Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende esketamin som korttids-behandling til patienter med depression, som har en akut øget selvmordsrisiko

Vers. 1.0

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering vedr. esketamin som akut korttidsbehandling

Til voksne med en moderat til svær depressionsepisode med henblik på hurtig reduktion af depressive symptomer, som udgør en akut øget selvmordsrisiko

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som 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.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
ECT	Elektrokonvulsiv terapi
OAD	Oral antidepressiv medicin
SAIP	Sygehusapotekernes indkøbspris

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
Medicinrådet estimerer, at de inkrementelle omkostninger ved anvendelse af esketamin som akut korttidsbehandling i tillæg til oral antidepressiva er ca. [redacted] DKK pr. patient sammenlignet med behandling med oral antidepressiva alene (klinisk spørgsmål 1). Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 17.600 DKK pr. patient. De inkrementelle omkostninger er drevet af lægemiddelomkostningerne til esketamin. Udgifterne opvejes delvist af, at hospitals-omkostningerne er en anelse højere for komparator pga. længere indlæggelsestid.

Medicinrådet præsenterer ikke en sundhedsøkonomisk model, der undersøger de inkrementelle omkostninger af esketamin sammenlignet med ECT (klinisk spørgsmål 2), fordi der ikke findes data, der tillader en sammenligning af disse to behandlinger. Medicinrådet præsenterer i stedet et estimat af omkostningerne til selve behandlingerne i ét behandlingsforløb uden at tage højde for eventuelt afledte omkostninger eller besparelser som fx indlæggelsestid. Lægemiddel- og administrationsomkostninger ved anvendelse af esketamin i et behandlingsforløb på 4 uger estimeres at være ca. [redacted] DKK, hvor behandlingsomkostninger til et ECT-forløb på 12 behandlinger over 4 uger estimeres at være i intervallet 17.800 - 62.400 kr.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af esketamin som akut korttidsbehandling som tillæg til oral antidepressiva til voksne patienter med en moderat til svær depressionsepisode, med henblik på hurtig reduktion af depressive symptomer, som udgør en akut øget selvmordsrisiko.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Janssen. Medicinrådet modtog ansøgningen den 22. september 2022.

3.1 Patientpopulation

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]. En mindre andel vil have særskilt behov for akut behandling med hurtigindsættende virkning på depressive symptomer, fordi de udviser alvorlig selvmordsadfærd.

Patienter med svær depression kan udvise selvmordstanker og -adfærd, der er så alvorlig, at det kan være nødvendigt med indlæggelse og akut behandling. Dette gælder også for et fåtal af patienter med moderat depression. Selvmordsrisikoen beror på et

klinisk skøn af den behandlende speciallæge i psykiatri og kan afdækkes ved en klinisk vurdering.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af esketamin på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med placebo i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko?

Klinisk spørgsmål 2:

Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med ECT i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for esketamin kombineret med oral antidepressiva sammenlignet med oral antidepressiva alene (OAD) og ECT. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Sammenligningen af esketamin tillagt OAD med OAD alene i klinisk spørgsmål 1 er lavet på baggrund af data fra ASPIRE-1 og 2[2,3]. Begge studier var randomiserede, dobbeltblindede, placebokontrollerede, multicenter fase-3 studer. Medicinrådet gennemgår denne model herunder.

For sammenligningen med ECT i klinisk spørgsmål 2, har ansøger antaget en ligeværdig klinisk effekt af esketamin for de relevante effektmål. Ansøger har valgt denne tilgang, da det ikke har været muligt at identificere det nødvendige data for at kunne sammenligne effekt af esketamin overfor ECT. Medicinrådet vurderer ikke, at det er rimeligt at antage en ligeværdig effekt af esketamin og ECT. Som følge deraf præsenterer Medicinrådet i stedet en beregning af, hvad 4-ugers behandling koster med hhv.

esketamin og ECT i resultatafsnittet uden at tage højde for eventuelle afledte omkostninger eller besparelser.

4.1.1 Modelbeskrivelse og analyseperspektiv

Ansøger har udarbejdet en sundhedsøkonomisk model, der estimerer omkostningerne forbundet med anvendelse af esketamin + OAD og ved anvendelse af OAD alene under et indlæggelsesforløb. Der er således både estimeret omkostninger til den medicinske behandling og omkostninger til selve indlæggelsen.

Der anvendes en tidshorisont på 90 dage, svarende til opfølgningstiden i ASPIRE-1 og 2. Over denne tidshorisont er patienterne initialt indlagt, hvorefter de udskrives og behandles ambulant. Antagelser om indlæggelsestid vil blive beskrevet i afsnit 4.2.2. Modellen har 16 cyklusser af forskellig længde, hvor cykluslængden afspejler opfølgningstidspunkterne i studierne.

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse.

Medicinrådets vurdering af ansøgers model og analyseperspektiv
Medicinrådet anvender ansøgers valg af tidshorisont.

Medicinrådet anvender også ansøgers valg af model og analyseperspektiv for klinisk spørgsmål 1, hvor der sammenlignes med OAD alene.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af esketamin + OAD sammenlignet med OAD alene. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger. Ansøger har ikke inkluderet bivirkningsomkostninger på baggrund af Medicinrådets tidligere vurdering af esketamin til patienter med behandlingsresistent depression, hvor det blev konkluderet, at bivirkningsprofilen ikke medførte yderligere omkostninger.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP).

Ansøger har anvendt dosis af esketamin angivet i produktresuméet (SPC). Patienter modtager en dosis på 84 mg pr. behandling, fordelt over tre doser med 5 minutters mellemrum. Ansøger har også inkluderet omkostninger til OAD.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 1

Tabel 1. Anvendte lægemiddelpriser, SAIP (januar 2022)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Esketamin	28 mg	3 stk.	[redacted]	Amgros

Medicinrådet anvender ikke omkostninger for OAD, da disse er ens for patienter i behandling med esketamin + OAD og OAD alene, og derfor ikke har betydning for resultatet. Medicinrådet anvender ansøgers antagelser vedr. esketamin.

4.2.2 Hospitalsomkostninger

Ansøger inkluderer omkostninger til administration og monitorering i forbindelse med behandling på hospitalet samt omkostninger i forbindelse med indlæggelser.

Administrations- og observationsomkostninger

Behandling med esketamin skal superviseres af en sundhedsprofessionel, efterfulgt af en observationsperiode. Ansøger har ikke inkluderet udgifter til administration af esketamin under indlæggelsesperioden, men har til estimering af udgifter efter endt indlæggelse anvendt DRG-taksten for et ambulant psykiatrisk besøg. Til observationsperioden, efter lægemidlet er blevet givet, har ansøger, i forligelighed med Medicinrådets vurdering af esketamin til behandlingsresistent depression, antaget, at en sygeplejerske kan monitorere tre patienter ad gangen. Observationsperioden post behandling er estimeret til at være 90 minutter, baseret på den gennemsnitlige observationstid i ASPIRE-1 og 2.

Der antages ingen administrationsomkostninger i forbindelse med administration af OAD.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet medregner udgifter til administration af esketamin under indlæggelse, fordi administrationen af esketamin indebærer en yderligere udgift sammenlignet med udgifter relateret til behandling af patienter, der er indlagt uden at modtage esketamin. Medicinrådet anvender enhedsomkostningen for en reservelæge til at estimere omkostninger forbundet med administration af esketamin under indlæggelse fremfor en DRG-takst. Det antages, at administration af esketamin tager 10 minutter pr. behandling. Administrationsomkostning efter afsluttet indlæggelse er, ligesom i ansøgers analyse, baseret på DRG-taksten for et ambulant psykiatrisk besøg.

Medicinrådet inkorporerer omkostninger til administration af esketamin under indlæggelse. Anvendte enhedsomkostninger kan ses i Tabel 2.

Tabel 2. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Kilde
Administrationsomkostning for esketamin under indlæggelse (10 min. pr. behandling)	86	Medicinrådets enhedsomkostninger
Administrationsomkostning pr. behandling efter endt indlæggelse	1.944	DRG 2022 (psykiatri)
Udgifter til observation efter behandling (pr. patient)	220,5	Medicinrådets enhedsomkostninger

Indlæggelsesomkostninger

Ansøger har anvendt DRG-takster til at estimere omkostningerne forbundet med psykiatriske indlæggelser. Efter samtale med egne kliniske eksperter har ansøger estimeret, at patienter i behandling med esketamin + OAD vil have en gennemsnitlig indlæggelsestid på 14 dage, mens patienter, der behandles med OAD alene, gennemsnitligt vil være indlagt 21 dage. Argumentet for, at patienter i behandling med esketamin vil være kortere tid indlagt, baseres på en forventning om, at disse patienter vil opnå en hurtigere respons sammenlignet med patienter, der behandles med OAD alene.

Medicinrådets vurdering af ansøgers antagelser om indlæggelsesomkostninger

Medicinrådet anvender den gennemsnitlige indlæggelsestid, der fremgår af ASPIRE-1, hvor indlæggelsestiden for esketamin + OAD og OAD var hhv. 21,6 og 19,1 dage (indlæggelsestid er ikke beskrevet i ASPIRE-2). I ASPIRE-1 indgik patienter fra USA, Europa, Asien og Sydafrika, hvorfor der kan være forskelle i praksis for indlæggelseslængde relativt til dansk klinisk praksis. Det forventes dog, at den relative forskel i indlæggelsestid mellem patienter i behandling med esketamin + OAD og OAD alene er overførbar til danske patienter. Ydermere er den gennemsnitlige indlæggelsestid observeret i ASPIRE-1 sammenlignelig med danske tal for indlæggelsestid (i 2017 varede den gennemsnitlige psykiatriske indlæggelse 16,5 dage, retspsykiatriske patienter ekskluderet)[4].

Medicinrådet anvender gennemsnitlig indlæggelsestid observeret i ASPIRE-1 (19,1 dage for esketamin + OAD og 21,1 dage for OAD).

Bivirkningsomkostninger

Ansøger har ikke inkluderet omkostninger til bivirkninger i den indsendte model. Dette er valgt på baggrund af Medicinrådets tidligere vurdering af esketamin til behandling af behandlingsresistent depression. Her blev det konkluderet, at det kun er dissociation, der kræver håndtering af en læge, men at der ikke vil være yderligere omkostninger til håndtering af dette, siden dette vil blive varetaget ved generelle monitoreringsbesøg.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Medicinrådet anvender ansøgers antagelser vedr. bivirkningsomkostninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af indlæggelsestid og tid brugt på administration af esketamin og monitorering efter udskrivelse. For hver indlæggelsesdag er der i ansøgers hovedanalyse anvendt en patienttid på 16 timer. Ansøger anvender en enhedsomkostning for patienttid på 181 DKK pr. time og transportomkostninger på 140 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

Ansøger har yderligere inkluderet patienttid for pårørende for 50 % af patienterne med en varighed af 2 timer pr. dag.

Medicinrådets anvender ansøgers antagelser vedr. patientomkostninger.

4.3 Opsummering af ændringer fra ansøgers analyse til Medicinrådets analyse.

Medicinrådet har foretaget ændringer til ansøgers hovedanalyse. Ændringerne er opsummeret i Tabel 3.

Tabel 3. Forskelle mellem ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Omkostning til administration af esketamin under indlæggelse	Ikke inkluderet	Medicinrådets enhedsomkostning for timeløn af reservelæger
Gennemsnitlig indlæggelsestid	14 og 21 dage for hhv. patienter i behandling med esketamin + OAD og patienter, som kun behandles med OAD. Baseret på antagelse efter samtale med kliniske eksperter	21,6 og 19,1 dage for hhv. esketamin + OAD og OAD baseret på gennemsnitlig indlæggelsestid observeret i ASPIRE-1

4.4 Opgørelse af behandlingsomkostninger til ECT.

Som beskrevet i 4.1, præsenterer Medicinrådet estimerede behandlingsomkostninger til ECT, baseret på materiale indsendt af ansøger, uden at tage højde for forskelle i afledte omkostninger eller besparelser. I alle tre scenarier er anvendt et gennemsnitligt antal behandlinger på 12 henover 4 uger baseret på et studie, der undersøgte brugen af ECT i Danmark [5].

Ansøger har estimeret omkostninger til behandling med ECT ved tre forskellige metoder. I første metode estimeres omkostninger ved anvendelse af DRG-takster. Ansøger har her via interaktiv DRG identificeret den mest relevante DRG-takst til at være en takst for et ambulant besøg på (DRG: 19MA98). Dette resulterer i en omkostning på 2.770 DKK pr. ECT-behandling

Den anden estimering af omkostninger til ECT, indsendt af ansøger, tager udgangspunkt i et *micro costing approach*. Der tages her højde for tid og timeløn til ansatte samt udgifter til anæstesi og ECT-apparatur. I forbindelse med løn for ansatte antages det, at der er en overlæge i anæstesi og tre sygeplejersker til at udføre selve behandlingen (15 min.). Derudover inkorporeres udgifter til portør ifm. transport af patient til opvågningsstue (5 min.) og SOSU-assistent til monitorering af patient under opvågning (30 min.). Timelønsomkostning er ganget med en faktor 2 for at tage højde for overhead omkostning.

Tredje metode er baseret på en analyse af ECT-omkostninger foretaget af NICE, der anvendes i en publiceret cost-utility analyse[6].

Medicinrådets vurdering af ansøgers antagelser om behandlingsomkostninger til ECT
Medicinrådet præsenterer alle tre metoder udarbejdet af ansøger. I micro-costing tilgangen foretages dog en række ændringer på baggrund af fagudvalgets udtalelser. På baggrund heraf inkorporerer Medicinrådet omkostninger for en psykiatrisk- og anæstesisygeplejerske ved selve behandlingen samt en anæstesilæge og en psykiater (ikke overlæge). Behandlingen vurderes at tage 25 minutter pr. patient i gennemsnit. Derudover vurderes det, at der én sygeplejerske til stede på opvågningsstuen, og at de gennemsnitligt håndterer 5 patienter ad gangen.

Medicinrådet fjerner også overheadomkostningen, da dette ikke længere er en del af Medicinrådets metode for værdisætning af enhedsomkostninger[7]. Omkostning pr. ECT-behandling fremgår af Tabel 4.

Tabel 4. Estimat af omkostning pr. ECT-behandling ved forskellige metoder

Omkostning pr. ECT-behandling ved forskellige metoder	
Metode	**Pris pr. behandling [DKK]**
DRG	2.770
Micro-costing	1.483
Estimat udarbejdet af NICE	5.196

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 10.

Den gennemsnitlige inkrementelle omkostning pr. patient ved anvendelse af esketamin + OAD bliver ca. [redacted] DKK sammenlignet med OAD alene i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 17.600 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 5.

Tabel 5. Resultatet af Medicinrådets hovedanalyse af esketamin + OAD ved sammenligning med OAD alene (klinisk spørgsmål 1), DKK

	Esketamin	OAD	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrationsomkostninger	3.820	-	3.820
Monitoreringsomkostninger	8.057	7.675	382
Indlæggelsesomkostninger	75.213	85.055	-9.842
Patientomkostninger	63.459	70.434	-6.975
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.2 Estimat af 4-ugers behandling med esketamin og ECT

Lægemiddel- og administrationsomkostninger ved 4-ugers behandling med esketamin		[redacted]
Metode	**Omkostning af behandlingsforløb [DKK]**	**Inkrementel omkostning ved anvendelse af esketamin [DKK]**
4-ugers ECT-behandling estimeret ved brug af DRG takst (12 behandlinger)	[redacted]	[redacted]

4 ugers ECT-behandling estimeret ved brug af micro-costing (12 behandlinger)	[redacted]	[redacted]
4-ugers ECT-behandling estimeret ved brug af estimat udarbejdet af NICE (12 behandlinger)	[redacted]	[redacted]

6. Budgetkonsekvenser

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

- esketamin bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- esketamin bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Estimat af patientantal og markedsandel

Ansøger estimerer, at der årligt er 1.126 patienter, der er kandidater til behandling med esketamin. I tilfælde af anbefaling estimeres det, at 24 % af patienterne vil blive behandlet med esketamin det første år, stigende til 66 % i år 5. Andel, der behandles med esketamin, i tilfælde af at lægemidlet ikke anbefales, vurderes at være 0 %.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
I protokollen for denne vurdering anslog fagudvalget, at 1.000-2.000 patienter ville være kandidater til behandling med esketamin i tilfælde af anbefaling. I forbindelse med deres arbejde med denne vurdering er deres estimat blevet revideret til at være 200-500 patienter. Medicinrådet anvender derfor et estimat på 300 patienter pr. år til at estimere budgetkonsekvenser, se Tabel 6.

Tabel 6. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Esketamin + OAD	300	300	300	300	300
OAD	826	826	826	826	826

	År 1	År 2	År 3	År 4	År 5
			Anbefales ikke		
Esketamin + OAD	0	0	0	0	0
OAD	1.126	1.126	1.126	1.126	1.126

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet er ændret til 300 patienter pr. år.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af esketamin vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 7.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca.7,2 mio. DKK i år 5.

Tabel 7. Medicinrådets 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 budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Medicinrådet estimerer, at 4 ugers behandling med esketamin tillagt oral antidepressiv medicin, under en moderat til svær depressiv episode med akut øget selvmordsrisiko, er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med oral antidepressiv medicin alene. De inkrementelle omkostninger er hovedsageligt drevet af lægemiddelomkostningerne til esketamin. Anvendelse af esketamin kan potentielt lede til en vis besparelse i indlæggelsesomkostninger, når der sammenlignes med behandling med OAD alene. Denne observation baserer sig på indlæggelsestiden i ASPIRE-1, hvor esketamin-armen var indlagt ca. 2 dage kortere end placebo-armen. Der er derfor en vis usikkerhed om, hvorvidt dette også vil gøre sig gældende i dansk klinisk praksis.

Den sundhedsøkonomiske analyse indeholder flere usikkerheder. Den mest nævneværdige er, at der i den sundhedsøkonomiske model ikke er taget højde for potentielle genindlæggelser og dermed en eventuel forskel i andel genindlæggelser på tværs af intervention og komparator. Dette har ikke været muligt at undersøge, siden der ikke forelægger data vedrørende dette i ASPIRE-1 og 2.

Som beskrevet i afsnit 4.1 har ansøger i sin indsendte analyse antaget ligeværdig klinisk effekt af esketamin og ECT, da det ikke har været muligt at identificere relevant studiedata for denne sammenligning. Medicinrådet har ikke anvendt denne analyse, men i stedet præsenteret et estimat af, hvad et behandlingsforløb koster med hhv. esketamin og ECT. De forskellige anvendte metoder til at estimere omkostning forbundet med ECT leder til forskellige resultater og er forbundet med usikkerhed. Opgørelsen tager ikke højde for evt. afledte besparelser eller meromkostninger i forbindelse med fx indlæggelsestid.

8. Referencer

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	20. januar 2023	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 90 dage. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 8.

Tabel 8. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Esketamin	OAD	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrationsomkostninger	7.268	-	7.268
Monitoreringsomkostninger	8.448	7.675	773
Indlæggelsesomkostninger	55.130	82.692	-27.562
Patientomkostninger	48.183	68.519	-20.336
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af Esketamin vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 9.

Tabel 9. Ansøgers hovedanalyse for 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 budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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20. december 2022
MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25. januar 2023
Leverandør	Janssen Cilag A/S
Lægemiddel	Spravato (esketamin)
Ansøgt indikation	Til voksne med en moderat til svær depressionsepisode med henblik på hurtig reduktion af depressive symptomer, som udgør en akut øget selvmordsrisiko

Forhandlingsresultat

Amgros har opnået følgende pris på Spravato (esketamin):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Nuværende SAIP	Forhandlet SAIP	Rabatprocent ift. AIP
Spravato (esketamin)	28 mg	2 stk.	2.857,21	[redacted]	[redacted]	[redacted]
Spravato (esketamin)	28 mg	3 stk.	4.141,08	[redacted]	[redacted]	[redacted]

Prisen er betinget af en anbefaling.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på området.

Tabel 2: Lægemiddeludgifter for Spravato (esketamin)

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP	Antal pakninger	Lægemiddeludgift for 4 ugers behandling SAIP
Spravato (esketamin)	84 mg 2 gange om ugen i 4 uger	28 mg (3 stk.)	[redacted]	8	[redacted]

Status fra andre lande

Norge: Under vurdering[1].
Sverige: Anbefalet[2]
England: Ikke vurderet

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/esketamin-spravato-indikasjon-ii
[2] https://janusinfo.se/download/18.13de125317a50669b3a54599/1625051143899/Esketamin-(Spravato)-210630.pdf

Fra:	Ehm Astrid Andersson Galijatovic
Til:	Koldby, Kasper [JACDK]
Cc:	Johansen, Mikkel [JACDK]; Riise, Jesper [JACDK]; Christian Skouenborg
Emne:	SV: Høring over vurderingsrapport og sundhedsøkonomiske afrapportering for esketamin som akut korttidsbehandling
Dato:	22. december 2022 09:14:00
Vedhæftede filer:	image002.png image003.png

Kære Kasper,

Tak for høringssvaret.
Vi har været i dialog med fagudvalgsformanden om høringssvaret.
Vi er herved blevet enige om, at vi vil lægge op til at slette usikkerheden vedr. benzodiazepiner fra vurderingsrapporten i en version 1.1. Dette vil blive forelagt Rådet sammen med anbefalingen i den skriftlige proces. Dette ændrer ikke på konklusionerne i rapporten.
Jeres øvrige kommentarer har ikke medført ændringer i rapporten.

Mh Ehm

Fra: Koldby, Kasper [JACDK] <KKoldby@ITS.JNJ.com>
Sendt: 9. december 2022 15:29
Til: Ehm Astrid Andersson Galijatovic <EAG@medicinraadet.dk>; Christian Skouenborg <CSC@medicinraadet.dk>
Cc: Johansen, Mikkel [JACDK] <MJohan12@ITS.JNJ.com>; Riise, Jesper [JACDK] <jriise@ITS.JNJ.com>
Emne: RE: Høring over vurderingsrapport og sundhedsøkonomiske afrapportering for esketamin som akut korttidsbehandling

Kære Ehm & Christian,

Endnu en gang mange tak for det det fremsendte. I finder nedenfor vores korte høringssvar til vurderingsrapporten og den sundhedsøkonomiske afrapportering.
I tager som altid bare fat i mig, hvis I har opfølgende spørgsmål eller kommentarer.

De bedste hilsner,
Kasper

Til Medicinrådet,

I forbindelse med modtagelsen af den kliniske vurderingsrapport og den sundhedsøkonomiske afrapportering for esketamin til akut korttidsbehandling finder vi det først og fremmest positivt, at fagudvalget i så høj grad anerkender værdien af og behovet for esketamin som en behandlingsmulighed til voksne patienter med moderat til svær depressionsepisode med akut øget selvmordsrisiko. Vi hæfter os særligt ved følgende budskaber fra fagudvalget:

- **Værdi for patienterne:** Der er tale om en højrisikogruppe med behov for hurtig krisestyring eller akut indlæggelse, hvor fagudvalget lægger vægt på, at patienterne ved behandling med esketamin opnår en hurtigt indsættende klinisk relevant reduktion i

depressive symptomer, og der bringes flere patienter i remission. Den hurtigt indsættende virkning fremhæves som særligt værdifuld for en gruppe af patienter i en meget forpint tilstand med svært nedsat livskvalitet.

- **Behovet for nye behandlingsmuligheder:** Der er i Danmark omfattende erfaring med håndtering af ECT, men til trods for behandlingens veletablerede effekt, så er den ikke en relevant eller optimal behandling for alle patienter. Disse patienter har ifølge fagudvalget brug for nye behandlingsalternativer, da mulighederne for dem lige nu er meget begrænsede.

- **Bivirkningsprofilen:** Fagudvalget konkluderer, at eventuelle bekymringer om bivirkninger er mindre relevante i den akutte setting, fordi behandlingen er kortvarig og foregår under indlæggelse på en psykiatrisk enhed i størstedelen af tiden. De bekymringer, som Medicinrådet gav udtryk for i vurderingen af esketamin til behandlingsresistent depression, vurderes således som mindre relevante for denne indikation. Samtidig vurderes bivirkningsprofilen ikke som værre end ved alternative behandlinger som fx ECT men blot af anderledes karakter.

Det kan endvidere nævnes, at fagudvalgets budskaber og samlede vurdering af esketamin er helt i overensstemmelse med den udvikling, som aktuelt pågår i Tyskland inden for det psykiatriske område, hvor de kliniske retningslinjer (NVL Unipolare Depression, PDF-version er vedhæftet) for nyligt er blevet opdateret med tilføjelsen af esketamin som en anbefalet behandling til patienter med øget selvmordsrisiko og andre akutte psykiatriske situationer.

Som en enkeltstående anmærkning til vurderingsrapporten undrer vi os over formuleringen *"merværdi af ukendt størrelse (formentlig lille) baseret på effekten på depressive symptomer"* i den samlede kategorisering af esketamins merværdi. Det ligger i kategoriseringens definition, at størrelsen af merværdien ikke kan bestemmes, og *"formentlig lille"* bryder således med den metodiske definition. En mere retvisende formulering i overensstemmelse med kategoriseringen af merværdien vil være *"som minimum lille"*.

Derudover hæfter vi os ved, at fagudvalget kort kommenterer på, hvorvidt der er en mulig indvirkning af benzodiazepiner på effekten af esketamin. Dette er blevet belyst i en publiceret artikel, som er vedhæftet denne mail som baggrundsinformation til fagudvalget. Publikationen fandt, at hovedparten af patienterne i ASPIRE studierne benyttede benzodiazepiner (68.5%, n=309/451) med en ligelig fordeling mellem de to arme. Forskellen i reduktionen af depressive symptomer mellem esketamin og placebo-armen var klinisk betydningsfuld uafhængigt af benzodiazepinforbrug, mens intervention med benzodiazepiner blandt esketamin-behandlede patienter ikke påvirkede den hurtigt indsættende antidepressive virkning af esketamin betydningsfuldt ved 24 timer post-dosis.

Som udgangspunkt har vi ikke yderligere bemærkninger til vurderingsrapporten, og fremsendte kan derfor betragtes som vores endelige høringssvar. Dette baserer sig naturligvis på en antagelse om, at Rådets konklusion og behandling af vurderingsrapporten på mødet d. 14. december forbliver i overensstemmelse med fagudvalgets indstilling og den nuværende version af vurderingsrapporten.

På vegne af Janssen-Cilag A/S,

Kasper Magaard Koldby
Country HEMAR Manager

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From: Ehm Astrid Andersson Galijatovic <EAG@medicinraadet.dk>
Sent: 2. december 2022 12:42
To: Koldby, Kasper [JACDK] <KKoldby@ITS.JNJ.com>
Cc: Christian Skouenborg <CSC@medicinraadet.dk>
Subject: [EXTERNAL] Høring over vurderingsrapport og sundhedsøkonomiske afrapportering for esketamin som akut korttidsbehandling

Kære Kasper

Sekretariatet fremsender hermed udkast til Medicinrådets vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for esketamin til akut kortidsbehandling.
Medicinrådet drøfter vurderingen af lægemidlets værdi og modelantagelserne for den sundhedsøkonomiske afrapportering den 14. december 2022. I får besked fra sekretariat, hvis Rådet har ændringer til vurderingen udarbejdet af fagudvalget.
I har i alt 20 dage til at sende eventuelle bemærkninger til kategoriseringen af lægemidlets værdi og den sundhedsøkonomiske afrapportering. **Jeres frist for at indgive kommentarer er derfor den 22. december 2022.** I er selvfølgelig velkomne til at sende eventuelle bemærkninger inden denne dato. I må også gerne meddele, hvis I ikke har kommentarer til kategoriseringen.
Vurderer sekretariatet og fagudvalget, at jeres kommentarer giver anledning til at revurdere kategoriseringen af lægemidlets værdi, skal Rådet drøfte vurderingen igen. Det vil med overvejende sandsynlighed udskyde tidspunktet for Rådets drøftelse af anbefalingen.
Jeres eventuelle kommentarer indgår i det materiale, som bliver fremlagt for Medicinrådet i

forbindelse med behandlingen af anbefalingen. Jeres eventuelle kommentarer bliver offentliggjort sammen med anbefalingen.

Mh Christian og Ehm

Med venlig hilsen

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Medicinrådet

Medicinrådets vurdering vedrørende esketamin som akut kortidsbehandling

Til voksne med en moderat til svær depressionsepisode med henblik på hurtig reduktion af depressive symptomer, som udgør en akut øget selvmordsrisiko

Version 1.1

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 bliver sammenfattet 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.

Dokumentoplysninger	
Godkendelsesdato	20. januar 2023
Dokumentnummer	159826
Versionsnummer	1.1

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at esketamin som korttidsbehandling samtidig med oral antidepressiv behandling til patienter med akut øget selvmordsrisiko har en merværdi af ukendt størrelse, som formentlig er lille, sammenlignet med oral antidepressiv behandling alene. Denne vurdering er baseret på esketamins effekt på reduktion i depressive symptomer i en relevant patientpopulation.

Der findes ikke komparative data, som kan bruges til en sammenligning mellem esketamin og ECT. Derfor kan værdien af esketamin ikke kategoriseres i sammenligningen med ECT.

Der er betydende bivirkninger ved esketamin, herunder særligt dissociation og blodtrykstigning. Medicinrådet er mindre bekymret over bivirkningsprofilen i denne patientgruppe, fordi patienterne skal have behandling i kort tid, og fordi behandlingen foregår under indlæggelse på en psykiatrisk enhed i størstedelen af tiden. Behandlingen kan dermed foregå under meget kontrollerede forhold, hvilket kan mindske risikoen for misbrug.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 20. januar 2023

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.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

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

CI:	Konfidensinterval
CGI-SS-R:	*Clinical Global Impression-Severity of Suicidality - Revised*
ECT:	Elektrokonvulsiv terapi
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
MADRS:	*Montgomery-Åsberg Depression Rating Scale*
MDD:	*Major Depressive Disorder*
ITT:	*Intention to treat*
OR:	*Odds ratio*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per Protocol*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*

3. Introduktion

Medicinrådets vurdering omhandler indikationen esketamin samtidig med oral antidepressiva til voksne med en moderat til svær depressionsepisode, som akut korttidsbehandling, med henblik på hurtig reduktion af depressive symptomer, som ud fra en klinisk vurdering udgør en akut øget selvmordsrisiko (eller akut psykiatrisk tilfælde jf. EMAs indikation).

Formålet med denne rapport er at vurdere den værdi, behandlingen har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en ansøgning fra Janssen. Medicinrådet modtog den endelige ansøgning den 22. september 2022.

De kliniske spørgsmål er:

1. Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med placebo i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko? (Patienter, som ikke behandles med elektrokonvulsiv terapi (ECT)).

2. Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med ECT i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko?

Fagudvalget havde i protokollen desuden ønsket behandlingseffekten belyst i en subpopulation med en *Clinical Global Impression-Severity of Suicidality - Revised* (CGI-SS-R)-score på 4 eller højere ved baseline.

3.1 Moderat til svær depression

Depression præsenterer sig typisk med symptomer som nedtrykthed og nedsat energi over længere tid, manglende selvværd, isolationstendens, selvbebrejdelser, nedsat eller øget appetit, tab af livslyst og ofte ved svær og moderat depression som selvmordstanker eller -planer [1]. I alvorlige tilfælde kan der være psykotiske symptomer i form af hallucinationer og vrangforestillinger [1]. 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 [1].

Depression diagnosticeres, jf. klassifikationssystemet *International Classification of Diseases and Related Health Problems-10* (ICD-10), ud fra en række grundliggende kriterier. Varighed samt antal og sværhedsgrad af depressive symptomer afgør, om der er tale om depression, og hvorvidt denne er af let, moderat eller svær grad. Depression ses ofte sammen med andre psykiske lidelser som f.eks. angstlidelser og

personlighedsforstyrrelser [1,2]. Herudover er alkohol og/eller stofmisbrug også almindeligt hos patienter med svær depression [1]. Især stofpåvirkede patienter kan optræde med akut opstået selvmordsadfærd. I sådanne tilfælde bør behandlingen tilrettelægges ud fra patientens psykiske tilstand efter afrusning.

Moderat til svær 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 [3,4]. Det skønnes, at kun 65 % af disse, svarende til ca. 72.400 voksne individer, bliver diagnosticeret og kan komme i behandling [4]. En mindre andel vil have særskilt behov for akut behandling med hurtigindsættende virkning på depressive symptomer, fordi de udviser alvorlig selvmordsadfærd.

Patienter med svær depression kan udvise selvmordstanker og -adfærd, der er så alvorlig, at det kan være nødvendigt med indlæggelse og akut behandling. Dette gælder også for et fåtal af patienter med moderat depression. Selvmordsrisikoen beror på et klinisk skøn af den behandlende speciallæge i psykiatri og kan afdækkes ved en klinisk vurdering og bl.a. følgende spørgsmål:

- Har patienten tidligere foretaget selvmordsforsøg? Er det for nyligt? Hvad var omstændighederne for selvmordsforsøget?
- Har patienten aktuelle selvmordstanker? Hvad omhandler selvmordstankerne?
- Har patienten aktuelle selvmordsplaner? Hvad omhandler selvmordsplanerne, og i hvilket omfang har patienten forberedt sig på at effektuere planerne?
- Kan patienten på troværdig vis tage afstand fra selvmordsimpulser? Hvilke modforestillinger har patienten? Kan der indgås en troværdig sikkerhedsplan med patienten?

Et selvmordsforsøg beskrives som en handling, hvor en person intentionelt udviser en adfærd, der kan have dødelig udgang. Selvmordstanker strækker sig fra forbigående forestillinger og overvejelser om at dø til mere vedvarende og påtrængende overvejelser og i sidste ende en endelig beslutning om at begå selvmord. Selvmordsadfærd dækker over egentlige selvmordsforsøg eller forberedelser herpå. For patienter med moderat til svær depression med akut øget selvmordsrisiko er der ofte tale om en risiko, der er øget i en igangværende depressionsepisode eller som led i en nyligt påbegyndt depressionsepisode. Årsagerne kan være mange, men sociale forhold og misbrug spiller ofte en rolle.

Patienter med selvmordsadfærd henvises til psykiatrisk intensivbehandling for hurtig akut behandling, og patienter diagnosticeres ofte i akutmodtagelsen eller som en del af en akut indlæggelsesvurdering. Patienter med moderat til svær depression med akut øget selvmordsrisiko udgør en højrisikogruppe med behov for hurtig krisestyring eller akut indlæggelse for at føre opsyn med patienten og nedbringe selvmordsrisikoen.

3.2 Esketamin

Esketamin (handelsnavn Spravato®) eller s-ketamin er ét af to spejlmolekyler af ketamin (s- og r-ketamin), hvor s-formen har størst specificitet i forhold til r-formen [5]. Esketamin påvirker bl.a. N-methyl-D-aspartat (NMDA)-receptoren i hjernen, hvilket tænkes at have betydning for reguleringen af affektiv og emotionel adfærd [6–8].

Til behandling af depression hos voksne er esketamin udviklet som en nasal formulering [9]. Den intranasale administrationsvej tillader en hurtig absorption og virkning, hvorimod det kan tage flere uger at opnå en ønsket effekt af andre behandlinger med f.eks. orale antidepressiva.

Oprindeligt blev esketamin (fleksibel dosering) i kombination med SSRI/SNRI godkendt af EMA i 2019 til voksne med behandlingsresistent moderat til svær depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva under den igangværende moderate til svære depressionsepisode [9]. I 2020 og ved en revurdering i 2022 anbefalede Medicinrådet ikke esketamin som mulig standardbehandling til denne indikation, bl.a. pga. manglende evidens for langtidseffekterne, og at patienterne, som indgik i de kliniske studier, ikke i tilstrækkelig grad afspejlede de relevante patienter i dansk praksis, Esketamin (Spravato) til moderat til svær depression (MDD) hos voksne med manglende respons (revurdering) (medicinraadet.dk).

Denne indikationsudvidelse omhandler esketamin givet sammen med oral antidepressiva til voksne med en moderat til svær depressionsepisode, som akut korttidsbehandling, med henblik på hurtig reduktion af depressive symptomer, som ud fra en klinisk vurdering udgør en akut øget selvmordsrisiko (eller udgør et akut psykiatrisk tilfælde jf. EMAs indikation) [9]. Indikationsteksten illustrerer, at EMA har vurderet, at esketamin kan reducere depressive symptomer, men at det ikke er dokumenteret, at esketamin kan forebygge selvmord eller reducere selvmordsrisikoen [10].

Den godkendte behandling til denne indikation består af en fast dosis intranasal esketamin 84 mg to gange om ugen i fire uger i samtidig med anden antidepressiv behandling [9]. Behandlingen forventes seponeret senest efter 4 uger. Fagudvalget finder, at voksne patienter med moderat til svær depressionsepisode med akut øget selvmordsrisiko kan være relevante kandidater til kortvarig behandling med esketamin.

3.3 Nuværende behandling

Ifølge den gældende behandlingsvejledning udarbejdet af Rådet for Anvendelse af Dyr Sygehusmedicin for medicinsk behandling af unipolær depression, behandles moderat depression (score på despressionsskala *Montgomery-Åsberg Depression Rating Scale* (MADRS) 22-29) med antidepressiva eller psykoterapi, mens svær depression (MADRS 30-60) bør behandles med antidepressiva og samtaler tilpasset patientens tilstand [11]. En patient med moderat til svær depression, der er i overhængende fare for at begå selvmord, vil typisk allerede være i behandling med et eller flere antidepressiva og evt. andre psykofarmaka. For nogle patienter er der tale om en ny episode, hvor patienten skal påbegynde antidepressiv behandling. For begge situationer gælder, at patienten som udgangspunkt bliver indlagt til psykiatrisk intensivbehandling, hvor det primære mål

vil være at afværge selvmordsfaren og derefter at sikre nattesøvnen, som ofte vil være svært forstyrret, og reducere agitation med f.eks. antidepressiva med sederende virkning, antipsykotika eller benzodiazepiner. Desuden skal de øvrige symptomer behandles. Som led i krisestyringen forsøges optimering eller ændring af patientens antidepressive behandling.

Ved umiddelbar bedring med disse tiltag gives ikke yderligere medicinsk behandling, og patienten forbliver indlagt, indtil der er nok bedring i tilstanden til, at patienten kan udskrives.

Ved vedvarende svære symptomer eller akut selvmordsrisiko er der indikation for elektrokonvulsiv terapi (ECT) [12]. Dette gælder særligt, hvis patienten tidligere har haft god gavn af ECT i en tilsvarende situation. Efter 1-3 ECT inden for en uge forventes en bedring i tilstanden, og typisk gives 8-12 behandlinger i alt, men behandlingsvarigheden varierer fra patient til patient. Patienter vil blive kontinuerligt observeret af personalet, indtil der er nok bedring i tilstanden til, at patienten kan udskrives. Mange patienter har god gavn af ECT. Den bedste effekt ses hos ældre patienter over 50-60 år og patienter med såkaldt psykotisk depression.

For nogle patienter er ECT ikke en relevant eller optimal behandling. Disse patienter har brug for andre behandlingsmuligheder. Dette gælder patienter, som ikke har haft tilstrækkeligt respons på tidligere ECT-serie, eller som har haft betydende bivirkninger efter tidligere ECT. Samtidig ønsker nogle patienter ikke ECT efter at have modtaget en grundig gennemgang af fordele og ulemper. Fagudvalget anslår, at dette gælder for ca. 300-500 patienter om året.

I Danmark er den gennemsnitlige indlæggelsesvarighed 19-20 dage, hvorefter patienterne udskrives til opfølgende ambulant behandling. Ca. 20-25 % genindlægges akut inden for 30 dage efter udskrivelsen.

I meget sjældne tilfælde begår nogle patienter selvmord under indlæggelsen på trods af akut behandling og forebyggende tiltag.

4. Metode

Medicinrådets protokol for vurdering vedrørende esketamin til kortvarig behandling af voksne med moderat til svær depressiv episode med akut øget selvmordsrisiko beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne, Medicinrådets protokol for vurdering vedr. esketamin i tillæg til antidepressiva til kortvarig behandling af voksne med moderat til svær depressiv episode med akut øget selvmordsrisiko-vers. 1.0 (medicinraadet.dk).

Protokolafvigelser:

EMA har vurderet, at esketamins effekt på reduktion af selvmordsrisiko ikke er tilstrækkeligt dokumenteret i studiedata. Derfor er indikationsteksten formuleret

således, at esketamin bør gives til disse patienter med henblik på hurtig reduktion af depressive symptomer i patientgruppen, som er i akut selvmordsrisiko (udgør et akut psykiatrisk tilfælde), og ikke med henblik på at reducere selvmordsrisikoen, idet denne effekt ikke er veldokumenteret, og derfor ikke kan forventes [10].

En del af protokollens effektmål omhandler selvmordsrisiko og disse vil blive gennemgået på et mere overordnet plan, fordi effekten ikke er anerkendt af EMA. Subpopulation med en *Clinical Global Impression-Severity of Suicidality - Revised* (CGI-SS-R)-score på 4 eller højere ved baseline, som var ønsket i protokollen, vurderes ikke længere at være relevant, idet der ikke kan påvises en effekt på selvmordsrisiko på denne score for hele patientgruppen.

5. Resultater

5.1 Klinisk spørgsmål 1

Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med placebo i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko? (Patienter, som ikke behandles med ECT).

5.1.1 Litteratur

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

Ansøgningen baserer sig på de 3 studier, der er angivet i protokollen.

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer
Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). Fu DJ, Ionescu DF, Li X, Lane R, Lim P, Sanacora G, et al. The Journal of Clinical Psychiatry. 2020. [13]	ASPIRE-I	NCT03039192

Publikationer	Klinisk forsøg	NCT-nummer
Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). Ionescu DF, Fu DJ, Qiu X, Lane R, Lim P, Kasper S, et al. The International Journal of Neuropsychopharmacology. 2020 [14].	ASPIRE-II	NCT03097133
Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. American Journal of Psychiatry. 2018 [15]	ESKETINSUI2001	NCT02133001

ASPIRE-I og ASPIRE-II

APSIRE-I og APSIRE-II (ASPIRE-I n=112, ASPIRE-II n=115) er to identiske kortvarige, randomiserede, dobbeltblindede, placebokontrollerede fase 3-multicenterstudier, som undersøgte esketamin 84 mg i tillæg til optimeret standardbehandling (defineret som optimering af AD eller augmentering, inklusive hospitalisering) [13,14,16].

Studierne inkluderede voksne patienter med moderat til svær depression (total MADRS-score > 28), som svarede bekræftende på MINI-spørgsmål B3 (”Haft tanker [selv kortvarigt] om at påføre dig selv skade, med i det mindste nogen hensigt eller viden om, at du kunne dø af det, eller haft tanker om selvmord [dvs. at slå dig selv ihjel]?”) og B10 (”Hensigt om at handle på tanker om at slå dig selv ihjel inden for de seneste 24 timer?”). Efter lægens vurdering var der klinisk begrundelse for akut indlæggelse på psykiatrisk afdeling på grund af akut selvmordsrisiko.

I disse studier fik patienterne behandling med esketamin 84 mg eller placebo som næsespray to gange om ugen i fire uger. Efter den første dosis blev en dosisreduktion til 56 mg tilladt én gang for patienter, som ikke tolererede 84 mg-dosis.

Alle patienter fik omfattende standardbehandling, herunder en indledende hospitalsindlæggelse og et nyligt initieret eller optimeret oralt antidepressivum (AD) (AD monoterapi eller AD plus augmentering) efter investigators valg. Patienterne skulle være indlagt i minimum 5 dage.

Studiet indeholdt en screeningsfase på 48 timer, hvor patienter, som blev indlagt på en psykiatrisk enhed grundet selvmordsrisiko, blev screenet for at undersøge, om de kunne indgå i studiet (in- og eksklusionskriterier ses længere nede i afsnittet). Herefter fulgte den dobbelt-blindede behandlingsfase på 4 uger. Efter den dobbeltblindede fase stoppede patienterne eksetamin og fortsatte den optimerede standardbehandling og

blev fulgt til dag 90. I follow-up fasen blev patienterne fulgt to gange om ugen i de første to uger (dag 28, 32, 35 og 39). Herefter én gang ugentligt, de næste to uger (dag 46 og 53) og herefter hver anden uge frem til dag 90 (dag 67 og 90).

Det primære endepunkt var ændring i MADRS-score 24 timer efter første dosis esketamin, og det sekundære endepunkt var ændring i CGI-SS-R 24 timer efter første dosis esketamin. Studierne opgør også resultater for disse effektmål for hele den dobbeltblindede periode, dag 25 og ved opfølgning til dag 90.

Sikkerhed blev opgjort ved uønskede hændelser og ved Clinician-Administered Dissociative States Scale (CADSS).

Baseline karakteristik kan findes herunder for den samlede population i ASPIRE I og II [16]. Karakteristik for de enkelte studier for sig kan ses i bilag 1.

TABLE 1. Demographics, Baseline Clinical Rating, and Psychiatric History (Efficacy Analysis Data Set)

Parameter	Placebo + Standard of Care (n = 225)	Esketamine 84 mg* + Standard of Care (n = 226)	All Patients (N = 451)
Age, mean (SD), y	39.6 (13.08)	40.5 (12.92)	40.1 (13.00)
Sex, n (%)			
Female	140 (62.2)	134 (59.3)	274 (60.8)
Male	85 (37.8)	92 (40.7)	177 (39.2)
Race, n (%)			
White	161 (71.6)	169 (74.8)	330 (73.2)
Asian	30 (13.3)	29 (12.8)	59 (13.1)
Black or African American	15 (6.7)	11 (4.9)	26 (5.8)
Other/not reported	19 (8.4)	17 (7.5)	36 (8.0)
Region, n (%)			
North America	65 (28.9)	58 (25.7)	123 (27.3)
Europe	106 (47.1)	117 (51.8)	223 (49.4)
Asia	27 (12.0)	26 (11.5)	53 (11.8)
South America	27 (12.0)	25 (11.1)	52 (11.5)
MADRS total score,† mean (SD)	40.4 (6.04)	40.3 (5.60)	40.4 (5.82)
CGI-SS-r,† n (%)			
Normal, not at all suicidal	0	0	0
Questionably suicidal	6 (2.7)	6 (2.7)	12 (2.7)
Mildly suicidal	17 (7.6)	16 (7.1)	33 (7.3)
Moderately suicidal	61 (27.1)	64 (28.4)	125 (27.8)
Markedly suicidal	84 (37.3)	86 (38.2)	170 (37.8)
Severely suicidal	55 (24.4)	46 (20.4)	101 (22.4)
Among the most extremely suicidal patients	2 (0.9)	7 (3.1)	9 (2.0)
Suicide attempt, n (%)			
Attempt in the last month	55 (24.4)	68 (30.1)	123 (27.3)
Attempt during lifetime†	140 (62.2)	144 (64.0)	284 (63.1)
Standard-of-care antidepressant,‡ n (%)			
Antidepressant monotherapy	108 (48.0)	104 (46.0)	212 (47.0)
Antidepressant plus augmentation therapy§	117 (52.0)	122 (54.0)	239 (53.0)

*Includes patients who had their dose reduced because of tolerability issues.
†Two hundred twenty-five for the esketamine + standard-of-care group.
‡As randomized.
§Augmentation therapy included an agent, such as a second antidepressant, an atypical antipsychotic, or a mood stabilizer.

Den mediane patientalder var 40 år (interval 18 til 64 år), 61 % var kvinder, og 63 % af patienterne havde mindst ét tidligere selvmordsforsøg. 27,3 % havde et selvmordsforsøg indenfor seneste måned. Før de indtrådte i studiet, fik 92 % af patienterne antidepressiva. Som en del af standardbehandlingen fik 40 % af patienterne AD monoterapi, 54 % af patienterne fik AD plus augmentering og 6 % fik både AD

monoterapi/AD plus augmentering under studiet. ECT er ikke tilladt. Dosering af andre lægemidler kan ændres i studiets første to uger.

De hyppigst anvendte psykofarmaka i studierne er (≥ 10 %) venlafaxin (26,5 %), quetiapin (21,2 %), escitalopram (16,6 %), duloxetin (15,0 %) og mirtazapin (14,2 %). Brug af benzodiazepiner var 73,6 % og 66,7 % i hhv. esketamin og placebogrupperne, og non-benzodiazepiner (hypnotika og anxiolytika) var 36,0 % og 31,7 % i hhv. esketamin og placebogrupperne.

Der er flere eksklusionskriterier i studierne, hvoraf kan nævnes: bipolar eller relateret sygdom, (antisocial personality disorder eller OCD), borderline personlighedsforstyrrelse, autisme, demens eller dårlig begavelse, psykose eller psykotiske træk og alkohol eller stofmisbrug inden for seneste 6 måneder.

ESKETINSUI2001 (PeRSEVERe)

ESKETINSUI2001 var et randomiseret, dobbeltblindet, placebokontrolleret fase 2-multicenter studie til proof-of-concept [15]. Det undersøgte 84 mg esketamin i tillæg til optimeret standardbehandling i 68 patienter. Studiedesign og kriterier for inklusion var ikke betydende forskelligt fra APSIRE-I og -II. Se afsnit ovenfor. Enkelte forskelle var at MADRS-scoren kun skulle være over 22 og at studiet kun blev udført på centre i USA. Det primære effektmål var ændring i MADRS score 4 timer efter første dosis esketamin. Effektmålet opgøres frem til dag 25. Baselinekarakteristisk kan ses i bilag 1.

Fagudvalgets vurdering af studierne

Fagudvalget vurderer, at patienterne, som er inkluderet i studierne, stemmer godt overens med de patienter, man forventer i dansk praksis med hensyn til karakteristik og sygdomsalvorlighed, hvis man ser bort fra de temmelig stramme inklusionskriterier. Det er således almindeligt forekommende i den psykiatriske klinik, at patienter har komorbide lidelser ved siden af deres depression, som fx autisme, OCD, personlighedsforstyrrelser, angstlidelser osv. Sådanne patienter er ikke indgået i de kliniske studier. Dog var angst alene ikke et eksklusionskriterie. Hertil kommer, at patienter med bipolar depression heller ikke er inkluderet.

Indlæggelsestiden i dansk praksis er altid længere end 5 dage, som var minimum i studierne.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Til hvert effektmål ses på effekten ved 24 timer og efter ca. 4 ugers behandling svarende til dag 25 i studierne.

Selvmordsrisiko/symptomer er undersøgt ved CGI-SS-R jf. protokollen. I analyserne for selvmordsrisiko indgår data fra ASPIRE I og II, som er kombineret i en metaanalyse.

Til at estimere en forskel i depressive symptomer på MADRS-score (remission, respons og ændring på den kontinuerlige skala) anvendes ASPIRE I, ASPIREII og ESKETINSUI2001-studierne, som kombineres i en metaanalyse. Analyserne følger protokollen.

Fagudvalget er enige med ansøger i, at de 3 studier er tilpas sammenlignelige til, at effektestimaterne kan samles i metaanalyser.

Bivirkninger adresseres ved en kvalitativ gennemgang.

5.1.3 Evidensens kvalitet

Medicinrådet 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.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at der er forbehold for risiko for bias. Dette skyldes primært den tvivlsomme blænding af interventionsgruppen. Der er god effekt af placebo plus SoC. Mens en del af dette formentlig skyldes en virksom SoC, kan en del også tilskrives placeboeffekt. Esketamin har for en del patienter tydelige psykiatriske bivirkninger, hvilket kan betyde, at en del patienter, som fik det aktive lægemiddel, har været klare over det, og at blindingen derfor ikke er intakt. Dog ses placeborespons efter de enkelte doseringer, hvilket kan tyde på, at nogle patienter, som får placebo, fortsat er blindede. Den tvivlsomme blinding kan påvirke de relevante effektmål. Disse forhold medfører nedgradering for risk of bias.

Der ses et nogenlunde ensartet frafald i studiearmene i både behandlings- og follow-up fasen.

Populationen svarer ikke helt overens med dansk praksis grundet stramme inklusionskriterier, som nævnt ovenfor, og der nedgraderes derfor for indirekthed.

For nogle effektmål er effekten ikke større end den prædefinerede mindste kliniske relevante forskel på de absolutte skalaer. Samlet set nedgraderes derfor for imprecision.

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 2. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Selvmordsrisiko	Gennemsnitlig forbedring fra baseline i selvmordssymptomer på CGI-SS-R (MKRF 3 point)	Kritisk	24 timer: -0,20 (-0,44; 0,04) Dag 25: -0,19 (-0,43; 0,04)	Ingen dokumenteret merværdi			Ingen dokumenteret merværdi
	Andel med resolution af selvmordstankerne (score på ≤ 2) på CGI-SS-R (MKRF 30 %-point)				24 timer: RR: 1,09 (0,91-1,13) Dag 25: RR: 1,05 (0,96-1,14)	Ingen dokumenteret merværdi	
	Andel med forværring (deterioration defineret som forværring på ≥ 1 point) af selvmordssymptomer på CGI-SS-R (MKRF 5 %-point)				24 timer: RR: 1,2 (0,48-3,0) Dag 25: RR: 0,8 (0,04-16,3)	Kan ikke kategoriseres	
Bivirkninger	Kvalitativ gennemgang af specifikke hændelser relevante for behandling og sygdom						Kan ikke kategoriseres
Depressive symptomer*							Merværdi af ukendt størrelse
Respons	50 %-reduktion i MADRS MKRF 20 %point)	Vigtigt	24 timer: 11,5 %-point (4,4-32,2) Dag 25: 6,2 %-point (-3,1-18,6)	Ingen dokumenteret merværdi	24 timer: RR: 1,5 (1,1-1,9), Dag 25: RR: 1,1 (0,95-1,3)	Lille merværdi Ingen dokumenteret merværdi	

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Remission	≤11 på MADRS (MKRF 15 %-point)	Vigtigt	24 timer: 12,7 %-point (9,4-53,3)	Merværdi af ukendt størrelse	24 timer: RR: 2,2 (1,4-3,4)	Stor merværdi	
			Dag 25: 12,1 %-point (3,8-30,9)	Ingen dokumenteret merværdi	Dag 25: RR: 1,3 (1,08-1,62),	Lille merværdi	
Ændring på kontinuer skala	Gennemsnitlig ændring fra baseline på MADRS (3 point)	Vigtigt	24 timer: -4,2 (-6,0; -2,4) Dag 25: -3,9 (-5,8; -1,9)	Merværdi af ukendt størrelse			

Konklusion	
Samlet kategori for lægemidlets værdi	Merværdi af ukendt størrelse (formentlig lille) baseret på effekten på depressive symptomer
Kvalitet af den samlede evidens	Meget lav

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko
*remission, respons og ændring på den kontinuerlige skala for MADRS er samlet i et effektmål; depressive symptomer

Selvmordsrisiko
Som beskrevet i protokollen er effektmålet selvmordsrisiko kritisk for vurderingen af lægemidlets værdi for patienterne, fordi der er behov for at nedbringe den overhængende risiko for, at patienten tager sit eget liv.

Samlet set oplevede patienter i begge behandlingsgrupper forbedring i sværhedsgraden af deres selvmordsadfærd som målt med CGI-SS-R-skalaen (Clinical Global Impression – Severity of Suicidality – revised) ved 24-timers endepunktet, men der var ingen statistisk signifikant forskel mellem behandlingsgrupperne.

Jf. EMA er den langsigtede virkning af esketamin på forebyggelse af selvmord ikke blevet fastlagt [9].

Fagudvalget vurderer, at esketamin ingen dokumenteret merværdi har vedr. selvmordsrisiko.

Bivirkninger
Bivirkninger og risici ved esketamin er udførligt gennemgået i Medicinrådets vurdering af esketamin til behandlingsresistent depression, se Medicinrådets hjemmeside (Udkast Medicinrådet revurdering af esketamin til behandling af behandlingsresistent depression-vers. 1.0_Blændet (medicinraadet.dk)).

Jf. EMAs produktresumé er de hyppigst observerede bivirkninger hos patienter på tværs af indikationer svimmelhed (31 %), dissociation (27 %), kvalme (27 %), hovedpine (23 %), somnolens (18 %), dysgeusi (18 %), vertigo (16 %), hypæstesi (11 %), opkastning (11 %) og forhøjet blodtryk (10 %) [9].

Til denne indikation anvendes en dosis på 84 mg to gange om ugen, som er den højeste af de mulige doser, som er godkendt til den foregående indikation. Der er ikke identificeret nogle nye risici eller bivirkninger i forhold til den tidligere gennemgang af esketamin i variabel dosis (56 eller 84 mg to gange om ugen i uge 1-4 i denne aldersgruppe). I alt 6,2 % vs. 3,6 % stoppede behandling grundet bivirkninger i ASPIRE I og II, pooled for hhv. esketamin og placebo. 15,4 % fik dosisreduktion vs. 1,8 %. Årsager var hyppigst dissociation, kvalme og svimmelhed [16].

Samlet set over de 3 studier var der en tilsvarende frekvens af events, som var relateret til selvmordsadfærd for esketamin og placebo i både den dobbeltblændede fase og i follow-up fasen. Ligeledes var der tilsvarende frekvens af selvmordsforsøg inkl. 1 selvmord i begge arme i begge faser samlet over de 3 studier.

Tabel 3. Overblik over uønskede hændelser relateret til selvmordsadfærd for esketaminstudier

Study, study phase	Treatment	N	Any TEAE potentially related to suicidality, n (%)	Suicide attempts and completed suicides, n (%)
Pooled ASPIRE I and ASPIRE II, DB	Placebo + SoC	225	17 (7.6%)	4 (1.8%)
	ESK NS + SoC	227	17 (7.5%)	4 (1.8%)
Pooled ASPIRE I and ASPIRE II, FU	Placebo + SoC	185	19 (10.3%)	3 (1.6%)
	ESK NS + SoC	190	21 (11.1%)	7 (3.7%)
Pooled ASPIRE I, ASPIRE II, and ESKETINSUI2001, DB	Placebo + SoC	256	17 (6.6%)	4 (1.6%)
	ESK NS + SoC	262	20 (7.6%)	4 (1.5%)
Pooled ASPIRE I, ASPIRE II, and ESKETINSUI2001, FU	Placebo + SoC	207	24 (11.6%)	6 (2.9%)
	ESK NS + SoC	217	23 (10.6%)	7 (3.2%)

[redacted] Når man kun ser på follow-up fasen for de to fase 3-studier (ASPIRE I og II), var der numerisk flere selvmordsforsøg i esketaminarmen (3,7 % vs. 1,6 %). Tallene er dog meget små og i det samlede materiale (ASPIRE I, ASPIRE II og ESKETINSUI2001) var der ikke forskel i andele i follow-up fasen (3,2 % vs. 2,9 %) og ej heller i den dobbeltblændende fase. Fagudvalget påpeger, at follow-up fasen udgør en sårbar tid, hvor patienterne forventes at stoppe esketaminbehandling, og der kan dermed være behov for øget opmærksomhed på tilbagefald i denne periode.

I sammenhæng med dette indeholder produktresuméet en advarsel omkring selvmordsrisiko: "*Spravatos virkning til at forhindre selvmord eller reducere selvmordstanker eller -adfærd er ikke blevet påvist (se pkt. 5.1). Anvendelse af Spravato udelukker ikke behovet for hospitalsindlæggelse, hvis det er klinisk indiceret, heller ikke selv om patienten oplever forbedring efter en indledende dosis af Spravato. Behandlingen bør ledsages af nøje monitorering af patienterne og særligt patienter i højrisikogruppen, især i starten af behandlingen og ved dosisændringer. Patienten (og patientens omsorgspersoner) skal orienteres om at holde øje med tegn på klinisk forværring, selvmordsadfærd eller selvmordstanker samt usædvanlige ændringer i patientens adfærd og om straks at søge lægehjælp, hvis disse symptomer opstår. Depression er forbundet med en forøget risiko for selvmordstanker, selvskade og selvmord (selvmordsrelaterede hændelser). Denne risiko varer ved, indtil signifikant remission forekommer, og derfor skal patienterne monitoreres nøje. Det er generel klinisk erfaring, at risikoen for selvmord kan stige i de tidlige stadier af bedring. Patienter med selvmordsforsøg i anamnesen, og patienter, der udviser en høj grad af selvmordstanker før igangsætningen af behandlingen, vides at have større risiko for selvmordstanker og selvmordsforsøg og skal derfor monitoreres tæt under behandlingen*" [9].

Fagudvalget vurderer, at denne advarsel og beskrivelse i tilstrækkelig grad favner den mulige risiko.

Fagudvalget udtrykker derfor fortsat generelt bekymring for dissociative symptomer (følelse af at forlade kroppen) og fremhæver, at nogle patienter højest sandsynligt vil opleve de dissociative symptomer som meget ubehageligt, ligesom nogen vil have en risiko for efterfølgende at få generende flashbacks relateret til disse. Fagudvalget fremhæver, at dissociative symptomer kan

variere betydeligt i deres sværhedsgrad og finder fortsat, at graden eller omfanget af de dissociative symptomer er utilstrækkeligt beskrevet for studiepopulationerne. Herudover mener fagudvalget fortsat ikke, at blodtryksstigninger forbundet med anvendelse af esketamin er tilstrækkeligt belyst. Fagudvalget tilslutter sig, at alle patienter, der behandles med esketamin, bør overvåges efter dosering på grund af muligheden for sedation, dissociation og forhøjet blodtryk. Overvågning skal ske af en sundhedsperson, indtil patienten anses for at være klinisk stabil og parat til at forlade klinikken (inkl. revurdering af patientens blodtryk efter ca. 40 minutter og efterfølgende, som det findes klinisk relevant). Fagudvalget vurderer, at lægemidlets påvirkning af nervesystemet, herunder svimmelhed, dissociation og somnolens, er bekymrende, sidstnævnte også i forhold til bilkørsel. Disse neuropsykiatriske og motoriske forstyrrelser er potentielt alvorlige bivirkninger og bekræftes af, at der kræves overvågning af sundhedsperson efter hver administration. Generelt er fagudvalget bekymret for, at esketamin kan vise sig at have lignende uønskede effekter, herunder misbrugspotentiale, som det ses fra studier med ketamin. Risikoen for misbrug er dog generelt mindre i den akutte setting, fordi patienterne overvejende er indlagt, mens behandlingen pågår, og at der er tale om en kortvarig behandling på 4 uger.

Fagudvalget bemærker, at disse patienter i forvejen har det rigtig dårligt og derfor vil være villige til at acceptere en risiko for bivirkninger for at opnå en bedring i deres tilstand.

Reduktion i depressive symptomer:
Fagudvalget har i protokollen efterspurgt effekt på depressive symptomer på MADRS-score med 3 forskellige opgørelser,

1) andel, der opnår remission MADRS ≤ 11,

2) andel, der opnår respons $\geq$ 50% reduktion på MADRS

3) ændring fra baseline på den kontinuerlige MADRS-skala.

Herunder ses i tabelform effekten i de enkelte studier og resultatet af metaanalysen ved hhv. 24 timer efter første dosis og på dag 25, Tabel 4 og 5.

Tabel 4. Resultater for sammenligningen mellem esketamin og placebo efter 24 timer for de enkelte studier og den samlede metaanalyse for MADRS-score hhv. andel, der opnår respons, andel, der opnår remission, og gennemsnitlig ændring fra baseline på MADRS-score.

