive Therapy
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (questionnaire)
ESK-NS	Esketamine Nasal Spray
FDA	Food and Drug Administration
F/U	Follow-up
HCP	Health Care Professional
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSI	Health Status Index
IA	Interim Analysis
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IDS-C30	Inventory of Depressive Symptomatology - Clinician-rated, 30-item
IDS-C_{ANX}	Inventory of Depressive Symptomatology – Clinician rating anxiety subscale
IWRS	Interactive Web Response System
LL	Lower Limit
LOCF	Last Observation Carried Forward
LS	Least Squares
LSD	Lsergic acid diethylamide
MA	Maintenance
MADRS	Montgomery-Åsberg Depression Rating Scale
MCI	Mild Cognitive Impairment
MDMA	3,4-methylenedioxy-metamphetamine

MDD	Major Depressive Disorder
MGH-ATRQ	Massachusetts General Hospital- Antidepressant Treatment Response Questionnaire
MINI	Mini International Neuropsychiatric Interview
MKRF	Mindste klinisk relevante forskel
MMRM	Mized-Effects Model Using Repeated Measures
MMSE	Mini Mental State Examination
NE	Not Estimable
NMDA	N-Methyl-D-Aspartate
NNT	Number Needed to Treat
OAD	Oral Antidepressant
PBO-NS	Placebo Nasal Spray
PCP	Phencyclidine
PHQ-9	Patient Health Questionnaire, 9-item
PWC-20	Physician Withdrawal Checklist, 20-item
RR	Relative Risk
SAE	Serious Adverse Events
SD	Standard Deviation
SDS	Sheehan Disability Scale
SE	Standard Error
SMD	Standardized mean difference
SNRI	Serotonin-Norephinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TEAE	Treatment Emergent Adverse Event
TRD	Treatment Resistant Depression
UL	Upper Limit
VNS	Vagus Nerve Stimulation
Wk	Week
XR	Extended-Release
Y	Year

3 Summary

Esketamine (Spravato®) in combination with a SSRI or SNRI is an innovative treatment approved by the European Commission on December 19th 2019 for the treatment of adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

Spravato® is the first antidepressant specifically indicated for TRD. Whereas almost all of the commonly used OADs act on the monoaminergic pathway, Spravato® has a unique mechanism of action, exerting its effect via transient N-methyl-D-aspartate (NMDA) receptor antagonism which is believed to alter the underlying pathophysiological process of depression. Spravato® is administered nasally providing a non-invasive, patient-acceptable, rapidly absorbed and readily bioavailable route of delivery.

This application presents the basis for the evaluation of the clinically added value of Spravato® in combination with SSRI or SNRI compared to placebo in combination with SSRI or SNRI for the treatment of adults with treatment resistant depression, which have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.
Based on the clinical trials included in this submission the data shows that flexible dosed Spravato® nasal spray, in combination with a SSRI or SNRI, provided statistically significant, clinically meaningful, rapid, and sustained improvement of depressive symptoms in patients with TRD versus placebo in combination with SSRI or SNRI.

The meta-analyses based on data from the three short-term induction studies TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 as well as the long-term maintenance study SUSTAIN-1, where Spravato® in combination with SSRI or SNRI was studied head to head with the comparator, placebo in combination with SSRI or SNRI showed that treatment with Spravato® results in:

- Significantly higher remission rates at induction and maintenance based on MADRS total score.
- Significantly higher response rates at induction and maintenance based on MADRS total score.
- Significantly increase in quality of life at induction and maintenance as measured by EQ-5D-5L mean difference change in health status index.
- No significant difference in serious adverse events
- No significant difference in discontinuation due to adverse events

Consequently, the recommendation of Spravato® in combination with a SSRI or SNRI, will provide TRD patients in Denmark with the possibility to get a new innovative treatment which provides significant, clinically meaningful, rapid, and sustained improvement of depressive symptoms with TRD who have failed at least two OADs, and provide the first new opportunity and hope in treatment for TRD in over 30 years. Subsequent improvements in a patient's quality of life will also likely have an additional positive impact on the lives of their careers, family and friends.

4 Introduction

The burden attributed by mental disorders and especially depression pose a massive challenge to Danish society and is a major public health concern. Depression is one of the most common psychiatric disorders and is the leading cause of disability worldwide. The global burden has increased steadily with 18% between 2005-2015 affecting more than 320 million people worldwide. (2) In addition to the depression being a debilitating disease for those affected, mental disorders were the overall contributor to loss of productivity including sick leave, reduced ability to work and disability pension. Importantly, the total costs related to treatment, care and loss of productivity was 4.3 billion DKK annually from depression alone. (3) Major depressive disorder (MDD) is a common debilitating disease characterized by the persistence of negative thoughts and emotions that disrupt mood, cognition, motivation and behavior. It is a highly recurrent psychiatric illness characterized by an increased risk of relapse with increasing frequency and severity of episodes over time. (4)

Treatment resistant depression (TRD) is defined as MDD that has not responded to treatment with at least two oral antidepressants in the current depressive episode. (5) TRD is a severely debilitating and potentially life-threatening disease. Symptoms include profound sleep disturbance, fatigue, change in appetite/weight, agitation or slowness of speech/action, diminished concentration, decreased libido, inability to enjoy usual activities, and feelings of worthlessness. These symptoms result in an impaired capacity and inability to work, to the point of complete inability to function, which substantially interferes with social connection, integration and relationships. (6) Symptoms of TRD may last for months or years. In many cases, patients with TRD feel weary of life or have suicidal ideation to the point of suicidal actions approximately 30% of patients with TRD attempt suicide at least once in their lifetime. (7) Furthermore, TRD may develop at any age, but disproportionally affects people of working age which places a substantial burden on care givers and loved ones, the healthcare system, and broader society (8-11)
TRD patients typically suffer from an inadequate treatment response and cycle through numerous OADs primarily SSRIs and SNRIs as there is no single preferred agent for TRD in Danish clinical practice.(8, 12) Despite the available pharmacological treatments, there is a serious unmet need for new and TRD specific treatments with a different mode of action since patients continue failing to achieve the overall treatment goal of remission and recovery with current treatment options. (13)

Designated as a Breakthrough Therapy by the US Food and Drug Administration and as stated above approved by the European Commission on December 19th 2019, Spravato® nasal spray is the first antidepressant specifically indicated for TRD. Data from TRANSFORM-2 and SUSTAIN-1 show that flexible dosed Spravato® nasal spray, in combination with a SSRI or SNRI, provided statistically significant, clinically meaningful, rapid, and sustained improvement of depressive symptoms in patients with TRD versus a newly initiated oral AD plus placebo nasal spray. The new mode of action combined with the unique route of administration results in a rapid response (as early as 24 hours) with clinical symptom improvement compared with currently available oral ADs. Co-administered with an oral AD, esketamine nasal spray has a rapid onset of action, 20% higher response and remission rates in the short-term, and 50% -70% lower relapse rates among stable remitters and responders, in the long-term versus a newly initiated oral AD plus placebo nasal spray.(14, 15) Consequently, the recommendation of Spravato® in combination with a SSRI or SNRI, will provide TRD patients in Denmark with the possibility to getting an innovative effective treatment.

5 Literature search

A systematic literature search was not conducted as specified in the Medicines Council protocol for evaluation of Spravato® for the treatment of treatment resistant depression in adults. The Medicine Council found that the following studies are consider relevant and can be used to conduct direct comparisons.

- TRANSFORM-1 (NCT02417064)
- TRANSFORM-2 (NCT02418585)
- TRANSFORM-3 (NCT02422186)
- SUSTAIN-1 (NCT02493868)

5.1 Relevant studies

Table 3 Relevant studies included in the assessment (14-21)

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Efficacy and Safety of fixed-dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1), Fedgchin et al., Int J Neuropsychopharmacol, 2019	TRANSFORM-1	NCT02417064	**Study Start Date:** August 10, 2015 **Study Completion Date:** February 20, 2018	1
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, Popova et al., Am J Psychiatry, 2019	TRANSFORM-2	NCT02418585	**Study Start Date:** August 7, 2015 **Study Completion Date:** November 6, 2017	1
Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients with Treatment-Resistant Depression – TRANSFORM-3, Am J of Geriatric Psychiatry, 2019	TRANSFORM-3	NCT02422186	**Study Start Date:** August 20, 2015 **Study Completion Date:** August 10, 2017	1
Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression, Daly et al., JAMA Psychiatry, 2019	SUSTAIN-1	NCT02493868	**Study Start Date:** Oct 1, 2015 **Study Completion Date:** February 15, 2018	1

5.2 Main characteristics of included studies

5.2.1 TRANSFORM-1

TRANSFORM-1 was a 4-week, randomised, double-blind, active-controlled, multicentre, Phase 3 trial that enrolled adult patients (aged 18–64 years) with recurrent or single-episode TRD (non-response to ≥1 but ≤5 OADs in the current episode of depression). The study consisted of a 4-7-week screening/prospective observational phase, a 4-week double-blind induction phase during which nasal spray treatment sessions occurred twice weekly, and a 24-week post-treatment follow-up phase. (17) Schematic illustrating the study design of TRANSFORM-1 is presented in figure 1 at the end of this section. Furthermore, a detailed overview of the main study characteristics of TRANSFORM-1 is available at table A2.
TRANSFORM-1 was conducted to evaluate the efficacy, safety and tolerability of fixed dose esketamine nasal spray plus a newly initiated OAD (ESK-NS-56mg or -84mg + OAD) versus a newly initiated OAD plus placebo nasal spray (OAD + PBO-NS) for the treatment of TRD in adults aged 18–64 years. The primary efficacy endpoint was change from baseline to day 28 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score defined as change in the 10-item clinician-administered MADRS total score (assessed by an independent, remote rater) from baseline (Day 1 prior to randomisation) to the end of the 4-week double-blind induction phase. (17) The secondary endpoints are available at table A2.

At entry of the study, patients had moderate-to-severe depression (Inventory of Depressive Symptomatology [IDS-C30] total score ≥34 and MADRS total score ≥28). In addition to non-response to ≥1 OAD (≤25% improvement) in the current depressive episode based on historical report, non-response to a different OAD taken at an adequate dose for a total duration of at least 6 weeks was observed prospectively in the screening/prospective observational phase. Subsequently non-responders (defined as ≤25% improvement in the MADRS total score from week 1 to week 4 and a MADRS total score ≥28 at weeks 2 and 4) who were eligible to enter the 4-week double-blind treatment phase discontinued all current antidepressant treatment(s). Consequently, at the time of randomization, patients met the study definition of TRD, which was non-response to ≥2 OADs in the current episode of depression. Key exclusion criteria were suicidal ideation with intent to act within the prior 6 months or suicidal behavior within the prior year; diagnosis of psychotic disorder, bipolar or related disorders; recent history (within prior 6 months) of moderate or severe substance use disorder; and, positive test result(s) for specified drugs of abuse. (17) Further details of the exclusion and inclusion criteria is available in table A2.

A total of 710 patients were screened and 346 enrolled patients were randomised 1:1:1, to receive following treatment regimens beginning from the 4-week induction phase (17):

- ESK-NS (56 mg [fixed dose[1]]) plus a newly initiated OAD twice weekly for 4 weeks (n=117)
- ESK-NS (84 mg [fixed dose]) plus a newly initiated OAD twice weekly for 4 weeks[2] (n=116)
- A newly initiated OAD plus PBO-NS twice weekly for 4 weeks (OAD + PBO-NS; n=113).

In general, the treatment groups were similar with respect to baseline characteristics and the full demographic. The baseline characteristics of patients enrolled in the full analysis set of TRANSFORM-1 are presented in table A2a. The mean (SD) age of all patients was 46.3 (11.19) years, ranging from 18–64 years. Most patients were female (70.5%) and white (76.6%). The majority (57.3%) initiated OAD treatment with an SNRI; 39.8% initiated OAD with duloxetine. Of enrolled patients, 45.3% were in North America, 24.9% in

[1] Not in line with licensed dosing for ESK-NS which is for flexible dosing of ESK-NS.
[2] Patients randomised to receive the 84 mg esketamine dose were started at Day 1 on 56 mg before increasing to 84 mg at Day 4.

Europe, and 29.8% from other regions. The mean (SD) baseline MADRS total score was 37.6 (5.52 [range: 18, 53]), corresponding to severe depression. (1) All patients had non-response to at least two OADs prior to randomisation, with non-response being confirmed prospectively during the screening/prospective observational phase for at least one of these antidepressant treatments. (17)

Most of the randomized patients (315/346) completed the double-blind phase, however a total of 6 (5.1%), 19 (16.4%), and 6 (5.3%) patients in the ESK-NS 56 mg + OAD, 84 mg + OAD, and OAD + PBO-NS groups, respectively, withdrew prior to completing the treatment phase. Worth mentioning, 11 of the 19 withdrawn patients in the ESK-NS 84 mg + OAD group were withdrawn after only receiving the first dose, which was 56 mg based on the fixed titration in the study design. The higher withdrawal rate in the ESK-NS 84 mg + OAD group did not appear to be due to any new or dose-related safety finding. (17)

As described above the ESK-NS dosing was fixed (56 mg or 84 mg) in TRANSFORM-1 and not in line with licensed dosing for ESK-NS which is for flexible dosing of ESK-NS. Patients randomly assigned to 84 mg ESK-NS received an 84 mg dose on Day 4 and for all subsequent nasal spray treatment sessions. No further adjustment to the ESK-NS dose was permitted for the duration of the double-blind induction phase. (17) Table 4 presents the titration schedule of nasal spray study medication (esketamine or placebo) which was dosed at each nasal spray treatment session in the double-blind induction phase of the TRANSFORM-1 trial.

Table 4: ESK-NS dose titration schedule during the double-blind induction phase in the TRANSFORM-1 study (22).

Study day	Esketamine dose	Dose titration guidance
TRANSFORM-1		
Day 1	56 mg	
Day 4	56 mg or 84 mg (as per randomisation)	No further adjustments to the esketamine dose were permitted for the duration of the double-blind induction phase

Dosing of the newly initiated OAD began on Day 1 of the induction phase of the TRANSFORM-1/2/3 trials. All patients were initiated, open-label, on one of four OADs from two classes: an SSRI (escitalopram or sertraline), or an SNRI (duloxetine or venlafaxine XR). Dosing of the OAD was according to local prescribing guidelines with protocol-specified titration to the maximally tolerated dose, as per the titration schedule presented in table 5. Use of the titration schedule was mandatory but if higher doses were not tolerated, a down-titration was permitted based on clinical judgment. However, the patient's dose was not to be lower than the following minimum therapeutic doses at the end of the induction phase (17, 22):

TRANSFORM-1/2:

- Duloxetine: 60 mg/day
- Escitalopram: 10 mg/day
- Sertraline: 50 mg/day
- Venlafaxine XR: 150 mg/day

Table 5: OAD dose titration schedule during the double-blind induction phase – TRANSFROM-1/2 (22).

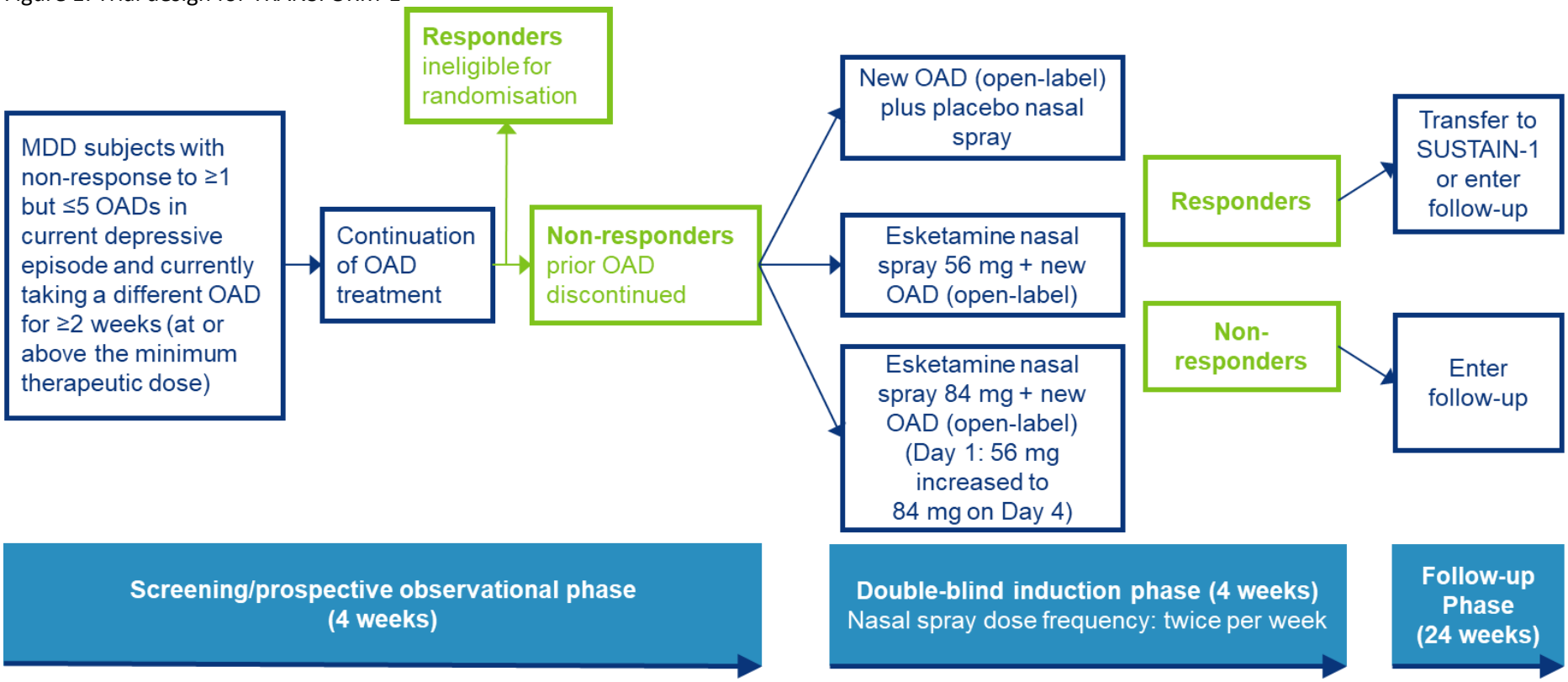
OAD	Titration schedule[a]			
	Week 1 (starting Day 1)	**Week 2 (starting Day 8)**	**Week 3 (starting Day 15)**	**Week 4 (starting Day 22)**
TRANSFORM-1/2				
Duloxetine	60 mg[b]	60 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg
Sertraline	50 mg	100 mg	150 mg	200 mg (**TRANSFORM-1**) 150 mg (**TRANSFORM-2**)
Venlafaxine XR	75 mg	150 mg	225 mg	225 mg

Abbreviations: OAD, oral antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; XR, extended release.

[a] Adjustments to the titration schedule may have been required in some countries in order to conform to local prescribing information.

[b] In TRANSFORM-1, patients who had a history of increased sensitivity towards SSRIs/SNRIs could, at the discretion of the treating physician, be initiated on a 30 mg dose of duloxetine and up-titrated to the therapeutic dose of 60 mg by the start of Week 2.

Figure 1: Trial design for TRANSFORM-1



Abbreviations: MDD, major depressive disorder; OAD, oral antidepressant.
Note: Patients who withdrew early from the double-blind induction phase and received at least one dose of nasal spray study medication had an early withdrawal visit and then proceeded to the follow-up phase.

5.2.2 TRANSFORM-2

TRANSFORM-2 was a phase 3, randomized, double-blind, active-controlled, multicenter study in adult participants (18-64 years) with recurrent or single-episode TRD (nonresponse to ≥1 to≤5 antidepressants in the current depression episode) to assess the efficacy, safety, and tolerability of flexibly dosed ESK-NS (56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator: escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS. TRANSFORM-2 consisted of a 4-7-week screening/prospective observational phase, , a 4-week double-blind induction phase during which nasal spray treatment sessions occurred twice weekly, and a 24-week post-treatment follow-up phase. (14) Schematic illustrating the study design of TRANSFORM-2 is presented in figure 2 at the end of this section. Furthermore, a detailed overview of the main study characteristics of TRANSFORM-2 is available at table A2.1.
The primary objective of TRANSFORM-2 was to evaluate the efficacy of ESK-NS (flexibly-dosed) + a newly initiated OAD versus newly initiated OAD + PBO-NS. The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1 prior to randomization) in clinician-administered MADRS total score (assessed by an independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28) to prove efficacy in the context of acute phase treatment. (14) The secondary endpoints are available at table A2.1.

At study entry, participants had documented (retrospectively) nonresponse ≤25% improvement) to ≥1 to ≤5 antidepressants (based on the Massachusetts General HospitalAntidepressant Treatment Response Questionnaire [MGH-ATRQ]) in the current depressive episode and were currently receiving a different OAD, to which they had been adherent (<4 missed days of treatment based on the Patient Adherence Questionnaire) for at least the previous 2 weeks at or above the minimum therapeutic dosage (or therapeutic blood level for specific tricyclic OAD), which was continued prospectively for another 4 weeks during the screening/prospective observational phase, providing a total duration of at least 6 weeks of the prospective OAD. Patients who had not responded to the prospective OAD treatment by the end of the screening phase (nonresponse was defined as ≤25% improvement in MADRS score from week 1 to week 4 and a MADRS score ≥28 at weeks 2 and 4) entered the 4-week double-blind treatment phase, at which time they discontinued all current OAD treatments and were randomly assigned to the intranasal treatment combined with a newly initiated OAD. (14) Key exclusion criteria were current or recent (past 6 months) homicidal ideation/intent or suicidal ideation with intent to act or suicidal behavior within the past year; diagnosis of psychotic disorder, major depressive disorder with psychotic features, bipolar or related disorders, borderline, antisocial, histrionic, or narcissistic personality disorder, obsessive-compulsive disorder (current), intellectual disability, autism spectrum disorder; uncontrolled hypertension; seizures; a recent history (past 6 months) of moderate or severe substance use disorder (including a lifetime history of ketamine use disorder) and positive urine test results for specified drugs of abuse. (14) Further details of the exclusion and inclusion criteria is available in table A2.1.

A total of 435 patients were screened for TRANSFORM-2 of which 227 patients met the inclusion criteria and were randomised to treatment during the double-blind induction phase with either (1, 19):

- ESK-NS (flexibly-dosed: 56 or 84 mg) + a newly initiated OAD (n=116), or
- A newly initiated OAD + PBO-NS (n=111).

However, the full analysis set for ESK-NS (flexibly-dosed: 56 or 84 mg) + OAD was n=114 and for the OAD + PBO-NS n=109. (14) Of the 227 patients randomly assigned to treatment, 197 (86.8%) patients completed the 28 day double-blind induction phase, and 30 (13.2%) patients withdrew. In total, 118 patients continued into SUSTAIN-1.(14)

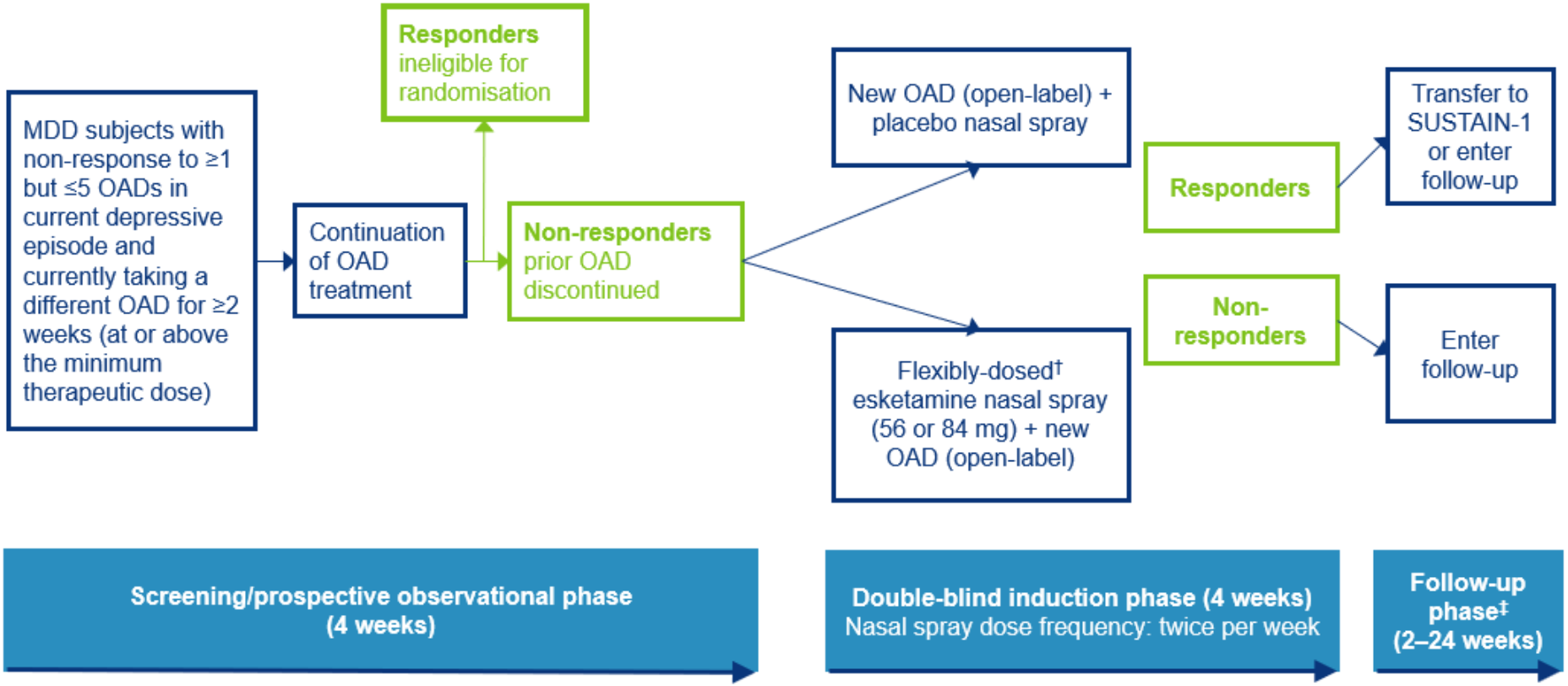
In general, treatment groups were similar with respect to baseline characteristics. The baseline characteristics of patients enrolled in the full analysis set of TRANSFORM-2 are presented in table A2.1a. Patients enrolled in TRANSFORM-2 had a mean baseline MADRS score of 37.1, corresponding to severe depression, a mean age of 45.7 years, and a mean duration of the current episode of MDD of 114.6 weeks. All patients had non-response to at least two OADs prior to randomisation, with non-response being confirmed prospectively during the screening/prospective observational phase for at least one of these OADs. (1, 14)

As described above TRANSFORM-2 evaluated the efficacy, safety, and tolerability of flexibly dosed ESK-NS (56 mg or 84 mg) + a newly initiated OAD (ESK-NS-56 mg or -84 mg + OAD) versus newly initiated OAD + PBO-NS).
During the double-blind induction phase of TRANSFORM-2, patients self-administered nasal spray treatment (esketamine or placebo) at treatment sessions twice per week for four weeks at the study site. The first nasal spray treatment session occurred on Day 1. On Day 1, patients randomised to receive ESK-NS started on a dose of 56 mg in TRANSFORM-2. (14) At subsequent nasal spray treatment sessions in TRANSFORM-2, the dose could have been titrated as described in table 6.
Dosing of the newly initiated OAD began on Day 1 of the induction phase of the TRANSFORM-2 trial and the subsequently OAD dose titration schedule during the double-blind induction phase is consistent with the titration schedule described in section 4.2.1. (14)

Table 6: ESK-NS dose titration schedule during the double-blind induction phase in the TRANSFORM-2 study (23).