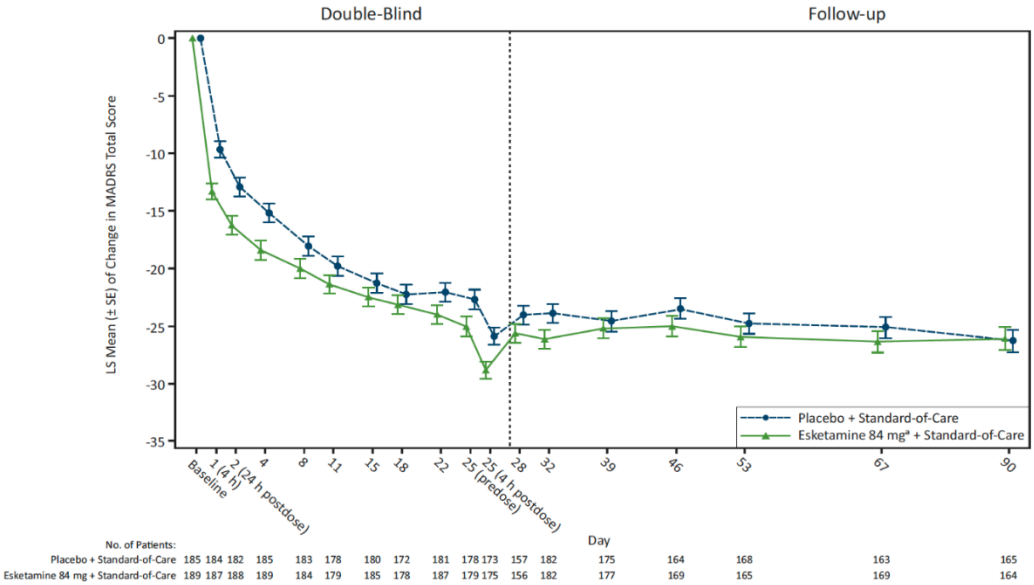
Andel, der opnår respons ≥ 50 % reduktion på MADRS	24 timer	
ESKETINSUI2001	ESK-NS 84 mg + SoC	54,3%
	PBO + SoC	29,0%
ASPIRE I og II	ESK-NS 84 mg + SoC	34,5
	PBO + SoC	25,3
Resultat af metanalyse: RR: 1,45 (1,1-1,9), 11,5 %-point (4,4-32,2)		
Andel der opnår remission MADRS ≤ 11	24 timer	
ESKETINSUI2001	ESK-NS 84 mg + SoC	34,3%
	PBO + SoC	16,1%
ASPIRE I og II	ESK-NS 84 mg + SoC	20,4 %
	PBO + SoC	9,8 %
Resultat af metanalyse: RR: 2,2 (1,4-3,4), 12,7 %-point (9,4-53,3)		
MADRS score, gennemsnitlig ændring fra baseline	24 timer	
ESKETINSUI2001	ESK-NS 84 mg + SoC	-18.9
	PBO + SoC	-11.7
ASPIRE I og II	ESK-NS 84 mg + SoC	−16.1 [11.73])
	PBO + SoC	−12.6 [10.56])
Resultat af metanalyse: -4,2 (-6,0; -2,4)		

Tabel 5. Resultater for sammenligningen mellem esketamin og placebo dag 25 for de enkelte studier og den samlede metaanalyse for MADRS-score hhv. respons, remission og gennemsnitlig ændring fra baseline på MADRS-score

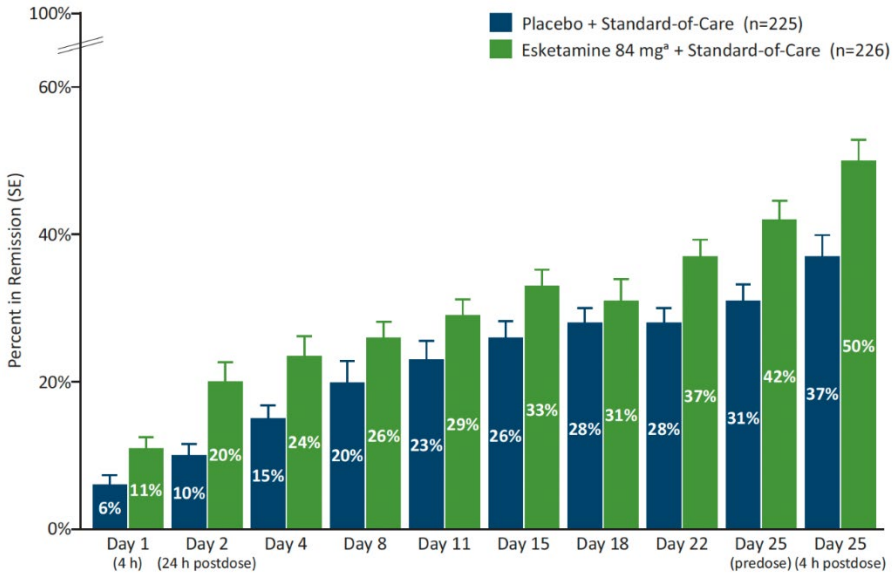
Andel, der opnår respons ≥ 50 % reduktion på MADRS	Dag 25	
ESKETINSUI2001	ESK-NS 84 mg + SoC	57,1%
	PBO + SoC	48,4%
ASPIRE I og II	ESK-NS 84 mg + SoC	65 %
	PBO + SoC	58 %
Resultat af metanalyse: RR: 1,15 (0,95-1,3), 6,2 %-point (-3,1-18,5)		
Andel der opnår remission MADRS ≤ 11	Dag 25	
ESKETINSUI2001	ESK-NS 84 mg + SoC	45,7%
	PBO + SoC	38,7%
ASPIRE I og II	ESK-NS 84 mg + SoC	50 %
	PBO + SoC	37 %
Resultat af metanalyse: RR: 1,3 (1,1-1,7), 12,1 %-point (3,8-30,9)		
MADRS-score, gennemsnitlig ændring fra baseline	Dag 25	
ESKETINSUI2001	ESK-NS 84 mg + SoC	-25,4
	PBO + SoC	-21,0
ASPIRE I	ESK-NS 84 mg + SoC	-28,1
	PBO + SoC	-23,2
ASPIRE II	ESK-NS 84 mg + SoC	-25,6
	PBO + SoC	-23.2
Resultat af metanalyse: -3,9 (-5,8; -1,9)		

Figur 1-3 herunder viser MADRS-scoren i den samlede population fra ASPIRE I og ASPIRE II med hhv. esketamin og placebo henover 4 ugers behandling og efterfølgende follow-up fase. Data vises for ændringer i den kontinuerlige score og for andel af patienter der opnår remission og respons.

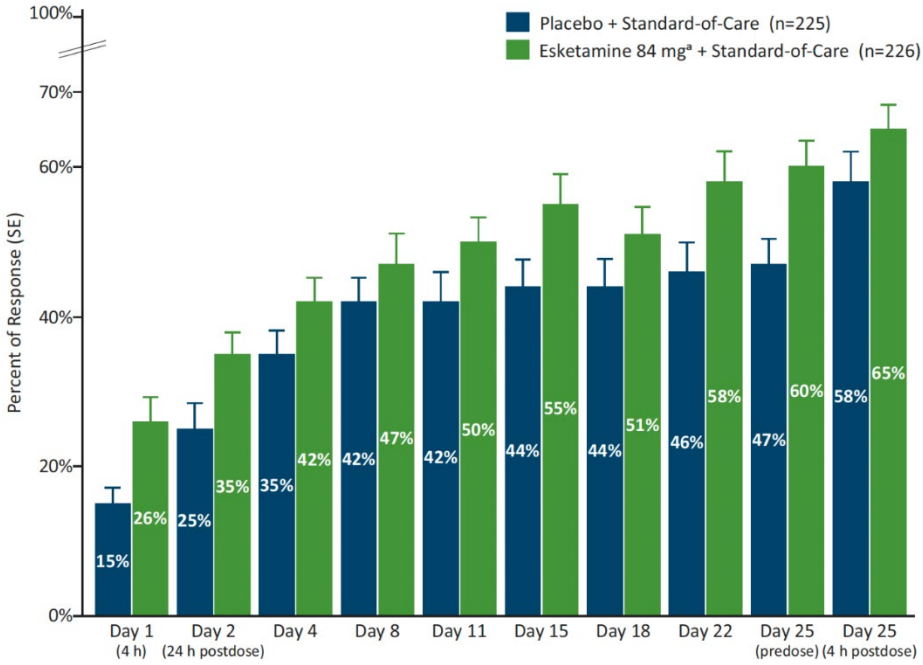
Figur 1. Udvikling i MADRS-score i den samlede population fra ASPIRE I og ASPIRE II med hhv. esketamin og placebo henover 4 ugers behandling og efterfølgende follow-up fase [16]



Figur 2: Andel patienter der opnår remission ved MADRS-score i den samlede population fra ASPIRE I og ASPIRE II med hhv. esketamin og placebo henover 4 ugers behandling og efterfølgende follow-up fase [16]



Figur 3: Andel patienter der opnår respons ved MADRS-score i den samlede population fra ASPIRE I og ASPIRE II med hhv. esketamin og placebo henover 4 ugers behandling og efterfølgende follow-up fase [16]



MADRS-scoren opgøres 10 gange hen over den 4 ugers dobbeltblindede fase med første måling 4 timer efter første dosis og sidste måling 4 timer efter sidste dosis.

I begge arme ses et fald i MADRS-score fra første måling og frem til den sidste måling på dag 25, hvilket betyder, at de depressive symptomer reduceres både med placebo + SoC og med esketamin + SoC. Det største fald sker i de første uger, se figur 1. Faldet i esketaminarmen er størst, og ved 24 timer ses en forskel i den gennemsnitlige ændring på MADRS-score på -4,2 (-6,0; -2,4) point (24 timer ASPIRE I og II samlet: esketamin: −16,1 [11,7]; placebo: −12,6 [10,6]). Forskellen på den kontinuerlige MADRS-score er klinisk relevant jf. de fastsatte kriterier i protokollen (MCID: 3 point).

Frem mod dag 25 sker der i begge arme en yderligere reduktion i depressive symptomer på MADRS-scoren. Forskellen mellem esketamin og placebo opretholdes hen over perioden og frem til dag 25, hvor der fortsat ses en forskel på omkring -3,9 point (-5,8; -1,9) på MADRS-scoren (dag 25 ASPIRE I og II samlet: Esketamin: −23,2; placebo: −25,6; -28,1). I ASPIRE I og II var der samlet set et frafald på 37/229 og 40/227 patienter for hhv. esketamin- og placebo-armene.

Efter 24 timer ses en effekt på både respons og remission for begge arme med en forskel på ca. 12 %-point for esketamin vs. placebo. Forskellen er klinisk relevant for remission men ikke for respons, jf. Medicinrådets metoder og kriterier for mindste klinisk relevante forskelle i protokollen.

Ved dag 25 ses fortsat den samme forskel i effekt for remission (ca. 12 %-point), mens effekten på respons ikke længere er statistisk signifikant og af mindre størrelsesorden.

Patienterne er fulgt i 90 dage, dvs. 75 dage efter sidste dosis esketamin. I poolede analyser af ASPIRE I og II er der på dette tidspunkt ikke længere forskel i MADRS-score imellem esketamin og placebo. MADRS-scoren ligger fortsat lavt, som den gjorde ved dag 25. Der var et frafald på hhv. 25 ud af 190 og 20 patienter ud af 185 for esketamin og placebo i opfølgningsfasen.

Fagudvalget vurderer, at esketamin har merværdi af ukendt størrelse for effektmålet reduktion i depressive symptomer, idet der er påvist klinisk merværdi for både den kontinuerlige score og for remission efter 24 timer, som opretholdes frem til dag 25.

5.1.5 Fagudvalgets vurdering af klinisk spørgsmål 1

Fagudvalget vurderer samlet set, at esketamin har merværdi af ukendt størrelse, som formentlig er lille sammenlignet med placebo.

Fagudvalget lægger vægt på, at der ses en hurtig indsættende klinisk relevant effekt af esketamin sammenlignet med placebo på reduktion i depressive symptomer, og at effektforskellen opretholdes uden at øges relativt til placebo i op til 4 uger. Esketamin kan bringe en større andel af patienter i remission, målt ved MADRS-scoren. Størrelsesordenen af denne effekt svarer til *numbers needed to treat* (NNT) på ca. 8. Efter 90 dage er værdien på MADRS-scoren for patienter, som blev behandlet med esketamin, fortsat på samme lave niveau, selvom patienterne stopper esketamin efter dag 25.

I sammenligning med den vurdering af esketamin, som Medicinrådet lavede for indikationen behandlingsresistent depression, er patienter i studierne til denne indikation mere svært syge og svarer bedre overens med de patienter, man ville behandle i dansk klinisk praksis, selvom de fortsat er selekteret med relativt stramme in- og eksklusionskriterier. Patientgruppen har aktuelt brug for nye behandlingsalternativer, og muligheden for at afprøve esketamin vil være værdifuldt for nogle patienter. Effekten som ses i de kliniske studier vurderes at være klinisk relevant for patienterne i forhold til en reduktion af de depressive symptomer. Effekten af esketamin vs. placebo på remission og den kontinuerlige MADRS-score er af tilsvarende størrelsesorden, som ses efter 4 uger i studierne, som undersøger patienter med behandlingsresistent depression i TRANSFORM 1-2 studierne. Dette styrker tiltroen til den observerede effekt.

Selvom der er betydende bivirkninger ved esketamin, vurderer fagudvalget, at patienterne vil være villige til at acceptere en risiko for bivirkninger, fordi der ikke er mange alternative behandlingsmuligheder, og fordi patienternes livskvalitet i forvejen er meget nedsat på dette tidspunkt. Samtidig er der også betydende bivirkninger ved alternative behandlinger som fx ECT. Se næste afsnit. Fagudvalget beskriver, at nogle patienter er meget forpinte og har brug for hurtigindsættende effekt, hvilket er vist for esketamin.

Fagudvalget er mindre bekymret for anvendelse esketamin i den akutte setting, fordi patienterne skal have behandling i kort tid, og fordi behandlingen foregår under

indlæggelse på en psykiatrisk enhed i størstedelen af tiden. Behandlingen kan dermed foregå under meget kontrollerede forhold, hvilket kan mindske risikoen for misbrug.

Fagudvalget bemærker, at der kan være nogle patienter, som man i klinisk praksis vil ønske at fortsætte i esketaminbehandling udover de 4 ugers behandling, svarende til indikationen for vedligeholdelsesbehandling med esketamin. Dog vurderer fagudvalget, at udgangspunktet for behandlingen bør være de 4 uger, også fordi langt de fleste patienter vil ønske at stoppe esketamin efter 4 uger og forsøge at forblive i bedring med traditionelle antidepressive behandlinger, som ikke kræver mange hospitalsbesøg.

Fagudvalget ønsker at opstille kriterier for anvendelsen af esketamin, se 5.4 herunder.

5.2 Klinisk spørgsmål 2

Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med ECT i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko?

Ansøger har ikke kunne identificeret studier, som vurderes at være egnede til at sammenligne effekten af esketamin med ECT. Ansøger har dog fundet et studie, KetECT, som er et randomiseret studie, som sammenligner ketamin med ECT i et noninferiority-design. I dette studie var ketamin inferiørt til ECT. Ansøger mener dog ikke, studiet er anvendeligt til at sammenligne med esketamin.

Ansøger påpeger generelt flere problematikker ved den ønskede sammenligning mellem esketamin og ECT. Randomisering til ECT er ofte ikke en mulighed i kliniske studier grundet etiske aspekter, studier inkluderer ikke patienter med akut øget selvmordsrisiko, og studier på ECT inkluderer patienter med psykose, hvor ECT har en rigtig god effekt, mens disse patienter ikke indgår i esketaminstudierne.

Fagudvalgets vurdering af klinisk spørgsmål 2
Værdien af esketamin overfor ECT kan ikke kategoriseres grundet manglende datagrundlag.

Fagudvalget er enige i, at der formentlig ikke findes studier, som vil være brugbare til en sammenligning, og at det medsendte KetECT-studie ikke kan anvendes i og med, at det er ketamin og ikke esketamin, som undersøges.

Fagudvalget har følgende betragtninger vedr. sammenligningen mellem esketamin og ECT.

ECT anvendes i dag som førstelinje behandling af psykotisk depression og til patienter, som tidligere har responderet godt på denne behandling. ECT bruges også til svær behandlingsrefraktær depression, hvor anden behandling har svigtet, samt ved patienter som er i akut øget selvmordsrisiko. Bemærkelsesværdigt i denne sammenhæng er, at ECT har en hurtigt indsættende virkning mod selvmordsovervejelser [17].

Der er risiko for kognitive bivirkninger ved ECT, herunder særligt erindringslakuner, som kan være generende for patienterne. Fagudvalget vurderer, at bivirkningsprofilen for

esketamin ikke er værre end for ECT, men at de ikke kan sammenlignes grundet de meget forskellige bivirkningstyper.

ECT har været anvendt over en lang årrække, og der er meget erfaring med at håndtere behandlingen samtidig med, at det er veletableret, at behandlingen har god effekt. Derfor vurderer fagudvalget, at ECT bør være førstevalg over esketamin til patientgruppen. Det vil dog stadig være gavnligt at have mulighed for at anvende esketamin i klinisk praksis som et alternativ til patienter, som ikke har gavn af, ikke tåler eller ikke ønsker ECT efter grundig information om effekt og bivirkninger. Disse patienter har lige nu meget begrænsede behandlingsmuligheder.

5.3 Fagudvalgets samlede konklusion

Fagudvalget vurderer, at esketamin (i tillæg til optimeret behandling) som korttidsbehandling til patienter med akut øget selvmordsrisiko har en merværdi af ukendt størrelse, som formentlig er lille, sammenlignet med placebo (i tillæg til optimeret behandling). Denne vurdering er baseret på esketamins effekt på reduktion i depressive symptomer i en relevant patientpopulation.

Der findes ikke komparative data, som kan bruges til en sammenligning mellem esketamin og ECT. Derfor kan værdien af esketamin ikke kategoriseres i sammenligningen med ECT.

Der er betydende bivirkninger ved esketamin, herunder særligt dissociation og blodtrykstigning. Fagudvalget er mindre bekymret over bivirkningsprofilen i denne patientgruppe, fordi patienterne skal have behandling i kort tid, og fordi behandlingen foregår under indlæggelse på en psykiatrisk enhed i størstedelen af tiden. Behandlingen kan dermed foregå under meget kontrollerede forhold, hvilket kan mindske risikoen for misbrug.

5.4 Kriterier for anvendelse

En implementering af esketaminbehandling kræver, at man forbereder patienterne på behandlingsforløbet og de bivirkninger, som kan optræde undervejs. Herudover kræves et trygt miljø omkring patienten under behandlingen og personale på afdelingen, som er trænet til at håndtere eventuelle bivirkninger.

Opstart:

- Patienten opfylder indikationen og er indlagt med en akut øget selvmorsrisiko jf. klinisk vurdering.
- Patientens sygdom har ikke tidligere haft tilstrækkelig gavn af ECT, der har været betydende svære bivirkninger ved ECT, eller patienten ønsker ikke at modtage ECT efter grundig gennemgang af fordele og ulemper ved behandlingen.
- Patienten må ikke udvise produktive psykotiske træk.
- Særlig forsigtighed bør udvises ved bipolar sygdom, OCD, borderline og autisme, da patienter med disse tilstande ikke indgik i studierne.

Opfølgning:
Behandlingen pågår som udgangspunkt i 4 uger. Efter 4 uger forventes patientens anden behandling at være optimeret, og behandling med esketamin kan stoppes.

Der er ikke anvisninger i produktresuméet, som peger på en specifik opfølgning grundet anvendt esketamin. Opfølgningen består typisk af tæt monitorering for tilbagefald i 6 måneder i psykiatrisk regi, hvilket også er udgangspunktet for patienter i nuværende praksis, som ikke får esketamin.

Hvis patienten oplever et tilbagefald, som hurtigt bedres igen med genbehandling med esketamin, bør det overvejes, om esketamin som vedligeholdelsesbehandling skal være en del af denne patients samlede behandlingsstrategi.

Fagudvalget mener, at det er vigtigt, at der opsamles data i psykiatrisk regi for anvendelsen af esketamin, så man kan følge op på forbrug, effekt og bivirkninger over tid.

6. Andre overvejelser

Fagudvalget har efterspurgt:

- CGI-SS-R-scoren præsenteret grafisk over perioden fra baseline til endt opfølgning som spaghetti-plots.
- en redegørelse for, om der er specifikke hændelser, som optræder med en anden frekvens i de pivotale studier, der lægger til grund for den aktuelle population, sammenlignet med de studier, der undersøger effekten af intranasal esketamin hos patienter med behandlingsresistent depression.
- hvor stor en andel patienter fra den aktuelle population, der forventes genbehandlet.

Ansøger har ikke kunne leveret spaghettiplots eller et estimat af andel patienter, der forventes genbehandlet.

En sammenligning mellem hændelser i de to studiepopulationer indgår i ansøgningen og er vurderet sammen med øvrige hændelser i afsnittet om bivirkninger.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende behandlingsresistent depression

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Poul Videbech *Professor, overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Gustav Bizik *Overlæge*	Region Nordjylland
Maike Andreasen *Overlæge*	Region Midtjylland
Claus Havregaard Sørensen *Overlæge*	Region Syddanmark
Dénes Langyel *Overlæge*	Region Sjælland
Lars Vedel Kessing *Professor, overlæge*	Region Hovedstaden
Niels August Willer Strand *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Jonas Meile *Speciallæge i almen medicin*	Dansk Selskab For Almen Medicin
Klaus Martiny *Professor, Overlæge*	Inviteret af formanden
Marin Balslev Jørgensen *Professor, Overlæge*	Inviteret af formanden
Leni Grundtvig Nielsen *Patientrepræsentant*	Danske Patienter
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**

Sammensætning af fagudvalg	
Louise Wulff *Patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.1	20. januar 2023	Usikkerheder vedr. brug af benzodiazepiner i de kliniske studier er slettet.
1.0	14. december 2022	Godkendt af Medicinrådet.

11. Bilag

11.1 Bilag 1: Baselinekarakteristik

ASPIRE-I

Characteristics	Placebo + SoC n= 112	Esketamine 84 mg + SoC n= 112	Total n= 224
Age, years, mean (SD)	37.9 (12.54)	40.8 (13.7)	39.3 (12.91)
Women, n (%)	73 (65.2)	65 (58.0)	138 (61.6)
Race, n (%)			
Asian	28 (25.0)	28 (25.0)	56 (25.0)
Black or African American	7 (6.3)	4 (3.6)	11 (4.9)
Native Hawaiian or other Pacific Islander	0	1 (0.9)	1 (0.4)
White	74 (66.1)	77 (68.8)	151 (67.4)
Other	2 (1.8)	1 (0.9)	3 (1.3)
Multiple	1 (0.9)	1 (0.9)	2 (0.9)
Weight (kg), mean (SD)	74.5 (20.66)	76.3 (22.82)	75.4 (21.74)
BMI (kg/m^2), mean (SD)	26.4 (7.13)	26.7 (6.28)	26.5 (6.70)
SoC AD treatment as randomized, n (%)			
Monotherapy	65 (58.0)	59 (52.7)	124 (55.4)
Augmentation	47 (42.0)	53 (47.3)	100 (44.6)
Baseline MADRS total score, mean (SD)	41.0 (6.29)	41.3 (5.87)	41.1 (6.07)
Baseline duration (months) of current depressive episode, median	13.3	15.9	13.7
CGI-SS-r 'moderately suicidal', n (%)	28 (25.0)	29 (26.1)	57 (25.6)
CGI-SS-r 'severely suicidal', n (%)	27 (24.1)	29 (26.1)	56 (25.1)
SIBAT: previous suicide attempt, n (%)	68 (60.7)	66 (59.5)	134 (60.1)
Suicide attempt within the last month: 'yes', n (%)	31 (27.7)	32 (28.6)	63 (28.1)

ASPIRE-II

Characteristics	Placebo + SoC n= 113	Esketamine 84 mg + SoC n= 114	Total n= 227
Age, years, mean (SD)	41.4 (13.43)	40.2 (12.73)	40.8 (13.07)
Women, n (%)	67 (59.3)	69 (60.5)	136 (59.9)
Race, n (%)			
American Indian or Alaska Native	1 (0.9)	0	1 (0.4)
Asian	2 (1.8)	1 (0.9)	3 (1.3)
Black or African American	8 (7.1)	7 (6.1)	15 (6.6)

Characteristics	Placebo + SoC n= 113	Esketamine 84 mg + SoC n= 114	Total n= 227
Native Hawaiian or other Pacific Islander	1 (0.9)	0	1 (0.4)
White	87 (77.0)	92 (80.7)	179 (78.9)
Other	6 (5.3)	6 (5.3)	12 (5.3)
Multiple	0	2 (1.8)	2 (0.9)
Not reported	8 (7.1)	6 (5.3)	14 (6.2)
Weight (kg), mean (SD)	80.6 (22.05)	78.6 (19.62)	79.6 (20.83)
BMI (kg/m2), mean (SD)	28.3 (7.56)	27.6 (6.40)	27.9 (6.99)
SoC AD treatment as randomized, n (%)			
Monotherapy	43 (38.1)	45 (39.5)	88 (38.8)
Augmentation	70 (61.9)	69 (60.5)	139 (61.2)
Baseline MADRS total score, mean (SD)	39.9 (5.76)	39.5 (5.19)	39.7 (5.48)
Baseline duration (months) of current depressive episode, median	21.2	16.5	17.1
CGI-SS-r 'moderately suicidal', n (%)	33 (29.2)	35 (30.7)	68 (30.0)
CGI-SS-r 'severely suicidal', n (%)	28 (24.8)	17 (14.9)	45 (19.8)
SIBAT: previous suicide attempt, n (%)	72 (63.7)	78 (68.4)	150 (66.1)
Suicide attempt within the last month: 'yes', n (%)	24 (21.2)	36 (31.6)	60 (26.4)

ESKETINSUI2001

Characteristics	Placebo + SoC n=31	Esketamine 84 mg + SoC n=35	Total n=66
Age, years, mean (SD)	36.0 (12.82)	35.7 (13.40)	35.8 (13.03)
Women, n (%)	21 (67.7)	22 (62.9)	43 (65.2)
Race, n (%)			
White	15 (48.4)	20 (57.1)	35 (53.0)
Black or African American	13 (41.9)	12 (34.3)	25 (37.9)
Asian	0	1 (2.9)	1 (1.5)
Multiple	1 (3.2)	0	1 (1.5)
Other	2 (6.5)	0	2 (3.0)
Not reported	0	2 (5.7)	2 (3.0)
Weight (kg), mean (SD)	76.1 (18.83)	83.5 (23.86)	80.0 (21.79)
BMI (kg/m^2), mean (SD)	26.8 (6.62)	30.1 (9.49)	28.5 (8.37)
SoC AD treatment as randomized, n (%)			
Monotherapy	25 (80.6)	25 (71.4)	50 (75.8)
Augmentation	6 (19.4)	10 (28.6)	16 (24.2)
Baseline MADRS total score, mean (SD)	38.8 (7.02)	38.5 (6.17)	38.6 (6.53)

Characteristics	Placebo + SoC n=31	Esketamine 84 mg + SoC n=35	Total n=66
SIBAT: previous suicide attempt, n (%)	21 (67.7)	20 (57.1)	41 (62.1)
Suicide attempt within the last month: 'yes', n (%)	13 (61.9)	11 (55.0)	24 (58.5)

Application for the assessment of Spravato® (esketamine) for the short-term treatment of adults with moderate to severe depressive episode with an acute increased suicide risk

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1 Basic information

Table 1: Contact information

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Area of responsibility	Medical
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Table 2: Overview of the pharmaceutical

Proprietary name	SPRAVATO®
Generic name	Esketamine
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 DK-3460 Birkerød
ATC code	N06AX27 (1)
Pharmacotherapeutic group	Psychoanaleptic, Other antidepressants
Active substance(s)	Esketamine hydrochloride (1)
Pharmaceutical form(s)	28 mg Nasal Spray, solution (1)
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 signaling which may contribute to the restoration of synaptic function in these brain regions involved with the regulation of mood and emotional behavior. 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. (1)
Dosage regimen	The recommended dosage of Spravato for adult patients (<65 years) is 84 mg twice per week for 4 weeks. Dosage reduction to 56 mg should be made

	based on tolerability. After 4 weeks of treatment with Spravato, the oral antidepressant (AD) therapy should be continued, per clinical judgement. Treatment with Spravato should be part of the comprehensive clinical care plan. (1)
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	SPRAVATO, co-administered with oral antidepressant therapy, is indicated in adult patients with a moderate to severe episode of major depressive disorder (MDD), as acute short-term treatment for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency. (1)
Other approved therapeutic indications	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. (1)
Will dispensing be restricted to hospitals?	Yes, dispensing code A§4-BEGR
Combination therapy and/or co-medication	Spravato co-administered with oral antidepressant therapy (1)
Packaging – types, sizes/number of units, and concentrations	SPRAVATO® (esketamine) 28 mg Dose Kit* (1) 1x28 mg Nasal Spray Device, 1 Device, 28 mg esketamine SPRAVATO® (esketamine) 56 mg Dose Kit* (1) 2x28 mg Nasal Spray Devices, 2 Devices, 56 mg esketamine SPRAVATO® (esketamine) 84 mg Dose Kit* (1) 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 (1)
Orphan drug designation	No

2 Abbreviations

AD	Antidepressants
AE	Adverse Events
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ANCOVA	Analysis of Covariance
CADSS	Clinician-Administered Dissociative States Scale
CGI-SR-I	Clinical Global Impression-Imminent Suicide Risk
CI	Confidence Interval
DMC	Danish Medicines Council
DSM-V	Diagnostic and Statistical Manual of Mental Health, 5th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Text Revision, 4th Edition
ECT	Electroconvulsive Therapy
ED	Emergency Department
ESK NS	Esketamine Nasal Spray
FAS	Full Efficacy Analysis Set
HCP	Healthcare Professional
ICD-10	International Classification of Diseases and Related Health Problems-10
ITT	Intention-To-Treat
LOCF	Last Observation Carried Forward
LS	Least Square
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MDSI	Major Depression with Suicidal Ideation and Intent
MINI	Mini-International Neuropsychiatric Interview
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl-D-aspartate
OECD	Organisation for Economic Co-operation and Development
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
RD	Risk Difference
RR	Relative Risk
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
SLR	Systematic Literature Review
SIBAT	Suicide Ideation and Behaviour Assessment Tool
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SoC	Standard of Care
SSRI	Selective Serotonin Reuptake Inhibitor
TRD	Treatment Resistant Depression

3 Summary

Esketamine nasal spray – a novel fast-acting anti-depressant

Esketamine nasal spray (ESK NS) is the first and only approved fast-acting antidepressant (AD) treatment indicated as an acute-short-term treatment for the rapid reduction of depressive symptoms. With its fixed 4-week treatment duration, ESK NS treats the acute crisis, providing significant symptomatic relief in patients with major depressive disorder (MDD) experiencing a psychiatric emergency until a longer-term, comprehensive treatment plan can take effect. ESK NS is a non-selective, non-competitive antagonist of the glutamatergic N-methyl-d-aspartic acid (NMDA) receptor, making it the first AD with a novel mechanism of action approved in the last 30 years (2). This underlines the lack of pharmacologic innovation that modern psychiatry has faced for decades, where current treatment strategies used for MDD patients with active suicidal ideation and intent (MDSI) show limited evidence in a severely impacted patient population.

ASPIRE trial design & overall results

The ESK NS clinical program is the first and only global registrational program enrolling patients with MDSI, having demonstrated significant and clinically meaningful benefits in this vulnerable population in phase III trials (the ASPIRE trials). ASPIRE I and II are two robust, identically designed, placebo-controlled phase III trials evaluating the efficacy and safety of ESK NS in adult patients with MDD assessed to be at imminent risk of suicide (3, 4). Both treatment groups (ESK NS and placebo) were evaluated in conjunction with an enhanced and comprehensive standard of care (SoC) that included initial hospitalization, newly initiated or optimized oral AD treatment (as monotherapy or with augmentation therapy), and an intensive level of clinician interaction.

The ASPIRE trials were designed to investigate the effectiveness of ESK NS + SoC at improving the overall symptom of MDD as a primary objective in the MDSI population that historically has been excluded in clinical trials. The primary objective follows the primary diagnosis of MDD included in the clinical trials. MDD includes a range of symptoms, of which suicidal ideation/behavior is one. Thus, a key secondary endpoint of the ASPIRE trials was to investigate the effectiveness of ESK NS + SoC at reducing the severity of suicidality. The focus on depression symptom reduction as the primary endpoint follows the intrinsic relationship between depression and suicidality, where the severity of depression serves as the underlying disease that drives the risk of suicidality (5-10). This relationship is further iterated by the FDA in the wording of ESK's indication, which directly targeted the treatment of "*depressive symptoms in adults with major depression disorder with acute suicidal ideation or behaviour*" (11). Measuring the treatment difference for suicidality in clinical trials comes with its own set of challenges. This is due to the substantial beneficial effects of inpatient psychiatric hospitalization in the ASPIRE trials, diffusing the acute suicidal crisis in subjects in both treatment groups. Additionally, during the double-blind phase, the effect of comprehensive SoC was enhanced by twice-weekly study visits which might have obscured a potential benefit of the experimental intervention (12). Finally, suicidal ideation and its risk factors often varies considerably over short periods of time (e.g. 4-8 hours) complicating the overall assessment at fixed time points (13).

As reflected in the results, ESK NS was shown to reduce depressive symptoms within 24 hours and rapidly induce remission, thus providing significant relief from depressive symptoms during the critical early hours and days of the psychiatric emergency. ESK NS + SoC demonstrated a rapid and clinically meaningful reduction of depressive symptoms within 24 hours (3.8-point superior reduction in the least square [LS] mean Montgomery–Åsberg Depression Rating Scale [MADRS] total score vs. placebo + SoC). Furthermore, the reduction of depressive symptoms with ESK NS + SoC occurred as early as 4 hours after dosing, hereby

meeting the critical and currently unmet need for a rapid-acting pharmacological treatment to reduce depression symptoms within acute psychiatry. At the 24-hour endpoint, both treatment groups experienced improvements in the severity of their suicidality, though there was no statistically significant difference between the treatment groups.

In addition to its demonstrated efficacy, ESK NS has a predictable and manageable safety profile in line with previous observations in the clinical trial program for treatment resistant depression (TRD). Furthermore, any concerns within TRD for potential long-term safety effects of ESK NS are significantly limited through the fixed 4-week treatment duration within the indication in scope for this submission. Most treatment-emergent adverse events (TEAEs) in ASPIRE I and II were of mild to moderate severity, with a transient and self-limiting nature, and resolved on the same day of dosing.

Electroconvulsive therapy as a comparator

Electroconvulsive therapy (ECT) is an important treatment option in Denmark for patients with unipolar depression (14), with an established treatment benefit in subgroups of patients especially psychotic depression (15). However, with regards to the comparison of ECT to ESK NS, our systematic literature review (SLR) found only one available randomized, clinically controlled studies of ECT versus a comparator, but was not in the population of interest for this assessment. The difficulty in studying ECT in clinical trials has also been acknowledged in ECT treatment guidelines in Denmark, citing ethical and practical issues when compared to alternative treatment options (14). This made it unfeasible to make a valid and meaningful comparison between ECT and ESK NS. Furthermore, despite the potential relevance of making a comparison between ECT and EKS NS, new fast-acting treatment alternatives are needed irrespectively of such a comparison to offer rapid and depressive symptom specific interventions. In addition, not all patients are eligible for ECT or may be prejudiced against ECT and may prefer other, less invasive therapies (16, 17). This creates a significant treatment need that is not currently addressed by other existing emergency treatments such as antidepressants that require weeks or months to achieve appreciable symptom remission.

The main benefits demonstrated in the clinical trials were the improvement in depressive symptoms, as measured with MADRS. As discussed in the EPAR, it is not certain whether the observed lack of a significant treatment effect versus comparator on the suicidality measures is due to a lack of true effect from ESK NS or due to the large impact of the enhanced SoC in the ASPIRE trials (18). Despite this, the European Medicines Agency (EMA) considered that the benefits of using ESK NS outweighed the risks (18), and we believe that the rapid-acting reduction of depressive symptoms meets a critical unmet need and is of significant benefit to this patient population as an alternative treatment option. For a depressed patient, a single day without symptom improvement means yet another day of suffering (19).

Differences from the TRD submission

As a final point, it is important to emphasize some of the key differences in the ESK NS treatment from this submission compared to the previous ESK NS submission within TRD:

- The short and fixed 4-week treatment duration contributes to the overall safety profile, ensuring a limitation of exposure to any risks associated with ESK NS during the treatment phase. Despite ESK NS being given at a higher dose (84 mg), the overall safety profile was in line with what was observed in the previous clinical trial programs for TRD.
- The short and fixed 4-week treatment duration significantly limits the budget impact and combined with the rapid-acting effect of ESK NS, this provides a cost-saving treatment option in comparison to ECT, which in addition can help free up sparse HCP personnel time for other tasks.

- The rapid-acting effects of ESK NS in reducing depression symptoms in an acute psychiatric emergency present ESK NS as a solution for the current unmet need within this indication were not all patients are eligible for or willing to receive ECT and were oral ADs are limited by a 4-6 week delay in the onset of their full effect (20, 21).
- The difference in cumulative incidence of stable remission between the ESK NS + SoC and placebo + SoC arms not only remained but continued to increase in favor of ESK NS + SoC from the end of the double-blind phase to the end of the follow-up phase. This was observed despite the discontinuation of ESK NS in the ESK NS + SoC arm during the follow-up phase, which indicates a long-lasting treatment effect of ESK NS following discontinuation.

4 Introduction

Major depressive disorder is the most prevalent mental health condition and the psychiatric diagnosis most commonly associated with suicide (22, 23). Up to 60% of patients with MDD experience suicidal ideation, and up to 20% attempt suicide over their lifetime, with an estimated lifetime risk of 3.4% for completed suicide in this population (24, 25). According to the proposal for a 10-year psychiatry plan by *Sundhedsstyrelsen*, patients who have been hospitalized due to a mental illness, such as MDD, have an approximately 20 times higher suicide rate compared to the background population, with the Organisation for Economic Cooperation and Development (OECD) ranking Denmark as the country with the highest proportion of suicide hospitalizations (26). In addition, due to depressive disorders, it is estimated that a total of 14.6 (males = 8.2; females 6.4) life years are lost in Denmark every year compared to the background population (26). The burden of this disease on Danish patients is part of the reason why a psychiatric reform is placed so high on the political agenda, and it highlights the need for capacity and a healthcare framework reform to start addressing the current unmet needs in the healthcare system starting with the individual patient's needs (26).

Depression with suicidal ideation is a particularly severe form of depression, tightly associated with the severity of depressive symptoms (5-10) and with a worse response to treatment (5, 9, 27-31). Furthermore, depression symptom severity is a key driver of the short-term risk of hospital encounters (27). These elements emphasize that MDSI patients constitute an extremely ill subpopulation that requires prompt intervention to ameliorate depression symptom severity and avert self-harm.

There is currently no fast-acting pharmacological treatment option available in routine clinical practice that induces rapid relief of depressive symptoms in the MDSI population. This is evident from the current guideline from *Rådet for Anvendelse af Dyr Sygehusmedicin* (RADS) for patients with unipolar MDD. Here, AD therapy and psychotherapy, often combined with hospitalization, are recommended as a first-line treatment for moderate to severe MDD, but without specific guidance for the management of a psychiatric emergency including suicidality (14).

While optimal care for MDSI patients includes initiation or optimization of oral ADs as well as hospitalization for many, standard ADs are limited by a 4–6-week delay in the onset of their full effect (20, 21). Hospitalization is generally helpful to establish a safe environment for evaluation and the initiation of treatment, but the benefits of hospitalization are short-lived and the risk for attempted and completed suicide remains high in the weeks immediately after discharge (32, 33).

A supplementary guideline on the use of ECT by the *Dansk Psykiatrisk Selskab* (34) proposes ECT as a potential first-line treatment for MDD patients who require immediate treatment to alleviate the suicide risk. Although ECT's impact on suicidality has been established in the literature, randomized studies of ECT versus comparators are lacking in the MDSI population, resulting in uncertainty about the comparative effectiveness of ECT within this group. This challenge has also been recognized by the ECT guideline (14).

Clinical trials of ADs have historically excluded MDD patients with suicidality which undermines the generalizability of the results and creates uncertainty about medication efficacy and safety in this severely ill and vulnerable patient population (35). The ASPIRE trials represented the first registration program to evaluate the rapid AD efficacy and safety of ESK NS systematically in a cohort of 451 adults with MDSI, which represents the largest sample of acutely suicidal patients to be studied in an AD treatment trial to date. As a result of the beneficial risk-benefit ratio in the target group, ESK NS was granted marketing authorization by

the European Medicines Agency with the label to treat 'psychiatric emergency of MDD' (1). In Denmark, the submission has been narrowed down to MDSI to reflect the patient population specifically studied in the clinical trial program and to be in line with Danish clinical practice. This population constitutes a large subgroup of psychiatric emergencies (36).

ESK NS thus presents as the first and only approved fast-acting AD that rapidly reduces the depressive symptoms in the critical early hours and days of the acute crisis and bridges the current unmet need until the effect of additional comprehensive therapeutic measures (including the onset of full oral AD effect) sets in. This underlines ESK NS's potential to improve the lives of patients with MDSI and at the same time provide a faster relieve from the heavy strain on HCP resources during the acute crisis until treatment effect sets in.

5 Literature search

For clinical question 1, the Danish Medicines Council (DMC) found that the following studies were considered relevant for the evaluation of esketamine for the treatment of moderate to severe depression in adults with an acute increased risk of suicide and can be used to conduct direct comparisons (36):

- ASPIRE-I (NCT03039192)
- ASPIRE-II (NCT03097133)
- ESKITINSUI2001 (NCT02133001)

Therefore, an SLR was not conducted for clinical question 1.

For clinical question 2, an SLR was conducted on the 7th of September 2021 according to the search strings and criteria in MEDLINE (via PubMed) and CENTRAL (via Cochrane Library) as specified in the DMC protocol (36).

This was done to extract data answering the clinical question:

What is the value of esketamine in addition to antidepressants compared to ECT in addition to antidepressants for adult patients in the current moderate to severe depressive episode with acute increased risk of suicide?

The selection of relevant studies was based on the inclusion and exclusion criteria specified by the DMC in the protocol and criteria specified in Table 73 in the appendix. Consequently, the included studies had to compare ECT in addition to antidepressants with esketamine/ketamine for a period of at least 4 weeks and include the relevant population i.e., moderate to severe depression in adults with acute increased risk of suicide. In addition, the studies had to include a minimum of one of the relevant efficacy endpoints specified in the protocol.

The literature search identified 175 potentially relevant publications from the databases MEDLINE (130) and CENTRAL (45) according to the search strings specified in the protocol (36). After removing 26 duplicates, the literature search resulted in 149 unique citations. Amongst these, a total of 141 citations were excluded during a title and abstract screening because they did not meet the pre-specified inclusion criteria. Among the set of 8 remaining citations, a total of 8 were furthermore excluded at a full-text screening phase, leaving 0 citations included to address clinical question 2 for the relevant patient population.

However, an additional study was identified after the conclusion of the SLR search through a manual hand search and is described in Section 5.2.3 below as a narrative assessment.

See Section 6.2.1 for more details on the currently available literature for ECT within the scope of this submission.

The PRISMA flow diagram for the selection of these studies is presented in Figure 24 in the appendix. Furthermore, the conducted search strings are available in Figure 25 and Figure 26 in the appendix whereas a list of excluded articles including reasons for exclusion can be seen in Table 74.

The studies selected by the DMC to answer clinical question 1 are presented in Table 3 and section 5.2.

5.1 Relevant Studies

Table 3: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). Fu DJ, Ionescu DF, Li X, Lane R, Lim P, Sanacora G, et al. The Journal of Clinical Psychiatry. 2020. (3)	ASPIRE-I	NCT03039192	**Study Start Date:** June 9, 2017 **Study Completion Date:** December 18, 2018	1 & 2
Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). Ionescu DF, Fu DJ, Qiu X, Lane R, Lim P, Kasper S, et al. The International Journal of Neuropsychopharmacology. 2020. (4)	ASPIRE-II	NCT03097133	**Study Start Date:** June 15, 2017 **Study Completion Date:** April 11, 2019	1 & 2
Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. American Journal of Psychiatry. 2018. (2)	ESKETINSUI2001	NCT02133001	**Study Start Date:** May 23, 2014 **Study Completion Date:** February 1, 2016	1 & 2
Joakim Ekstrand, Christian Fattah, Marcus Persson, Tony Cheng, Pia Nordanskog, Jonas Åkeson, Anders Tingström, Mats B Lindström, Axel Nordenskjöld, Pouya Movahed Rad, Racemic Ketamine as an Alternative to Electroconvulsive Therapy for Unipolar Depression: A Randomized, Open-Label, Non-Inferiority Trial (KetECT), International Journal of Neuropsychopharmacology, Volume 25, Issue 5, May 2022, Pages 339–349 (37)	KetECT	NCT02659085	**Study Start Date:** Not specified **Study Completion Date:** Not specified	2

5.2 Main Characteristics of Included Studies

5.2.1 ASPIRE I & II

Study characteristics of ASPIRE-I and ASPIRE-II trials are presented summarized in this section and presented in detail in Appendix 8.2.1 and 8.2.2.

Study design

The ASPIRE-I and ASPIRE-II trials were randomized, double-blinded, placebo-controlled, multicenter, Phase III trials that investigated the efficacy and safety of ESK NS 84 mg in addition to comprehensive SoC (defined as AD monotherapy or augmentation, including hospitalization and the initiation/optimization of AD treatment) in adult subjects with MDD assessed to be at imminent risk of suicide (3, 4). The trials were

identical in design, and they consisted of three key phases (a schematic illustration of the study design is presented in Figure 1 at the end of this section):

- Screening period (within 48 hours prior to Day 1 intranasal dose)
- Double-blind treatment phase (Day 1 to Day 25)
- Follow-up phase (Day 26 to Day 90)

If possible, screening occurred within 24 hours prior to the Day 1 intranasal dose. It is important to note that patients received considerable psychiatric care before randomization e.g., subjects who had recently attempted suicide, were hospitalized for medical stabilization, and continued to be at imminent risk for suicide, or subjects who were admitted directly into the inpatient psychiatric unit due to imminent risk for suicide, were also screened to determine eligibility. Thus, patients could have been hospitalized for 48 hours before the 1st dose (screening period) and so a patient would have received intensive medical attention for up to 3 days at the time of the endpoint measurement. The acute suicidal crisis could hereby have been diffused during inpatient psychiatric hospitalization.

On Day 1 of the double-blind treatment phase, subjects were randomized in a 1:1 ratio to receive either ESK NS 84 mg + SoC (ASPIRE-I n=114, ASPIRE-II n=115) or intranasal placebo + SoC (ASPIRE-I n=112, ASPIRE-II n=115), administered twice a week for 4 weeks. Subjects self-administered their allocated study treatment under the supervision of an on-site staff member (3, 4).

Due to the vulnerability of the population, all subjects enrolled in the ASPIRE trials were treated in the context of comprehensive SoC, including initial hospitalization and newly initiated or optimized AD therapy (3, 4):

- Subjects were hospitalized for a minimum of 5 days, with shorter or longer hospitalization permitted if clinically warranted per local practice guidance
- All subjects in the trials participated only if they had adequate capacity to give consent and after fully understanding the potential risks, benefits, and adverse events (AE) of the study. Subjects also agreed to be hospitalized voluntarily and to take SoC AD therapy.
- SoC AD therapy, either as monotherapy or augmentation therapy, was initiated or optimized at the time of randomization on Day 1. Augmentation agents could consist of a second AD, an atypical antipsychotic, or a mood stabilizer
- Permitted concomitant medications (e.g., benzodiazepines) and psychotherapy per SoC
- Alternative therapies such as ECT were excluded in the ASPIRE trials based on the study set-up

Additionally, the comprehensive SoC was enhanced by twice-weekly study visits with extensive clinical contact (during initial hospitalization and after hospital discharge) during the double-blind phase (3, 4). This aspect of the program is important to consider when interpreting the results as it can be expected to have a considerable impact on both treatment arms.

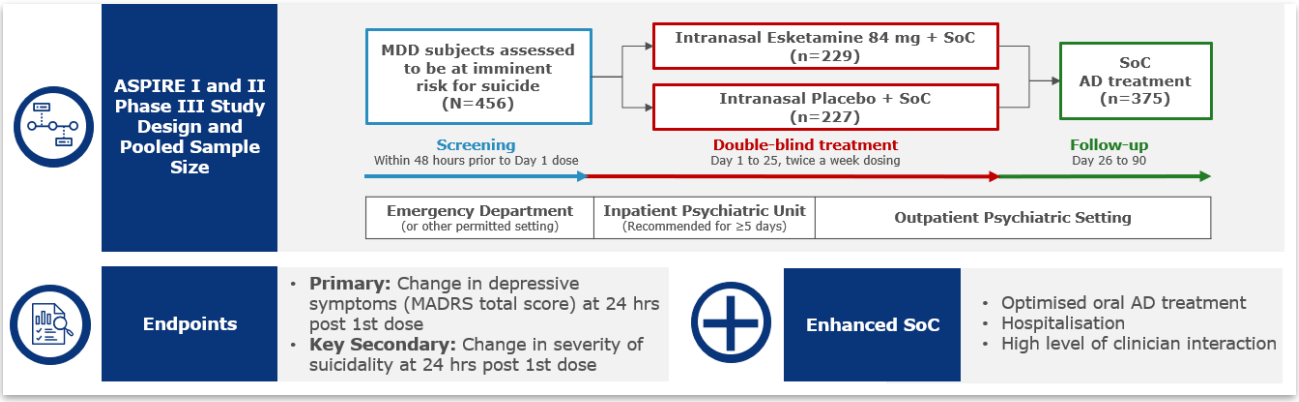
After Day 1, a one-time, blinded, dose reduction to ESK NS 56 mg or intranasal placebo was permitted if a patient was unable to tolerate the ESK NS 84 mg or placebo dose assigned at randomization. No further dose adjustment was permitted during the double-blind treatment phase (3, 4).

The severity of depressive symptoms was assessed using the structured interview guide for MADRS on Day 1 (pre-dose and 4 hours post-dose), Day 2 (24 hours post-dose), all subsequent visits (pre-dose), at 4 hours post-dose on Day 25 during the double-blind phase, and all visits during the follow-up phase (twice weekly through Day 39, weekly through Day 53, and every other week through Day 90) (3, 4).

The Suicide Ideation and Behaviour Assessment Tool (SIBAT) was used to assess efficacy related to suicidal ideation and behavior on all visit days during the double-blind and follow-up phases. The SIBAT contains both patient and clinician-reported outcomes, including the Clinical Global Impression-Severity of Suicidality Revised version (CGI-SS-r; rated from 0 [normal, not all suicidal] to 6 [among the most extremely suicidal patients])(3, 4).

Safety was evaluated by AE and the Clinician-Administered Dissociative States Scale (CADSS) (3, 4).

Figure 1: ASPIRE I & II trial design



Abbreviations: *AD = antidepressant; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; SoC = standard of care*

Patient population and key eligibility criteria

Key eligibility criteria used in the phase III studies were designed to accurately reflect patients with MDD at imminent risk of suicide. Patients enrolled in ASPIRE-I and ASPIRE-II had moderate to severe MDD, without psychotic features (as determined by the Diagnostic and Statistical Manual of Mental Health, 5th Edition [DSM-V] criteria), confirmed by a Mini-International Neuropsychiatric Interview (MINI). Patients were required to have a MADRS score of >28 and the clinician assessed current suicidal ideation and intent, which in the physician's opinion, warranted acute psychiatric hospitalization due to imminent risk for suicide (3, 4). For the full list of eligibility criteria, see Sections 8.2.1 and 8.2.2

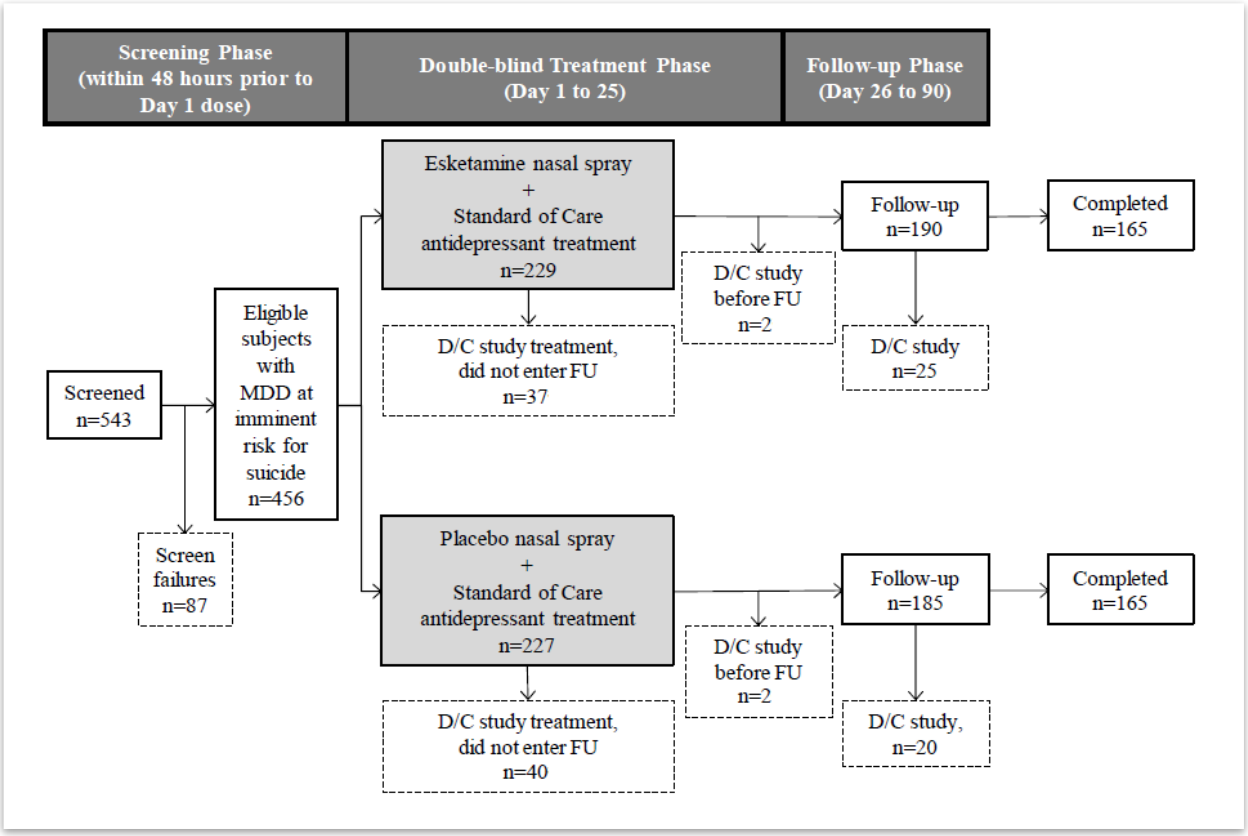
Safety was analyzed for all randomized patients who received ≥1 dose of double-blind study medication during the double-blind phase and were included in the safety analysis population. The full efficacy analysis set (FAS) population included all patients in the safety analysis population who had a baseline and ≥1 postbaseline assessment with the MADRS or CGI-SS-r during the double-blind phase. The follow-up population included all patients who completed the double-blind treatment phase and entered the follow-up phase or provided AE data (3, 4).

Patient flow through the ASPIRE-I and ASPIRE-II trials is summarized in Figure 2 below. A total of 456 patients were randomized and 379 completed the double-blind study treatment. Patient demographics and baseline psychiatric characteristics were generally similar across treatment groups and the two phase III trials (38).

- The mean age was 40.1 years (range 18 to 64)
- The majority of patients were female (61%)
- Prior to entering the study, 92% of patients were receiving AD therapy
- The mean MADRS score at baseline was 40.4 (range 29 to 58)
- The median duration of current depressive episode was 15.8 months (range 1 to 445)

- The majority of patients (90%) were assessed by a clinician to be moderately (3 out of 6) to extremely (6 out of 6) suicidal as measured by the CGI-SS-r scale
- The majority of patients had prior history of suicide attempt (63%) and more than one in four (27%) reported a suicide attempt within the last month

Figure 2: ASPIRE I & II patient flow diagram



Abbreviations: *D/C = discontinued; MDD = major depressive disorder; FU = follow-up*

5.2.2 ESKETINSUI2001

Study characteristics of the ESKETINSUI2001 trial are presented summarized in this section and presented in detail in Appendix 8.2.3.

Study design

The ESKETINSUI2001 trial (PeRSEVERe) was a randomized, double-blind, placebo-controlled, multicentre, Phase II, proof-of-concept trial which investigated the efficacy and safety of ESK NS 84 mg plus SoC (defined as newly initiated or augmented oral AD treatment), compared to placebo plus SoC, in patients with MDD at imminent risk for suicide. The trial consisted of three key phases (a schematic illustration of the study design is presented in Figure 3 below) (2):

- Screening evaluation (within 24 to 48 hours prior to Day 1)

- Double-blind treatment phase (Day 1 to Day 25)
- Follow-up phase (Day 26 to 81)

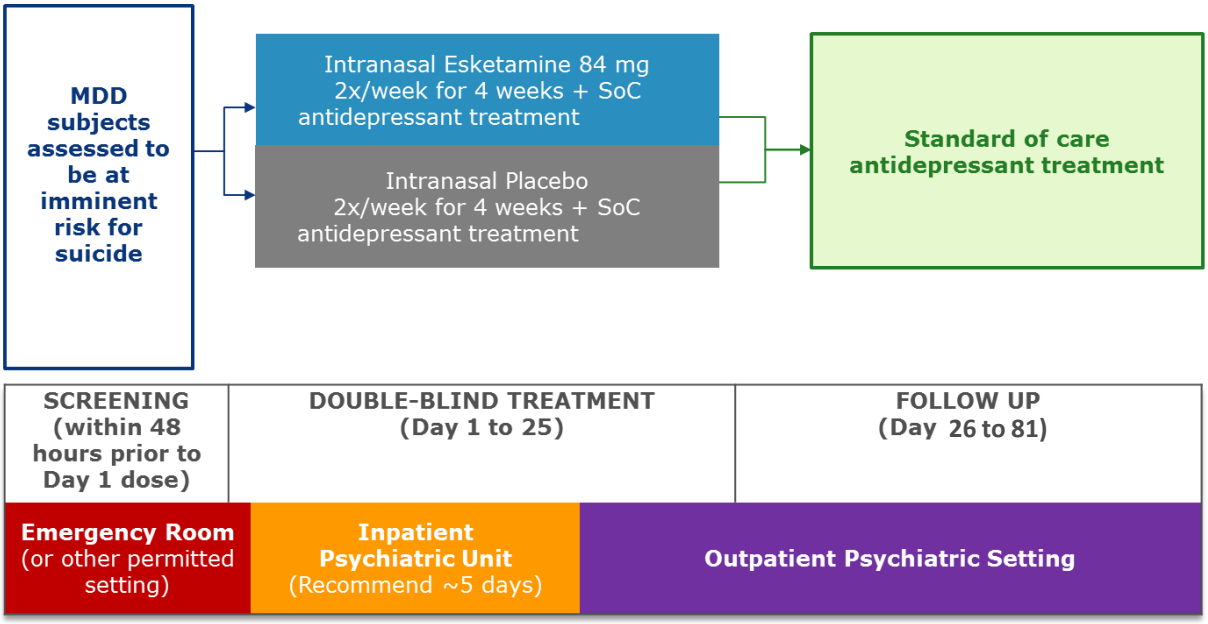
On Day 1 of the double-blind treatment period, 68 patients were randomized in a 1:1 ratio to receive either ESK NS 84 mg (n=36) or intranasal placebo 84 mg (n=32), administered two times per week for four weeks (Day 1, 4, 8, 11, 15, 18, 22, and 25). Randomization was stratified by the study center, physician's assessment of the patient's needs for SoC AD treatment (i.e., AD monotherapy or AD plus augmentation therapy) prior to randomization on Day 1 (2).

After Day 1, a one-time dose reduction to ESK NS 56 mg or intranasal placebo, made in a blinded manner was permitted if a subject was unable to tolerate the esketamine 84 mg or placebo dose (as per the investigator's judgment). Once reduced, patients received the decreased doses for the remainder of the trial duration (2).

The first dose of study medication was administered in the emergency room (or other permitted settings). All patients enrolled in the study were treated in the context of SoC, defined as AD monotherapy or augmentation, including hospitalization and the initiation/optimization of AD treatment. Dose titration/adjustments of newly initiated or optimized SoC ADs occurred during the first two weeks of the double-blind treatment phase, with doses remaining stable until the end of the double-blind phase (Day 25) (2).

Study participants in the ESKETINSUI2001 trial remained in an inpatient psychiatric unit for a recommended duration of five days, with shorter or longer hospitalizations permitted if clinically warranted. Once discharged, subjects were then treated in an outpatient psychiatric setting (2).

Figure 3. ESKETINSUI2001 phase 2 trial design



Standard antidepressant treatment was initiated or optimized on day 1

Abbreviations: *MDD = major depressive disorder; SoC = standard of care*

Patient population and key eligibility criteria

The study enrolled adults (19–64 years of age) who had a diagnosis of major depressive disorder without psychotic features according to Diagnostic and Statistical Manual of Mental Disorders Text Revision, 4th Edition (DSM-IV-TR) criteria and confirmed by the MINI. Candidates were screened shortly after presenting to an emergency department or an inpatient psychiatric unit. Eligibility criteria required that participants respond affirmatively to MINI questions B5 ("Think about suicide [killing yourself]?") in the present and B9 ("Intend to act on thoughts of killing yourself?") in the past 24 hours, that they be in clinical need of acute psychiatric hospitalization due to imminent risk for suicide, and that they have a score ≥22 on the MADRS on day 1 before dosing (2). For the full list of eligibility criteria, please see section 8.2.3.

Safety was analyzed for all randomized patients who received ≥1 dose of double-blind study medication during the double-blind phase and were included in the safety analysis population. The Intention-To-Treat (ITT) population included all patients in the safety analysis population who had a baseline and ≥1 post-baseline assessment with the MADRS during the double-blind phase. The follow-up population included all patients who completed the double-blind treatment phase and entered the follow-up phase or provided AE data (2).

Participants had to agree voluntarily to standard-of-care treatment, including hospitalization (for 5 days after randomization, unless a longer or shorter period was clinically warranted) and initiation or optimization of one or more non-investigational antidepressants (2).

Several psychiatric comorbidities were exclusionary, including a current diagnosis of bipolar disorder, moderate to severe substance use disorder, intellectual disability, antisocial personality disorder, borderline personality disorder, or a current or past diagnosis of a psychotic disorder (2).

In general, the treatment groups were comparable in terms of baseline characteristics and an extensive overview is available in section 8.2.3.

- The mean age at baseline for all patients was 35.8 years (range 19 to 64)
- The majority of patients in the trial were female (65.2%)
- The majority of patients received AD monotherapy (as randomized) alongside either ESK NS or placebo (75.8%).
- Baseline MADRS total score was similar between the placebo + SoC and ESK NS + SoC groups (38.8 versus 38.5, respectively)

5.2.3 KetECT

The KetECT trial was a randomized, parallel, open-label multicenter, non-inferiority trial comparing racemic ketamine to ECT and was conducted in Sweden in patients with unipolar depression. The aim of the trial was to test the hypothesis that ketamine is non-inferior to ECT in antidepressant efficacy (37).

The trial included hospitalized patients who were scheduled for ECT between the ages of 18-85 years with diagnosed unipolar depression according to DSM-IV with a MADRS score of ≥20. Patients were randomized to 1:1 to receive either 12 treatment sessions of intravenous ketamine at a fixed dose of 0.5mg/kg over 40 minutes or ECT until remission or maximal antidepressant effect. Patients were then followed up 1 week and 3, 6 and 12 months after completed treatment (37).

The primary outcome of the trial was remission after completed treatment, which was defined as a MADRS score ≤10 over at least 2 subsequent treatment sessions or a minimum of 5 days. Patients were classified as responders if MADRS scores decreased by 50% following a complete treatment series. Secondary outcomes included change in MADRS, total number of sessions and number of sessions to remission, relapse rate and adverse events (37).

The KetECT trial was able to demonstrate in the ITT and old population a better remission for ECT compared to ketamine (ITT: ECT = 61% vs ketamine = 45%; Old: ECT = 77% vs ketamine = 37%), however ketamine was numerically higher for remission in the young population compared to ECT (ECT = 50% vs ketamine = 61%), while a non-statistical difference was shown for psychotic depression (ECT=79% vs ketamine=50%). The KetECT trial confirmed the differences in adverse event profiles between the two different therapies, with ECT having a significant predominance of long-term adverse events, whereas there was a predominance of specific short-term side effects of ketamine (37).

However, there are several limitations in the KetECT study which ultimately makes it unsuitable for the purposes of comparative effectiveness for this submission. The most important factors to consider are that the KetECT study did not specifically screen for unipolar depressed patients in a psychiatric emergency with imminent risk of suicide before randomization (37). Thus, despite the fact that approximately 50% of patients had records of prior suicide attempt, there is no knowledge of their status in the current episode. The KetECT patient population is thus different to the patient population described in the ASPIRE I & II and ESKETINSUI2001 trials and is not within the scope of this submission. Further, patients were specifically screened for ECT treatment, and were then randomized into one of the two treatment arms, which may have introduced selection bias towards ECT given that 37% and 42% in the ECT and ketamine arm, respectively, have previously been treated with ECT, of which, 71% and 67% have had an effect with ECT, respectively (37). The trial was not rater-blinded which may also have introduced a risk of bias (37). As shown in Table 4 below, there was an uneven distribution of young patients in the ECT arm vs ketamine arm, and vice versa for the older population, which may introduce a skewing of data (37). Also, the study included patients with psychotic depression, although of smaller size, which was an exclusion criteria in the ASPIRE trials. Of practical importance, the drop-out rate within the first 2 weeks was higher in the ketamine arm vs the ECT arm, which potentially could be explained by the fact that the study was conducted at 6 ECT clinics in Sweden specialized in ECT, but without prior experience with i.v. ketamine. This is supported by the article supplementary material where the remission rates for i.v. ketamine was higher at sites who had treated more patients with ketamine. Finally, the comparison was conducted between ECT and i.v. ketamine, and not with intranasal esketamine, which limits its usefulness for this submission.