Study day	Esketamine dose	Dose titration guidance
TRANSFORM-2		
Day 1	56 mg	
Day 4	56 mg or 84 mg	The dose could remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
Days 8 and 11	56 mg or 84 mg	The dose could remain the same or be increased to 84 mg (if the previous dose was 56 mg) or be reduced to 56 mg (if the previous dose was 84 mg) as determined by the investigator based on efficacy and tolerability.
Day 15	56 mg or 84 mg	A dose reduction from 84 mg to 56 mg was permitted if required for tolerability; no dose increase was permitted on Day 15.
Days 18, 22, and 25	56 mg or 84 mg	The dose was to remain unchanged. If there was no nasal spray treatment session on Day 15, a dose reduction from 84 mg to 56 mg was permitted on Day 18 if required for tolerability; no dose increase was permitted.

Figure 2: Trial design for TRANSFORM-2



Abbreviations: MDD, major depressive disorder; OAD, oral antidepressant.
† On Day 1 of the induction phase, all patients randomised to receive ESK-NS started with a dose of 56 mg. Thereafter, ESK-NS could be dosed flexibly (56 or 84 mg) based on efficacy and tolerability up until Day 15 (or Day 18 if the Day 15 treatment session did not occur). Beyond Day 15, the ESK-NS dose was to remain unchanged. Note: Patients who withdrew early from the double-blind induction phase and received at least one dose of nasal spray study medication had an early withdrawal visit and then proceeded to the follow-up phase.
‡ From the follow-up phase, patients could also transfer to SUSTAIN-3 (ongoing). Non-responders remained double-blinded on their nasal spray treatment.

5.2.3 TRANSFORM-3

TRANSFORM-3 was a 4-week, randomised, double-blind, active-controlled, multicentre, Phase 3 trial that enrolled adult patients (aged ≥65 years) with recurrent or single-episode TRD (non-response to ≥1 but ≤8 OADs in the current episode of depression). Patients aged ≥65 years are generally excluded from Phase 3 antidepressant clinical trials. The ESK-NS clinical trial programme, however, included this dedicated short-term study in patients aged ≥65 with TRD to assess the efficacy, safety, and tolerability of flexibly dosed ESK-NS (28 mg, 56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator: escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS in this vulnerable population. (16)

TRANSFORM-3 consisted of a 4-7-week screening/prospective observational phase assessing response to current OAD treatment, a 4-week double-blind induction phase with flexibly dosed nasal spray study medication (esketamine or placebo) plus a newly-initiated OAD, and a 2-week post-treatment follow-up phase assessing safety and tolerability, including potential withdrawal symptoms. Furthermore, following the 4-week double-blind induction phase, regardless of treatment response, patients could participate in a long-term open-label safety study. Schematic illustrating the study design of TRANSFORM-2 is presented in figure 3 at the end of this section. The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1) in MADRS total score (as assessed by an independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28) (16, 20)
Furthermore, a detailed overview of the main study characteristics of TRANSFORM-3 is available at table A2.2.

A total of 302 patients were screened for TRANSFORM-3 of which 138 patients met the inclusion criteria and were randomised 1:1 to treatment during the double-blind induction phase with either (16):

- ESK-NS (flexibly-dosed: 28 mg, 56 mg, or 84 mg) plus a newly initiated OAD twice weekly for 4 weeks (n=72), or
- A newly initiated OAD + PBO-NS twice weekly for 4 weeks (n=66).

In general, the treatment groups were similar with respect to baseline characteristics, see table A2.2a. The mean (SD) age of all patients was 70.0 (4.52) years. Most patients were female (62.0%) and white (94.9%). The majority (55.5%) initiated OAD treatment with an SSRI. Of enrolled patients, 51.1% were in North America, 43.1% in Europe, and 5.8% from other regions. The mean (SD) baseline MADRS total score was 35.2 (6.16 [range: 19, 51]), corresponding to severe depression. Based on Clinical Global Impression-Severity (CGI-S) scores, patients ranged between “mildly ill” and “among the most extremely ill patients”, with approximately half of patients (49.6%) being “markedly ill” and approximately one quarter of patients (24.8%) being “severely ill”. The mean (SD) duration of the current episode of depression was 215.8 (341.71) weeks. Approximately one third (31.9%) of patients had a history (lifetime) of suicidal ideation, assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), and 14.1% had a history (lifetime) of suicidal behaviour. (1)
All patients had non-response to at least two OADs prior to randomisation, with non-response being confirmed prospectively during the screening/prospective observational phase for at least one of these OAD treatments. (16)

Of the 138 subjects randomly assigned to treatment, 122 (88.4%) subjects completed the 28-day double-blind induction phase, and 16 (11.6%) subjects were withdrawn. A total of 77.8% patients in the ESK-NS+OAD, and 81.5% in the OAD + PBO-NS+ group received treatment on all eight dosing days. (16)

As described above TRANSFORM-3 evaluated the efficacy, safety, and tolerability of flexibly dosed ESK-NS (56 mg or 84 mg) + a newly initiated OAD (ESK-NS-56 mg or -84 mg + OAD) versus newly initiated OAD + PBO-NS in elderly population. (16)
During the double-blind induction phase of TRANSFORM-3, patients self-administered nasal spray treatment (esketamine or placebo) at treatment sessions twice per week for four weeks at the study site. The first nasal spray treatment session occurred on Day 1. On Day 1, patients randomised to receive esketamine nasal spray started on a dose of 28 mg in TRANSFORM-3. (16) At subsequent nasal spray treatment sessions in TRANSFORM-3, the dose could have been titrated as described in table 7.

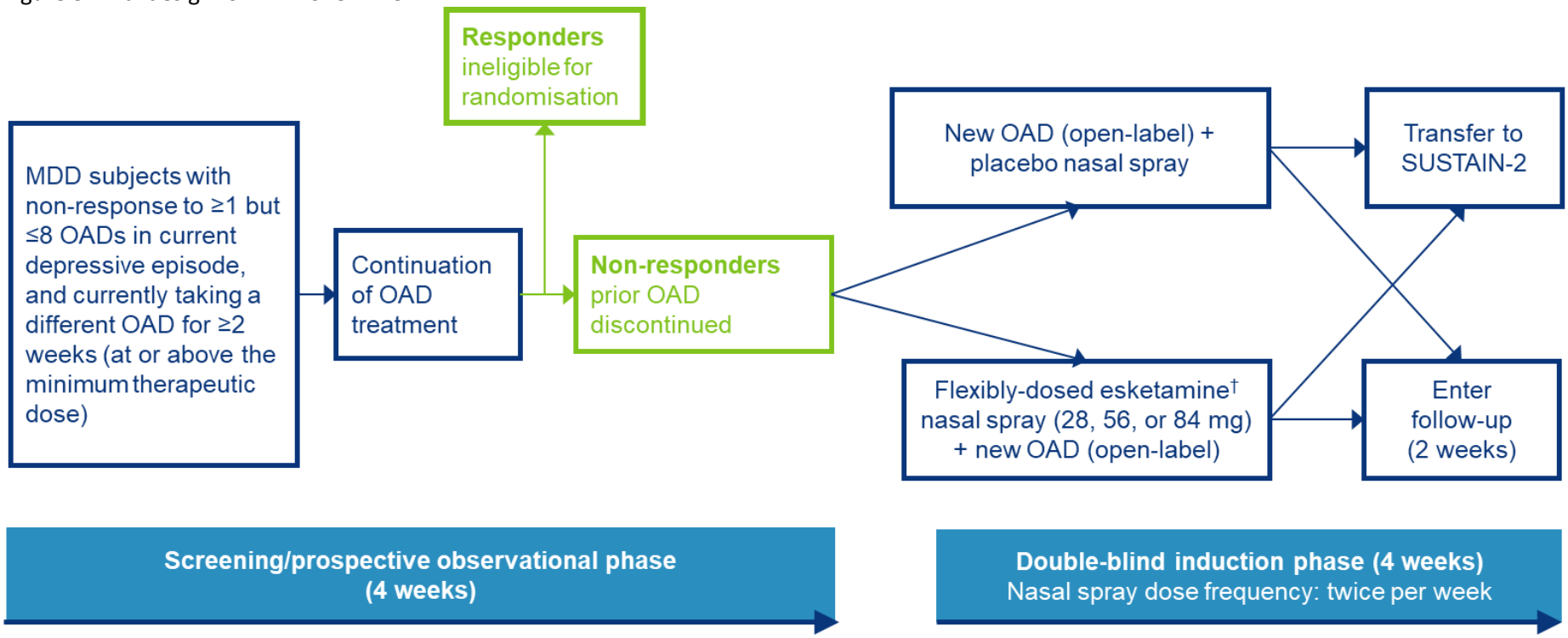
Table 7: ESK-NS dose titration schedule during the double-blind induction phase in the TRANSFORM-3 study. (16)

Study day	Esketamine dose	Dose titration guidance
TRANSFORM-3		
Day 1	28 mg	
Day 4	28 mg or 56 mg	The dose could remain at 28 mg or be increased to 56 mg, as determined by the investigator based on efficacy and tolerability.
Days 8, 11, and 15	28 mg, 56 mg, or 84 mg	The dose could remain the same or increased or reduced by 28 mg from the previous dose, as determined by the investigator based on efficacy and tolerability. No dose increase was permitted beyond Day 15.
Days 18, 22, and 25	28 mg, 56 mg, or 84 mg	No dose increase was permitted beyond Day 15. If needed for tolerability, a dose reduction by 28 mg from the previous dose was permitted on Days 18, 22, and 25.

Dosing of the new OAD began on Day 1 of the induction phase of the TRANSFORM-3 and dosed was given as following (20):

- Duloxetin: The minimum therapeutic dose is 60 milligram per day (mg/day).
- Escitalopram: will be given at a dose of 10 mg/day throughout the Double-Blind Induction Phase. This dose (10 mg/day) is the also the minimum therapeutic dose.
- Sertraline: may be titrated up to a dose of 150 mg/day, but if not tolerated the dose can be reduced to the minimum therapeutic dose of 50 mg/day.
- Venlafaxine XR: may be titrated up to a dose of 150 mg/day, but if not tolerated the dose can be reduced to the minimum therapeutic dose of 75 mg/day.

Figure 3: Trial design for TRANSFORM-3



Abbreviations: MDD, major depressive disorder; OAD, oral antidepressant.
† On Day 1 of the induction phase, all patients randomised to receive esketamine nasal spray started with a dose of 28 mg. On Day 4, patients could either receive 28 or 56 mg. Thereafter, esketamine could be dosed flexibly (28, 56, or 84 mg) based on efficacy and tolerability up until Day 15 beyond which no dose increases were permitted. If needed for tolerability, dose reduction by 28 mg from the previous dose was permitted on Days 18, 22, and 25.
Note: Patients who withdrew early from the double-blind induction phase and received at least one dose of nasal spray study medication had an early withdrawal visit and then proceeded to the follow-up phase.

5.2.4 SUSTAIN-1

SUSTAIN-1 was a phase 3, double-blind, active-controlled, multicenter, relapse prevention study using a randomized withdrawal design in adults (18-64 years) with recurrent or single-episode TRD (nonresponse to ≥1 to≤5 antidepressants in the current depression episode) who have achieved stable remission or stable response after an induction and optimization course (16 weeks) of treatment with ESK NS + OAD.
SUSTAIN-1 consisted of an open-label induction phase (4 weeks; direct-entry patients only), an optimisation phase (12 weeks; both direct-entry and transferred-entry patients), and a double-blind maintenance phase. Transferred-entry patients from the OAD + PBO-NS arms of the acute ESK-NS trials (TRANSFORM-1 and TRANSFORM-2) were included in SUSTAIN-1 to maintain the blinding of the ongoing acute treatment trials and to capture safety data for OAD + PBO-NS beyond 4 weeks. (15) Schematic illustrating the study design of SUSTAIN-1 is presented in figure 4 at the end of this section. Furthermore, a detailed overview of the main study characteristics of TRANSFORM-2 is available at table A2.3.

The primary objective of this study was to assess the efficacy, safety and tolerability of flexibly doses ESK-NS + OAD (ESK-NS-56 or -84 + OAD) compared with an OAD (active comparator) + PBO-NS in delaying relapse of depressive symptoms in adult patients (18-64 years) with TRD who are in stable remission and response after an induction (4 weeks) and optimization (12 weeks) course of ESK-NS + OAD. Additionally, to investigate the safety and tolerability of ESK-NS + OAD compared with an OAD + PBO-NS. The primary efficacy endpoint was the time from randomization to the first relapse during the maintenance phase (up to 92 weeks) in esketamine-treated subjects who achieved stable remission at the end of optimization phase after treatment with ESK-NS + OAD (based on MADRS). (15) The secondary efficacy endpoints are available at table A2.3.

A total of 1,097 patients were screened for SUSTAIN-1 of which 705 were enrolled (1):

- 437 direct-entry patients
- 268 transferred-entry patients from either TRANSFORM-1 or TRANSFORM-2

Transferred-entry patients who were on an OAD + PBO-NS were not included in efficacy analyses but were included in safety analyses. Of the patients who directly entered the open-label induction phase of SUSTAIN-1 and transferred-entry patients on ESK-NS + OAD, 455 met the criteria for response and started the optimisation phase.(1) Of the 455 patients who entered the optimisation phase, 176 met the criteria for stable remission and 121 met the criteria for stable response at the end of the optimisation phase and were therefore eligible to be randomised to receive treatment with either ESK-NS (flexibly-dosed: 56 or 84 mg) + OAD or OAD + PBO-NS during the maintenance phase. Of the 176 stable remitters 90 were randomized to receive ESK-NS + OAD and last 86 stable remitters were randomised to OAD + PBO-NS whereas 62 and 59 of the 121 stable responders were randomized to receive ESK-NS + OAD and OAD + PBO-NS, respectively. (15)

Further detailed description of the enrolled patients in SUSTAIN-1 from baseline to endpoint (up to 92 weeks) (1):

Induction phase (4 weeks)
Of the 437 direct-entry patients, 273 (62.5%) subjects completed the 28-day induction phase and 164 (37.5%) subjects withdrew.

Optimization phase (12 weeks)
Of the 455 esketamine-treated subjects entering the optimization phase (including 182 esketamine-treated transferred-entry subjects), 297 completed the 12-week optimization phase and 158 (34.7%) subjects withdrew.

Maintenance phase (variable length
Remitters
Of the 176 subjects in the Full (stable remitters) analysis set, 159 (90.3%) subjects completed the maintenance phase. (1)
Median exposure to intranasal esketamine during the maintenance phase was 17.7 weeks in stable remitters and 19.4 weeks in stable responders.(15)

Responders
Of the 121 subjects in the Full (stable responders) analysis set, 113 (93.4%) subjects completed the maintenance phase. (1)
Median exposure to placebo during the maintenance phase was 10.2 weeks among stable remitters and 10.1 weeks among stable responders.(15)

In general, the treatment groups were comparable with respect to baseline characteristics and an extensive overview of the baseline characteristics of patients is available in table A2.3a.
The mean (standard deviation [SD]) age of all subjects was 46.1 (11.10) years, ranging from 18 to 64 years. The majority of subjects entering the study were female (64.8%) and white (90.1%). In addition, the majority of subjects (62.9%) initiated OAD treatment with an SNRI and 46.2% of subjects received duloxetine. Medical history of hypertension was observed in 20.9% of subjects. The highest percentage of subjects was enrolled in the United States (27.0%), followed by Poland (18.7%), the Czech Republic (14.0%), Brazil (9.1%), and Turkey (7.5%); The mean (SD) baseline MADRS total score was 37.9 (5.50), ranging from 4 (1 subject, with a score >28 at screening with an unexpected significant score decrease on Day 1, who ultimately discontinued after the induction phase) to 53. Based on CGI-S scores, the majority of subjects (58.4%) were markedly ill (CGI-S score of 5). The mean (SD) duration of the current episode of depression was 132.2 (209.18) weeks (median 64.0 weeks). Subjects reported a family history of depression (45.1%), alcohol abuse (13.5%), and anxiety disorder (9.1%). A total of 27.4% of subjects had a history (lifetime) of suicidal ideation as assessed using the C-SSRS and 14.9% had a history of suicidal behavior. The mean (SD) IDS-C30 total score at screening was 47.2 (7.26), corresponding to severe depression. (1)

As described above SUSTAIN-1 evaluated the efficacy, safety and tolerability of flexibly doses ESK-NS + OAD (ESK-NS-56 mg or -84 mg + OAD) compared with an OAD (active comparator) + PBO-NS. Regarding the details of the flexible dosage and frequency of nasal spray treatments during the open-label induction, optimisation, and maintenance phases, a detail description is outlined below. Note that no nasal spray study medication was administered during the screening/prospective observational or follow-up phases. (15)

Open-label induction phase

During the open-label induction phase, patients self-administered nasal spray treatment with esketamine (56 mg or 84 mg) at treatment sessions twice per week for four weeks as a flexible-dose regimen at the study site (15, 21). Dose titration was performed as described in table 9.

Table 9: ESK-NS dose titration schedule during the open-label induction phase of the SUSTAIN-1 study. (21)

Study day	Esketamine dose	Dose titration guidance
Day 1	56 mg	
Day 4	56 mg or 84 mg	The dose could remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
Days 8, 11, 15, 18, and 22	56 mg or 84 mg	The dose could remain the same or be increased to 84 mg (if the previous dose was 56 mg) or be reduced to 56 mg (if the previous dose was 84 mg) as determined by the investigator based on efficacy and tolerability.
Day 25	56 mg or 84 mg	A dose reduction from 84 mg to 56 mg was permitted if required for tolerability. No dose increase was permitted.

Optimisation phase

Transferred-entry patients continued the same double-blind nasal spray study drug (at the same dose) from the double-blind induction phase of TRANSFORM-1 or TRANSFORM-2. Direct-entry patients continued the same open-label ESK-NS treatment (at the same dose) from the open-label induction phase. (15)

During the optimisation phase, the MADRS was performed weekly by an independent, remote rater, and used to assign the frequency of nasal spray treatment sessions every four weeks. For all patients, the frequency of nasal spray treatment sessions was reduced from the twice weekly frequency used in the induction phase to weekly for the first four weeks of the optimisation phase (Week 5 to Week 8). (15)

Maintenance phase

All patients received double-blind nasal spray study drug during the maintenance phase. Patients were assessed weekly using the MADRS by an independent, remote rater, and treatment administration frequency during the maintenance phase was based on an algorithm using the MADRS score and was reevaluated every 4 weeks, with nasal spray treatment self-administered either once weekly or every 2 weeks. (15)

OAD administration

Screening/prospective observational phase (direct-entry patients only)
At the start of the screening/prospective observational phase of the SUSTAIN-1 trial, direct-entry patients were already receiving an OAD with a documented non-response in their current episode of depression (on the basis of MGH-ATRQ). Patients continued to take this same OAD for four weeks to confirm non-response. Upon completion of four weeks of prospective treatment and assessment of OAD response, the OAD, if clinically indicated, could be tapered over a period of up to three weeks as per country-specific prescribing information. (15)

Open-label induction phase (direct-entry patients only)
Starting on Day 1, a new, open-label OAD was initiated in direct-entry patients and continued for at least the duration of the open-label induction phase. Doses were not to exceed the maximum doses as specified (21):

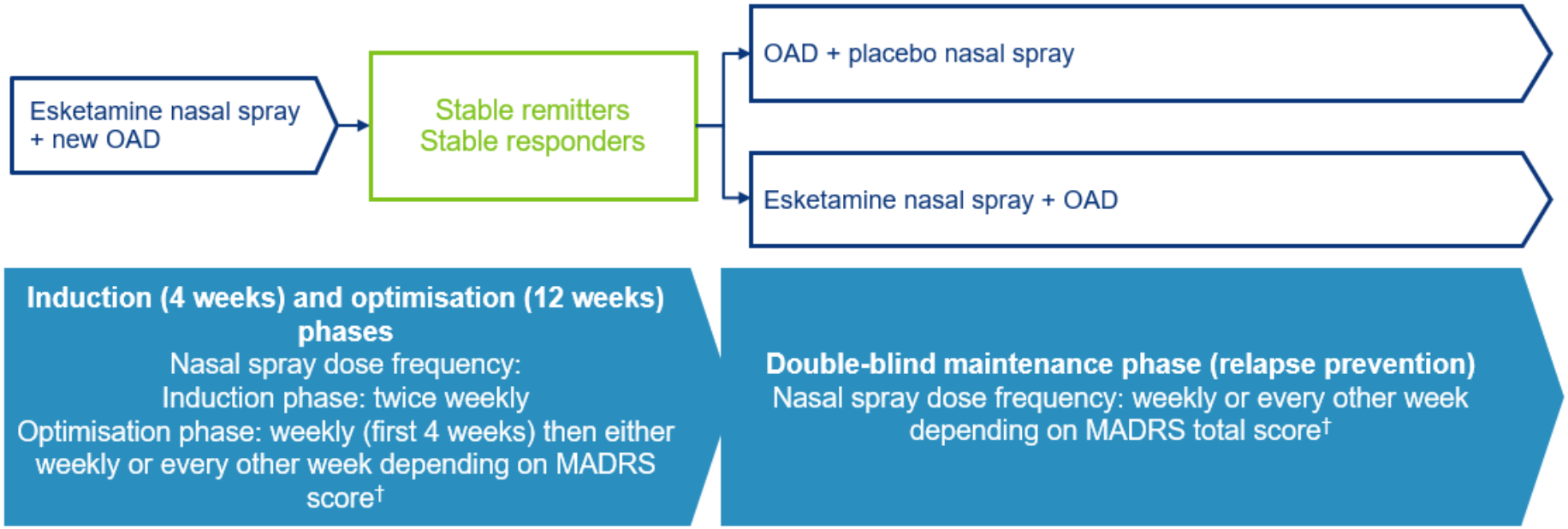
- Duloxetine: 60mg/day
- Escitalopram: 20 mg/day
- Sertraline: 200 mg/day
- Venlafaxine XR: 225 mg/day

If higher doses were not tolerated, a down-titration was permitted based on clinical judgment. However, the patient's dose was not to be lower than the following minimum therapeutic doses at the end of the induction phase (21):

- Duloxetine: 60 mg/day
- Escitalopram: 10 mg/day
- Sertraline: 50 mg/day
- Venlafaxine XR: 150 mg/day

Optimisation and maintenance phases
For both direct-entry and transferred-entry patients, the same OAD initiated on Day 1 of induction (the induction phase of TRANSFORM-1/2 in the case of transferred-entry patients) was continued throughout the optimisation and maintenance phase. The OAD dosage at the end of the induction phase was to remain unchanged. (15)

Figure 4: Trial design for SUSTAIN-1



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; TRD, treatment-resistant depression.
SUSTAIN-1 was a randomised, double-blind, long-term trial in adults (aged 18–64 years) with TRD who had achieved stable remission or stable response that compared the maintenance of efficacy of continued flexibly-dosed ESK-NS + OAD treatment with that of OAD + PBO-NS. The study ended upon 84 relapses occurring. An interim analysis was performed at 30 relapses. Efficacy analyses included direct-entry patient as well as patients transferred from TRANSFORM-1 and TRANSFORM-2 who were on ESK-NS + OAD and during these studies. Patients who were on OAD + PBO-NS during TRANSFORM-1 and TRANSFORM-2 could also enter the study but these patients were only considered in safety analyses. These patients were included in SUSTAIN-1 to maintain the blinding of the ongoing acute treatment trials, TRANSFORM-1 and TRANSFORM-2, and to capture safety data for OAD + PBO-NS beyond 4 weeks

6 Clinical questions

6.1 What is the clinically added value of esketamine in combination with SSRI or SNRI compared to placebo in combination with SSRI or SNRI for the treatment of adults with treatment resistant depression, which have not responded on a least two different treatments with antidepressants in the current moderate to severe depressive episode.

6.1.1 Presentation of relevant studies

The clinical evidence for ESK-NS is derived from four Phase 3 trials: three acute, 4-week treatment studies (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3), and one maintenance study (SUSTAIN-1), see table 10.

- In TRANSFORM-1, with the exception of the first dose (56 mg), ESK-NS was administered at fixed doses of either 56 mg or 84 mg, which is not reflective of the approved licence .
- The TRANSFORM-2 study evaluated the efficacy of flexible dosing (56mg/84mg) of ESK-NS, which is in line with its licence and use in clinical practice.
- TRANSFORM-3 enrolled patients with TRD ≥65 years and for tolerability considerations, the starting dose of ESK-NS was 28 mg which was below the minimum effective dose (56 mg).
- SUSTAIN-1 is a randomised, double-blind, long-term trial in adults (18–64 years) with TRD who had achieved stable remission or stable response comparing the maintenance of efficacy of continued flexible-dosed ESK-NS + OAD with OAD + PBO-NS.

Table 10: Overview of clinical trials

Trial	**TRANSFORM-1**	**TRANSFORM-2**	**TRANSFORM-3**	**SUSTAIN-1**
Study design	Randomised, double-blind, parallel-group, active-controlled, multicentre, Phase 3			
Population	Adults (aged 18–64 years) with recurrent or single-episode TRD		Adults (aged ≥65 years) with recurrent or single-episode TRD	Adults (aged 18–64 years) with recurrent or single-episode TRD.
Intervention(s)	Fixed dose ESK-NS (56 mg OR 84 mg) twice weekly for 4 weeks (starting dose for all patients: 56 mg) + newly initiated OAD	Flexibly-dosed ESK-NS (56 mg/84 mg) twice weekly for 4 weeks (starting dose for all patients: 56 mg) + newly initiated OAD	Flexibly-dosed ESK-NS (28 mg /56 mg/84 mg) twice weekly for 4 weeks (starting dose for all patients: 28 mg) + newly initiated OAD	Flexibly-dosed ESK-NS (56 mg/ 84 mg) weekly, or every other week in the maintenance phase until relapse or study termination plus + initiated OAD
Comparator(s)	Newly initiated OAD + PBO-NS twice weekly for 4 weeks			Newly initiated OAD + PBO-NS twice weekly, or every other week until relapse or study termination

6.1.2 Results per study

6.1.3 TRANSFORM-1

Data from TRANSFORM-1 show that ESK-NS + a newly initiated OAD, provided clinically meaningful, rapid improvement of depressive symptoms in patients with TRD versus a newly initiated OAD + PBO-NS. The primary endpoint measured improvement in depressive symptoms, as assessed by the change in MADRS total score from baseline to Day 28 of induction (which numerically favoured the ESK-NS-56 mg + OAD and ESK-NS-84 mg + OAD arms over OAD + PBO-NS. (17)
Since the difference between the ESK-NS-84 mg + OAD and OAD + PBO-NS arms was not statistically significant (LS mean difference: –3.2; 1-sided p=0.044), in accordance with the predefined testing sequence, the ESK-NS-56 mg + OAD arm could not be formally evaluated. Similarly, the key secondary endpoints of onset of clinical response by Day 2 (maintained to Day 28) could not be formally evaluated. (17)

Serious adverse events

There were no deaths in the study however, two subjects experienced an serious adverse event (SAE) during the double-blind induction phase, see table 11. One subject in the ESK-NS 56 mg + OAD treatment group experienced an SAE of depression (reported term of "worsening of depression") on Day 15 of the double-blind induction phase. The investigator considered the event possibly related to ESK-NS+OAD. Another subject in the ESK-NS 56 mg + OAD treatment group experienced an SAE of headache (reported term of "headache") on Day 12 of the double-blind induction phase. The investigator considered the event probably related to ESK-NS and not related to OAD. (1, 17)
No patients in the OAD + PBO-NS group experienced SAEs during the double-blind induction phase. (1, 17)

Table 11: Overall incidence of serious adverse events in TRANSFORM-1 (1)

TRANSFORM-1 (Fixed-Dose)	Treatment (+ Oral AD)	N	SAE	SAE Considered as at Least Possibly Related
Induction Phase	ESK-NS 56 mg:	115	2 (1.7%)	2
	ESK-NS 84 mg:	116	0 (0%)	0
	Total ESK-NS (56 mg and 84 mg)	231	2 (0.87%)	2
	PBO-NS:	113	0 (0%)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

In total, 10 subjects experienced 1 or more treatment emergent adverse events (TEAEs) leading to discontinuation of intranasal study medication during the double-blind induction phase, see table 12. Subjects who experienced a TEAE leading to discontinuation of intranasal study medication could have continued treatment with the OAD study medication in the follow-up phase if clinically appropriate.