Table 4: Site data for KetECT trial (37)

No. of Patients[a]	Remission levels[b]	Age[c]	Female gender
Malmö 25 (11/14)	14/25 (56% 64% 50%)	47±17 (45±18, 49±17)	68%
Lund 114(58/56)	67/114 (59% 60% 57%)	51±19 (49±18, 54±18)	62%
Helsingborg 18(9/9)	8/18 (44% 67% 22%)	57±12(60±13, 54±11)	72%
Örebro 23(12/11)	10/23 (43% 67% 18%)	59±19 (54±19, 65±18)	61%
Halmstad 1(0/1)	1/1 (100% n/a 100%)	65 (65, N/A)	100%

No. of Patients[a]	Remission levels[b]	Age[c]	Female gender
Linköping 5(1/4)	1/5 (20%, 100% 0%)	57±13 (37, 62±9)	20%

(*a) Total number of participants per site that received at least one treatment. Numbers in parenthesis are the number of participants receiving treatment with ECT and ketamine respectively. (b) Number of patients achieving remission. Percentages in parenthesis indicate the proportion of remitters for the site as a whole, and in the ECT and ketamine group respectively. (c) Age per site and, in parenthesis, for the ECT and ketamine group respectively.*

To the authors knowledge, this is the first randomized controlled trial comparing ketamine with ECT with an adequate sample size (37). However, the KetECT trial had several internal validity limitations which may have biased the results towards ECT. In addition, when considering the inclusion of patients with unipolar depression who have not been screened to be at imminent risk of suicide, and thus a different population group, the results of this trial cannot be used for the comparative effectiveness of ESK NS to ECT.

6 Clinical Questions

6.1 What is the value of esketamine in addition to antidepressants compared to placebo in addition to antidepressants for adult patients in the current moderate to severe depressive episode with acute increased risk of suicide?

6.1.1 Presentation of Relevant Studies

The clinical evidence for ESK-NS is derived from two phase 3 trials (ASPIRE-I, ASPIRE-II) and one proof-of-concept phase 2 trial (ESKETINSUI2001).

ASPIRE-I and ASPIRE-II were randomized, double-blinded, placebo-controlled, multicenter, Phase III trials which investigated the efficacy and safety of ESK NS 84 mg in addition to comprehensive standard of care (SoC, defined as AD monotherapy or augmentation, including hospitalization and the initiation/optimization of AD treatment) in adult patients with MDD assessed to be at imminent risk of suicide. (3, 4)

ESKETINSUI2001 was a randomized, double-blind, placebo-controlled, multicentre, Phase II, proof-of-concept trial which investigated the efficacy and safety of ESK NS 84 mg plus SoC (defined as newly initiated or augmented oral AD treatment), compared to placebo plus SoC, in patients with MDD at imminent risk for suicide. (2)

It is worth mentioning at this point the limitations inherent in the study designs of the above trials which should be considered when interpreting the results for clinical question 1:

- The ASPIRE I & II trials were not designed to evaluate suicide prevention, rather, the primary objective was to assess the efficacy in rapidly reducing the depression symptoms of MDD in patients with active suicidal ideation and intent.
- ESKENTINSUI2001 was a phase 2 proof-of-concept study and thus is limited by the relatively small sample size. Further, the study only enrolled participants from the US in contrast to the ASPIRE phase 3 trials.

The studies were similar across most patient and study characteristics, but some of the key differences between them were:

- The ASPIRE I & II trials had an inclusion criterion for participants with a MADRS total score of greater than (>) 28 predose on Day 1, whereas the ESKETINSUI2001 required participants with a MADRS total score of greater than (>) 22 predose on Day 1.
- The ASPIRE I & II trials used the CGI-SS-r tool to assess the clinician's impression of a participant's severity of suicide as part of its secondary outcome assessing the change from baseline in CGI-SS-r Score at 24 Hours After the First Dose (Day 2). The CGI-SS-r tool was not used in the phase II ESKENTISUI2001 trial and consequently, did not assess the change from baseline in CGI-SS-r Score at 24 Hours After the First Dose (Day 2).
- The ESKETINSUI2001 trial did not include subpopulation analyses based on patients with a CGI-SS-r score of ≥ 4.
- The ESKETINSUI2001 trial had a slightly shorter follow-up phase compared to the ASPIRE I & II trials (81 days vs 90 days, respectively)

Overall, all three trials match the population relevant for answering clinical question 1 as stated in the DMC protocol (36).

6.1.2 Results per Study

6.1.2.1 ASPIRE-I

The ASPIRE-I trial demonstrated the value of ESK NS + SoC compared to placebo + SoC in the treatment of MDSI in several key clinical outcomes for the FAS population and the subpopulation of patients with a CGI-SS-r of ≥ 4.

Notably, the ASPIRE-I trial met its primary endpoint in the FAS population, as patients in the ESK NS + SoC group achieved a statistically significant (2-sided p-value: 0.006) rapid improvement in symptoms of depression compared to patients who received placebo + SoC, as measured by the change in MADRS total score from baseline to 24 hours after the first dose (Day 2) (Figure 7). At 24 hours, the mean changes from baseline (SD) were -16.4 (11.95) in the ESK NS + SoC group and -12.8 (10.73) in the placebo + SoC group with a statistically significant difference of LS Means of -3.8 (95% CI: -6.56; -1.09). The difference was maintained during the double-blind treatment phase, increasing to -4.9 (95% CI: -7.60; -2.12) on day 25.

AEs for this population were consistent with the known safety profile of ESK NS.

In this section, results of ASPIRE-I are presented in detail for each outcome of interest to the DMC for both the FAS population and the subpopulation of patients with a CGI-SS-r of ≥ 4.

Mean improvement in suicidal symptoms based on CGI-SS-r

In the analysis of the key secondary endpoint, numerical improvements in the severity of suicidality, defined as change from baseline in CGI-SS-r to 24 hours post-dose, were observed across both patients receiving ESK NS + SoC and placebo + SoC, but no statistically significant treatment difference was observed.

Results for the change in CGI-SS-r from baseline to 24 hours after the first dose are shown in Table 5. The median changes from baseline (range) at 24 hours were -1.0 (-6; 2) in the ESK NS + SoC group and -1.0 (-5; 1) in the placebo + SoC group, the estimated treatment difference was not statistically significant (2-sided p-value: 0.107). Furthermore, the LS mean changes from baseline at 24 hours were -1.5 in the ESK NS + SoC group and -1.3 in the placebo + SoC group with an LS mean difference of -0.3 (95% CI: -0.59; 0.08).

Results for the change in CGI-SS-r from baseline to the endpoint on day 25 after the first dose are shown in Table 6. The median changes from baseline (range) at day 25 were -3.0 (-6; 1) in the ESK NS + SoC group and -2.5 (-5; 1) in the placebo + SoC group. Furthermore, the LS mean changes from baseline at day 25 were -2.7 in the ESK NS + SoC group and -2.5 in the placebo + SoC group with an LS mean difference of -0.2 (95% CI: -0.54; 0.09).

Table 5. CGI-SS-r score change from baseline to 24 hours post first dose (ANCOVA LOCF) on ranks, double-blind treatment phase, full efficacy analysis set – ASPIRE I (39)

	Placebo + SoC n= 112	Esketamine 84 mg + SoC n= 112
Baseline (DB)		
N	112	111
Median (Range)	4.0 (1; 6)	4.0 (1; 6)
Day 2 (DB) LOCF[a]		
N	112	112
Median (Range)	2.5 (0; 5)	2.0 (0; 6)
Change from baseline		
N	112	111
Median (Range)	-1.0 (-5; 1)	-1.0 (-6; 2)
2-sided p-value (minus placebo)[b]	p=0.107	
N	112	111
LS Mean (SE)	-1.3 (0.13)	-1.5 (0.13)
Hodges-Lehmann Est. of Treatment Diff. (95% CI)	0.0 (-1.00; 0.00)	
Difference of LS Means (95% CI)	-0.3 (-0.59; 0.08)[b]	

[a]Day 2 (DB) is 24 hours post first dose.

[b]Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.

Note: CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition.

Negative change in score indicates improvement.

***Abbreviations**: ANCOVA: Analysis of covariance; DB: Double-blind; CGI-SS-r: Clinical Global Impression of Severity of Suicidality Revised; LOCF: Last Observation Carried Forward; SoC: Standard of Care*

Table 6: CGI-SS-r score change from baseline to day 25 (ANCOVA LOCF) on ranks, double-blind treatment phase, full efficacy analysis set – ASPIRE I (39)

	Placebo + SoC n= 112	Esketamine 84 mg + SoC n= 112
Baseline (DB)		
N	112	111
Median (Range)	4.0 (1; 6)	4.0 (1; 6)
Day 25 (DB) LOCF[a]		
N	112	112
Median (Range)	1.0 (0; 5)	1.0 (0; 5)
Change from baseline		
N	112	111
Median (Range)	-2.5 (-5; 1)	-3.0 (-6; 1)
N	112	111
LS Mean (SE)	-2.5 (0.12)	-2.7 (0.12)
Hodges-Lehmann Est. of Treatment Diff. (95% CI)	0.0 (-1.00; 0.00)	
Difference of LS Means (95% CI)	-0.2 (-0.54; 0.09)[b]	

[a]*Day 25 (DB) is predose*

[b]*Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.*

Note: CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition.

Negative change in score indicates improvement.

***Abbreviations**: ANCOVA: Analysis of covariance; DB: Double-blind; CGI-SS-r: Clinical Global Impression of Severity of Suicidality Revised; LOCF: Last Observation Carried Forward; SoC: Standard of Care*

Mean improvement in suicidal symptoms based on CGI-SS-r – subpopulation with a CGI-SS-r score of ≥ 4

[redacted]

[redacted]

Table 7: CGI-SS-r score change from baseline to 24 hours post first dose (ANCOVA LOCF) on ranks, double-blind treatment phase - subpopulation with a CGI-SS-r score of ≥ 4 – ASPIRE I (40)

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

[a]*Day 2 (DB) is 24 hours post first dose.*

[b]*Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.*

Note: CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition.

Negative change in score indicates improvement.

***Abbreviations**: ANCOVA: Analysis of Covariance; DB: Double-blind; CGI-SS-r: Clinical Global Impression of Severity of Suicidality Revised; LOCF: Last Observation Carried Forward; SoC: Standard of Care*

Table 8: CGI-SS-r score change from baseline to day 25 (ANCOVA LOCF) on ranks, double-blind treatment phase - subpopulation with a CGI-SS-r score of ≥ 4 – ASPIRE I (40)

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

[a]*Day 25 (DB) is predose*

[b]*Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.*

Note: CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition.

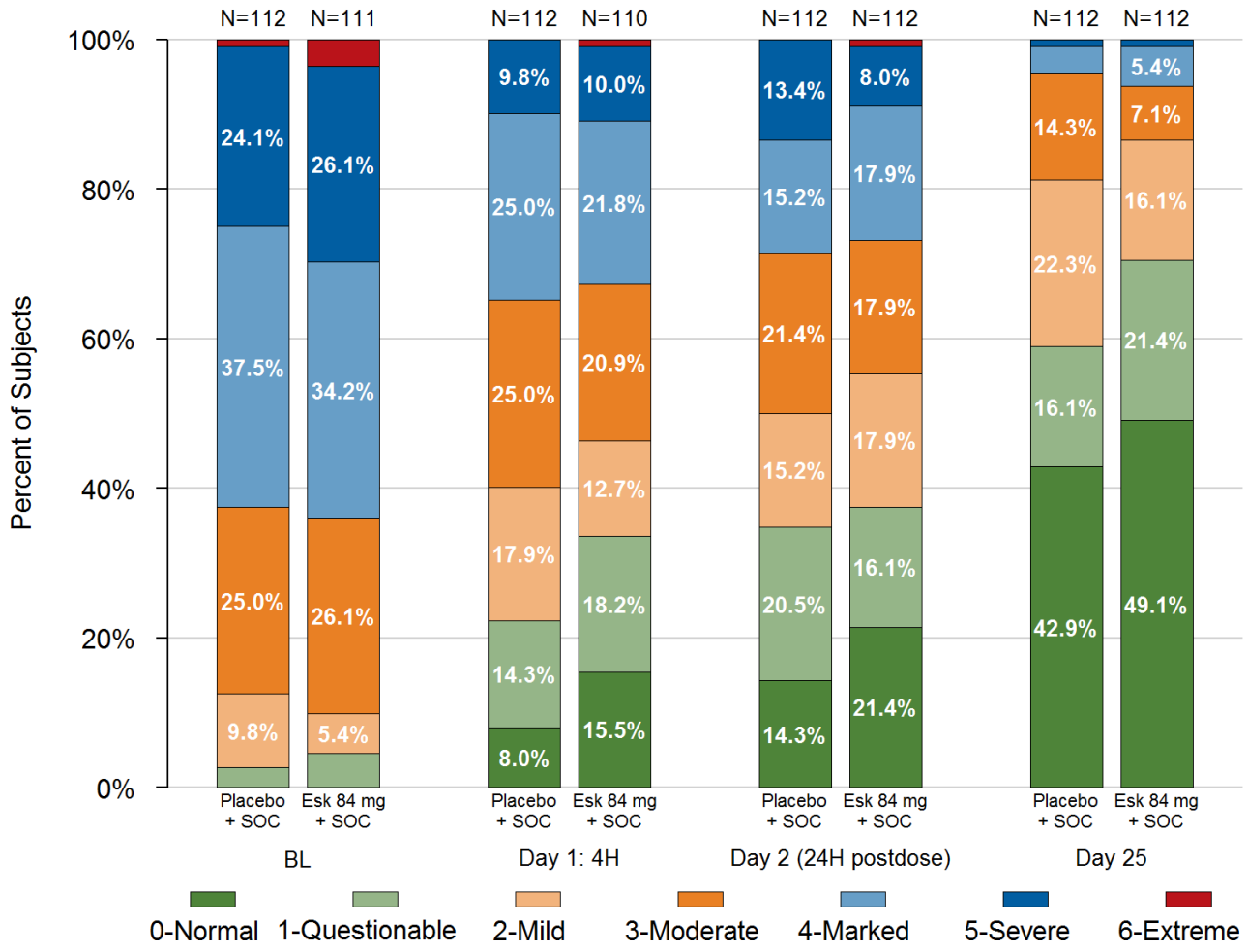
Negative change in score indicates improvement.

***Abbreviations**: ANCOVA: Analysis of covariance; DB: Double-blind; CGI-SS-r: Clinical Global Impression of Severity of Suicidality Revised; LOCF: Last Observation Carried Forward; SoC: Standard of Care*

Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r

The proportion of patients achieving resolution of suicidality (based on a CGI-SS-r score of 0 [normal, not at all suicidal], 1 [questionably suicidal], or 2 [mildly suicidal]) in ASPIRE-I was numerically higher among patients receiving ESK NS + SoC vs. placebo + SoC at all but one point during the double-blind treatment phase. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on risk ratios (RR) and risk difference (RD). See Figure 4 and Table 9 for resolution of suicidality results in ASPIRE-I.

Figure 4. Frequency Distribution of CGI-SS-r Score at Baseline, 4 Hours Post-Dose, 24 Hours Post-Dose and Day 25 (LOCF), double-blind treatment phase, full efficacy analysis set - ASPIRE I (39)



***Abbreviations:** CGI-SS-r = Clinical Global Impression – Severity of Suicidality – Revised; LOCF = Last Observation Carried Forward; SOC = Standard of Care*

Table 9: Proportion of patients achieving resolution of suicidality (score of ≤ 2) (LOCF), double-blind treatment phase, full efficacy analysis set – ASPIRE I (39)

n, %	ASPIRE I			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	109	107		
Day 2, 24 hours post first dose				
Patients with resolution of suicidality	53 (48.6%)	56 (52.3%)	1.12 (0.88; 1.44); 0.3511	5.8% (-6.3%; 17.9%); 0.3471
Day 25, predose				
Patients with resolution of suicidality	88 (80.7%)	91 (85.0%)	1.05 (0.93; 1.19); 0.4298	4.1% (-6.3%; 14.5%); 0.4389

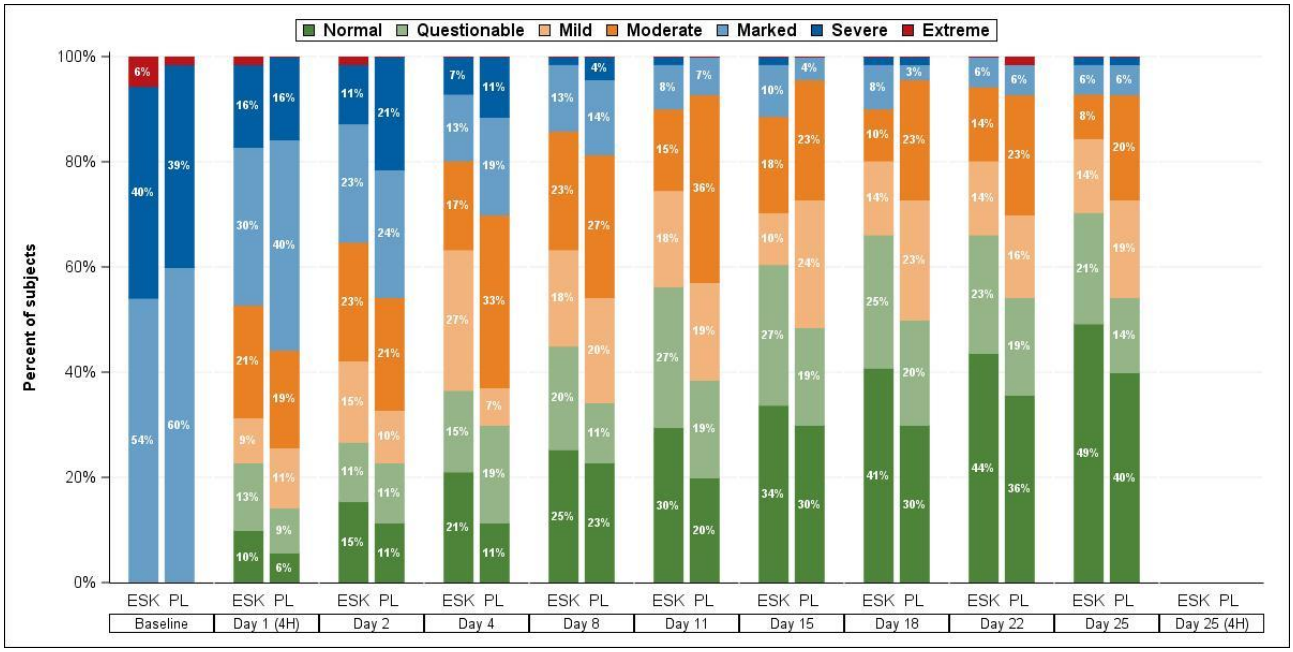
Note: resolution of suicidality is based on a CGI-SS-r score of 0 [normal, not at all suicidal], 1 [questionably suicidal] or 2 [mildly suicidal] Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to have resolution of suicidality.

Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD

Abbreviations: *ESK NS = Esketamine Nasal Spray; LOCF = Last Observation Carried Forward; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

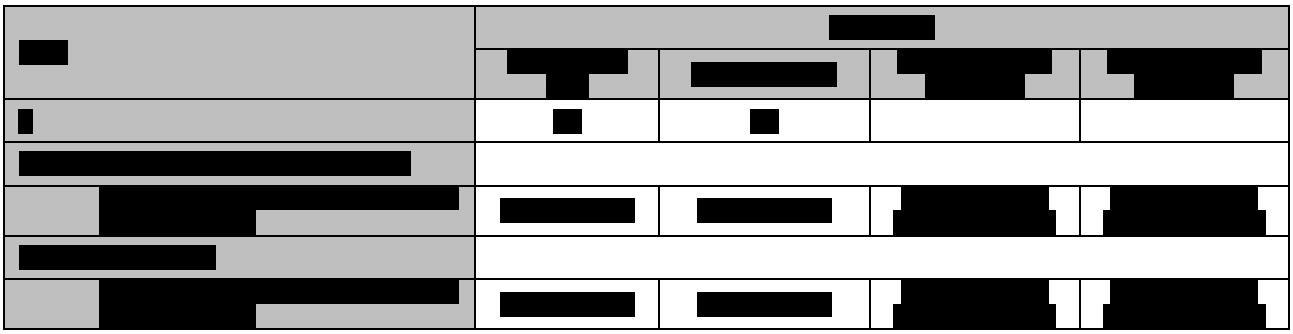
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r – subpopulation with a CGI-SS-r score of ≥ 4

[redacted]



Abbreviations: *CGI-SS-r = Clinical Global Impression – Severity of Suicidality – Revised; ESK = Esketamine; LOCF = Last observation carried forward; PL = Placebo*

Table 10: Proportion of patients achieving resolution of suicidality (score of ≤ 2)(LOCF), double-blind treatment phase - subpopulation with a CGI-SS-r score of ≥ 4 – ASPIRE I (40)



Note: resolution of suicidality is based on a CGI-SS-r score of 0 [normal, not at all suicidal], 1 [questionably suicidal], or 2 [mildly suicidal] Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to have resolution of suicidality.
Note: subgroup analyses were performed by Mantel-Haenszel estimate of the common RR/RD
Abbreviations: *ESK NS = Esketamine Nasal Spray; CGI-SS-r = Clinical Global Impression-Severity of Suicidality Revised; LOCF = Last observation carried forward; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r

The proportion of patients who experienced an exacerbation of suicidal symptoms is defined as an increase of ≥1 point in CGI-SS-r. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered. The proportion of patients who deteriorated from Day 2, 24 hours post first dose to day 25 in the ASPIRE-I was, for the full population, observed in both patient groups receiving the ESK NS + SoC vs placebo vs SoC throughout the double-blind treatment phase. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. See Table 11 for the deterioration of suicidality symptoms results in ASPIRE-I.

Table 11: Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r, double-blind treatment phase, full efficacy analysis set – ASPIRE I (39)

n, %	ASPIRE I			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	112	114		
Day 2, 24 hours post first dose				
Patients with exacerbation of ≥ 1 point on CGI-SS-r	4 (3.6%)	7 (6.1%)	1.47 (0.42; 5.15); 0.5430	1.8% (-4.1% ; 7.7%); 0.5485
Day 25, predose				
Patients with exacerbation of ≥ 1 point on CGI-SS-r	1 (0.9%)	3 (2.6%)	4.00 (0.35; 45.22); 0.2626	2.3% (-1.4% ; 6.1%); 0.2241

Note: A subject is defined as a having deterioration at a given time point if there is an exacerbation of 1 ≥ point of CGI-SS-r. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered as having a deterioration.
Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD
Abbreviations: *ESK NS = Esketamine Nasal Spray; CGI-SS-r = Clinical Global Impression-Severity of Suicidality Revised; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r - subpopulation with a CGI-SS-r score of ≥ 4

[redacted]

Table 12: Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r, double-blind treatment phase – subpopulation with a CGI-SS-r score of ≥ 4 - ASPIRE I (40)

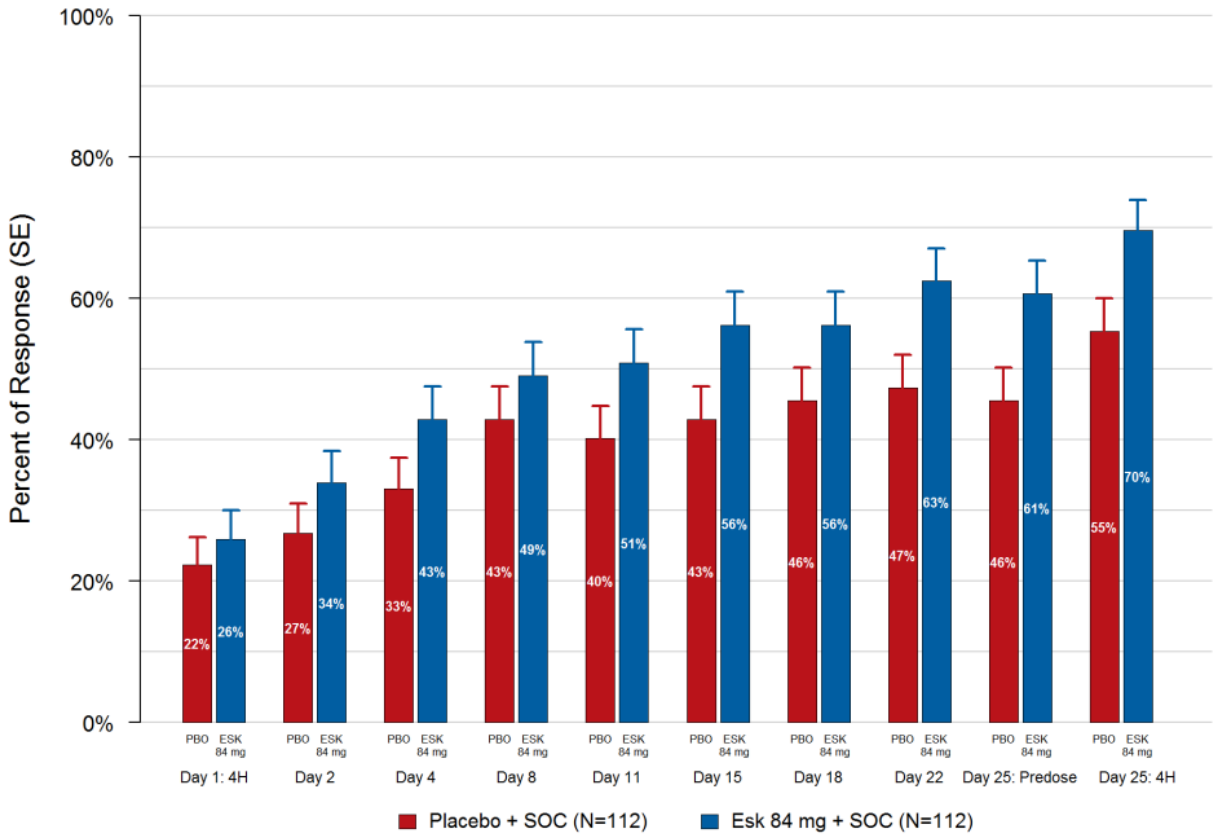
[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: A subject is defined as a having deterioration at a given time point if there is an exacerbation of 1 ≥ point of CGI-SS-r. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered as having a deterioration.
Note: subgroup analyses were performed by Mantel-Haenszel estimate of the RR/RD
Abbreviations: *ESK NS = Esketamine Nasal Spray; CGI-SS-r = Clinical Global Impression-Severity of Suicidality Revised; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Response

A patient was considered to achieve response at a given time point if the percent improvement in MADRS total score was at least 50%. Patients who did not meet the criterion or discontinued prior to the time point for any reason were not considered to achieve a response. The percentage of patients who achieved response directionally favored the ESK NS + SoC group over the placebo + SoC group at all timepoints during the double-blind treatment phase as seen in Figure 5. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. The treatment difference between treatment groups in the percentage of patients who achieved response over time during the double-blind treatment phase is shown in Table 13. On Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was 5.6% (-5.6%; 16.7%) with a risk ratio (95% CI) of 1.21 (0.82; 1.78). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was 11.6% (-1.7%; 24.8%) with a risk ratio (95% CI) of 1.21 (0.97; 1.51).

Figure 5. MADRS total score: Frequency distribution of patients who achieved response of MDD over time, double-blind treatment phase, full efficacy analysis set – ASPIRE I (39)



Abbreviations: *ESK: Esketamine; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; PBO: Placebo; SE: Standard Error; SoC: Standard of Care*

Table 13: Response rates (percent improvement in MADRS total score was at least 50%) over time, double-blind treatment phase, full efficacy analysis set - ASPIRE I (39)

n, %	ASPIRE I			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	112	114		
Day 2, 24 hours post first dose				
Patients with Response	30 (26.8%)	38 (33.3%)	1.21 (0.82; 1.78); 0.3335	5.6% (-5.6% ; 16.7%); 0.3270
Day 25 (4 hours post-dose)				
Patients with Response	62 (55.4%)	78 (68.4%)	1.21 (0.97; 1.51); 0.0981	11.6% (-1.7% ; 24.8%); 0.0880

Note: A subject is defined as a responder at a given time point if the percent improvement from baseline in MADRS total score is at least 50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder

Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD

Abbreviations: *ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Response – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 14: Response rates (percent improvement in MADRS total score was at least 50%) over time, double-blind treatment phase – subpopulation with a CGI-SS-r score ≥ 4 - ASPIRE I (40)

[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: A subject is defined as a responder at a given time point if the percent improvement from baseline in MADRS total score is at least 50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder

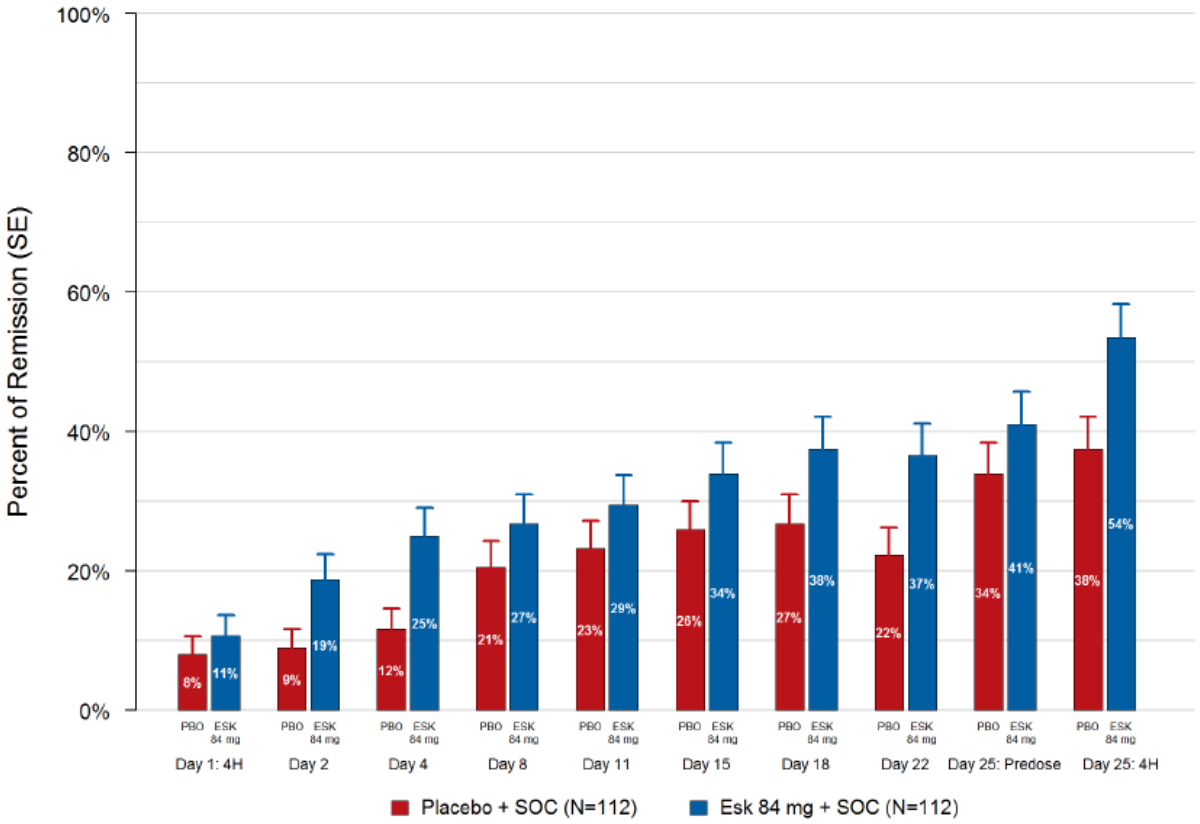
Note: subgroup analyses were performed by Mantel-Haenszel estimate of RR/RD

***Abbreviations**: ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Remission

According to pre-defined criteria, patients were considered to have achieved remission of MDD at a given time point if the MADRS total score was ≤12. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered to be in remission. The percentage of patients who achieved remission directionally favored the ESK NS + SoC versus the placebo + SoC group at all timepoints during the double-blind treatment phase (see Figure 6 and Table 15). The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. On Day 2, 24 hours after the first dose, a statistically significant treatment risk difference (95% CI) of 9.6% (1.6%; 17.5%) was observed with a statistically significant risk ratio (95% CI) of 2.31 (1.09; 4.93). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was 14.6% (2.1%; 27.2%) with a statistically significant risk ratio (95% CI) of 1.39 (1.03; 1.87).

Figure 6. MADRS total score: frequency distribution of patients who achieved remission of MDD over time, double-blind treatment Phase, full efficacy analysis set – ASPIRE I (39)



Abbreviations: *ESK: Esketamine; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: Major depressive disorder; PBO: Placebo; SE: Standard error; SoC: Standard of care*

Table 15: Remission rates (MADRS total score ≤12) over time, double-blind treatment phase, full efficacy analysis set - ASPIRE I (39)

n, %	ASPIRE I			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	112	114		
Day 2, 24 hours post first dose				
Patients with Remission of MDD	10 (8.9%)	21 (18.4%)	2.31 (1.09; 4.93); 0.0297	9.6% (1.6% ; 17.5%); 0.0183
Day 25 (4 hours post-dose)				
Patients with Remission of MDD	42 (37.5%)	60 (52.6%)	1.39 (1.03; 1.87); 0.0299	14.6% (2.1% ; 27.2%); 0.0224

Note: According to pre-defined criteria, patients were considered to have achieved remission of MDD at a given time point if the MADRS total score was ≤12. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered to be in remission.

Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD

Abbreviations: *ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; SoC = Standard of Care*

Remission – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 16: Remission rates (MADRS total score ≤12) over time, double-blind treatment phase – subpopulation with a CGI-SS-r score ≥ 4 - ASPIRE I (40)

[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: According to pre-defined criteria, patients were considered to have achieved remission of MDD at a given time point if the MADRS total score was ≤12. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered to be in remission.

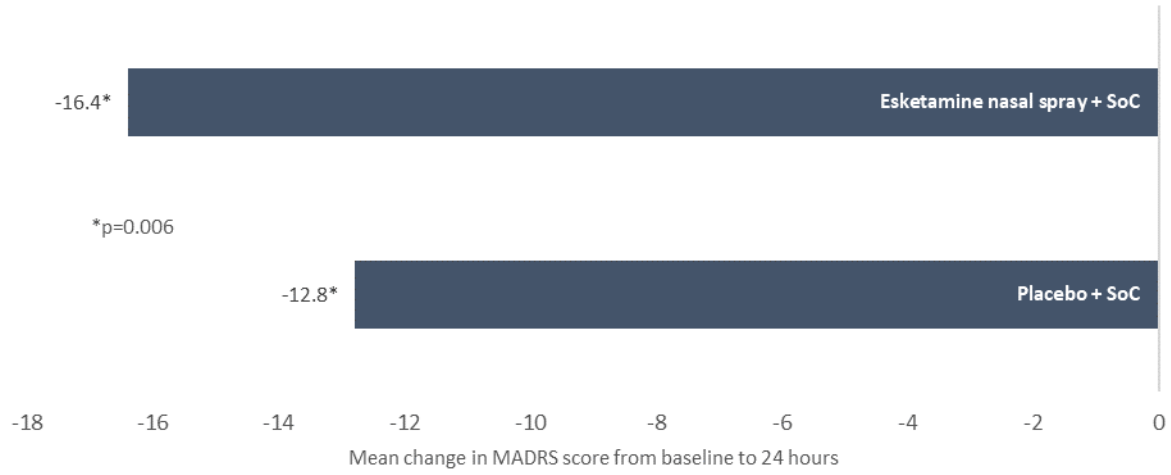
Note: subgroup analyses were performed by Mantel-Haenszel estimate of the RR/RD

Abbreviations: *ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Mean change in MADRS total score from baseline

The primary efficacy endpoint for ASPIRE-I was the change in MADRS total score from baseline (Day 1, pre-dose) to 24 hours after the first dose (Day 2) in the double-blind treatment phase. MADRS total scores range from 0 to 60, and a decrease in scores indicates an improvement. The primary efficacy analysis was performed on the full efficacy analysis set with LOCF data using an ANCOVA model. Patients in the ESK NS + SoC group achieved a statistically significant (2-sided p-value: 0.006) rapid improvement in symptoms of depression and suicidality compared to patients who received placebo + SoC, as measured by the change in MADRS total score from baseline to 24 hours after the first dose (Day 2) shown in Figure 7. At 24 hours, the LS mean changes from baseline (SD) were -15.9 in the ESK NS + SoC group and -12.0 in the placebo + SoC group (Table 17) with a statistically significant difference of LS Means of -3.8 (-6 .56; -1.09). The difference as measured by the difference in LS mean was maintained during the full double-blind treatment phase, increasing to -4.9 (-7 .60; -2.12) on day 25.

Figure 7: Mean changes in MADRS score from baseline (Day 1, pre-dose) to 24 hours after the first dose (Day 2); double-blind treatment phase; full efficacy analysis set – ASPIRE I (39)



**p=0.006*
Abbreviations: *MADRS: Montgomery-Asberg Depression Rating Scale; SoC: Standard of Care*

Table 17: MADRS total score change from baseline to 24 hours post first dose and day 25 at endpoint (ANCOVA LOCF), double-blind treatment phase, full efficacy analysis set – ASPIRE I (39)

	Placebo + SoC n= 112	Esketamine 84 mg + SoC n= 112
Baseline (DB)		
N	112	111
Mean (SD)	41.0 (6.29)	41.3 (5.87)
Day 2 (DB) LOCF[a]		
N	112	112
Mean (SD)	28.2 (11.97)	24.7 (12.12)
Change from baseline at Day 2		
N	112	111
LS Mean (SE)	-12.0 (1.02)	-15.9 (1.04)
Diff. of LS Means [95% CI]	-3.8 [-6.56; -1.09]	
Day 25 (DB) LOCF		
N	112	112
Mean (SD)	17.1 (11.69)	12.5 (10.33)
Change from baseline at Day 25[b]		
N	112	111
LS Mean (SE)	-23.2 (1.02)	-28.1 (1.05)
Diff. of LS Means [95% CI]	-4.9 [-7.60; -2.12]	

[a]Day 2 (DB) is 24 hours post first dose.

[b]Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.

Negative change in score indicates improvement.

***Abbreviations**: ANCOVA: Analysis of Covariance; DB: Double-blind; LOCF: Last Observation Carried Forward; MADRS: Montgomery-Asberg Depression Rating Scale; SD: Standard Deviation, SE: Standard Error; SoC: Standard of Care*

Mean change in MADRS total score from baseline – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 18. MADRS total score change from baseline to 24 hours post first dose and day 25 at endpoint (ANCOVA LOCF), double-blind treatment phase, full efficacy analysis set –subpopulation with a CGI-SS-r score ≥ 4 - ASPIRE I (40)

[redacted]

[a]*Day 2 (DB) is 24 hours post first dose.*
[b]*Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.*
Negative change in score indicates improvement.
***Abbreviations**: ANCOVA: Analysis of Covariance; DB: Double-blind; LOCF: Last Observation Carried Forward; MADRS: Montgomery-Asberg Depression Rating Scale; SD: Standard Deviation, SE: Standard Error; SoC: Standard of Care*

Adverse events

Summaries of AEs and other safety data for the double-blind treatment phase were based on all randomized patients who received at least 1 dose of the study drug in the double-blind treatment phase. This is referred to as the safety analysis set (3).

The safety analysis set included 225 patients:

- 112 patients in the placebo + SoC group
- 113 patients in the ESK NS + SoC group

Summaries of AEs and other safety data from the follow-up phase were based on the follow-up analysis set. The follow-up analysis set included all patients who completed the double-blind treatment phase and entered the follow-up phase or provided AE data (3).

The follow-up analysis set included 192 patients:

- 91 patients from the placebo + SoC group

- 101 patients from the ESK NS + SoC group

The AEs observed in this study are consistent with the safety profile of ESK NS established in previous studies in patients with MDD with active suicidal ideation and intent, and those with treatment-resistant depression.

Most of the AEs which occurred in the ASPIRE-I trial were mild to moderate in severity with a transient and self-limiting nature which resolved within the same day of dosing as per the comprehensive risk management plan designed for ESK NS (41).

Double-blind treatment phase

There were no TEAEs leading to death during the double-blind treatment phase. There were 100 (88.5%) in the ESK NS + SoC group and 83 (74.1%) in the placebo + SoC group that experienced one or more TEAEs in the double-blind treatment phase. Table 19 provides a summary of the TEAEs experienced during the double-blind treatment phase.

Table 19: Overall summary of TEAEs, double-blind treatment phase, safety analysis set – ASPIRE I (39)

	Placebo + SoC (n=112)	Esketamine 84 mg + SoC (n=113)
Patients with 1 or more:		
TEAEs	83 (74.1%)	100 (88.5%)
TEAEs leading to death[a]	0	0
Serious TEAEs	6 (5.4%)	4 (3.5%)
Severe TEAEs	6 (5.4%)	10 (8.8%)
TEAEs leading to discontinuation of study agent	5 (4.5%)	5 (4.4%)

aTEAEs leading to death are based on TEAE outcome of Fatal.
Note: Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
***Abbreviations**: SoC: Standard of care; TEAE: Treatment-emergent adverse event*

The TEAEs reported in at least 5% of patients in either treatment group during the double-blind treatment phase are summarized in Table 20. The most common TEAEs (reported by ≥10% patients) were observed more frequently in the ESK NS + SoC group versus placebo + SoC group were dizziness (35.4% vs 8.9%), dissociation (29.2% vs 3.6%), nausea (20.4% vs 13.4%), headache (18.6% vs 17.9%), somnolence (18.6% vs 9.8%), blood pressure increased (16.8% vs 5.4%), dysgeusia (14.2% vs 9.8%), and constipation (13.3% vs 4.5%). The most common TEAEs (reported by ≥5% patients) observed more frequently in the placebo + SoC treatment group were anxiety (8.0% vs 5.3%) and insomnia (6.3% vs 6.2%). Most of the TEAEs in both treatment groups occurred on the intranasal dosing days. 91.0% of the TEAEs in the ESK NS + SoC group occurred during the dosing days while 70.3% of the TEAEs in the placebo + SoC group occurred during the dosing days. However, the effects of the TEAEs seemed to be transient in nature and numerically favored ESK NS, with 94.9% of the TEAEs in the ESK NS + SoC group resolving on the same day versus 85.7% in the placebo + SoC group.

Table 20: Number of patients with TEAEs with frequency of at least 5% in any treatment group by system organ class and preferred term, double-blind treatment phase, safety analysis set – ASPIRE I (39)

	Placebo + SoC (n=112)	Esketamine 84 mg + SoC (n=113)
Patients with 1 or more TEAEs	83 (74.1%)	100 (88.5%)
System organ class Preferred term		
Nervous system disorders	47 (42.0%)	77 (68.1%)
Dizziness	10 (8.9%)	40 (35.4%)
Headache	20 (17.9%)	21 (18.6%)
Somnolence	11 (9.8%)	21 (18.6%)
Dysgeusia	11 (9.8%)	16 (14.2%)
Hypoaesthesia	2 (1.8%)	8 (7.1%)
Sedation	2 (1.8%)	7 (6.2%)
Dizziness postural	2 (1.8%)	6 (5.3%)
Psychiatric disorders	29 (25.9%)	51 (45.1%)
Dissociation	4 (3.6%)	33 (29.2%)
Insomnia	7 (6.3%)	7 (6.2%)
Anxiety	10 (8.9%)	6 (5.3%)
Gastrointestinal disorders	30 (26.8%)	43 (38.1%)
Nausea	15 (13.4%)	23 (20.4%)
Constipation	5 (4.5%)	15 (13.3%)
Vomiting	7 (6.3%)	8 (7.1%)
Investigations	11 (9.8%)	28 (24.8%)
Blood pressure increased	6 (5.4%)	19 (16.8%)
Eye disorders	5 (4.5%)	13 (11.5%)
Vision blurred	5 (4.5%)	10 (8.8%)
Ear and labyrinth disorders	3 (2.7%)	9 (8.0%)
Vertigo	1 (0.9%)	7 (6.2%)

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
***Abbreviations**: SoC: Standard of care; TEAE: Treatment-emergent adverse event*

The proportion of patients experiencing one or more serious adverse events (SAE) was comparable between the treatment groups, with 4 (3.5%) in the ESK NS + SoC group and 6 (5.4%) in the placebo + SoC group. Details of SAEs in both phases of the study are discussed in the next section. None of the SAEs were considered possibly, probably, or very likely related to ESK NS.

In the ESK NS + SoC group, 10 patients reported 1 or more severe TEAEs (dissociation [3 patients], anxiety, blood pressure increased, blood pressure systolic increased, depression, depression suicidal, dizziness, hallucination (visual), muscle rigidity, mutism, nausea, retrograde amnesia, and suicide attempt [1 patient each]). In the placebo + SoC treatment group, 6 patients reported 1 severe TEAEs (aggression, depression, depression suicidal, dysgeusia, erectile dysfunction, and suicidal ideation [1 patient each]). As with the non-serious TEAEs reported above, most of the severe TEAEs in both treatment groups occurred on the intranasal dosing days. 81.3% of severe TEAEs in the ESK NS + SoC group occurred during the dosing days while 50.0%

severe TEAEs in the placebo + SoC group occurred during the dosing days. However, the effects of the TEAEs seemed to be transient in nature as well and numerically favored ESK NS, with 84.6% of the severe TEAEs in the ESK NS + SoC group resolving on the same day versus 33.3% in the placebo + SoC group. Three patients in the ESK NS + SoC group who reported a severe TEAE of dissociation had resolved within 1.5 hours.

Ten patients experienced 1 or more TEAEs leading to discontinuation of study agent. In the ESK NS + SoC treatment group, 5 (4.4%) of 113 patients discontinued study agent due to TEAEs (dizziness [1 patient], hallucination, visual (1 patient, blood pressure increased and dissociation (1 patient), headache and somnolence (1 patient), and confusional state, hypoaesthesia, pharyngeal hypoaesthia, and sedation (1 patient). In the placebo + SOC treatment group, 5 (4.5%) of 112 patients discontinued the study agent due to TEAEs (aggression, suicidal ideation, blood pressure diastolic increased, atrioventricular block first degree, and hypertransaminasaemia [1 patient each]).

Follow-up phase

There was one AE leading to death during the follow-up phase in the ESK NS + SoC group, a narrative summary of the event will be presented below. There were 49 (48.5%) in the ESK NS + SoC group and 39 (42.9%) in the placebo + SoC group that experienced one or more AEs during the follow-up phase. Table 21 provides a summary of the AEs experienced during the follow-up phase.

Table 21: Overall summary of AEs, follow-up phase, follow-up analysis set – ASPIRE I (39)

	Placebo + SoC (n=91)	Esketamine 84 mg + SoC (n=101)
Patients with 1 or more:		
AEs	39 (42.9%)	49 (48.5%)
AEs leading to death[a]	0	1 (1.0%)
Serious AEs	10 (11.0%)	13 (13.9%)
Severe AEs	6 (6.6%)	6 (5.9%)

aTEAEs leading to death are based on TEAE outcome of Fatal.
Note: Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
***Abbreviations**: AE: Adverse event; SoC: Standard of care*

The AEs reported in at least 5% of patients in either treatment group during the follow-up phase are summarized in Table 22. The most common AE (reported by ≥5% patients) observed more frequently in the ESK NS + SoC group versus placebo + SoC group was depression (10.9% vs 3.3%). The most common AEs (reported by ≥5% patients) observed more frequently in the placebo + SoC group were anxiety (9.9% vs 3.0%), headache (7.7% vs 5.9%), and suicidal ideation (5.5% vs 5.0%).

Table 22: Number of patients with AEs with frequency of at least 5% in any treatment group by system organ class and preferred term, follow-up phase, follow-up analysis set – ASPIRE I (39)

	Placebo + SoC (n=91)	Esketamine 84 mg + SoC (n=101)
Patients with 1 or more AEs	39 (42.9%)	49 (48.5%)
System organ class Preferred term		
Psychiatric disorders	20 (22.0%)	28 (27.7%)
Depression	3 (3.3%)	11 (10.9%)
Suicidal ideation	5 (5.5%)	5 (5.0%)
Anxiety	9 (9.9%)	3 (3.0%)
Nervous system disorders	12 (13.2%)	14 (13.9%)
Headache	7 (7.7%)	6 (5.9%)

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
***Abbreviations**: AE: Adverse event; SoC: Standard of care*

The proportion of patients experiencing one or more SAE was comparable between the treatment groups, with 13 (13.9%) in the ESK NS + SoC group and 10 (11.0%) in the placebo + SoC group.

12 patients reported 1 or more severe TEAEs in both treatment groups with 6 (5.9%) in the ESK NS + SoC group and 6 (6.6%) in the placebo + SoC group.

Deaths, other serious adverse events, and other significant adverse events

Deaths

[redacted]

Serious adverse events

As mentioned in the above section, SAEs were comparable in both treatment groups during the double-blind phase with 4 (3.5%) in the ESK NS + SoC group and 6 (5.4%) in the placebo + SoC group. An overview of SAEs experienced in both groups is shown in Table 23.

In the ESK NS group, 2 (1.8%) patients were depression suicidal, 1 (0.9%) patient had depression, 1 (0.9%) patient had a suicide attempt and 1 (0.9%) patient had diabetic ketoacidosis. In the placebo + SoC, 2 (1.8%) patients had suicidal ideation, 1 (0.9%) patient had depression suicidal, 1 (0.9%) patient had depression, 1 (0.9%) patient had a suicide attempt, 1 (0.9%) experienced aggression and 1 (0.9%) patient had hypertransaminasaemia.

Table 23: Number of patients with treatment-emergent serious adverse events by system organ class and preferred term, double-blind treatment phase, safety analysis set – ASPIRE I (39)

	Placebo + SoC (n=112)	Esketamine 84 mg + SoC (n=113)
Patients with 1 or more serious TEAEs	6 (5.4%)	4 (3.5%)
System organ class Preferred term		
Psychiatric disorders	5 (4.5%)	3 (2.7%)
Depression **suicidal**	1 (0.9%)	2 (1.8%)
Depression	1 (0.9%)	1 (0.9%)
Suicide attempt	1 (0.9%)	1 (0.9%)
Aggression	1 (0.9%)	0
Suicidal ideation	2 (1.8%)	0
Metabolism and nutrition disorders	0	1 (0.9%)
Diabetic ketoacidosis	0	1 (0.9%)
Hepatobiliary disorders	1 (0.9%)	0
Hypertransaminasaemia	1 (0.9%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
***Abbreviations**: SoC: Standard of care; TEAE: Treatment-emergent adverse event*

During the follow-up phase of the study, 23 patients experienced SAEs: 13 (12.9%) in the ESK NS + SoC group and 10 (11.0%) patients in the placebo + SoC group. A detailed list of SAEs experienced in both groups is shown in Table 24.

In the ESK NS group, 5 (5.0%) patients were depression suicidal, 3 (3.0%) patients had suicide attempts, 2 (2.0%) patients had depression, 2 (2.0%) patients had suicidal ideation, 1 (1.0%) patient had major depression and 1 (1.0%) patient had a completed suicide. In the placebo + SoC, 3 (3.3%) patients were depression suicidal, 3 (3.3%) patients were suicidal ideation, 2 (2.2%) patients had a suicide attempt, 1 (1.1%) patient had depression and 1 (1.1%) patient had rhabdomyolysis.

Table 24: Number of patients with serious adverse events by system organ class and preferred term, follow-up phase, follow-up analysis set – ASPIRE I (39)

	Placebo + SoC (n=91)	Esketamine 84 mg + SoC (n=101)
Patients with 1 or more serious AEs	10 (11.0%)	13 (12.9%)
System organ class Preferred term		
Psychiatric disorders	9 (9.9%)	13 (12.9%)
Depression **suicidal**	3 (3.3%)	5 (5.0%)
Suicide attempt	2 (2.2%)	3 (3.0%)
Depression	1 (1.1%)	2 (2.0%)
Suicidal ideation	3 (3.3%)	2 (2.0%)
Completed suicide	0	1 (1.0%)
Major depression	0	1 (1.0%)
Musculoskeletal and connective tissue disorders	1 (1.1%)	0
Rhabdomyolysis	1 (1.1%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
***Abbreviations**: AE: Adverse event; SoC: Standard of care*

Adverse events leading to discontinuation of study medication

The number of patients who experienced TEAEs leading to discontinuation of study agent by system organ class and preferred term is provided in Table 25. In the ESK NS + SoC group, TEAEs leading to discontinuation of study agent occurred on Day 1, except for 1 patient with TEAEs of headache and somnolence on Day 7. TEAEs leading to discontinuation of study agent in the placebo + SoC group occurred on Day 1, Day 4, Day 9, Day 10, and Day 24. Most of the TEAEs in the ESK NS + SoC treatment group were mild to moderate in severity and probably or very likely related to study agent. 2 patients in the ESK NS + SoC group experienced nonserious, severe TEAEs which were assessed by the investigator to be very likely related to study agent. In the placebo + SoC group, 3 patients experienced SAEs of moderate or severe intensity assessed by the investigator to be not related to study agent and 2 patients experienced mild nonserious TEAEs, 1 of which was assessed by the investigator to be possibly related to study agent.

Table 25: Number of patients with treatment-emergent adverse events leading to discontinuation of study agent by system organ class and preferred term, double-blind treatment phase, safety analysis set – ASPIRE I (39)

	Placebo + SoC (n=112)	Esketamine 84 mg + SoC (n=113)
Patients with 1 or more TEAEs	5 (4.5%)	5 (4.4%)
System organ class Preferred term		
Nervous system disorders	0	3 (2.7%)
Dizziness	0	1 (0.9%)
Headache	0	1 (0.9%)
Hypoaesthesia	0	1 (0.9%)
Sedation	0	1 (0.9%)
Somnolence	0	1 (0.9%)
Psychiatric disorders	2 (1.8%)	3 (2.7%)
Confusional state	0	1 (0.9%)
Dissociation	0	1 (0.9%)
Hallucination. Visual	0	1 (0.9%)
Aggression	1 (0.9%)	0
Suicidal ideation	1 (0.9%)	0
Investigations	1 (0.9%)	1 (0.9%)
Blood pressure increased	0	1 (0.9%)
Blood pressure diastolic increased	1 (0.9%)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.9%)
Pharyngeal hypoaesthesia	0	1 (0.9%)
Cardiac disorders	1 (0.9%)	0
Atrioventricular block first degree	1 (0.9%)	0
Hepatobiliary disorders	1 (0.9%)	0
Hypertransaminasaemia	1 (0.9%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
***Abbreviations**: SoC: Standard of care; TEAE: Treatment-emergent adverse event*

Adverse events of special interest - suicidality

Seven patients in each treatment group reported TEAEs potentially related to suicidality during the double-blind treatment phase. In the ESK NS + SoC group, patients reported preferred terms of depression suicidal (2 patients), intentional self-injury (2 patients), suicidal ideation (2 patients), suicide attempt, and intentional overdose (1 patient each). In the placebo + SoC group, patients reported preferred terms of suicidal ideation (3 patients), intentional self-injury (2 patients), depression suicidal, and suicide attempt (1 patient each). Most TEAEs potentially related to suicidality were considered by the investigator to be not related to study agent. Two patients (1 in each treatment group) experienced nonserious, moderate TEAEs of intentional self-injury considered by the investigator to be possibly related to study agent.

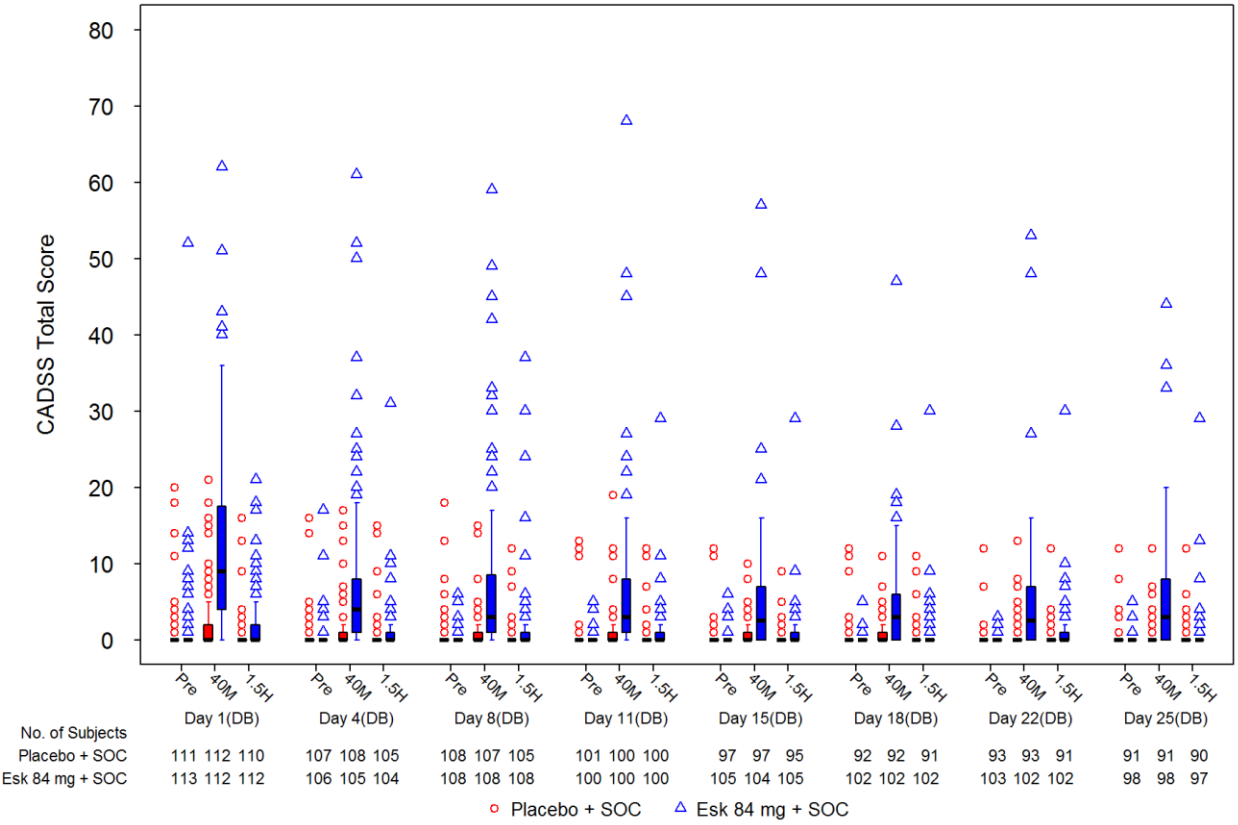
Twenty-two patients reported 1 or more AEs potentially related to suicidality in the follow-up phase. In the ESK NS + SoC group, 12 patients reported preferred terms of depression suicidal (5 patients), suicidal ideation (5 patients), suicide attempt (3 patients), and completed suicide (1 patients). In the placebo + SoC group, 10 patients reported preferred terms of depression suicidal (3 patients), suicidal ideation (5 patients), suicide attempt (2 patients), and intentional self-injury (2 patients). None of the AEs potentially related to suicidality in the follow-up phase were considered by the investigator to be possibly, probably, or very likely related to study agent. No patients in the ESK NS + SoC group. The occurrence of suicide attempts in the follow-up phase was dispersed over the follow-up phase without an apparent pattern suggestive of rebound.

Adverse events of special interest - dissociation

The CADSS is a clinician administered scaled used for the assessment of treatment-emergent dissociative and perceptual change symptoms. The subject's responses are recorded on a 5-point scale (0 = not at all and 4 = extremely, with a score of ≤4 considered within the normal range). Total scores range from 0 to 92, with a higher score representing a more severe condition. The CADSS were measured prior to intranasal dosing of study drug and at 40 minutes, 2 hours and 4 hours post dose, on each dosing day of the double-blind phase (42).

A consistently greater proportion of patients in the ESK NS + SoC group had an increase in CADSS total score over pre-dose on all dosing days (ranging from 65.7% to 84.1%) compared with the placebo + SoC group (15.4% to 30.6%). It is notable that mean CADSS total scores peaked at 40 minutes post-dose in patients receiving ESK NS + SoC and returned towards baseline at 90 minutes post-dose. The transient and self-limiting nature of this AE falls within the time frame specified in the risk management plan for ESK NS (41). Further, the CADSS total score was reduced with an increasing number of treatment sessions underlining that the dissociative symptoms diminished over time. Results for assessment of CADSS total score over time for ASPIRE I are summarized in Figure 8.

Figure 8: CADSS total score: box plot over time; double-blind treatment phase; safety analysis set – ASPIRE I (39)



***Abbreviations**: CADSS: Clinician-administered dissociative states scale; DB: Double-blind; SOC: Standard of care.*

Adverse events of special interest - euphoria

4 (3.5%) patients in the ESK NS + SoC group experienced euphoria during the double-blind treatment phase while there were none in the placebo + SoC group. None of the euphoria TEAES were reported as SAEs and occurred during the dosing days. All euphoria TEAEs were resolved on the same day.

6.1.2.2 ASPIRE-II

Similarly, to the ASPIRE-I trial, ASPIRE-II demonstrated the value of ESK NS + SoC compared to placebo + SoC in the treatment of MDSI in a number of key clinical outcomes for the ITT population and the subgroup of patients with a CGI-SS-r ≥ 4.

Most importantly, ASPIRE-II met its primary endpoint. Patients in the ESK NS + SoC group achieved a statistically significant (2-sided p-value: 0.006) rapid improvement in symptoms of depression and suicidality compared to patients who received placebo + SoC, as measured by change in MADRS total score from baseline to 24 hours after the first dose (Day 2) (Figure 12). At 24 hours, the mean (SD) changes from baseline were -15.7 (11.56) in the ESK NS + SoC group and -12.4 (10.43) in the placebo + SoC group (Table 28) with a statistically significant difference of LS Means of -3.9 (95% CI: -6.60; -1.11).

In ASPIRE-II, results in terms of improvement in suicidal symptoms based on CGI-SS-r score were in line with current standard of care, with a median change from baseline (range) at 24 hours of -1.0 (-6; 2) in the ESK NS + SoC group and of -1.0 (-5; 2) in the placebo + SoC group. This difference was not statistically significant (2-sided p-value: 0.379). However, the LS mean changes from baseline at 24 hours were -1.4 in the ESK NS + SoC group and -1.3 in the placebo + SoC group with a LS mean difference of -0.1 (95% CI: -0.48; 0.19).

The value of ESK NS + SoC as compared to placebo + SoC is further demonstrated by the results in the Response and Remission outcomes.

In terms of response to treatment, the percentage of patients who achieved response directionally favored the ESK NS + SoC group over the placebo + SoC group at all but one timepoint (day 25, 4 hours post dose) during the double-blind treatment phase (Figure 9). At Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was statistically significant at 13.7% (2.2%; 25.3%) with a statistically significant risk ratio (95% CI) of 1.62 (1.07; 2.46). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was -0.3% (-14.5%; 13.9%) with a risk ratio (95% CI) of 0.99 (0.79-1.26).

In terms of remission, the percentage of patients who achieved remission directionally favored the ESK NS + SoC group versus the placebo + SoC group at all but one timepoint (day 18) during the double-blind treatment phase (Figure 12). At Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was statistically significant at 13.9% (4.1%; 23.8%) with a statistically significant risk ratio (95% CI) of 2.53 (1.26; 5.09). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was 11.1% (-2.2%; 24.5%) with a risk ratio (95% CI) of 1.31 (0.95; 1.81).

AEs for this trial were consistent with the known safety profile of ESK NS.

In this section, results of ASPIRE-II are presented in detail for each outcome of interest to the DMC for both the FAS population and the subpopulation of patients with a CGI-SS-r ≥ 4.

Mean improvement in suicidal symptoms based on CGI-SS-r

As described in section 6.1.2.1, the analysis of the key secondary endpoint, numerical improvements in severity of suicidality, defined as change from baseline in CGI-SS-r to 24 hours post-dose, were observed across both patients receiving ESK NS + SoC and patients receiving placebo + SoC, but no statistically significant treatment difference was observed.

Results for the change in CGI-SS-r from baseline to 24 hours after the first dose are shown in Table 26. The median changes from baseline (range) at 24 hours were -1.0 (-6; 2) in the ESK NS + SoC group and -1.0 (-5; 2) in the placebo + SoC group, this difference was not statistically significant (2-sided p-value: 0.379). Furthermore, the LS mean changes from baseline at 24 hours were -1.4 in the ESK NS + SoC group and -1.3 in the placebo + SoC group with a LS mean difference of -0.1 (95% CI: -0.48; 0.19).

Results for the change in CGI-SS-r from baseline to endpoint at day 25 after the first dose are shown in Table 27. The median changes from baseline (range) to day 25 were -3.0 (-6; 2) in the ESK NS + SoC group and -3.0 (-6; 4) in the placebo + SoC group. Furthermore, the LS mean changes from baseline to day 25 were -2.7 in the ESK NS + SoC group and -2.5 in the placebo + SoC group with a LS mean difference of -0.1 (95% CI: -0.50; 0.20).