- Among 115 subjects in the ESK-NS 56 mg + OAD treatment group, 1 (0.9%) subject discontinued ESK-NS on Study Day 15 of the double-blind induction phase due to a TEAE of depression (reported term of "worsening of depression"). (17)
- Among 116 subjects in the ESK-NS 84 mg + OAD treatment group, a total of 7 (6.0%) subjects discontinued ESK-NS due to TEAEs. The reported TEAEs were single events of anxiety, disturbance in attention, extrasystoles, headache, mania, motion sickness, panic attack, and tachycardia, and 2 events each of dizziness, nausea, and vomiting. (17)
- The majority of these subjects (5 of 7 subjects) discontinued after receiving only 1 intranasal dose of esketamine; per the study design, subjects in the ESK-NS 84 mg + OAD treatment group were to receive ESK-NS 56 mg on Day 1, followed by ESK-NS 84 mg on Day 4 and for all subsequent intranasal treatment sessions. Of the other 2 subjects, 1 subject discontinued ESK-NS due to TEAEs of nausea and vomiting on Day 14 (after receiving 4 intranasal doses), and the other subject discontinued due to a TEAE of panic attack on Day 5 (after receiving 2 intranasal doses). (17)
- Among 113 subjects in the PBO+OAD treatment group, 1 (0.9%) subject discontinued intranasal placebo due to a TEAE of insomnia, and 1 (0.9%) subject discontinued intranasal placebo due to a TEAE of erectile dysfunction. (17)

Table 12: Proportion of patients experiencing 1 or more TEATs leading to discontinuation of intranasal study medication in TRANSFORM-1 (17).

Trial	**Randomised interventions**	**N**	**Definition of discontinuation**	**Incidence of discontinuation**	
				n	%
TRANSFORM-1	ESK-NS 56 mg + OAD	115	Patients experiencing ≥1 TEAE leading to discontinuation of intranasal study medication	1	0.9
	ESK-NS 84 mg + OAD	116		7	6
	Total ESK-NS	231		8	3.5
	PBO-NS	113		2	1.8

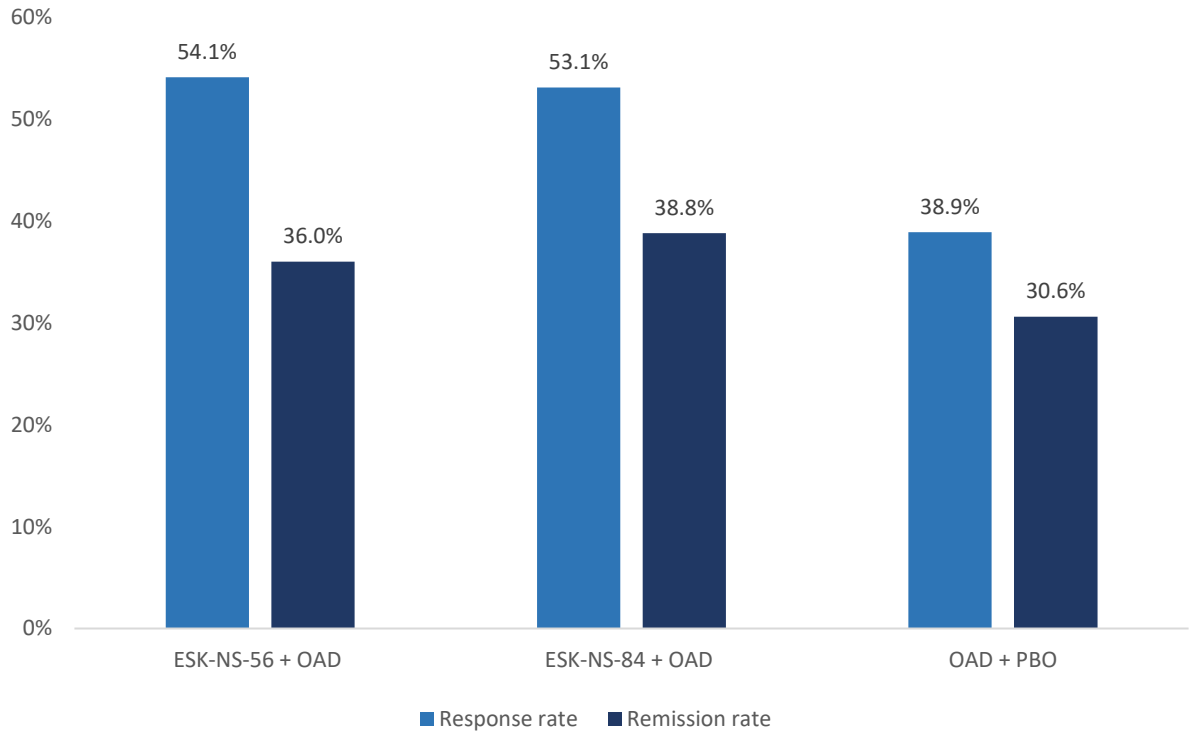
Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 5.1.7 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Response rates based on MADRS total score (response defined as ≥50% reduction from baseline in MADRS total score) and remission rates based on MADRS total score (remission defined as MADRS total score ≤12) during the double-blind induction phase are presented in figure 5. The proportion of responders at Day 28 based on the MADRS total score (observed cases) were 60 of 111 subjects (54.1%), 52 of 98 subjects (53.1%), and 42 of 108 subjects (38.9%) for the ESK-NS 56 mg + OAD, the ESK-NS 84 mg + OAD, and the OAD + PBO-NS+ treatment groups, respectively. Furthermore, The proportion of subjects in remission at Day 28 were 40 of 111 subjects (36.0%), 38 of 98 subjects (38.8%), and 33 of 108 subjects (30.6%) for the ESK-NS 56 mg + OAD, the ESK-NS 84 mg + OAD, and OAD + PBO-NS treatment groups, respectively. (17)

Figure 5: Day 28 response and remission rates based on MADRS (observed cases) in TRANSFORM-1 (17).



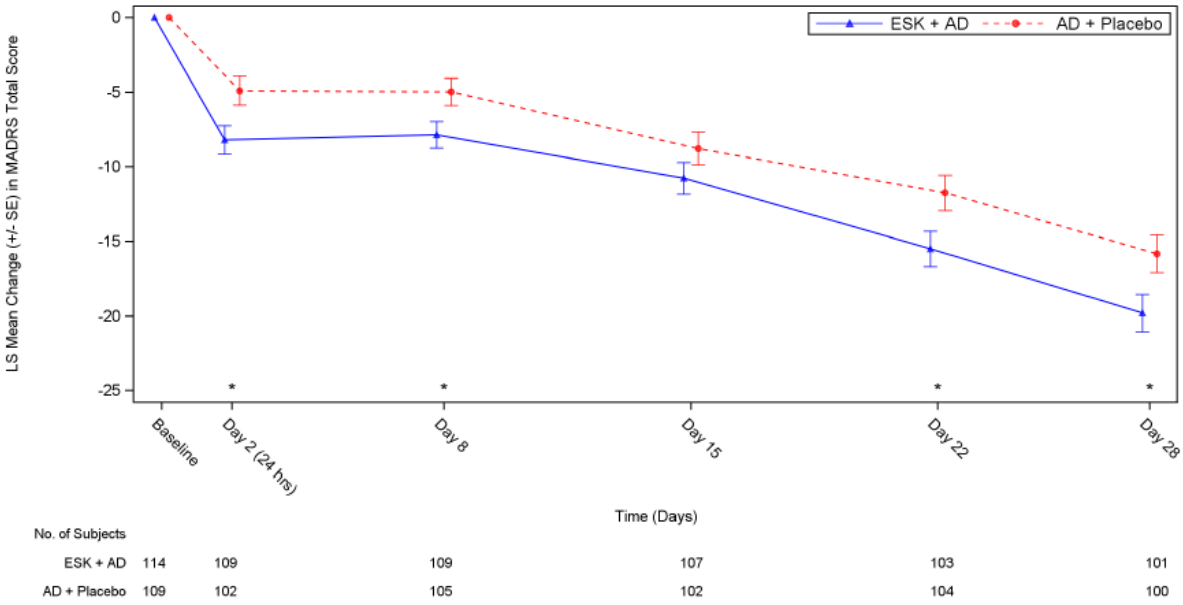
Quality of life

Mean (SD) changes in Health Status Index (HSI) from baseline to the endpoint of the double-blind induction phase were 0.224 (0.2481) for subjects treated with ESK-NS 56 mg + OAD, 0.243 (0.2395) for subjects treated with ESK-NS 84 mg + OAD, and 0.181 (0.2495) for those treated with PBO-NS+OAD.(17)

6.1.4 TRANSFORM-2

Data from TRANSFORM-2 show that ESK-NS + a newly initiated OAD, provided statistically significant, clinically meaningful, rapid improvement of depressive symptoms in patients with TRD versus a newly initiated OAD + PBO-NS. Additionally, ESK-NS has shown to act more quickly (as fast as 24 hours post-dose) compared with currently available antidepressant drugs. The TRANSFORM-2 study shows that ESK-NS + OAD induces about 20% higher response and remission levels at four weeks. TRANSFORM-2 met its primary endpoint, showing a statistically significant and clinically meaningful improvement in depressive symptoms, as assessed by MADRS, with ESK-NS + a newly initiated OAD versus a newly initiated OAD + PBO-NS. (14) The mean (SD) change in MADRS total score from baseline to the end of the double-blind 4-week induction phase (Day 28) was –21.4 (12.32) in the ESK-NS + OAD arm and –17.0 (13.88) in the OAD + PBO-NS arm; LS mean (SE) difference was –4.0 (1.69; p=0.010), based on Mixed-effects model using repeated measures (MMRM), see figure 6. Most importantly, the superiority of ESK-NS + OAD compared with OAD + PBO-NS in change in MADRS total score at Week 4 translates into considerably higher remission and response rates. (14)

Figure 6: LS mean (SE) changes in MADRS total score over time (observed cases MMRM; full analysis set) (14)



Abbreviations: AD, antidepressant; ESK, esketamine; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; SE, standard error.
Note: Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline MADRS value were covariates.
* 1-sided p<0.020.

Serious adverse events

One patient treated with ESK-NS + OAD experienced SAEs of road traffic accident and multiple injuries Day 16 of the double-blind induction phase, 1 day (approximately 28 hours) after receiving a dose of ESK-NS and study medication was withdrawn. This patient subsequently died on Day 55, 40 days after the last dose of ESK-NS. The investigator considered the events of road traffic accident and multiple injuries not related to ESK-NS and not related to OAD. Furthermore, one patient in the OAD + PBO-NS group experienced an SAE in the double-blind induction phase (1, 14). See table 13 for an overview of SEAs.

Table 13: Overall incidence of serious adverse events in TRANSFORM-2 (1)

TRANSFORM-2 (Flexible-Dose)	Treatment (+ Oral AD)	N	SAE	SAE Considered as at Least Possibly Related
Induction Phase	Esk-NS 56-84 mg:	115	1 (0.9%)	0
	PBO-NS:	109	1 (0.9%)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

In total, 9 patients experienced 1 or more TEAEs leading to discontinuation of intranasal study medication: 8 (7.0%) of 115 patients in the ESK-NS + OAD group, and 1 (0.9%) of 109 patients in the OAD + PBO-NS group, see table 14. Patients in the ESK-NS + OAD group discontinued ESK-NS due to TEAEs of anxiety, depression, depressive symptom, panic attack, drug intolerance, feeling drunk, dizziness, headache, vertigo, nausea, multiple injuries and road traffic accident. One patients in the OAD + PBO-NS group discontinued intranasal placebo due to a TEAE of rash generalized. (14)

Table 14: Proportion of patients experiencing 1 or more TEAEs leading to discontinuation of intranasal study medication in TRANSFORM-2 (14).

Trial	**Randomised interventions**	**N**	**Definition of discontinuation**	**Incidence of discontinuation**	
				n	%
TRANSFORM-2	ESK-NS + OAD	115	Patients experiencing ≥1 TEAE leading to discontinuation of intranasal study medication	8	7
	OAD + PBO-NS	109		1	0.9

Abbreviations; SNRI, serotonin–norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event.

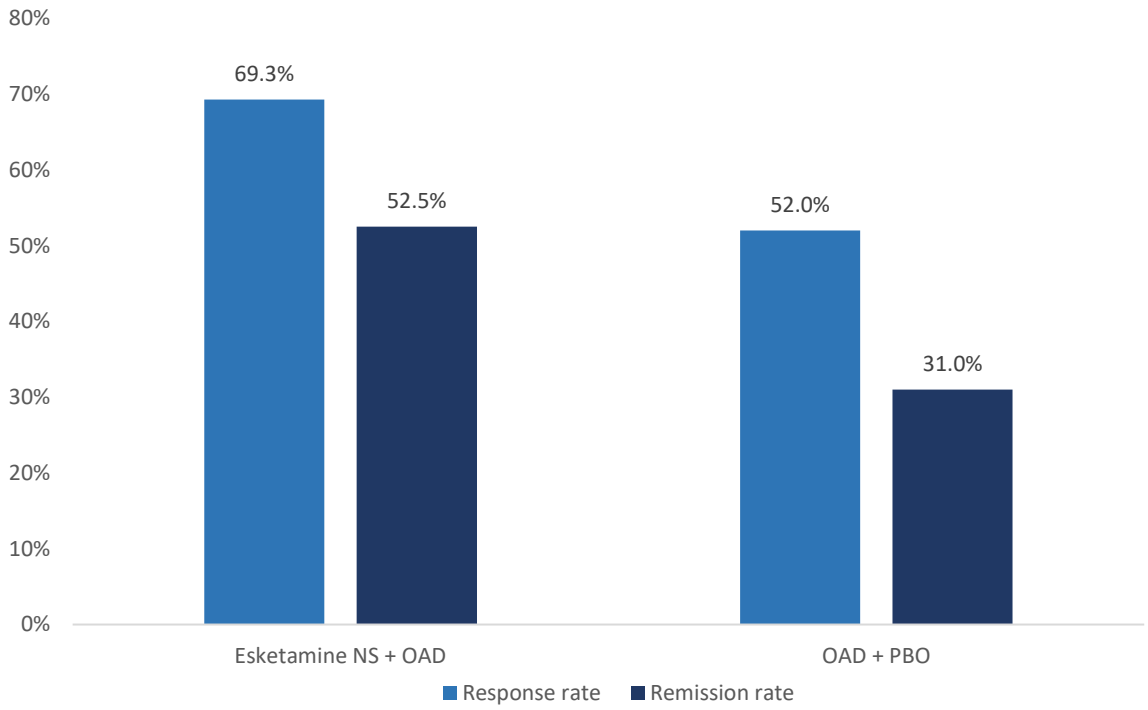
Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 5.1.7 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Based on MADRS, higher response (≥50% reduction from baseline in MADRS total score) and remission (MADRS total score of ≤12) rates were achieved among patients treated with ESK-NS + OAD versus OAD + PBO-NS at week 4, see figure 7. Specifically, at Day 28, 70 (69.3%) of 101 subjects in the ESK-NS + OAD group and 52 (52.0%) of 100 subjects in the OAD + PBO-NS group were responders and 53 (52.5%) of 101 subjects in the ESK-NS + OAD group and 31 (31.0%) of 100 subjects in the OAD + PBO-NS group were in remission. (14) Furthermore a odds ratio of 2.4 (CI;1.30-4.54) was reported comparing the proportion of responders in the ESK-NS + OAD versus OAD + PBO-NS group at day 28. (14)
From a patient perspective, improved response and remission rates likely translate into greater improvements in mood, appetite, sleep, and concentration. Furthermore, these improved response and remission rates lead to a higher number of patients being able to care for themselves and their relatives as well as friends, go back to work, and live normal lives again.

Figure 7: Day 28 response and remission rates based on MADRS (observed cases) in TRANSFORM-2. (14)



Quality of life

ESK-NS + OAD treatment resulted in a greater improvement in health-related quality of life (HRQoL) versus OAD + PBO-NS, as shown by the increase from baseline in mean (SD) EQ-5D Health Status Index (HSI) score to Day 28 of induction. The Mean (SD) changes in HSI from baseline to the endpoint of the double-blind induction phase were 0.288 (0.2317) for subjects treated with ESK-NS+OAD and 0.231 (0.2506) for those treated with OAD+PBO-NS. Compared to OAD + PBO-NS, ESK-NS + OAD treatment resulted in more patients being able to care for themselves, who are more mobile, experience less pain and depression or anxiety, and a significant higher number of patients being able to resume their usual activities compared with OAD + PBO-NS. (1)

6.1.5 TRANSFORM-3

Data from TRANSFORM-3 show that ESK-NS + a newly initiated OAD, provided clinically meaningful, rapid improvement of depressive symptoms in elderly patients with TRD versus a newly initiated OAD + PBO-NS. Though not statistically significant, improvement in depressive symptoms, as assessed by the change in MADRS total score from baseline to Day 28 of induction (MMRM), numerically favoured ESK-NS + OAD over OAD + PBO-NS for the treatment of adult patients aged ≥65 years with TRD.
Improvement in depressive symptoms, as assessed by the mean (SD) change in MADRS total score from baseline in the ESK-NS + OAD arm was –10.0 (12.74) versus –6.3 (8.86) in the OAD + PBO-NS arm (LS mean difference: –3.6; two-sided p = 0.059) (16)

Serious adverse events

There were no deaths in the study however five subjects reported a serious TEAE during the double-blind induction phase, see table 15.
In the ESK-NS + OAD group, one subject reported a serious TEAE of anxiety disorder. The investigator considered the event possibly related to ESK-NS and possibly related to OAD. Furthermore, one subject in the ESK-NS + OAD group reported a serious TEAE of blood pressure (BP) increased which the investigator considered the event probably related to ESK-NS and not related to OAD. The last patient in the ESK-NS + OAD group reported a hip fracture. The investigator considered the event not related to ESK-NS and not related to OAD. (16)

For the OAD + PBO-NS group one subject reported serious TEAEs of gait disturbance which the investigator considered be possibly related to PBO-NS and very likely related to OAD. Furthermore, one subject in the OAD + PBO-NS group reported a serious TEAE of dizziness. The investigator considered the event to be doubtfully related to PBO-NS and doubtfully related to OAD. (16)

Table 15: Overall incidence of serious adverse events in TRANSFORM-3 (1)

TRANSFORM-3 (Flexible-Dose)	Treatment (+ Oral AD)	N	SAE	SAE Considered as at Least Possibly Related
Induction Phase	Esk-NS 28-84 mg:	72	3 (4.2%)	2
	PBO-NS:	65	2 (3.1%)	1

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

Four of 72 (5.6%) subjects in the ESK-NS + OAD group, and 2 of 65 (3.1%) subjects in the OAD + PBO-NS group experienced 1 or more TEAEs leading to discontinuation of intranasal study medication, see table 16. Subjects in the ESK-NS + OAD group discontinued ESK-NS due to TEAEs of anxiety disorder, BP increased, BP systolic increased, and hip fracture. (16)

Table 16: Proportion of patients experiencing 1 or more TEATs leading to discontinuation of intranasal study medication in TRANSFORM-3. (16)

Trial	Randomised interventions	N	Definition of discontinuation	Incidence of discontinuation	
				n	%
TRANSFORM-2	ESK-NS + OAD	72	Patients experiencing ≥1 TEAE leading to discontinuation of intranasal study medication	4	5.6
	OAD + PBO-NS	65		2	3.1

Abbreviations; SNRI, serotonin–norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event.

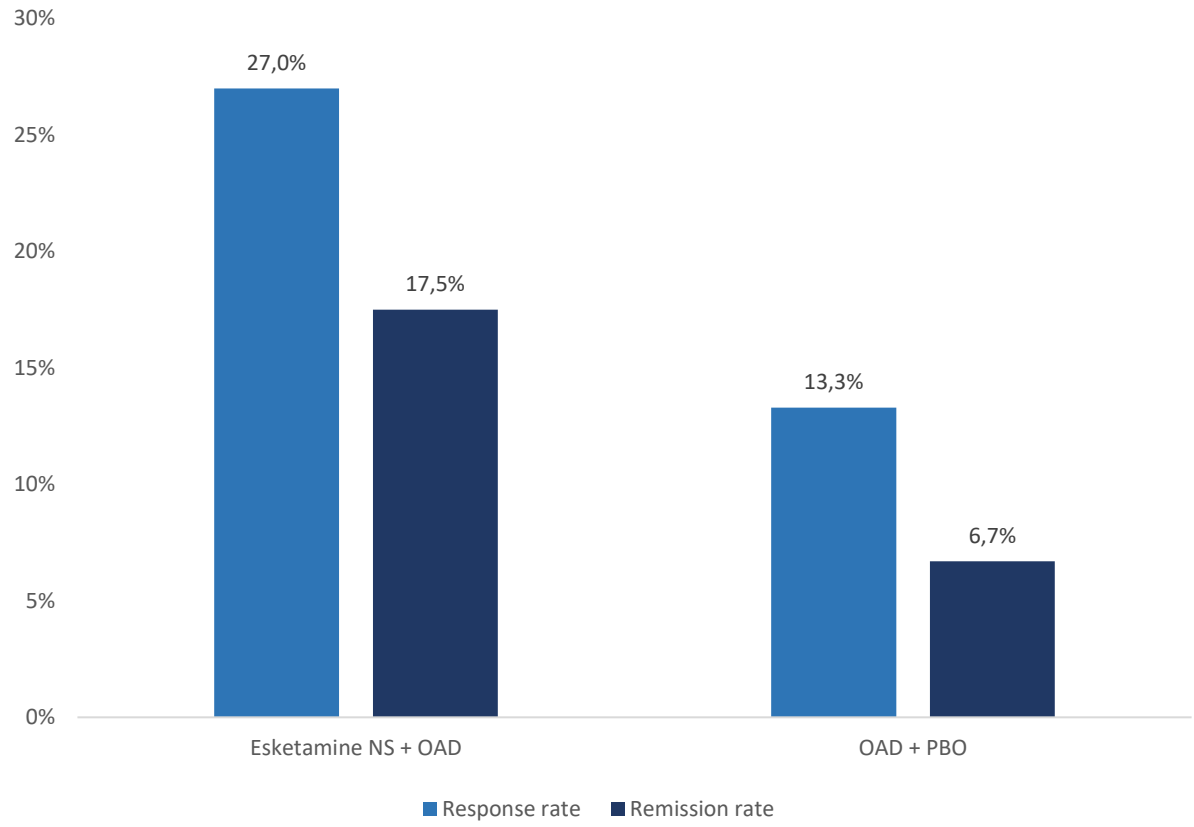
Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 5.1.7 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Response rates based on MADRS total score (response defined as ≥50% reduction from baseline in MADRS total score) and remission (MADRS total score of ≤12) rates during the double-blind induction phase are presented in figure 8. The proportion of responders in both treatment groups generally increased over time during the double-blind induction phase. Overall response rates at Day 28 numerically favored the ESK-NS + OAD group (17 of 63 [27.0%] subjects) compared with OAD + PBO-NS (8 of 60 [13.3%] subjects). At Day 28, 11 of 63 (17.5%) subjects in the ESK-NS + OAD group and 4 of 60 (6.7%) subjects in the OAD + PBO-NS group were in remission. (16)

Figure 8: Day 28 response and remission rates based on MADRS (observed cases) in TRANSFORM-3. (16)



Quality of life

Mean (SD) changes in HSI from baseline to the endpoint of the double-blind induction phase were 0.081 (0.2624) for subjects treated with ESK-NS + OAD and 0.026 (0.2235) for those treated with OAD + PBO-NS. (24).

6.1.6 SUSTAIN-1

In SUSTAIN-1, maintenance treatment with ESK-NS + OAD significantly reduced relapse rates in patients with TRD aged 18–64 years. Relapse rates were lower both in patients in stable remission and those in stable response who, at randomisation, continued ESK-NS + OAD compared with those who, at randomisation, continued the same OAD but switched to PBO-NS from ESK-NS.
After 16 weeks of initial treatment with EKS-NS, ongoing ESK-NS + OAD treatment also significantly delayed worsening of symptom severity and functional impairment during the maintenance phase compared with OAD + PBO-NS, based on mean changes over time in MADRS (in both stable remitter and responder patients). In a consistent manner, continuing ESK-NS + OAD treatment was associated with smaller deterioration in HRQoL (EQ-5D-5L HSI) over the duration of the maintenance phase, compared with those who continued their OAD but switched to PBO-NS. (15)
Overall, the SUSTAIN-1 data show that after 16 weeks of initial ESK-NS treatment, maintenance treatment with ESK-NS + OAD is associated with sustained improvement in patient social and occupational functioning and quality of life, which will have a positive impact on not only the patients themselves, but also their family, friends and carers. (15)

Serious adverse events

SAEs were reported in the ESK-NS + OAD group by 13 of 437 (3.0%) subjects during the open-label induction phase, 11 of 455 (2.4%) subjects during the optimization phase, and 4 of 152 (2.6%) subjects during the maintenance phase, see table 17. In the OAD + PBO-NS group, SAEs were reported during the maintenance phase by one subject (0.7%) in the safety (MA) analysis set. (1) SAEs considered by the investigator as related to study drug were reported for 6 patients in the ESK-NS + OAD group (autonomic nervous system imbalance, disorientation, hypothermia, lacunar stroke [ie, ischemic lesion, day 1, 6 hours after dosing], sedation, simple partial seizures [day 5, 45 minutes after dosing; no seizure history], and suicidal ideation) during the induction phase. (15)

Table 17: Overall incidence of SAEs in SUSTAIN-1. (1)

SUSTAIN-1	Treatment (+ Oral AD)	N	SAE	SAE Considered as at Least Possibly Related
Induction phase	Esk-NS 56-84 mg:	437	13 (3.0%)	6 (1.4%)
Optimization phase	Esk-NS 56-84 mg:	455	11 (2.4%)	0
Maintenance Phase	Esk-NS 56-84 mg:	152	4 (2.6%)	0
	PBO-NS:	145	1 (0.7%)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

Seven patients experienced 1 or more AEs during the maintenance phase, leading to discontinuation of the intranasal study drug, see table 18; 4 (2.6%) of 152 were in the ESK-NS + OAD group (worsening depression, 3 patients; anxiety and confusional state [transient], 1 patient) and 3 (2.1%) of 145 were in the OAD + PBO-NS (worsening depression for each). (15)

Table 18: Proportion of patients experiencing 1 or more TEATs leading to discontinuation of intranasal study medication during the maintenance phase of SUSTAIN-1.

Trial	Randomised interventions	N	Definition of discontinuation	Incidence of discontinuation	
				n	%
SUSTAIN-1	ESK-NS + OAD	152	Patients experiencing ≥1 TEAE leading to discontinuation of intranasal study medication	4	2.6
	OAD + PBO-NS	145		3	2.1

Abbreviations; SNRI, serotonin–norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event.

Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 5.1.7 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Based on MADRS definitions, the proportions of patients in stable remission and stable response, who had maintained their remitter/responder status by the end of the maintenance phase, were consistently higher among ESK-NS + OAD patients than OAD + PBO-NS, see table 19. (24) Overall, the results of SUSTAIN-1 indicate sustained improvements in the physician-reported symptoms of depression (mood, tension, sleep, appetite, concentration, lassitude, and empathy) as well as in patient-reported depressive symptoms and functional impairment/disability.

Table 19: Response and remission rates over the duration of the maintenance (MA) phase based on MADRS. (24)

	Full (stable remitters) analysis set N=176		Full (stable responders) analysis set N=121	
	ESK-NS + OAD N=90	OAD + PBO-NS N=86	ESK-NS + OAD N=62	OAD + PBO-NS N=59
Response/remission based on MADRS, n/N (%)				
Responder at beginning of MA	90/90 (100.0)	86/86 (100.0)	62/62 (100.0)	59/59 (100.0)
Responder at end of MA	67/89 (75.3)	48/86 (55.8)	41/62 (66.1)	20/59 (33.9)
Remitter at beginning of MA	90/90 (100.0)	85/86 (98.8)[a]	37/62 (59.7)	38/59 (64.4)
Remitter at end of MA	58/89 (65.2)	36/86 (41.9)	29/62 (46.8)	15/59 (25.4)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; MA, maintenance phase; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] one patient was incorrectly randomised.

Overall, among patients who achieved stable remission, 24 patients (26.7%) in the ESK-NS + OAD and 39 patients (45.3%) in the OAD + PBO-NS group experienced a relapse event during the maintenance phase; among the patients who achieved stable response, 16 patients (25.8%) in the ESk-NS + OAD group and 34 patients (57.6%) in the OAD + PBO-NS group experienced relapse, see table 20 and 21. Continued treatment with Esk-NS + OAD significantly delayed relapse compared with treatment with OAD + PBO-NS. Patients who achieved stable remission, see figure 9: Hazard ration(HR), 0.49; 95% CI, 0.29-0.84; *P* = .003, number needed to treat [NNT], 6. Patients who achieved stable response, figure 10: HR, 0.30; 95% CI, 0.16-0.55: *P* < .001, NNT, 4).(15)

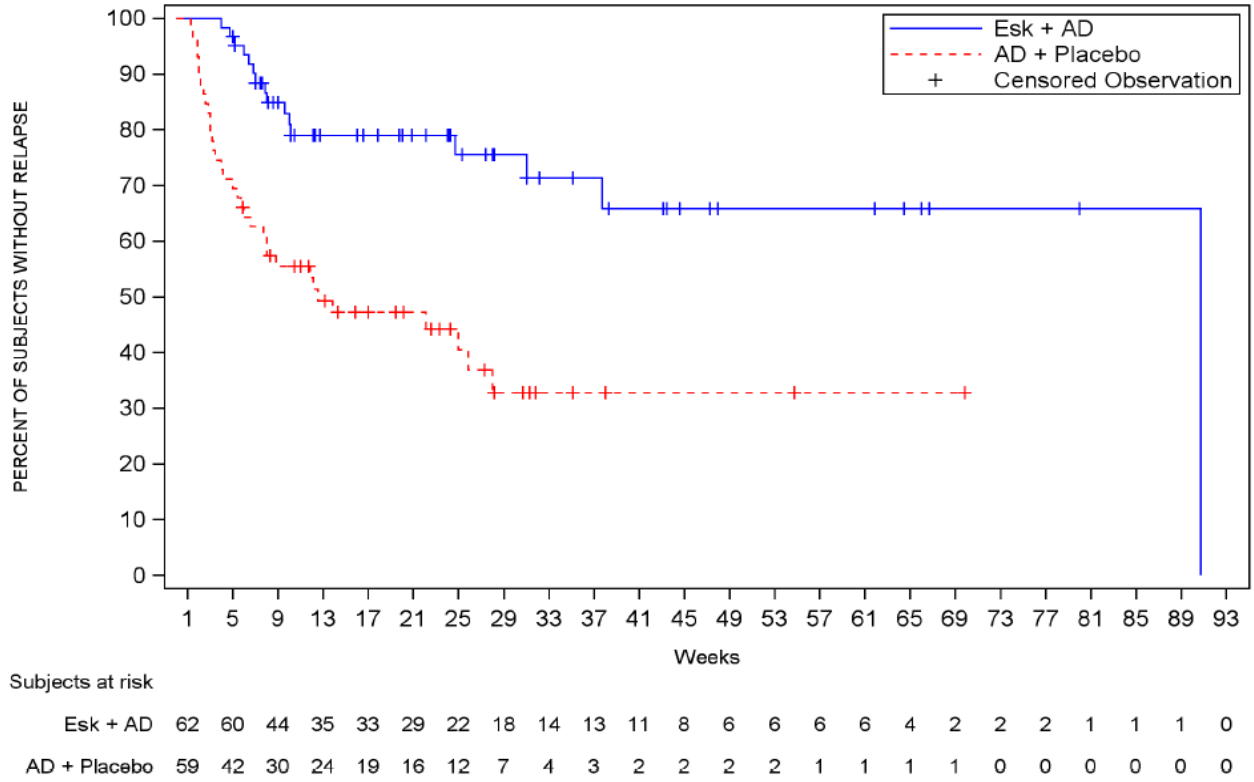
Table 20: Time to relapse and proportions of patients remaining relapse-free/stable responders (15)

	ESK-NS + OAD N=62	OAD + PBO-NS N=59
Time to relapse (days)[a]		
Patients assessed, n (%)	62 (100.0)	59 (100.0)
Patients censored, n (%)	46 (74.2)	25 (42.4)
Relapses, n (%)	16 (25.8)	34 (57.6)
25th percentile (95% CI)	217.0 (56.0; 635.0)	24.0 (17.0; 46.0)
Median (95% CI)	635.0 (264.0; 635.0)	88.0 (46.0; 196.0)
75th percentile (95% CI)	635.0 (NE)	NE
HR (95% CI)[b]	0.30 (0.16; 0.55)	
2-sided p-value[c]	<0.001	

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HR, hazard ratio; NE, not estimable; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Based on Kaplan-Meier product limit estimates.

[b] Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor.
[c] Log-rank test.

Figure 9: Cumulative proportion of patient who remained relapse-free/stable remitters (15)



Abbreviations: AD, antidepressant; Esk, esketamine.

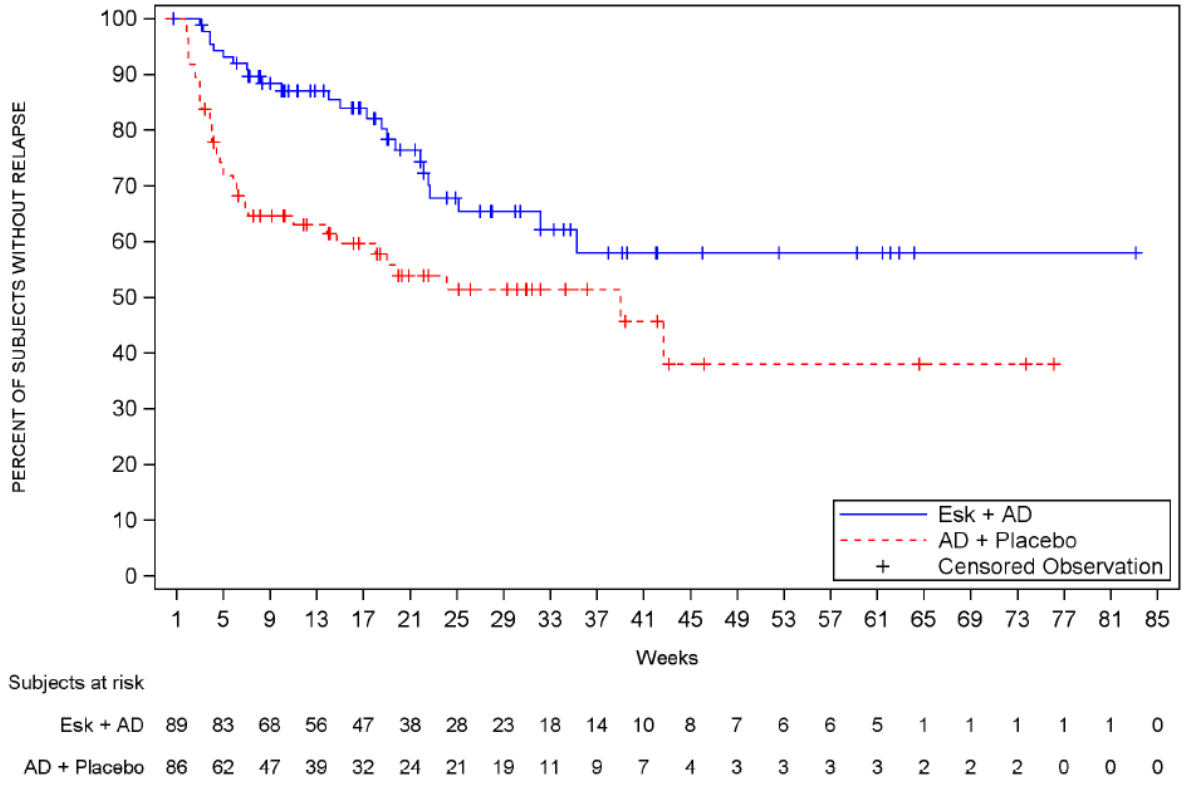
Table 21. Time to relapse and proportions of patients remaining relapse-free/stable remitters (15)

	ESK-NS + OAD N=90	**OAD + PBO-NS N=86**
Time to relapse (days)[a]		
Patients assessed, n (%)	90	86
Patients censored, n (%)	66 (73.3)	47 (54.7)
Relapses, n (%)	24 (26.7)	39 (45.3)
25th percentile (95% CI)	153.0 (105.0; 225.0)	33.0 (22.0; 48.0)
Median (95% CI)	NE	273.0 (97.0; NE)
75th percentile (95% CI)	NE	NE
HR (95% CI)[b]	0.49 (0.29; 0.84)	-
2-sided p-value[c]	0.003	-

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HR, hazard ratio; NE, not estimable; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Based on Kaplan-Meier product limit estimates.

[b] HRs and CIs are weighted estimates based on Wassmer (2006) (25) and calculated using R.
[c] Based on the final test statistic which is a weighted combination of the log-rank test statistics calculated on the interim full analysis set and on the full analysis set in stable remitters.

Figure 10: Cumulative proportion of patient who remained relapse-free/stable remitters (15)



Abbreviations: AD, oral antidepressant; Esk, esketamine nasal spray.

Quality of life

In both stable remitters and stable responders, those in the ESK-NS + OAD arm experienced smaller reductions in HRQoL (EQ-5D-5L HSI) compared with those in the OAD + PBO-NS arm over the duration of the maintenance phase. Mean (SD) changes in HSI from baseline of the maintenance phase to the endpoint of the maintenance phase among stable remitters were -0.067 (0.1180) for subjects treated with ESK-NS + OAD and -0.096 (0.1484) for those treated with OAD + PBO-NS. (24) In addition the mean (SD) changes in HSI for stable responders were -0.023 (0.0753) for subjects treated with ESK-NS + OAD and -0.073 (0.1383) for those treated with OAD + PBO-NS. (24)

These results show that ESK-NS + OAD treatment maintained the increase in quality of life more sufficiently over the cause of the maintenance phase compared to OAD + PBO-NS. Consequently, more patients will remain being able to care for themselves, being more mobile, experience less pain and depression or anxiety, and a higher number of patients will remain being able to resume their usual activities compared with OAD + PBO-NS.

6.1.7 Narrative review of specific incidents, death for whatever reason and suicide attempts

In the primary safety analysis set across the included phase 3 studies in TRD, there was 1 death among patients with ESK-NS + OAD and no deaths occurred in the OAD + PBO-NS groups, see table 22.

Table 22: Overview of deaths observed in the included studies of this application.(1)

Subject Number (Study)	Age Sex	Dictionary-derived Term (Reported Term)	Study Day of Onset	Protocol Phase	Onset Dose	Investigator's assessment of Relationship
COMPLETED STUDIES						
Phase 3 TRD Studies (esketamine + newly initiated oral AD)						
TRANSFORM-2	41 Male	Multiple injuries (Multiple injuries following a road traffic accident)	16[b]	DB	<84>	Not related

In regards to TRANSFORM-2, one patient in the ESK-NS + OAD group experienced multiple injuries following a road traffic (motorbike) accident on day 16 of the double-blind phase and subsequently died on day 55, 40 days after the last dose of esketamine. The motor vehicle accident with fatal outcome occurred ~28 hours after the patient's last dose of esketamine. Information on drug levels at the time of death is not available, as it was not collected in the emergency room. This patient underwent pre-dose cognitive testing evaluation, which included reaction time measurement on the day of the final dosing preceding the accident, with normal results. The patient did not experience other adverse events. No history of suicidal behavior and no suicidal ideations (C-SSRS was 0 at all timepoints) were reported. In the SAE report narrative provided by the site, the verbatim description of the event was: "The accident was not patient's fault, but he ended up falling down and hitting a tree." The investigator assessed the road traffic accident as doubtfully related to esketamine or antidepressant. An autopsy was performed, however the report was not shared with investigator or Sponsor based on the family's wishes. (23)
The Sponsor's internal Safety Management Team (a product-based, cross-functional collaborative team responsible for review, assessment, and evaluation of Medical Safety data arising from any source) also reviewed the case as part of the Safety Oversight and, based on the available evidence, considered it not related to the study treatment. Similarly, the case was reviewed by an Independent Data Monitoring Committee (IDMC) established for the esketamine phase 3 TRD studies
Esketamine has a short half-life and is rapidly cleared from the plasma (which tightly parallels the rates of the drop in brain concentrations and receptor occupancy), therefore it seems unlikely that esketamine played a role in this accident. Moreover, we conducted two formal studies of the effects of esketamine nasal spray on driving, which supported the safety of driving on the day following esketamine dosing. Per protocol, patients were discharged from the clinical site accompanied by a responsible adult and were not allowed to drive a car or operate machinery within 24 hours following an intranasal session. (23)

6.1.8 Comparative analyses

ESK-NS (Spravato®) + a newly initiated OAD has been directly compared with OAD + NS-PBO in four Phase 3 clinical trials: three acute, 4-week treatment studies (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3), and one maintenance study (SUSTAIN-1). As per the Handbook of the Medicines Council's process and methodologies for new pharmaceuticals and indication expansions version 2.4, a meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model. (26)
Forest plots available in section 8.3 show the risk ratio and mean difference results of the performed meta-analyses. All the I^2 statistic were less than 50% and chi-squared test were non-significant, thus the tests for heterogeneity does not indicate presence of heterogeneity (27). Consequently, the meta-analyses are all based on fixed effects estimates.

The absolute differences in effect were calculated using the estimated risk ratio (RR) from the meta-analyses as well as the event rates and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4. (28)

Serious adverse events at induction

The relative difference in RR between Spravato® + OAD and OAD + PBO-NS in the proportion of patients experiencing a SAE in the induction period is 1.398 (0.369-5.295). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinically added value cannot be categorized, see table 23.
In addition, the estimated difference on absolute effect is 0.4% (-0.07%-4.5%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 2.5%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 4.5% is neither equal to; upper limit (UL) ≤ -2.5%-point nor is it equal to; UL < 2.5%-point and the lower bound of -0.7% is not equal to; LL > MKRF 2.5%-point.

Table 23: Clinically added value of Spravato® in regards to SAEs at induction.

Clinically added value – Serious adverse events		
Absolute difference - SAE	**Adjusted least clinically relevant difference** -2.5%	**Estimated CI**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	
Negativ merværdi	LL > MKRF (statistisk signikant forskel)	
Kan ikke kategoriseres		0.4% (-0.7%-4.5%)
Relative difference - SAE	**Specified confidence limit - SAE**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75=<UL<0.90 eller (UL<0.75 og risiko < 5%)	
Lille merværdi	0.90 =< UL < 1.00 og LL =< 0.75	
Merværdi af ukendt størrelse	0.90 =< UL < 1.00 og LL<0.75	
Ingen dokumenteret merværdi	1.00=<UL<1.11 og LL=<1.00	
Negativ merværdi	LL>1.00	

Kan ikke kategoriseres		1.398 (0.369-5.295)

Serious adverse events at maintenance

Regarding the relative difference between Spravato® + OAD and OAD + PBO-NS in the proportion of patients experiencing a SAE in the maintenance period, the RR is 3.816 (0.432-33.739).
As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinically added value cannot be categorized, see table 24.
In addition, the estimated difference on absolute effect is 1.9% (-0.4%-22.6%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 2.5%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 22.6% is neither equal to; upper limit (UL) ≤ -2.5%-point nor is it equal to; UL < 2.5%-point and the lower bound of -0.4% is not equal to; LL > MKRF 2.5%-point.

Table 24: Clinically added value of Spravato® in regards to SAEs at maintenance.

Clinically added value – Serious adverse events		
Absolute difference - SAE	**Adjusted least clinically relevant difference -2.5%**	**Estimated CI_high**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	
Negativ merværdi	LL > MKRF (statistisk signikant forskel)	
Kan ikke kategoriseres		1.9% (-0.4%-22.6%)
Relative difference - SAE	**Specified confidence limit - SAE**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75=<UL<0.90 eller (UL<0.75 og risiko < 5%)	
Lille merværdi	0.90 =< UL < 1.00 og LL =< 0.75	
Merværdi af ukendt størrelse	0.90 =< UL < 1.00 og LL<0.75	
Ingen dokumenteret merværdi	1.00=<UL<1.11 og LL=<1.00	
Negativ merværdi	LL>1.00	
Kan ikke kategoriseres		3.816 (0.432-33.739)

Discontinuation due to adverse events at induction

The relative difference in RR between Spravato® + OAD and OAD + PBO-NS in the proportion of patients discontinuing treatment due to adverse events in the induction period is 2.598 (0.966-6.985). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinically added value cannot be categorized, see table 25.
In addition, the estimated difference on absolute effect is 2.8% (-0.1%-10.4%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 10%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 10.4% is neither equal to;

upper limit (UL) ≤ -10%-point nor is it equal to; UL < 10%-point and the lower bound of -0.1% is not equal to; LL > MKRF 2.5%-point.

Table 25: Clinically added value of Spravato® in regards to discontinuation at induction.

Clinically added value - Discontinuation		
Absolute difference – Discontinuation	**Adjusted least clinically relevant difference** -10%	**Estimated CI_high**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	
Negativ merværdi	LL > MKRF (statistisk signikant forskel)	
Kan ikke kategoriseres		2.8% (-0.1%-10.4%)
Relative difference - Discontinuation	**Specified confidence limit - Discontinuation**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75=<UL<0.90 eller (UL<0.75 og risiko < 5%)	
Lille merværdi	0.90 =< UL < 1.00 og LL =< 0.75	
Merværdi af ukendt størrelse	0.90 =< UL < 1.00 og LL<0.75	
Ingen dokumenteret merværdi	1.00=<UL<1.11 og LL=<1.00	
Negativ merværdi	LL>1.00	
Kan ikke kategoriseres		2.598 (0.966-6.985)

Discontinuation due to adverse events at maintenance

Regarding the relative difference between Spravato® + OAD and OAD + PBO-NS in the proportion of patients experiencing a SAE in the maintenance period, the RR is 1.272 (0.290-5.585). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinically added value cannot be categorized, see table 26.
In addition, the estimated difference on absolute effect is 0.6% (-1.5%-9.5%). Thus, the preliminary added value falls under the category no documented added value. This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 10%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 9.5% which is equal to; UL < 10%-point.

Table 26: Clinically added value of Spravato® in regards to discontinuation at maintenance.

Clinically added value - Discontinuation		
Absolute difference – Discontinuation	**Adjusted least clinically relevant difference -10%**	**Estimated CI_high**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	0.6% (-1.5%-9.5%)
Negativ merværdi	LL > MKRF (statistisk signikant forskel)	
Kan ikke kategoriseres		
Relative difference - Discontinuation	**Specified confidence limit - Discontinuation**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75=<UL<0.90 eller (UL<0.75 og risiko < 5%)	
Lille merværdi	0.90 =< UL < 1.00 og LL =< 0.75	

Merværdi af ukendt størrelse	0.90 =< UL < 1.00 og LL<0.75	
Ingen dokumenteret merværdi	1.00=<UL<1.11 og LL=<1.00	
Negativ merværdi	LL>1.00	
Kan ikke kategoriseres		1.272 (0.290-5.585)

Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 5.1.7 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission at induction

The relative difference in RR between Spravato® + OAD and OAD + PBO-NS in the proportion of patients achieving remission at the end of the induction period at day 28 is 1.4 (1.163-1.860).
In addition, the absolute difference in effect following induction is 11.9% (4.1%-21.8%). The RR point estimate of 1.473 in favor of Spravato® + OAD suggests that the likelihood of having remission at day 28 is 1.473 times higher when treated with Spravato® + OAD compared to OAD + PBO-NS. Furthermore, as the lower confidence interval of the relative difference is above 1.11 the preliminary clinically added value is moderate as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, see table 27. (28) The absolute effect point difference in favor of Spravato® + OAD is above the 10%-point difference defined as being the least clinically relevant difference. Furthermore, as the lower confidence interval of 4.1% is above the negative adjusted least clinically relevant difference (LL > -5%-point) but not equal to LL ≥ 5%-point, the preliminary categorization of clinically added value is no documented added value.

Table 27: Clinically added value of Spravato® in regards to remission at induction.

Clinically added value - Remission		
Absolute difference - Remission	**Adjusted least clinically relevant difference – 7.5%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	11.9% (4.1%-21.8%)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)	
Relative difference - Remission	**Specified confidence limit - Remission**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	1.470 (1.163-1.860)
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	

Remission at maintenance

Regarding the relative difference between Spravato® + OAD and OAD + PBO-NS in the proportion of patients achieving remission at the end of the maintenance period for the stable remitters, the RR is 1.557 (1.163-2.084) whereas it for stable responders is 1.840 (1.103-3.068)
In addition, the absolute difference in effect following maintenance is 23.3% (6.8%-45.4%) and 21.4% (2.6%-52.6%) for stable remitters and stable responders, respectively. The RR point estimates of 1.557 and 1.840 in favor of Spravato® + OAD suggests that the likelihood of having remission at the end of the maintenance period is 1.557 and 1.840 times higher when treated with Spravato® + OAD compared to OAD + PBO-NS for stable remitters and stable responders, respectively. Furthermore, as the lower confidence interval of the relative difference is above 1.11 for the stable remitters the preliminary clinically added value is moderate as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, see table 28. (28) Furthermore, the preliminary clinically added value is of unknown size for the stable responders as the lower confidence interval is placed between 1.11 and 1.00, and the upper confidence interval is above 1.33
The absolute effect point difference of 23.3% for stable remitters and 21.4% for stable responders in favor of Spravato® + OAD is well above the 15%-point difference defined as being the least clinically relevant difference. Furthermore, as the lower confidence interval of 6.8% and 2.6% for stable remitters and stable responders, respectively, is above the negative adjusted least clinically relevant difference (LL > -7.5%-point), the preliminary categorization of clinically added value is no documented added value.

Table 28: Clinically added value of Spravato® in regards to remission at maintenance.

Clinically added value - Remission			
Absolute difference - Remission	**Adjusted least clinically relevant difference – 7.5%**	**Estimated (CI) Stable remitters**	**Estimated (CI) Stable responders**
Merværdi af ukendt størrelse	LL ≥ MKRF		
Ingen dokumenteret merværdi	LL > -MKRF	23.3% (6.8%-45.4%)	21.4% (2.6%-52.6%)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)		
Relative difference - Remission	**Specified confidence limit - Remission**	**RR (CI) Stable remitters**	**RR (CI) Stable responders**
Stor merværdi	LL>1.33		
Moderat merværdi	1.33 ≥ LL > 1.11	1.557 (1.163-2.084)	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33		
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33		1.840 (1.103-3.068)
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00		
Negativ merværdi	UL<1.00		

Response at induction

The relative difference in RR between Spravato® + OAD and OAD + PBO-NS in the proportion of patients achieving response at the end of the induction period at day 28 is 1.379 (1.164-1.634).
In addition, the absolute difference in effect following induction is 14.4% (6.2%-24.1%). The RR point estimate of 1.379 in favor of Spravato® + OAD suggests that the likelihood of having response at day 28 is 1.379 times higher when treated with Spravato® + OAD compared to OAD + PBO-NS. Furthermore, as the

lower confidence interval of the relative difference is above 1.11 the preliminary clinically added value is moderate as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, see table 29. (28) Furthermore, as the lower confidence interval of the absolute difference of 6.2% is above the negative adjusted least clinically relevant difference (LL > -10%-point) but not equal to LL ≥ 10%-point, the preliminary categorization of clinically added value is no documented added value.

Table 29: Clinically added value of Spravato® in regards to response at induction.

Clinically added value - Response		
Absolute difference - Response	**Adjusted least clinically relevant difference – 10%**	**Estimated (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	14.4% (6.2%-24.1%)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)	
Relative difference - Response	**Specified confidence limit - Response**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	1.379 (1.164-1.634)
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	

Response at maintenance

Regarding the relative difference between Spravato® + OAD and OAD + PBO-NS in the proportion of patients achieving response at the end of the maintenance period for the stable remitters, the RR is 1.349 (1.080-1.685) whereas it for stable responders is 1.951 (1.310-2.906). In addition, the absolute difference in effect following maintenance is 19.5% (4.5%-38.2%) and 32.2% (10.5%-64.5%) for stable remitters and stable responders, respectively. The RR point estimates of 1.349 and 1.951 in favor of Spravato® + OAD suggests that the likelihood of having remission at the end of the maintenance period is 1.349 and 1.951 times higher when treated with Spravato® + OAD compared to OAD + PBO-NS for stable remitters and stable responders, respectively. Furthermore, as the lower confidence interval of the relative difference is placed between 1.33 and 1.11 the preliminary clinically added value is moderate for the stable responders as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, see table 30. (28) Furthermore, the preliminary clinically added value is of unknown size for the stable remitters as the lower confidence interval is placed between 1.11 and 1.00, and the upper confidence interval is above 1.33

The absolute effect point difference of 19.5% for stable remitters and 32.2% for stable responders in favor of Spravato® + OAD is very close to and above the 20%-point difference defined as being the least clinically relevant difference. Furthermore, as the lower confidence interval of 10.5% is above the adjusted least clinically relevant difference (LL ≥ 10%-point), the preliminary categorization of clinically added value is added value of unknown size for stable responders. For stable remitters the lower limit confidence interval of 4.5% is above the negative adjusted least clinically relevant difference (LL > -10%-point).

Table 30: Clinically added value of Spravato® in regards to response at maintenance.

Clinically added value - Response			
Absolute difference - Response	**Adjusted least clinically relevant difference – 10%**	**Estimated (CI) Stable remitters**	**Estimated (CI) Stable responders**
Merværdi af ukendt størrelse	LL ≥ MKRF		32.2% (10.5%-64.5%)
Ingen dokumenteret merværdi	LL > -MKRF	19.5% (4.5%-38.2%)	
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)		
Relative difference - Response	**Specified confidence limit - Response**	**RR (CI) Stable remitters**	**RR (CI) Stable responders**
Stor merværdi	LL>1.33		
Moderat merværdi	1.33 ≥ LL > 1.11		1.951 (1.310-2.906)
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33		
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	1.349 (1.080-1.685)	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00		
Negativ merværdi	UL<1.00		

Quality of life at induction

The mean difference change in health status index from baseline to the endpoint of the double-blind induction between Spravato® + OAD and OAD + PBO-NS of 0.054 (0.017-0.092) demonstrate an improvement in quality of life in patients with TRD. However, as the lower confidence interval of the absolute difference of 0.021 is above the negative adjusted least clinically relevant difference (LL > -0.035 points) but not equal to LL ≥ 0.035 points, the preliminary categorization of clinically added value is no documented added value, see table 31.