Table 26. CGI-SS-r score change from baseline to 24 hours post first dose (ANCOVA LOCF) on ranks, double-blind treatment phase, full efficacy analysis set – ASPIRE II (43)

	Placebo + SoC n= 113	**Esketamine 84 mg + SoC n= 114**
Baseline (DB)		
N	113	114
Median (Range)	4.0 (1; 6)	4.0 (1; 6)
Day 2 (DB) LOCF[a]		
N	113	113
Median (Range)	3.0 (0; 6)	2.0 (0; 5)
Change from baseline		
N	113	113
Median (Range)	-1.0 (-5; 2)	-1.0 (-6; 2)
2-sided p-value (minus Placebo)[b]	0.379	
N	113	113
LS Mean (SE)	-1.3 (0.13)	-1.4 (0.12)
Hodges-Lehmann Est. of Treatment Diff. (95% CI)	0.0 (0.00; 0.00)	
Difference of LS Means (95% CI)	-0.1 (-0.48; 0.19)[b]	

[a]Day 2 (DB) is 24 hours post first dose.

[b]Based on analysis of covariance (ANCOVA) model on ranks with treatment (placebo, esketamine 84 mg), analysis center and standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors, and baseline value (unranked) as a covariate.

Note: CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition.

Negative change in score indicates improvement.

***Abbreviations**: ANCOVA: Analysis of Covariance; CGI-SS-r: Clinical Global Impression of Severity of Suicidality Revised; DB: Double Blind; LOCF: Last Observation Carried Forward; SoC: Standard of Care*

Table 27: CGI-SS-r score change from baseline to day 25 post first dose (ANCOVA LOCF) on ranks, double-blind treatment phase, full efficacy analysis set – ASPIRE II (43)

	Placebo + SoC n= 113	Esketamine 84 mg + SoC n= 114
Baseline (DB)		
N	113	114
Median (Range)	4.0 (1; 6)	4.0 (1; 6)
Day 25 (DB) LOCF[a]		
N	113	113
Median (Range)	1.0 (0; 5)	0.0 (0; 6)
Change from baseline		
N	113	114
Median (Range)	-3.0 (-6; 4)	-3.0 (-6; 2)
LS Mean (SE)	-2.5 (0.12)	-2.7 (0.13)
Hodges-Lehmann Est. of Treatment Diff. (95% CI)	0.0 (0.00; 0.00)	
Difference of LS Means (95%)	-0.1 (-0.50; 0.20)[b]	

[a]*Day 25 (DB) is predose.*
[b]*Based on analysis of covariance (ANCOVA) model on ranks with treatment (placebo, esketamine 84 mg), analysis center and standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors, and baseline value (unranked) as a covariate.*
Note: CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition.
Negative change in score indicates improvement.
***Abbreviations**: ANCOVA: Analysis of Covariance; CGI-SS-r: Clinical Global Impression of Severity of Suicidality Revised; DB: Double Blind; LOCF: Last Observation Carried Forward; SoC: Standard of Care*

Mean improvement in suicidal symptoms based on CGI-SS-r – subpopulation with a CGI-SS-r score of ≥ 4

[redacted]

Table 28: CGI-SS-r score change from baseline to 24 hours post first dose (ANCOVA LOCF) on ranks, double-blind treatment phase - subpopulation with a CGI-SS-r score of ≥ 4 – ASPIRE II (40)

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

[a]*Day 2 (DB) is 24 hours post first dose.*
[b]*Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.*
Note: CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition.
Negative change in score indicates improvement.
***Abbreviations**: ANCOVA: Analysis of Covariance; DB: Double-Blind; CGI-SS-r: Clinical Global Impression of Severity of Suicidality Revised; LOCF: Last Observation Carried Forward; SoC: Standard of Care*

Table 29: CGI-SS-r score change from baseline to day 25 (ANCOVA LOCF) on ranks, double-blind treatment phase - subpopulation with a CGI-SS-r score of ≥ 4 – ASPIRE II

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

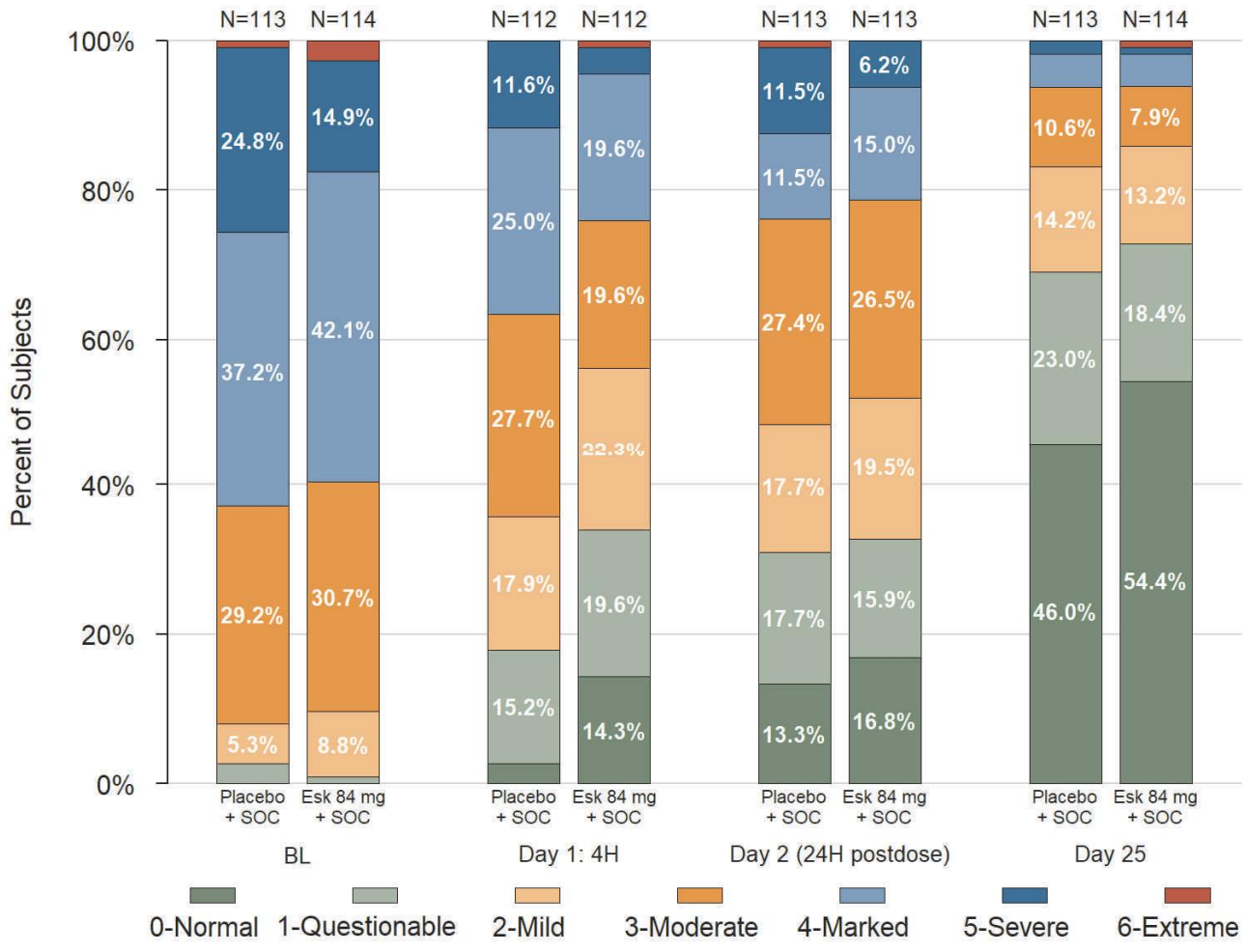
[a]*Day 25 (DB) is predose*
[b]*Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.*
Note: CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition.
Negative change in score indicates improvement.

***Abbreviations**: ANCOVA: Analysis of Covariance; DB: Double-Blind; CGI-SS-r: Clinical Global Impression of Severity of Suicidality Revised; LOCF: Last Observation Carried Forward; SoC: Standard of Care*

Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r

The proportion of patients achieving resolution of suicidality (based on a CGI-SS-r score of 0 [normal, not at all suicidal], 1 [questionably suicidal] or 2 [mildly suicidal]) in ASPIRE-II was numerically higher at all points among patients receiving ESK NS + SoC vs. Placebo + SoC throughout the double-blind treatment phase and demonstrating a clear rapid effect compared to Placebo + SoC. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. See Figure 9 and Table 30 for resolution of suicidality results in ASPIRE-II.

Figure 9. Frequency Distribution of CGI-SS-r Score at Baseline, 4 Hours Post-Dose, 24 Hours Post-Dose and Day 25 (LOCF), double-blind treatment phase, full efficacy analysis set - ASPIRE II (43)



***Abbreviations**: CGI-SS-r = Clinical Global Impression – Severity of Suicidality – Revised; ESK = Esketamine; LOCF = Lost Observation Carried Forward; SOC = Standard of Care*

Table 30: Proportion of patients achieving resolution of suicidality (score of ≤ 2) (LOCF), double-blind treatment phase, full efficacy analysis set – ASPIRE II (43)

n, %	ASPIRE II			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	110	113		
Day 2, 24 hours post first dose				
Patients with resolution of suicidality	52 (47.3%)	59 (52.2%)	1.06 (0.81; 1.39); 0.6849	2.7% (-10.2% ; 15.5%); 0.6828
Day 25, predose				
Patients with resolution of suicidality	92 (83.6%)	97 (85.8%)	1.04 (0.92; 1.18); 0.5048	3.5% (-6.9% ; 13.9%); 0.5105

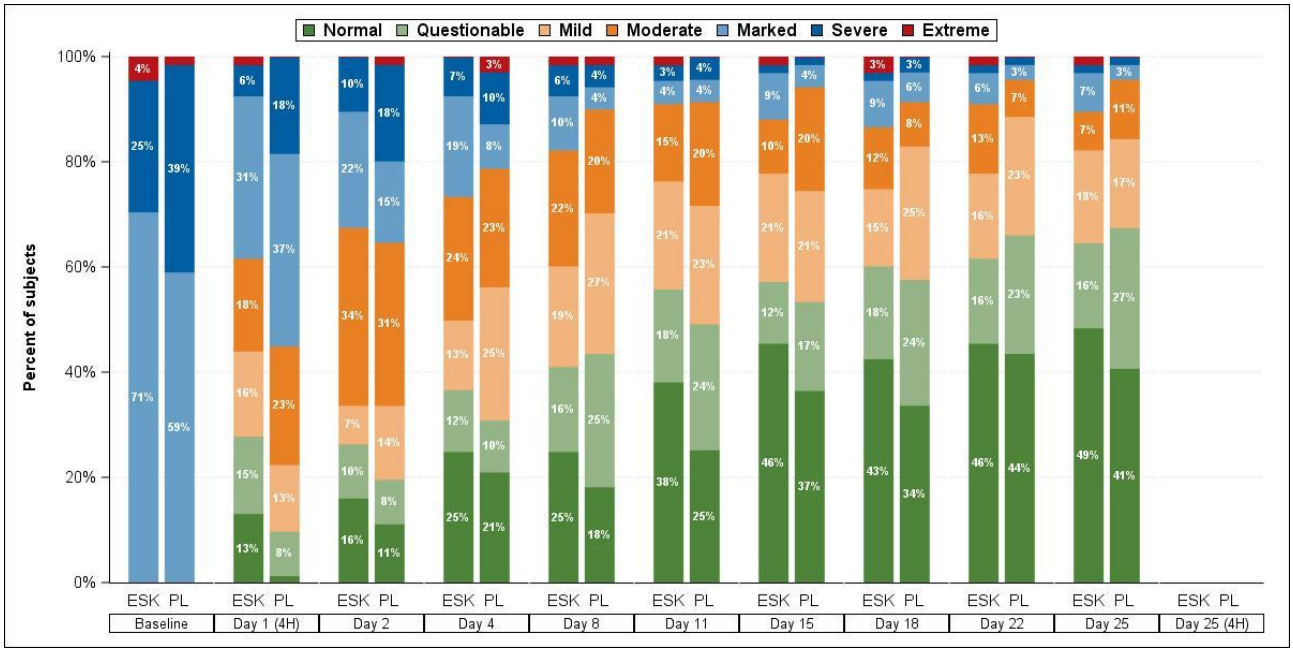
Note: resolution of suicidality is based on a CGI-SS-r score of 0 [normal, not at all suicidal], 1 [questionably suicidal] or 2 [mildly suicidal] Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to have resolution of suicidality.

Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD

Abbreviations: *ESK NS = Esketamine Nasal Spray; CGI-SS-r = Clinical Global Impression-Severity of Suicidality Revised; LOCF = Last Observation Carried Forward; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

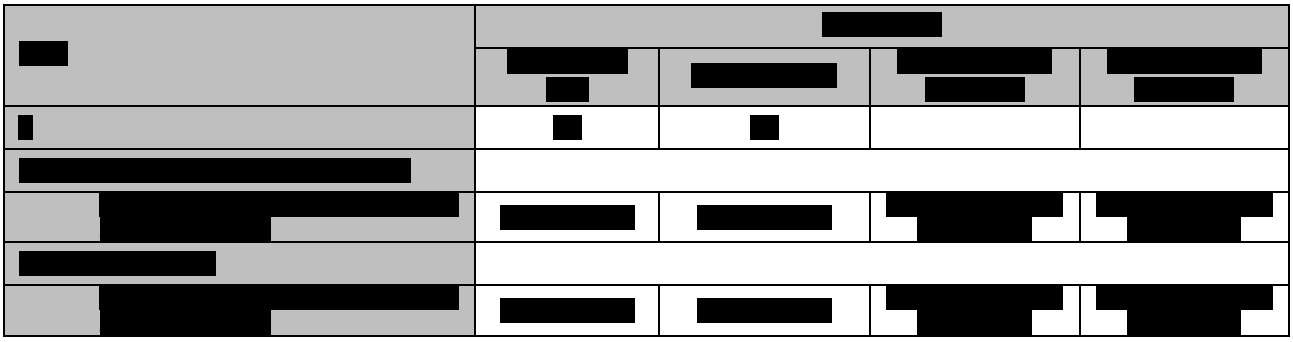
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r – subpopulation with a CGI-SS-r score of ≥ 4

[redacted]



Abbreviations*: CGI-SS-r = Clinical Global Impression – Severity of Suicidality – Revised; ESK = Esketamine; PL = Placebo*

Table 31: Proportion of patients achieving resolution of suicidality (score of ≤ 2) (LOCF), double-blind treatment phase – subpopulation with a CGI-SS-r score of ≥ 4 - ASPIRE II (40)



Note: resolution of suicidality is based on a CGI-SS-r score of 0 [normal, not at all suicidal], 1 [questionably suicidal] or 2 [mildly suicidal] Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to have resolution of suicidality.
Note: subgroup analyses were performed by Mantel-Haenszel estimate of the RR/RD
Abbreviations: *ESK NS = esketamine nasal spray; CGI-SS-r = Clinical Global Impression-Severity of Suicidality Revised; LOCF = Last observation carried forward; SoC = standard of care*

Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r

The proportion of patients who experienced an exacerbation of suicidal symptoms is defined as an increase of ≥1 point in CGI-SS-r. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. The proportion of patients who deteriorated from Day 2, 24 hours post first dose to 4 hours post dose on day 25 in the ASPIRE-II was, for the full population, observed in both patient groups receiving the ESK NS + SoC vs placebo vs SoC throughout the double-blind treatment phase. See Table 32 for the deterioration of suicidality symptoms results in ASPIRE-II.

Table 32: Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (LOCF), double-blind treatment phase, full efficacy analysis set – ASPIRE II (43)

n, %	ASPIRE II			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	115	115		
Day 2, 24 hours post first dose				
Patients with exacerbation of ≥ 1 point on CGI-SS-r	5 (4.3%)	5 (4.3%)	0.97 (0.25; 3.72); 0.9598	-0.1% (-5.6% ; 5.3%); 0.9578
Day 25, predose				
Patients with exacerbation of ≥ 1 point on CGI-SS-r	5 (4.3%)	1 (0.9%)	0.18 (0.02; 1.32); 0.0916	-4.4% (-9.1% ; 0.4%); 0.0703

Note: A subject is defined as a having deterioration at a given time point if there is an exacerbation of 1 ≥ point of CGI-SS-r. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered as having a deterioration.
Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD
Abbreviation: *ESK NS = Esketamine Nasal Spray; CGI-SS-r = Clinical Global Impression-Severity of Suicidality Revised; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r - subpopulation with a CGI-SS-r score of ≥ 4

[redacted]

Table 33: Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r, double-blind treatment phase – subpopulation with a CGI-SS-r score of ≥ 4 - ASPIRE II (40)

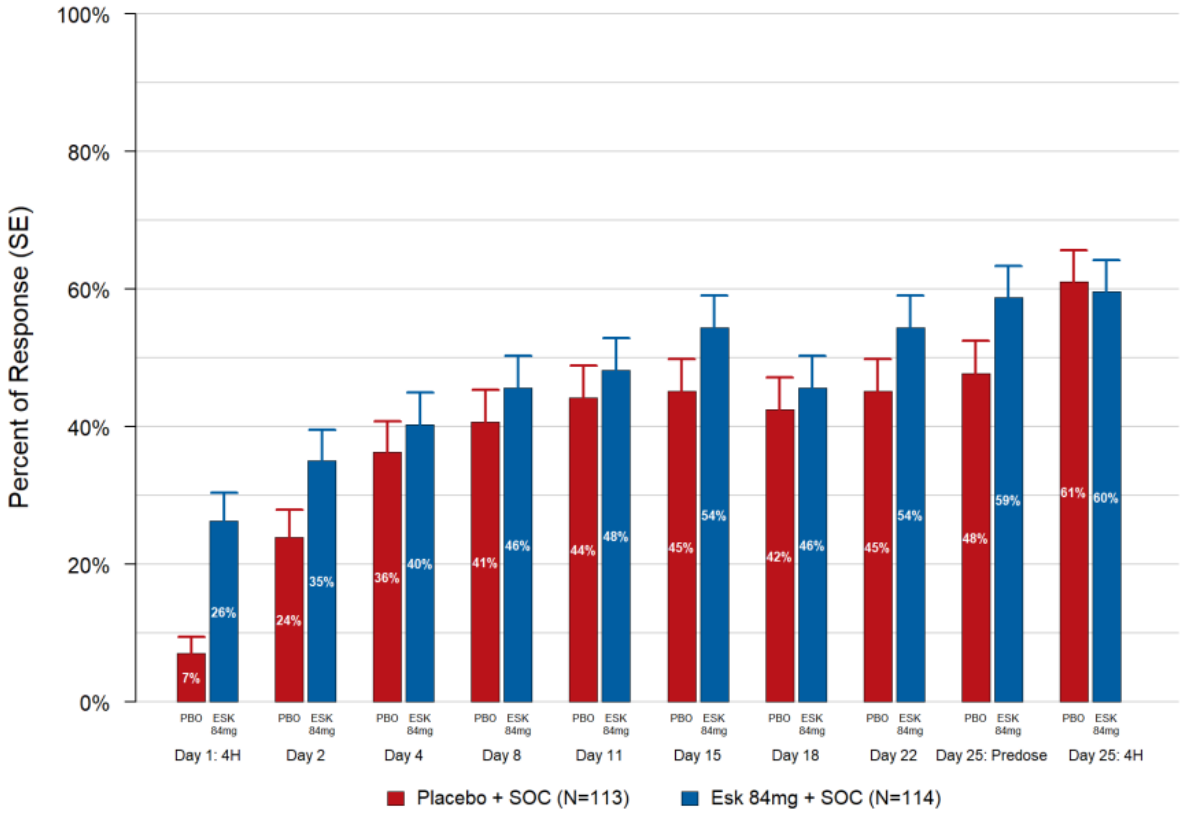
[redacted]	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: A subject is defined as a having deterioration at a given time point if there is an exacerbation of 1 ≥ point of CGI-SS-r. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered as having a deterioration.
Note: subgroup analyses were performed by Mantel-Haenszel estimate of the RR/RD
Abbreviation: *ESK NS = esketamine nasal spray; CGI-SS-r = Clinical Global Impression-Severity of Suicidality Revised SoC = standard of care*

Response

A patient was considered to achieve response at a given time point if the improvement in MADRS total score was at least 50%. Patients who did not meet the criterion or discontinued prior to the time point for any reason were not considered to achieve response. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. The percentage of patients who achieved response directionally favored the ESK NS + SoC group over the placebo + SoC group at all but one timepoint (day 25, 4 hours post dose) during the double-blind treatment phase (Figure 11). The treatment difference between treatment groups in percentage of patients who achieved response over time during the double-blind treatment phase is shown in Table 34. At Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was statistically significant at 13.7% (2.2%; 25.3%) with a statistically significant risk ratio (95% CI) of 1.62 (1.07; 2.46). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was -0.3% (-14.5%; 13.9%) with a risk ratio (95% CI) of 0.99 (0.79; 1.26).

Figure 11: MADRS total score: frequency distribution of patients who achieved remission of MDD over time, double-blind treatment Phase, full efficacy analysis set – ASPIRE II (43)



Abbreviations: *ESK: Esketamine; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; PBO: Placebo; SE: Standard Error; SoC: Standard of Care*

Table 34: Response rates (percent improvement in MADRS total score was at least 50%) over time, double-blind treatment phase, full efficacy analysis set – ASPIRE II (43)

n, %	ASPIRE II			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	115	115		
Day 2, 24 hours post first dose				
Patients with Response	27 (23.5%)	40 (34.8%)	1.62 (1.07; 2.46); 0.0231	13.7% (2.2% ; 25.3%); 0.0198
Day 25 (4 hours post-dose)				
Patients with Response	69 (60.0%)	68 (59.1%)	0.99 (0.79; 1.26); 0.9626	-0.3% (-14.5% ; 13.9%); 0.9626

Note: A subject is defined as a responder at a given time point if the percent improvement from baseline in MADRS total score is at least 50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder

Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD

Abbreviations: *ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; RD = Risk Difference; RR = Risk ratio; SoC = Standard of Care*

Response – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 35: Response rates (percent improvement in MADRS total score was at least 50%) over time, double-blind treatment phase – subpopulation with a CGI-SS-r score ≥ 4 - ASPIRE II (40)

[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]		
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: A subject is defined as a responder at a given time point if the percent improvement from baseline in MADRS total score is at least 50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder

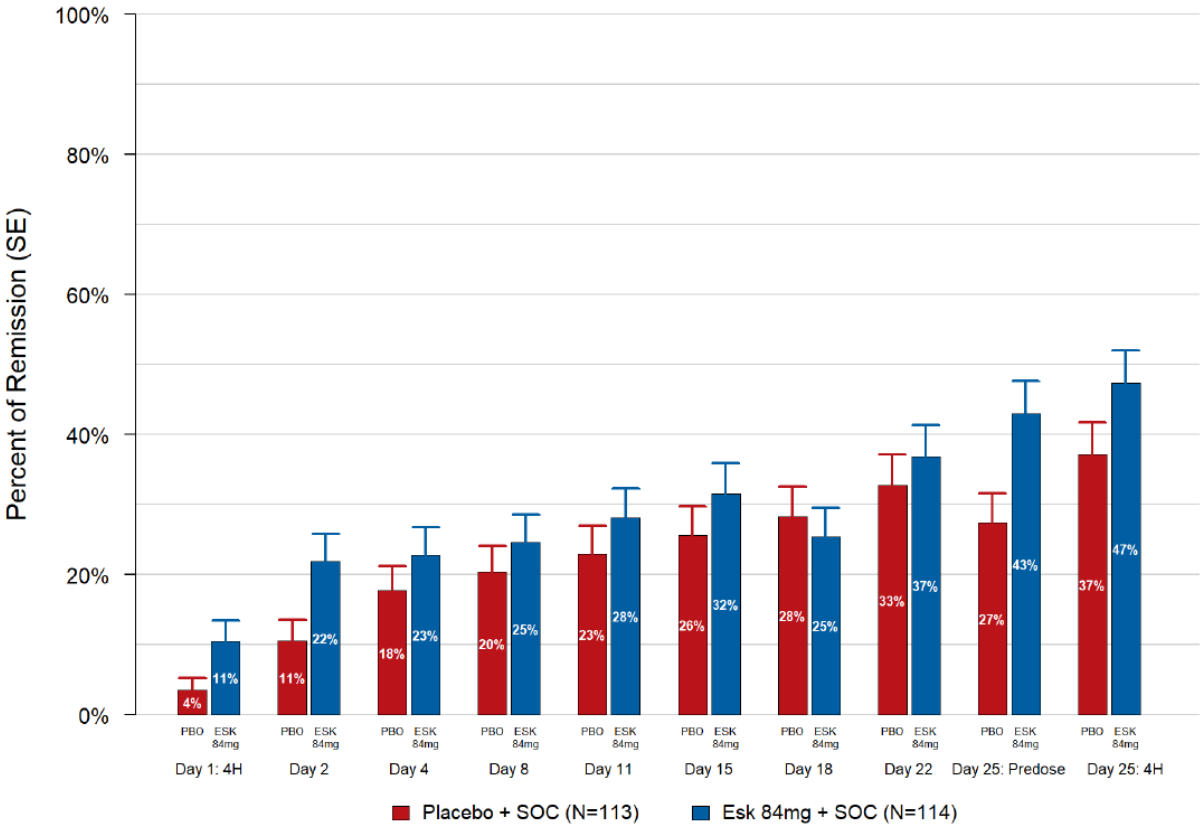
Note: subgroup analyses were performed by Mantel-Haenszel estimate of the RR/RD

***Abbreviations:** ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Remission

According to pre-defined criteria, patients were considered to have achieved remission of MDD at a given time point if the MADRS total score was ≤ 12. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered to be in remission. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. The percentage of patients who achieved remission directionally favored the ESK NS + SoC group versus the placebo + SoC group at all but one timepoint (day 18) during the double-blind treatment phase. See Figure 12 and Table 36 for the remission rates in the ASPIRE-II study. At Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was statistically significant at 13.9% (4.1%; 23.8%) with a statistically significant risk ratio (95% CI) of 2.53 (1.26; 5.09). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was 11.1% (-2.2%; 24.5%) with a risk ratio (95% CI) of 1.31 (0.95; 1.81).

Figure 12. MADRS total score: frequency distribution of patients who achieved remission of MDD over time, double-blind treatment phase, full efficacy analysis set – ASPIRE II (43)



Abbreviations: *ESK: Esketamine; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; PBO: Placebo; SE: Standard Error; SoC: Standard of Care*

Table 36. Remission rates (MADRS total score ≤12) over time, double-blind treatment phase, full efficacy analysis set - ASPIRE II (43)

n, %	ASPIRE II			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	115	115		
Day 2, 24 hours post first dose				
Patients with Remission of MDD	12 (10.4%)	25 (21.7%)	2.53 (1.26; 5.09); 0.0094	13.9% (4.1% ; 23.8%); 0.0055
Day 25 (4 hours post-dose)				
Patients with Remission of MDD	42 (36.5%)	54 (47.0%)	1.31 (0.95; 1.81); 0.1054	11.1% (-2.2% ; 24.5%); 0.1022

Note: According to pre-defined criteria, patients were considered to have achieved remission of MDD at a given time point if the MADRS total score was ≤12. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered to be in remission.

Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD

Abbreviations: *ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Remission – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 37: Remission rates (MADRS total score ≤12) over time, double-blind treatment phase – subpopulation with a CGI-SS-r score ≥ 4 – ASPIRE II (40)

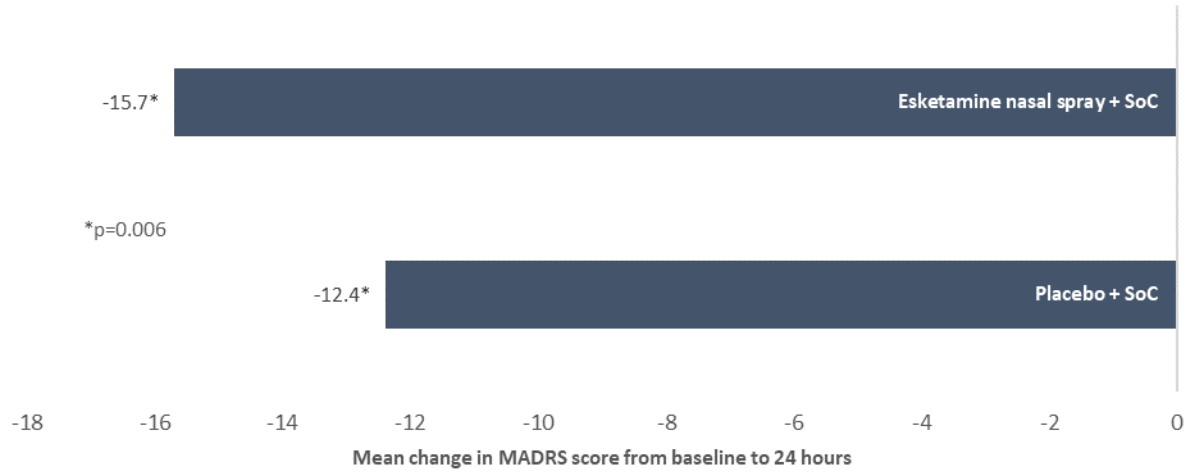
[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: According to pre-defined criteria, patients were considered to have achieved remission of MDD at a given time point if the MADRS total score was ≤12. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered to be in remission.
Note: subgroup analyses were performed by Mantel-Haenszel estimate of the RR/RD
Abbreviations: *ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; SoC = Standard of Care*

Mean change in MADRS total score from baseline

The primary efficacy analysis was performed on the full efficacy analysis set with LOCF data using an ANCOVA model. Patients in the ESK NS + SoC group achieved a statistically significant (2-sided p-value: 0.006) rapid improvement in symptoms of depression and suicidality compared to patients who received placebo + SoC, as measured by change in MADRS total score from baseline to 24 hours after the first dose (Day 2) (Figure 13). At 24 hours, the mean (SD) changes from baseline were -15.7 (11.56) in the ESK NS + SoC group and -12.4 (10.43) in the placebo + SoC group (Table 38) with a statistically significant difference of LS Means of -3.9 (95% CI: -6.60; -1.11). Despite a smaller difference, the trend toward efficiency applies throughout the full double-blind treatment phase with a difference of LS Means of -2.3 (95% CI: -5.50; 0.86) at day 25.

Figure 13. Mean changes in MADRS score from baseline (Day 1, pre-dose) to 24 hours after first dose (Day 2), double-blind treatment phase, full efficacy analysis set – ASPIRE II (43)



Abbreviations: *MADRS: Montgomery-Asberg Depression Rating Scale; SoC: Standard of Care*
**p=0.006*

Table 38. MADRS total score change from baseline to 24 hours post first dose (ANCOVA LOCF) double-blind treatment phase, full efficacy analysis set – ASPIRE II (43)

	Placebo + SoC n=113	Esketamine 84 mg + SoC n=114
Baseline (DB)		
N	113	114
Mean (SD)	39.9 (5.76)	39.5 (5.19)
Day 2 (DB) LOCF[a]		
N	113	113
Mean (SD)	27.5 (11.13)	23.7 (11.75)
Change from baseline at Day 2		
N	113	113
LS Mean (SE)	-12.2 (1.05)	-16.0 (1.02)
Diff. of LS Means (95% CI)	-3.9 (-6.60; -1.11)	
Day 25 (DB) LOCF		
N	113	114
Mean (SD)	16.2 (12.17)	13.6 (11.47)
Change from baseline at Day 25[b]		
N	113	114
LS Mean (SE)	-23.2 (1.22)	-25.6 (1.18)
Diff. of LS Means (95% CI)	-2.3 (-5.50; 0.86)	

[a]Day 2 (DB) is 24 hours post first dose.
[b]Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.
Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition.
Negative change in score indicates improvement.
***Abbreviations**: ANCOVA: Analysis of Covariance; DB: Double-Blind; LOCF: Last Observation Carried Forward; MADRS: Montgomery-Asberg Depression Rating Scale; SD: Standard Deviation, SE: Standard Error; SoC: Standard of Care*

Mean change in MADRS total score from baseline – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 39. MADRS total score change from baseline to 24 hours post first dose and day 25 at endpoint (ANCOVA LOCF), double-blind treatment phase – subpopulation with a CGI-SS-r score ≥ 4 – ASPIRE II (40)

	[redacted]	[redacted]
[redacted]		
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[redacted]		
[redacted]	[redacted]	[redacted]
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[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

[a]Day 2 (DB) is 24 hours post first dose.
[b]Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), analysis center, standard of care antidepressant treatment as randomized (antidepressant monotherapy, antidepressant plus augmentation therapy) as factors and baseline value as a covariate.
Negative change in score indicates improvement.
***Abbreviations**: ANCOVA: Analysis of Covariance; DB: Double-Blind; LOCF: Last Observation Carried Forward; MADRS: Montgomery-Asberg Depression Rating Scale; SD: Standard Deviation; SE: Standard Error; SoC: Standard of Care*

Adverse events

Summaries of AEs and other safety data for the double-blind treatment phase were based on all randomized patients who received at least 1 dose of study drug in the double-blind treatment phase. This is referred to as the safety analysis set (4).

The safety analysis set included 227 patients:

- 113 patients in the placebo + SoC group
- 114 patients in the ESK NS + SoC group

Summaries of AEs and other safety data from the follow-up phase were based on the follow-up analysis set. The follow-up analysis set included all patients who completed the double-blind treatment phase and entered the follow-up phase or provided AE data (4).

The follow-up analysis set included 183 patients:

- 94 patients from the placebo + SoC group
- 89 patients from the ESK NS + SoC group

The AEs observed in this study are consistent with the safety profile of ESK NS established in previous studies in patients with MDD with active suicidal ideation and intent, and those with treatment-resistant depression.

Most of the AEs which occurred in the ASPIRE-II trial were mild to moderate in severity with a transient and self-limiting nature which resolved within the same day of dosing as per the comprehensive risk management plan designed for ESK NS (41).

Double-blind treatment phase

There were no TEAEs leading to death during the double-blind treatment phase. There were 104 (91.2%) in the ESK NS + SoC group and 87 (77.0%) in the placebo + SoC group that experienced one or more TEAEs in the double-blind treatment phase. Table 40 provides a summary of the TEAEs experienced during the double-blind treatment phase.

Table 40: Overall summary of TEAEs, double-blind treatment phase, safety analysis set – ASPIRE II (43)

	Placebo + SoC (n=113)	Esketamine 84 mg + SoC (n=114)
Patients with 1 or more:		
TEAEs	87 (77.0%)	104 (91.2%)
TEAEs leading to death[a]	0	0
Serious TEAEs	6 (5.3%)	5 (4.4%)
Severe TEAEs	7 (6.2%)	21 (18.4%)
TEAEs leading to discontinuation of study agent	3 (2.7%)	9 (7.9%)

aTEAEs leading to death are based on TEAE outcome of Fatal.
Note: Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
Abbreviations: *SoC: Standard of care; TEAE: Treatment-emergent adverse event*

The TEAEs reported in at least 5% of patients in either treatment group during the double-blind treatment phase are summarized in Table 41. The most common TEAEs (reported by ≥10% patients) were observed more frequently in the ESK NS + SoC group versus placebo + SoC group were dizziness (41.2% versus 18.6%), dissociation (38.6% versus 8%), nausea (33.3% versus 14.2%), dysgeusia (25.4% versus 15.9%), somnolence (22.8% versus 10.6%), paresthesia (20.2% versus 6.2%), vomiting (15.8% versus 4.4%), anxiety (14.9% versus 6.2%), vision blurred (14.9% versus 5.3%), sedation (14% versus 2.7%), paresthesia oral (12.3% versus 2.7%), euphoric mood (11.4% versus 0.9%), and hypoesthesia (10.5% versus 0.9%). The most common TEAEs (reported by ≥10% patients) observed more frequently in the placebo + SoC treatment group was headache (23% versus 21.9%). Most of the TEAEs in both treatment groups occurred on the intranasal dosing days. 89.1% of the TEAEs in the ESK NS + SoC group occurred during the dosing days while 68.0% of the TEAEs in the placebo + SoC group occurred during the dosing days. However, the effects of the TEAEs seemed to be transient in nature and numerically favored ESK NS, with 94.9% of the TEAEs in the ESK NS + SoC group resolving on the same day versus 84.9% in the placebo + SoC group.

Table 41: Number of patients with TEAEs with frequency of at least 5% in any treatment group by system organ class and preferred term, double-blind treatment phase, safety analysis set – ASPIRE II (43)

	Placebo + SoC (n=112)	Esketamine 84 mg + SoC (n=113)
Patients with 1 or more TEAEs	87 (77.0%)	104 (91.2%)
System organ class, Preferred term		
Nervous system disorders	54 (47.8%)	86 (75.4%)
Dizziness	21 (18.6%)	47 (41.2%)
Dysgeusia	18 (15.9%)	29 (25.4%)
Somnolence	12 (10.6%)	26 (22.8%)
Headache	26 (23.0%)	25 (21.9%)
Paraesthesia	7 (6.2%)	23 (20.2%)
Sedation	3 (2.7%)	16 (14.0%)
Hypoaesthesia	1 (0.9%)	12 (10.5%)
Dizziness postural	1 (0.9%)	9 (7.9%)
Psychiatric disorders	34 (30.1%)	74 (64.9%)
Dissociation	9 (8.0%)	44 (38.6%)
Anxiety	7 (6.2%)	17 (14.9%)
Euphoric mood	1 (0.9%)	13 (11.4%)
Depersonalisation/derealisation disorder	0	9 (7.9%)
Insomnia	11 (9.7%)	9 (7.9%)
Suicidal ideation	6 (5.3%)	5 (4.4%)
Gastrointestinal disorders	36 (31.9%)	59 (51.8%)
Nausea	16 (14.2%)	38 (33.3%)
Vomiting	5 (4.4%)	18 (15.8%)
Paraesthesia oral	3 (2.7%)	14 (12.3%)
Dry mouth	5 (4.4%)	8 (7.0%)
Constipation	9 (8.0%)	7 (6.1%)
Hypoaesthesia oral	2 (1.8%)	7 (6.1%)
Respiratory, thoracic and mediastinal disorders	24 (21.2%)	32 (28.1%)
Nasal discomfort	9 (8.0%)	10 (8.8%)
Oropharyngeal pain	3 (2.7%)	6 (5.3%)
Throat irritation	4 (3.5%)	6 (5.3%)
General disorders and administration site conditions	11 (9.7%)	29 (25.4%)
Feeling drunk	1 (0.9%)	6 (5.3%)
Eye disorders	8 (7.1%)	21 (18.4%)
Vision blurred	6 (5.3%)	17 (14.9%)
Diplopia	0	6 (5.3%)
Skin and subcutaneous tissue disorders	9 (8.0%)	14 (12.3%)
Hyperhidrosis	3 (2.7%)	6 (5.3%)

	Placebo + SoC (n=112)	Esketamine 84 mg + SoC (n=113)
Investigations	10 (8.8%)	12 (10.5%)
Blood pressure increased	3 (2.7%)	7 (6.1%)
Ear and labyrinth disorders	3 (2.7%)	11 (9.6%)
Vertigo	0	7 (6.1%)

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: *SoC: Standard of care; TEAE: Treatment-emergent adverse event*

The proportion of patients experiencing one or more SAEs was comparable between the treatment groups, with 5 (4.4%) in the ESK NS + SoC group and 6 (5.3%) in the placebo + SoC group. Details of SAEs in both phases of the study are discussed in the next section. None of the SAEs were considered possibly, probably, or very likely related to intranasal study agent except 2 SAEs of suicide attempt and depersonalization/derealization disorder experienced by one patient each in the ESK NS + SoC group. The 2 SAEs were considered as possibly related to study agents by the investigator.

In the ESK NS + SoC group, 21 (18.4%) patients reported 1 or more severe TEAEs (dissociation [6 patients], nausea [4 patients], anxiety and blood pressure increased [3 patients each], depersonalization/derealization disorder, vomiting, and suicide attempt [2 patients each], suicidal ideation and depression [1 patient each]). In the placebo + SoC group, 7 (6.2%) patients reported 1 or more severe TEAEs (depression, suicide attempt, and suicidal ideation [2 patients each], anxiety [1 patient]). As with the non-serious TEAEs reported above, most of the severe TEAEs in both treatment groups occurred on the intranasal dosing days. 90.0% of severe TEAEs in the ESK NS + SoC group occurred during the dosing days while 22.2% severe TEAEs in the placebo + SoC group occurred during the dosing days. However, the effects of the TEAEs seemed to be transient in nature as well and numerically favored ESK NS, with 97.2% of the severe TEAEs in the ESK NS + SoC group resolving on the same day versus none of these resolved on the same day in the placebo + SoC group.

Twelve patients experienced 1 or more TEAEs leading to discontinuation of study agent. In the ESK NS + SoC group, 9 (7.9%) of 114 patients discontinued study agent due to TEAEs (dissociation [2 patients], dizziness postural, blood pressure increased, paresthesia oral, depersonalization/ derealization disorder [1 patient each], nausea and vomiting [both events in 1 patient], depersonalization/ derealization disorder, nausea, and throat irritation [all 3 events in 1 patient], nasal discomfort and dyspepsia [both events in 1 patient]. In the placebo + SoC group, 3 (2.7%) of 113 patients discontinued the study agent due to TEAEs (pericardial effusion and depression suicidal [1 patient each] and arrhythmia and pneumothorax [both events in 1 patient]).

Follow-up phase

There was no AE leading to death during the follow-up phase. There were 53 (59.6%) in the ESK NS + SoC group and 55 (58.5%) in the placebo + SoC group that experienced one or more AEs during the follow-up phase. Table 42 provides a summary of the AEs experienced during the follow-up phase.

Table 42: Overall summary of AEs, follow-up phase, follow-up analysis set – ASPIRE II (43)

	Placebo + SoC (n=94)	Esketamine 84 mg + SoC (n=89)
Patients with 1 or more:		
AEs	55 (58.5%)	53 (59.6%)
AEs leading to death[a]	0	0
Serious AEs	12 (12.8%)	9 (10.1%)
Severe AEs	10 (10.6%)	6 (6.7%)

aAEs leading to death are based on AE outcome of Fatal.
Note: Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
Abbreviations: *AE: Adverse event; SoC: Standard of care*

The AEs reported in at least 5% of patients in either treatment group during the follow-up phase are summarized in Table 43. The most common AE (reported by ≥5% patients) observed more frequently in the ESK NS + SoC group versus placebo + SoC group was insomnia (9% vs 7.4%). The most common AEs (reported by ≥5% patients) observed more frequently in the placebo + SoC group vs ESK NS + SoC group were headache (10.6% vs 7.9%), anxiety (9.6% vs 9%), suicidal ideation (7.4% vs 5.6%), and diarrhea (5.3% vs 3.4%).

Table 43: Number of patients with AEs with frequency of at least 5% in any treatment group by system organ class and preferred term, follow-up phase, follow-up analysis set – ASPIRE II (43)

	Placebo + SoC (n=94)	Esketamine 84 mg + SoC (n=89)
Patients with 1 or more AEs	55 (58.5%)	53 (59.6%)
System organ class Preferred term		
Psychiatric disorders	28 (29.8%)	30 (33.7%)
Anxiety	9 (9.6%)	8 (9.0%)
Insomnia	7 (7.4%)	8 (9.0%)
Suicidal ideation	7 (7.4%)	5 (5.6%)
Nervous system disorders	19 (20.2%)	13 (14.6%)
Headache	10 (10.6%)	7 (7.9%)
Gastrointestinal disorders	14 (14.9%)	11 (12.4%)
Diarrhoea	5 (5.3%)	3 (3.4%)

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: *AE: Adverse event; SoC: Standard of care*

The proportion of patients experiencing one or more SAE was comparable between the treatment groups, with 9 (10.1%) in the ESK NS + SoC group and 12 (12.8%) in the placebo + SoC group.

16 patients reported 1 or more severe AEs in both treatment groups with 6 (6.7%) in the ESK NS + SoC group and 10 (10.6%) in the placebo + SoC group.

Deaths, other serious adverse events, and other significant adverse events

Deaths

There were no AEs leading to death during the double-blind treatment phase and follow-up phase. No AEs resulting in death after the double-blind treatment phase for patients who discontinued from the double-blind phase or after the follow-up phase for patients who discontinued from the follow-up phase were reported.

Serious adverse events

As mentioned in the above section, SAEs were comparable in both treatment groups during the double-blind phase with 5 (4.4%) in the ESK NS + SoC group and 6 (5.3%) in the placebo + SoC group. An overview of SAEs experienced in both groups is shown in Table 44.

In the ESK NS group, 3 (2.6%) patients experienced a suicide attempt, 1 (0.9%) patient had depersonalization/derealization disorder, and 1 (0.9%) patient experienced a suicidal ideation. In the placebo + SoC, 3 (2.6%) patients experienced a suicide attempt, 2 (1.8%) patients had suicidal ideation, 1 (0.9%) patient had depression, 1 (0.9%) patient had an arrhythmia, 1 (0.9%) experienced a pericardial effusion and 1 (0.9%) patient had a pneumothorax.

Table 44: Number of patients with treatment-emergent serious adverse events by system organ class and preferred term, double-blind treatment phase, safety analysis set – ASPIRE II (43)

	Placebo + SoC (n=113)	Esketamine 84 mg + SoC (n=114)
Patients with 1 or more serious TEAEs	6 (5.3%)	5 (4.4%)
System organ class Preferred term		
Psychiatric disorders	4 (3.5%)	5 (4.4%)
Suicide attempt	3 (2.7%)	3 (2.6%)
Depersonalization/derealization disorder	0	1 (0.9%)
Suicidal ideation	2 (1.8%)	1 (0.9%)
Depression	1 (0.9%)	0
Cardiac disorders	2 (1.8%)	0
Arrhythmia	1 (0.9%)	0
Pericardial effusion	1 (0.9%)	0
Respiratory, thoracic and mediastinal disorders	1 (0.9%)	0
Pneumothorax	1 (0.9%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: *SoC: Standard of care; TEAE: Treatment-emergent adverse event*

During the follow-up phase of the study, 21 patients experienced SAEs: 9 (10.1%) in the ESK NS + SoC group and 12 (12.8%) patients in the placebo + SoC group. A detailed list of SAEs experienced in both groups is shown in Table 45.

In the ESK NS group, 9 (10.1%) patients reported an SAE of system organ class preferred term psychiatric disorders and 1 (1.1%) patient in respiratory, thoracic and mediastinal disorders. In the placebo + SoC group, 6 (6.4%) patients reported an SAE of system organ class preferred term psychiatric disorders, 3 (3.2%) patients in infections and infestations, 1 (1.1%) patient in injury, poisoning and procedural complications, 1

(1.1%) patient in neoplasms benign, malignant & unspecified and 1 (1.1%) patient in nervous system disorders.

Table 45: Number of patients with treatment-emergent serious adverse events by system organ class and preferred term, follow-up phase, follow-up analysis set – ASPIRE II (43)

	Placebo + SoC (n=94)	Esketamine 84 mg + SoC (n=89)
Patients with 1 or more serious AEs	12 (12.8%)	9 (10.1%)
System organ class Preferred term		
Psychiatric disorders	6 (6.4%)	9 (10.1%)
Suicide **attempt**	1 (1.1%)	4 (4.5%)
Suicidal ideation	3 (3.2%)	3 (3.4%)
Acute stress disorder	0	1 (1.1%)
Major depression	0	1 (1.1%)
Depression suicidal	2 (2.1%)	0
Homicidal ideation	1 (1.1%)	0
Respiratory, thoracic and mediastinal disorders	0	1 (1.1%)
Haemothorax	0	1 (1.1%)
Infections and infestations	3 (3.2%)	0
Erysipelas	1 (1.1%)	0
Pyelonephritis	1 (1.1%)	0
Staphylococcal bacteraemia	1 (1.1%)	0
Injury, poisoning and procedural complications	1 (1.1%)	0
Overdose	1 (1.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.1%)	0
Papillary thyroid cancer	1 (1.1%)	0
Nervous system disorders	1 (1.1%)	0
Encephalopathy	1 (1.1%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: *AE: Adverse event; SoC: Standard of care*

Adverse events leading to discontinuation of study medication

The number of patients who experienced TEAEs leading to discontinuation of study agent by system organ class and preferred term is provided in Table 46. In the ESK NS + SoC group, TEAEs leading to discontinuation of study agent occurred on Day 1, Day 3, Day 4, Day 5, Day 7, and Day 11 from start of study agent. TEAEs leading to discontinuation of study agent in the placebo + SoC group occurred on Day 4, Day 8, Day 20, and Day 23 from the start of study agent. TEAEs leading to discontinuation of study agent in the ESK NS + SoC group had wide range of severity grades (5 TEAEs were mild, 4 TEAEs were moderate, and 4 TEAEs were severe) and all were nonserious AEs. Nine TEAEs were considered very likely related, 2 TEAEs each were considered as probably related and possibly related to study agent by the investigator. In the placebo + SoC group, 2 SAEs of moderate intensities, 1 SAE of severe intensity assessed by the investigator to be not related

to study agent and 1 moderate nonserious TEAEs was assessed by the investigator to be not related to study agent.

Table 46: Number of patients with treatment-emergent adverse events leading to discontinuation of study agent by system organ class and preferred term, double-blind treatment phase, safety analysis set – ASPIRE II (43)

	Placebo + SoC (n=113)	Esketamine 84 mg + SoC (n=114)
Patients with 1 or more TEAEs	3 (2.7%)	9 (7.9%)
System organ class Preferred term		
Gastrointestinal disorders	0	4 (3.5%)
Nausea	0	2 (1.8%)
Dyspepsia	0	1 (0.9%)
Paraesthesia oral	0	1 (0.9%)
Vomiting	0	1 (0.9%)
Psychiatric disorders	1 (0.9%)	4 (3.5%)
Depersonalization/derealization disorder	0	2 (1.8%)
Dissociation	0	2 (1.8%)
Depression suicidal	1 (0.9%)	0
Respiratory, thoracic and mediastinal disorders	1 (0.9%)	2 (1.8%)
Nasal discomfort	0	1 (0.9%)
Throat irritation	0	1 (0.9%)
Pneumothorax	1 (0.9%)	0
Investigations	0	1 (0.9%)
Blood pressure increased	0	1 (0.9%)
Nervous system disorders	0	1 (0.9%)
Dizziness postural	0	1 (0.9%)
Cardiac disorders	2 (1.8%)	0
Arrhythmia	1 (0.9%)	0
Pericardial effusion	1 (0.9%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: *SoC: Standard of care; TEAE: Treatment-emergent adverse event*

Adverse events of special interest - suicidality

Ten patients in each treatment group reported TEAEs potentially related to suicidality in the double-blind phase. In the ESK NS + SoC group, patients reported preferred terms of intentional self-injury and suicidal ideation (5 patients each), and suicide attempt (3 patients). In the placebo + SoC group, patients reported preferred terms of suicidal ideation (6 patients), suicide attempt (3 patients), intentional self-injury and depression suicidal (1 patient each). Most TEAEs potentially related to suicidality were considered by the investigator to be not related to study agent. In the ESK NS + SoC group, one patient each experienced TEAEs of intentional self-injury (nonserious, moderate) and suicide attempt (serious, mild) considered by the investigator to be possibly related to study agent.

Two patients who discontinued from the double-blind phase reported AEs potentially related to suicidality after discontinuation: 1 (0.9%) of 114 patients in the ESK NS + SoC group (preferred term of suicidal ideation) and 1 (0.9%) of 113 patients in the placebo + SoC group (preferred terms of intentional self-injury).

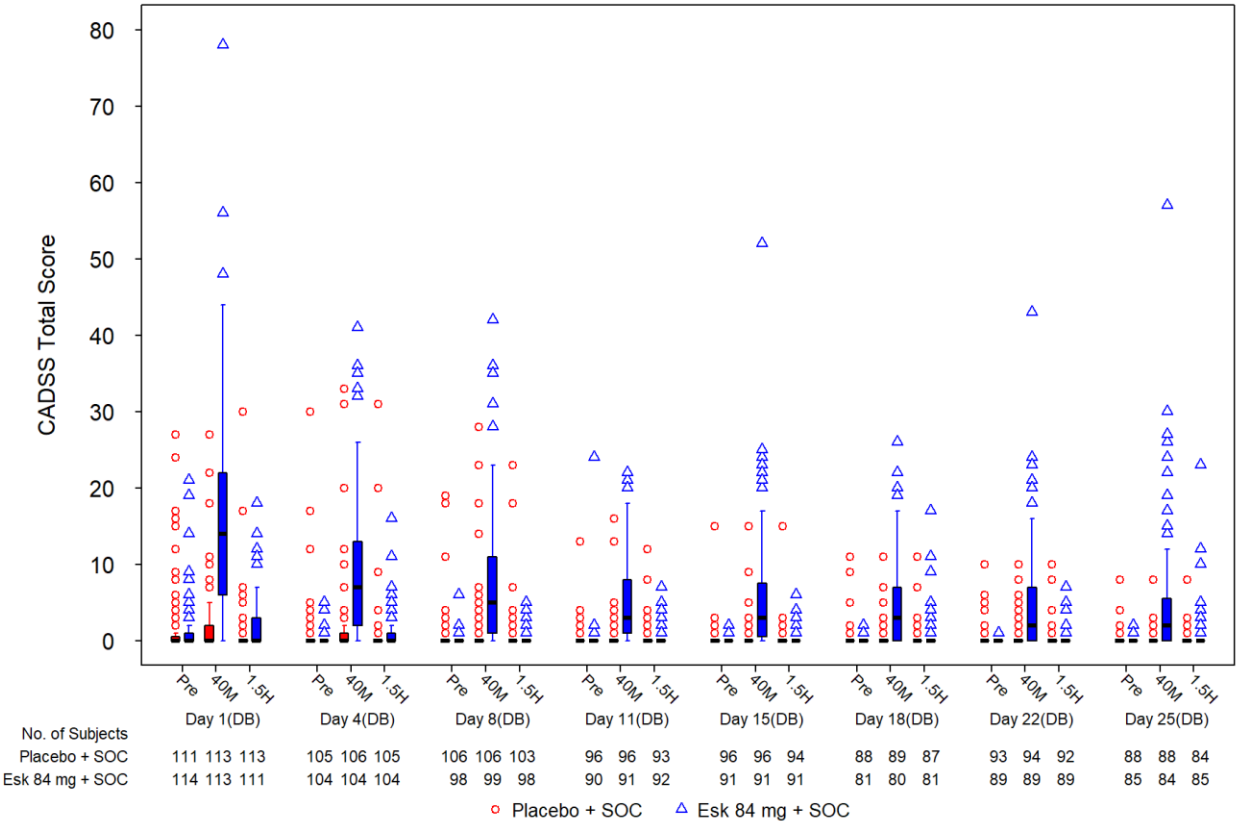
Eighteen patients reported 1 or more AEs potentially related to suicidality in the follow-up phase: 9 patients in the ESK NS + SoC group (preferred terms of suicidal ideation [5 patients], suicide attempt [4 patients], and intentional self-injury [3 patients]) and 9 patients in the placebo + SoC group (preferred terms of suicidal ideation [7 patients], depression suicidal [2 patients], and suicide attempt [1 patient]). None of the AEs potentially related to suicidality in the follow-up phase were considered by the investigator to be possibly, probably, or very likely related to study agent. No patients in the ESK NS + SoC and placebo + SoC groups who discontinued from the follow-up phase reported AEs potentially related to suicidality after the follow-up phase. The occurrence of these suicide attempts in the follow-up phase was dispersed over the follow-up phase without an apparent pattern suggestive of rebound.

Adverse events of special interest - dissociation

The CADSS is a clinician administered scaled used for the assessment of treatment-emergent dissociative and perceptual change symptoms. The subject's responses are recorded on a 5-point scale (0 = not at all and 4 = extremely, with a score of ≤4 considered within the normal range). Total scores range from 0 to 92, with a higher score representing a more severe condition. The CADSS were measured prior to intranasal dosing of study drug and at 40 minutes, 2 hours and 4 hours post dose, on each dosing day of the double-blind phase (42).

A consistently greater proportion of patients in the ESK NS + SoC group had an increase in CADSS total score over pre-dose on all dosing days (65.2% to 23.8%) compared with the placebo + SoC group (4.5% to 25.2%). It is notable that mean CADSS total scores peaked at 40 minutes post-dose in patients receiving ESK NS + SoC and returned towards baseline at 90 minutes post-dose. The CADSS total score was reduced with an increasing number of treatment sessions underlining that the dissociative symptoms diminished over time. Results for assessment of CADSS total score over time for ASPIRE II are summarized in Figure 14.

Figure 14: CADSS total score: box plot over time; double-blind treatment phase; safety analysis set – ASPIRE II (43)



CADSS: Clinician-administered dissociative states scale; SOC: Standard of care

Adverse events of special interest - euphoria

13 (11.4%) patients in the ESK NS + SoC group experienced euphoria during the double-blind treatment phase while 1 (0.9%) patient in the placebo + SoC group experienced euphoria. All the euphoria TEAEs in both treatment groups were not serious TEAEs in severity and occurred during the dosing days. All euphoria TEAEs in the placebo + SoC group were resolved on the same day, while 92.3% in the ESK NS + SoC group were resolved on the same day.

6.1.2.3 ESKETINSUI2001

Similarly, to the ASPIRE-I and ASPIRE-II trials, the ESKETINSUI2001 trial demonstrated the value of ESK NS + SoC compared to Placebo + SoC in the treatment of MDSI in a number of key clinical outcomes for the ITT population. No subpopulation analyses were carried out in this study based on the CGI-SS-r scale.

The ESKETINSUI2001 trial met its primary endpoint by demonstrating that patients who received ESK NS (84 mg) in combination with SoC achieved statistically significantly reduced symptoms of depression, as measured by MADRS total score, when compared to placebo + SoC from baseline to Day 2 (~24 hours post-dose), using a two-sided significance level of 0.20 (p=0.015) (2). At 24 hours, the mean (SD) changes from baseline were -19.3 (12.02) in the ESK NS + SoC group and -12.8 (9.77) in the placebo + SoC group (see Table 49) with a statistically significant difference of LS Means (SE) of -7.2 (2.85). Despite a smaller difference, the trend toward efficiency applies throughout the full double-blind treatment phase with a difference of LS Means (SE) of -4.5 (3.14) at day 25.

The value of ESK NS + SoC in comparison to placebo + SoC was further confirmed in the ESKETINSUI2001 trial through the analyses of Response and Remission.

The percentage of patients who achieved response directionally favored the ESK NS + SoC group over the placebo + SoC group during the double-blind of the study. At Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was statistically significant at 26.8% (-0.1%; 53.7%) with a risk ratio (95% CI) of 1.82 (0.97; 3.40). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was 7.9% (-17.4%; 33.1%) with a risk ratio (95% CI) of 1.16 (0.72-1.85).

The percentage of patients who achieved remission directionally favored the ESK NS + SoC group versus the placebo + SoC group at all but one timepoint (day 1, 4 hours post dose) during the double-blind treatment phase. At Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was 14.9% (-8.5%; 38.3%) with a risk ratio (95% CI) of 1.73 (0.75; 3.99). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was 4.1% (-23.6%; 31.7%) with a risk ratio (95% CI) of 1.10 (0.58; 2.09).

In this section, results of the ESKETINSUI2001 trial are presented in detail for the ITT population.

Mean improvement in suicidal symptoms based on CGI-SS-r

Not available as CGI-SS-r was not included as an endpoint in the ESKETINSUI2001 study.

Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r

Not available as CGI-SS-r was not included as an endpoint in the ESKETINSUI2001 study.

Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r

Not available as CGI-SS-r was not included as an endpoint in the ESKETINSUI2001 study.

Response

A patient was considered to achieve response at a given time point if the improvement in MADRS total score was at least 50%. Patients who did not meet the criterion or discontinued prior to the time point for any reason were not considered to achieve response. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. The percentage of patients who achieved response directionally favored the ESK NS + SoC group over the placebo + SoC group during the double-blind treatment phase of the study. The proportion of response rates between treatment groups in percentage of patients who achieved response over time during the double-blind treatment phase is shown in Table 47. At Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was statistically significant at 26.8% (-0.1%; 53.7%) with a risk ratio (95% CI) of 1.82 (0.97; 3.40). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was 7.9% (-17.4%; 33.1%) with a risk ratio (95% CI) of 1.16 (0.72-1.85).

Table 47: Response rates (percent improvement in MADRS total score was at least 50%) over time, double-blind treatment phase, ITT analysis set - ESKETINSUI2001 (44)

n, %	ESKETINSUI2001			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	31	35		
Day 2, 24 hours post first dose				
Patients with Response of MDD	9 (29.0%)	19 (54.3%)	1.82 (0.97; 3.40); 0.0611	26.8% (-0.1% ; 53.7%); 0.0511
Day 25 (Endpoint)				
Patients with Response of MDD	15 (48.4%)	20 (57.1%)	1.16 (0.72; 1.85); 0.5409	7.9% (-17.4% ; 33.1%); 0.5403

Note: A subject is defined as a responder at a given time point if the percent improvement from baseline in MADRS total score is at least 50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder

Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD

Abbreviations: *ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Remission

According to pre-defined criteria, patients were considered to have achieved remission of MDD at a given time point if the MADRS total score was ≤ 12. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered to be in remission. The treatment difference between the groups was assessed in a post-hoc analysis using the Mantel-Haenszel estimate on RR/RD. The percentage of patients who achieved remission directionally favored the ESK NS + SoC group versus the placebo + SoC group at all timepoints during the double-blind treatment phase. See Table 48 for the remission rates in the ESKETINSUI2001 study. At Day 2, 24 hours after the first dose, the treatment risk difference (95% CI) was 14.9% (-8.5%; 38.3%) with a risk ratio (95% CI) of 1.73 (0.75; 3.99). At the last MADRS assessment during the double-blind treatment phase on Day 25, 4 hours post dose, the treatment risk difference (95% CI) was 4.1% (-23.6%; 31.7%) with a risk ratio (95% CI) of 1.10 (0.58; 2.09).

Table 48. Remission rates (MADRS total score ≤12) over time, double-blind treatment phase, ITT analysis set - ESKETINSUI2001 (44)

n, %	ESKETINSUI2001			
	Placebo + SoC	ESK NS + SoC	RR (95% CI): p-value	RD (95% CI): p-value
N	31	35		
Day 2, 24 hours post first dose				
Patients with Remission of MDD	5 (16.1%)	12 (34.3%)	1.73 (0.75; 3.99); 0.2028	14.9% (-8.5% ; 38.3%); 0.2116
Day 25 (Endpoint)				
Patients with Remission of MDD	12 (38.7%)	16 (45.7%)	1.10 (0.58; 2.09); 0.7717	4.1% (-23.6% ; 31.7%); 0.7728

Note: According to pre-defined criteria, patients were considered to have achieved remission of MDD at a given time point if the MADRS total score was ≤12. Patients who did not meet this criterion or discontinued prior to the time point for any reason were not considered to be in remission.
Note: full population analyses were performed by Mantel-Haenszel estimate of the common RR/RD
Abbreviations: *ESK NS = Esketamine Nasal Spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; RD = Risk Difference; RR = Risk Ratio; SoC = Standard of Care*

Mean change in MADRS total score from baseline

Patients who received ESK NS + SoC achieved statistically significantly reduced symptoms of depression, as measured by MADRS total score, when compared to placebo + SoC from baseline to Day 2 (~24 hours post-dose), using a two-sided significance level of 0.20 (p=0.015)(2).

The primary efficacy analysis was performed on the ITT analysis set with LOCF data using an ANCOVA model. At Day 2, 24 hours post first dose, the mean (SD) changes from baseline were -19.3 (12.02) in the ESK NS + SoC group and -12.8 (9.77) in the placebo + SoC group (see Table 49) with a statistically significant difference of LS Means (SE) of -7.2 (2.85). Despite a smaller difference, the trend toward efficiency applies throughout the full double-blind treatment phase with a difference of LS Means (SE) of -4.5 (3.14) at Day 25.

Table 49: MADRS total score changes from baseline to day 2 (24 hours post dose) and day 25 at endpoint (ANCOVA LOCF), double-blind treatment phase, ITT analysis set – ESKETINSUI2001 (44)

	Placebo + SoC n=31	Esketamine 84 mg + SoC n=35
Baseline (DB)		
N	31	35
Mean (SD)	38.8 (7.02)	38.5 (6.17)
Day 2 (DB) LOCF[a]		
N	31	35
Mean (SD)	26.0 (12.85)	19.2 (11.23)
Change from baseline at Day 2		
N	31	35
LS Mean	-11.7	-18.9
Diff. of LS Means (SE); p-value	-7.2 (2.85); 0.015	
Day 25 (DB) LOCF[a]		
N	31	35
Mean (SD)	15.8 (12.59)	12.1 (11.90)
Change from baseline at Day 25		
N	31	35
LS Mean	-21.0	-25.4
Diff. of LS Means (SE); p-value	-4.5 (3.14); 0.159	

[a]Based on analysis of covariance (ANCOVA) model with treatment and AD therapy and analysis center as factors, and baseline value as covariate.
Note: Negative change in score indicates improvement.
***Abbreviations**: ANCOVA: Analysis of Covariance; DB: Double Blind; ITT: Intention-To-Treat; LOCF: Last Observation Carried Forward; LS: Least Square; MADRS, Montgomery-Asberg Depression Scale; SD: Standard Deviation: SE: Standard Error; SoC: Standard of Care*

Adverse events

Summaries of AEs and other safety data for the double-blind treatment phase were based on all randomized patients who received at least 1 dose of study drug in the double-blind treatment phase. This is referred to as the safety analysis set (44).

The safety analysis set included 66 patients:

- 31 patients in the placebo + SoC group
- 35 patients in the ESK NS + SoC group

Summaries of AEs and other safety data from the follow-up phase were based on the follow-up analysis set. The follow-up analysis set included all patients and included all subjects who had at least 1 visit during the follow-up phase (44).

The follow-up analysis set included 49 patients:

- 22 patients from the placebo + SoC group
- 27 patients from the ESK NS + SoC group

The AEs observed in this study are consistent with the safety profile of ESK NS established in previous studies in patients with MDD with active suicidal ideation and intent, and those with treatment-resistant depression.

Most of the AEs which occurred in the ASPIRE-I trial were mild to moderate in severity with a transient and self-limiting nature which resolved within the same day of dosing as per the comprehensive risk management plan designed for ESK NS (41).

Double-blind treatment phase

There were no TEAEs leading to death during the double-blind treatment phase. There were 33 (94.3%) in the ESK NS + SoC group and 25 (80.6%) in the placebo + SoC group that experienced one or more TEAEs in the double-blind treatment phase. Table 50 provides a summary of the TEAEs experienced during the double-blind treatment phase.

Table 50: Overall summary of TEAEs, double-blind treatment phase, safety analysis set – ESKETINSUI2001 (44)

	Placebo + SoC (n=31)	Esketamine 84 mg + SoC (n=35)
Patients with 1 or more:		
TEAEs	25 (80.6%)	33 (94.3%)
TEAEs leading to death[a]	0	0
Serious TEAEs	0	4 (11.4%)
TEAEs leading to discontinuation of study agent	1 (3.2%)	5 (14.3%)

aTEAEs leading to death are based on TEAE outcome of Fatal.
Note: Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
Abbreviations: *SoC: Standard of care; TEAE: Treatment-emergent adverse event*

The TEAEs reported in at least 5% of patients in either treatment group during the double-blind treatment phase is summarized in Table 51. The most common TEAEs (reported by ≥10% patients) were observed more frequently in the ESK NS + SoC group versus placebo + SoC group were dizziness (34.3% versus 12.9%), dysgeusia (31.4% versus 16.1%), headache (31.4% versus 25.8%), paraesthesia (17.1% versus 3.2%), sedation (17.1% versus 6.5%), somnolence (11.4% versus 6.5%), dissociation (31.4% versus 12.9%), anxiety (17.1% versus 3.2%), euphoric mood (11.4% versus 6.5%), nausea (37.1% versus 3.2%), vomiting (20.0% versus 0%) and vertigo (11.4% versus 0%).

The most common TEAEs (reported by ≥5% patients) observed more frequently in the placebo + SoC treatment group was panic attack (6.5% versus 0%), flatulence (6.5% versus 2.9%), abdominal pain (6.5% versus 0%), constipation (9.7% versus 0%), toothache (6.5% versus 0%), nasal congestion (6.5% versus 0%), epitaxis (6.5% versus 0%), intranasal paraesthesia (6.5% versus 0%), rhinalgia (6.5% versus 0%), rhinorrhoea (6.5% versus 0%), blepharospasm (6.5% versus 0%), rash (9.7% versus 2.9%), upper respiratory tract infection (6.5% versus 0%) and pollakiuria (6.5% versus 0%).

Table 51: Number of patients with TEAEs with frequency of at least 5% in any treatment group by system organ class and preferred term, double-blind treatment phase, safety analysis set – ESKETINSUI2001 (44)

	Placebo + SoC (n=31)	Esketamine 84 mg + SoC (n=35)
Patients with 1 or more TEAEs	25 (80.6%)	33 (94.3%)
System organ class, Preferred term		
Nervous system disorders	16 (51.6%)	25 (71.4%)
Dizziness	4 (12.9%)	12 (34.3%)
Dysgeusia	5 (16.1%)	11 (31.4%)
Headache	8 (25.8%)	11 (31.4%)
Paraesthesia	1 (3.2%)	6 (17.1%)
Sedation	2 (6.5%)	6 (17.1%)
Somnolence	2 (6.5%)	4 (11.4%)
Hypoaesthesia	0	3 (8.6%)
Dizziness postural	0	2 (5.7%)
Psychiatric disorders	10 (32.3%)	20 (57.1%)
Dissociation	4 (12.9%)	11 (31.4%)
Anxiety	1 (3.2%)	6 (17.1%)
Euphoric mood	2 (6.5%)	4 (11.4%)
Agitation	0	3 (8.6%)
Insomnia	2 (6.5%)	3 (8.6%)
Suicidal ideation	0	2 (5.7%)
Panic attack	2 (6.5%)	0
Gastrointestinal disorders	11 (35.5%)	19 (54.3%)
Nausea	1 (3.2%)	13 (37.1%)
Vomiting	0	7 (20.0%)
Diarrhoea	0	3 (8.6%)
Dry mouth	0	3 (8.6%)
Hypoaesthesia oral	0	2 (5.7%)
Paraesthesia oral	0	2 (5.7%)
Flatulence	2 (6.5%)	1 (2.9%)
Abdominal pain	2 (6.5%)	0
Constipation	3 (9.7%)	0
Toothache	2 (6.5%)	0
General disorders and administration site conditions	2 (6.5%)	10 (28.6%)
Feeling abnormal	0	3 (8.6%)
Fatigue	1 (3.2%)	2 (5.7%)
Feeling cold	0	2 (5.7%)
Ear and labyrinth disorders	1 (3.2%)	9 (25.7%)
Vertigo	0	4 (11.4%)
Hyperacusis	0	2 (5.7%)

	Placebo + SoC (n=31)	Esketamine 84 mg + SoC (n=35)
Tinnitus	0	2 (5.7%)
Respiratory, thoracic and mediastinal disorders	8 (25.8%)	9 (25.7%)
Nasal discomfort	1 (3.2%)	3 (8.6%)
Throat irritation	0	3 (8.6%)
Oropharyngeal pain	1 (3.2%)	2 (5.7%)
Pharyngeal hypoaesthesia	0	2 (5.7%)
Nasal congestion	2 (6.5%)	1 (2.9%)
Epistaxis	2 (6.5%)	0
Intranasal paraesthesia	2 (6.5%)	0
Rhinalgia	2 (6.5%)	0
Rhinorrhoea	2 (6.5%)	0
Eye disorders	2 (6.5%)	7 (20.0%)
Vision blurred	0	3 (8.6%)
Diplopia	0	2 (5.7%)
Blepharospasm	2 (6.5%)	0
Investigations	1 (3.2%)	5 (14.3%)
Blood pressure increased	0	2 (5.7%)
Weight increased	0	2 (5.7%)
Skin and subcutaneous tissue disorders	4 (12.9%)	5 (14.3%)
Acne	0	2 (5.7%)
Hyperhidrosis	0	2 (5.7%)
Rash	3 (9.7%)	1 (2.9%)
Infections and infestations	4 (12.9%)	1 (2.9%)
Upper respiratory tract infection	2 (6.5%)	0
Renal and urinary disorders	2 (6.5%)	1 (2.9%)
Pollakiuria	2 (6.5%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: *SoC: Standard of care; TEAE: Treatment-emergent adverse event*

One or more serious TEAEs were reported by 4 (11.4%) of the 35 patients in the ESK NS + SoC group, but none were reported in the placebo + SoC group. With the exception of one serious TEAE in the ESK NS + SoC group (exacerbation of depressive symptoms) which was considered as 'possibly' related to the intranasal study agent, none of the other serious TEAEs were considered to be related to the intranasal study agent. Details of serious TEAEs in both phases of the study are discussed in the next section.

Six patients experienced 1 or more TEAEs leading to discontinuation of study agent. In the ESK NS + SoC group, 5 (14.3%) of 35 patients discontinued study agent due to TEAEs (dizziness, dysgeusia, aggression, agitation, ventricular extrasystoles, nausea, and dyspnea [one subject each]). In the placebo + SoC group, 1 (3.2%) of 31 patients discontinued the study agent due to TEAEs (dissociative disorder and panic attack).

Follow-up phase

There was no AE leading to death during the follow-up phase. There were 13 (48.1%) in the ESK NS + SoC group and 17 (77.3%) in the placebo + SoC group that experienced one or more AEs during the follow-up phase.

Table 52 provides a summary of the AEs experienced during the follow-up phase.

Table 52: Overall summary of TEAEs, follow-up phase, follow-up analysis set – ESKETINSUI2001 (44)

	Placebo + SoC (n=22)	Esketamine 84 mg + SoC (n=27)
Patients with 1 or more:		
AEs	17 (77.3%)	13 (48.1%)
AEs leading to death[a]	0	0
Serious AEs	5 (22.7%)	1 (3.7%)

aTEAEs leading to death are based on TEAE outcome of Fatal.
Note: Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
Abbreviations: *AE: Treatment-emergent adverse event; SoC: Standard of care*

The AEs reported in at least 5% of patients in either treatment group during the follow-up phase are summarized in Table 53. The most common AE (reported by ≥5% patients) observed more frequently in the ESK NS + SoC group versus placebo + SoC group was insomnia (11.1%), dry mouth, headache, tremor and pharyngitis (7.4% subjects, each). The most common AEs (reported by ≥5% patients) observed more frequently in the placebo + SoC group vs ESK NS + SoC group were suicide attempt and cellulitis (each reported by 3 out of 22 subjects [13.6%]), and headache (2 subjects [9.1%]).

Table 53: Number of patients with AEs with frequency of at least 5% in any treatment group by system organ class and preferred term, follow-up phase, follow-up analysis set – ESKETINSUI2001 (44)

	Placebo + SoC (n=22)	Esketamine 84 mg + SoC (n=27)
Patients with 1 or more AEs	17 (77.3%)	13 (48.1%)
System organ class Preferred term		
Gastrointestinal disorders	4 (18.2%)	6 (22.2%)
Dry mouth	0	2 (7.4%)
Nervous system disorders	3 (13.6%)	6 (22.2%)
Headache	2 (9.1%)	2 (7.4%)
Tremor	0	2 (7.4%)
Psychiatric disorders	8 (36.4%)	5 (18.5%)
Insomnia	0	3 (11.1%)
Suicide attempt	3 (13.6%)	0
Infections and infestations	8 (36.4%)	3 (11.1%)
Pharyngitis	0	2 (7.4%)
Cellulitis	3 (13.6%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.

Abbreviations: *AE: Treatment-emergent adverse event; SoC: Standard of care*

The number of patients experiencing one or more SAEs was higher in the placebo + SoC group, with 1 (3.7%) in the ESK NS + SoC group and 5 (22.7%) in the placebo + SoC group.

Deaths, other serious adverse events, and other significant adverse events

Deaths

There were no AEs leading to death during the double-blind treatment phase and follow-up phase of the study.

Serious adverse events

As mentioned in the above section, serious TEAEs only occurred in the ESK NS + SoC group during the double-blind phase with 4 (11.4%). An overview of SAEs experienced is shown in Table 54.

In the ESK NS + SoC group, 2 (5.7%) patients experienced an exacerbation of suicidal ideation, 1 (2.9%) experienced increased agitation, and 1 (2.9%) experienced exacerbation of depressive symptoms.

Table 54: Number of patients with treatment-emergent serious adverse events by system organ class and preferred term, double-blind treatment phase, safety analysis set – ESKETINSUI2001 (44)

	Placebo + SoC (n=31)	Esketamine 84 mg + SoC (n=35)
Patients with 1 or more serious TEAEs	0	4 (11.4%)
System organ class Preferred term		
Psychiatric disorders	0	4 (11.4%)
Suicidal ideation	0	2 (5.7%)
Agitation	0	1 (2.9%)
Depressive symptoms	0	1 (2.9%)

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: *SoC: Standard of care; TEAE: Treatment-emergent adverse event*

During the follow-up phase of the study, 6 patients experienced SAEs: 1 (3.7%) in the ESK NS + SoC group and 5 (22.7%) patients in the placebo + SoC group. A detailed list of SAEs experienced in both groups is shown in Table 55.

In the ESK NS group, 1 (3.7%) patient reported a SAE of suicidal ideation which require hospitalization but was considered by the investigator as ‘not related’ to the intranasal study agent and resolved within 16 days. 1 (1.1%) patient in respiratory, thoracic and mediastinal disorders.

In the placebo + SoC group: 1 (4.5%) patient reported an SAE of suicidal ideation but was considered by the investigator as ‘not related’ to intranasal study agent; 3 (13.6%) patients reported suicide attempts, of which 2 were considered by the investigator as ‘not related’ to intranasal study agent and 1 was considered by the investigator as ‘doubtfully’ in relation to the intranasal study agent and 1 (4.5%) patient reported cellulitis and was considered ‘not related’ to the study medication.

Table 55: Number of patients with serious adverse events by system organ class and preferred term, follow-up phase, follow-up analysis set – ESKETINSUI2001 (44)

	Placebo + SoC (n=22)	Esketamine 84 mg + SoC (n=27)
Patients with 1 or more serious AEs	5 (22.7%)	1 (3.7%)
System organ class Preferred term		
Psychiatric disorders	4 (18.2%)	1 (3.7%)
Suicidal ideation	1 (4.5%)	1 (3.7%)
Suicide attempt	3 (13.6%)	0
Infections and infestations	1 (4.5%)	0
Cellulitis	1 (4.5%)	0

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
***Abbreviations**: AE: Treatment-emergent adverse event; SoC: Standard of care*

Adverse events leading to discontinuation of study medication

The number of patients who experienced TEAEs leading to discontinuation of study agent by system organ class and preferred term is provided in Table 56. In the ESK NS + SoC group, TEAEs leading to discontinuation of study agent occurred on Day 1, Day 3, and Day 18 from start of study agent. TEAEs leading to discontinuation of study agent in the placebo + SoC group occurred on Day 4 from the start of study agent.

TEAEs leading to discontinuation of study agent in the ESK NS + SoC group had wide range of severity grades (3 TEAEs were mild, 3 TEAEs were moderate, and 1 TEAEs were severe). The severe TEAE (agitation) was considered not related to the intranasal study agent, 2 TEAEs each were considered as very likely (dysgeusia and ventricular extrasystoles), 3 TEAEs each were considered as probable (dizziness, dyspnoea and nausea) and 1 TEAE was considered as doubtful (aggression).

In the placebo + SoC group, the 2 TEAEs were considered to be of moderate severity (dissociative disorder and panic attack) and was assessed by the investigator to be possibly related to the intranasal study agent.

Table 56: Number of patients with treatment-emergent adverse events leading to discontinuation of study agent by system organ class and preferred term, double-blind treatment phase, safety analysis set – ESKETINSUI2001 (44)

	Placebo + SoC (n=31)	Esketamine 84 mg + SoC (n=35)
Patients with 1 or more TEAEs	1 (3.2%)	5 (14.3%)
System organ class Preferred term		
Nervous system disorders	0	2 (5.7%)
Dizziness	0	1 (2.9%)
Dysgeusia	0	1 (2.9%)
Psychiatric disorders	1 (3.2%)	2 (5.7%)
Aggression	0	1 (2.9%)
Agitation	0	1 (2.9%)
Dissociative disorder	1 (3.2%)	0
Panic attack	1 (3.2%)	0
Cardiac disorders	0	1 (2.9%)
Ventricular extrasystoles	0	1 (2.9%)
Gastrointestinal disorders	0	1 (2.9%)
Nausea	0	1 (2.9%)
Respiratory, thoracic and mediastinal disorders	0	1 (2.9%)
Dyspnoea	0	1 (2.9%)

Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: *SoC: Standard of care; TEAE: Treatment-emergent adverse event*

Adverse events of special interest - suicidality

2 (5.7%) out of 35 patients in the ESK NS + SoC group reported a TEAE potentially related to suicidality (suicidal ideation) during the double-blind phase but none in the placebo + SoC group. In 1 patient, the suicidal ideation was classified as being moderate in severity and was considered as 'doubtful in relation to the intranasal study agent by the investigator. The other patient, the suicidal ideation was classified as severe in severity, but was considered as 'not related' to the intranasal study agent. Both patients recovered within 5 days and were able to complete the study.

5 patients reported 1 or more AEs potentially related to suicidality in the follow-up phase: In the ESK + SoC group (1 [3.7%] patient), reported suicidal ideation, and in the placebo, + SoC group (4 patients [18.2%], reported suicidal ideation (1 patient) and attempted suicide (3 patients).

For suicidal ideation, the patient in the ESK NS + SoC group, the suicidal ideation was classified as severe in severity and was considered as 'not related' to the intranasal study agent. For the patient in the placebo + SoC group, the suicidal ideation was classified as 'severe' and was considered as 'not related' to the intranasal study agent. Both patients recovered after 16 and 17 days respectively and were able to complete the follow-up phase of the study.

For attempted suicide, all the patients were in the placebo + SoC group. 1 patient reported an attempted suicide which was classified as severe in severity and was considered as 'doubtful' in relation to the intranasal

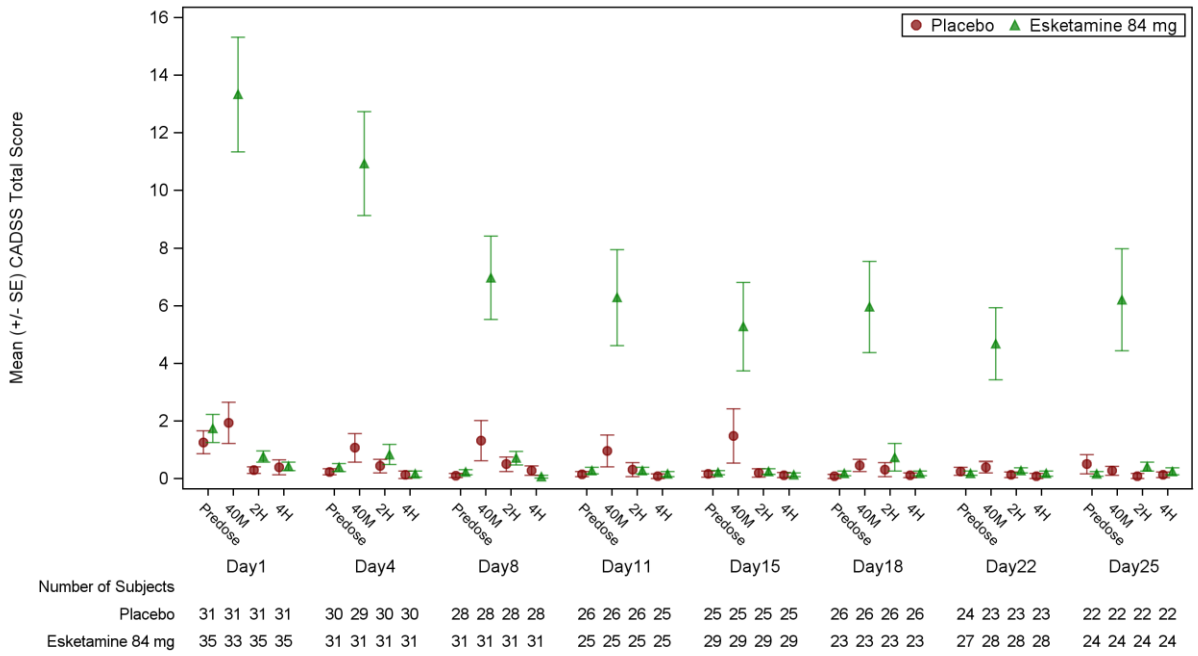
study agent. 2 patients reported attempted suicides which were classified as moderate in severity and were both considered as 'not related' to the intranasal study agent. All the patients recovered after 13, 2 and 1 days respectively and were able to complete the follow-up phase of the study.

Adverse events of special interest - dissociation

The CADSS is a clinician administered scaled used for the assessment of treatment-emergent dissociative and perceptual change symptoms. The subject's responses are recorded on a 5-point scale (0 = not at all and 4 = extremely, with a score of ≤4 considered within the normal range). Total scores range from 0 to 92, with a higher score representing a more severe condition. The CADSS were measured prior to intranasal dosing of study drug and at 40 minutes, 2 hours and 4 hours post dose, on each dosing day of the double-blind phase (42).

The percentage of patients with an increase in CADSS total score at any time during the double-blind phase was higher in the ESK NS + SoC group (85.7%) than in the placebo + SoC group (54.8%). It is notable that mean CADSS total scores peaked at 40 minutes post-dose in patients receiving ESK NS + SoC and returned towards baseline at 2 hours post-dose. In addition, the CADSS total score was reduced with an increasing number of treatment sessions underlining that the dissociative symptoms diminished over time. Results for assessment of the arithmetic mean CADSS total score over time for ESKETINSUI2001 are summarized in Figure 15.

Figure 15: Arithmetic Mean (+/- SE) CADSS total score over time observed case; double-blind treatment phase; safety analysis set – ESKETINSUI2001 (44)



CADSS: Clinician-administered dissociative states scale; SE: Standard error

Adverse events of special interest - euphoria

4 (11.4%) patients in the ESK NS + SoC group experienced euphoria during the double-blind treatment phase while 2 (6.5%) patients in the placebo + SoC group experienced euphoria. None of the euphoria TEAEs in the two treatment groups were classified as severe TEAEs in severity. In the ESK NS + SoC group, all 4 of the patients were considered as 'very likely' related to the intranasal study agent by the investigator. In the placebo + SoC group, 1 patient was considered as 'doubtful' and the other patient was considered as 'very likely' in relation to the intranasal study agent by the investigator.

6.1.3 Comparative Analyses

As mentioned in section 5.1, ESK NS + SoC has been directly compared to placebo + SoC in two Phase 3 head-to-head trials (ASPIRE-I and ASPIRE-II), and one Phase 2 head-to-head trial (ESKETINSUI2001) which informs the comparative analyses related to answering clinical question 1. Since head-to-head evidence was available from these trials, no indirect comparisons were carried out. A full summary of the results of the head-to-head trials is presented in detail for the outcomes outlined in the protocol in Table 81, Table 82, and Table 83 for each of the respective trials. To synthesize the evidence, a meta-analysis of the outcomes of the trials was carried out for ASPIRE-I, ASPIRE-II, and ESKETINSUI2001 using a random-effects model (45). Forest plots for both the main population and the subpopulation with a CGI-SS-r score ≥ 4 are available in sections 8.5 and 8.6 respectively. Results of the meta-analyses are reported as risk ratios and mean differences.

Since the ESKETINSUI2001 trial did not use the CGI-SS-r score as a measure of suicidality, the relevant outcomes outlined in the protocol using the CGI-SS-r measure as well as all the subpopulation results could not be reported. Therefore, a comparative analysis could only be done for response, remission, and mean change in MADRS total score in the main population for the ESKETINSUI2001 trial.

The absolute differences (AD) in effect for each outcome were calculated using the estimated risk ratios (RR) from the meta-analyses, the combined incidence of the comparator arm, Placebo + SoC which was used as the event rate and the formula provided in Appendix 5 the Handbook of the DMCs process and methodologies version 2.8 (46), details of which are shown in Table 84 in the appendix.

For the mean change in CGI-SS-r and MADRS scores, the difference in LS means was used in the meta-analyses for each outcome and the results were reported as the mean difference from the meta-analysis.

The results of the comparative analysis for clinical question 1 are presented in Table 84 in the appendix.

The result of the comparative analysis is presented in the next section, where the AD will be compared to the minimum clinically relevant difference set out in the DMC protocol for each outcome at the time points of interest (24 hours post first dose [Day 2] and 4 weeks after the first dose [Day 25]) (36).

Mean improvement in suicidal symptoms based on CGI-SS-r – full population

A meta-analysis was carried out to compare the mean improvement in suicidal symptoms based on CGI-SS-r scores for the full population of ASPIRE-I and ASPIRE-II trials and is summarized in Table 57. The results show that, although not statistically significant, ESK NS + SoC provided an absolute difference (negative value indicates the treatment effect in favor of ESK NS + SoC) of -0.200 on the CGI-SS-r score at 24 hours post first dose compared to placebo + SoC.

The treatment effect continues at day 25 in favor of ESK NS + SoC, with an absolute difference of -0.191 on the CGI-SS-r score compared to placebo + SoC, however, this was not statistically significant either.

The outcomes for both time points did not meet the 3-points threshold specified in the DMC protocol.

Table 57: Summary of mean improvements in suicidal symptoms based on CGI-SS-r - ASPIRE-I & ASPIRE-II in the full population

Outcome	AD (95% CI)	RD (95% CI)	p-value
Mean improvement in suicidal symptoms based on CGI-SS-r (24 hours)	-0.200 (-0.437 - 0.037)	NA	0.098*
Mean improvement in suicidal symptoms based on CGI-SS-r (Day 25)	-0.191 (-0.426 - 0.043)	NA	0.109*

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; NA, not available; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
*Note: *, p-value for AD.*

Mean improvement in suicidal symptoms based on CGI-SS-r – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 58: Summary of mean improvements in suicidal symptoms based on CGI-SS-r - ASPIRE-I & ASPIRE-II in the subpopulation with a CGI-SS-r score ≥ 4

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
*Note: *, p-value for AD.*

Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r -full population

A meta-analysis was carried out in the full population to compare the proportion of patients with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r between patients receiving ESK NS + SoC and patients receiving placebo + SoC in the full population of the ASPIRE-I and ASPIRE-II trials. The results are summarized in Table 59. The results show that at 24 hours post first dose, although not statistically significant, ESK NS + SoC was associated with a 4.41% increase in the proportion of patients with resolution of suicidal thoughts compared to placebo + SoC.

Similarly, on day 25, the meta-analysis results show that ESK NS + SoC was associated with a 3.70% increase in the proportion of patients with resolution of suicidal thoughts compared to placebo + SoC.

At both time points, however, ESK NS + SoC did not meet the 30% increase threshold specified in the DMC protocol.

Table 59: Summary of proportion with resolution of suicidal thoughts on CGI-SS-r - ASPIRE-I & ASPIRE-II in the full population

Outcome	AD (95% CI)	RD (95% CI)	p-value	Event Rate
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (24 hours)	4.41% (-4.81% - 16.36%)	1.092 (0.908 - 1.313)	0.350#	47.9%
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (Day 25)	3.70% (-3.76% - 12.13%)	1.045 (0.97 - 1.14)	0.331#	82.2%

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
Note: #, p-value for RD.

Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 60: Summary of proportion with resolution of suicidal thoughts on CGI-SS-r - ASPIRE-I & ASPIRE-II in the subpopulation with CGI=SS-R score ≥ 4

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
Note: #, p-value for RD.

Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r – full population

The results of the meta-analysis for the proportion of deterioration of suicide symptoms in the full population of the ASPIRE-I and ASPIRE-II trials are summarized in Table 61 below. At 24 hours post first dose, ESK NS + SoC was associated with a none statistically significant 0.84% increased chance of experiencing a deterioration when compared to placebo + SoC.

On day 25, placebo + SoC was associated with a none statistically significant -0.57% increase in the proportion of patients experiencing a deterioration when compared to ESK NS + SoC.

The results strongly indicate that there is no difference between the ESK NS + SoC and placebo + SoC treatment groups in the risk of deterioration. The very low risk of deterioration in both groups is likely to be due to the strong effect of the enhanced SoC with close clinical contact in the ASPIRE trials.

ESK NS + SoC was not associated with a significant increase in the deterioration of suicide symptoms during the double-blind treatment phase compared to placebo + SoC. Besides not being statistically significant, the difference is also below the 5% absolute difference threshold set out in the DMC protocol.

Table 61: Summary of proportion with deterioration of suicide symptoms on CGI-SS-r - ASPIRE-I & ASPIRE-II in the full population

Outcome	AD (95% CI)	RD (95% CI)	p-value	Event Rate
Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (24 hours)	0.84% (-2.70% - 10.64%)	1.211 (0.484 - 3.030)	0.682[#]	4.0%
Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (Day 25)	-0.57% (-1.68% - 26.70%)	0.783 (0.038 – 16.288)	0.875[#]	2.6%

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
Note: #, p-value for RD.

Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 62: Summary of proportion with deterioration of suicide symptoms on CGI-SS-r - ASPIRE-I & ASPIRE-II in the subpopulation with a CGI-SS-r score ≥ 4

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
Note: #, p-value for RD.

Response – full population

A meta-analysis was carried out in the full population to compare the proportion of patients experiencing a response between patients receiving ESK NS + SoC and patients receiving placebo + SoC in the full population of the ASPIRE-I and ASPIRE-II and & ESKETINSUI2001 trials. The results are summarized in Table 63. The results show that at 24 hours post first dose, EKS NS + SoC was associated with a statistically significant 11.51% increase in the proportion of patients experiencing a response, compared to placebo + SoC.

Similarly, on day 25, the meta-analysis results show that ESK NS + SoC was associated with an 6.22% increase in the proportion of patients experiencing a response compared to placebo + SoC.

At both time points, however, ESK NS + SoC did not meet the 20% difference threshold specified in the DMC protocol.

Table 63: Summary of response - ASPIRE-I, ASPIRE-II & ESKETINSUI2001 in the full population

Outcome	AD (95% CI)	RD (95% CI)	p-value	Event Rate
Response (24 hours)	11.51% (4.41% - 32.22%)	1.450 (1.120 - 1.877)	0.005#	25.6%
Response (Day 25)	6.22% (-3.08% - 18.55%)	1.110 (0.951 - 1.295)	0.185#	56.6%

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
Note: #, p-value for RD.

Response – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 64: Summary of response – ASPIRE I && ASPIRE II in the subpopulation with a CGI-SS-r score ≥ 4

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
Note: #, p-value for RD.

Remission – full population

A meta-analysis was carried out in the full population of the ASPIRE-I and ASPIRE-II and & ESKETINSUI2001 trials to compare the proportion of patients going into remission between patients receiving ESK NS + SoC and patients receiving placebo + SoC. The results are summarized in Table 65. The results show that at 24 hours post first dose, ESK NS + SoC was associated with a 12.67% statistically highly significant increase in the proportion of patients going into remission, compared to placebo + SoC.

Similarly, on day 25, the meta-analysis results show that ESK NS + SoC was associated with a statistically significant 12.06% increase in the proportion of patients going into remission compared to placebo + SoC.

At both time points, ESK NS + SoC came very close to the 15% minimum clinically relevant difference threshold specified in the DMC protocol.

Table 65: Summary of remission – ASPIRE I, ASPIRE II & ESKETINSUI2001 in the full population

Outcome	AD (95% CI)	RD (95% CI)	p-value	Event Rate
Remission (24 hours)	12.67% (9.38% - 53.30%)	2.211 (1.427 - 3.426)	<0.001#	10.5%
Remission (Day 25)	12.06% (3.79% - 30.92%)	1.324 (1.077 - 1.628)	0.008#	37.2%

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
Note: #, p-value for RD.

Remission – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 66: Summary of remission – ASPIRE I & ASPIRE II in the subpopulation with a CGI-SS-r score ≥ 4

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
Note: #, p-value for RD.

Mean change in MADRS total score from baseline – full population

Results from the meta-analysis for the mean change in MADRS total score from baseline for the full population of ASPIRE-I, ASPIRE-II & ESKETINSUI2001 are summarized in Table 67 below. ESK NS + SoC was associated with a statistically highly significant absolute difference (negative value indicates the treatment effect in favor of ESK NS + SoC) in MADRS total score from baseline of -4.201 at 24 hours post first dose compared to placebo + SoC.

On day 25, ESK NS + SoC continued to demonstrate its ability in reducing depressions symptoms, with a statistically highly significant absolute difference of -3.852 in MADRS total score from baseline compared to placebo + SoC.

Both outcomes meet the 3-points threshold specified in the DMC protocol and demonstrate ESK NS + SoC ability in reducing depression symptoms throughout the double-blind treatment phase compared to placebo + SoC.

Table 67: Summary of mean change in MADRS total score – ASPIRE I, ASPIRE II & ESKETINSUI2001 in the full population

Outcome	AD (95% CI)	RD (95% CI)	p-value
Mean change in MADRS total score from baseline (24 hours)	-4.201 (-6.031; -2.370)	NA	<0.001*
Mean change in MADRS total score from baseline (Day 25)	-3.852 (-5.818; -1.885)	NA	<0.001*

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; NA, not available; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
*Note: *, p-value for AD.*

Mean change in MADRS total score from baseline – subpopulation with a CGI-SS-r score ≥ 4

[redacted]

Table 68: Summary of mean change in MADRS total score – ASPIRE I & ASPIRE II in the subpopulation with a CGI-SS-r score ≥ 4

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: AD, absolute difference; CI, Confidence Interval; NA, not available; RD, relative difference; SoC, standard of care; ESK NS, esketamine nasal spray.*
*Note: *, p-value for AD.*

Adverse events

In general, the AEs experienced by patients in ASPIRE-I, ASPIRE-II, and ESKETINSUI2001 were consistent with the safety profile of ESK NS as stated in the summary of product characteristics and the recent ESK NS submission for treatment-resistant depression to the DMC (1, 47).

Most AE's which occurred was determined to not be related to ESK NS and were resolved within a few hours from the dosing period. The transient and self-limiting nature of the AEs were handled within the time frame of the comprehensive risk management program designed for ESK NS (41). Despite ESK NS being administered at a high dose of 84 mg throughout the double-blind phase, there was no major difference in the AE profile in comparison to placebo. Additionally, it should be noted that the fixed 4-week treatment period would be expected to negate any long-term AEs concerns for ESK NS as any long-term cumulative risks of ESK NS are hereby avoided.

Results for AEs potentially related to suicidality for pooled Phase III trials ASPIRE-I, ASPIRE-II, and ESKETINSUI2001 are summarized in Table 69. Overall, the rates of AEs potentially related to suicidality (including suicide attempts and one completed suicide) in Phase II and III studies were similar between the ESK NS + SoC and placebo + SoC treatment groups during the double-blind and follow-up phases.

[redacted]

Table 69: Overall incidence of TEAEs potentially related to suicidality in completed Phase II (ESKETINSUI2001) and Phase III (ASPIRE I and ASPIRE II) studies

Study, study phase	Treatment	N	Any TEAE potentially related to suicidality, n (%)	Suicide attempts and completed suicides, n (%)
Pooled ASPIRE I and ASPIRE II, DB	Placebo + SoC	225	17 (7.6%)	4 (1.8%)
	ESK NS + SoC	227	17 (7.5%)	4 (1.8%)
Pooled ASPIRE I and ASPIRE II, FU	Placebo + SoC	185	19 (10.3%)	3 (1.6%)
	ESK NS + SoC	190	21 (11.1%)	7 (3.7%)
Pooled ASPIRE I, ASPIRE II, and ESKETINSUI2001, DB	Placebo + SoC	256	17 (6.6%)	4 (1.6%)
	ESK NS + SoC	262	20 (7.6%)	4 (1.5%)
Pooled ASPIRE I, ASPIRE II, and ESKETINSUI2001, FU	Placebo + SoC	207	24 (11.6%)	6 (2.9%)
	ESK NS + SoC	217	23 (10.6%)	7 (3.2%)

Note: TEAEs in the category of suicidality included completed suicide, depression suicidal, intentional overdose, intentional self-injury, multiple drug overdose [intentional], poisoning [deliberate], self-injurious behaviour, self-injurious ideation, suicidal behaviour, suicidal ideation, suicide attempt. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

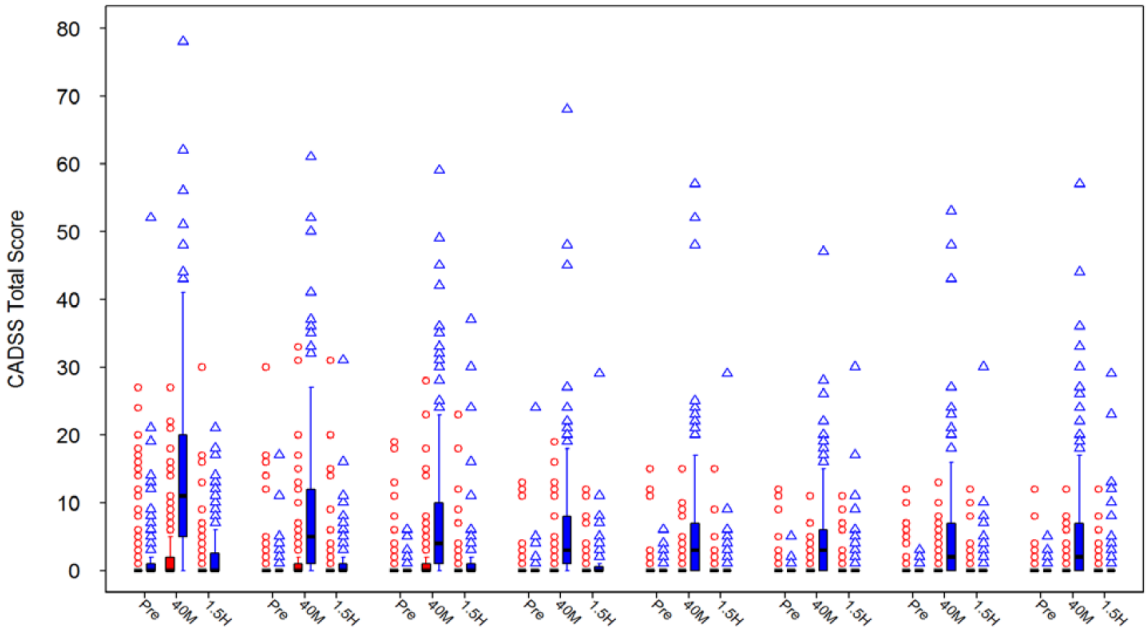
***Abbreviations**: DB: Double-blind; ESK NS: Esketamine nasal spray; FU: Follow-up; SoC: Standard of Care; TEAE: Treatment-emergent adverse events*

Dissociation (CADSS, treatment phase)

In the pooled Phase III studies, an increase in CADSS total score was observed in 67.0% to 88.9% of subjects in the ESK NS + SoC group on each dosing day, and the majority of subjects (83.6%) had an increase in CADSS total score of >4 at some point during the study. However, as with most of the AEs observed in the trial, the dissociations were within the same day of dosing and were within the window of HCP (Healthcare professional) monitoring time. Further, the CADSS total score was reduced with an increasing number of

treatment sessions underlining that the dissociative symptoms diminished over time. Despite the expectation that dissociative symptoms would only be reported in ESK NS + SoC treated subjects, some subjects in the placebo + SoC group also experienced an increase in CADSS total score on each dosing day (10.1% to 27.9%) and 11.1% experienced an increase of >4 points. Results for assessment of CADSS total score over time for ASPIRE-I and ASPIRE-II are summarized in Figure 16.

Figure 16: CADSS total score: box plot over time – pooled analysis (ASPIRE I and ASPIRE II)



Abbreviations: CADSS: Clinician-administered dissociative states scale

Conclusion

In conclusion, for the short-term treatment of adults with MDSI, ESK NS + SoC demonstrated its value compared to placebo + SoC in a number of important health outcomes, as measured by the ASPIRE-I, ASPIRE-II, and ESKETINSUI2001 in both the ITT and the subpopulation of with a CGI-SS-r score ≥ 4. In particular, ESK NS + SoC demonstrated statistically significant positive results compared to placebo + SoC in mean change in MADRs total score for baseline across both population groups throughout the entire treatment period. The AD effect of ESK NS + SoC was observed as early as 4 hours after 1st administration and was independent of the type of AD SoC being used, concomitant use of benzodiazepines, severity of disease, and history of prior suicide attempt (48-50). In addition, patients in the ESK NS + SoC arm experienced a statistically significant higher remission of MADRS score over placebo + SoC across both population groups.

Depression with suicidal ideation is a particularly severe form of depression tightly associated with the severity of depressive symptoms and with a worse treatment outcome. Therefore, the importance of the improvement of MADRS scores and remission rates is significant given that depression is the underlying disease for suicidality and the primary diagnosis of the MDD population. The ability of ESK NS to reduce depressive symptoms within 24 hours and rapidly induce remission during the critical hours and days of the psychiatric emergency highlights the importance of ESK NS as a treatment option in Danish clinical practice to ameliorate depression symptoms and avert the risk of suicidality.

6.1.4 Other Considerations

Suicide risk as a secondary endpoint

Oral ADs constitute a key component of the first-line treatment for patients with MDSI, as they target the underlying psychiatric disorder. Despite this, conventional oral ADs are of limited use in the acute treatment phase due to the delayed onset of action. Thus, there is a clear unmet medical need for a novel pharmacological treatment that can rapidly reduce symptoms of depression in this severe patient population.

The ASPIRE trials were designed to investigate the effectiveness of ESK NS + SoC at improving the overall depression symptoms as a primary objective in the MDSI population that historically has been excluded in clinical trials. The primary objective follows the primary diagnosis of MDD included in the clinical trials. The MDD diagnosis includes a range of symptoms, of which suicidal ideation/behavior is one. Thus, a key secondary endpoint of the ASPIRE trials was to investigate the effectiveness of ESK NS + SoC at reducing the severity of suicidality as it has been associated with the symptom severity of depression (5-10).

The focus on depression symptom reduction as the primary endpoint follows the intrinsic relationship between depression and suicidality, where the severity of depression serves as the underlying disease that drives the risk of suicidality (5-10), and not vice versa. This has also been confirmed by Danish clinicians in an advisory board (51). The ASPIRE trials were able to demonstrate a numerical improvement in suicidality in both arms, but there was no statistically significant difference between the treatment arms. There are several reasons why this may have been the case:

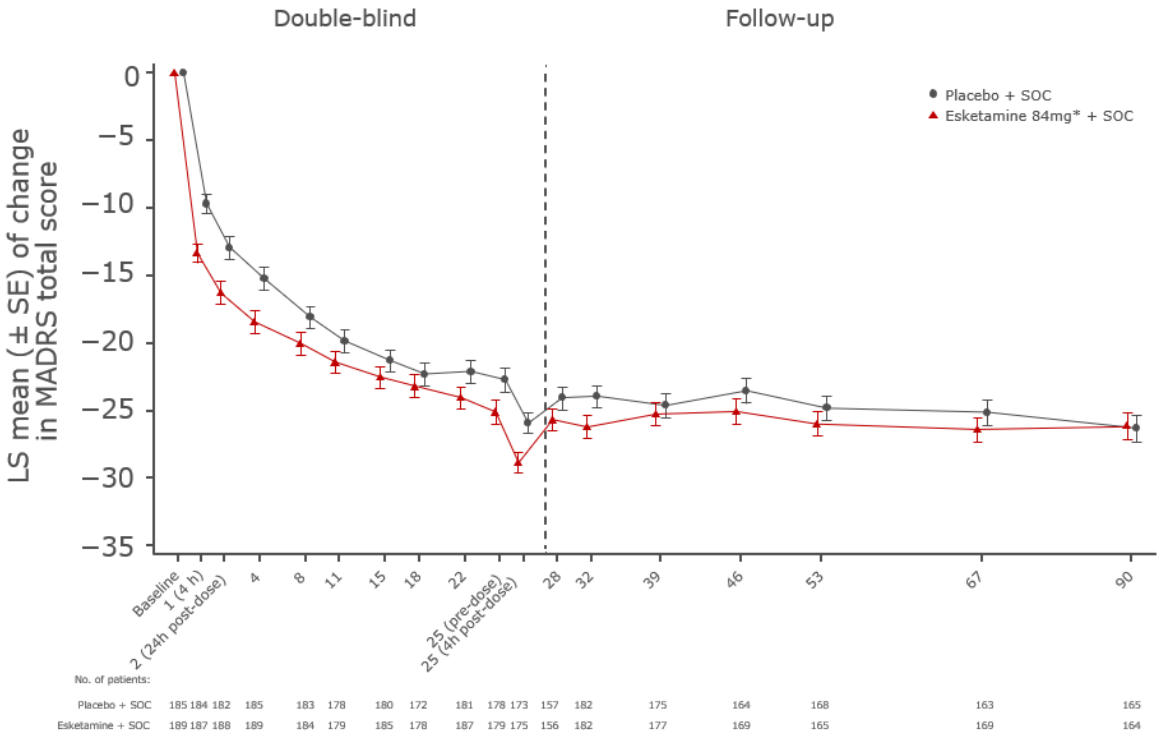
1) As a result of having suicidality as the secondary endpoint, the ASPIRE trials were not sufficiently powered to detect a significant difference in treatment effect. The lack of statistical power may have been amplified by the substantial impact of extensive and close clinical contact in the studies common to both treatment arms (52)
2) Since patients may have been in inpatient psychiatric hospitalization 48 hours before being randomized in the trials, this may have diffused the acute clinical suicidal crisis before the first dose of ESK NS could be received, thus decreasing the possible efficacy within suicidality (52)
3) Suicidal ideation and its risk factors (e.g., hopelessness, burdensomeness and loneliness) varies considerable over short periods of time complicating the overall assessment at fixed time points (13).

Even though the secondary endpoint of suicide risk was not met, this should not be seen as a failed outcome, but rather as a safety parameter in this vulnerable group of patients who have previously been excluded from clinical trials (51). The clinical trial program clearly demonstrates the ability of ESK NS to improve the underlying depressive symptoms in a very severe group of patients with suicidal ideation in urgent need of depressive symptom relief, but with limited treatment options in psychiatric emergency settings.

Continuous symptom reduction in the follow-up phase

Figure 17 illustrates the LS mean changes in MADRS total score over time for the two comparative treatment arms, ESK NS + SoC vs placebo + SoC. The figure illustrates the ability of the ESK NS + SoC arm to maintain the reduction in MADRS scores during the follow-up phase despite the discontinuation of ESK NS on Day 25. This underlines that ESK NS can safely be discontinued after 4 weeks of treatment as the symptom improvement remains stable with continuous longer-term SoC treatment.

Figure 17: ASPIRE I & II pooled analysis: Changes in MADRS total score over time*(48)



**Includes patients who had their dose reduced due to tolerability issues.*
Abbreviations: *LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; SOC, standard of care.*

Rapid effect and limitations of the current standard of care

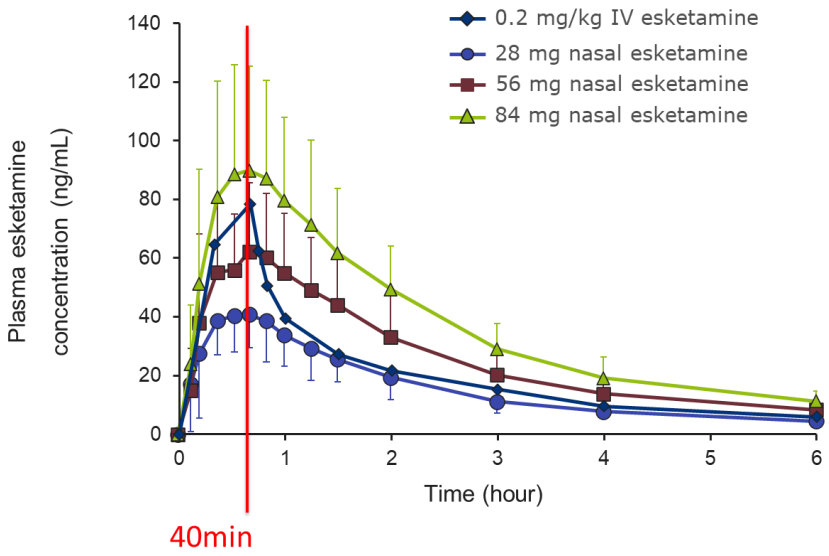
As mentioned above, oral ADs constitute a key component of the first-line treatment for patients with MDSI, as they target the underlying core symptoms of depression (i.e. MDD). Despite this, conventional oral ADs are of limited use in the acute treatment phase due to their delayed onset of action, taking up to 4-6 weeks to reach their optimal AD effect (20, 21). As such, there is a clear unmet medical need for a novel treatment that can rapidly reduce core symptoms of depression in these patients. The lack of rapid effect of oral ADs increases the length of hospitalization for these patients, places a significant strain on the personnel and internal resource capacity and prolongs the suffering for patients.

There has been a lack of new treatment options within this field, and ESK NS is the first AD with a novel mechanism of action that has been approved in the last 30 years and has been characterized as a breakthrough therapy by the FDA (2).

Pharmacokinetic profile of ESK

ESK is both able to be rapidly absorbed to provide a rapid response while also being rapidly eliminated from the patient's body, thereby limiting safety issues. Consistent with the rapid plasma clearance, dissociative symptoms and dizziness were transient and mostly resolved within 1.5 hours after dosing. As shown in Figure 18, absorption typically occurs ≤7 minutes after a dose of ESK NS, with the time to reach maximum ESK plasma concentration between 20-40 minutes after the last administration (11, 53). Notably, the rapid clearance from plasma, the short half-life and the low frequency of dosing (2x per week) led to no accumulation and a complete elimination of ESK (11, 53).

Figure 18: Pharmacokinetic profile of IV and nasal ESK (11, 53)

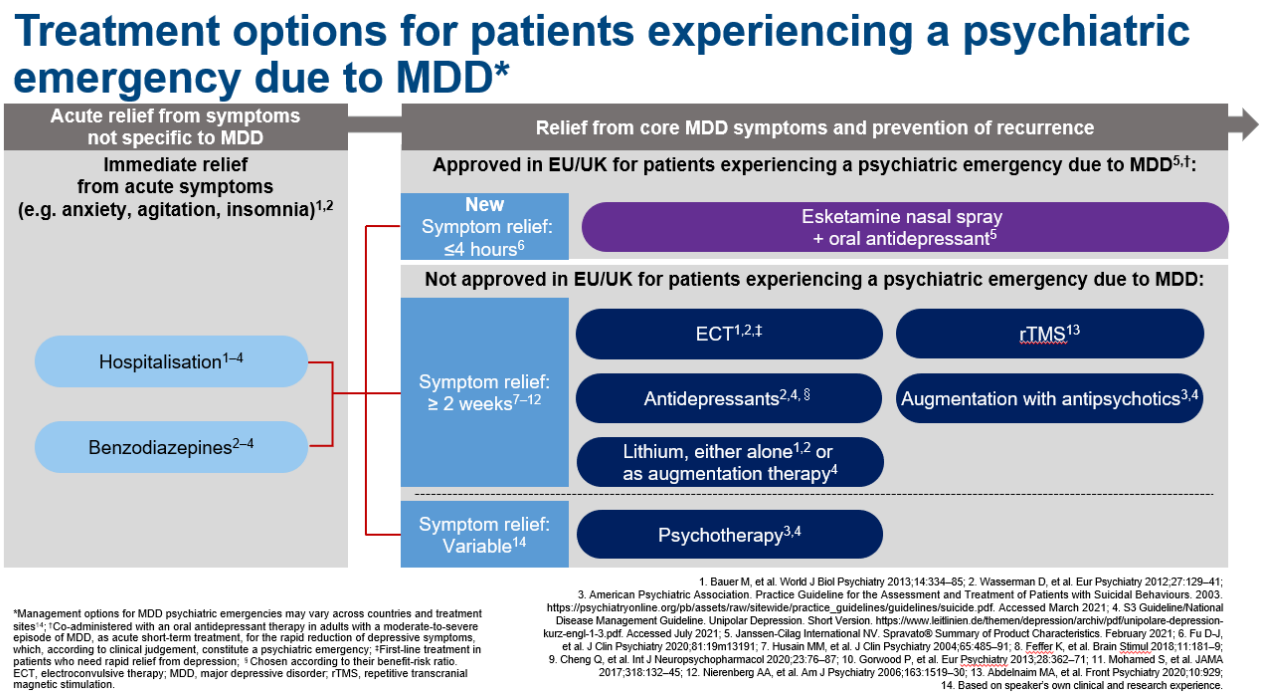


The current treatment landscape for MDD experiencing a psychiatric emergency

The current treatment landscape for rapidly acting therapies within the MDD population experiencing a psychiatric emergency remains quite limited. While hospitalization and benzodiazepines induce acute relief from symptoms that are not specific to MDD (e.g. anxiety, agitation, psychotic features and insomnia), an unmet need exists for rapid symptom relief of core MDD symptoms as outlined in Figure 19. Further, administration of benzodiazepines poses a risk of "unmasking the danger of suicide" by the emergence of suicidal ideation (54).

ESK NS + SoC is the only approved therapy within this indication that provides symptom relief of MDD within a few hours (55). Other therapies such as ECT, repetitive transcranial magnetic stimulation (rTMS), and AD therapy have not obtained regulatory approval for MDD patients experiencing a psychiatric emergency and are, despite the comprehensive clinical experience with some of them, unable to provide the same level of evidence as ESK NS + SoC for rapid-acting symptom relief in this specific and severely ill patient population. In addition, while ECT may be perceived as an effective treatment option, the recurrence of serious depression after successful ECT is common, with a Norwegian study reporting that 72% of patients suffered a relapse of depressive symptoms after an average of 13 months (median 3 months) (56).

Figure 19: Current treatment landscape within MDD patients experiencing a psychiatric emergency (55)



***Abbreviations**: ECT = Electro convulsion therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation*

Rapid response of ESK NS

To further highlight the rapid-acting nature of ESK NS + SoC, Table 70 illustrates the response rates, which is the percentage improvement in MADRS total score of at least 50%, at 4 hours post first dose from the ASPIRE-I, ASPIRE-II, and ESKETINSUI2001 trials. The difference in response rates favored ESK NS + SoC in all three studies, with a percentage difference (95% CI) of 3.6 (-7.62; 14.76) for ASPIRE-I, 19.2 (9.87; 28.60) for ASPIRE-II and 12.8 (NR) for ESKETINSUI2001 (39, 43, 44).

Table 70: Response rates (percent improvement in MADRS total score was at least 50%) at 4 hours post first dose – ASPIRE I, ASPIRE II and ESKETINSUI2001 (39, 43, 44)

n, %	ASPIRE I	
	Placebo + SoC	ESK NS + SoC
N	112	112
Day 1, 4 hours post first dose		
Patients with Response	25 (22.3%)	29 (25.9%)
Difference in % (95% CI)	-	3.6 (-7.62; 14.76)
n, %	ASPIRE II	
	Placebo + SoC	ESK NS + SoC
N	113	114
Day 1, 4 hours post first dose		
Patients with Response	8 (7.1%)	30 (26.3%)
Difference in % (95% CI)	-	19.2 (9.87; 28.60)
n, %	ESKETINSUI2001	
	Placebo + SoC	ESK NS + SoC
N	31	35
Day 1, 4 hours post first dose		
Patients with Response	4 (12.9%)	9 (25.7%)
Difference in % (95% CI)	-	12.8 (NR)

Note: A subject is defined as a responder at a given time point if the percent improvement from baseline in MADRS total score is at least 50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder

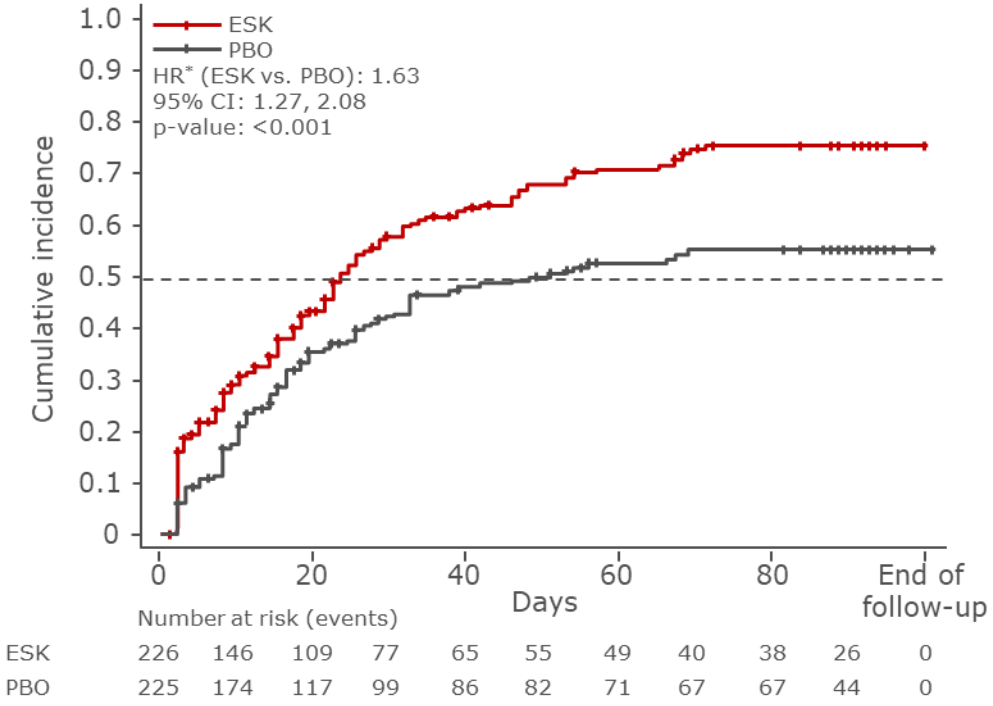
**The confidence intervals are based on Wald statistic.*

***Abbreviations**: ESK NS = esketamine nasal spray; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; SoC = standard of care*

Post-hoc analysis on stable remission in the ASPIRE trials

Pooled post-hoc analyses of the ASPIRE-I and ASPIRE-II trials also demonstrated that patients treated with ESK NS + SoC achieved first remission significantly faster than patients treated with placebo + SoC (median time, 15 vs. 23 days; HR: 1.47; 95% CI: 1.13, 1.92; p=0.005) (52). When analyzing whether this benefit was sustained over time, results from the ASPIRE trials showed that the median time to achieve stable remission (defined as MADRS score ≤12 for at least two consecutive visits) in patients treated with ESK NS + SoC was 23 days vs 50 days in patients treated with placebo + SoC (adjusted HR: 1.50; 95% CI: 1.12, 2,00; p=0.007, Figure 20).

Figure 20. Time to Stable Remission (MADRS Total Score ≤12 for 2 Consecutive Visits) (ASPIRE I and II Pooled Analyses). (52)



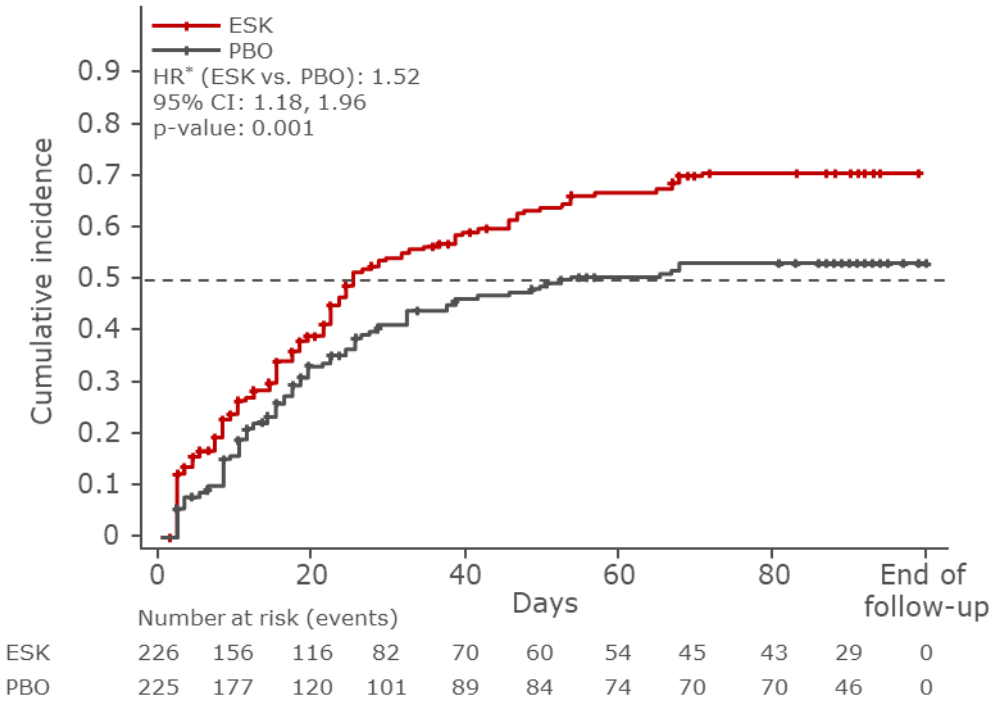
**Unadjusted HR*

Abbreviations: *CI = confidence interval; ESK = esketamine nasal spray; HR = hazard ratio; MADRS = Montgomery-Åsberg Depression Rating Scale; PBO = placebo*

At the end of the double-blind phase and follow-up phase, 54.2% and 75.0% of patients had achieved stable remission in the ESK NS + SoC arm, respectively, compared to 39.8% and 55.0% in the placebo + SoC arm, respectively (52).

A stricter analysis was further carried out which assessed the time to stable remission together with suicidality severity defined as patients with a CGI-SS-r ≤1 as a combined endpoint (52). The results showed an identical trend as noted above, and demonstrated that the median time to stable remission in patients treated with ESK NS + SoC was 25 days vs 52 days in patients treated with placebo + SoC (adjusted HR: 1.42; 95% CI: 1.06, 1.91; p=0.007, Figure 21)

Figure 21: Time to Stable Remission (MADRS Total Score ≤12 for 2 Consecutive Visits) of patients with MDD and a CGI-SS-r ≤1 (ASPIRE I and II Pooled Analyses) (52)



**Unadjusted HR*

Abbreviations: *CI = confidence interval; ESK = esketamine nasal spray; HR = hazard ratio; MADRS = Montgomery-Åsberg Depression Rating Scale; PBO = placebo*

At the end of the double-blind phase and follow-up phase, 51.8% and 71.1% of patients had achieved stable remission in the ESK NS + SoC arm, respectively, compared to 39.0% and 53.5% in the placebo + SoC arm respectively (52).

The difference in cumulative incidence of stable remission between the ESK NS + SoC and placebo + SoC arms not only remained but continued to increase in favor of ESK NS + SoC from the end of the double-blind phase to the end of the follow-up phase. This was observed despite the discontinuation of ESK NS in the ESK NS + SoC arm during the follow-up phase, which indicates a long-lasting treatment effect of ESK NS following discontinuation. Thus, acute short-term treatment with ESK NS could contribute to keeping patients on continuous long-term SoC treatment in remission following the critical period around discharge from the hospital.

Taken together, these results indicate that adding ESK NS to SoC will improve both the likelihood of achieving remission and the time to and on, remission, which is the end goal of any treatment for MDD patients (29, 57, 58).

The safety profile of ESK NS within the indicated population

As stipulated in the protocol for this submission, the expert committee wanted to understand how the current safety profile of ESK NS in this population differs in comparison to what was seen in the TRD submission of ESK NS and possible implications of using the highest dose, as well as the implications on an older population.

Safety in TRD vs ASPIRE trials

As described in Section 6.1.3 under adverse events, the AEs experienced by patients in ASPIRE-I, ASPIRE-II, and ESKETINSUI2001 were consistent with the safety profile of ESK NS as stated in the summary of product characteristics and the recent ESK NS submission for treatment-resistant depression to the DMC (1, 47). As within TRD, most AE's were resolved within a few hours from the dosing period. The transient and self-limiting nature of the AEs were handled within the time frame of the comprehensive risk management program designed for ESK NS (41). No direct comparison was formally prepared across the two patient populations of TRD and MDSI as AE reporting is variable based on the clinicians' experience and judgement. Furthermore, intranasal ESK was administered together with a newly initiated antidepressant (SSRI/SNRI) in the TRD population whereas the treatment consisted of intranasal ESK + SoC (AD monotherapy or augmentation therapy [e.g., second antidepressant, atypical antipsychotic or mood stabilizer] initiated or optimized at randomization) in the MDSI population. Therefore, AE information from clinical trials is useful for identifying drug-related AEs and for approximating rates, but not necessarily for direct comparison across different studies.

Below is a summary of the most frequently reported (≥10% of patients in either treatment group) TEAEs shown for the pooled data of the short-term trials ASPIRE I and II (MDSI, Table 71) and TRANSFORM-1 and TRANSFORM-2 (TRD, Table 72). The selection of data is based on a similar age range (18-64 years) and trial design (short-term trials). Events are presented in descending order in the ESK group and in alphabetical order for the events with the same incidence.