Table 31: Clinically added value of Spravato® in regards to EQ-5D at induction.

Clinically added value - EQ-5D		
Absolute difference – EQ-5D	**Adjusted least clinically relevant difference – 0.035 points**	**Estimated (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	0.054 (0.017-0.092)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)	

Quality of life at maintenance

The mean difference change in health status index from baseline of the maintenance phase to the endpoint of the maintenance phase between Spravato® + OAD and OAD + PBO-NS of 0.029 (-0.011-0.069) and 0.050 (0.010-0.090) demonstrate an improvement in quality of life in patients with TRD. However, as the lower confidence interval of the absolute difference of -0.011 for stable remitters and 0.010 for stable responders is above the negative adjusted least clinically relevant difference (LL > -0.035 points) but not equal to LL ≥ 0.035 points, the preliminary categorization of clinically added value is no documented added value, see table 32.

Table 32: Clinically added value of Spravato® in regards to EQ-5D at maintenance.

Clinically added value - EQ-5D			
Absolute difference – EQ-5D	**Adjusted least clinically relevant difference – 0.035 points**	**Estimated (CI) Stable remitters**	**Estimated (CI) Stable responders**
Merværdi af ukendt størrelse	LL ≥ MKRF		
Ingen dokumenteret merværdi	LL > -MKRF	0.029 (-0.011-0.069)	0.050 (0.010-0.090)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)		

6.1.9 Other considerations

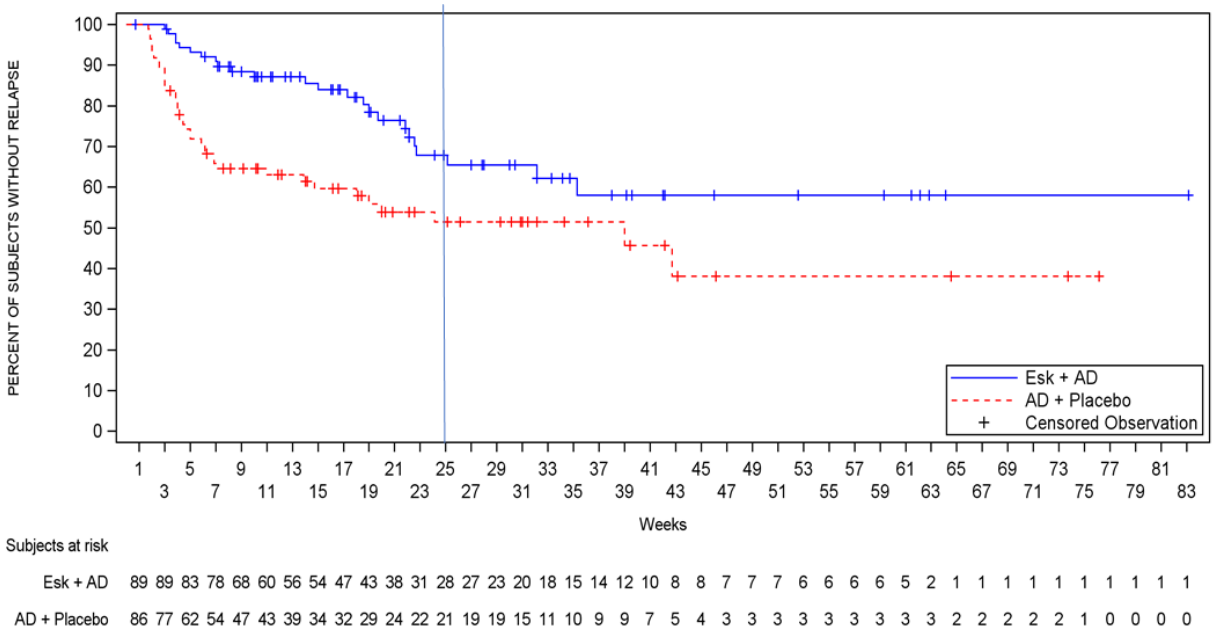
Treatment length

For the patients who achieve response or remission at the end of the induction phase (4 weeks), as stated in the SmPC, it is expected that they will discontinue esketamine nasal spray when there is no clinical need for further treatment (treatment is recommended for at least 6 months with the need for continued treatment re-examined periodically as stated in the SmPC). In clinical practice, it is expected that physicians would aim to reduce the esketamine nasal spray treatment length as much as possible based on individual patient needs. But as TRD patients have a severe depression (long time since first diagnosis and long/recurrent episodes), it is expected that the majority of patients will require Spravato® nasal spray treatment for 6-12 months.

In average 9 months (approx. 36 weeks) after the induction phase is defined as the timepoint of recovery, hence the time a patient can stop esketamine treatment. This 36 weeks definition (recovery definition) was supported by clinical data on relapse among stable remitters from the SUSTAIN-1 trial.
SUSTAIN-1 consisted of an open-label induction phase (4 weeks; direct-entry patients only), an optimisation phase (12 weeks; both direct-entry and transferred-entry patients), and a double-blind maintenance phase. After 24 weeks of maintenance therapy, patients showed a reduced risk of relapse, see figure 11. This corresponds to 36 weeks after the induction treatment period (12 weeks optimization + 24 weeks maintenance). Thus, patients before this timepoint are in remission and are subject to higher relapse risk compared to patients who had passed 36 weeks post-acute treatment, where their relapse risk is lower.(15)

Conclusive we assume the treatment length of Spravato® in combination with a SSRI or SNRI to be 4 weeks of induction + approx. 36 weeks of maintenance treatment as the clinicians can be more sustain that the patients will remain stable after the discontinuation of Spravato®.

Figure 3: Kaplan-meier curve over proportion of patient who remained relapse-free/stable remitters(15)



Reflections related to practical aspect of Spravato® administration

Spravato® is intended to be self-administered by the patient under the direct supervision of a healthcare professional (HCP) as Spravato® has been reported to cause adverse events during the clinical trials that may blood pressure, impair attention, judgment, thinking, reaction speed and motor skills. Therefore, patients should be monitored under the supervision of an HCP at each treatment session to assess when the patient is considered stable and ready to leave the clinic based on clinical judgement and the risk minimization document "ready to leave checklist" (5) A post hoc analysis observed that ≥90% of patients were considered ready for discharge at 90 minutes after Spravato® administration. (29) Furthermore, based on the trial investigators' experience, the supervision of self-administration of a group of six patients in a clinic could be managed by one or two nurses. (30)

There is also attached a benefit to the direct supervision by an HCP as it ensures proper guidance and support of the patient during the self-administration of esketamine as well as compliance transparency with the treatment. (5)

From a patient perspective we recognize that the supervision required at each administration session could interfere with patients' everyday life, especially during the initial induction phase (first 4 weeks). However, in this context it is equally important to emphasize the suffering caused by an insufficiently treated TRD. TRD is a severely debilitating and potentially life-threatening disease. Symptoms include profound sleep disturbance, fatigue, change in appetite/weight, agitation or slowness of speech/action, diminished concentration, decreased libido, inability to enjoy usual activities, and feelings of worthlessness. These symptoms result in an impaired capacity and inability to work, to the point of complete inability to function, which substantially interferes with social connection, integration and relationships. (6)
Thus, the possible benefit of Spravato® treatment has been a key driver for many patients' engagement in the esketamine trials as it has outweighed the need for regular visits.

Reflections related to compliance

With respect to the raised concern regarding lack of compliance, data from the long-term study SUSTAIN-1 showed that no patients were withdrawn from the esketamine treatment group during the maintenance phase due to non-compliance. (24) These results underline that patients with a satisfying initial treatment response are prone to adhere to the treatment. As the treatment with esketamine requires supervision, any potential compliance issues will be fully transparent to the HCP and allow them to act accordingly to avoid any serious consequences for the patient. (5)

Secondly, ketamine, the racemic mixture of arketamine and esketamine, is listed as a narcotic agent in Denmark with a well-known potential for recreational abuse. Spravato® contains esketamine however, there were no reports of drug-seeking behavior (e.g. requests for dosing changes and/or diversion of Spravato®), no reports of patients requesting an increase in dose or dosing frequency (a potential early indicator of drug-seeking behavior) or evidence of a distinct withdrawal syndrome after cessation of treatment (PWC-20 results) in the Phase 3 clinical trials of Spravato® (5, 31) To minimize any potential risk of abuse, misuse and diversion associated with the self-administration of Spravato® the product is to be administered under the direct supervision of an HCP.
Whether any patients would initiate self-medication with illegal ketamine caused by lack of compliance during continuous treatment cannot be excluded. However, the illicit use of ketamine has been reported on a relatively small global scale for several decades. (32) In line with this the Danish Health Authorities conducted a survey in 2017 concluding that only 2% of all respondents aged 16-44 years had experience with the illicit use of ketamine, whereas persons above 44 years were excluded due to a very limited use of illegal drugs. (33) These data underlines that ketamine is not a commonly misused drug in Denmark, which reduces the overall risk of self-medication. Further, to minimize the risk of any drug abuse related to Spravato® treatment, risk minimization material for all psychiatrists will be provided addressing how to carefully assess each patient's risk for abuse and misuse prior to prescribing Spravato®. This information should also increase the awareness among HCPs to monitor each patient for signs of drug abuse. Based on this we find it unlikely that well-treated patient would discontinue Spravato® and initiate illicit ketamine self-medication. (5, 31)

Summary of registered manic events during treatment and follow-up.

Emergence of symptoms of hypomania or mania have been reported with the use of oral AD in patients with MDD. Emergence of such symptoms may be related to undiagnosed bipolar disorder.

Patients with current or prior DSM-5 diagnosis of bipolar disorder or related disorders (as assessed by the Mini International Neuropsychiatric Interview [MINI]) were excluded from enrollment in the esketamine clinical phase 3 trials. Further, the use of lithium, anticonvulsants (valproate, carbamazepine), and antipsychotics were prohibited during the study.

In the phase 3 esketamine clinical trial program, the observed rate of mania/hypomania was <0.5%. A confounding factor was all subjects initiated a newly initiated oral AD at the time of study entry. Across completed phase 2 and 3 studies, treatment-emergent adverse events (TEAEs) of mania/hypomania were reported in 2 patients exposed to esketamine + an oral antidepressant (case 1 and case 2). (1) A third subject was reported to have hypomania during the study (case 3) but was defined as euphoria instead during follow-up by investigator.

Below in table 33 and 34 is a list of the reported treatment emergent adverse events of mania/hypomania in the clinical phase 3 trial program of esketamine (Short-term trials: TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3) (Long-term trial: SUSTAIN-1) during treatment and follow-up periods. A short description of each of the individual cases is also presented. (24)

Table 33: Treatment emergent adverse events of mania/hypomania in TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3

Short-term trials						
TEAE; Mania	**TRANSFORM-1**		**TRANSFORM-2**		**TRANSFORM-3**	
	Esk-NS+oAD (n=231)	PBO+oAD (N=113)	Esk-NS+oAD (n=116)	PBO+oAD (n=111)	Esk-NS+oAD (n=72)	PBO+oAD (n=66)
Treatment	1 (0.4%)	0	0	0	0	0
Follow-up	0	0	0	0	0	0

Table 34: Treatment emergent adverse events of mania/hypomania in TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3

Long-term trial							
TEAE; Mania/hypomania	**SUSTAIN-1 (OL Induction Phase)**	**SUSTAIN-1 (optimization phase)**		**SUSTAIN-1 (Db Maintenance phase)**		**SUSTAIN-1 (Follow-up Phase)**	
	Esk-NS+oAD (n=437)	Esk-NS+oAD (n=455)	PBO+oAD (n=86)	Esk-NS+oAD (n=152)	PBO+oAD (n=145)	Esk-NS+oAD (n=481) for any phases	PBO+oAD (n=64) for any phases
Treatment	1 (0.2%)	0	0	0	0	-	-
Follow-up	-	-	-	-	-	1 (0.2%)	0

Safety analysis set

TRANSFORM-1: short description of case

- Case 1 (Mania): There was 1 reported AE of mania in a 20-year-old male on day 2 of the double-blind induction phase in a short-term phase 3 trial (TRANSFORM-1). The patient had received esketamine 56 mg + newly initiated daily duloxetine 60 mg the previous day. This AE led to withdrawal from the study, was resolved on day 7 without treatment, and was assessed as probably related to esketamine by the investigator. The investigator confirmed the subject had no prior history of bipolar disorder, no family history of bipolar disorder and no history of drug or alcohol use prior to the visit. (24)

SUSTAIN-1: short description of cases

- Case 2 (Mania): One direct-entry male subject aged 61-years, with no family history of bipolar disorder, was withdrawn from the induction phase at day 31 as he did not meet the criteria for continuing into the next phase. The subject had received eskteamin 56 mg + newly initiated daily sertraline 50 mg on day 1, was increased to 84 mg esketamine on day 5. The subject entered into the follow-phase by Day 32 and started experiencing depressive symptoms and was hospitalized on day 35 due to worsening symptoms. At the time, the patient was on sertraline 200 mg daily, and the dose was reduced to 100 mg daily on day 37. On day 38, the patient's depression resolved,

however a manic episode was reported the same day. Medications administered during the manic episode included sertraline, valproic acid, haloperidol, olanzapine, clonazepam, and lithium carbonate. The last dose of sertraline was on day 42, and the patient completed the follow-up phase on day 43. On day 65, the mania resolved, and the patient was discharged. This AE was assessed as not related to esketamine by the investigator and possibly related to sertraline. (24)

- Case 3 (euphoria): One direct-entry subject experience 4 separate adverse events (Day 1, 4, Day 18 and Day 25) that were initially reported as hypomania (moderate: first 3 events; mild: one event) in the open-label induction phase in a long-term relapse prevention study (SUSTAIN-1). However, on follow-up the investigator clarified that the symptoms lasted only 30 minutes on each occasion and agreed these events would be better defined as euphoria. This subject had no personal or family history of bipolar disorder. (24)

1. Data on co-morbidities among patients at study inclusion

Subjects with a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorder (confirmed by the MINI), comorbid obsessive-compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8 and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder were excluded from the phase 3 clinical esketamine trials.

The pooled incidence of common psychiatric comorbidities upon enrollment in the phase 3 TRD trials in adults 18-64 years (TRANSFORM-1, TRANSFORM-2 and SUSTAIN-1) and separately in adults ≥65 years (TRANSFORM-3) is presented in the table 35 below. Results of the Mini-International Neuropsychiatric Interview (MINI) was used to identify the presence of comorbid psychiatric conditions. This diagnostic interview was conducted at the site at the first screening visit to conform patient eligibility. (24)

Table 35: Pooled incidence of common psychiatric comorbidities upon enrollment in TRANSFORM-1, TRANSFORM-2 and SUSTAIN-1 and incidence in TRANSFORM-3.

	Pooled Incidence (TRANSFORM-1, TRANSFORM-2 & SUSTAIN-1) ESK patients (n=773)	TRANSFORM-3 ESK patients (n=72)
Generalized Anxiety Disorder	9.2% (n=71)	13.9% (n=10)
Panic Disorder	5.4% (n=42)	5.6% (n=4)
Social Anxiety Disorder	4.7% (n=36)	5.6% (n=2)
Agoraphobia	4.5% (n=35)	2.8% (n=2)
Posttraumatic Stress Disorder	1.6% (n=12)	0

Additionally, a pooled post hoc analysis of TRANSFORM-1 and TRANSFORM-2 looked at patients with TRD and comorbid anxiety at baseline based on 3 definitions: 1) presence of anxious depression, based on the Inventory of Depressive Symptomatology – Clinician rating (IDS-C) anxiety subscale (IDS-C_{ANX}) score ≥8; 2) comorbid anxiety disorder as evaluated by the Mini-International neuropsychiatric Interview (MINI); and 3) presence of anxious distress, based on a score ≥2 on at least 2 items of GAD-7 scale among the following items: item 1 (feeling anxious), 2 (unable to stop worrying), 5 (restlessness), and 7 (being afraid). At baseline, 22.3% (126/564), 14.2% (80/565) and 72.9% (412/565) of patients had anxious depression, comorbid anxiety disorder, or anxious distress, respectively. (34)

The proportion of comorbid psychiatric disorders in TRD patients of the clinical esketamine trial program is in line with a recent Swedish register-based cohort study reporting a psychiatric comorbidity of 26.4% among TRD patients (35) Further, the presence of comorbid anxiety disorder (14.2%) among TRD patients in the clinical trials is consistent with another recent Danish register-based cohort study (14.9%) (8). Thus, the TRD patient population included in the clinical trials has comparable psychiatric comorbidities with the general TRD population.

No summary data of somatic comorbidities were available from the clinical trials. Thus, it is only the psychiatric comorbidities that are presented in this section.

Data on average remission and response scores over time during treatment and follow up

Data on average remission and response scores over time are presented from the long-term relapse prevention study (SUSTAIN-1) in the below figure 11a and 11b (a: Patients who were stable Remitters; b: Patients who were stable Responders). (36)

Figure 11a: Mean (± SE) in MADRS total score over time LOCF during the Induction, optimization and maintenance Phases in patients who were Stable Remitters (36)

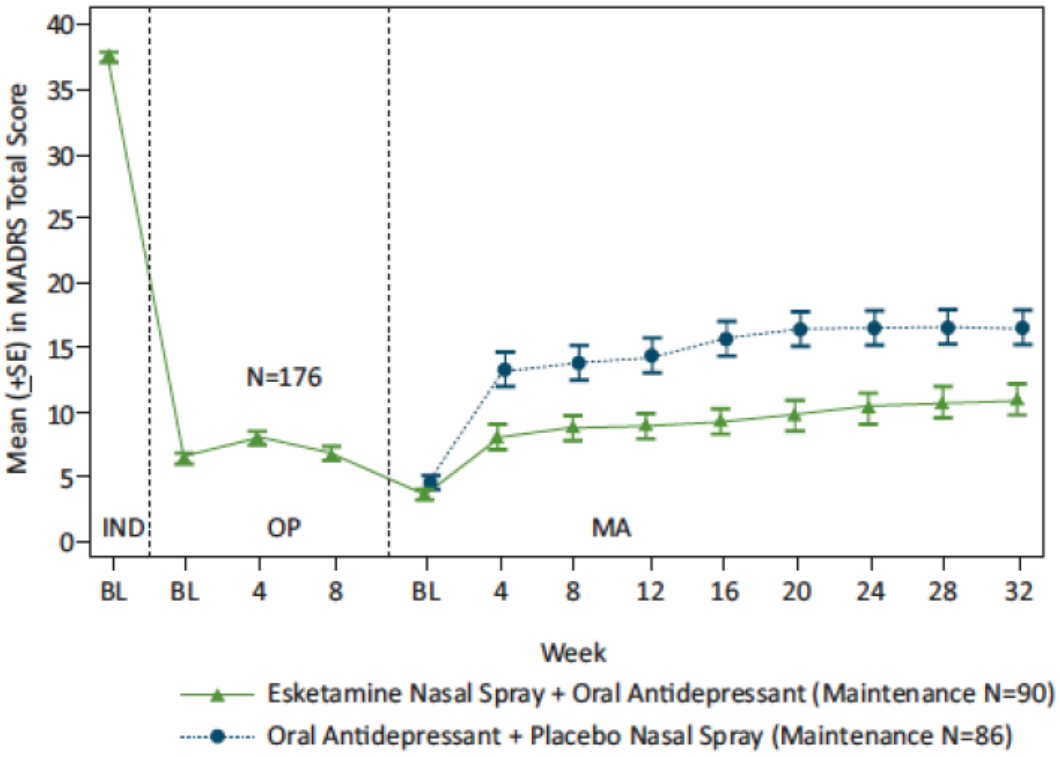
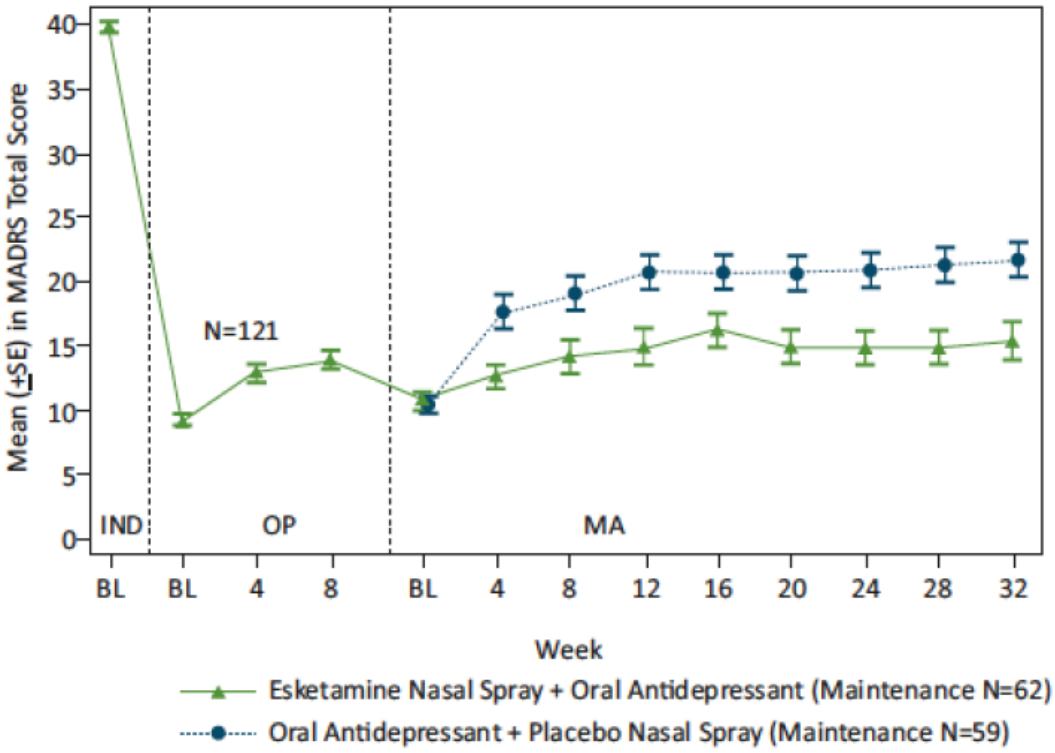


Figure 11b: Mean (± SE) in MADRS total score over time LOCF during the Induction, optimization and maintenance Phases in patients who were Stable Responders (36)



At baseline (induction phase), the mean (SD) MADRS total score was 37.7 (5.50) in esketamine-treated subjects (n=430), decreasing to 15.4 (12.44) at endpoint (induction phase). At baseline (optimization phase), the mean (SD) MADRS total score was 8.5 (5.93) in esketamine-treated subjects (n=452), and at endpoint (optimization phase), mean (SD) MADRS total score was 12.2 (10.57) (n=451). For stable remitters, both treatment groups showed an increase in mean MADRS total score from baseline (maintenance phase) to endpoint (maintenance phase). However, the mean (SD) increase was lower in subjects randomized to continue on intranasal esketamine (7.5 [11.59]) compared to subjects who discontinued intranasal esketamine (12.5 [13.63]). The LS mean (95% CI) difference between treatment groups was -5.2 (-8.77; -1.58), p<0.005. Similarly, among stable responders, the mean (SD) increase was 4.4 (11.38) in subjects randomized to continue intranasal esketamine + oral antidepressant compared to a mean (SD) increase of 11.4 (12.00) in subjects who were randomized to discontinue intranasal esketamine. The LS mean (95% CI) difference between treatment groups was -7.4 (-11.30; -3.55), p<0.001.