Table 71: Summary of most frequently reported* treatment-emergent adverse events during double-blind phase for ASPIRE I & II (59)

	Pooled ASPIRE 1/2 data	
Adverse Event	PBO + SoC (n=225)	ESK-NS + SoC (n=227)
Dizziness	31 (13.8)	87 (38.3)
Dissociation	13 (5.8)	77 (33.9)
Nausea	31 (13.8)	61 (26.9)
Somnolence	23 (10.2)	47 (20.7)
Headache	46 (20.4)	46 (20.3)
Dysgeusia	29 (12.9)	45 (19.8)
Blurred vision	11 (4.9)	27 (11.9)
Blood pressure increased	9 (4.0)	26 (11.5)
Paresthesia	7 (3.1)	26 (11.5)
Vomiting	12 (5.3)	26 (11.5)
Anxiety	17 (7.6)	23 (10.1)
Sedation	5 (2.2)	23 (10.1)

**Most frequently reported is defined as ≥10% of patients in either treatment group during the double-blind phase. Events are presented in descending order in the Esketamine group and in alphabetical order for the events with the same incidence.*

Table 72: Summary of most frequently reported* treatment-emergent adverse events for Transform I & II (53)

	Pooled TRANSFORM-1/2 data (Esketamine Product Monograph – Canada)	
Adverse Event	PBO + SSRI/SNRI (n=222)	ESK-NS + SSRI/SNRI (n=346)
Dissociation	21 (9)	142 (41)
Dizziness	17 (8)	101 (29)
Nausea	19 (9)	98 (28)

	Pooled TRANSFORM-1/2 data (Esketamine Product Monograph – Canada)	
Sedation	21 (9)	79 (23)
Vertigo	6 (3)	78 (23)
Headache	38 (17)	70 (20)
Dysgeusia	30 (14)	66 (19)
Hypoesthesia	5 (2)	63 (18)
Anxiety	14 (6)	45 (13)
Lethargy	12 (5)	37 (11)
Blood pressure increased	6 (3)	36 (10)

**Most frequently reported is defined as ≥10% of patients in either treatment group. Events are presented in descending order in the Esketamine group and in alphabetical order for the events with the same incidence*

Exclusion of elderly (≥65 years) from MDSI trials and significance of higher doses

The age range in the Phase 2 study ESKETINSUI2001 (19 to 64 years) and the Phase 3 studies ASPIRE 1 and ASPIRE 2 (18 to 64 years) was selected to confirm the efficacy and safety of ESK NS in the proposed indication in adults at a dose level of 84 mg, the dose anticipated to offer the most rapid and sustained benefit in the context of a psychiatric emergency. It was decided not to enroll elderly subjects in these studies, as the 84 mg dose had not been investigated as a starting dose for elderly patients.

Although the pharmacokinetics, efficacy, and safety of ESK (across a dose range of 28-84 mg) was well characterized in the elderly population during the TRD program, it is recognized that the new proposed patient population differs from the TRD population. The proposed dosing regimen for the new indication (i.e., starting at a dose of 84 mg) also differs from the approved TRD dosing regimen. Thus, the efficacy and safety of intranasal esketamine in elderly patients with a psychiatric emergency is currently not established.

Estimation of patients expected to be re-treated after ESK NS treatment

The expert committee had in the protocol requested an estimation of the proportion of patients who would be re-hospitalized and re-treated after completing a course of ESK + NS 84 mg (36). However, there is currently a data gap on this matter and consequently, Janssen is unable to provide an estimate of this for the DMC at this point in time.

Spaghetti plot of changes in the CGI-SS-r scores presented from baseline toto completed follow-up

The expert committee had in the protocol requested changes in the CGI-SS-R score presented graphically over the period from baseline for completed follow-up as spaghetti plots for patients with a score of 4 or above and for patients with a score of 3 or less to assess whether there is one correlation between treatment and change in suicidal symptoms over shorter time intervals and/or at the individual level. However, Janssen is unable to provide this for the DMC. The reasoning for this is that Janssen cannot share any kind of patient level data externally due to data privacy rules.

6.2 What is the value of esketamine in addition to antidepressants compared to ECT in addition to antidepressants for adult patients in the current moderate to severe depressive episode with acute increased risk of suicide?

6.2.1 Presentation of Relevant Studies

As stated in Section 5, the SLR revealed only one trial of randomized, comparative scientific evidence available for ECT, however the population of the trial was not within the indication specified by the DMC and had several internal validity issues which do not make it appropriate to use for this submission. This is a general challenge from a comparative point of view as noted in the ECT guideline by *Dansk Psykiatrisk Selskab,* emphasizing that comparative randomization trials most likely would not be allowed from an ethical aspect in modern times due to the severe, vulnerable state many ECT patients are in (34).

As stated in Section 8.1.4 which provides details on the full-text review, the systematic review showed that:

- The MDD population in the full-text articles did not have a clear inclusion of MDSI patients, rendering a population comparison inappropriate for this submission (60-67)
- In addition, one study contained MDD patients with psychosis, an exclusion criterion for this submission (66)
- There was an inclusion of TRD as opposed to MDD in one study, which is not within the scope of this submission (65)

ECT is an essential treatment option in Danish clinical practice, with established treatment effects on unipolar depression, especially within psychotic depression (15), and is recommended as first-line treatment for psychotic depression as per the *Rådet for Anvendelse af Dyr Sygehusmedicin* (14). Additionally, ECT has been shown to reduce the risk of suicide in the most severely depressed patients (68). However, the effects of ECT have generally been demonstrated in case series or cohort studies, citing limited controlled clinical trials, especially within suicidality (69).

As shown above in the findings of the SLR, the current limitations in the literature within ECT make any direct and indirect comparisons between ESK NS and ECT a difficult task for the purposes of this submission. The level of high-quality, randomized, comparative evidence required is not available for ECT within the indicated population. This is due to a combination of ethical aspects and the historical exclusion of the MDSI population from clinical trials due to the level of vulnerability of these patients (35).

ECT was an exclusion criterion in the ASPIRE trials based on the mentioned ethical concerns as well as the potential study design challenges an inclusion would have raised. Despite not including ECT as a comparator, the randomized controlled trials of ESK NS constitute the golden standard for studying causal relationships by prospectively measuring the comparative effectiveness versus SoC in a homogenous patient population identified as MDD with suicidal intent. Thus, the clinical trial program of ESK NS clearly shows the effectiveness and safety of ESK NS vs SoC in randomized controlled trials of the MDSI population, but similar evidence allowing for an indirect comparison is unfortunately not currently available for ECT.

6.2.2 Results per Study

6.2.2.1 ASPIRE-I

The results presented under clinical question 1 for EKS NS + SoC in section 6.1.3 are also representative for clinical question 2.

6.2.2.2 ASPIRE-II

The results presented under clinical question 1 for EKS NS + SoC in section 6.1.4 are also representative for clinical question 2.

6.2.2.3 ESKETINSUI2001

The results presented under clinical question 1 for EKS NS + SoC in section 6.1.5 are also representative for clinical question 2.

6.2.3 Comparative Analyses

A comparative analysis was not possible to conduct since there were no studies available to compare ESK NS + SoC directly or indirectly against ECT.

However, in the next section, aspects surrounding the practical and ethical nature of the current treatment pathway for patients with MDSI will be highlighted, and how ESK NS + SoC could positively impact the treatment pathway.

6.2.4 Other Considerations

Current treatment pathway in Denmark

Currently, there is no fast-acting pharmacological treatment option approved in routine clinical practice that induces rapid relief of depressive symptoms for adult patients with MDSI. Patients with moderate to severe depression are currently managed with SoC primarily consisting of AD therapy and psychotherapy as first-line treatments. However, these patients may still experience a psychiatric emergency and are generally admitted into psychiatric intensive care where the primary goal is to ameliorate depression severity and avert the risk of suicide. When hospitalized, AD therapy may be initiated, optimized, or augmented in the intensive care to manage the depression severity and the suicidal episode, but the benefits of the AD therapy can take up to 4-6 weeks to take full effect, limiting the utility in emergencies (20, 21). The limitations of ADs in emergency settings are supported by a Danish registry study outlining that the suicide rates were 3-4 times higher during the first 28 days after AD initiation than in the following year, which likely reflects the disease severity and the delay in mood response (70). Further, while hospitalization is generally helpful to establish a safe environment for evaluation and the initiation of treatment, the benefits are short-lived and the risk for worsening of depression and attempting and completing suicide remains high in the weeks immediately after discharge (33, 71).

The current RADS guideline for unipolar depression available by the health authorities in Denmark offers recommendations for the treatment of MDD in general but without specific guidance for the management of a psychiatric emergency including suicidality. The RADS guideline recommends that hospitalized MDD patients should be initiated/optimized on AD therapy as a first-line approach and allow 2-4 weeks after achieving the optimal dose before augmenting treatment with other pharmacologic options such as lithium or antipsychotics (14). Only after these additional medications have failed to adequately control for MDD, ECT is indicated. The guideline does not specifically indicate ECT for the treatment of suicidal risk itself, but

rather as the last line of treatment for hospitalized MDD patients. In contrast, ECT is specifically indicated as a first-line treatment for patients with psychotic depression (14).

A supplementary guideline on the use of ECT by *Dansk Psykiatrisk Selskab* (34), proposes ECT as a potential first-line treatment for MDD patients who are in need of immediate treatment to alleviate the suicide risk. Although ECT's impact on suicidality has been established in the literature, especially in decreasing the risk of suicide in those with psychotic features and aged >45 years, the comparative effectiveness is limited by the lack of randomized studies in the most severe psychiatric patients as recognized by the ECT guideline (68, 69). In addition, a recent study highlighted that ECT appears less likely to be effective in younger patients, with non-psychotic depressive episode, suicidal intent or (suspected) personality disorder (17), which underlines that ECTs treatment potential is higher in certain subpopulations. Therefore, while ECT might be an effective treatment option for several MDD subgroups, other patient groups might not be eligible for ECT, willing to accept the treatment or experience sufficient effect, and this underlines the need for new fast-acting treatment options.

According to the ECT guideline, patients will typically undergo 3 treatments of ECT per week and will receive on average a total of 12 treatments over a period of approximately 28 days (34).

Limitations within the treatment pathway

Depression with suicidal ideation is a particularly severe form of depression tightly associated with the severity of depressive symptoms (5-10) and a worse response to treatment (5, 9, 27-31). Research suggests that depression severity mediates suicidality, supporting treatment of depression as the mainstay for suicidal relief (28). Furthermore, depression symptom severity is a key driver of short-term risk of hospital encounters (27), which emphasizes that MDSI patients constitute an extremely ill subpopulation that requires prompt intervention to ameliorate depression symptom severity and avert self-harm.

In both guidelines mentioned above, there does not seem to be a clear distinction as to whether patients should receive ECT due to their MDD condition or because of their risk of suicide. In general, both guidelines appear to follow the notion that the risk of suicide is mediated by the patient's depression severity in line with the described intrinsic relationship above (14, 34). Further, the role of ECT in suicide prevention is also confounded by the fact that ECT-treated patients are among the sickest psychiatric patients, with the highest prevalence of suicidal ideation and behavior (69). In addition, there are no clear-cut inclusion criteria for ECT treatment based on the severity of suicide (such as the CGI-SS-r), but rather only on the depression severity (HAMD).

While ECT has shown to provide rapid response in the symptomatic relief of depression for patients with MDD, these effects have not been sufficiently studied in controlled clinical trials, and to a lesser degree among those at risk of suicide (69). When considered together with the limited comparative evidence available, it is difficult to compare the effects of ECT to other treatment alternatives for MDSI patients with the majority of the literature being based on case studies and cohort studies (69).

While ECT is used for severe conditions of depressive disorder in Denmark, many patients are still reluctant to receive the treatment due to the stigma attached to its use, and may prefer other, less invasive therapies (16, 17). This emphasizes the need for new treatment alternatives such as ESK NS for MDD patients experiencing a psychiatric emergency. ECT use is generally hampered by the cognitive side effects, which are also rated by patients as the most troublesome (72). During the wakening phase after an ECT session, many will have acute disturbances in consciousness and postictal disorientation, or even delirium may occur (73). ECT can cause memory impairment in patients, consisting of anterograde and retrograde amnesia.

Anterograde amnesia leads to a deficit in the learning of variable degrees in patients and may last from days to months, but it appears to depend upon techniques used in the administration of ECT (74, 75). While a meta-analysis reported that functional levels primarily normalize within 15 days (76), there is still a strong debate as to the long-lasting nature of these memory impairments (77). Retrograde amnesia is the most common persistent and critical side effect of ECT. Shortly after ECT, most patients have gaps in the memory of events that occurred before the treatment, and retrograde amnesia may extend back months to years before the course (72, 78). The memory of autobiographical information seems less affected by ECT than the memory of events of an impersonal nature (79). Although retrograde amnesia often improves during the first few months after ECT, for many patients, recovery is incomplete, with prolonged amnesia regarding events that occurred close to the time of treatment (78). The potential cognitive adverse events associated with the therapy limit the broader use of ECT treatment in psychiatry, and this leaves a need for alternative rapid-acting treatment options.

Practical considerations of ECT

The use of ECT is always carried out in a hospital setting, and as illustrated in the micro-costing analysis in the health economic submission, it is a resource-intensive treatment. Generally, the procedure requires the patient to be under general anesthesia along with other pretreatment medications such as a muscle relaxant at least an hour before the treatment (34). The treatment requires the presence of trained medical personnel including the attending psychiatrist, anesthetist, and experienced nurses (34). After the ECT treatment, the patient is monitored for any AEs that may occur afterward, which can generally take up to a day to recover from. This process is then repeated 3 times per week, for a minimum of 6 sessions (80), but on average ranges between 8-16 sessions (81, 82). The patient is required to be hospitalized during the entire process (34).

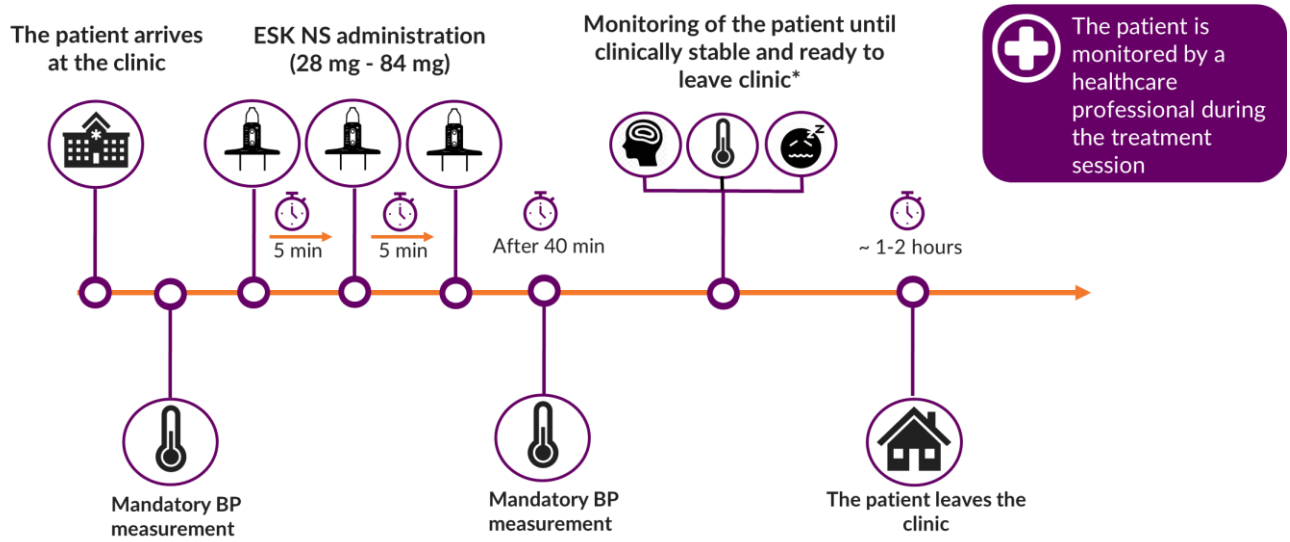
What is often not highlighted in guidelines such as the one mentioned above is how this applies in clinical practice. The application of ECT is often limited from an organizational and practical perspective as the treatment for many hospitals is performed 2-3 times per week (81, 83) on specific weekdays (e.g., Monday, Wednesday, and Fridays) with ECT often not being conducted on the weekends (82). Differences in the organization of acute ECT treatment do occur on both regional and hospital level, such as in Region Nordjylland, where intensive ECT bloc-treatment is given for a minimum of three consecutive days for patients at risk of suicide (80). Though acute ECT bloc-treatment can be initiated in special circumstances, there will still at many hospitals be a risk that MDSI patients who arrive for ECT treatment on a Friday, will not be able to receive it before Monday, or even Wednesday after proper assessment and planning have been carried out (51). In this situation, a patient may go almost a week without receiving acute treatment and in an emergency such as this, the patient must be able to receive treatment immediately. The need for rapid response is not only crucial in relieving the patient from an extreme level of suffering and resolving the immediate risk of suicidality, but also to free up personnel time and reduce the current strain on resources on the healthcare sector, particularly since hospitalization and extensive clinical contact often are required during this time.

Implementation of ESK + NS in clinical practice

In one of the previously mentioned advisory boards, the issue of how ESK NS + SoC would be implemented in clinical practice was discussed (51). The members of the advisory board agreed that the current setup for ECT in the psychiatric intensive care and the outpatient setting could be used if a positive recommendation for ESK NS was received. This would ensure a quick and efficient uptake of ESK NS in clinical practice with trained staff and the necessary facilities already available for patients eligible to receive the treatment (51). Thus, the existing infrastructure allows for implementation of ESK NS in Danish clinical practice, hereby providing immediate patient access to a rapid-acting pharmacologic treatment that only requires self-

administration by patients under the supervision of an HCP and demonstrated in Figure 22 showing a proposed treatment course in the Danish clinics.

Figure 22: Proposed course of treatment with ESK NS (11)



**Following the checklist for healthcare professionals*

Abbreviations: *BP = blood pressure; ESK NS = esketamine nasal spray*

Hospitalization and healthcare professionals resource use

As mentioned in the practical considerations of the ECT section above, the current treatment pathway for the patient population of this submission highlights the resource-intensive nature due to:

- The number of ECT procedures needed to stabilize the patient
- The number of specialized healthcare personnel needed to carry out each ECT procedure
- The need for hospitalization during the entire ECT procedure along with extensive monitoring

This resource intensiveness may present a challenge for hospitals in emergencies where immediate care needs to be allocated to each patient, but where personnel time is often a limited resource. The implementation of ESK NS into clinical practice may be resource-saving given the rapid effect combined with the simple and immediate administration which is carried out by the patients themselves under the supervision of an HCP. As highlighted in the health economic technical report of this submission, ESK NS is cost-saving in the Danish healthcare system within the scope of MDSI. Furthermore, the potential opportunity cost related to healthcare personnel time could be significant in this case and therefore an important factor to consider when assessing the recommendation of ESK NS.

Cost-utility study on ECT vs ESK NS

A recent cost-utility analysis study was conducted which compared ECT to ESK NS and found ECT to be cost-effective in all scenarios conducted by the authors (84). While this does seem to be a stark contrast to the cost-saving result mentioned above, it is important to note that this analysis was conducted for a completely different decision problem (TRD indication), which renders its conclusions irrelevant for this submission. A key differentiating aspect to highlight is the fixed 4-week treatment duration for MDSI patients which significantly limits the cost of ESK NS.

Threshold analysis of the cost-saving benefits of ESK in the Danish healthcare system

A threshold analysis was performed to investigate different costing assumptions of ECT (the details of which can be found in the health economic technical report of this submission) and the number of ECT sessions versus ESK NS. This was done to determine the number of ECT sessions that needed to be done in clinical practice before the total treatment cost overtook ESK NS treatment. As shown in Figure 23, the highlighted sections in green below indicate that ESK NS becomes cost-saving after 7 ECT treatments under all the costing assumptions. Given that for most patients, 6 ECT treatments sessions are needed as a minimum and most likely will require additional sessions ranging between 8-16 sessions are to be used on average (80-82), ESK NS will, on average, be cost-saving compared to ECT in the Danish healthcare system. This reiterates ESK NS ability to free up resources within the healthcare system while being able to provide an immediate and rapid reduction in depression symptoms in this vulnerable population group.

Figure 23: Threshold analysis with 3 different costing approaches

	DRG tariff DK	Micro costing	NICE tariff
Cost per session	DKK 2.770,00	DKK 5.228,69	DKK 5.196,46

Mean number of ECT sessions	Incremental cost (ESK vs. ECT)		
	DRG tariff DK	Micro costing	NICE tariff
1	DKK 124.521,31	DKK 122.063,34	DKK 122.095,56
2	DKK 100.231,13	DKK 95.315,20	DKK 95.379,64
3	DKK 78.198,45	DKK 70.824,56	DKK 70.921,22
4	DKK 61.037,62	DKK 51.205,76	DKK 51.334,64
5	DKK 43.876,78	DKK 31.586,96	DKK 31.748,06
6	DKK 19.586,60	DKK 4.838,82	DKK 5.032,14
7	DKK 2.425,77	-DKK 14.779,98	-DKK 14.554,44
8	-DKK 14.735,07	-DKK 34.398,78	-DKK 34.141,02
9	-DKK 36.773,51	-DKK 58.895,19	-DKK 58.605,21
10	-DKK 53.934,35	-DKK 78.513,99	-DKK 78.191,79
11	-DKK 71.095,18	-DKK 98.132,79	-DKK 97.778,37
12	-DKK 95.385,36	-DKK 124.880,94	-DKK 124.494,29
13	-DKK 112.546,20	-DKK 144.499,73	-DKK 144.080,87
14	-DKK 129.707,03	-DKK 164.118,53	-DKK 163.667,45
15	-DKK 151.749,49	-DKK 188.618,96	-DKK 188.135,65
16	-DKK 168.910,33	-DKK 208.237,76	-DKK 207.722,23
17	-DKK 186.071,16	-DKK 227.856,56	-DKK 227.308,81
18	-DKK 210.361,34	-DKK 254.604,70	-DKK 254.024,73
19	-DKK 227.522,18	-DKK 274.223,50	-DKK 273.611,31
20	-DKK 244.683,01	-DKK 293.842,30	-DKK 293.197,89

***Abbreviations**: DKK = Danish krone; DRG = Diagnose Related Group; ECT = Electroconvulsive therapy; ESK = Esketamine; NICE = National Institute for Health and Care Excellence*

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8 Appendices

8.1 Literature search

8.1.1 Inclusion & Exclusion Criteria

Table 73: Inclusion and exclusion criteria for SLR

Category	Inclusion Criteria	Exclusion Criteria
Population	Adult patients (≥18 years) with moderate to severe depression (MDD) with acute risk of suicide meeting one of following criteria*: Adult patients (≥18 years) with MDD with active suicidal ideation and intent. Patients with MDD, including TRD, with suicidal ideation and intent, or who are assessed to have active or acute suicidal ideation and active intent as defined in primary studies (clinically and/or with validated scales) Patients with primary diagnosis of MDD in inpatient settings Had ≥1 diagnoses for MDD or general depression and ≥1 diagnoses for suicidal ideation and/or suicide attempt, and treated with ≥1 antidepressants medication during hospitalization, ER visits, community setting, or other similar settings MDD in need of acute hospitalization, ER visits, or ER clinic visits	Studies that did not enroll or excluded adults who were actively suicidal or severely suicidal, having active suicidal intent or plan, had significant risk for suicide, had significant suicide ideation, or had suicidal thoughts Studies conducted in a mixed population and that did not report outcomes for MDD with active suicidal ideation and intent subgroup Studies of adults with MDD and >80% psychosis or history of psychosis Paediatric studies Studies primarily (with >80% patients) enrolling patients with comorbid substance or alcohol abuse disorder, except nicotine or caffeine Studies conducted primarily (with >80% patients) among patients with comorbid psychotic disorders, schizophrenia, bipolar disorder, personality disorders including borderline, antisocial, and obsessive-compulsive disorder, autism, dementia, or intellectual disability
Interventions/comparators	Electroconvulsive therapy Electroconvulsive therapy in addition to antidepressants	Any comparator not being electroconvulsive therapy No comparator
Outcomes†	**Efficacy and effectiveness:** At least one of the following: Response (as defined in the studies as reduction of at least 50% on MADRS) Remission (defined as MADRS score <10 or <12) Mean change from baseline in the following measures: MADRS total score, CGI-SS-r Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r **Safety:** All-cause mortality Treatment-related mortality All drug harms and tolerability and AEs (number of patients with) Overall total AEs Discontinuations overall Discontinuations due to AEs	Pharmacokinetic or pharmacodynamic or other publications that do not report data on eligible outcomes

Category	Inclusion Criteria	Exclusion Criteria
Study designs	RCTs (phase II or III), including follow-up data	Phase I RCTs, crossover RCTs Uncontrolled case series, chart reviews Case reports Single-arm trials (including uncontrolled clinical trials) and non-comparative RWE studies evaluating hospitalized MDD populations‡
Publication types	Full-text articles Trial outcomes or CSR as reported on clinicaltrials.gov when results are not available otherwise	Publications of the following types: Animal, in vitro, or genetic studies Narrative publications Editorials Conference abstracts^
Timing and language	Articles published in English language	Journal articles not available in English

** Full-text articles will be included in the SLR if ≥80% of the study population meets the inclusion criteria (the threshold of 80% was selected as it is commonly used in evidence reviews supporting NICE clinical guidelines and it is also recommended in the IQWiG methods).*

† Various measures of endpoints will be considered—including those using Kaplan-Meier curves, mean differences, hazard and odds ratios, and relative risks—based on data availability. The selection of outcomes follows HTA methodologies published by NICE and IQWiG.

‡ Non-comparative RWE studies or uncontrolled, single-arm trials in hospitalized MDD populations that do not assess a least two interventions/treatments, but otherwise meet inclusion criteria will be tagged separately.

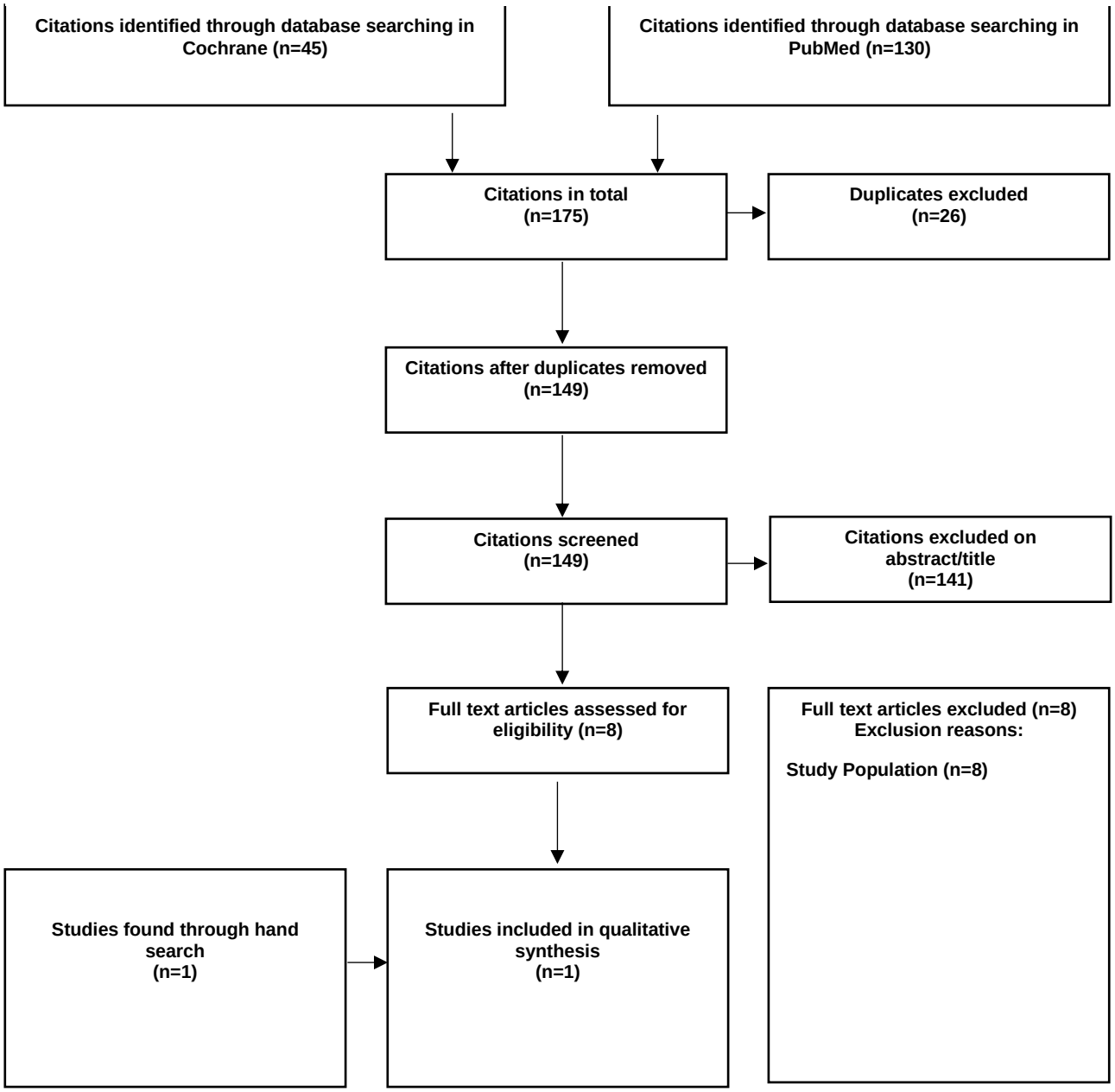
§ Individual AEs were limited to: Aggression, Anxiety, Blood pressure (increased), Blood pressure (systolic), Cystitis, Constipation, Depersonalization/derealization disorder, Dissociation, Dizziness, Dysgeusia, Euphoric mood, Hallucination (visual), Headache, Hypoeasthesia,, Impaired cognition, Increased heart rate, Insomnia, Nasal discomfort, Nausea, Parasthesia, Sedation, Somnolence, Vertigo, Vision (blurred), Vomiting.

^Conference abstract will be listed in study listing but will not be extracted during data extraction due to the insufficient background information it contains. Abstracts reporting relevant data from otherwise unpublished studies may be eligible for extraction upon request by Janssen.

***Abbreviations:** AE = adverse effect; CGI-SS-r = Clinical Global Impression of Severity of Suicidality Scale; CSR = clinical study report; ER = emergency room; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; RCT = randomized controlled trial; RWE = real-world evidence; SLR = systematic literature review*

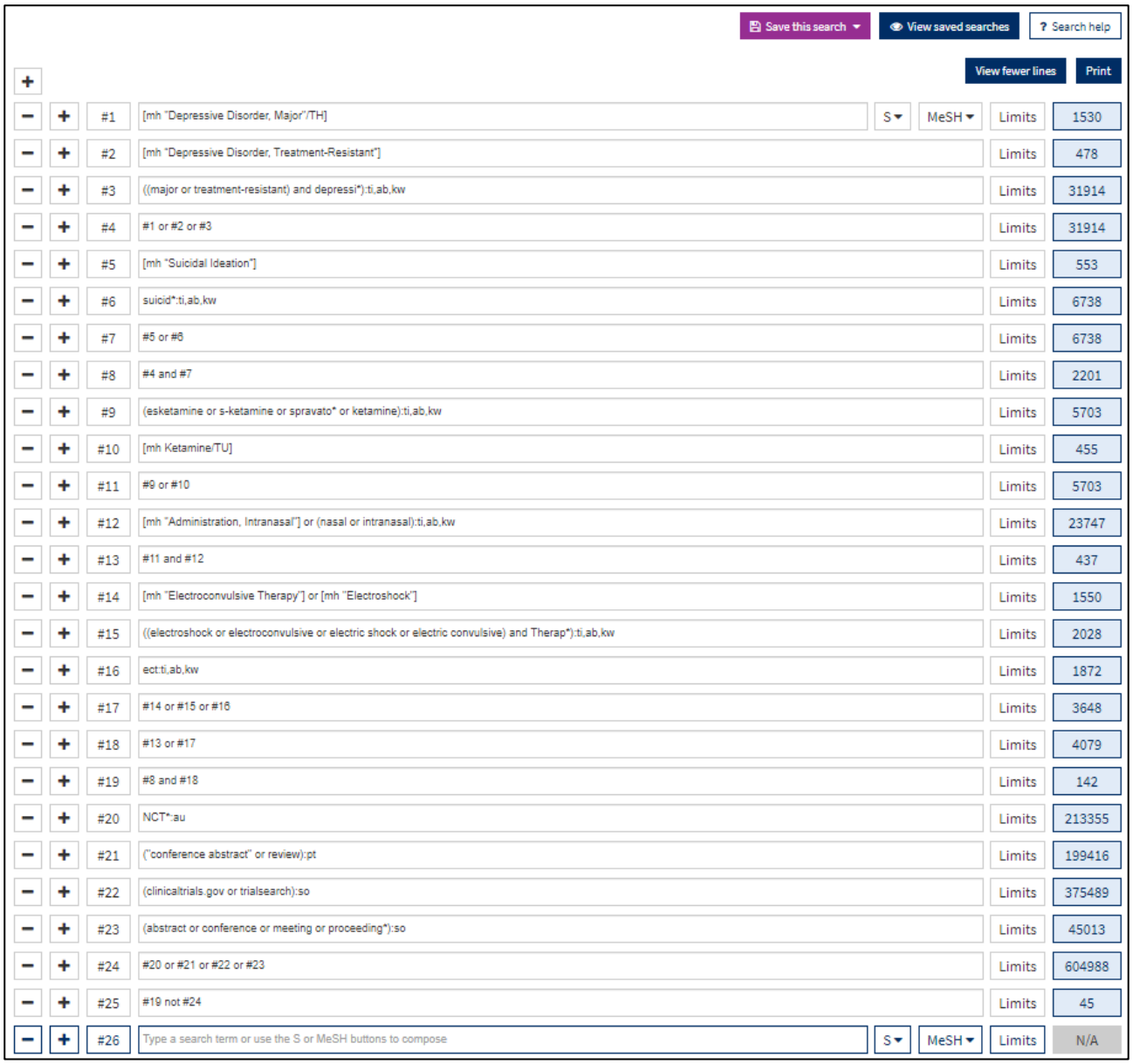
8.1.2 PRISMA Diagram

Figure 24: PRISMA flow diagram of study selection for systematic review



8.1.3 Search Strings

Figure 25: Screenshot of literature search conducted in CENTRAL (via Cochrane Library)



Save this search | View saved searches | Search help

View fewer lines | Print

#1	[mh "Depressive Disorder, Major"/TH]	S MeSH	Limits	1530
#2	[mh "Depressive Disorder, Treatment-Resistant"]		Limits	478
#3	((major or treatment-resistant) and depressi*):ti,ab,kw		Limits	31914
#4	#1 or #2 or #3		Limits	31914
#5	[mh "Suicidal Ideation"]		Limits	553
#6	suicid*:ti,ab,kw		Limits	6738
#7	#5 or #6		Limits	6738
#8	#4 and #7		Limits	2201
#9	(esketamine or s-ketamine or spravato* or ketamine):ti,ab,kw		Limits	5703
#10	[mh Ketamine/TU]		Limits	455
#11	#9 or #10		Limits	5703
#12	[mh "Administration, Intranasal"] or (nasal or intranasal):ti,ab,kw		Limits	23747
#13	#11 and #12		Limits	437
#14	[mh "Electroconvulsive Therapy"] or [mh "Electroshock"]		Limits	1550
#15	((electroshock or electroconvulsive or electric shock or electric convulsive) and Therap*):ti,ab,kw		Limits	2028
#16	ect:ti,ab,kw		Limits	1872
#17	#14 or #15 or #16		Limits	3648
#18	#13 or #17		Limits	4079
#19	#8 and #18		Limits	142
#20	NCT*:au		Limits	213355
#21	("conference abstract" or review):pt		Limits	199416
#22	(clinicaltrials.gov or trialsearch):so		Limits	375489
#23	(abstract or conference or meeting or proceeding*):so		Limits	45013
#24	#20 or #21 or #22 or #23		Limits	604988
#25	#19 not #24		Limits	45
#26	Type a search term or use the S or MeSH buttons to compose	S MeSH	Limits	N/A

Figure 26: Screenshot of literature search conducted in MEDLINE (via PubMed)

History and Search Details

Download Delete

Search	Actions	Details	Query	Results	Time
#20	•••	›	Search: **#18 NOT #19**	130	03:47:04
#19	•••	›	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]**	6,937,872	03:46:48
#18	•••	›	Search: **#7 AND #17**	283	03:46:29
#17	•••	›	Search: **#12 OR #16**	35,331	03:46:14
#16	•••	›	Search: **#13 OR #14 OR #15**	34,869	03:45:53
#15	•••	›	Search: **ECT[tiab]**	8,977	03:45:36
#14	•••	›	Search: **(electroshock[tiab] OR electroconvulsive[tiab] OR electric shock[tiab] OR electric convulsive[tiab]) AND Therap*[tiab]**	10,520	03:45:15
#13	•••	›	Search: **"Electroconvulsive Therapy"[Mesh] OR "Electroshock"[MeSH]**	29,756	03:45:00
#12	•••	›	Search: **#10 AND #11**	470	03:44:33
#11	•••	›	Search: **Administration, Intranasal[Mesh] OR nasal[tiab] OR intranasal[tiab]**	143,177	03:44:13
#10	•••	›	Search: **#8 OR #9**	20,603	03:43:55
#9	•••	›	Search: **esketamine[tiab] OR s-ketamine[tiab] OR spravato*[tiab] OR ketamine[tiab]**	19,952	03:43:40
#8	•••	›	Search: **"Esketamine" [Supplementary Concept] OR "Ketamine/therapeutic use"[Mesh]**	6,628	03:43:25
#7	•••	›	Search: **#3 AND #6**	6,727	03:43:06
#6	•••	›	Search: **#4 OR #5**	85,626	03:42:45
#5	•••	›	Search: **suicid*[tiab]**	85,166	03:42:29
#4	•••	›	Search: **"Suicidal Ideation"[Mesh]**	9,015	03:42:01
#3	•••	›	Search: **#1 OR #2**	78,532	03:41:43
#2	•••	›	Search: **(major[tiab] OR treatment-resistant[tiab]) AND depressi* [tiab]**	73,591	03:41:28
#1	•••	›	Search: **"Depressive Disorder, Major/therapy"[Mesh] OR "Depressive Disorder, Treatment-Resistant"[Mesh**	16,704	03:41:02

Showing 1 to 20 of 20 entries

8.1.4 Full Text Review

Table 74. List of excluded articles based on full text review

Reference (title, author, journal, year)	Exclusion Criteria
A Novel Strategy for Continuation ECT in Geriatric Depression: phase 2 of the PRIDE Study. Kellner CH et al. American Journal of Psychiatry. 2016. (63)	Inappropriate population group
Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. Kayser S et al. Journal of Psychiatric Research. 2011. (65)	Inappropriate population group
Bitemporal Versus High-Dose Unilateral Twice-Weekly Electroconvulsive Therapy for Depression (EFFECT-Dep): a Pragmatic, Randomized, Non-Inferiority Trial. Semkovska M et al. American Journal of Psychiatry. 2016. (67)	Inappropriate population group
Comparison of Rapid Antidepressant and Antisuicidal Effects of Intramuscular Ketamine, Oral Ketamine, and Electroconvulsive Therapy in Patients With Major Depressive Disorder: A Pilot Study. Kheirabadi D et al. Journal of Clinical Psychopharmacology. 2020. (62)	Inappropriate population group
Effects of Low-Dose Ketamine on the Antidepressant Efficacy and Suicidal Ideations in Patients Undergoing Electroconvulsive Therapy. Chen Q et al. Journal of ECT. 2020. (60)	Inappropriate population group
Relief of expressed suicidal intent by ECT: a consortium for research in ECT study. Kellner CH et al. American Journal of Psychiatry. 2005. (66)	Inappropriate population group
Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for the treatment of major depressive disorder, a randomized controlled clinical trial. Keshtkar M et al. Journal of ECT. 2011. (61)	Inappropriate population group
Suicide, attempted suicide, and relapse rates in depression. Avery D et al. JAMA Psychiatry (formerly "Archives of General Psychiatry"). 1978. (64)	Inappropriate population group

8.2 Main Characteristics of Included Studies

8.2.1 ASPIRE-I

Table 75: Main study characteristics of ASPIRE-I (3, 85)

Trial name	**ASPIRE-I**
NCT number	NCT03039192
Objective	The purpose of the study is to evaluate the efficacy of intranasal esketamine 84 milligram (mg) compared with intranasal placebo in addition to comprehensive standard of care in reducing the symptoms of Major Depressive Disorder (MDD), including suicidal ideation, in participants who are assessed to be at imminent risk for suicide, as measured by the change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at 24 hours post first dose.
Publications – title, author, journal, year	Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). Fu DJ, Ionescu DF, Li X, Lane R, Lim P, Sanacora G, et al. The Journal of Clinical Psychiatry. 2020.
Study type and design	A phase 3, double-blind, randomized, placebo-controlled, multicenter study to evaluate the efficacy and safety of intranasal esketamine in addition to comprehensive standard of care for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in adult subjects assessed to be at imminent risk for suicide.
Follow-up time	The study consisted of a screening evaluation performed within 48 hours prior to the Day 1 intranasal dose immediately followed by a 25-day double-blind treatment phase (Day 1 to 25), and a 65 day follow-up phase (Day 26 to Day 90).
Population (inclusion and exclusion criteria)	Inclusion criteria • Patient must be between the age of 18 to 64 years (inclusive) • Participant must meet Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) diagnostic criteria for Major Depressive Disorder (MDD), without psychotic features, based upon clinical assessment and confirmed by the Mini International Psychiatric Interview (MINI) • In the physician's opinion, acute psychiatric hospitalization is clinically warranted due to participant's imminent risk of suicide • Participants must have current suicidal ideation with intent, confirmed by a "Yes" response to Question B3 [Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (i.e., about killing yourself)?] and Question B10 [Intend to act on thoughts of killing yourself?] obtained from the MINI. Note: the response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If the screening period is longer than 24 hours, assessment of B3 and B10 of MINI must be repeated prior to randomization to confirm eligibility • Participant has a Montgomery Asberg Depression Rating Scale (MADRS) total score of greater than (>) 28 predose on Day 1 • As part of standard of care treatment, participant agrees to be hospitalized voluntarily for a recommended period of 5 days after randomization (may be shorter or longer if clinically warranted in the investigator's opinion) and take prescribed non-investigational antidepressant therapy(ies) for at least the duration of the double-blind treatment phase (Day 25) • Participant is comfortable with self-administration of intranasal medication and able to follow instructions provided Exclusion criteria • Participant has a current DSM-5 diagnosis of bipolar (or related disorders), antisocial personality disorder, or obsessive-compulsive disorder • Participant currently meets DSM-5 criteria for borderline personality disorder. Participant not meeting full DSM-5 criteria for borderline personality disorder but exhibiting recurrent suicidal gestures, threats, or self-mutilating behaviors should also be excluded • Participant has a current clinical diagnosis of autism, dementia, or intellectual disability • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder, or MDD with psychotic features • Participant meets the DSM-5 severity criteria for moderate or severe substance or alcohol use disorder, (except for nicotine or caffeine), within the 6 months before screening. A history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder is exclusionary

Intervention	Esketamine + Standard of care • Participants received intranasal esketamine 84 milligram (mg) two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) along with standard of care (SOC) antidepressant treatment.
Comparator	Placebo + Standard of care • Participants received intranasal placebo two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) along with standard of care antidepressant treatment.
Baseline characteristics	See Table 76
Primary and secondary endpoints	Primary outcome • Change From Baseline in Montgomery Asberg Depression Rating Scale (MADRS) Total Score at 24 Hours After the First Dose (Day 2) (Last Observation Carried Forward [LOCF] Data) During Double-blind Phase [Time Frame: Baseline (Day 1, predose) and 24 hours first post dose (Day 2)] Secondary outcome • Change From Baseline in Clinical Global Impression of Severity of Suicidality- Revised (CGI-SS-r) Score at 24 Hours After the First Dose (Day 2) (LOCF Data) During Double-blind Phase [Time Frame: Baseline (Day 1, predose) and 24 hours first post dose (Day 2)] • Number of Participants Who Achieved Remission (MADRS Total Score Less Than or Equal to [<=] 12) Through the Double-blind Phase [Time Frame: Days 1 (4 hours postdose), 2, 4, 8, 11, 15, 18, 22 and Day 25 (predose and 4 hours postdose)] • Change From Baseline in Montgomery Asberg Depression Rating Scale Total Score at Days 1, 2, 4, 8, 11, 15, 18, 22 and 25 During Double-blind Phase [Time Frame: Baseline and Days 1, 2, 4, 8, 11, 15, 18, 22 and 25 (predose and 4 hours postdose)] • Change From Baseline in Clinical Global Impression- Severity of Suicidality-Revised (CGI-SS-r) at Days 1, 2, 4, 8, 11, 15, 18, 22 and 25 During Double-blind Phase [Time Frame: Baseline and Days 1, 2, 4, 8, 11, 15, 18, 22 and 25] • Number of Participants Who Achieved Resolution of Suicidality (CGI-SS-r Score of 0 or 1) Through Double-blind Phase [Time Frame: Days 1, 2, 4, 8, 11, 15, 18, 22 and 25] • Change From Baseline in Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) Scale Total Score at Days 1, 2, 4, 8, 11, 15, 18, 22 and 25 During Double-blind Phase [Time Frame: Baseline and Days 1, 2, 4, 8, 11, 15, 18, 22 and 25] • Change From Baseline in Beck Hopelessness Scale (BHS) Total Score at Days 8 and 25 During Double-blind Phase [Time Frame: Baseline, Days 8 and 25] • Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) at Days 2, 11 and 25 During Double-blind Phase: Health Status Index [Time Frame: Baseline and Days 2, 11 and 25] • Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) at Days 2, 11 and 25 During Double-blind Phase: EQ-Visual Analogue Scale (EQ-VAS) [Time Frame: Baseline, Days 2, 11 and 25] • Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) at Days 2, 11 and 25 During Double-blind Phase: Sum Score [Time Frame: Baseline, Days 2, 11 and 25] • Change From Baseline in Quality of Life in Depression Scale (QLDS) Total Score at Days 2, 11 and 25 During Double-blind Phase [Time Frame: Baseline and Days 2, 11 and 25] • Treatment Satisfaction Questionnaire for Medication (TSQM-9) Total Score at Days 15 and 25 During Double-blind Phase [Time Frame: Days 15 and 25] • Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 5 (My Risk) Question 3 (Patient-reported FoST) Total Score at Days 1, 2, 4, 8, 11, 15, 18, 22 and 25 During Double-blind Phase [Time Frame: Baseline, Days 1, 2, 4, 8, 11, 15, 18, 22 and 25] • Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 7 - Clinician-rated FoST Total Score at Days 1, 2, 4, 8, 11, 15, 18, 22 and 25 During Double-blind Phase [Time Frame: Baseline and Days 1, 2, 4, 8, 11, 15, 18, 22 and 25] • Number of Participants With Treatment Emergent Adverse Events (TEAEs): DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With Treatment Emergent Abnormal Laboratory Values: DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With Abnormal Nasal Examinations at Day 25: DB Treatment Phase [Time Frame: At Day 25] • Number of Participants With Treatment Emergent Abnormal Electrocardiogram (ECG) Values at Any Time: DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With Abnormal Arterial Oxygen Saturation (SpO2) Levels (Less Than [<] 93%) as Assessed by Pulse Oximetry at Any Time: DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With Treatment Emergent Vital Signs Abnormalities: DB Treatment Phase [Time Frame: Up to Day 25]

	• Number of Sedated Participants as Assessed by Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Score at Any Time: DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With an Increase in Clinician-administered Dissociative States Scale (CADSS) Total Score Over Time: DB Treatment Phase [Time Frame: Days 1, 4, 8, 11, 15, 18, 22 and 25]
Method of analysis	Patients who received at least one dose of double-blind study medication who have both a baseline and a post dose evaluation for the MADRS total score were included in the full analysis set. All randomized patients who received at least one dose of double-blind study medication were included in the safety analysis set. The sample size for ASPIRE I was calculated assuming an effect size of 0.45 (based on results of the Phase II ESKETINSUI2001 trial) for the MADRS total score at 24 hours post first dose (Day 2), a one-sided significance level of 0.025, and a drop out-rate at 24 hours of 5%. Therefore, 112 patients would be needed to be randomized to each treatment group to achieve 90% power. The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model, which included factors for treatment, center, SoC AD treatment, and baseline MADRS total score as a covariate. Last observation carried forward was used for missing data.
Subgroup analyses	Prespecified subgroup analyses were conducted on sex, race, age, region, baseline MADRS total score, standard-of-care antidepressant treatment as randomized, prior suicide attempt and baseline suicide attempt within the last month using an ANCOVA model. The outcome analyzed was MADRS total score from baseline.

Table 76. Baseline characteristics and demographics of patients enrolled in ASPIRE-I (full analysis set) (39)

Characteristics	Placebo + SoC n= 112	Esketamine 84 mg + SoC n= 112	Total n= 224
Age, years, mean (SD)	37.9 (12.54)	40.8 (13.7)	39.3 (12.91)
Women, n (%)	73 (65.2)	65 (58.0)	138 (61.6)
Race, n (%)			
Asian	28 (25.0)	28 (25.0)	56 (25.0)
Black or African American	7 (6.3)	4 (3.6)	11 (4.9)
Native Hawaiian or other Pacific Islander	0	1 (0.9)	1 (0.4)
White	74 (66.1)	77 (68.8)	151 (67.4)
Other	2 (1.8)	1 (0.9)	3 (1.3)
Multiple	1 (0.9)	1 (0.9)	2 (0.9)
Weight (kg), mean (SD)	74.5 (20.66)	76.3 (22.82)	75.4 (21.74)
BMI (kg/m^2), mean (SD)	26.4 (7.13)	26.7 (6.28)	26.5 (6.70)
SoC AD treatment as randomized, n (%)			
Monotherapy	65 (58.0)	59 (52.7)	124 (55.4)
Augmentation	47 (42.0)	53 (47.3)	100 (44.6)
Baseline MADRS total score, mean (SD)	41.0 (6.29)	41.3 (5.87)	41.1 (6.07)
Baseline duration (months) of current depressive episode, median	13.3	15.9	13.7
CGI-SS-r 'moderately suicidal', n (%)	28 (25.0)	29 (26.1)	57 (25.6)
CGI-SS-r 'severely suicidal', n (%)	27 (24.1)	29 (26.1)	56 (25.1)
SIBAT: previous suicide attempt, n (%)	68 (60.7)	66 (59.5)	134 (60.1)
Suicide attempt within the last month: 'yes', n (%)	31 (27.7)	32 (28.6)	63 (28.1)

Abbreviations: AD: Antidepressant, BMI: Body Mass Index; CGI-SS-r: Clinical Global Impression of Severity of Suicidality – Revised; MADRS: Montgomery-Asberg Depression Scale; SD: Standard Deviation; SIBAT: Suicide Ideation and Behavior Assessment Tool; SoC: Standard of Care

8.2.2 ASPIRE-II

Table 77: Main study characteristics of ASPIRE-II (4, 86)

Trial name	**ASPIRE-II**
NCT number	NCT03097133
Objective	The purpose of this study is to evaluate the efficacy of intranasal esketamine 84 milligram (mg) compared with intranasal placebo in addition to comprehensive standard of care in reducing the symptoms of Major Depressive Disorder (MDD), including suicidal ideation, in participants who are assessed to be at imminent risk for suicide, as measured by the change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at 24 hours post first dose.
Publications – title, author, journal, year	Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). Ionescu DF, Fu DJ, Qiu X, Lane R, Lim P, Kasper S, et al. The International Journal of Neuropsychopharmacology. 2020.
Study type and design	A phase 3, double-blind, randomized, placebo-controlled, multicenter study to evaluate the efficacy and safety of intranasal esketamine in addition to comprehensive standard of care for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in adult subjects assessed to be at imminent risk for suicide.
Follow-up time	The study consisted of a screening evaluation performed within 48 hours prior to the Day 1 intranasal dose immediately followed by a 25-day double-blind treatment phase (Day 1 to 25), and a 65 day follow-up phase (Day 26 to Day 90).
Population (inclusion and exclusion criteria)	Inclusion criteria • Patient must be between the age of 18 to 64 years (inclusive) • Participant must meet Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) diagnostic criteria for major depressive disorder (MDD), without psychotic features, based upon clinical assessment and confirmed by the Mini International Psychiatric Interview (MINI) • Participants must have current suicidal ideation with intent, confirmed by a "Yes" response to Question B3 [Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (i.e., about killing yourself)?] AND Question B10 [Intend to act on thoughts of killing yourself?] obtained from the MINI • In the physician's opinion, acute psychiatric hospitalization is clinically warranted due to participant's imminent risk of suicide • Participant has a Montgomery Asberg Depression Rating Scale (MADRS) total score of greater than (>) 28 predose on Day 1 • As part of standard of care treatment, participant agrees to be hospitalized voluntarily for a recommended period of 14 days after randomization (may be shorter or longer if clinically warranted in the investigator's opinion) and take prescribed non-investigational antidepressant therapy(ies) for at least the duration of the double-blind treatment phase (Day 25) Exclusion criteria • Participant has a current DSM-5 diagnosis of bipolar (or related disorders), antisocial personality disorder, or obsessive compulsive disorder • Participant currently meets DSM-5 criteria for borderline personality disorder. Note: Participant not meeting full DSM-5 criteria for borderline personality disorder but exhibiting recurrent suicidal gestures, threats, or self-mutilating behaviors should also be excluded • Participant has a current clinical diagnosis of autism, dementia, or intellectual disability • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder, or MDD with psychotic features • Participant meets the DSM-5 severity criteria for moderate or severe substance or alcohol use disorder, (except for nicotine or caffeine), within the 12 months before Screening. A history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder is exclusionary • Participant has a history or current signs and symptoms of liver or renal insufficiency, clinically significant cardiac (including unstable coronary artery disease and congestive heart failure, tachyarrhythmias and recent myocardial infarction) or vascular, pulmonary, gastrointestinal, endocrine (including uncontrolled hyperthyroidism), neurologic (including current or past history of seizures except uncomplicated childhood febrile seizures with no sequelae), hematologic, rheumatologic, or metabolic (including severe dehydration/ hypovolemia) disease

	• Participant has known allergies, hypersensitivity, intolerance or contraindications to esketamine or ketamine or its excipients
Intervention	Esketamine + Standard of care • Participants received intranasal esketamine 84 milligram (mg) two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) along with standard of care (SOC) antidepressant treatment.
Comparator	Placebo + Standard of care • Participants will receive intranasal placebo two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) along with standard of care antidepressant treatment.
Baseline characteristics	See Table 78
Primary and secondary endpoints	<u>Primary outcomes</u> • Change From Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score at 24 Hours Post First Dose (Last Observation Carried Forward [LOCF] Data): Double-blind (DB) Treatment Phase [Time Frame: Baseline (Day 1, predose) and 24 hours first post dose (Day 2)] <u>Secondary outcomes</u> • Change From Baseline in Clinical Global Impression-Severity of Suicidality - Revised (CGI-SS-r) Scale at 24 Hours Post First Dose (LOCF Data): DB Treatment Phase [Time Frame: Baseline (Day 1, predose) and 24 hours first post dose (Day 2)] • Number of Participants With Remission of Major Depressive Disorder (MADRS Total Score Less Than or Equal to [<=] 12): DB Treatment Phase [Time Frame: Days 1 (4 hours [h] postdose), 2, 4, 8, 11, 15, 18, 22 and 25 (predose and 4 hours postdose)] • Change From Baseline in MADRS Total Score at 4 Hours Post First Dose at Day 1 (4 Hours Post First Dose), and 2, 4, 8, 11, 15, 18, 22 and 25: DB Treatment Phase[Time Frame: Baseline (Day 1, predose), Days 1 (4 hours postdose), 2, 4, 8, 11, 15, 18, 22 and 25 (predose and 4 hours postdose)] • Change From Baseline in CGI-SS-r Score at 4 Hours Post First Dose at Day 1 (4 Hours Post First Dose), and 2, 4, 8, 11, 15, 18, 22 and 25: DB Treatment Phase [Time Frame: Baseline (Day 1, predose), Days 1 (4 hours postdose), 2, 4, 8, 11, 15, 18, 22 and 25] • Number of Participants Who Achieved Resolution of Suicidality (CGI-SS-r Score of 0 or 1): DB Treatment Phase [Time Frame: Days 1 (4 hours postdose), 2, 4, 8, 11, 15, 18, 22 and 25] • Change From Baseline in Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) at Days 1, 2, 4, 8, 11, 15, 18, 22 and 25: DB Treatment Phase [Time Frame: Baseline (Day 1, predose), Days 1 (4 hours postdose), 2, 4, 8, 11, 15, 18, 22 and 25] • Change From Baseline in Beck Hopelessness Scale (BHS) Total Score at Days 8 and 25 in DB Treatment Phase [Time Frame: Baseline, Days 8 and 25] • Change From Baseline in European Quality of Life Group, 5-Dimension, 5-Level (EQ-5D-5L) Sum Score at Days 2, 11 and 25 of the DB Treatment Phase [Time Frame: Baseline, Days 2, 11 and 25] • Change From Baseline in European Quality of Life Group, Visual Analogue Scale (EQ-VAS) Score at Days 2, 11 and 25 of the DB Treatment Phase [Time Frame: Baseline, Days 2, 11 and 25] • Change From Baseline in EQ-5D-5L Health Status Index at Days 2, 11 and 25 of the DB Treatment Phase [Time Frame: Baseline, Days 2, 11 and 25] • Change From Baseline in Quality of Life in Depression Scale (QLDS) Total Score at Days 2, 11 and 25 of the DB Treatment Phase [Time Frame: Baseline, Days 2, 11 and 25] • Treatment Satisfaction Questionnaire for Medication (TSQM-9) Domain Score at Days 15 and 25: DB Treatment Phase [Time Frame: Days 15 and 25] • Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 5 (My Risk) Question 3 (Participant-Reported Frequency of Suicidal Thinking) Score at Days 1, 2, 4, 8, 11, 15, 18, 22 and 25: DB Treatment Phase [Time Frame: Baseline, Days 1 (4h postdose), 2, 4, 8, 11, 15, 18, 22 and 25] • Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 7 (Clinician-rated Frequency of Suicidal Thinking [FoST]) Score at Days 1, 2, 4, 8, 11, 15, 18, 22 and 25: DB Treatment Phase [Time Frame: Baseline, Days 1 (4 hours postdose), 2, 4, 8, 11, 15, 18, 22 and 25] • Number of Participants With Treatment Emergent Adverse Events (TEAEs): DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With Treatment Emergent Abnormal Laboratory Values: DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With Abnormal Nasal Examinations at Day 25: DB Treatment Phase [Time Frame: At Day 25] • Number of Participants With Treatment Emergent Abnormal Electrocardiogram (ECG) Values at Any Time: DB Treatment Phase [Time Frame: Up to Day 25]

	• Number of Participants With Abnormal Arterial Oxygen Saturation (SpO2) Levels (Less Than [<] 93%) as Assessed by Pulse Oximetry at Any Time: DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With Treatment Emergent Vital Signs Abnormalities: DB Treatment Phase [Time Frame: Up to Day 25] • Number of Sedated Participants as Assessed by Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Score at Any Time: DB Treatment Phase [Time Frame: Up to Day 25] • Number of Participants With an Increase in Clinician-administered Dissociative States Scale (CADSS) Total Score Over Time: DB Treatment Phase [Time Frame: Days 1, 4, 8, 11, 15, 18, 22 and 25]
Method of analysis	Patients who received at least one dose of double-blind study medication who have both a baseline and a post dose evaluation for the MADRS total score were included in the full analysis set. All randomized patients who received at least one dose of double-blind study medication were included in the safety analysis set. The sample size for ASPIRE II was calculated assuming an effect size of 0.45 (based on results of the Phase II ESKETINSUI2001 trial) for the MADRS total score at 24 hours post first dose (Day 2), a one-sided significance level of 0.025, and a drop out-rate at 24 hours of 5%. Therefore, 112 patients would be needed to be randomized to each treatment group to achieve 90% power. The primary efficacy variable was analyzed using an ANCOVA model, which included factors for treatment, center, SoC AD treatment, and baseline MADRS total score as a covariate. Last observation carried forward was used for missing data.
Subgroup analyses	Prespecified subgroup analyses were conducted on sex, race, age, region, baseline MADRS total score, standard-of-care antidepressant treatment as randomized, prior suicide attempt and baseline suicide attempt within the last month using an ANCOVA model. The outcome analyzed was MADRS total score from baseline and CGI-SS-r score.

Table 78: Baseline characteristics and demographics of patients enrolled in ASPIRE-II (full analysis set) (43)

Characteristics	Placebo + SoC n= 113	Esketamine 84 mg + SoC n= 114	Total n= 227
Age, years, mean (SD)	41.4 (13.43)	40.2 (12.73)	40.8 (13.07)
Women, n (%)	67 (59.3)	69 (60.5)	136 (59.9)
Race, n (%)			
American Indian or Alaska Native	1 (0.9)	0	1 (0.4)
Asian	2 (1.8)	1 (0.9)	3 (1.3)
Black or African American	8 (7.1)	7 (6.1)	15 (6.6)
Native Hawaiian or other Pacific Islander	1 (0.9)	0	1 (0.4)
White	87 (77.0)	92 (80.7)	179 (78.9)
Other	6 (5.3)	6 (5.3)	12 (5.3)
Multiple	0	2 (1.8)	2 (0.9)
Not reported	8 (7.1)	6 (5.3)	14 (6.2)
Weight (kg), mean (SD)	80.6 (22.05)	78.6 (19.62)	79.6 (20.83)
BMI (kg/m2), mean (SD)	28.3 (7.56)	27.6 (6.40)	27.9 (6.99)
SoC AD treatment as randomized, n (%)			
Monotherapy	43 (38.1)	45 (39.5)	88 (38.8)
Augmentation	70 (61.9)	69 (60.5)	139 (61.2)
Baseline MADRS total score, mean (SD)	39.9 (5.76)	39.5 (5.19)	39.7 (5.48)
Baseline duration (months) of current depressive episode, median	21.2	16.5	17.1
CGI-SS-r 'moderately suicidal', n (%)	33 (29.2)	35 (30.7)	68 (30.0)
CGI-SS-r 'severely suicidal', n (%)	28 (24.8)	17 (14.9)	45 (19.8)

Characteristics	Placebo + SoC n= 113	Esketamine 84 mg + SoC n= 114	Total n= 227
SIBAT: previous suicide attempt, n (%)	72 (63.7)	78 (68.4)	150 (66.1)
Suicide attempt within the last month: 'yes', n (%)	24 (21.2)	36 (31.6)	60 (26.4)

Abbreviations: *AD: Antidepressant, BMI: Body Mass Index; CGI-SS-r: Clinical Global Impression of Severity of Suicidality – Revised; MADRS: Montgomery-Asberg Depression Scale; SD: Standard Deviation; SIBAT: Suicide Ideation and Behavior Assessment Tool; SoC: Standard of Care*

8.2.3 ESKETINSUI2001

Table 79: Main study characteristics of ESKETINSUI2001 (2, 87)

Trial name	**ESKETINSUI2001**
NCT number	NCT02133001
Objective	The purpose of this study is to evaluate the efficacy of intranasal esketamine 84 milligram (mg) compared with intranasal placebo along with standard care treatment, in reducing the symptoms of major depressive disorder (MDD) (an affective disorder manifested by either a dysphoric mood or loss of interest or pleasure in usual activities, the mood disturbance is prominent and relatively persistent), including the risk for suicide as assessed by the Investigator, in participants who will be assessed to be at imminent risk for suicide.
Publications – title, author, journal, year	Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. American Journal of Psychiatry. 2018.
Study type and design	A phase 2, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intranasal esketamine for the rapid reduction of the Symptoms of major depressive disorder, including suicidal ideation, in subjects who are assessed to be at imminent risk for suicide.
Follow-up time	The study consisted of a screening evaluation performed within 24 to 48 hours prior to Day 1, followed by a 4-week double-blind treatment phase (Day 1 to Day 25), and then an 8 weeks posttreatment follow-up phase (Day 26 to 81).
Population (inclusion and exclusion criteria)	Inclusion criteria • Patient must be between the age of 18 to 64 years (inclusive) • Participants must meet Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnostic criteria for major depressive disorder • Participants must have current suicidal ideation with intent • In the Investigator's opinion, participant must be in need of acute psychiatric hospitalization due to imminent risk of suicide • Participant has a Montgomery Asberg Depression Rating Scale (MADRS) total score of greater than or equal to (>=) 22 predose on Day 1 • As part of standard of care treatment, participant agrees to be hospitalized voluntarily for a recommended period of 5 days after randomization (that is, through Day 5), and take prescribed non-investigational antidepressant therapy(ies) for at least the duration of the double-blind treatment phase (Day 25) Exclusion criteria • Participant has a current clinical diagnosis of bipolar or related disorders, intellectual disability, or cluster b personality disorder (example, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, and narcissistic personality disorder) • Participant meets DSM-IV criteria for borderline personality disorder, based on clinical interview • Participant has a current or prior diagnosis of a psychotic disorder, major depressive disorder (MDD) with psychosis, or obsessive-compulsive disorder • Participant with a history or current signs and symptoms of liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disturbances • Participant has uncontrolled hypertension (systolic blood pressure greater than [>] 160 millimeter of mercury [mmHg] or diastolic blood pressure > 90 mmHg) despite diet, exercise or a stable dose of an allowed anti-hypertensive treatment at Screening; or any past history of hypertensive crisis
Intervention	Esketamine + Standard of care • Participants received intranasal esketamine 84 milligram (mg) two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) along with standard of care (SOC) antidepressant treatment.
Comparator	Placebo + Standard of care • Participants received intranasal placebo two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) along with standard of care (SOC) antidepressant treatment.
Baseline characteristics	See Table 80

Primary and secondary endpoints	Primary outcomes • Change From Baseline to Day 1: 4-Hour Post-dose in Montgomery Asberg Depression Rating Scale (MADRS) Total Score (Double-blind Phase) [Time Frame: Baseline (Day 1-Predose) to Day 1: 4-hours post-dose] Secondary outcomes • Percentage of Participants With Sustained Response Based on MADRS Total Score (Double-blind Phase) [Time Frame: Day 1 to Day 25] • Change From Baseline to Day 2 in MADRS Total Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Day 2] • Change From Baseline to Double-blind Phase-End Point (Day 25) in MADRS Total Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Double-blind Phase-End Point (Day 25)] • Percentage of Participants With Response Based on MADRS Total Score During the Double-Blind Phase [Time Frame: Day 1 (4 hours postdose), Day 2 (double blind phase), Double blind phase -Endpoint (Day 25)] • Percentage of Participants With Response Based on MADRS Total Score at Follow up Phase Endpoint [Time Frame: Follow up phase-endpoint (Day 81)] • Change From Baseline to Day 1: 4-hours Post-dose in Suicide Ideation and Behavior Assessment Tool (SIBAT)-Clinical Global Judgment of Suicide Risk (CGJ-SR) Module 8 Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Day 1: 4-hours Postdose] • Change From Baseline to Day 2 in Suicide Ideation and Behavior Assessment Tool (SIBAT)-Clinical Global Judgment of Suicide Risk (SIBAT CGJ-SR) Module 8 Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Day 2] • Change From Baseline to Double-blind Phase-Endpoint (Day 25) Suicide Ideation and Behavior Assessment Tool (SIBAT)-Clinical Global Judgment of Suicide Risk (SIBAT CGJ-SR) Module 8 (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Double-blind Phase-Endpoint (Day 25)] • Change From Baseline to Follow-up Phase-Endpoint (Day 81) in Suicide Ideation and Behavior Assessment Tool (SIBAT)-Clinical Global Judgment of Suicide Risk Score (Follow-up Phase) [Time Frame: Baseline (Day 1-predose) to Follow-up Phase-Endpoint (Day 81)] • Change From Baseline to Day 1: 4- Hours Postdose in SIBAT-Patient-Reported Global Assessment of Suicide Risk (Module 6) Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Day 1: 4-hours postdose] • Change From Baseline to Day 2 in Suicide Ideation and Behavior Assessment Tool Patient-Reported Global Assessment of Suicide Risk (Module 6) Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Day 2] • Change From Baseline to Double Blind Phase-Endpoint (Day 25) in Suicide Ideation and Behavior Assessment Tool Patient-Reported Global Assessment of Suicide Risk (Module 6) Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Double-blind Phase-Endpoint (Day 25)] • Change From Baseline to Follow-up Phase-Endpoint (Day 81) in Suicide Ideation and Behavior Assessment Tool Patient-Reported Global Assessment of Suicide Risk (Module 6) Score (Follow-up Phase) [Time Frame: Baseline (Day 1-predose) to Follow-up Phase Endpoint (Day 81)] • Change From Baseline to Day 1: 4-Hours Postdose in Beck Scale for Suicidal Ideation (BSS) Total Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Day 1: 4-hours postdose] • Change From Baseline to Day 2 in Beck Scale for Suicidal Ideation (BSS) Total Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Day 2] • Change From Baseline to Double-blind Phase-Endpoint (Day 25) in Beck Scale for Suicidal Ideation Total Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Double-blind Phase-endpoint (Day 25)] • Change From Baseline to Follow-up Phase-Endpoint (Day 81) in Beck Scale for Suicidal Ideation Total Score (Follow-up Phase) [Time Frame: Baseline (Day 1-predose) to Follow-up Phase-Endpoint (Day 81)] • Change From Baseline to Day 1: 4-Hours Postdose in Beck Hopelessness Scale (BHS) Total Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Day 1: 4-hours Postdose] • Change From Baseline to Double-blind Phase-Endpoint (Day 25) in Beck Hopelessness Scale Total Score (Double-blind Phase) [Time Frame: Baseline (Day 1-predose) to Double-blind Phase-Endpoint (Day 25)]
Method of analysis	The sample size for the Phase II ESKETINSUI2001 trial was determined based on the assumption of a treatment difference of at least six points in the mean change from baseline to Day 1 (four hours post dose) in MADRS total score between esketamine and placebo groups. A standard deviation of nine was used for both groups. Using a 2-sample t-test, 32 patients in each group were required to detect the treatment difference of six points with a power of 91% at an overall one-sided significance level of 0.10. Therefore, assuming 8% of randomized patients discontinue before providing post-baseline efficacy measurements, 35 patients were required for each treatment group.