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8 Appendices

Main characteristics of included studies

8.1 Study characteristics

Table A2 Main study characteristics of TRANSFORM-1 (17, 18)

Trial name	TRANSFORM-1
NCT number	NCT02417064
Objective	The purpose of this study is to evaluate the efficacy, safety and tolerability of switching adult subjects (18-64 years) with TRD from a prior antidepressant treatment (to which they have not responded) to either fixed doses of ESK-NS (56 mg or 84 mg) + a newly initiated OAD or to a newly initiated OAD (active comparator) + PBO-NS
Publications – title, author, journal, year	Efficacy and Safety of fixed-dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1), Fedgchin et al., Int J Neuropsychopharmacol, 2019
Study type and design	This is a phase 3, randomized, double-blind, active-controlled, multicenter study in adult participants (18-64 years) with moderate to severe TRD (nonresponse to ≥1 to ≤5 antidepressants in the current depression episode) to assess the efficacy, safety, and tolerability of fixed doses of ESk-NS (56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator; escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS. Eligible subjects were randomly assigned at a 1:1:1 ratio by computer-generated randomization schedule (IWRS randomization codes) to either ESK-NS 56 mg, ESK-NS 84 mg or PBO-NS. Randomization was balanced by using randomly permuted blocks (blocks size of 6) and was stratified by country and by class of oral antidepressant (SSRI or SNRI). Patients, investigators, site personnel, those assessing outcomes, and those analyzing the data were blind to treatment assignment The ESK-NS and PBO-NS devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug. The same number of nasal spray devices (three) were given to patients to self-administer regardless of what dose of esketamine nasal spray (56 mg/84 mg) or treatment (esketamine or placebo) they were taking. The study consists of 3 phases: 1. Screening/Prospective Observational Phase: 4 Weeks + optional antidepressant taper period ≤3 weeks 2. Double-blind Induction Phase 4-weeks 3. Post-treatment follow-up Phase: 24-weeks (only for those participants ineligible or unwilling to participate in subsequent long-term study SUSTAIN-1 following double-blind induction phase. Thus, eligible participants rollover into a SUSTAIN-1 and was not part of the Follow-up Phase)

Follow-up time	**Double-blind induction phase (4 weeks)** Of the 346 subjects randomly assigned to treatment, 315 (91%) subjects completed the 28-day double-blind induction phase, and 31 (9%) subjects were withdrawn **Follow-up phase (24 weeks)** 168 subjects entered the follow-up phase, 36 (21.4%) of these subjects completed the follow-up phase and 132 (78.6%) of these subjects were withdrawn from the follow-up phase (17) **Maintenance study enrollment (SUSTAIN-1)** 150 subjects continued into the SUSTAIN-1 maintenance of effect study (only responders defined as ≥50% reduction in the MADRS total score from baseline to the end of the 4-week double-blind induction phase were eligible).
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • At the time of signing the informed consent form (ICF), participant must be a man or woman 18 (or older if the minimum legal age of consent in the country in which the study is taking place is greater than [>]18) to 64 years of age, inclusive • At the start of the screening/prospective observational phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) (if single-episode MDD, the duration must be greater than or equal to [>=] 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At the start of the screening/prospective observational phase, participant must have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of greater than or equal to (>=) 34 • At the start of the screening/prospective observational phase, participants must have had non-response (less than or equal to [<=25] percent [%] improvement) to >=1 but less than or equal to (<=) 5 (if current episode is >2 years, upper limit is applicable to only the last 2 years) oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by medical history and pharmacy/prescription records, for the current episode of depression. • Participant is taking a different oral antidepressant treatment on the MGH-ATRQ for at least the previous 2 weeks at or above the minimum therapeutic dose • The participant's current major depressive episode, depression symptom severity (Week 1 MADRS total score >=28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using a Site Independent Qualification Assessment **Exclusion Criteria:** • Participants who have previously demonstrated nonresponse of depressive symptoms to esketamine or ketamine in the current major depressive episode, to all 4 of the oral antidepressant treatment options available for the double-blind induction phase (i.e, duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT • Participant has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression

	• Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) • Participants with history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria
Intervention	**Double blind Induction phase (4 weeks)** Beginning from the double-blind induction phase, patients (n=346) were randomized 1:1:1 to receive: • ESK-NS 56 mg + OAD (n=117) • ESK-NS 84 mg + OAD (n=116) • Active comparator: OAD + PBO-NS (n=113)
Baseline characteristics	*See table A2a*
Primary and secondary endpoints	**Primary endpoints** The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1) in MADRS total score (independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28). **Secondary endpoints** The key secondary endpoints assessed: • The proportion of participants with onset of clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind phase with 1 excursion (i.e., ≥25% reduction relative to baseline MADRS allowed on days 8, 15 or 22) • Change from baseline in SDS total score to end of double-blind induction phase • Change from baseline in PHQ-9 total score to end of double-blind induction phase
Method of analysis	**Sample Size, power calculation** The maximum sample size planned was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between ESK-NS + OAD and OAD + PBO-NS arms, a SD of 12 , a 2-sided significance level of 0.025, and a drop-out rate of 25%. 116 patients were required to be randomized to each treatment group to achieve 90% power using a fixed design assuming no interim analysis. **Efficacy analyses**

	Efficacy analyses were performed on the full analysis set (all randomized subjects who received at least 1 dose of intranasal study mediation and 1 dose of oral antidepressant medication during the double-blind induction phase) using a truncated fixed sequence parallel gatekeeping procedure to adjust for multiplicity and to strongly control type I error. For each endpoint, testing of the ESK-NS 56 mg dose group was conducted only if the 84 mg dose group was significant. Sequential testing of the endpoints (in the order 1) Change in MADRS total score, 2) onset of clinical response by Day 2, 3) change in SDS total score, and 4) change in PHQ-9 total score) was performed for both dose groups only if they were significant for the previous endpoint in the hierarchy (84 mg dose group at 2-sided 0.05 level, 56 mg dose group at 2-sided 0.0425 level). If only the 84 mg dose group was significant for an endpoint, testing of the other endpoints down the hierarchy was conducted only for this dose group at the 2-sided 0.0075 level. **Primary efficacy endpoint** Primary efficacy was analysed using a mixed-effects repeated measures model (MMRM) with baseline MADRS total score as a covariate; treatment, region, oral antidepressant class (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects; and a random patient effect. The change from baseline for all post-baseline MADRS assessments (days 2, 8, 15, 22 and 28) were included in the model as the repeated measure. To account for sample size reassessment during the interim analysis, a weighted combination test was used for treatment comparisons, with the test statistic defined as an equally weighted sum of the test statistics determined before (stage 1) and after (stage 2) the interim analysis. The two stages were weighted equally in the combination test. A similar MMRM model was used for a post hoc, unweighted analysis of the primary endpoint combining the 2 ESK-NS dose groups, with the exception that the fixed effect for treatment included pooled ESK-NS + OAD and OAD + PBO-NS groups. Unweighted analyses were also conducted for various subgroups with a similar MMRM model as was used for the primary endpoint. **Secondary efficacy endpoints** <u>Key secondary endpoints</u> • Analysis of the weighted differences in the proportion of patients showing onset of clinical response by day 2 (24 hours) that was maintained for the duration of the double-blind induction phase (day 28) with 1 excursion allowed ((i.e. ≥25% reduction relative to baseline MADRS allowed on days 8, 15, or 22) in the ESK-NS + OAD (both dosing groups 56 mg/84 mg) arm versus OAD + PBO-NS was planned using a Cochran-Mantel-Haenszel chi square test adjusting for country and class of antidepressant (SSRI or SNRI). • The second and third key secondary efficacy endpoints, change from baseline in SDS and PHQ-9 total score at end of double-blind induction phase (day 28),respectively, were analyzed using the MMRM model and weighted combination test described for the primary efficacy analysis but using the respective baseline score (SDS or PHQ-9) as covariate. •
Subgroup analyses	In prespecified exploratory analyses, the point estimate (least squares mean) of the treatment difference (for each treatment comparison) of change from baseline (95% CI) to day 28 for MADRS total score (primary endpoint) were assessed by an

	unweighted MMRA analysis in the double-blind induction phase for each of the following subgroups (full analysis set): • sex (male/female) • age group (<45 years/≥45 years) • baseline MADRS total score (≤Median/>Median) • Number of previous treatment failures in current episode (1 or 2/ 3 or more) • Functional impairment based on baseline SDS (moderate/marked/extreme) • race (black/white/other) • class of antidepressant study medication (SNRI/SSRI)

Table A2a Baseline characteristics and demographics of patients enrolled in TRANSFORM-1 (full analysis set) (17).

	ESK-NS 56 mg + OAD N = 115	ESK-NS 84 mg + OAD N = 114	OAD + PBO-NS N = 113	Total N = 342
Age, years				
Mean (SD)	46.4 (11.18)	45.7 (11.10)	46.8 (11.36)	46.3 (11.19)
Range	22–64	18–64	18–64	18–64
Sex, n (%)				
Male	34 (29.6%)	35 (30.7%)	32 (28.3%)	101 (29.5%)
Female	81 (70.4%)	79 (69.3%)	81 (71.7%)	241 (70.5%)
Race, n (%)				
Asian	2 (1.7%)	1 (0.9%)	2 (1.8%)	5 (1.5%)
Black or African American	7 (6.1%)	7 (6.1%)	5 (4.4%)	19 (5.6%)
White	91 (79.1%)	85 (74.6%)	86 (76.1%)	262 (76.6%)
Other	8 (7.0%)	12 (10.5%)	10 (8.8%)	30 (8.8%)
Multiple	0	0	1 (0.9%)	1 (0.3%)
Not reported	7 (6.1%)	9 (7.9%)	9 (8.0%)	25 (7.3%)
Baseline body mass index (kg/m2)				
Mean (SD)	28.8 (6.70)	28.4 (5.86)	29.2 (6.69)	28.8 (6.42)
Range	18–56	17–50	19–50	17–56
Employment status[a], n (%)				
Any type of employment	60 (52.2%)	67 (58.8%)	67 (59.3%)	194 (56.7%)
Any type of unemployment	41 (35.7%)	41 (36.0%)	36 (31.9%)	118 (34.5%)
Other	14 (12.2%)	6 (5.3%)	10 (8.8%)	30 (8.8%)
Country, n (%)				
Belgium	8 (7.0%)	9 (7.9%)	12 (10.6%)	29 (8.5%)
Brazil	20 (17.4%)	19 (16.7%)	18 (15.9%)	57 (16.7%)
Canada	7 (6.1%)	7 (6.1%)	6 (5.3%)	20 (5.8%)
Estonia	3 (2.6%)	4 (3.5%)	3 (2.7%)	10 (2.9%)
France	11 (9.6%)	10 (8.8%)	10 (8.8%)	31 (9.1%)
Hungary	3 (2.6%)	1 (0.9%)	1 (0.9%)	5 (1.5%)
Mexico	14 (12.2%)	16 (14.0%)	15 (13.3%)	45 (13.2%)

Slovakia	4 (3.5%)	3 (2.6%)	3 (2.7%)	10 (2.9%)
United States	45 (39.1%)	45 (39.5%)	45 (39.8%)	135 (39.5%)
Age when diagnosed with MDD, years				
Mean (SD)	30.3 (12.34)	32.1 (12.86)	31.8 (12.44)	31.4 (12.54)
Range	11–61	9–59	10–63	9–63
Duration of current episode, weeks				
Mean (SD)	202.8 (277.25)	212.7 (327.62)	193.1 (264.10)	202.9 (290.24)
Range	12–1525	12–2288	6–1720	6–2288
No. of previous antidepressant				
medications[b,c], n (%)				
1 or 2	79 (69.9%)	59 (51.8%)	67 (59.3%)	205 (60.3%)
≥3	34 (30.1)	55 (48.2%)	46 (40.7%)	135 (39.7%)
Class of oral antidepressant[d], n (%)				
SNRI	65 (56.5%)	67 (58.8%)	64 (56.6%)	196 (57.3%)
SSRI	50 (43.5%)	47 (41.2%)	49 (43.4%)	146 (42.7%)
Oral antidepressant, n (%)				
Duloxetine	49 (42.6%)	43 (37.7%)	44 (38.9%)	136 (39.8%)
Escitalopram	26 (22.6%)	23 (20.2%)	24 (21.2%)	73 (21.3%)
Sertraline	24 (20.9%)	24 (21.1%)	25 (22.1%)	73 (21.3%)
Venlafaxine extended release (XR)	16 (13.9%)	24 (21.1%)	20 (17.7%)	60 (17.5%)

Abbreviations: CGI-S, Clinical Global Impression–Severity; MDD, major depressive disorder; PHQ, Patient Health Questionnaire; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a]Any type of employment includes: any category containing "employed", sheltered work, housewife or dependent husband, and student; any type of unemployment
includes: any category containing "unemployed"; other includes: retired and no information available.

[b]In accordance with the protocol, patients entering the induction phase had nonresponse to at least 2 oral AD medications prior to randomization. The data presented
is the number of AD medications with nonresponse (defined as ≤25% improvement) taken for at least 6 weeks during the current episode as obtained from
Massachusetts General Hospital Antidepressant Treatment Response Questionnaire at the beginning of the screening/prospective observational phase.

[c]Ns for the previous antidepressant medications are 113, 114, 113, and 340 for esketamine 56 mg/antidepressant, esketamine 84 mg/antidepressant, antidepressant/
placebo, and total, respectively.

[d]Assigned by the investigator at randomization.

Table A2.1 Main study characteristics of TRANSFORM-2 (14, 19)

Trial name	TRANSFORM-2
NCT number	NCT02418585
Objective	The purpose of this study is to evaluate the efficacy, safety and tolerability of switching adult subjects (18-64 years) with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly dosed ESK-NS (56 mg or 84 mg) plus a newly initiated OAD or to a newly initiated OAD (active comparator) + PBO-NS
Publications – title, author, journal, year	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, Popova et al., Am J Psychiatry, 2019
Study type and design	This is a phase 3, randomized, double-blind, active-controlled, multicenter study in adult participants (18-64 years) with moderate to severe TRD (nonresponse to ≥1 to≤5 antidepressants in the current depression episode) to assess the efficacy, safety, and tolerability of flexibly dosed ESK-NS (56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator: escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS. Eligible subjects were randomly assigned at a 1:1 ratio by computer-generated randomization schedule (IWRS randomization codes) to either ESK-NS (56 mg or 84 mg) or PBO-NS. Randomization was balanced by using randomly permuted blocks (blocks size of four) and was stratified by country and by class of oral antidepressant (SSRI or SNRI). Patients, investigators, site personnel, those assessing outcomes, and those analyzing the data were blind to treatment assignment. The ESK-NS and PBO-NS devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug. Throughout TRANSFORM-2, and during the double-blind maintenance phase of SUSTAIN-1, the same number of nasal spray devices (three) were given to patients to self-administer regardless of what dose of ESk-NS (56 mg/84 mg) or treatment (esketamine versus placebo) they were taking.
Follow-up time	**Double-blind induction phase (4 weeks)** Of the 227 subjects randomly assigned to treatment, 197 (86.8%) subjects completed the 28-day double-blind induction phase, and 30 (13.2%) subjects were withdrawn **Follow-up phase (24 weeks)** 86 subjects entered the follow-up phase, 43 (50.0%) of these subjects completed the follow-up phase and 43 (50.0%) of these subjects were withdrawn from the follow-up phase **Maintenance study rollover (SUSTAIN-1)** 118 subjects continued into the SUSTAIN-1 maintenance of effect study (only responders defined as ≥50% reduction in the MADRS total score from baseline to the end of the 4-week double-blind induction phase were eligible).
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • At the time of signing the informed consent form (ICF), participant must be a man or woman 18 (or older if the minimum legal age of consent in the

	country in which the study is taking place is greater than [>]18) to 64 years of age, inclusive • At the start of the screening/prospective observational phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) (if single-episode MDD, the duration must be greater than or equal to [>=] 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At the start of the screening/prospective observational phase, participant must have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of greater than or equal to (>=) 34 • At the start of the screening/prospective observational phase, participant must have had non-response (greater than or equal to [<=25] percent [%] improvement) to ≥1 but less than or equal to (<=) 5 (if current episode is >2 years, upper limit is applicable to only the last 2 years) oral antidepressant treatments in the current episode of depression, assessed using the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by medical history and pharmacy/prescription records, for the current episode of depression. In addition, the participant is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose • The participant's current major depressive episode, depression symptom severity (Week 1 MADRS total score >=28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using a Site Independent Qualification Assessment **Exclusion Criteria:** • Participants who have previously demonstrated nonresponse of depressive symptoms to esketamine or ketamine in the current major depressive episode, to all 4 of the oral antidepressant treatment options available for the double-blind induction phase (i.e., duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT • Participant has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), comorbid obsessive-compulsive disorder, intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) • Participants with history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria

Intervention	**Double blind Induction phase (4 weeks)** Beginning from the double-blind induction phase, patients (N=227) were randomized 1:1 to receive: • ESk-NS - 56 mg or - 84 mg + OAD (n=116) • Active comparator: OAD + PBO-NS (n=111)
Baseline characteristics	*See table A2.1a*
Primary and secondary endpoints	**Primary endpoints** The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1 prior to randomization) in clinician-administered MADRS total score (independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28) **Secondary endpoints** The key secondary endpoints assessed: • the proportion of participants with onset of MADRS clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind phase with 1 excursion (i.e., ≥25% reduction relative to baseline MADRS allowed on days 8, 15 or 22) • Change from baseline in Sheehan Disability Scale (SDS) total score to end of double-blind induction phase • Change from baseline in Patient Health Questionnaire-9 (PHQ-9) total score to end of the double-blind induction phase.
Method of analysis	**Sample Size, power calculation** The sample size planned was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between ESK-NS + OAD and the OAD + PBO-NS arms, a SD of 12, based on the results of a phase 2 study of ESK-NS for TRD (ESKETINTRD2003) and clinical judgment, a 2-sided significance level of 0.05, and a drop-out rate of 25%. 98 patients were required to be randomized to each treatment group to achieve 90% power using a fixed design assuming no interim analysis. **Efficacy analyses** Efficacy analyses were performed on the full analysis set (all randomized subjects who received at least 1 dose of intranasal study mediation and 1 dose of oral antidepressant medication during the double-blind induction phase) using a truncated fixed sequence parallel gatekeeping procedure to adjust for multiplicity and to strongly control type I error across the primary (change in MADRS total score) and the 3 key secondary efficacy endpoints (onset of clinical response by Day 2, change in SDS total score, and change in PHQ-9 total score). Statistical tests were conducted at a two-sided significance level 0.05. **Primary efficacy endpoint** Primary efficacy endpoint, change in MADRS score from baseline (day 1) to endpoint (day 28) of the double-blind induction phase was analyzed using a mixed-effects repeated measures model (MMRM) with baseline MADRS total score as a covariate and treatment, country, oral antidepressant class (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects; and a random patient effect. A delta adjustment

	tipping point sensitivity analysis was conducted to evaluate the robustness of the MMRM analysis to increasing deviations from the missing-at-random assumption **Secondary efficacy endpoints** The three key secondary endpoints were analyzed sequentially and considered significant at the two-sided 0.05 level only if the endpoint individually and previous endpoints in the hierarchy, including the primary endpoint, were significant at the two-sided 0.05 level. • The first key secondary efficacy endpoint compared the proportion of participants with onset of clinical response in MADRS score by day 2 with 1 excursion (i.e. ≥25% reduction relative to baseline MADRS allowed on days 8, 15, or 22) maintained to the end of the double-blind induction phase using a Cochran-Mantel-Haenszel chi-square test adjusting for country and antidepressant class. • The second and third key secondary efficacy endpoints- change from baseline to week 4 in SDS and PHQ-9 scores, respectively – were analyzed using the MMRM model described for the primary efficacy analysis but using the respective baseline score for the instrument as a covariate. •
Subgroup analyses	Prespecified exploratory subgroup analyses included age, sex, baseline severity, antidepressant class, number of previous treatment failures, functional impairment, and region

Table A2.1a Baseline characteristics and demographics of patients enrolled in TRANSFORM-2 (full analysis set) (14)

Characteristic	ESK-NS + OAD (N=114)		OAD + PBO-NS (N=109)	
	Mean	SD	Mean	SD
Age (years)	44.9	12.58	46.4	11.14
Age at diagnosis of major depression (years)	32.1	12.53	35.3	13.04
Duration of current episode (weeks)	111.4	124.28	118.0	187.37
Montgomery-Åsberg Depression Rating Scale score	37.0	5.69	37.3	5.66
Body mass index (calculated as kg/m2)	27.5	5.84	28.6	6.24
	N	%	N	%
Sex				
Male	39	34.2	46	42.2
Female	75	65.8	63	57.8
Race				
Asian	1	0.9	1	0.9
Black or African American	6	5.3	5	4.6

White	106	93.0	102	93.6
Multiple	1	0.9	1	0.9
Employment status[a]				
Any type of employment	68	59.6	63	57.8
Any type of unemployment	34	29.8	35	32.1
Other	12	10.5	11	10.1
Country				
Czech Republic	30	26.3	28	25.7
Germany	10	8.8	10	9.2
Poland	20	17.5	18	16.5
Spain	9	7.9	9	8.3
United States	45	39.5	44	40.4
Number of previous antidepressant medications[b]				
1 or 2	78	68.4	72	66.1
≥3	36	31.6	37	39.9
Class of antidepressant				
Serotonin-norepinephrine reuptake inhibitor	77	67.5	75	68.8
Selective serotonin reuptake inhibitor	37	32.5	34	31.2
Antidepressant				
Duloxetine	60	52.6	61	56.0
Escitalopram	21	18.4	17	15.6
Sertraline	16	14.0	16	14.7
Venlafaxine extended-release	17	14.9	15	13.8

[a] Any type of employment includes any category containing “employed,” sheltered work, housewife or dependent husband, and student; any type of unemployment
includes any category containing “unemployed”; “other” includes retired and no information available.
[b] Number of previous antidepressant medications indicates antidepressants taken for at least 6 weeks with nonresponse (defined as #25% improvement) during
the current episode in addition to one prospective antidepressant.

Table A2.2 Main study characteristics of TRANSFORM-3 (16, 20)

Trial name	TRANSFORM-3
NCT number	NCT02422186
Objective	The purpose of this study is to evaluate the efficacy, safety and tolerability of switching elderly subjects (≥65 years) with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly dosed ESk-NS (28 mg, 56 mg or 84 mg) + a newly initiated OAD or to a newly initiated OAD (active comparator) + PBO-NS.
Publications – title, author, journal, year	Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients with Treatment-Resistant Depression – TRANSFORM-3, Am J of Geriatric Psychiatry, 2019
Study type and design	This is a phase 3, randomized, double-blind, active-controlled, multicenter study in elderly participants (≥65 years) with TRD (nonresponse to ≥1 to ≤8 antidepressants in the current depression episode) to assess the efficacy, safety, and tolerability of flexibly dosed ESK-NS (28 mg, 56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator: escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS. Eligible subjects were randomly assigned at a 1:1 ratio by computer-generated randomization schedule (IWRS randomization codes) to either ESK-NS (56 mg or 84 mg) or PBO-NS. Randomization was balanced by using randomly permuted blocks (block size of four) and was stratified by country and by class of oral antidepressant (SSRI or SNRI). Patients, investigators, site personnel, those assessing outcomes, and those analyzing the data were blind to treatment assignment The ESK-NS and PBO-NS devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug.
Follow-up time	**Double-blind induction phase (4 weeks)** Of the 138 subjects randomly assigned to treatment, 122 (88.4%) subjects completed the 28-day double-blind induction phase, and 16 (11.6%) subjects were withdrawn. A total of 77.8% patients in the ESK-NS + OAD, and 81.5% in the OAD + PBO-NS group received treatment on all eight dosing days. **Follow-up phase (24 weeks)** 15 (10.9%) subjects entered the follow-up phase, 11 (73.3%) of these subjects completed the follow-up phase and 4 (33.3%) of these subjects were withdrawn from the follow-up phase **Maintenance study rollover (SUSTAIN-2, not part of this application)** 111 (80.4%) subjects continued into the SUSTAIN-2 (NCT02497287) long-term safety and efficacy study and 2 (1.4%) subjects continued into SUSTAIN-3 (NCT02782104, not part of this application) long-term safety extension study after completing the 28-day double-blind induction phase
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • At the time of signing the informed consent form (ICF), participant must be a man or woman 65 years of age or older • At the start of the Screening/prospective observational Phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) [if

	single-episode MDD, the duration must be greater than or equal to (>=) 2 years] or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At the start of the Screening/Prospective observational Phase, participant must have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of greater than or equal to (>=) 31 • At the start of the Screening/Prospective observational Phase, participants must have had nonresponse (less than or equal to 25% improvement) to >=1 but less than or equal to (<=) 8 oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented records by medical and pharmacy/prescription records, or a letter from the treating physician, for the current episode of depression • Participant must be taking one of the oral antidepressant treatments with nonresponse that is documented on the MGH-ATRQ at the start of the screening/prospective observational phase • The participant's current major depressive episode, depression symptom severity (Week 1 MADRS total score greater than or equal to 24 required) and treatment response to antidepressant treatments used in the current depressive episode (retrospectively assessed) must be confirmed for participation in a clinical study based on a Site-Independent Qualification Assessment • Participant must be medically stable on the basis of clinical laboratory tests performed in the screening/prospective observational phase **Exclusion Criteria:** • The participant's depressive symptoms have previously demonstrated nonresponse to: Esketamine or ketamine in the current major depressive episode per clinical judgment, or all of the 4 oral antidepressant treatment options available for the double-blind induction Phase (Duloxetine, Escitalopram, Sertraline, and Venlafaxine extended release [XR]) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral ECT • Participants who has received vagal nerve stimulation (VNS) or who has received deep brain stimulation (DBS) in the current episode of depression • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current episode only), intellectual disability (intellectual disability [DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319]), borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the Investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the Screening/prospective observational Phase, per the Investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) and also includes history of suicidal behavior within the past year prior to start of the screening/prospective observational phase • Participant has a history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder

	• Participant has a Mini Mental State Examination (MMSE) < 25 or <22 for those participants with less than an equivalent of high school education • Participant has neurodegenerative disorder (e.g., Alzheimer's Disease, Vascular dementia, Parkinson's disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment (MCI) • Participant has a history of uncontrolled hypertension; current or past history of significant pulmonary insufficiency/condition; clinically significant ECG abnormalities; current or past history of seizures; clinically significant cardiovascular disorders including cerebral and cardiac vascular disease
Intervention	**Double blind Induction phase (4 weeks)** ESK-NS 28 mg, 56 mg or 84 mg + OAD (n=72) Active comparator: OAD + PBO-NS (n=66)
Baseline characteristics	*See table A2.2a*
Primary and secondary endpoints	**Primary endpoints** The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1) in MADRS total score (independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28) **Secondary endpoints** Secondary endpoints included: • Rates of response (≥50% reduction from baseline in the MADRS total score) at double-blind induction phase (day 28) • Rates of remission (MADRS ≤12 at endpoint) at double-blind induction phase (day 28) • Change from baseline to endpoint of double-blind induction phase in: • CGI-S total score • PHQ-9 total score • SDS total score
Method of analysis	**Sample Size, power calculation** The maximum sample size planned was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between ESK-NS + OAD and the OAD + PBO-NS arms, a SD of 12, based on the results of a phase 2 study of esketamine nasal spray for treatment-resistant depression (SYNAPSE, NCT01998958) and clinical judgment, a 2-sided significance level of 0.05, and a drop-out rate of 25%. 74 patients were required to be randomized to each treatment group to achieve 80% power using a fixed design assuming no interim analysis (IA). **Efficacy analyses** Efficacy analyses were performed on the full analysis set (all randomized subjects who received at least 1 dose of intranasal study mediation and 1 dose of oral antidepressant medication during the double-blind induction phase). Statistical tests were conducted at a two-sided significance level 0.05 unless otherwise specified. **Primary efficacy endpoint** Primary efficacy endpoint changes in MADRS score from baseline (day 1) to endpoint (day 28) of the double-blind induction phase was analyzed using a mixed-effects repeated measures model (MMRM) with baseline MADRS total score as a covariate and treatment, region, oral antidepressant class (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects. Least square means (i.e., adjusted for terms included in the MMRM model) were provided for each timepoint. To adjust for the

	interim analysis (IA), the primary endpoint was analyzed using a weighted combination test that defined test statistics from the MMRM analyses as a weighted sum of stage 1 (pre-IA) and stage 2 (post-IA) test statistics. Stages were weighted equally regardless of the sample size in each stage. The median-unbiased estimate and flexible CI were used for estimation of the treatment difference from antidepressant/placebo at Day 28. **Secondary efficacy endpoints** Additional measures of efficacy including: • The proportion of responders (≥50% reduction from baseline in MADRS total score) and remitters (MADRS ≤12) at end of double-blind induction phase • The average number of patients needed to produce one more responder/remitter in the ESK-NS + OAD group than in the OAD + PBO-NS group was calculated for response and remission. • The odds ratio for an improved CGI-S was estimated by mapping the ordinal scale to a continuous scale using item response modeling via the logit model and analyzed using an ANCOVA model. • Descriptive statistics of actual values and changes from baseline to end of double-blind induction phase in PHQ-9 and SDS total score. • The number needed to treat (NNT) was estimated for both response and remission at day 28 on the MADRS total score
Subgroup analyses	Preplanned assessment of age (65-74 or ≥75 years) and a post-hoc assessment of age at MDD onset (<55 or ≥55 years) by the change from baseline (day 1) in MADRS total score to the end of the double-blind induction phase using MMRM models with baseline MADRS total score as a covariate, and treatment, region, class of antidepressant (SSRI or SNRI), age, day, treatment-by-day, treatment-by-age and treatment by-day-by-age interaction as fixed effects..

Table A2.2a Baseline characteristics and demographics of patients enrolled in TRANSFORM-3 (full analysis set) (16)

	ESK-NS + OAD (N = 72)	OAD + PBO-NS (N = 65)	Total (N = 137)
Age (years), mean (SD)	70.6 (4.79)	69.4 (4.15)	70.0 (4.52)
Male	27 (37.5)	25 (38.5)	52 (38.0)
Female	45 (62.5)	40 (61.5)	85 (62.0)
Age category (years), n (%)			
65−74	59 (81.9)	57 (87.7)	116 (84.7)
≥75	13 (18.1)	8 (12.3)	21 (15.3)
Race, n (%)			
White	66 (91.7)	64 (98.5)	130 (94.9)
Multiple	4 (5.6)	0	4 (2.9)
Not reported	1 (1.4)	1 (1.5)	2 (1.5)
Unknown	1 (1.4)	0	1 (0.7)
Region, n (%)			
European Union	35 (48.6)	24 (36.9)	59 (43.1)
United States	34 (47.2)	36 (55.4)	70 (51.1)
Other	3 (4.2)	5 (7.7)	8 (5.8)
Class of oral AD, n (%)			
SNRI	31 (43.1)	30 (46.2)	61 (44.5)
SSRI	41 (56.9)	35 (53.8)	76 (55.5)
Oral AD			
Duloxetine	25 (34.7)	23 (35.4)	48 (35.0)
Escitalopram	25 (34.7)	25 (38.5)	50 (36.5)

Sertraline	15 (20.8)	10 (15.4)	25 (18.2)
Venlafaxine XR	7 (9.7)	7 (10.8)	14 (10.2)
Age when diagnosed with MDD (years), mean (SD)	42.6 (16.18)	43.7 (16.28)	43.1 (16.18)
Baseline MADRS total score, mean (SD)	35.5 (5.91)	34.8 (6.44)	35.2 (6.16)[a]
Screening IDS-C30 total score, mean (SD)	44.2 (6.50)	43.1 (6.71)	43.7 (6.60)
Duration of current episode (weeks), mean (SD)	163.1 (277.04)	274.1 (395.47)	215.8 (341.71)
Baseline CGI-S, mean (SD)	5.1 (0.76)	4.8 (0.80)	5.0 (0.79)
Number of previous AD trial in addition to 1 AD trial assessed prospectively,[b] n (%)			
1	15(20.8)	6 (9.2)	21 (15.3)
2	31 (43.1)	32 (49.2)	63 (46.0)
3	13 (18.1)	17 (26.2)	30 (21.9)
4	12 (16.7)	4 (6.2)	16 (11.7)
≥5	1 (1.4)	6 (9.2)	7 (5.1)

AD: antidepressant; CGI-S: Clinical Global Impression-Severity; Esk: esketamine; IDS-C30: Inventory of Depressive Symptoms-Clinician rated-30-
item; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MGH-ATRQ: Massachusetts General Hospital Antidepressant
Treatment Response Questionnaire; SD: standard deviation; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin
reuptake inhibitor; XR: extended release.