	The primary efficacy analyses in the Phase II ESKETINSUI2001 trial was based on the intention-to-treat (ITT) analysis set, which included all randomized patients who received at least one dose of study drug and had both the baseline and the Day 1, four hours post dose values for the MADRS total score. The primary efficacy analysis was analyzed using an ANCOVA model, with factors for treatment, center, AD treatment, and baseline score as a continuous covariate. The comparison between esketamine and placebo was tested at the one-sided significance level of 0.10 (equivalent to a two-sided significance level of 0.20).

Table 80. Baseline characteristics and demographics of patients enrolled in ESKETINSUI2001 (ITT) (44)

Characteristics	Placebo + SoC n=31	Esketamine 84 mg + SoC n=35	Total n=66
Age, years, mean (SD)	36.0 (12.82)	35.7 (13.40)	35.8 (13.03)
Women, n (%)	21 (67.7)	22 (62.9)	43 (65.2)
Race, n (%)			
White	15 (48.4)	20 (57.1)	35 (53.0)
Black or African American	13 (41.9)	12 (34.3)	25 (37.9)
Asian	0	1 (2.9)	1 (1.5)
Multiple	1 (3.2)	0	1 (1.5)
Other	2 (6.5)	0	2 (3.0)
Not reported	0	2 (5.7)	2 (3.0)
Weight (kg), mean (SD)	76.1 (18.83)	83.5 (23.86)	80.0 (21.79)
BMI (kg/m^2), mean (SD)	26.8 (6.62)	30.1 (9.49)	28.5 (8.37)
SoC AD treatment as randomized, n (%)			
Monotherapy	25 (80.6)	25 (71.4)	50 (75.8)
Augmentation	6 (19.4)	10 (28.6)	16 (24.2)
Baseline MADRS total score, mean (SD)	38.8 (7.02)	38.5 (6.17)	38.6 (6.53)
SIBAT: previous suicide attempt, n (%)	21 (67.7)	20 (57.1)	41 (62.1)
Suicide attempt within the last month: 'yes', n (%)	13 (61.9)	11 (55.0)	24 (58.5)

Abbreviations: AD: Antidepressant, BMI: Body Mass Index; CGJ-SR: Clinical Global Judgment of Suicide Risk; ITT: Intention-To-Treat; MADRS: Montgomery-Asberg Depression Scale; SD: Standard Deviation; SIBAT: Suicide Ideation and Behavior Assessment; SoC: Standard of Care

8.3 Results per study

Table 81: Results of the ASPIRE-I study

Trial name: ASPIRE I						
NCT number: NCT03039192						
	Data extracted from ASPIRE-I			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Mean improvement in suicidal symptoms based on CGI-SS-r (24 hours)	ESK-NS 84 mg + SoC	111	-1.5*	-0.3**	-0.59; 0.08**	*Reported as the change from baseline least square mean of CGI-SS-r per treatment as stated in ASPIRE-I. **No relative difference in effect is reported, but the difference in change from baseline least square means of CGI-SS-r as stated in ASPIRE-I.
	PBO + SoC	112	-1.3*			
Mean improvement in suicidal symptoms based on CGI-SS-r (Day 25)	ESK-NS 84 mg + SoC	111	-2.7*	-0.2**	-0.54; 0.09**	*Reported as the change from baseline least square mean of CGI-SS-r per treatment as stated in ASPIRE-I. **No relative difference in effect is reported, but the difference in change from baseline least square means of CGI-SS-r as stated in ASPIRE-I.
	PBO + SoC	112	-2.5*			
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Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (24 hours)	ESK-NS 84 mg + SoC	56/107	52.34%	1.12*	0.88-1.44*	*Data based on post-hoc full population analysis of ASPIRE-I. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	53/109	48.62%			
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (Day 25)	ESK-NS 84 mg + SoC	91/107	85.05%	1.05*	0.93-1.19*	*Data based on post-hoc full population analysis of ASPIRE-I. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	88/109	80.73%			
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Proportion of patients with deterioration defined as	ESK-NS 84 mg + SoC	7/114	6.14%	1.47*	0.42-5.15*	*Data based on post-hoc full population analysis of ASPIRE-I. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.

exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (24 hours)	PBO + SoC	4/112	3.57%			
Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (Day 25)	ESK-NS 84 mg + SoC	3/114	2.63%	4.00*	0.35-45.22*	*Data based on post-hoc full population analysis of ASPIRE-I. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	1/112	0.89%			
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Response (24 hours)	ESK-NS 84 mg + SoC	38/114	33.33%	1.21*	0.82-1.78*	*Data based on post-hoc full population analysis of ASPIRE-I. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	30/112	26.79%			
Response (Day 25)	ESK-NS 84 mg + SoC	78/114	68.42%	1.21*	0.97-1.51*	*Data based on post-hoc full population analysis of ASPIRE-I. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	62/112	55.36%			

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Remission (24 hours)	ESK-NS 84 mg + SoC	21/114	18.42%	2.31*	1.09-4.93*	*Data based on post-hoc full population analysis of ASPIRE-I. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	10/112	8.93%			
Remission (Day 25)	ESK-NS 84 mg + SoC	60/114	53.63%	1.39*	1.03-1.87*	*Data based on post-hoc full population analysis of ASPIRE-I. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	42/112	37.5%			
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Mean change in MADRS total score from baseline (24 hours)	ESK-NS 84 mg + SoC	111	-15.9*	-3.8**	-6.56; -1.09**	*Reported as the change from baseline least square mean of MADRS per treatment as stated in ASPIRE-I. **No relative difference in effect is reported, but the difference in change from baseline least square means of MADRS as stated in ASPIRE-I.
	PBO + SoC	112	-12.0*			
Mean change in MADRS total score from baseline (Day 25)	ESK-NS 84 mg + SoC	111	-28.1*	-4.9**	-7.60; -2.12**	*Reported as the change from baseline least square mean of MADRS per treatment as stated in ASPIRE-I. **No relative difference in effect is reported, but the difference in change from baseline least square means of MADRS as stated in ASPIRE-I.
	PBO + SoC	112	-23.2*			
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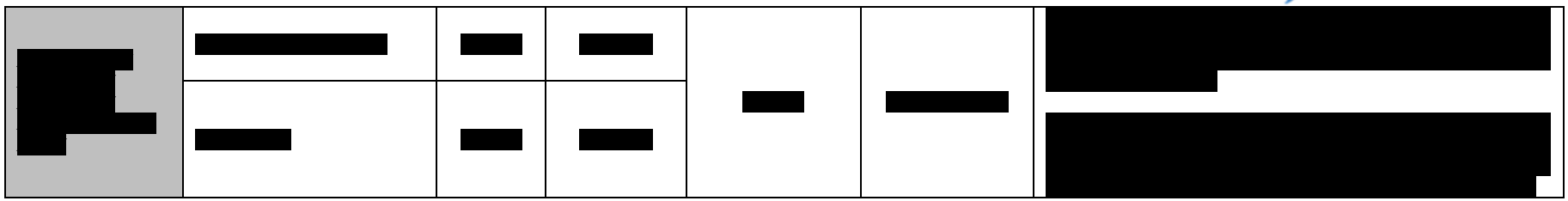

Table 82: Results of the ASPIRE II study

Trial name: ASPIRE-II						
NCT number: NCT03097133						
	Data extracted from ASPIRE-II			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Mean improvement in suicidal symptoms based on CGI-SS-r – Full population (24 hours)	ESK-NS 84 mg + SoC	113	-1.4*	-0.1**	-0.48; 0.19**	*Reported as the change from baseline least square mean of CGI-SS-r per treatment as stated in ASPIRE-II. **No relative difference in effect is reported, but the difference in change from baseline least square means of CGI-SS-r as stated in ASPIRE-II.
	PBO + SoC	113	-1.3*			
Mean improvement in suicidal symptoms based on CGI-SS-r – Full population (Day 25)	ESK-NS 84 mg + SoC	114	-2.7*	-0.1**	-0.50; 0.20**	*Reported as the change from baseline least square mean of CGI-SS-r per treatment as stated in ASPIRE-II. **No relative difference in effect is reported, but the difference in change from baseline least square means of CGI-SS-r as stated in ASPIRE-II.
	PBO + SoC	113	-2.5*			
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Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (24 hours)	ESK-NS 84 mg + SoC	59/113	52.21%	1.06*	0.81-1.39*	*Data based on post-hoc full population analysis of ASPIRE-II. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	52/110	47.27%			
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (Day 25)	ESK-NS 84 mg + SoC	97/113	85.84%	1.04*	0.92-1.18*	*Data based on post-hoc full population analysis of ASPIRE-II. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	92/110	83.64%			
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Proportion of patients with deterioration defined as	ESK-NS 84 mg + SoC	5/115	4.35%	0.97*	0.25-3.72*	*Data based on post-hoc full population analysis of ASPIRE-II. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.

exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (24 hours)	PBO + SoC	5/115	4.35%			
Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (Day 25)	ESK-NS 84 mg + SoC	1/115	0.87%	0.18*	0.02-1.32*	*Data based on post-hoc full population analysis of ASPIRE-II. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	5/115	4.35%			
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Response (24 hours)	ESK-NS 84 mg + SoC	40/115	34.78%	1.62*	1.07-2.46*	*Data based on post-hoc full population analysis of ASPIRE-II. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	27/115	23.48%			
Response (Day 25)	ESK-NS 84 mg + SoC	68/115	59.13%	0.99*	0.79-1.26*	*Data based on post-hoc full population analysis of ASPIRE-II. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	69/115	60.00%			
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Remission (24 hours)	ESK-NS 84 mg + SoC	25/115	21.74%	2.53*	1.26-5.09*	*Data based on post-hoc full population analysis of ASPIRE-II. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	12/115	10.43%			
Remission (Day 25)	ESK-NS 84 mg + SoC	54/115	46.96%	1.31*	0.95-1.81*	*Data based on post-hoc full population analysis of ASPIRE-II. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	42/115	36.52%			
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Mean change in MADRS total score from baseline (24 hours)	ESK-NS 84 mg + SoC	113	-16.0*	-3.9**	-6.60; -1.11**	*Reported as the change from baseline least square mean of MADRS per treatment as stated in ASPIRE-II. **No relative difference in effect is reported, but the difference in change from baseline least square means of MADRS as stated in ASPIRE-II.
	PBO + SoC	113	-12.2*			
Mean change in MADRS total score from baseline (Day 25)	ESK-NS 84 mg + SoC	114	-25.6*	-2.3**	-5.50; 0.86**	*Reported as the change from baseline least square mean of MADRS per treatment as stated in ASPIRE-II. **No relative difference in effect is reported, but the difference in change from baseline least square means of MADRS as stated in ASPIRE-II.
	PBO + SoC	113	-23.2*			
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Table 83: Results of the ESKETINSUI2001 study

Trial name: ESKETINSUI2001						
NCT number: NCT02133001						
	Data extracted from ESKETINSUI2001			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Mean improvement in suicidal symptoms based on CGI-SS-r – Full population (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	CGI-SS-r was not measured in the study; therefore, no results are available for these outcomes for ESKETINSUI2001.
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Mean improvement in suicidal symptoms based on CGI-SS-r – Full population (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Mean improvement in suicidal symptoms based on CGI-SS-r – Subpopulation with a CGI-SS-r ≥ 4 (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Mean improvement in suicidal symptoms based on CGI-SS-r – Subpopulation with a CGI-SS-r ≥ 4 (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	

Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	CGI-SS-r was not measured in the study; therefore, no results are available for these outcomes for ESKETINSUI2001.
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r – Subpopulation with a CGI-SS-r ≥ 4 (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r – Subpopulation with a CGI-SS-r ≥ 4 (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	

Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	CGI-SS-r was not measured in the study; therefore, no results are available for these outcomes for ESKETINSUI2001.
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r – Subpopulation with a CGI-SS-r ≥ 4 (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Response (24 hours)	ESK-NS 84 mg + SoC	19/35	54.29%	1.82*	0.97-3.40*	*Data based on post-hoc full population analysis of ESKETINSUI2001. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	9/31	29.03%			
Response (Day 25)	ESK-NS 84 mg + SoC	20/35	57.14%	1.16*	0.72-1.85*	*Data based on post-hoc full population analysis of ESKETINSUI2001. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	15/31	48.39%			
Response R – Subpopulation with a CGI-SS-r ≥ 4 (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	CGI-SS-r was not measured in the study; therefore, no results are available for these outcomes for ESKETINSUI2001.
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Response R – Subpopulation with a CGI-SS-r ≥ 4 (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	

Remission (24 hours)	ESK-NS 84 mg + SoC	12/35	34.29%	1.73*	0.75-3.99*	*Data based on post-hoc full population analysis of ESKETINSUI2001. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	5/31	16.13%			
Remission (Day 25)	ESK-NS 84 mg + SoC	16/35	45.71%	1.10*	0.58-2.09*	*Data based on post-hoc full population analysis of ESKETINSUI2001. Relative difference is provided as adjusted risk ratio based on Mantel-Haenszel estimate of the common RR/RD.
	PBO + SoC	12/31	38.71%			
Remission R – Subpopulation with a CGI-SS-r ≥ 4 (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	CGI-SS-r was not measured in the study; therefore, no results are available for these outcomes for ESKETINSUI2001.
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Remission R – Subpopulation with a CGI-SS-r ≥ 4 (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Mean change in MADRS total score from baseline (24 hours)	ESK-NS 84 mg + SoC	35	-18.9*	-7.2 (SD: 23.154) **	*n/a*	*Reported as the change from baseline least square mean of MADRS per treatment as stated in ESKETINSUI2001. **No relative difference in effect is reported, but the difference in change from baseline least square means of MADRS as stated in ESKETINSUI2001. SD based on the reported SE of 2.850 and number of patients in this outcome (n=66)
	PBO + SoC	31	-11.7*			
Mean change in MADRS total score from baseline (Day 25)	ESK-NS 84 mg + SoC	35	-25.4*	-4.5 (SD: 25.509) **	*n/a*	*Reported as the change from baseline least square mean of MADRS per treatment as stated in ESKETINSUI2001. **No relative difference in effect is reported, but the difference in change from baseline least square means of MADRS as stated in ESKETINSUI2001. SD based on the reported SE of 3.140 and number of patients in this outcome (n=66)
	PBO + SoC	31	-21.0*			
Mean change in MADRS total score from baseline R – Subpopulation with a CGI-SS-r ≥ 4 (24 hours)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	CGI-SS-r was not measured in the study; therefore, no results are available for these outcomes for ESKETINSUI2001.
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
Mean change in MADRS total score from baseline R – Subpopulation with a CGI-SS-r ≥ 4 (Day 25)	ESK-NS 84 mg + SoC	*n/a*	*n/a*	*n/a*	*n/a*	
	PBO + SoC	*n/a*	*n/a*	*n/a*	*n/a*	

8.4 Results per PICO

Table 84. Results referring to clinical question 1

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	*P* value	Risk Ratio	95% CI	*P* value	
Mean improvement in suicidal symptoms based on CGI-SS-r (24 hours)	ASPIRE-I ASPIRE-II	-0.200	-0.437; 0.037	0.098	*n/a*	*n/a*	*n/a*	A meta-analysis was used to combine the difference in change from baseline least square means of the ASPIRE-I and ASPIRE-II studies using continuous random effects model and is reported as mean difference.
Mean improvement in suicidal symptoms based on CGI-SS-r (Day 25)	ASPIRE-I ASPIRE-II	-0.191	-0.426; 0.043	0.109	*n/a*	*n/a*	*n/a*	A meta-analysis was used to combine the difference in change from baseline least square means of the ASPIRE-I and ASPIRE-II studies using continuous random effects model and is reported as mean difference.
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion with resolution of	ASPIRE-I ASPIRE-II	4.41%	-4.81% - 16.36%	*n/a*	1.092	0.908 - 1.313	0.350	A meta-analysis was used to combine the results of the Mantel-Haenszel risk ratios of

suicidal thoughts (score of ≤ 2) on CGI-SS-r (24 hours)								the ASPIRE-I and ASPIRE-II studies using random effects model and is reported as adjusted risk ratios. 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 2.8. The event rate of the placebo + SoC arm was 47.9% and is based on the meta-analysis which was used to calculate the absolute difference.
Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r (Day 25)	ASPIRE-I ASPIRE-II	3.70%	-3.76% - 12.13%	*n/a*	1.045	0.956 - 1.142	0.331	A meta-analysis was used to combine the results of the Mantel-Haenszel risk ratios of the ASPIRE-I and ASPIRE-II studies using random effects model and is reported as adjusted risk ratios. 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 2.8. The event rate of the placebo + SoC arm was 82.2% and is based on the meta-analysis which was used to calculate the absolute difference.
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Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (24 hours)	ASPIRE-I ASPIRE-II	0.84%	-2.70% - 10.64%	*n/a*	1.211	0.484 - 3.030	0.682	A meta-analysis was used to combine the results of the Mantel-Haenszel risk ratios of the ASPIRE-I and ASPIRE-II studies using random effects model and is reported as adjusted risk ratios. 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 2.8. The event rate of the placebo + SoC arm was 4.0% and is based on the meta-analysis which was used to calculate the absolute difference.
Proportion of patients with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r (Day 25)	ASPIRE-I ASPIRE-II	-0.57%	-1.68% - 26.70%	*n/a*	0.783	0.038–16.288	0.875	A meta-analysis was used to combine the results of the Mantel-Haenszel risk ratios of the ASPIRE-I and ASPIRE-II studies using random effects model and is reported as adjusted risk ratios. 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 2.8. The event rate of the placebo + SoC arm was 2.6% and is based on the meta-analysis which was used to calculate the absolute difference.
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Response (24 hours)	ASPIRE-I ASPIRE-II PeRSERVERe	11.51%	4.41% - 32.22%	*n/a*	1.450	1.120 - 1.877	0.005	A meta-analysis was used to combine the results of the Mantel-Haenszel risk ratios of the ASPIRE-I, ASPIRE-II and PeRSERVERe studies using random effects model and is reported as adjusted risk ratios. 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 2.8. The event rate of the placebo + SoC arm was 25.6% and is based on the meta-analysis which was used to calculate the absolute difference.
Response (Day 25)	ASPIRE-I ASPIRE-II PeRSERVERe	6.22%	-3.08% - 18.55%	*n/a*	1.110	0.951 - 1.295	0.185	A meta-analysis was used to combine the results of the Mantel-Haenszel risk ratios of the ASPIRE-I, ASPIRE-II and PeRSERVERe studies using random effects model and is reported as adjusted risk ratios. 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 2.8. The event rate of the placebo + SoC arm was 56.6% and is based on the meta-analysis which was used to calculate the absolute difference.

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Remission (24 hours)	ASPIRE-I ASPIRE-II PeRSERVERe	12.67%	9.38% - 53.30%	*n/a*	2.211	1.427 - 3.426	<0.001	A meta-analysis was used to combine the results of the Mantel-Haenszel risk ratios of the ASPIRE-I, ASPIRE-II and PeRSERVERe studies using random effects model and is reported as adjusted risk ratios. 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 2.8. The event rate of the placebo + SoC arm was 10.5% and is based on the meta-analysis which was used to calculate the absolute difference.
Remission (Day 25)	ASPIRE-I ASPIRE-II PeRSERVERe	12.06%	3.79% - 30.92%	*n/a*	1.324	1.077 - 1.628	0.008	A meta-analysis was used to combine the results of the Mantel-Haenszel risk ratios of the ASPIRE-I, ASPIRE-II and PeRSERVERe studies using random effects model and is reported as adjusted risk ratios.

								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 2.8. The event rate of the placebo + SoC arm was 37.2% and is based on the meta-analysis which was used to calculate the absolute difference.
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in MADRS total score from baseline (24 hours)	ASPIRE-I ASPIRE-II PeRSERVERe	-4.201	-6.031; -2.370	<0.001	*n/a*	*n/a*	*n/a*	A meta-analysis was used to combine the difference in change from baseline least square means of the ASPIRE-I, ASPIRE-II and PeRSERVERe studies using continuous random effects model and is reported as mean difference.
Mean change in MADRS total score from baseline (Day 25)	ASPIRE-I ASPIRE-II PeRSERVERe	-3.852	-5.818; -1.885	<0.001	*n/a*	*n/a*	*n/a*	A meta-analysis was used to combine the difference in change from baseline least square means of the ASPIRE-I, ASPIRE-II and PeRSERVERe studies using continuous random effects model and is reported as mean difference.

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.5 Forest plots for clinical question 1 – full population

8.5.1 Mean improvement in suicidal symptoms based on CGI-SS-r at Day 2 (24 hours)

study names weights

ASPIRE-1: 49.998%

ASPIRE-2: 50.002%

Continuous Random-Effects Model

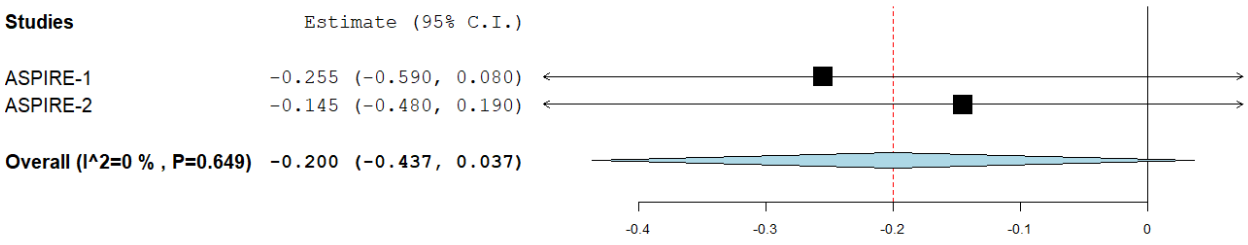
Metric: Mean Difference

Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
-0.200	-0.437	0.037	0.121	0.098

Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
0.000	0.207	0.649	0



8.5.2 Mean improvement in suicidal symptoms based on CGI-SS-r at Day 25 (Endpoint)

study names weights

ASPIRE-1: 55.240%

ASPIRE-2: 44.760%

Continuous Random-Effects Model

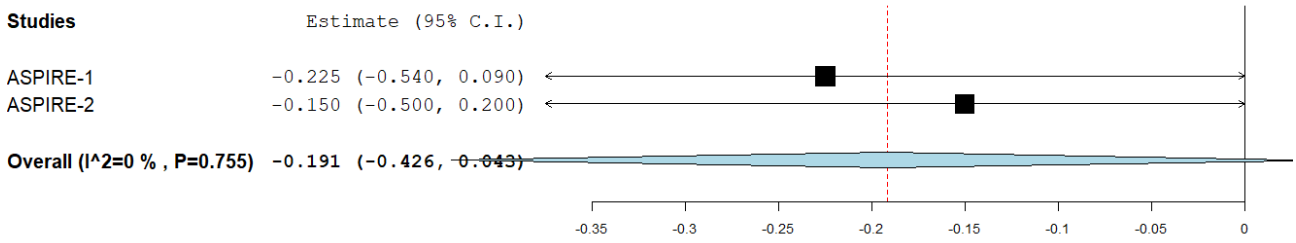
Metric: Mean Difference

Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
-0.191	-0.426	0.043	0.119	0.109

Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
0.000	0.097	0.755	0



8.5.3 Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r at Day 2 (24 hours)

study names weights

ASPIRE-1: 53.770%

ASPIRE-2: 46.230%

Binary Random-Effects Model

Metric: Relative Risk

Model Results

Estimate Lower bound Upper bound p-Value

1.092 0.908 1.313 0.350

Heterogeneity

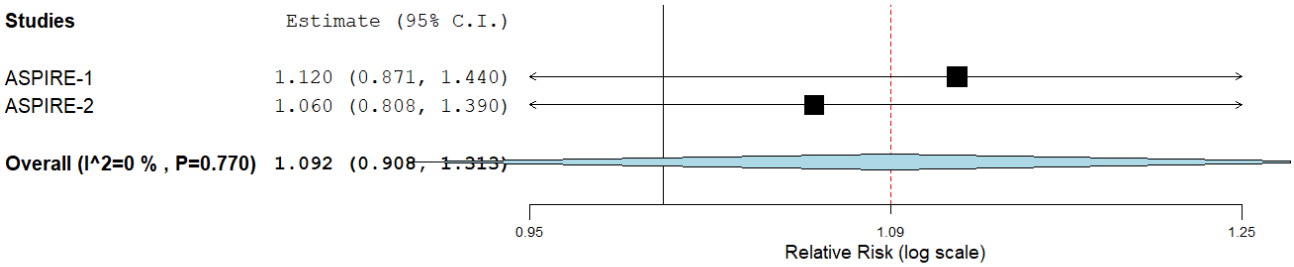
tau^2 Q(df=1) Het. p-Value I^2

0.000 0.085 0.770 0

Results (log scale)

Estimate Lower bound Upper bound Std. error

0.088 -0.096 0.272 0.094



8.5.4 Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r at Day 25 (Endpoint)

study names weights

ASPIRE-1: 50.450%

ASPIRE-2: 49.550%

Binary Random-Effects Model

Metric: Relative Risk

Model Results

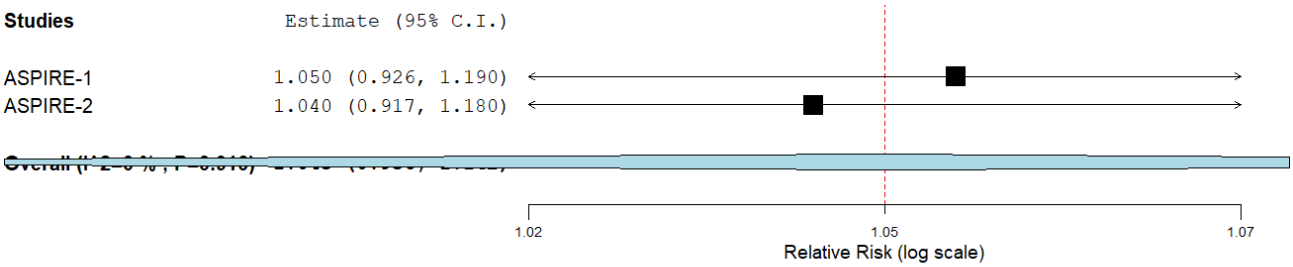
Estimate	Lower bound	Upper bound	p-Value
1.045	0.956	1.142	0.331

Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
0.000	0.011	0.916	0

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.044	-0.045	0.133	0.045



8.5.5 Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r at Day 2 (24 hours)

study names weights

ASPIRE-1: 53.477%

ASPIRE-2: 46.523%

Binary Random-Effects Model

Metric: Relative Risk

Model Results

Estimate Lower bound Upper bound p-Value

1.211 0.484 3.030 0.682

Heterogeneity

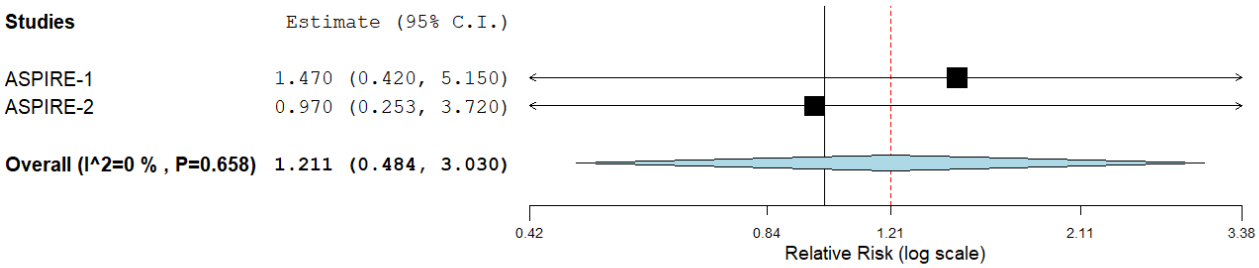
tau^2 Q(df=1) Het. p-Value I^2

0.000 0.196 0.658 0

Results (log scale)

Estimate Lower bound Upper bound Std. error

0.192 -0.725 1.109 0.468



8.5.6 Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r at Day 25

study names weights

ASPIRE-1: 47.412%

ASPIRE-2: 52.588%

Binary Random-Effects Model

Metric: Relative Risk

Model Results

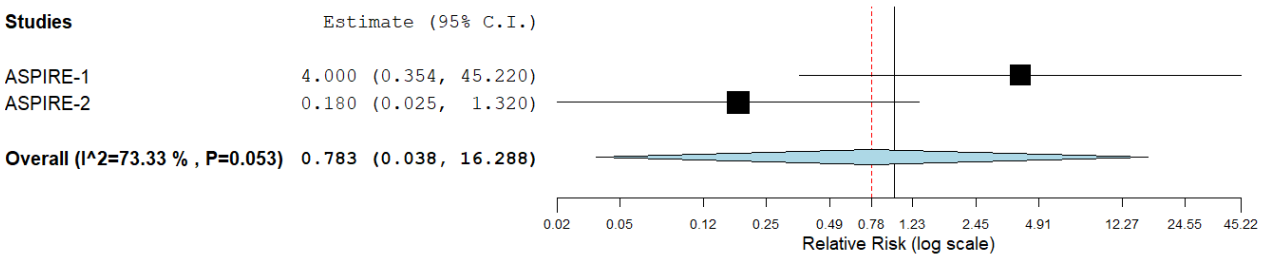
Estimate	Lower bound	Upper bound	p-Value
0.783	0.038	16.288	0.875

Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
3.526	3.750	0.053	73.333

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
-0.245	-3.279	2.790	1.548



8.5.7 Response at Day 2 (24 hours)

study names weights

ASPIRE-1 : 44.737%

ASPIRE-2 : 38.196%

PERSERVERE: 17.067%

Binary Random-Effects Model

Metric: Relative Risk

Model Results

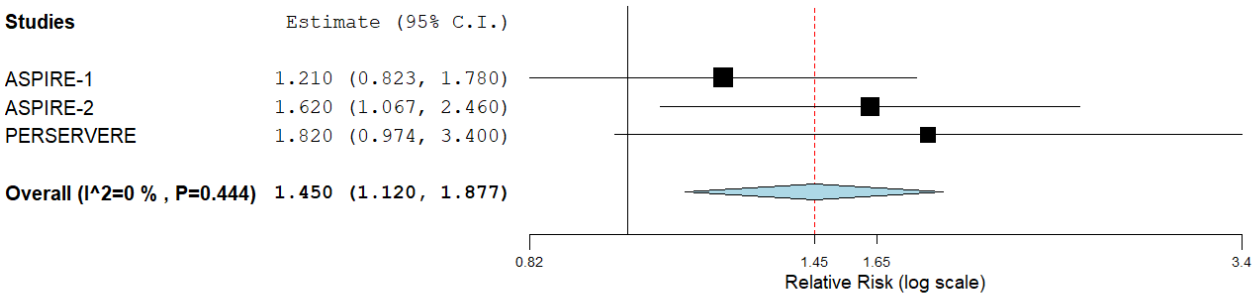
Estimate	Lower bound	Upper bound	p-Value
1.450	1.120	1.877	0.005

Heterogeneity

tau^2	Q(df=2)	Het. p-Value	I^2
0.000	1.623	0.444	0

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.372	0.114	0.630	0.132



8.5.8 Response at Day 25 (Endpoint)

study names weights

ASPIRE-1 : 48.340%

ASPIRE-2 : 40.775%

PERSERVERE: 10.885%

Binary Random-Effects Model

Metric: Relative Risk

Model Results

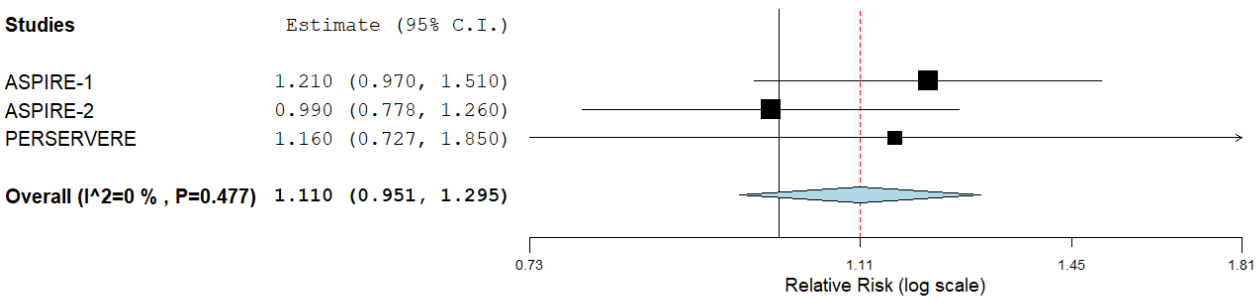
Estimate	Lower bound	Upper bound	p-Value
1.110	0.951	1.295	0.185

Heterogeneity

tau^2	Q(df=2)	Het. p-Value	I^2
0.000	1.481	0.477	0

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.104	-0.050	0.258	0.079



8.5.9 Remission at Day 2 (24 hours)

study names weights

ASPIRE-1 : 33.345%

ASPIRE-2 : 39.214%

PERSERVERE: 27.441%

Binary Random-Effects Model

Metric: Relative Risk

Model Results

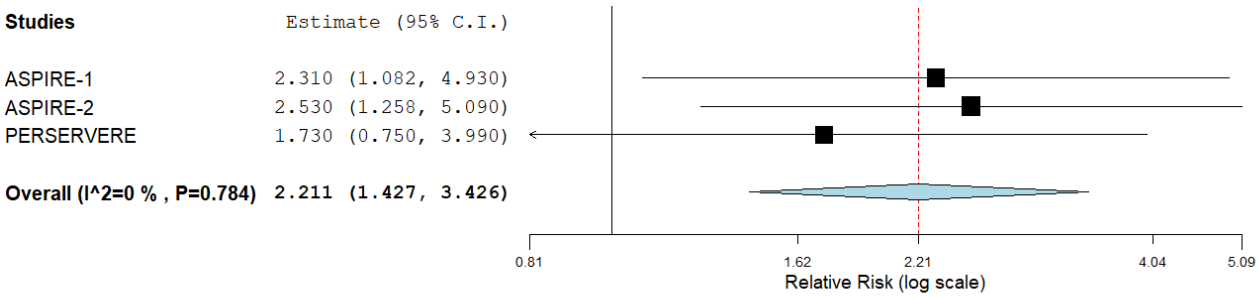
Estimate	Lower bound	Upper bound	p-Value
2.211	1.427	3.426	< 0.001

Heterogeneity

tau^2	Q(df=2)	Het. p-Value	I^2
0.000	0.487	0.784	0

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.794	0.356	1.231	0.223



8.5.10 Remission at Day 25 (Endpoint)

study names weights

ASPIRE-1 : 48.652%

ASPIRE-2 : 40.957%

PERSERVERE: 10.391%

Binary Random-Effects Model

Metric: Relative Risk

Model Results

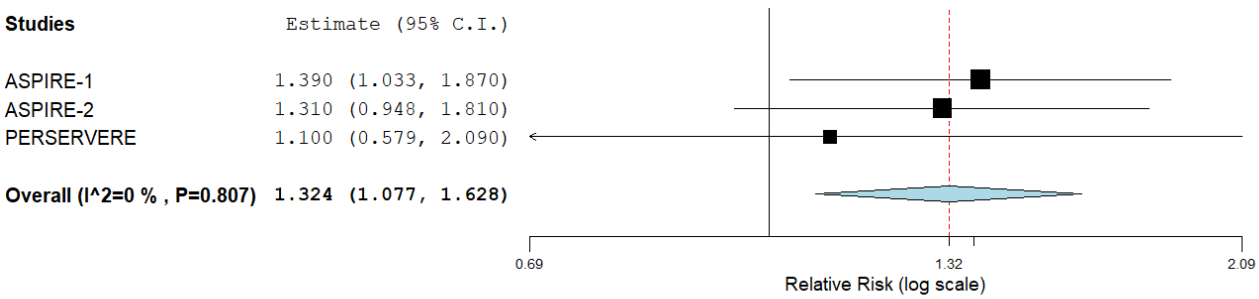
Estimate	Lower bound	Upper bound	p-Value
1.324	1.077	1.628	0.008

Heterogeneity

tau^2	Q(df=2)	Het. p-Value	I^2
0.000	0.428	0.807	0

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.281	0.074	0.488	0.106



8.5.11 Mean change in MADRS total score from baseline at Day 2 (24 hours)

study names weights

ASPIRE-1 : 44.793%

ASPIRE-2 : 44.469%

PERSERVERE: 10.738%

Continuous Random-Effects Model

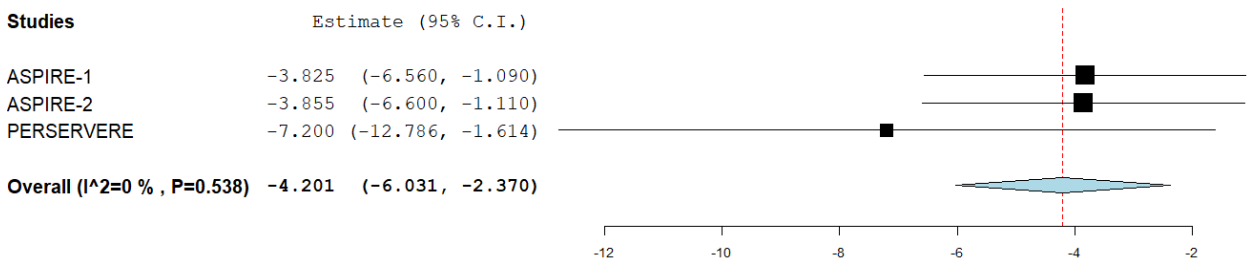
Metric: Mean Difference

Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
-4.201	-6.031	-2.370	0.934	< 0.001

Heterogeneity

tau^2	Q(df=2)	Het. p-Value	I^2
0.000	1.241	0.538	0



8.5.12 Mean change in MADRS total score from baseline at Day 25 (Endpoint)

study names weights

ASPIRE-1 : 51.530%

ASPIRE-2 : 38.256%

PERSERVERE: 10.214%

Continuous Random-Effects Model

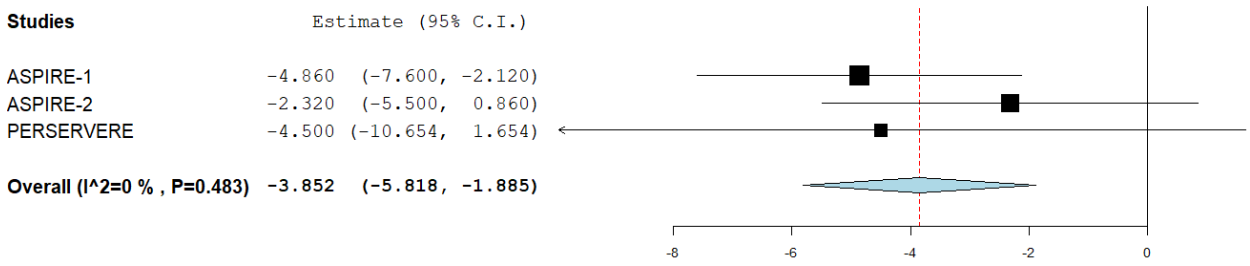
Metric: Mean Difference

Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
-3.852	-5.818	-1.885	1.004	< 0.001

Heterogeneity

tau^2	Q(df=2)	Het. p-Value	I^2
0.000	1.454	0.483	0



8.6 Forest plots for clinical question 1 – subpopulation with a CGI-SS-r score ≥ 4

8.6.1 Mean improvement in suicidal symptoms based on CGI-SS-r at Day 2 (24 hours)

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8.6.2 Mean improvement in suicidal symptoms based on CGI-SS-r at Day 25 (Endpoint)

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8.6.3 Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r at Day 2 (24 hours)

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8.6.4 Proportion with resolution of suicidal thoughts (score of ≤ 2) on CGI-SS-r at Day 25 (endpoint)

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8.6.5 Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r at Day 2 (24 hours)

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8.6.6 Proportion with deterioration defined as exacerbation of ≥ 1 point of suicide symptoms on CGI-SS-r at Day 25

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8.6.7 Response at Day 2 (24 hours)

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8.6.8 Response at Day 25 (Endpoint)

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8.6.9 Remission at Day 2 (24 hours)

[redacted]

8.6.10 Remission at Day 25 (Endpoint)

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8.6.11 Mean change in MADRS total score from baseline at Day 2 (24 hours)

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8.6.12 Mean change in MADRS total score from baseline at Day 25 (Endpoint)

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SPRAVATO® (esketamine) for the treatment of adult patients with a moderate to severe episode of MDD with acute increased risk of suicide

Health economic technical report for the Danish Medicines Council

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List of abbreviations

AD	Antidepressants
AE	Adverse Events
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor
CGI-SS-R-I	Clinical Global Impression-Imminent Suicide Risk
DKK	Danish Krone
DMC	Danish Medicines Council
ECT	Electroconvulsive Therapy
ED	Emergency Department
FoST	Frequency of Suicidal Thinking
HCC	Half cycle correction
HCP	Healthcare professional
ICD-10	International Classification of Diseases and Related Health Problems-10
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MDSI	Major Depression with Suicidal Ideation and Intent
Mg	milligrams
NMDA	N-methyl-D-aspartate
OS	Overall Survival
SIBAT	Suicide Ideation and Behaviour Assessment Tool
SmPC	Summary of Product Characteristics
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SoC	Standard of Care
SSRI	Selective Serotonin Reuptake Inhibitor

Summary in Danish

Baggrund

Den 17. marts 2021 offentliggjordes Medicinrådets protokol for vurdering af esketamin (SPRAVATO®) til kortvarig behandling af voksne med en moderat til svær depressiv episode med akut øget selvmordsrisiko (MDSI). Protokollen omfattede følgende kliniske spørgsmål:

1. Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med placebo i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko?
2. Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med elektrokonvulsiv terapi (ECT) i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko?

Dette tekniske dokument beskriver de økonomiske analyser, hhv. omkostningsanalyser og budgetkonsekvensanalyser, som er udarbejdet som en del af ansøgningen til Medicinrådets for ovenstående kliniske spørgsmål. Formålet med dette dokument er at beskrive de økonomiske modeller, deres funktioner, datagrundlaget, antagelserne, samt de overordnede resultater.

Metode

En Markov-model med tre stadier (Bedring af sygdom [Remission], Respons, Svær depressiv episode [MDE]) blev udviklet for at estimere de inkrementelle omkostninger per patient for esketamin i kombination med antidepressiva sammenlignet med antidepressiva alene (standardbehandling) for klinisk spørgsmål 1 og ECT i kombination med antidepressiva for klinisk spørgsmål 2. Omkostningsanalysen er delvist indlejret i budgetkonsekvensmodellen, og resultaterne fra omkostningsanalysen er således anvendt som direkte input til budgetkonsekvensmodellen.

Modellen er primært baseret på resultaterne fra ASPIRE-I og ASPIRE-II, to randomiserede fase III-studier der undersøgte effekten og sikkerheden af esketamin i kombination med antidepressiva sammenlignet med placebo i kombination med antidepressiva som kortvarig behandling til patienter med en moderat til svær depressiv episode med akut øget selvmordsrisiko. Eftersom der ikke findes tilstrækkelige data for effekten af ECT til en komparativ analyse, blev det antaget at effekten af ECT er lig effekten af esketamin. Således sammenlignes udelukkende omkostningerne for brugen af disse behandlingsalternativer.

Modellen anvender en 90-dages tidshorisont, hvilket afspejler både varigheden af de kliniske forsøg samt det kliniske forløb for den akutte tilstand. Omkostningerne diskonteres af denne grund ikke i overensstemmelse med Medicinrådets og Finansministeriets vejledninger for diskontering. Modellen har et begrænset samfundsperspektiv og inkluderer lægemiddelomkostninger, administrationsomkostninger, monitoreringsomkostninger, omkostninger til uønskede hændelser, omkostninger i forbindelse med indlæggelse samt patient- og transportomkostninger.

Resultater

Base-case-analysen viser en gennemsnitlig inkrementel omkostning per patient på [redacted] for esketamin + antidepressiva sammenlignet med antidepressiva alene, og [redacted] for esketamin + antidepressiva sammenlignet med ECT + antidepressiva.

Budgetkonsekvenserne estimeres i år 5 til at være [redacted] og [redacted] ved anbefaling af esketamin + antidepressiva som kortvarig behandling af patienter med MDSI for henholdsvis klinisk spørgsmål 1 og 2.

1 Introduction

Moderate to severe unipolar depression or Major Depressive Disorder (MDD) will, according to the WHO, within a period of 20 years be among the two most debilitating diseases in the world in terms of disease burden and economic consequences for society. In Denmark, the prevalence of moderate to severe depression among adults is estimated to be approx. 3%, corresponding to approx. 111,000 adult individuals [1, 2]. Of these, it is estimated that only 65.3%, corresponding to approx. 72,400 adult individuals, are diagnosed and can receive treatment [2]. Furthermore, a smaller proportion of 1,000 to 2,000 adult individuals per year will have a special need for acute treatment with a rapid onset effect on depressive symptoms because they exhibit serious suicidal behaviour.

Depression is typically presented with symptoms such as sadness and decreased energy over time, lack of self-esteem, tendency to isolate, self-blame, decreased or increased appetite, loss of zest for life and often with severe and moderate depression such as suicidal thoughts or plans [3]. In severe cases, there may be psychotic symptoms in the form of hallucinations and delusions [3]. Depression can be triggered by prolonged somatic illness, stress, loss of loved ones and existential crises, but often the triggers are unknown. Genetic predisposition and personality predisposing factors contribute to increasing the risk of the disease [3].

Depression is diagnosed according to the International Classification of Diseases and Related Health Problems-10 (ICD-10) classification system, based on a set of basic criteria. Duration as well as the number and severity of depressive core and accompanying symptoms determine whether it is depression, and it is severity. Depression is often seen with other mental disorders such as anxiety disorders and personality disorders [3, 4]. In addition, alcohol and/or substance abuse are also common in patients with major depression [3]. Particularly drug-addicted patients may occur with acute suicidal behaviour. In such cases, treatment should be organized according to the patient's mental state after detoxification. Patients with major depression may exhibit suicidal thoughts and behaviours that are so severe that hospitalisation and emergency treatment may be necessary. This is also true for a small number of patients with moderate depression. The risk of suicide is based on a clinical assessment by the treating specialist in psychiatry and can be covered by a clinical assessment and i.e., the following questions:

- Has the patient previously attempted suicide? Is it recently? What were the circumstances of the suicide attempt?
- Does the patient have current suicidal thoughts? What are the suicidal thoughts about?
- Does the patient have current suicide plans? What are the suicide plans and to what extent has the patient prepared to carry out the plans?
- Can the patient credibly distance himself from suicidal impulses? What counter-perceptions does the patient have? Can a credible safety plan be made with the patient?

A suicide attempt is described as an act in which a person intentionally exhibits behaviour that can have a fatal outcome. Suicidal thoughts range from transient notions and considerations of dying to more persistent and intrusive considerations and ultimately a final decision to commit suicide. Suicidal behaviour covers actual suicide attempts or preparations for them. For patients with moderate to severe depression with an acutely increased risk of suicide, it is often a risk that is increased in an ongoing depression episode or as part of a recently started depression episode. Several reasons can be underlying for patients to try to commit suicide, but social conditions and abuse often play a role.

Patients with MDD is currently treated with standard of care (SoC), consisting of antidepressants (selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI)). Patients with suicidal behaviour are referred to psychiatric intensive care for rapid acute care, and patients are often

diagnosed in the emergency department or as part of an acute hospitalisation assessment. Patients with moderate to severe depression with acutely increased suicide risk constitute a high-risk group in need of rapid crisis management or acute hospitalisation to supervise the patient and reduce the risk of suicide. When patients are hospitalized, they will continue treatment with SoC, and some patients will as a supplement receive electroconvulsive therapy (ECT). However, 4 to 6 weeks is required for antidepressants to exert their full effect, which constitutes an unmet medical need for patients who requires acute treatment [5, 6]. The same is true for patients eligible for ECT. The treatment with ECT is performed over three to six weeks with the administration of ECT three times per week. This results in a total of 6 to 20 ECT procedures, which each time requires the patient to be placed under general anaesthesia [7].

Janssen has developed esketamine (SPRAVATO®), an S-enantiomer of racemic ketamine that provides a new mode of action in the treatment of MDD. Esketamine has been studied in the trials, ASPIRE-I and ASPIRE-II, as a supplement to SoC for patients with Major Depression with Suicidal Ideation and Intent (MDSI). 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-isoxazole propionic 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.

1.1 Decision problems (Clinical questions)

The Danish Medicines Council (DMC) have presented two clinical questions in the protocol [8]:

1) *What is the value of esketamine as a supplement to antidepressants compared to placebo as a supplement to antidepressants for adults currently affected by a moderate to severe depressive disorder episode with acutely increased risk of suicide?*

2) *What is the value of esketamine as a supplement to antidepressants compared to ECT as a supplement to antidepressants for adults currently affected by a moderate to severe depressive disorder episode with acutely increased risk of suicide?*

1.2 Objective

The economic model was developed to estimate the mean incremental costs per patient as well as the budget impact of recommending esketamine as standard treatment in Denmark for adult patients affected by a moderate to severe depressive episode with acutely increased risk of suicide as defined by the clinical questions in the protocol [8]. For the health economic assessment, two patient populations were of interest; MDSI patients ineligible for ECT and MDSI patients eligible for ECT corresponding to clinical questions 1 and 2, respectively, with a subgroup analysis of patients with a CGI-SS-R ≥4 for both clinical questions. The model applies a restricted societal perspective, thereby including patient- and transportation costs as set out in the method guidelines of the DMC [9].

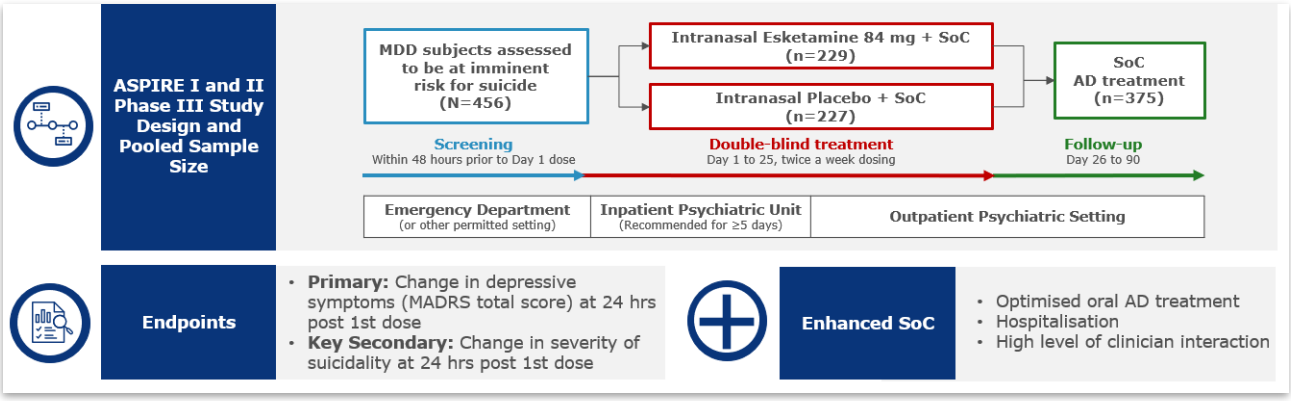
The economic analysis was based on the evidence from the two phase III trials, ASPIRE-I and ASPIRE-II, investigating the efficacy and safety of esketamine as an add-on short-term therapy as per the protocol received from the DMC [8]. Furthermore, evidence and estimations from Danish clinical experts and published literature informed the assumptions for the ECT-arm in the model as no robust data for the clinical efficacy of ECT for these patients is available.

2 Clinical trials: ASPIRE-I and ASPIRE-II

The clinical trials, ASPIRE-I and ASPIRE-II, were randomized, double blinded, placebo-controlled, multicentre, phase III trials which investigated the effect and safety of esketamine nasal spray 84 mg in addition to comprehensive standard of care (SoC, defined as AD monotherapy or augmentation, including hospitalisation and the initiation/optimization of AD treatment) in adult patients with MDD assessed to be at imminent risk of suicide [10, 11].

On Day 1 of the double-blind treatment phase, patients were randomized in a 1:1 ratio to receive either esketamine intranasal 84 mg plus SoC or intranasal placebo plus SoC, administered twice a week for 4 weeks. Patients self-administered their allocated study treatment under the supervision of an on-site staff member [10, 11]. The trial design of ASPIRE-I and ASPIRE-II was identical and is presented in Figure 1.

Figure 1. Trial design ASPIRE-I and ASPIRE-II



Abbreviations: *AD = Antidepressants, Hrs = Hours, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, SoC = Standard of Care*

The severity of depressive symptoms was assessed using the Structured Interview Guide for Montgomery-Åsberg Depression Rating Scale (MADRS) on Day 1 (pre-dose and 4 hours post-dose), Day 2 (24 hours post-dose), all subsequent visits (pre-dose), at 4 hours post-dose on Day 25 during the double-blind phase, and all visits during the follow-up phase (twice weekly through Day 39, weekly through Day 53, and every other week through Day 90) [10, 11].

The Suicide Ideation and Behaviour Assessment Tool (SIBAT) was used to assess efficacy related to suicidal ideation and behaviour on all visit days during the double-blind and follow-up phases. The SIBAT contains both patient and clinician-reported outcomes, including the Clinical Global Impression-Severity of Suicidality Revised version (CGI-SS-r; rated from 0 [normal, not all suicidal] to 6 [among the most extremely suicidal patients]), Clinical Global Impression-Imminent Suicide Risk (CGI-SR-I) and Frequency of Suicidal Thinking (FoST) measures [10, 11]

2.1 Disease progression

The MADRS is a clinician-administered assessment for depression severity developed by Stuart Montgomery and Marie Åsberg in 1979. This instrument includes questions, each rated on a 0–6-point scale, that cover 10 depressive symptoms: (1) apparent sadness; (2) reported sadness; (3) inner tension; (4) reduced sleep; (5) reduced appetite; (6) concentration difficulties; (7) lassitude; (8) inability to feel; (9) pessimistic thoughts; and (10) suicidal thoughts. Since its inception, a self-reported version of MADRS (MADRS-S) was created and has been proven through research to be an effective assessment instrument [12].

The primary efficacy endpoint in ASPIRE-I and ASPIRE-II was the change of MADRS total score at 24 hours post first dose. Patients' MADRS score was evaluated at several time points throughout the trials, e.g., day two, day four, day eight, day 11, etc. The following definitions are used for the health states used by the model:

- Major Depressive Episode (MDE): patients experiencing moderate to severe symptoms of MDD, with a MADRS ≥28, and who at baseline have acute suicidal ideation or behaviour
- Response: defined as ≥50% improvement from baseline in the MADRS score, but excluding those patients who achieve MADRS ≤12
- Remission: a patient is considered to achieve remission when their MADRS score is ≤ 12

A key secondary efficacy endpoint in ASPIRE-I and ASPIRE-II was the CGI-SS-r at 24 hours post first dose. Patients with a CGI-SS-R score = 0 or 1 are said to have a resolution of suicidality.

2.2 Study population

Key eligibility criteria used in the phase III studies were designed to accurately reflect patients with MDD at imminent risk of suicide. Subjects enrolled in ASPIRE-I and -II had moderate to severe MDD, without psychotic features (as determined by DSM-V criteria), confirmed by a Mini-International Neuropsychiatric Interview (MINI). Patients were required to have a MADRS score of >28 and the clinician assessed current suicidal ideation and intent, which in the physician's opinion, warranted acute psychiatric hospitalisation due to imminent risk for suicide (1, 2). For the full list of eligibility criteria, see section 5.2.1 in the clinical application.

3 Health economic model

3.1 Health economic analysis

In the economic model, the incremental costs of esketamine plus SoC were compared to SoC alone and esketamine plus SoC compared to ECT plus SoC. Table 1 presents the key features of the model.

Table 1. Key features of the analysis

Feature	Input	Notes
Software	*Microsoft Excel*	
Model type	*Markov model*	*Appropriate for long-term chronic conditions and conditions featuring recurrent events, such as MDE.* *Allows for clear and reproducible model outcomes*
Perspective	*Danish restricted societal perspective*	*Following the DMC methodological guidelines [13]*
Time horizon	*90 Days*	*90 days was chosen as esketamine is assessed as a short-term treatment for acute episodes of MDSI*
Discount rate	*3.5%*	*Discounting rates refer to the guidelines from the DMC and Danish Ministry of Finance [14]*
Cycle length	*Variable cycle length*	*Corresponding to every point at which efficacy outcomes were captured during the trial, see section 3.2.1.*
Half-cycle correction	*Not applied*	*Not necessary as the variable cycle length accounts for this*
Comparators and relevant populations	Esketamine *plus SoC compared to:* • *SoC alone (MDSI population, ineligible for ECT)* • *SoC alone (CGI-SS-R ≥4, ineligible for ECT)* • *ECT plus SoC (MDSI population, eligible for ECT)* • *ECT plus SoC (CGI-SS-R ≥4, eligible for ECT)*	*As per the DMC protocol [8]*
Treatment efficacy measure (RCT/NMA/STC)	*Efficacy estimates up to day 90 were informed by a pooled data analysis from ASPIRE-I and ASPIRE-II trials.*	
TTD assumption	*Assumed to include all-cause treatment discontinuation except for lack of efficacy*	*Only applies for esketamine, while these patients will continue to receive SoC.*
Mortality estimation	*Survival of general population, stratified by age and sex as baseline risk of death.*	

Drug acquisition costs (DKK)	*Drug costs/Treatment costs*	*As per the DMC methodological guidelines [13]*
Administration costs (DKK)	*Included*	*As per the DMC methodological guidelines [13]*
Adverse event management costs (DKK)	*Not included explicitly*	*Previous assessments of esketamine from DMC excluded the cost of AEs as these are assumed to be treated at the controls or under admission to the hospital*
Hospitalisation costs (DKK)	*Included*	*As per the DMC methodological guidelines [13]*
Patient's costs (DKK)	*Included*	*As per the DMC methodological guidelines [13]*
Travel costs (DKK)	*Included*	*As per the DMC methodological guidelines [13]*
Model outcomes	*Incremental costs*	*As per the DMC methodological guidelines [13]*

Abbreviations: *AE = Adverse events, CGI-SS-R = Clinical Global Impression-Imminent Suicide Risk, DMC = Danish Medicines Council, ECT = Electroconvulsive Therapy, MADRS = Montgomery-Åsberg Depression Rating Scale, MDSI = Major Depression with Suicidal Ideation and Intent, SoC = Standard of Care*

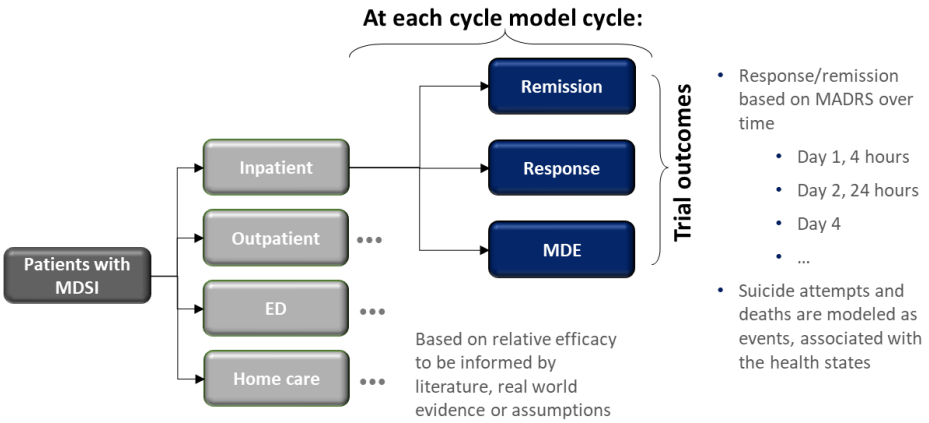
3.2 Modelling approach and rationale

3.2.1 Model structure

A Markov cohort model was developed in Microsoft Excel® to accurately model disease progression and costs experienced by patients throughout the model time horizon. The model was set to a time horizon of 90 days, matching the duration of the follow-up period from the key clinical trials, however, the model can be set to a long-term evaluation of the acute treatment with a time horizon of up to one year. The short-term model uses efficacy data (MADRS score) observed in the trials ASPIRE-I and ASPIRE-II. Patients were assessed before the first dose of esketamine, four hours post-administration and 24 hours post-administration of the first dose (day 1 and 2 in the model) and at all the other days of treatment with esketamine up to day 25. Patients were further assessed at all post-treatment follow-up visits: twice weekly days 26–39, weekly days 40–53, and bi-weekly days 54–90. Whereas the long-term model (up to 1 year) required additional clinical data to make projections beyond the ASPIRE-I and -II trials follow-up period, see appendix 9.1.