[a] Range: 19−51. In some cases, the baseline MADRS score was obtained after patients were qualified to enter the trial so the baseline MADRS
could be ≤24.

[b] Number of antidepressant medications with nonresponse (defined as <25% improvement) taken for at least 6 weeks during the current episode
as obtained from MGH-ATRQ.

Table A2.3 Main study characteristics of SUSTAIN-1 (15, 21)

Trial name	SUSTAIN-1
NCT number	NCT02493868

Objective	The purpose of this study is to assess the efficacy of flexibly doses ESK-NS + OAD (56 mg/84 mg) compared with OAD (active comparator) + PBO-NS in delaying relapse of depressive symptoms in adult patients (18-64 years) with treatment-resistant depression (TRD) who are in stable remission and response after an induction (4 weeks) and optimization (12 weeks) course of ESK-NS + OAD. Additionally, to investigate the safety and tolerability of ESK-NS + OAD compared with OAD + PBO-NS.
Publications – title, author, journal, year	Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients with Treatment-Resistant Depression, Daly et al., JAMA Psychiatry, 2019
Study type and design	This is a phase 3, double-blind, active-controlled, multicenter, relapse prevention study using a randomized withdrawal design* in adults (18-64 years) with TRD (nonresponse to ≥1 to≤5 antidepressants in the current depression episode) who have achieved stable remission or stable response after an induction and optimization course of treatment with ESK-NS + OAD. The study compared the maintenance of efficacy of continued flexibly-doses ESK-NS + OAD treatment with that of OAD + PBO-NS. The study continued until requisite number of relapses occurred, specified by a preplanned interim analysis (31 relapses to assess early efficacy) Investigators and site personnel were not provided with the IWRS randomization codes a remained blinded to treatment assignments until all patients had completed the study. The ESK-NS and PBO-NS devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug. * Subjects were randomized in a 1:1 ratio in the maintenance phase to either continue ESK-NS (same dose) or to discontinue ESK-NS; all subjects continued the same OAD, at the same dose. Randomization was achieved centrally via an IWRS, balanced using randomly permuted blocks (block size of four), stratified by country. The same number of nasal spray devices (three) were given to patients to self-administer regardless of what dose of ESK-NS (56 mg/84 mg) or treatment (esketamine or placebo) they were taking. Transfer entry patients who achieved stable remission or stable response at the end of the optimization phase after treatment with an OAD + PBO-NS continued to receive the same treatment.
Follow-up time	**Time frame: baseline and endpoint (up to 92 weeks):** **Induction phase (4 weeks):** Of the 437 safety set subjects (direct-entry subjects only, 273 (62.5%) subjects completed the 28-day induction phase and 164 (37.5%) subjects withdrew **Optimization phase (12 weeks):** Of the 455 esketamine-treated subjects entering the optimization phase (including 182 esketamine-treated transferred-entry subjects), 297 (65.3%) completed the 12-week optimization phase and 158 (34.7%) subjects withdrew. **Maintenance phase (variable length:** <u>Remitters</u> Of the 176 subjects in the Full (stable remitters) analysis set, 159 (90.3%) subjects completed the maintenance phase.

	Median exposure to ESK-NS during the maintenance phase was 17.7 weeks in stable remitters and 19.4 weeks in stable responders. <u>Responders</u> Of the 121 subjects in the Full (stable responders) analysis set, 113 (93.4%) subjects completed the maintenance phase. Median exposure to PBO-NS during the maintenance phase was 10.2 weeks among stable remitters and 10.1 weeks among stable responders
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** <u>For Direct-Entry Participants</u> • At the time of signing the informed consent form (ICF), participant must be a man or woman 18 (or older if the minimum legal age of consent in the country in which the study is taking place is greater than [>]18) to 64 years of age, inclusive - At the start of the screening/prospective observational phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) (if single-episode MDD, the duration must be greater than or equal to [>=] 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At the start of the screening/prospective observational phase, participant must have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of greater than or equal to (>=) 34 • At the start of the screening/prospective observational phase, participants must have had nonresponse (less than or equal to 25 percent [%] improvement) to greater than or equal to (>=1) but less than or equal to (<=) 5 oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using the Massachusetts General Hospital (MGH-ATRQ) • MGH-ATRQ and documented by medical history and pharmacy/prescription records, for the current episode of depression. In addition, the participant is taking different ongoing oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimal therapeutic dose • The participant's current major depressive episode, depression symptom severity (Week 1 MADRS total score >=28 required), and treatment response to antidepressant treatments used in the current depressive episode (retrospectively assessed) must be deemed valid for participation in a clinical study based on a Site-Independent Qualification Assessment for Transferred-Entry Participants • The participant must have completed the double-blind induction phase in ESKETINTRD3001 or ESKETINTRD3002 and must have demonstrated response at the end of that phase (>=50% reduction in the MADRS total score from baseline [Day 1 pre-randomization] at the end of the 4-week double-blind induction phase) **Exclusion Criteria:** • Participants who have previously demonstrated nonresponse of depressive symptoms to esketamine or ketamine in the current major depressive episode, to all 4 of the oral antidepressant treatment options available for the double-blind induction phase (i.e., duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with

	electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT • Participant has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) • Participants with history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria
Intervention	<u>Intranasal esketamine 56 mg or 84 mg plus oral antidepressant</u> ***Open label induction phase (direct-entry patients only; n=437)*:** ***Optimization phase (direct-entry and transferred-entry patients (TRANSFORM1/2); n=455):*** ***Maintenance phase (n=297)*:** Patients in stable remission (n=176) were randomized 1:1 to either: • Continued with ESK-NS (same dose) and the same OAD (n=90), or • Continued with the same OAD, but switched to PBO-NS(n=86) Patients with stable response (but who were not in stable remission; n=121) were randomized 1:1 to either: • Continued with ESK-NS (same dose) and the same OAD (n=62), or • Continued with the same OAD but switched to PBO-NS (n=59,)
Baseline characteristics	*See table A2.3a*
Primary and secondary endpoints	**Primary efficacy endpoint** Primary efficacy endpoint was the time from randomization to the first relapse during the maintenance phase (up to 92 weeks) in esketamine-treated subjects who achieved stable remission at the end of optimization phase after treatment with ESK-NS + OAD (based on MADRS) **Secondary and other efficacy endpoints** Key secondary endpoint: • time from randomization to the first relapse during the maintenance phase (up to 92 weeks) in esketamine-treated subjects who achieved stable response (not in remission) at the end of the optimization phase after treatment with ESK-NS + OAD (based on MADRS)
Method of analysis	SUSTAIN-1 was implemented as a random withdrawal design to perform analyses on time to relapse (i.e. survival analyses). As such, the follow-up duration was different between patients, depending on their inclusion date and time remaining until study termination. The study was not set up to analyse patients' outcomes at fixed timepoints. For this reason, response and remission rates over time were not

	measured at a fixed date but at the endpoint, which corresponds to the last record available for the patients. This can be viewed as analysis of covariance (ANCOVA) based on last observation carried forward (LOCF) at the longest observed follow-up per patient. **Sample Size, power calculation** On the basis of assumptions, 211 patients who achieved stable remission needed to be randomized (1:1 ratio) to obtain 84 relapses, providing 90% power to detect a HR of 0.49 at a 2-sided alpha of 0.05 for a fixed-sample design to detect superiority of ESK-NS + OAD over OAD + PBO-NS in delaying time to relapse of depressive symptoms. A 2-stage group-sequential design was implemented for the analysis set of patients who achieved stable remission, and an independent data-monitoring committee performed a pre-specified interim analysis at 31 relapses to assess early efficacy. **Efficacy endpoints** The primary efficacy analysis was based on the full (stable remitters) analysis set and the relapse (based on MADRS total score) collected during the maintenance phase. The cumulative distribution function of time to relapse during the maintenance phase among patients who achieved stable remission (primary endpoint) and those who achieved stable response without remission (secondary endpoint) was estimated by the Kaplan-Meier method. Relapse was defined as a MADRS total score of 22 or higher for 2 consecutive assessments separated by 5 to 15 days or hospitalization for worsening depression, suicide attempt, suicide prevention or completed suicide, or another clinically relevant event suggestive of relapse (assessed by a relapse adjudication committee) The between-group difference in time to relapse was analyzed using a 2-sided log-rank test (weighted combination [interim and final analyses] for patients who achieved stable remission because of conducting an interim analysis). The estimated HRs and 95% CIs were based on weighted estimates for patients who achieved stable remission and, on a Cox proportional hazards regression model with treatment as a factor for patients who achieved stable response. A similar post hoc analysis was performed combining the analysis set of patients who achieved stable remission and the analysis set of patients who achieved stable response
Subgroup analyses	n/a

Table A2.3a Baseline characteristics of SUSTAIN-1 (15)

Characteristic[a]	Stable Remission at Baseline		Stable Response at Baseline	
	ESK-NS + OAD (n = 90)	OAD + PBO-NS (n = 86)	ESK-NS + OAD (n = 62)	OAD + PBO-NS (n = 59)
Age, mean (SD) [range], y	45.4 (12.12) [19-64]	46.2 (11.16) [19-64]	47.2 (11.00) [23-63]	46.7 (9.76) [24-64]
Sex				
Male	32 (35.6)	27 (31.4)	24 (38.7)	17 (28.8)
Female	58 (64.4)	59 (68.6)	38 (61.3)	42 (71.2)
Race				
American Indian or Alaskan Native	0	1 (1.2)	0	0
Asian	0	0	0	1 (1.7)
Black	4 (4.4)	6 (7.0)	2 (3.2)	1 (1.7)
White	80 (88.9)	76 (88.4)	57 (91.9)	55 (93.2)
Other	2 (2.2)	1 (1.2)	3 (4.8)	1 (1.7)
Multiple	1 (1.1)	0	0	1 (1.7)
Not reported	3 (3.3)	2 (2.3)	0	0
Region				
Europe	52 (57.8)	50 (58.1)	34 (54.8)	35 (59.3)
North America	22 (24.4)	20 (23.3)	18 (29.0)	16 (27.1)
Brazil and Mexico	16 (17.8)	16 (18.6)	10 (16.1)	8 (13.6)
Age diagnosed with MDD, mean (SD) [range], y	32.5 (11.42) [5-55]	33.4 (11.41) [10-60]	36.2 (13.25) [15-61]	34.0 (10.54) [14-60]
Duration of current episode, mean (SD) [range], wk	112.2 (171.30) [12-1040]	110.5 (147.41) [9-884]	121.6 (193.85) [13-1080]	141.8 (254.43) [9-1248]
No. of previous antidepressants before screening				
≤2	71 (78.9)	62 (73.8)	41 (66.1)	34 (57.6)
>2	19 (21.1)	22 (26.2)	21 (33.9)	25 (42.4)
History of suicidal ideation in previous 6mo	18 (20.0)	14 (16.3)	20 (32.3)	14 (23.7)
Class of oral antidepressant				
SNRI	62 (68.9)	58 (67.4)	35 (56.5)	36 (61.0)
SSRI	28 (31.1)	28 (32.6)	27 (43.5)	23 (39.0)
Baseline MADRS total score, mean (SD)				
All patients	37.4 (5.20)	37.6 (4.66)	40.1 (5.56)	38.9 (4.92)
Direct-entry patients[b]	37.8 (5.28)	37.8 (4.26)	40.5 (4.88)	38.5 (4.65)
Transfer-entry patients[c]	36.8 (5.10)	37.3 (5.38)	39.6 (6.22)	39.9 (5.49)
Baseline PHQ-9 score, mean (SD)	19.2 (4.16)	19.8 (3.43)	20.5 (4.12)	20.4 (4.15)
Dose of esketamine before randomization[d]				
56 mg	40 (44.4)	33 (38.4)	20 (32.3)	19 (32.2)
Direct-entry patients	14 (15.6)	9 (10.5)	7 (11.3)	6 (10.2)
Transfer-entry 3001 patients[e]	5 (5.6)	4 (4.7)	5 (8.1)	3 (5.1)

Transfer-entry 3002 patients[f]	21 (23.3)	20 (23.3)	8 (12.9)	10 (16.9)
84 mg	50 (55.6)	53 (61.6)	42 (67.7)	40 (67.8)
Direct-entry patients	12 (13.3)	11 (12.8)	8 (12.9)	2 (3.4)
Transfer-entry 3001 patients[e]	5 (5.6)	6 (7.0)	11 (17.7)	7 (11.9)
Transfer-entry 3002 patients[f]	33 (36.7)	36 (41.9)	23 (37.1)	31 (52.5)
Dosing frequency at baseline				
Weekly	37 (41.1)	41 (47.7)	51 (83.6)	43 (72.9)
Every other week	53 (58.9)	45 (52.3)	10 (16.4)	16 (27.1)
Missing	0	0	1	0

Abbreviations: MADRS, Montgomery-Asberg Depression Rating scale; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire 9; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Patients who achieved stable remission: 54 for esketamine nasal spray and oral antidepressant and 56 for oral antidepressant and placebo nasal spray; patients who achieved stable response: 31 for esketamine nasal spray and oral antidepressant and 41 for oral antidepressant and placebo nasal spray.

[c] Patients who achieved stable remission: 36 for esketamine nasal spray and oral antidepressant and 30 for oral antidepressant and placebo nasal spray; patients who achieved stable response: 31 for esketamine nasal spray and oral antidepressant and 18 for oral antidepressant and placebo nasal spray.

[d] During the optimization phase and before randomization.

[e] The 3001 indicates transferred from Janssen-sponsored fixed-dose esketamine study TRD3001.

[f] The 3002 indicates transferred from Janssen-sponsored flexible-dose esketamine study TRD3002.

8.2 Results per study

Table A3a Results of the TRANSFORM-1 study

Trial name:	*TRANSFORM-1*					
NCT number:	NCT02417064					
	Data extracted from TRANSFORM-1			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	Pooled ESK-NS 56-84 mg + OAD	2/231	1.7%	2.457*	0.12-50.75*	*Data extracted as stated in the study or EPAR. Relative difference is provided as unadjusted risk ratio* **In TRANSFORM-1, there is no SAE in the OAD+PBO arm, meaning a probability of 0, and then a non-computable relative risk (divide by 0). Consequently, classical approach with adding 0.5 subject to those having outcome and 0.5 to those not having an outcome given an extra fictional participant in both treatment arms was conducted.*
	OAD+PBO	0/113	0%			
Discontinuation due to adverse events	Pooled ESK-NS 56-84 mg + OAD	8/231	3.5%	1.957	0.442-9.064	
	OAD+PBO	2/113	1.8%			
Response	Pooled ESK-NS 56-84 mg + OAD	112/209	53.5%	1.378	1.054-1.801	
	OAD+PBO	42/108	38.9%			
Remission	Pooled ESK-NS 56-84 mg + OAD	78/209	37.3%	1.221	0.874-1.706	
	OAD+PBO	33/108	30.5%			
EQ-5D-5L	ESK-NS 56 mg + OAD	113	0.224 (SD;0.248)	0.043**	-0.022-0.108**	**Unpublished post-hoc analysis of mean difference pooled (56mg + 84mg) results for study TRANSFORM-1 on EQ-5D-5L.* ***No relative difference in effect reported but the mean difference change in health status index.*
	ESK-NS 84 mg + OAD	112	0.243 (SD;0.239)	0.062**	-0.002-0.126**	
	Pooled ESK-NS 56-84 + OAD	225*	0.233(SD: 0.244)*	0.052**	-0.004-0.108**	
	OAD+PBO	113	0.181 (SD;0.249)	n/a	n/a	

Table A3b Results of the TRANSFORM-2 study

Trial name:	*TRANSFORM-2*					
NCT number:	NCT02418585					
	Data extracted from TRANSFORM-2			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	ESK-NS 56-84 mg + OAD	1/115	0.9%	0.948	0.060-14.966	*Data extracted as stated in the study or EPAR. Relative difference is provided as unadjusted risk ratio.*
	OAD+PBO	1/109	0.9%			
Discontinua-tion due to adverse events	ESK-NS 56-84 mg + OAD	8/115	7%	7.583	0.964-59.629	
	OAD+PBO	1/109	0.9%			
Response	ESK-NS 56-84 mg + OAD	70/101	69.3%	1.333	1.060-1.675	
	OAD+PBO	52/100	52%			
Remission	ESK-NS 56-84 mg + OAD	53/101	52.5%	1.693	1.197-2.393	
	OAD+PBO	31/100	31%			
EQ-5D-5L	ESK-NS 56-84 mg + OAD	114	0.288 (SD;0.2317)	0.057*	-0.007-0.121*	**No relative difference in effect reported but the mean difference change in health status index.*
	OAD+PBO	109	0.231 (SD;0.2506)			

Table A3c Results of the TRANSFORM-3 study

Trial name:	*TRANSFORM-3*					
NCT number:	NCT02422186					
	Data extracted from TRANSFORM-3			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	Pooled ESK-NS 28-56-84 mg + OAD	3/72	4.2%	1.354	0.234-7.851	*Data extracted as stated in the study or EPAR. Relative difference is provided as unadjusted risk ratio.*
	OAD+PBO	2/65	3.1%			
Discontinuation due to adverse events	Pooled ESK-NS 28-56-84 mg + OAD	4/72	5.6%	1.806	0.342-9.534	
	OAD+PBO	2/65	3.1%			
Response	Pooled ESK-NS 28-56-84 mg + OAD	17/63	27%	2.024	0.944-4.338	
	OAD+PBO	8/60	13.3%			
Remission	Pooled ESK-NS 28-56-84 mg + OAD	11/63	17.5%	2.619	0.882-7.777	
	OAD+PBO	4/60	6.7%			
EQ-5D-5L	Pooled ESK-NS 28-56-84 mg + OAD	70	0.081 (SD;0.2624)	0.055*	-0.027-0.137*	**No relative difference in effect reported but the mean difference change in health status index.*
	OAD+PBO	64	0.026 (SD;0.2235)			

Table A3d Results of the SUSTAIN-1 study

Trial name:	*SUSTAIN-1*					
NCT number:	NCT02417064					
	Data extracted from SUSTAIN-1			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
*Serious adverse events**	Pooled ESK-NS 56-84 mg + OAD	4/152	2.6%	3.816	0.432-33.739	*Data extracted as stated in the study or EPAR. Relative difference is provided as unadjusted risk ratio.*
	OAD+PBO	1/145	0.7%			
*Discontinuation due to adverse events**	Pooled ESK-NS 56-84 mg + OAD	4/152	2.6%	1.272	0.290-5.585	
	OAD+PBO	3/145	2.1%			
Response - stable remitters	Pooled ESK-NS 56-84 mg + OAD	67/89	75.3%	1.349	1.080-1.685	
	OAD+PBO	48/86	55.8%			
Response - stable responders	Pooled ESK-NS 56-84 mg + OAD	41/62	66.1%	1.951	1.310-2.906	
	OAD+PBO	20/59	33.9%			
Remission - stable remitters	Pooled ESK-NS 56-84 mg + OAD	58/89	65.2%	1.557	1.163-2.084	
	OAD+PBO	36/86	41.9%			

Remission - stable responders	Pooled ESK-NS 56-84 mg + OAD	29/62	46.8%	1.840	1.103-3.068	
	OAD+PBO	15/59	25.4%			
EQ-5D-5L among stable remitters	Pooled ESK-NS 56-84 mg + OAD	88	-0.067 (SD;0.1180)	0.029*	-0.011-0.069*	**No relative difference in effect reported but the mean difference change in health status index.*
	OAD+PBO	86	-0.096 (SD;0.1484)			
EQ-5D-5L among stable responders	Pooled ESK-NS 56-84 mg + OAD	61	-0.023 (SD;0.0753)	0.050*	0.010-0.090*	**No relative difference in effect reported but the mean difference change in health status index.*
	OAD+PBO	58	-0.073 (SD;0.1383)			

Results per PICO

Table A4 Results referring to the clinical question.

Results per outcome								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Risk ratio	CI	*P* value	
Serious adverse events	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	0.4%	-0.7%-4.5%	n/a	1.398	0.369-5.295	0.622 No significant difference as indicated by the CI containing the value 1.	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model.* *Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based on the meta-analysis used to calculate the absolute difference was 1.0%*
	SUSTAIN-1	1.9%	-0.4%-22.6%	n/a	3.816	0.432-33.739	No significant difference as indicated by the CI containing the value 1.	*Absolute difference in effect were calculated using the reported relative difference provided as unadjusted risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm used to calculate the absolute difference was 0.7%*
Discontinuation due to adverse events	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	2.8%	-0.1%-10.4%	n/a	2.598	0.966-6.985	0.059	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-*

							No significant difference as indicated by the CI containing the value 1.	*2 and TRANSFORM-3 studies using fixed effects inverse variance model.* *Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based on the meta-analysis used to calculate the absolute difference was 1.7%*
	SUSTAIN-1	0.6%	-1.5%-9.5%	n/a	1.272	0.290-5.585	No significant difference as indicated by the CI containing the value 1.	*Absolute difference in effect were calculated using the reported relative difference provided as unadjusted risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based used to calculate the absolute difference was 2.1%*
Response	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	14.4%	6.2%-24.1%	n/a	1.379	1.164-1.634	< 0.001	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model.* *Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based on the meta-analysis used to calculate the absolute difference was 38.1%*

	SUSTAIN-1 stable remitters	19.5%	4.5%-38.2%	n/a	1.349	1.080-1.685		*Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based on the meta-analysis used to calculate the absolute difference was 55.8%*
	SUSTAIN-1 stable responders	32.2%	10.5%-64.5%	n/a	1.951	1.310-2.906		*Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based on the meta-analysis used to calculate the absolute difference was 33.9%*
Remission	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	11.9%	4.1%-21.8%	n/a	1.470	1.163-1.860	0.001	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model.* *Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based on the meta-analysis used to calculate the absolute difference was 25.4%*

	SUSTAIN-1 stable remitters	23.3%	6.8%-45.4%	n/a	1.557	1.163-2.084		*Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based on the meta-analysis used to calculate the absolute difference was 41.9%*
	SUSTAIN-1 stable responders	21.4%	2.6%-52.6%	n/a	1.840	1.103-3.068		*Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO arm based on the meta-analysis used to calculate the absolute difference was 25.4%*
EQ-5D-5L	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	0.054	0.017-0.092	0.004	n/a	n/a	n/a	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using Continuous Fixed-Effect Model for the metric, mean difference.*
	SUSTAIN-1 stable remitters	0.029	-0.011-0.069		n/a	n/a	n/a	*Mean difference change in health status index among stable remitters*
	SUSTAIN-1 stable responders	0.050	0.010-0.090		n/a	n/a	n/a	*Mean difference change in health status index among stable responders*

8.3 Forest plot

8.3.1 SAE – TRANSFORM-1, 2 and 3

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

Model Results

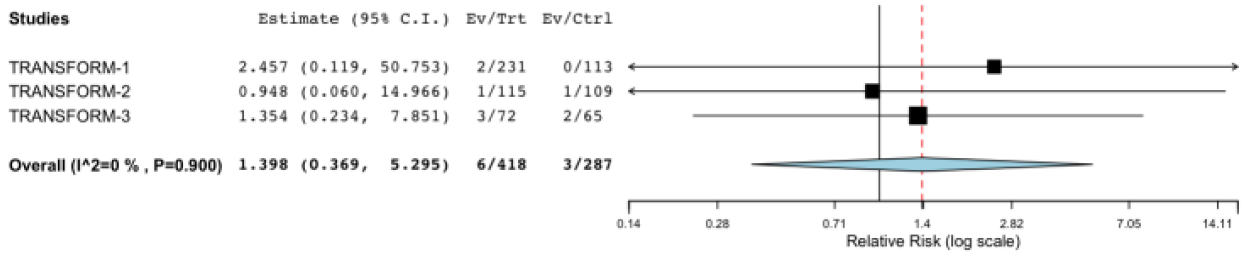
Estimate	Lower bound	Upper bound	p-Value
1.398	0.369	5.295	0.622

Heterogeneity

Q(df=2)	Het. p-Value
0.211	0.900

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.335	-0.966	1.667	0.679



8.3.2 Discontinuation - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

Model Results

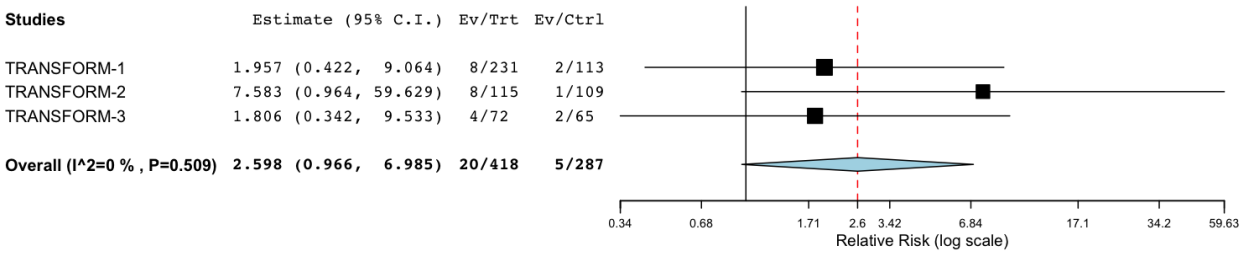
Estimate	Lower bound	Upper bound	p-Value
2.598	0.966	6.985	0.059

Heterogeneity

Q(df=2)	Het. p-Value
1.351	0.509

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.955	-0.035	1.944	0.505



8.3.3 Remission - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

Model Results

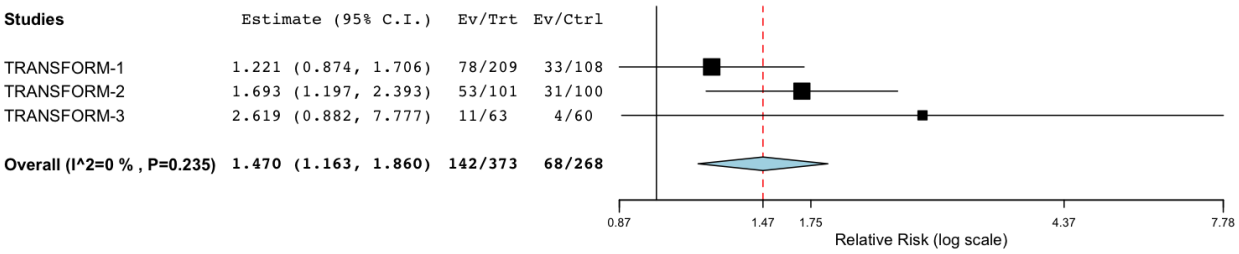
Estimate	Lower bound	Upper bound	p-Value
1.470	1.163	1.860	0.001

Heterogeneity

Q(df=2)	Het. p-Value
2.900	0.235

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.386	0.151	0.620	0.120



8.3.4 Response - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

Model Results

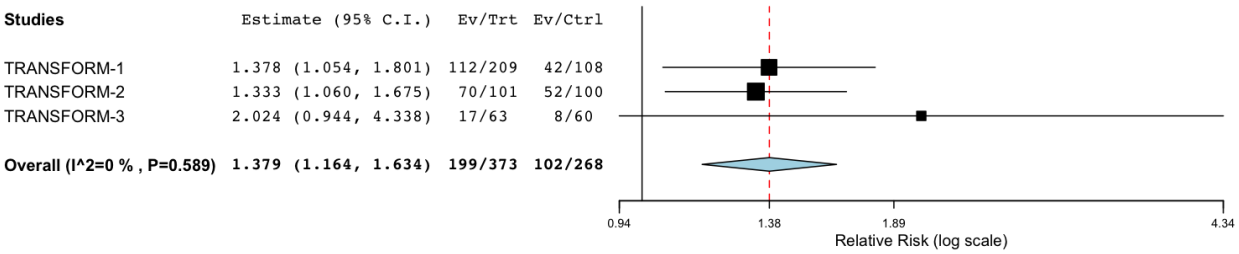
Estimate	Lower bound	Upper bound	p-Value
1.379	1.164	1.634	< 0.001

Heterogeneity

Q(df=2)	Het. p-Value
1.058	0.589

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.321	0.152	0.491	0.087



8.3.5 EQ-5D - TRANSFORM-1, 2 and 3

Summary:

Continuous Fixed-Effect Model

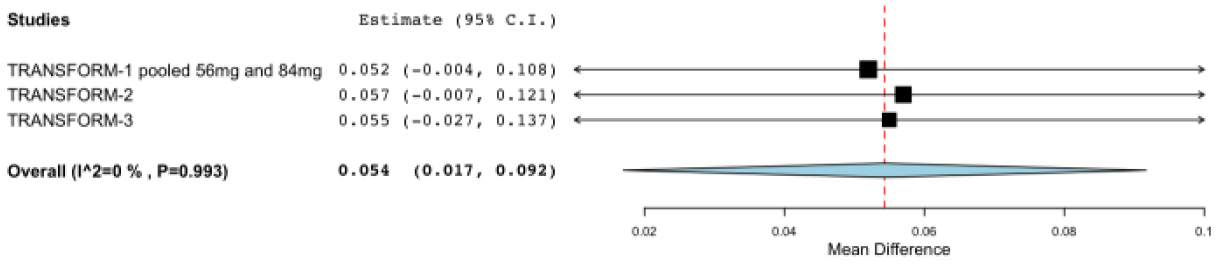
Metric: Mean Difference

Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
0.054	0.017	0.092	0.019	0.004

Heterogeneity

Q(df=3)	Het. p-Value
0.014	0.993



Medicinrådet

Medicinrådets protokol for vurdering af esketamin til behandling af behandlingsresistent depression hos voksne – vers. 1.1

Versionsnr.: 1.1

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	4. december 2019
Ikrafttrædelsesdato	4. december 2019
Dokumentnummer	65906
Versionsnummer	1.1

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 4. december 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Spravato
Generisk navn	Esketamin
Firma	Janssen-Cilag
ATC-kode	N01AX14
Virkningsmekanisme	Formodet non-kompetitiv glutamatreceptormodulator, med antidepressiv effekt via N-methyl-D-aspartatreceptor antagonisme.
Administration/dosis	Intranasal administration, ét tryk pr. næsebor. Induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg* eller 56 mg esketamin plus nyligt initieret daglig oralt antidepressivum, som ikke har indgået i behandling tidligere, på dag 1 efterfulgt af administration med 28 mg*, 56 mg eller 84 mg esketamin plus nyligt initieret daglig oralt antidepressivum ved efterfølgende behandling. Vedligeholdelsesbehandling med esketamin 28 mg*, 56 mg eller 84 mg en gang ugentlig fra uge 5-8 og fra uge 9 hver anden uge eller ugentligt samt vedligeholdelse af oralt antidepressivum administreret under induktionsfasen. *patienter ≥ 65 år
Forventet EMA-indikation	Kombinationsbehandling med en serotoninoptagshæmmer- eller noradrenalingenoptagelseshæmmer til voksne med moderat til svær unipolar depression, *Major Depressive Disorder*, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode.

2 Forkortelser

AMPAR:	*α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid Receptor*
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HDRS:	*Hamilton Depression Rating Scale*
HR:	*Hazard Ratio*
HTA:	*Health Technology Assessment*
ICD-10:	*Classification of Diseases-10*
MADRS:	*Montgomery–Åsberg Depression Rating Scale*
MDD:	*Major Depressive Disorder*
NaSSA:	Hæmmere af adrenerge receptorer
NICE:	*National Institute for Health and Care Excellence*
NMDA:	N-methyl-D-aspartat
OR:	*Odds ratio*
RADS:	Rådet for Anvendelse af Dyr Sygehusmedicin
RR:	Relativ risiko
SMD:	Standardiseret middelforskel
SNRI:	Serotonin-/noradrenalingenoptagelseshæmmer
SSRI:	Serotoningenoptagshæmmer
TCA:	Tricykliske antidepressiva

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af esketamin i kombination med serotoninoptagshæmmere (SSRI'er) eller noradrenalingenoptagelseshæmmere (SNRI'er) som mulig standardbehandling af voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode. I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende esketamin modtaget den 2. september 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af esketamin sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem esketamin i kombination med et SSRI eller SNRI og placebo i kombination med et SSRI eller SNRI af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

Svær unipolar depression, eller *Major Depressive Disorder* (MDD), vil ifølge WHO inden for en tidsramme af 20 år være blandt de to mest belastende sygdomme i verden, hvad angår sygdomsbyrde og økonomiske konsekvenser for samfundet. I Danmark anslås prævalensen af moderat til svær depression blandt voksne at være ca. 3 % svarende til ca. 111.000 voksne individer [1,2]. Det skønnes, at kun 65,3 % af disse, svarende til ca. 72.400 voksne individer, bliver diagnosticeret og kan komme i behandling [2]. Ca. 14 % svarende til ca. 10.100 voksne individer har ikke en tilfredsstillende effekt af behandlingen [2,3] og er mulige kandidater til behandling med esketamin.

Depression viser sig på mange måder, men præsenterer sig typisk med symptomer som en følelse af at være trist og træt over længere tid, manglende selvværd, isolationstendens, selvbebrejdelser, nedsat eller øget appetit, tab af livslyst og måske selvmordstanker eller -planer [4]. I alvorlige tilfælde kan der være psykotiske symptomer i form af hallucinationer og vrangforestillinger [4].

Depression inddeles i mild, moderat og svær depression. Patienter med svær depression har en overhyppighed af selvmord, og tilbagefald er hyppige og forekommer med stigende frekvens afhængigt af, hvor mange depressioner man tidligere har haft [5]. Nogle får kronisk depression, hvor de depressive symptomer fortsætter igennem flere år [4]. Depression ses ofte sammen med andre psykiske lidelser som f.eks. angst og personlighedsforstyrrelser og kan optræde parallelt til alvorlige fysiske lidelser som f.eks. diabetes, kræft og hjertesygdom [4]. Herudover er misbrugsproblemer også almindeligt hos patienter med svær depression [4].

Depression kan udløses af længerevarende somatisk sygdom, stress, tab af nærtstående og eksistentielle kriser, men ofte er de udløsende faktorer ukendte. Genetisk prædisposition og personlighedsmæssige disponerende forhold bidrager til at øge risikoen for sygdommen [4]. Den nuværende medicinske behandling virker bl.a. ved at regulere signalstofferne serotonin og noradrenalin i hjernen. En stigende mængde evidens indikerer desuden, at dysregulering af glutamatsignaleringen i hjernen også kan være involveret i depression [6].

Nogle patienter responderer ikke på den nuværende medicinske behandling og beskrives som havende behandlingsresistent depression. Definitionen af denne population er varierende. Ifølge Sundhedsstyrelsen omfatter behandlingsresistent depression voksne patienter over 18 år (både ambulante og indlagte) med moderat til svær depression, diagnosticeret efter ICD-10 (WHO's diagnoseliste) kriterier, der ikke har

responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger), eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling eller er vurderet behandlingsresistent på *Rating Scale for Treatment-Resistant Depression* (f.eks. Maudsley) [7].

Hvis patienten med depression tidligere har haft maniske eller hypomane episoder, betegnes depressionen som en bipolar depression, der er led i en bipolar lidelse. En andel af patienterne med behandlingsresistent depression vil have en ikkediagnosticeret bipolar depression, hvor de senere i forløbet vil udvikle mani eller hypomani [5,8].

5 Nuværende behandling

Diagnosticering af depression kan være vanskelig, og kun omkring halvdelen af alle patienter med depression får stillet en korrekt diagnose, hvis der ikke anvendes flere samtaler [7]. Langt de fleste med depression behandles i almen praksis [4].

Behandlingen af behandlingsresistent depression er ikke defineret i den gældende behandlingsvejledning for medicinsk behandling af unipolær depression udarbejdet af Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) i 2015. En national klinisk retningslinje vedrørende vanskelig behandlelig depression er under udarbejdelse af en arbejdsgruppe under Sundhedsstyrelsen. I henhold til RADS' vejledning bør behandlingen af patienter med moderat til svær depression tilgås som følgende:

Den indledende behandling af ikkehospitaliserede patienter skal bestå af SSRI som førstelinjebehandling, der gives over 1-3 måneder. En fuld effekt af antidepressiva kan først ventes efter 4-6 uger. Opnår patienten en tilfredsstillende effekt ved behandlingen, fortsættes i en vedligeholdelsesfase i ca. 6-12 måneder eller længere, afhængigt af kliniske forhold. Hvis der ikke er tegn på bedring efter ca. 2-4 uger på optimal dosis (i praksis ofte længere), skiftes der til andenlinjebehandling, som består af enten SSRI, SNRI, hæmmere af adrenerge receptorer (NaSSA) eller tricykliske antidepressiva (TCA). Er der fortsat ikke tegn på bedring, henvises der til psykiater eller indlæggelse på psykiatrisk afdeling. Blandt indlagte/hospitaliserede patienter med svær depression skal overvejes start med SNRI eller TCA.

Dansk registerdata viser, at SSRI og SNRI er de hyppigst anvendte tredjelinjebehandlinger i Danmark [3].

Behandlingsvarigheden varierer fra patient til patient. Til patienter, der er refraktære overfor behandling med antidepressiva, overvejes en række alternativer til medicinsk behandling. Disse inkluderer: psykoterapi, elektrochok og i særlige tilfælde magnetstimulation.

Ketamin har været kendt for sine bedøvende egenskaber siden 1960'erne. I Danmark er ketamin udelukkende godkendt som anæstetikum, men benyttes dog også som misbrugsstof. Ketamin har igennem knap 20 år været undersøgt i kliniske forsøg som middel mod svær depression og har vist både god og hurtigindsættende effekt [9,10]. Der er dog tale om en relativt kortvarig effekt ved den indledende behandling uden en efterfølgende vedligeholdelsesfase [10]. Ketamin anvendes i dag som off-label-behandling af behandlingsresistent depression i flere europæiske lande, men ifølge fagudvalget stort set ikke i Danmark. Undersøgelser viser, at ketamin har en akut indsættende antiselvmordseffekt [10,11].

Målet med behandling af behandlingsresistent depression er at opnå remission af depressive symptomer, øge livskvaliteten og forhindre selvmord blandt en patientgruppe med øget selvmordstendens.

6 Esketamin

Esketamin, eller s-ketamin, er ét af to spejlmolekyler af ketamin (s- og r-ketamin). Brugen af s-ketamin fremfor r-ketamin forventes at øge specificiteten og derved mindske bivirkninger ved brug [12]. Esketamin

udøver sin effekt i hjernen via N-methyl-D-aspartat (NMDA)-receptoren, der er et modtagermolekyle for glutamat. Glutamat frigives normalvis som et signalmolekyle i kontaktfladen mellem nerveceller i hjernen. Esketamin leder til en forbigående forøgelse i frigivelsen af glutamat, som trinvist fører til en forøgelse i neurotrofisk signalering, der er essentiel for nervecellernes funktion og overlevelse [6,13,14]. Dette antages at bidrage til at genoprette funktionen i hjerneområder involveret i reguleringen af affektiv og emotionel adfærd [6,13,14]. Intravenøs esketamin anvendes allerede på sygehuse i Danmark som anæstetikum ved mindre indgreb og indledningsvist ved længerevarende bedøvelse i særlige tilfælde. Esketamin, som ketamin, har dissociative effekter, der typisk efterlader brugeren med en følelse af at forlade kroppen [12]. Andre psykotomimetiske effekter er også beskrevet.

Til behandlingen af behandlingsresistent depression hos voksne er esketamin udviklet som en nasal formulering [2]. Den intranasale administrationsvej tillader en hurtig indsættende effekt og absorptionen er i modsætning til peroral indgift langt mere stabil, mens det kan tage flere uger at opnå en ønsket effekt af andre traditionelt, anvendte orale antidepressiva [2]. Esketamin har været administreret i kliniske forsøg som monoterapi og som add-on terapi med antidepressiva [15–17]. Den nuværende anbefalede behandling inkluderer en induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg eller 56 mg (afhængigt af alder, effektivitet og tolerabilitet) nasal esketamin plus nyligt initieret daglig oralt antidepressivum, som ikke har indgået i behandling tidligere, på dag 1 efterfulgt af administration med 28 mg, 56 mg eller 84 mg esketamin plus nyligt initieret daglig oralt antidepressivum ved efterfølgende behandling [2]. Efter induktionsfasen følger en vedligeholdelsesbehandling med nasal esketamin 56 mg eller 84 mg en gang ugentlig fra uge 5-8 og herefter hver anden uge eller ugentligt samt vedligeholdelse af oralt antidepressivum administreret under induktionsfasen [2]. Hvornår/om, behandlingen kan eller skal stoppes, er endnu uafklaret.

7 Kliniske spørgsmål

7.1 Klinisk spørgsmål 1

Hvad er værdien af esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode?

Population
Patienter over 18 år med behandlingsresistent depression. Ved dette forstås patienter, der ikke har responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger), eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling eller er vurderet behandlingsresistent på *rating scale for treatment-resistant depression*.

Intervention
Induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg* eller 56 mg esketamin plus nyligt initieret daglig oralt antidepressivum, som ikke har indgået i behandling tidligere, på dag 1 efterfulgt af administration med 28 mg*, 56 mg eller 84 mg esketamin plus nyligt initieret daglig oralt antidepressivum ved efterfølgende behandling.

Vedligeholdelsesbehandling med esketamin 28 mg*, 56 mg eller 84 mg en gang ugentlig fra uge 5-8 og fra uge 9 hver anden uge eller ugentligt samt vedligeholdelse af oralt antidepressivum administreret under induktionsfasen.

* Patienter ≥ 65 år

Komparator
Placebo, intranasalt, i kombination med SSRI eller SNRI, oralt.

Effektmål
Listet i Tabel 1.

7.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og effektmålsgruppe. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den *retningsgivende* mindste klinisk relevante forskel er fremkommet på samme måde som under den gamle metode og afspejler den mindste forskel, fagudvalget vurderer, er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den *justerede* mindste klinisk relevante forskel. Den justerede værdi vil være det halve af den retningsgivende værdi i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende MKRF* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre effektmålsgrupper ("dødelighed" "livskvalitet, alvorlige symptomer og bivirkninger" og "ikkealvorlige symptomer og bivirkninger").

Effektmål*	Vigtighed	Effektmålsgruppe	Måleenhed	Retningsgivende mindste klinisk relevante forskel	Justeret mindste klinisk relevante forskel
Uønskede hændelser	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel der oplever alvorlige uønskede hændelser (SAE'er)	5 %-point	2,5 %-point
			Andel der ophører behandling	20 %-point	10 %-point
			Narrativ gennemgang af specifikke hændelser, død uanset årsag og selvmordsforsøg	-	-

Remission	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	HDRS-17 eller MADRS. Andel der reducerer score til hhv. ≤ 7 point og ≤ 11 point	15 %-point	7,5 %-point
Respons	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	HDRS-17 eller MADRS. Andel der reducerer score fra baseline med 50 %	20 %-point	10 %-point
Livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på WHO-5 eller EQ-5D i prioriteret rækkefølge	10 point/0,07 point	5 point/0,035 point

Generelt om måletidspunkter

To måletidspunkter, efter endt behandling (induktionsfasen) og efter endt opfølgning (endt vedligeholdelsesfase eller længst mulig follow-up), gælder for samtlige effektmål. Måletidspunktet for endt behandling skal være minimum fire uger efter første administration ud fra rationalet om, at antidepressiva (komparator) først har begyndende effekt efter fire uger. Måletidspunktet for endt opfølgning skal være minimum seks måneder efter første administration ud fra rationalet om, at tilbagefald efter at have opnået remission af seks måneders varighed, ikke tæller som relaps, men tæller som en ny depressiv episode. De to måletidspunkter vægtes lige højt og anses af fagudvalget for at være et udtryk for hhv. en umiddelbar effekt af behandling og vedvarende (*sustained*) effekt af behandling. En umiddelbar effekt målt på remission eller respons kan muligvis have en akut antiselvmordseffekt, mens en vedvarende effekt anses for at være kurativ.

Kritiske effektmål

Uønskede hændelser
Alvorlige uønskede hændelser: Alvorlige uønskede hændelser (SAE'er) har stor betydning for den enkelte patients livskvalitet. Fagudvalget lægger vægt på, at der er tale om en behandling for en patientgruppe med en overhyppighed af selvmordsforsøg, der i samspil med de associative effekter af esketamin potentielt kan øge dødelighed og selvskade. Mindste klinisk relevante forskel vurderes af fagudvalget som en forskel på 5 %-point.

Fagudvalget ønsker behandlingsophør forårsaget af uønskede hændelser opgjort. Fagudvalget fremhæver, at der er tale om væsentligt syge patienter med tilsyneladende god mulighed for bedring. Derfor må der accepteres et vist niveau af behandlingsophør, hvis den andel af patienter, som forbliver i behandling, oplever en relevant bedring. Hvis der findes information om specifikke årsager til at patienterne ophører behandling, vil fagudvalget også inddrage denne information i vurderingen af dette effektmål, idet frafald generelt er højt i studier indenfor depression, og i tilfælde hvor der er tale om reversible, mindre alvorlige bivirkninger vil være relevant at forsøge behandling på trods af risiko for behandlingsophør. Fagudvalget fastsætter den mindste klinisk relevante forskel til 20 %-point.

Fagudvalget vil foretage en kvalitativ gennemgang af uønskede hændelser og død uanset årsag. Gennemgangen vil tage udgangspunkt i publicerede studier, produktresuméer og EPAR med henblik på at vurdere, om der er forskel mellem grupperne mht. alvorlighed, håndterbarhed og hyppighed af uønskede hændelser og død uanset årsag.

Remission
Remission betyder, at patienten ikke længere har symptomer på depression. Depression og remission af

depression måles ofte på sværhedsgraden af depressive symptomer på en skala som Hamilton Depression Rating Scale (HDRS) (interval 0-52 point) og Montgomery–Åsberg Depression Rating Scale (MADRS) (interval 0-60 point). HDRS er den mest almindeligt anvendte depressionsskala på verdensplan, herunder også i Danmark. MADRS er udviklet med det formål at være mere følsom overfor de ændringer, der er forårsaget af antidepressiva, men der er en høj korrelation mellem de scorer, der opnås med hhv. HDRS og MADRS [18]. Fagudvalget vurderer, at remission kan opgøres med begge skalaer og anslår, at remissionsraten med den nuværende standardbehandling med antidepressiva hos patienter, som tidligere har svigtet på to behandlinger, er 13-14 %. Dette estimat er baseret på evidens fra STAR*D-studiet, som er en stor anerkendt undersøgelse, der bl.a. estimerer remisionsrater efter flere sekventielle behandlinger hos patienter med svær depression [19].

Den engelske HTA-institution NICE har tidligere foreslået en forskel på tre point på HDRS eller 0,5 standardiseret middelforskel (SMD) som klinisk betydende [20]. Disse grænsetærskler er siden blevet kritiseret og anbefales ikke længere, selvom de stadig anvendes som reference i flere kliniske forsøg [20]. Fagudvalget vurderer, at en forskel i andel, der reducerer scoren til, hvad der er beskrevet som et relativt nulpunkt hhv. ≤ 7 på HDRS-17 og ≤ 11 på MADRS [21,22] uanset udgangspunkt og opgjort ved: 1) endt behandling, skal udgøre mindst 15 %-point og 2) efter længst mulig opfølgningstid, skal udgøre mindst 15 %-point for at være klinisk relevant.

Vigtige effektmål

Respons
Remission vurderes af fagudvalget at være svært opnåeligt hos patienter med behandlingsresistent depression. Når remission ikke kan opnås, har det stadig afgørende betydning for patienten, at den depressive tilstand bedres. Respons måles også, som det er tilfældet med remission vha. HDRS- eller MDRS-skalaen og betyder, at patienten som minimum har fået halveret sine symptomer målt som en reduktion i score på mindst 50 % fra baseline. Fagudvalget vurderer, at respons er et vigtigt effektmål til at vurdere en given effekt af behandlingen, da depressionssymptomer kan forværres eller bedres over ganske kort tid. Fagudvalget anslår, at responsraten med den nuværende standardbehandling med antidepressiva er 20 %. Fagudvalget vurderer, at en forskel i andel, der opnår respons opgjort ved: 1) endt behandling, skal udgøre mindst 20 %-point og 2) opgjort efter længst mulig opfølgningstid, skal udgøre mindst 20 %-point for at være klinisk relevant.

Livskvalitet
Fagudvalget er ikke bekendt med et værktøj til vurdering af livskvalitet, der er tilstrækkeligt valideret til patienter med behandlingsresistent depression. Fagudvalget mener, at en vurdering af livskvalitet ved hjælp af et generisk værktøj er behæftet med megen usikkerhed [23] og nedjusterer derfor livskvalitet fra et kritisk til et vigtigt effektmål. Fagudvalget ønsker livskvalitet opgjort med WHO-5. WHO-5 er et velvalideret generisk måleinstrument, der er udarbejdet for at kunne måle niveauet af mental sundhed ud fra trivsel og velbefindende. Spørgsmålene er formuleret positivt, men bliver også brugt til at vurdere negative aspekter af mental sundhed, eksempelvis ved screening af forøget risiko for depression [24]. Scoren går fra 0-100. Gennemsnittet for befolkningen som helhed er 68 pointtal, men ved pointtal over 50 er der ikke umiddelbart risiko for depression eller langvarig stressbelastning [25]. Pointtal mellem 0-35 angiver, at der er stor risiko for depression eller stressbelastning [25]. En forøgelse (eller forringelse) på 10 pointtal anses for en klinisk signifikant forskel, dvs. en forskel i trivsel der er så stor, at den kan tilskrives indsatsen [25,26]. På denne baggrund fastsætter fagudvalget en mindste klinisk relevant forskel til 10 pointtal for WHO-5. Hvis der ikke findes data opgjort med WHO-5, ønsker fagudvalget livskvalitet opgjort med EQ-5D. EQ-5D er et velvalideret, generisk spørgeskema udfyldt af patienten til vurdering af livskvalitet [27]. Spørgeskemaet består af fem dimensioner (bevægelighed, personlig pleje, sædvanlige aktiviteter, smerte/ubehag og angst/depression) og indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkelige

helbred) til 100 (bedst tænkelige helbred). Fagudvalget er opmærksomt på, at 2 ud af 5 delskalaer i EQ-5D måler somatiske forhold (bevægelighed, smerter), som ikke nødvendigvis er relevante for mennesker med depression, og som i høj grad kan skyldes anden (somatisk) sygdom. Fagudvalget er ikke bekendt med en valideret mindste klinisk relevant forskel specifikt for depression og læner sig op ad amerikanske værdier og en mindste klinisk relevante forskel på mellem 0,05-0,08 i EQ-5D index score for posttraumatisk stresssyndrom [28]. Den mindste klinisk relevante forskel er på denne baggrund fastsat af fagudvalget til 0,07 point i EQ-5D index score.

8 Litteratursøgning

Vurderingen af lægemidlets værdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere randomiserede studier, hvor esketamin er sammenlignet direkte med placebo.

Sekretariatet fandt følgende studier, som vurderes relevante, og som derfor kan anvendes til direkte sammenligning for de definerede effektmål:

Korttidsstudier

- TRANSFORM-1 (NCT02417064)
- TRANSFORM-2 (NCT02418585)
- TRANSFORM-3 (NCT02422186)

Vedligeholdelsesstudier

- SUSTAIN-1 (NCT02493868)

Virksomheden skal ikke søge efter yderligere studier. EMAs European public assessment reports (EPAR) konsulteres for det aktuelle lægemiddel.

9 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention to treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

10 Andre overvejelser

På nuværende har ansøger ikke angivet en forventet behandlingsvarighed. Fagudvalget ønsker en vurdering af forventet varighed af behandling med esketamin.

Fagudvalget finder, at der er nogle praktiske aspekter, som må overvejes i forbindelse med Medicinrådets vurdering af esketamin som mulig standardbehandling. Esketamin skal administreres under kontrollerede forhold under opsyn af fagfolk indledningsvist to gange om ugen og under vedligeholdelsesfasen én gang om ugen eller hver anden uge. Dette anses af fagudvalget at være et stort indgreb i patienterne hverdag, særligt i det lys, at det endnu ikke vides, hvor længe patienterne forventes at være i behandling. Fagudvalget vurderer, at der potentielt kan opstå et adhærensproblem, som muligvis vil lede nogle patienter til selvmedicinering med ketamin i stedet eller lede dem til at afbryde behandlingen muligvis med alvorlige følger. Fagudvalget ønsker ansøgers refleksion over denne problemstilling.

Fagudvalget ønsker en opgørelse af, hvor mange events i form af mani, der er registreret under behandling og under follow-up. Baggrunden for dette er, at en andel af patienterne, der diagnosticeres med unipolar depression, har en underliggende bipolar lidelse.

Fagudvalget ønsker data på komorbiditet f.eks. en oversigt over komorbiditeter, patienterne havde på inklusionstidspunktet til studierne. Baggrunden for dette er at bestemme heterogeniteten i studiepopulationen for at vurdere, om studiepopulationen er repræsentativ for patienter med behandlingsresistent depression, der ofte har andre psykiske eller somatiske lidelser.

Fagudvalget ønsker data på, hvordan remission-/responsmiddelværdiscoren ændrer sig over tid både under behandling og under opfølgning, hvis disse data eksisterer. Baggrunden for dette er at få indblik i en eventuel sammenhæng mellem behandling og respons over kortere tidsintervaller. Data foreslås at blive præsenteret grafisk.

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12 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende behandlingsresistent depression hos voksne

Formand	**Indstillet af**
Poul Videbech Professor, overlæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
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Claus Havregaard Sørensen Overlæge	Region Syddanmark
Dénes Langyel Overlæge	Region Sjælland
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13 Versionslog

Version	Dato	Ændring
1.0	4. december 2019	Godkendt af Medicinrådet.
1.1	9. december 2019	ATC-kode ændret fra ’ N01AX14’ til ’ATC-kode NO6AX27’