The model in Figure 2 is the short-term modelling of disease progression. The average MADRS score observed in pooled data from ASPIRE-I and ASPIRE-II was combined with the defined health states (Remission, Response, MDE) to determine how patients were distributed across these health states up to day 90.

Figure 2. Model structure for the short-term model



Abbreviations: *ED = emergency department, MDSI = major depressive disorder with acute suicidal ideation or behaviour, MDE = major depressive episode*

Mortality was applied during the short-term modelling for each cycle (I.e., at every time point at which efficacy was evaluated in the ASPIRE-I and ASPIRE-II trails). The mortality was modelled using the lifetables for the Danish general population and disease-specific mortality, reflecting the suicide-related death between the different health states [15, 16]. The impact on mortality for each treatment arm was captured through the state transitions in the model, given that suicide-related death is expected to differ between health states.

During the trials, the patients were treated in a hospital (inpatient setting). This is the treatment setting captured in the model by default. However, as illustrated in Figure 2, the model includes three additional treatment settings: outpatient, emergency department (ED) and home care. The model includes inputs for the proportion of patients treated in every setting, however, only an inpatient setting was considered relevant for this assessment of esketamine for patients with MDSI with increased risk of suicide in Denmark.

3.2.2 Choice of health states

The health states used in the model were based on the definitions used in the clinical trials and these align with the relevant disease-specific outcomes and the disease progression.

The following three health states were defined:

- Remission
- Response
- MDE

The definition of each health state is described in section 2.1.

The model was developed to accurately reflect the patient pathway, however, state transitions in the model have a neglectable impact on the results since these transitions are only driven by the overall survival (OS) differences. To illustrate the limited impact on the state-transition model versus a simple cost model, a simplified analysis was developed, where the costs were not based on underlying state transitions. This can be found in appendix 9.3.

3.2.3 Half cycle correction

No half cycle correction (HCC) was applied in the model. This was omitted due to the varying cycle length, corresponding to every point at which efficacy outcomes were measured during the trials. The short time horizon of 90 days reflects the ASPIRE-I and ASPIRE-II follow-up.

3.3 Patient population and comparators

3.3.1 Patient population

The DMC protocol defined the patient population for both clinical question 1 and clinical question 2 as follows:

1) *"Inpatients over 18 years of age with MDD, where the doctor assesses that there is a need for urgent treatment to reduce the risk of suicide, and who cannot be treated with ECT, e.g., because ECT is contraindicated or because the patient has refused treatment with ECT"*

2) *"Inpatients over 18 years of age with MDD, where the doctor assesses that acute treatment is needed to reduce the risk of suicide"*

Therefore, to align with the DMC assessment for this submission, the base case analysis has been conducted for patients with an acute increased risk of suicide from the ASPIRE-I and ASPIRE-II trials used for both populations in clinical question 1 and 2 due to the lack of data on the efficacy of ECT for this patient population, see clinical submission section 5 for more details. Furthermore, subgroup analyses were conducted in line with the DMC protocol for patients with CGI-SS-r ≥4 at baseline [8]. This subgroup can be selected in the "*Settings*" sheet in the health economic model.

3.3.2 Comparators

The model compared esketamine plus SoC to SoC alone and ECT plus SoC, respectively, as defined in the DMC protocol [8].

4 Model inputs

4.1 Perspective

The perspective of the economic model was a restricted societal perspective, which included costs related to drug acquisition, drug administration, monitoring, adverse events, patient time, and transportation. Indirect (productivity) costs were not included as per the DMC's guidelines [13]

4.2 Time horizon

For the base case, a time horizon of 90 days was applied to reflect an acute episode of MDSI. A time horizon of 90 days was expected to be sufficiently long enough to capture all important differences in costs or clinical outcomes between the comparators for short-term acute treatment for patients with MDSI. The 90 days did further align with the period patients were followed in the ASPIRE-I and ASPIRE-II trials.

4.3 Discounting

The discounting approach in the model is in line with the guidelines from the DMC that refers to the Danish Ministry of Finance guidelines with an annual discounting rate for future costs of 3.5% for model years >1 to ≤35 and 2.5% for model year 35 to 70. The health economic model time horizon is set to 90 days and consequently, discounting will not affect the results as the first year is not discounted.

4.4 Clinical inputs

4.4.1 Treatment Discontinuation

To reflect the actual dosing used in clinical practice (as opposed to the intended dosing specified in the summary of product characteristics [SmPC]), the model includes all-cause treatment discontinuation risk to account for patients who discontinue treatment for other reasons than lack of response. Table 2 shows the risk of discontinuation derived from ASPIRE-I and ASPIRE-II trials. The discontinuation risk was only applied for patients on treatment with esketamine, while these patients will continue to receive SoC.

Table 2. All-cause discontinuation risk [10, 11]

	Esketamine + SoC
Discontinuation risk (per day)	0.007

Abbreviations: *SoC = Standard of Care*

4.4.2 Health state transitions

4.4.2.1 MSDI population

Efficacy estimates up to day 90 were informed by the pooled data analysis of ASPIRE-I and ASPIRE-II trials for the esketamine plus SoC arm and the SoC alone arm. Patients were assessed at every administration of esketamine and post-treatment follow-up visits, see section 3.2.1 or the clinical section of the application, section 5.2.1.

Due to the lack of relevant efficacy data for ECT, efficacy estimates for the ECT plus SoC arm were assumed to be similar to the esketamine plus SoC arm.

Table 3 and Table 4 shows the observed efficacy outcomes for all patients in the pooled ASPIRE-I and ASPIRE-II analysis [17]. The tables show the state membership per specific measurement during the time horizon observed in the ASPIRE trials for esketamine plus SoC and SoC alone.

Table 3. Response and Remission Inpatient Setting – esketamine + SoC, MDSI population

Clinical data of Esketamine + SoC			
	Remission	Response	MDE
Day 1*	10.6%	15.9%	73.4%
Day 2	20.4%	14.6%	65.0%
Day 4	23.9%	18.1%	57.9%
Day 8	25.7%	22.1%	52.1%
Day 11	28.8%	20.8%	50.2%
Day 15	32.7%	23.0%	44.0%
Day 18	31.4%	19.9%	48.3%
Day 22	36.7%	22.1%	40.8%
Day 25†	42.0%	17.7%	39.8%
Day 28§	45.3%	13.2%	41.1%
Day 32	52.6%	21.1%	25.8%
Day 39	46.3%	18.4%	34.6%
Day 46	44.7%	17.9%	36.7%
Day 53	51.6%	11.6%	36.0%
Day 67	52.6%	12.6%	33.8%
Day 90	51.6%	9.0%	38.2%

Abbreviations: *SoC = standard of care; MDE = Major depressive episode*

*Evaluated at 4-hour post-dose; †Evaluated on day 25 pre-dose; §Start of the follow-up phase

Table 4. Response and Remission Inpatient Setting – SoC alone, MDSI population

Clinical data of SoC alone			
	Remission	Response	MDE
Day 1*	5.8%	8.9%	85.3%
Day 2	9.8%	15.6%	74.7%
Day 4	14.7%	20.0%	65.3%
Day 8	20.4%	21.3%	58.2%
Day 11	23.1%	19.1%	57.8%
Day 15	25.8%	18.2%	56.0%
Day 18	27.6%	16.4%	56.0%
Day 22	27.6%	18.7%	53.8%
Day 25†	30.7%	16.0%	53.3%
Day 28§	30.3%	21.1%	48.6%
Day 32	41.1%	22.7%	36.2%
Day 39	40.0%	26.0%	34.0%
Day 46	36.8%	19.5%	43.8%
Day 53	40.5%	21.1%	38.4%
Day 67	40.5%	25.4%	34.0%
Day 90	50.3%	12.4%	37.3%

Abbreviations: *SoC = standard of care; MDE = Major depressive episode*

*Evaluated at 4-hour post-dose; †Evaluated on day 25 pre-dose; §Start of the follow-up phase

4.4.2.2 CGI-SS-R ≥4 subgroup

Efficacy estimates up to day 90 were informed by the pooled data analysis of ASPIRE-I and ASPIRE-II trials for the esketamine plus SoC arm and the SoC alone arm. For ECT, the same approach was applied as for the overall population.

Table 5 and Table 6 shows the observed data efficacy outcomes for patients with a CGI-SS-R ≥4 from the pooled ASPIRE-I and ASPIRE-II analysis.

Table 5. Response and Remission Inpatient Setting – esketamine + SoC, CGI-SS-R ≥4 subgroup

Clinical data of esketamine + SoC subgroup			
	Remission	Response	MDE
Day 1*	7.1%	15.8%	77.1%
Day 2	16.4%	12.2%	71.4%
Day 4	20.0%	20.0%	60.0%
Day 8	24.3%	22.1%	53.6%
Day 11	26.4%	22.2%	51.4%
Day 15	29.3%	25.7%	45.0%
Day 18	30.0%	20.7%	49.3%
Day 22	33.6%	25.0%	41.4%
Day 25†	36.4%	24.3%	39.3%
Day 28§	38.6%	13.5%	47.9%
Day 32	42.9%	17.1%	40.0%
Day 39	37.1%	15.8%	47.1%
Day 46	36.4%	12.2%	51.4%
Day 53	42.9%	9.2%	47.9%
Day 67	41.4%	11.5%	47.1%
Day 90	41.4%	9.3%	49.3%

Abbreviations: *SoC = standard of care*

*Evaluated at 4-hour post-dose; †Evaluated on day 25 pre-dose; §Start of the follow-up phase

Table 6. Response and Remission Inpatient Setting – SoC alone, CGI-SS-R ≥4 subgroup

Clinical data for SoC alone, subgroup			
	Remission	Response	MDE
Day 1*	3.5%	10.7%	85.8%
Day 2	8.5%	13.5%	78.0%
Day 4	11.3%	19.2%	69.5%
Day 8	18.4%	20.6%	61.0%
Day 11	22.7%	23.4%	53.9%
Day 15	26.2%	18.5%	55.3%
Day 18	27.0%	16.3%	56.7%
Day 22	26.2%	22.0%	51.8%
Day 25†	32.6%	17.8%	49.6%
Day 28§	24.1%	19.9%	56.0%
Day 32	32.6%	20.6%	46.8%
Day 39	30.5%	23.4%	46.1%
Day 46	31.2%	19.2%	49.6%
Day 53	35.5%	19.1%	45.4%
Day 67	34.0%	21.3%	44.7%
Day 90	44.7%	10.6%	44.7%

Abbreviations: *SoC = standard of care*

*Evaluated at 4-hour post-dose; †Evaluated on day 25 pre-dose; §Start of the follow-up phase

4.4.3 Mortality

MDD represents a major source of risk for suicidality [18]. The model captured survival through both background mortality and disease-specific mortality. Firstly, the survival of the general population from Denmark Statistics, HISB8 table for the period 2019 to 2020, stratified by age and sex, was used to set the background risk of death [19].

The model specifically captures the rate of suicide attempts stratified by health state, and the proportion of these fatal suicide attempts. These were informed by estimates of excess mortality for patients with MDD from published literature, see Table 7 [15, 16].

Table 7. Suicide-related Death risk

Health State	Suicide Attempts (Rate per-day)	% Of Fatal Suicide Attempts
Remission[15]	0.0004	0.0626
Response*	0.0020	0.0817
MDE[16]	0.0036	0.1009

Abbreviations: *MDE = major depressive episode*

*Assumed mid-point between MDE and remission

Table 8 presents survival predictions in the model for each treatment arm and the estimated difference between Esketamine and the comparators. Since the same efficacy data was applied for esketamine- and ECT-arms, mortality predictions are not different between these two arms are. The accumulated difference in mortality between esketamine and SoC was 0.15% at the end of the 90 day time horizon. Consequently, this element has a very minor impact on the outcomes of the model.

Table 8. Survival predictions for 90 days for esketamine + SoC, SoC, and ECT + SoC

Health State	Proportion alive at day 90	Difference esketamine vs. comparator
Esketamine + SoC	0.983588	
SoC alone	0.982125	-0.001463
ECT + SoC	0.983588	0.000000

Abbreviations: *ECT = Electroconvulsive Therapy, SoC = Standard of Care*

4.5 Health care resource use and costs

To understand the patient pathway and resource use associated with the patient populations of scope in Denmark, four clinical experts within the treatment of MDSI patients in Denmark were consulted [20].

Given the clinical practice of treating MDSI patients in Denmark, it was assumed that patients would not be discharged from the hospital before their condition had stabilised. Consequently, health state specific costs were not applied to avoid double counting, since all the relevant costs were assumed to be accrued and included in the hospital admission.

All costs reported were in Danish kroner (DKK) and were based on DRG tariffs, official unit cost catalogues, and medicinpriser.dk. All drug costs were reported as the pharmacy purchase prices (AIP), where the lowest cost alternative was used in the health economic assessment [21].

4.5.1 Treatment costs

4.5.1.1 Esketamine

Esketamine is a nasal spray administrated at a dose of 84 mg. A nasal spray consists of 28 mg of esketamine and is administrated over three administrations with 5 minutes between each administration. This is equivalent to three units of esketamine per administration. Package and strength per unit of esketamine are

illustrated in Table 9. The drug acquisition cost of esketamine is 4,082.73 DKK per dose when using the cheapest alternative of the available packs [21]. Patients with MDSI will receive esketamine two times a week over a four-week period (up to 8 doses in total with the last dose on day 25).

Table 9. AIP price of esketamine per unit of 28 mg[21]

Esketamine (SPRAVATO®)	Unit per pack	Strength per unit (mg)	Price AIP (DKK)	Price per unit (DKK)
SPRAVATO® (499425)	1	28	[redacted]	[redacted]
SPRAVATO® (546611)	2	28	[redacted]	[redacted]
SPRAVATO® (484104)	3	28	[redacted]	[redacted]
			Price applied in model (DKK)	[redacted]

Abbreviations: *mg = milligram; AIP = Pharmacies purchase price; DKK = Danish krone*

4.5.1.2 Antidepressants, SSRI and SNRI (SoC)

Treatment costs of SoC were based on the currently available guidelines informed by The Council for the Use of Expensive Hospital Medicines (RADS) from 2015 [22]. The current SoC in Denmark consists of antidepressants, SSRI and SNRI. The latest recommendation from 2015, does not include a specific guideline for the treatment of patients with MDSI. It is recommended that adult patients with unipolar depression should receive treatment consisting of SSRI. The first choice recommended SSRI is sertraline for these patients and the second choice is either SSRIs; citalopram or escitalopram, or SNRIs; duloxetine or venlafaxine [22]. In the ASPIRE-I and ASPIRE-II trials, patients with MDSI were treated with oral SSRI and/or SNRI once daily. After an acute episode of MDSI patients would continue the treatment with SSRI and SNRI.

As no updated recommendation has been issued to inform this analysis, four SSRI/SNRI were included in the model in line with the current guidelines. This is in line with the approach used in the submission of esketamine assessed by the DMC for patients with treatment-resistant depression (TRD) [23, 24].

Table 10 shows the market share, daily dose, units, strength, price per unit and per pack of the included drugs [21]. The doses presented for SSRI and SNRI was used for calculating the drug cost associated with SSRI and SNRI for both the MSDI population and the CGI-SS-R ≥4 subpopulation. The AIP prices of sertraline, escitalopram, duloxetine, and venlafaxine were sourced from medicinpriser.dk. As no data about the market shares between these drugs were available for these patients specifically, equal market shares were assumed. This approach was also used in the submission of esketamine for patients with TRD which was accepted by the DMC. The cost of SoC is estimated to be 0.85 DKK per day, see Table 10. The cost of SoC is very low and will have minimal impact on the results of the analysis.

Table 10. Overview of the market share distribution between the OAD, number of doses per week, daily dosage, unit cost per mg and weighted acquisition cost per day [23, 24]

Oral AD	Market share (%)	Daily dose per day (mg)	Strength per unit (mg)	Units per pack	Cost per pack (DKK)
Sertraline "Accord" (38009)	25	200	100	100	32
Escitalopram "Accord" (182023)	25	20	20	98	24.1
Duloxetine "Accord" (440477)	25	120	60	98	53.1
Venlafaxine "Medical Valley" (586579)	25	375	150	110	62.8
Weighted acquisition cost per day					0.85

Abbreviations: *mg = milligram; DKK = Danish krone*

Other antidepressants than those included in this analysis can be used in the treatment of patients with MDSI. Additional antidepressants were used in the trials, such as mirtazapine, which is recommended for patients who further suffer from anxiety and insomnia [22]. However, since SoC was used in all treatment arms as background therapy in this model and the difference in mortality between esketamine and SoC stated in section 4.4.3 is expected to be limited, the impact on the costs is expected to be negligible.

4.5.1.3 ECT

Clinical experts were asked to estimate the resource use associated with ECT treatment in Denmark, including the time healthcare professionals (HCP) spend on the procedure and post-monitoring of the patient [20].

Three costing approaches can be selected in the model: the first approach is a Danish DRG tariff-based approach, the second approach is a micro-costing approach, see appendix 9.4, and third is a tariff derived from the National Institute for Health Care Excellence (NICE), used in a recent published Swedish cost utility analysis (CUA) of esketamine compared to ECT within TRD.

The Swedish CUA was investigating treatment of esketamine compared to ECT for TRD patients [25]. Thus, even though the results of this analysis are not relevant for this application, due to the different indication and local population, the cost per ECT session of £558 from NICE could be informative to explore the impact on the result. The ECT cost per session was converted to Danish Kroner [29/03/2022] and converted to 2022 values costs using consumer price index, leading to a cost of 5,196 DKK per session of ECT. This cost is very similar to the micro-costing scenario in this model. The Danish DRG-based approach was applied in the base case to be both conservative in favour of ECT and to align with the approach applied for estimating other unit costs in the model. A scenario analysis was performed using the micro-costing approach and the NICE tariff to see the impact on the results, see section 5.2.2. Furthermore, to provide a simple overview of the impact of the ECT session numbers and costs, a threshold analysis was developed, presenting the incremental results versus ECT of 1 to 20 sessions for all three costing approaches compared to esketamine, see section 5.2.3.

The treatment- and monitoring costs associated with ECT were based on clinical experts' testimonies and associated DRG tariffs [20, 26].

Clinical experts stated that ECT would be administrated in blocks of 3 sessions per week and patients would be admitted to the hospital throughout the entire treatment period of ECT. The estimated cost of ECT was based on a Danish DRG tariff of 2,770 DKK per treatment session [20, 26].

According to the ECT guideline published in 2020, patients with depression receive 6 to 12 sessions of ECT [7]. According to a study done by Bjørnshauge et al., which is used in the ETC guideline, the number of sessions per patient has been increasing in recent years [7]. Bjørnshauge et al. estimated the average number of ECT sessions per patient to be 11.5 sessions in 2017 [7].

No published data on the number of ECT sessions for patients with MDSI is available, for further details, see section 6.2.4 of the clinical submission. Consequently, to estimate the treatment duration of ECT in Danish clinical practice for MDSI patients, elicitations from three Danish clinical experts were used. The clinical experts stated that the number of sessions ranged from 6 to 20 sessions per patient.

Based on the clinical expert testimonies and the study used in the ECT guideline, the average number of ECT sessions was assumed to be 12 for the base case analysis for both the MDSI full population and the subpopulation with a CGI-SS-r ≥4. However, this estimate might be conservative for the CGI-SS-r ≥4 patients due to the more severe state of the disease. The total cost of ECT was applied as a one-time cost of 33,231 DKK in cycle 1 in the health economic model, see Table 11. Scenario analyses were performed assuming 6 and 20 ECT sessions to illustrate the impact of the result when the number of sessions was lower and higher, respectively.

Table 11. Total cost of ECT sessions

	Unit cost (DKK)	Number of sessions	Total cost (DKK)*	DRG code
ECT	2,770.00	12	**33,231.00**	Diagnosis: DF332, Procedure: BRXA1, DRG group: 19MA98

Abbreviations: *ECT = Electroconvulsive Therapy; DKK = Danish krone*

***Note:** Total cost aligns with the model results, total cost was multiplied with the proportion of patients on treatment in cycle 1.*

4.5.2 Drug administration and monitoring costs

4.5.2.1 Administration cost

4.5.2.1.1 Esketamine

Esketamine is a self-administered treatment but needs to be administered under the supervision of an HCP. During and after administration, patients are monitored for sedation and dissociation until the patient is stable, based on clinical judgement. Patients will typically need to wait 5 minutes between self-administering each dose, and so the typical administration time is assumed to be 10 minutes for the 84 mg dose (three doses).

Following the administration, patients will need to be observed for a minimum of 40 minutes. Requirements for HCP supervision and post-dose observation as per the SmPC for esketamine are stated to be until the HCP confirms the patient is clinically stable and is allowed to leave the clinic/facility where esketamine has been administered [27].

In the ASPIRE-I and ASPIRE-II trials, patients were observed for up to 90 minutes post-dose [10, 11]. Previous trials for patients with TRD showed that patients on average would be monitored for 90 minutes before being discharged [24]. Thus, the monitoring period after each session was assumed to be 90 minutes in this assessment.

It was assumed that an administration of esketamine would correspond to a psychiatric outpatient visit cost of 1,944 DKK including the administration of esketamine. The post-dose monitoring was assumed to be handled by a nurse, assuming the nurse can monitor three patients simultaneously, leading to a cost of 220 DKK per patient (441 DKK x 1,5 / 3), see Table 12. The assumption is in line with the previous assessment of esketamine for patients with TRD, where the DMC assumed that the administration of esketamine consisted of a DRG tariff of a psychiatric outpatient visit and post-dose monitoring by a nurse with the same assumption of being able to monitor three patients simultaneously [23, 24].

Patients with an acute episode of MDSI will be hospitalised for an extended period, see section 4.5.4. It was assumed that cost of administration and monitoring would be included within the cost of hospitalisation. For this reason, the administration and monitoring cost of esketamine is only applied to model cycles after patients have been discharged from the hospital. Administration and monitoring costs relating directly to esketamine are excluded when patients have completed all administrations of esketamine on day 25. Patients will then continue treatment with SoC, including monitoring visits, section 4.5.2.1.2 and 4.5.2.2.

The average administration for a patient treated with esketamine nasal spray is presented in Table 12. The average cost was estimated to be DKK 2,164.5 per session including the DRG tariff of a psychiatric outpatient visit of 1,944 DKK and the hourly rate of a nurse of 441 DKK, based on the Medicines Council´s valuation of unit costs 2022[28].

Table 12. Administration and monitoring resource use and costs for patients treated with esketamine [28] [26]

Resource use	Cost per session/hour (DKK)	Total duration required (hours)	Number of patients in cohort	Cost per patient	Average cost per session per patient (DKK)
Administration of esketamine, DRG for psychiatric ambulant visit	1,944.00	-	1	1,944.00	2,164.50
Nurse	441.00	1.5	3	220.50	

Abbreviations: *DKK = Danish krone*

4.5.2.1.2 SSRI and SNRI (SoC)

Oral treatment is self-administrated, for that reason no administration costs were assumed for SoC treatment consisting of oral administration of SSRI and SNRI. Since patients were on SoC before an event occurs, no one-off administration training was expected for SoC.

4.5.2.2 Monitoring costs

There are no Danish guidelines describing how often patients with MDSI should be monitored. One clinical expert provided information on how patients with MDSI are generally observed in Danish clinical practice. Therefore, the monitoring assumptions for patients with MDSI were based on one clinical expert statement. It was assumed that patients with MDSI would be monitored closely under and after an acute episode of MDSI. For that reason, patients were assumed to visit the hospital every 14 days for monitoring after the initial discharge from the hospital.

In the previous assessment of esketamine for TRD patients, it was accepted by the DMC to assume that patients would be monitored monthly [23, 24]. However, we assumed that patients will be monitored more closely and frequently after an episode of MDSI.

For all interventions it was assumed that any monitoring costs were captured in the hospitalisation costs, i.e., no additional monitoring costs were applied during the hospitalisation period. According to the Danish clinical experts, patients receiving ECT would be admitted for the whole administration period, whereas patients treated with esketamine would be discharged before ending the administration period of 25 days. Consequently, patients receiving esketamine would return to the hospital for any remaining administrations following their hospital discharge[20]. Monitoring is expected to be counted from the last day of administration or hospital discharge. Therefore, the number of monitoring visits for esketamine were based on the maximum administration period of 25 days (see section 4.5.2.1.1), whereas the number of monitoring visits for SoC and ECT were based on the length of the hospitalisation stays (21 and 28 days), see section 4.5.4. This was assumed as all administrations and monitoring were supervised at the hospital for these periods. The number of monitoring visits were calculated by dividing the remaining days following the treatment duration or hospitalisation by the 14 days interval between visits. The monitoring costs for the different comparators was estimated as follows:

- *Esketamine: (90 – 25 days)/14 = 4.64 ≈ 4 actual visits*
  - 90 days (time horizon)
  - 25 days (treatment duration for esketamine)
  - 14 days (intervals between monitoring visits)
- *SoC: (90 days – 21 days)/14 = 4.92 ≈ 4 actual visits*
  - 90 days (time horizon)
  - 21 days (days of hospitalisation)

    - 14 days (intervals between monitoring visits)
- *ECT: (90 days – 28 days)/14 = 4.43 ≈ 4 actual visits*
    - 90 days (time horizon)
    - 21 days (days of hospitalisation)
    - 14 days (intervals between monitoring visits)

This was modelled manually for each comparator sheet column named "Cost flag (after discharge)". However, the number of monitoring visits all interventions irrespective on the calculation approach, since only actual visits within the 90 days time horizon were counted.

The monitoring cost was estimated as a psychiatric outpatient ambulatory visit at a cost of 1,944 DKK, based on the psychiatric DRG tariff 2022, resulting in a total monitoring cost of 7,776 DKK for the 90 day time horizon [26].

4.5.3 Adverse events costs

Patients with MDSI will be closely monitored and admitted to the hospital for adverse events (AE). Consequently, the occurrence of AEs would be expected to be discovered and resolved during the hospitalisation or monitoring visits. A full description of the AEs experienced by patients in the ASPIRE-I and -II trials is provided in sections 6.1.2.1 and 6.1.2.2 of the clinical application. For this reason, no AE costs were included in this economic assessment of esketamine. This assumption is in line with the previous assessment of esketamine for patients with TRD, where the DMC applied a similar rationale by removing AE costs [23].

ECT is a well-established treatment approach used within psychiatry, however, the evidence of its comparative efficacy and safety is limited within the MDSI population. ECT is generally hampered by the cognitive side effects such as anterograde and retrograde amnesia, which is also rated by patients as the most troublesome [29]. However, due to the lack of relevant data, we have not been able to quantify these. For that reason and to maintain consistency in the approach for all included interventions, the costs of AEs for ECT were not included in the health economic assessment. Furthermore, the same assumption of AEs being diagnosed and treated while already being hospitalized can be assumed for ECT. However, a clinical expert stated that patients treated with ECT could be admitted for up to an extra week to treat potential AEs while most AEs for esketamine were shown to resolve within a few hours [10, 11, 20]. For this reason, the exclusion of AEs will potentially underestimate the total cost in the ECT arm.

4.5.4 Hospitalisation costs

Danish clinical expert testimonies were used to inform the hospitalisation admission lengths for patients treated with esketamine, SoC alone, and ECT + SoC.

Hospitalisation costs were included in the economic assessment as patients with MDSI will be admitted to the hospital. The health economic model includes the cost of hospitalisation as a one-off cost when patients enter the model. A hospital bed day was costed at a rate of 3,939 DKK per day, based on the interactive DRG tariff for psychiatry 2022 [26, 28].

Clinical experts expect the treatment with esketamine will lead to shorter hospital admissions as the treatment with esketamine results in a quicker response compared to SoC. A Danish clinical expert stated that patients treated with SoC would be admitted for at least 14 days and often up to a month as the efficacy of ADs can take up to 4-6 weeks to show a positive effect for patients [10, 11, 20]. Consequently, 21 hospitalisation days (average of 14 and 28 days) were assumed for patients treated with SoC alone, based on the clinical expert statements.

The clinical experts stated that patients with MDSI would be admitted to the hospital for at least 3-4 weeks and more likely 5-6 weeks if patients are not experienced in receiving ECT [20]. Based on this, patients treated with ECT were expected to be admitted to the hospital for 28 days (4 weeks), where they would receive treatment with ECT three times a week for four consecutive weeks.

For esketamine, clinicians expect patients to be admitted for around 14 days initially, and this duration is expected to be reduced over time as the clinicians familiarise themselves with the treatment.

The hospitalisation days were also captured in the ASPIRE-I and ASPIRE-II trials. The weighted average for the two trials was 19 and 18 hospitalisation days for esketamine and SoC alone, respectively. This should be interpreted with caution since this is more a reflection of both trial guidelines and local clinical practice in the countries, where the trials were conducted. To be reflective of Danish clinical practice, the Danish clinical expert statements were consequently used for the base case. The hospitalisations days from the weighted analysis of the trial data is presented in a scenario analysis, see section 5.2.

The hospitalisation cost for patients treated with esketamine, SoC and ECT is presented in Table 13 and was estimated to be 55,146 DKK, 82,719 DKK, and 110,292 DKK respectively.

Table 13. Hospitalisation costs

	Number of days	Cost of a bed day (DKK) [28]	Total cost (DKK)
Esketamine + SoC	14	3,939.00	55,146.00
SoC alone	21		82,719.00
ECT + SoC	28		110,292.00

Abbreviations: *SoC = Standard of Care; ECT = Electroconvulsive Therapy*

4.5.5 Patient and transportation cost

Patients and transportation costs were based on the assumptions described in the previous sections 4.5.1, 4.5.2, and 4.5.4, however using different unit costs, i.e., the cost of patient time and transportation in line with the DMC method guidelines [13].

The unit cost per patient hour was estimated to be 181 DKK and the transportation cost was estimated to be 3.51 DKK per km with the assumption of an average distance to the hospital of 40 km (roundtrip) in line with the DMC guidelines, see Table 14 [28, 30]. It was further assumed that patients would spend 30 minutes on transportation per visit (roundtrip).

Table 14. Patient and transportation unit costs [28]

	Unit costs (DKK)	Source
Patient cost per hour	181.00	Medicinrådets værdisætning af enhedsomkostninger, 2022 [28]
Transportation cost (roundtrip)	140.40	

Abbreviations: *DKK = Danish krone*

Table 15 shows the patient and transportation cost associated with the administration of esketamine over the 90-day time horizon. Patients going to the hospital after being discharged from the last four administrations of esketamine resulting in a patient and transportation cost of 2,009.6 DKK for the remaining treatment period.

Table 15. Patient and transportation associated with administration of esketamine

	Number of administrations	Hours per administration	Hours used on transport per admin.	Patient hours	Cost per hour (DKK)	Cost (DKK)	Transportation (units)	Cost per transportation (DKK)	Cost (DKK)	Total cost (DKK)
Esketamine	4	1.5	0.5	8	181.00	1,448.00	4	140.40	561.60	2,009.60

Abbreviations: *DKK = Danish krone, Admin = Administration*

Table 16 shows the patient time and transportation cost for all three comparators including the assumed patient hours and frequency of administration and monitoring visits. According to the clinical expert, a monitoring visit is estimated to have a duration of 30 minutes. As all three interventions are expected to be associated with the same number of visits, see sections 4.5.1.3 and 4.5.2, the patient and transportation cost for monitoring for all treatment arms was estimated to be 1,286 DKK for the 90-day time horizon.

Table 16. Patient and transportation costs associated with monitoring – All treatments

	Number of administrations	Hours per administration	Hours used on transport per visit	Patient hours	Cost per hour (DKK)	Cost (DKK)	Transportation (units)	Cost per transportation (DKK)	Cost (DKK)	Total cost (DKK)
Esketamine, SoC, and ECT	4	0.5	0.5	4	181.00	724.00	4	140.40	561.60	1,285.60

Abbreviations: *DKK = Danish krone*

For patient- and transportation costs related to hospitalisation, an additional assumption was applied, related to the number of patient hours spent per admitted day. In the base case, only 16 hours per day were assumed, as this was expected to be the time patients can use on other activities if they are not admitted to the hospital (i.e., assumed 8 hours of sleep per day). The cost of patient time and transportation cost were applied as a one-off cost in cycle 1 for each comparator in the model. Table 17 shows the total patient- and transportation cost for the admission period of 40,775 DKK, 61,047 DKK and 81,319 DKK for patients treated with esketamine plus SoC, SoC alone, and ECT plus SoC, respectively.

Table 17. Patient and transportation costs associated with hospitalisation

	Days admitted	Hours per day	Hours used on transport per visit	Patient hours	Cost per hour (DKK)	Cost (DKK)	Transportation (units)	Cost per transportation (DKK)	Total cost (DKK)
Esketamine + SoC	14	16	0.5	224.5	181.00	40,634.50	1	140.40	40,774.90
SoC alone	21			336.5		60,906.50			61,046.90
ECT + SoC	28			448.5		81,178.50			81,318.90

Abbreviations: *DKK = Danish krone*

It is expected that patients admitted to the hospital with an acute episode of MDSI will be accompanied by a caregiver during their hospitalisation. During the admission period stated in section 4.5.4, it was assumed that 50% of patients in each of the three treatment arms would have a caregiver once a day for two hours, see Table 18. This equals a total relative time and transportation costs of 4,151 DKK, 6,225 DKK, and 8,301DKK for caregivers to patients treated with esketamine plus SoC, SoC alone, and ECT plus SoC respectively.

Table 18. Patient and transportation costs associated with caregiver visits

	Proportion of relatives visiting every day (%)	Number of hospitalisation days	Number of hours per visit	Hours used on transport per visit	Caregiver' hours	Cost per hour caregiver (DKK)	Cost (DKK)	Transportation (units)	Cost per transportation (DKK)	Cost (DKK)	Total cost (DKK)
Esketamine + SoC	50	14	2	0.5	17.5	181.00	3,167.50	7	140.40	982.80	4,150.30
SoC alone	50	21			26,25		4,751.25	10.5		1,474.20	6,225.45
ECT + SoC	50	28			35.0		6,335.00	14		1,965.60	8,300.60

Abbreviations: *DKK = Danish krone*

The caregiver and transportation costs were included in the total patient time and transportation cost. Table 19 presents the total patient and transportation cost of 47,400 DKK, 68,519 DKK, and 89,597 DKK for patients treated with esketamine plus SoC, SoC alone, and ECT plus SoC respectively for the entire time horizon.

Table 19. Total patient and transportation cost

	Patient time cost (DKK)	Transportation cost (DKK)	Total patient and transportation cost (DKK)*
Esketamine + SoC	45,974.00	2,246.40	**48,183.02**
SoC alone	66,381.75	2,176.20	**68,519.30**
ECT + SoC	88,237.50	2,667.60	**90,863.58**

Abbreviations: *DKK = Danish krone*

***Note:** Total cost aligns with the model results.*

5 Results

5.1 Base case results

5.1.1 Patients ineligible for ECT

Results of the base case analysis for patients ineligible for ECT is presented below in Table 20. The analysis estimated a mean incremental cost per patient of esketamine plus SoC compared to SoC alone of [redacted] over a time horizon of 90 days.

Table 20. Base case analysis patients ineligible for ECT

	Esketamine + SoC (DKK)	SoC alone (DKK)	Incremental costs (DKK)
Drug cost	[redacted]	75.61	[redacted]
Administration cost	6,725.63	0.00	6,725.63
Monitoring cost	8,447.71	7,674.54	773.17
AE cost	0.00	0.00	0.00
Hospitalisation	55,129.73	82,692.10	-27,562.40
Patient time and transportation	48,183.02	68,519.30	-20,336.36
Total cost	[redacted]	[redacted]	[redacted]

Abbreviations: *SoC = Standard of Care; AE = Adverse events; mg = milligram; DKK = Danish krone*

5.1.1.1 CGI-SS-r ≥4 subpopulation

The results of the subpopulation for patients ineligible for ECT is presented below in Table 21. The analysis estimated a mean incremental cost per patient of esketamine plus SoC compared to SoC alone of [redacted] over a time horizon of 90 days for the subpopulation of patients with a CGI-SS-r ≥4.

Table 21. Subpopulation analysis ineligible for ECT

	Esketamine + SoC (DKK)	SoC alone (DKK)	Incremental costs (DKK)
Drug cost	[redacted]	75.55	[redacted]
Administration cost	6,724.77	0.00	6,724.77
Monitoring cost	8,436.00	7,666.64	769.36
AE cost	0.00	0.00	0.00
Hospitalisation	55,129.06	82,691.76	-27,562.70
Patient time and transportation	48,180.31	68,517.72	-20,337.40
Total cost	[redacted]	[redacted]	[redacted]

Abbreviations: *SoC = Standard of Care; AE = Adverse events; mg = milligram; DKK = Danish krone*

5.1.2 Patients eligible for ECT

Results of the base case analysis for patients eligible for ECT is presented below in Table 22. The analysis estimated a mean incremental cost per patient of esketamine plus SoC compared to ECT plus SoC of [redacted] over a time horizon of 90 days. Esketamine was associated with fewer costs with regards to drug/treatment cost, hospitalisation costs and patient and transportation cost compared to ECT in the time horizon of 90 days.

Table 22. Base case analysis patients eligible for ECT

	Esketamine + SoC (DKK)	ECT + SoC (DKK)	Incremental costs (DKK)
Drug cost	[redacted]	1,595.03	[redacted]
ECT sessions	[redacted]	33,306.38	-33,305.90
Administration cost	6,725.63	0.00	6,725.63
Monitoring cost	8,447.71	7,684.85	-478.80
AE cost	0.00	0,00	0.00
Hospitalisation	55,129.73	110,259.45	-55,516.93
Patient time and transportation	48,183.02	90,863.58	-43,463.70
Total cost	[redacted]	[redacted]	[redacted]

Abbreviations: *ECT = Electroconvulsive Therapy; SoC = Standard of Care; mg = milligram; DKK = Danish krone*

5.1.2.1 CGI-SS-r ≥4 subpopulation

Results of the subpopulation for patients eligible for ECT is present below in Table 22. The analysis estimated a mean incremental cost per patient of esketamine plus SoC compared to ECT plus SoC of [redacted] over a time horizon of 90 days. Esketamine was associated with fewer costs with regards to drug/treatment cost, hospitalisation costs and patient and transportation cost compared to ECT in the time horizon of 90 days for the subpopulation of patients with a CGI-SS-r ≥4.

Table 23. Subpopulation analysis eligible for ECT

	Esketamine + SoC (DKK)	ECT + SoC (DKK)	Incremental costs (DKK)
Drug cost	[redacted]	1,595.03	[redacted]
ECT sessions	[redacted]	33,305.40	-33,305.40
Administration cost	6,724.77	0.00	6,724.77
Monitoring cost	8,436.00	7,673.30	762.70
AE cost	0.00	0,00	0,00
Hospitalisation	55,129.06	110,258.13	-55,129.07
Patient time and transportation	48,180.31	90,860.60	-24,680.3
Total cost	[redacted]	[redacted]	[redacted]

Abbreviations: *ECT = Electroconvulsive Therapy; SoC = Standard of Care; mg = milligram; DKK = Danish krone*

5.2 Scenario analysis

The results of the different scenario analyses are presented in Table 24, Table 25, and Table 26.

5.2.1 Number of ECT sessions

A Scenario analysis was performed to investigate the impact of patients receiving more/fewer sessions of ECT. In the scenario with 6 sessions, hospitalisation was shortened to 14 days (manually) for the ECT arm. The scenario resulted in a total incremental cost of [redacted], see Table 24. The fewer sessions of ECT led to fewer treatment costs, patient time and transportation costs than esketamine which resulted in ECT being less costly compared to esketamine.

Table 24. Scenario, ECT eligible patients

	Esketamine + SoC (DKK)	ECT + SoC (DKK)	Incremental cost (DKK)
Drug cost	[redacted]	797.76	[redacted]
ECT sessions	0.00	16,690.79	-16,690.79

Administration cost	6,725.63	0.00	6,752.63
Monitoring cost	8,447.71	7,684.85	762.86
AE cost	0.00	0.00	0.00
Hospitalisation	55,129.73	55,129.73	0.00
Patient time and transportation	48,183.02	46,182.47	2,000.55
Total cost	[redacted]	**126,485.60**	[redacted]

Abbreviations: *ECT = Electroconvulsive Therapy; SoC = Standard of Care; AE = Adverse events; DKK = Danish krone*

In the scenario where patients would receive 20 sessions of ECT, patients would be admitted for 46 days (set manually) and then monitored three times within the 90 day time horizon. The scenario resulted in a total incremental cost of [redacted], see Table 25. More sessions of ECT led to an increase in the cost of treatment (drug cost), hospitalisation, patient time and transportation cost supporting esketamine in being less costly compared to ECT.

Table 25. Subgroup scenario, ECT eligible patients

	Esketamine + SoC (DKK)	ECT + SoC (DKK)	Incremental costs (DKK)
Drug cost	[redacted]	2,659.22	27,178.63
ECT sessions	0.00	55,459.34	-55,459.34
Administration cost	6,725.63	0.00	6,725.63
Monitoring cost	8,447.71	5,756.02	2,691,69
AE cost	0.00	0.00	0.00
Hospitalisation	55,129.73	181,140.53	-126,010.80
Patient time and transportation	48,183.02	147,991.84	-99,808.82
Total cost	[redacted]	**395,006.95**	[redacted]

Abbreviations: *ECT = Electroconvulsive Therapy; SoC = Standard of Care; AE = Adverse events; DKK = Danish krone*

5.2.2 ECT costing approach

A scenario analysis was performed to investigate the impact of the costing approach for ECT. The scenario using micro-costing resulted in a total incremental cost of [redacted], see Table 26. The incremental cost compared to the base case with the DRG costing approach would thereby increase by [redacted] in favour of esketamine.

The other scenario applying the NICE tariff resulted in a total incremental cost of [redacted], see Table 27. In this scenario, additional savings of 29,109 DKK for esketamine versus ECT were observed compared to the base case.

Consequently, if a micro-costing approach or the NICE tariff were used, the savings associated with esketamine compared to ECT would have been even greater than in the base case.

Table 26. Micro costing ECT, patients eligible for ECT

	Esketamine + SoC (DKK)	ECT + SoC (DKK)	Incremental costs (DKK)
Drug cost	[redacted]	1,595.53	[redacted]
ECT sessions	0.00	62,801.46	-62801.46
Administration cost	6,725.63	0.00	6,725.63
Monitoring cost	8,447.71	7,684.85	762.86

AE cost	0.00	0,00	0.00
Hospitalisation	55,129.73	110,259.45	-55,129.73
Patient time and transportation	48,183.02	90,863.58	-42,680.57
Total cost	[redacted]	[redacted]	[redacted]

Abbreviations: *ECT = Electroconvulsive Therapy; SoC = Standard of Care; AE = Adverse events; DKK = Danish krone*

Table 27. NICE tariff ECT, patients eligible for ECT

	Esketamine + SoC (DKK)	ECT + SoC (DKK)	Incremental costs (DKK)
Drug cost	[redacted]	1,595.53	28,242.32
ECT sessions	0.00	62,414.81	-62,414.81
Administration cost	6,725.63	0.00	6,725.63
Monitoring cost	8,447.71	7,684.85	762.86
AE cost	0.00	0,00	0.00
Hospitalisation	55,129.73	110,259.45	-55,129.73
Patient time and transportation	48,183.02	90,863.58	-42,680.57
Total cost	[redacted]	[redacted]	[redacted]

Abbreviations: *ECT = Electroconvulsive Therapy; SoC = Standard of Care; AE = Adverse events; DKK = Danish krone*

5.2.3 Threshold analysis, ECT costing approach

A threshold analysis was performed to investigate the impact of the costing approaches and average number of sessions for ECT. Length on hospital stays and number of monitoring visits were adjusted corresponding to the method used in section 4.5.2.2. The threshold analysis showed that esketamine would be cost saving using both the micro-costing approach and NICE tariff when patients on average are treated with more than six sessions. When applying the Danish DRG tariff, esketamine would be cost saving in patients receiving more than a mean of 7 sessions of ECT, see Figure 3. 7 and 8 sessions are significantly lower than the mean number of sessions applied in Denmark. Therefore, esketamine is expected to be cost saving compared to ECT irrespective of the scenario applied in the analysis.

Figure 3. Threshold analysis, ECT costing approach

	DRG tariff DK	Micro costing	NICE tariff
Cost per session	DKK 2.770,00	DKK 5.228,69	DKK 5.196,46

Mean number of ECT sessions	Incremental cost (ESK vs. ECT)		
	DRG tariff DK	Micro costing	NICE tariff
1	DKK 124.521,31	DKK 122.063,34	DKK 122.095,56
2	DKK 100.231,13	DKK 95.315,20	DKK 95.379,64
3	DKK 78.198,45	DKK 70.824,56	DKK 70.921,22
4	DKK 61.037,62	DKK 51.205,76	DKK 51.334,64
5	DKK 43.876,78	DKK 31.586,96	DKK 31.748,06
6	DKK 19.586,60	DKK 4.838,82	DKK 5.032,14
7	DKK 2.425,77	-DKK 14.779,98	-DKK 14.554,44
8	-DKK 14.735,07	-DKK 34.398,78	-DKK 34.141,02
9	-DKK 36.773,51	-DKK 58.895,19	-DKK 58.605,21
10	-DKK 53.934,35	-DKK 78.513,99	-DKK 78.191,79
11	-DKK 71.095,18	-DKK 98.132,79	-DKK 97.778,37
12	-DKK 95.385,36	-DKK 124.880,94	-DKK 124.494,29
13	-DKK 112.546,20	-DKK 144.499,73	-DKK 144.080,87
14	-DKK 129.707,03	-DKK 164.118,53	-DKK 163.667,45
15	-DKK 151.749,49	-DKK 188.618,96	-DKK 188.135,65
16	-DKK 168.910,33	-DKK 208.237,76	-DKK 207.722,23
17	-DKK 186.071,16	-DKK 227.856,56	-DKK 227.308,81
18	-DKK 210.361,34	-DKK 254.604,70	-DKK 254.024,73
19	-DKK 227.522,18	-DKK 274.223,50	-DKK 273.611,31
20	-DKK 244.683,01	-DKK 293.842,30	-DKK 293.197,89

Abbreviations: *ECT = Electroconvulsive Therapy; ESK = Esketamine; DKK = Danish krone, DRG = Diagnose Related Group*

6 Budget impact analysis

6.1 Methods

The budget impact model was developed to estimate the expected budget impact of recommending esketamine as a possible standard treatment in Denmark for MDSI patients as presented in the DMC protocol [8]. The budget impact was estimated per year for the first 5 years after the introduction of esketamine in Denmark.

The cost per patient model was partially nested within the budget impact model, and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the population in the cost per patient model.

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where esketamine is recommended as a standard treatment and the scenario where esketamine is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios. The budget impact model is built to distinguish between the two clinical questions and the subpopulation. Clinical question one was defined as ECT ineligible and clinical question two as ECT eligible in the dropdown selection in the “Market Shares” sheet in the model.

6.1.1 Incidence of patients each year

Janssen-Cilag estimated the incidence and prevalence of patients with MDSI population and patients with a CGI-SS-r ≥4 based on the same approach as the preliminary application and the ASPIRE trials, and Janssen-Cilag analysis in collaboration with an external partner were used (Table 28 and Table 29)[31] as well as the market uptake of the new drug with or without a recommendation, see section 6.1.2. The proportion of patients with a CGI-SS-R ≥4 score was based on the population in the ASPIRE trials, equivalent to 61.7% of the full MDSI population. The current lack of data prevents an exact estimate of patients eligible and ineligible for ECT. For this reason, it was assumed that the distribution between patients eligible and ineligible was 1:1.

Table 28. Prevalence and incidence of patients applied in the budget impact model, MDSI full population

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	1,126	1,126	1,126	1,126	1,126

Table 29. Prevalence and incidence of patients applied in the budget impact model, subpopulation with CGI-SS-R ≥4[10, 11]

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	695	695	695	695	695

6.1.2 Market Share

Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. Regardless, the estimates will be associated with uncertainty. The potential market share for esketamine with or without a recommendation is reported in Table 30 and Table 31 for patients ineligible for ECT and Table 32 and Table 33 for patients eligible for ECT.

Table 30. Yearly percentage of incident patients on esketamine or SoC alone, without a recommendation, MDSI population ineligible for ECT

Treatment	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
Esketamine	0.00	0.00	0.00	0.00	0.00
SoC	100.00	100.00	100.00	100.00	100.00

Abbreviations: *SoC = Standard of Care*

Table 31. Yearly percentage of incident patients on esketamine or SoC alone, with a recommendation, subpopulation with CGI-SS-R ≥4 ineligible for ECT

Treatment	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
Esketamine	24.00	43.00	56.00	63.00	66.00
SoC	76.00	57.00	44.00	37.00	34.00

Abbreviations: *SoC = Standard of Care*

Table 32. Yearly percentage of incident patients on esketamine or ECT, without a recommendation, MDSI population eligible for ECT

Treatment	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
Esketamine	0.00	0.00	0.00	0.00	0.00

ECT	100.00	100.00	100.00	100.00	100.00

Abbreviations: *ECT = Electroconvulsive Therapy*

Table 33. Yearly percentage of incident patients on esketamine or ECT, with a recommendation, subpopulation with CGI-SS-R ≥4 eligible for ECT

Treatment	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
Esketamine	24.00	43.00	56.00	63.00	66.00
ECT	76.00	57.00	44.00	37.00	34.00

Abbreviations: *ECT = Electroconvulsive Therapy*

6.1.3 Costs

Included costs in the budget impact model were drug costs, administration costs, monitoring costs, AE costs, and hospitalisation costs. Patient and transportation costs were not included as these are not part of the regional budgets. Discounting was not used in the budget impact model in line with DMC's methods guidelines [13].

6.2 Results

6.2.1 Base case results

Based on the base case assumptions, the estimated budget impact of recommending esketamine as a possible standard treatment in Denmark for the full population ineligible for ECT was [redacted] in year 5, shown in Table 34. Even though esketamine is associated with reduced costs compared to SoC in the cost per patient analysis for clinical question 1, esketamine is expected to have a positive net budget impact for clinical question 1, since patient and transportation costs are excluded from the budget impact analysis.

Table 34. Base case analysis, patients ineligible for ECT

Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *DKK = Danish krone*

Based on the base case assumptions, the estimated budget impact of recommending esketamine as a possible standard treatment in Denmark for the subpopulation ineligible for ECT was [redacted] in year 5, shown in Table 35.

Table 35. Subpopulation analysis, patients ineligible for ECT

Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *DKK = Danish krone*

Based on the base case assumptions, the estimated budget impact of recommending esketamine as a possible standard treatment in Denmark for the full population eligible for ECT was [redacted] in year 5, shown in Table 36

Table 36. Base case analysis, patients eligible for ECT

Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *DKK = Danish krone*

Based on the base case assumptions, the estimated budget impact of recommending esketamine as a possible standard treatment in Denmark for the subpopulation eligible for ECT was [redacted] in year 5, shown in Table 37.

Table 37. Subpopulation analysis, patients eligible for ECT

Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *DKK = Danish krone*

7 Discussion and conclusion

The economic assessment estimated that treatment with esketamine for patients with MDSI would be cost saving with an incremental cost of [redacted] versus SoC alone for the full population ineligible for ECT and an incremental cost of [redacted] versus ECT plus SoC for the full population eligible for ECT. For the subpopulation with a CGI-SS-r score ≥4, the incremental cost was [redacted] versus SoC and [redacted] versus ECT plus SoC for patients ineligible and eligible for ECT, respectively.

Esketamine + SoC was estimated to be cost saving compared to the treatment arm with SoC. This saving was due to the expected reduction in hospitalisation time for esketamine compared to SoC. The reduction in hospitalisation time was based only on Danish KOL testimony, which inherently makes the results very uncertain. However, the estimates are based on the best available evidence and is in line with the clinical pathway, considering esketamine has a considerable faster onset of treatment effects compared to SoC. In addition, this short and fixed treatment duration presents as a cost- and resource saving treatment given the rapid acting effect and the need for less personnel to be involved in the treatment administration and monitoring, thereby freeing up some of the limited resources.

Esketamine + SoC was also estimated to be cost saving compared to the ECT + SoC treatment arm. These costs were driven by the cost of the ECT procedure and the associated hospitalisation time. For this comparison, the estimates for the treatment duration of ECT were based on Danish clinical guidelines as well as testimony from several Danish clinical experts, which consequently reflects the expected costs of ECT in Danish clinical practice. Only in the scenario where the lowest number of expected ECT procedures were assumed, ECT was a less costly alternative. However, based on the expert testimony the actual mean number of procedures per patient is significantly higher than this scenario. Furthermore, the result of esketamine being cost saving compared to ECT was supported by the threshold analysis. This showed patients receiving more than seven sessions of ECT would result in higher costs compared to the treatment with esketamine when using the DRG tariff in the base case. The two other costing approaches illustrated that esketamine would be cost saving for patients receiving more than six sessions of ECT. These number of sessions are significantly lower than the mean number of sessions applied in Denmark. Therefore, esketamine is expected to be cost saving compared to ECT irrespective of the scenario applied in the analysis.

The expected mean drug cost per patient for esketamine was [redacted] for the full population and [redacted] for the subgroup of patients with CGI-SS-R ≥4. The limited total drug cost per patient is a result of the short treatment duration. Consequently, as the discontinuation rate is minimal, the uncertainty around the expected drug cost associated with the use of esketamine is considered low. Three scenario analyses were performed, two regarding the number of ECT sessions and one scenario where a micro-costing approach for the ECT sessions was used instead of the tariff-based approach. The scenarios with the number of ECT sessions resulted in an incremental cost of [redacted] and [redacted] when exploring 6 or 20 sessions of ECT, respectively. In the scenario where a micro-costing approach for the ECT sessions was used instead of the tariff-based approach, the incremental cost for esketamine + SoC vs. ECT + SoC was estimated to be [redacted], which is an additional cost saving of [redacted] compared to the base case scenario, illustrating that the cost base case scenario is the most conservative of the two approaches in favour of ECT. The same was observed for the scenario where the NICE tariff for a ECT session was used estimated an incremental cost for esketamine + SoC vs. ECT + SoC. The incremental cost was [redacted], with an additional cost saving of [redacted] for esketamine versus ECT compared to the base case.

The expected budget impact associated with recommending esketamine for the full population was estimated to be [redacted] in year 5, which is the result of a limited positive budget impact of [redacted] for clinical question 1 and a higher negative budget of [redacted] impact for clinical question 2.

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9 Appendix

9.1 Long-term model

As described, a Markov cohort model was developed in Microsoft Excel® to track the disease progression and costs experienced by patients throughout the model time horizon of 90 days. This model can, however, be set for a long-term evaluation with a time horizon of up to one year (370 days). In addition to the efficacy data observed in the trials (ASPIRE-I and ASPIRE-II), the long-term model was dependent on additional clinical data for post-trial projections.

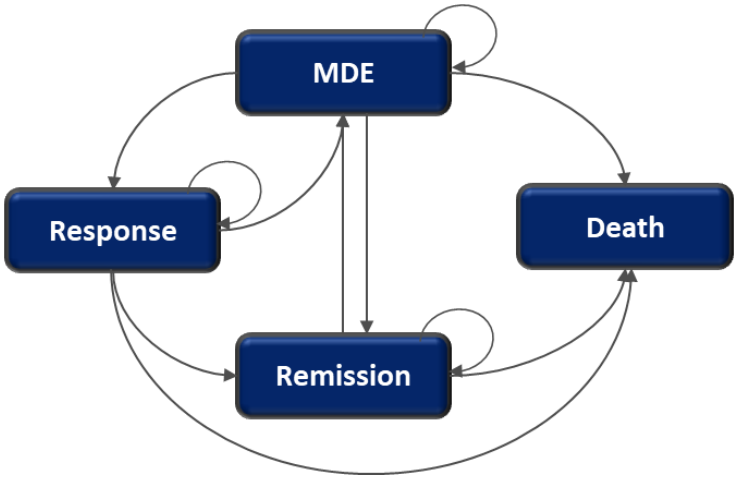
The patient characteristics, economic perspective, treatment comparators, model structure, mortality, outcome measure, clinical outcomes, cost outcomes, and treatment discontinuation are presented in the main analysis.

9.1.1 Disease progression

The short-term modelling of disease progression is common to both short- and long-term models and is described in section 2.1.

The long-term modelling of disease progression corresponds to projections after the 90 days of follow-up captured in the trials (alternatively, trial data up to day 28 can be used, representing the time during which patients were on esketamine treatment), and after that using long-term efficacy data. Figure 4 shows the model structure used in long term modelling. The long-term modelling uses 28-days cycles.

Figure 4. Long-term Model Structure



MDE = major depressive episode

At every model cycle, patients who responded to treatment may:

- Remain in the Response health state
- Improve their depressive symptoms further and transition into the Remission health state
- Lose treatment response and return to the MDE health state
- Die

Patients who achieved Remission to treatment may:

- Remain in the Remission health state
- Experience a relapse (i.e., return to the MDE health state)
- Die

Patients who achieve remission or response may also experience relapses/loss of response, transitioning back to the MDE health state, where patients have a chance to achieve remission or response (as a result of continuing to be treated with SoC). Patients cycle between these health states—MDE, Response, and Remission—during the long-term treatment phase.

9.1.2 Discounting

The model uses an annual discount rate for future costs of 3.5% for model years ≤35 and 2.5% for model years 35-70, derived from the Ministry of Finance per the DMC guidelines.

Discounting is used to discount future cost a year in the future, meaning no discount is normally used within the first year. The model allows a maximum time horizon of 370 days, for this reason applying discounting would not be relevant.

9.2 Data sources and input

This section summarizes the inputs and sources used to inform the long-term model.

Discontinuation, adverse events, mortality, cost (drug acquisition and administration) and disease management are described in the main analysis.

9.2.1 Efficacy

In the long-term model, patients are assumed to receive SoC, and their transitions between health states are governed by the probabilities given in Table 38 (probabilities for 28-day cycles). Efficacy estimates up to day 90 were informed by the pooled data analysis from ASPIRE-I and ASPIRE-II trials. Long-term efficacy for SoC (except the response to remission estimate) were sourced from Edwards et al. [32]. Reported risks from Edward's health states "response discontinue", "remission discontinue", "relapse from response discontinue", and "relapse from remission discontinue" were used to inform response, remission, loss of response, and relapse for this model, respectively. Standard methodology was used to convert two-month risks to four-week risks [33]. The response to remission probability was derived from STAR*D (Step 4 remission rate at follow-up entry) [34] with data converted to 4-week risks using standard formulae.

Table 38. Long-term efficacy

Probability of:	Remission	Response	Response to Remission	Relapse	Loss of Response
Value	0.004	0.008	0.028	0.042	0.104

9.3 Simplified cost analysis

This analysis was performed to demonstrate that the results of the more complex state-transition model used to inform the base case, are very similar to the results when conducting a simple a costing analysis without state-transitions.

The largest main difference between the results of these approaches was the absolute and incremental drug costs were slightly higher for esketamine + SoC in the simple approach. This is the result of assuming that no patients would discontinue treatment with esketamine, which is not a plausible assumption.

Table 39. Esketamine total cost, simplified cost analysis

Esketamine	Units	Unit cost (DKK)	Total cost (DKK)
Drug cost	24	[redacted]	[redacted]
Antidepressants	90	0.85	76.50
Administration cost	4	1,944.00	7,776.00
Monitoring cost	4	220.50	882.00
Monitoring cost (SoC)	4	1,944	7,776.00
AE cost	0	0.00	0.00
Hospitalisation	14	3939.00	55,146.00
Patient time (hours)	254	181.00	45,974.00
Patient transportation (roundtrips)	16	140.40	2,246.40
	Total		[redacted]

Table 40. SoC total cost, simplified cost analysis

SoC	Units	Unit cost (DKK)	Total cost (DKK)
Drug cost	90	0.85	76.50
Administration cost	0	0.00	0.00
Monitoring cost	4	1,944	7,776.00
AE cost	0	0.00	0.00
Hospitalisation	21	3,939.00	82,719.00
Patient time (hours)	366.5	181.00	66,336.5
Patient transportation	16	140.40	2,246.4
	Total		[redacted]

Table 41. ECT total cost, simplified cost analysis

ECT	Units	Unit cost (DKK)	Total cost (DKK)
Drug cost	12	133.00	1,596.00
ECT sessions	12	2,770.00	33,240.00
Antidepressants	90	0.85	76.50
Administration cost	0	0.00	0.00
Monitoring cost	4	1,944	7,776.00
AE cost	0	0.00	0.00
Hospitalisation	28	3,939.00	110,292.00
Patient time (hours)	487.5	181.00	88,237.50
Patient transportation	19	140.40	2,667.60
	Total		[redacted]

Table 42. Incremental cost, simplified cost analysis

	Esketamine (DKK)	SoC (DKK)	ECT (DKK)
Costs	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	0.00	1,596.00
Antidepressants	76,50	76.50	76,50

ECT sessions	0.00	0.00	33,240.00
Administration cost	7,776.00	0.00	0.00
Monitoring cost	8,658.00	7,776.00	7,776.00
AE cost	0.00	0.00	0.00
Hospitalisation	55,146.00	82,719.00	110,292.00
Patient time and transportation	48,880.40	68,582.90	90,905.10
Total incremental costs (DKK)		[redacted]	[redacted]
Total incremental cost vs. state-transition model (DKK)		[redacted]	[redacted]

9.4 ECT session, Micro-costing approach

Instead of using DRG tariffs, the other costing approach for ECT was to use a micro-costing approach, where the same rationale for the number of 12 sessions as the DRG costing also applied.

Table 43 summarizes the administration and monitoring cost per session applied for patients treated with ECT. The Danish clinical experts estimate that the resource use of the involved team of HCPs consists of two nurses (441 DKK per hour), one specialised anaesthesiologist (1,024 DKK per hour), one anaesthesia nurse (441 DKK per hour), and one hospital porter (542 DKK per hour) for an ECT procedure. For the post-ECT observation, a social and health care assistant at a cost of 414 DKK per hour was estimated to be observing the patient for 0.5 to 1 hour [20]. The hourly rate of all HCPs was based on the Medicine Council´s valuation of unit cost [28].

Table 43. Administration and observation resource use and costs associated with ECT

Resource use	Cost per hour (DKK)[28]	Number of professionals	Units	Total duration required (hours)	Average cost per session per patient (DKK)
Nurse	441	2	1	0.25	220.50
Specialized anæstesiologis" overlæge, ikke ledende"	1,024	1	1	0.25	256.00
Anaesthesia nurse "sygeplejerske"	441	1	1	0.25	110.25
Social and healthcare assistant	414	1	1	0.50	207.00
Hospital porter "sygehusportør"	362	1	1	0.17	60.33
Measurement of vital parameters "Social and healthcare assistant"	414	1	*48	0.08	1,655.93
			Total cost per session DKK		**2,510.00**

Abbreviations: *DKK = Danish krone*

***Note:** Clinical expert statement, vital parameters will be measured twice an hour. Assumed to take 5 minutes per measurement.*

ECT is not a pharmaceutical treatment. However, the ECT procedure involves patients being pre-medicated and given anaesthesia, see Table 44. The newest Danish ECT guideline from 2020 does not specify which anaesthetic is used for the ECT procedure. A Danish clinical expert stated that patients would receive chlorprothixene (Truxal®) (25-100 mg) before the procedure and an ECT guideline by Aarhus university hospital 2018 stated that atropine (0.3-0.5 mg) is administrated to counteract airway secretion followed by the short-acting anaesthetic thiomebumal (100-500 mg) and the muscle relaxants suxamethonium (30-70 mg), resulting in an average cost of 133.00 DKK per session of ECT [20, 35].

Table 44. Anaesthetic costs for ECT

	Dose (mg)	Strength per unit (mg)	Units per pack	Cost per pack (DKK)*	Average cost per mg (DKK)	Average cost per session (DKK)
Pre-medication						
Chlorprothixene Truxal® (149815)	50	25	100	30.01	0.012	0.60
Anaesthetics						
Atropine" Aguettant" (581377)	0.4	0.5	10	530	106.00	53.00
Thiomebumal/ pentocur (444362)	250	1000	10	1600	0.16	40.00
Suxamethonium (136223)	50	100	10	1000	1.00	50.00

Total cost per session (DKK)	133.00

Abbreviations: *mg = milligram; DKK = Danish krone*

A Danish clinical expert estimated an acquisition cost of 150,000 DKK for an ECT device (depreciated over 10 years) and 5,000-10,000 DKK for the wires connecting the device to the patients (which needs to be replaced after 100 procedures) equalling to a total of 75.15 DKK in materials per ECT session, see Table 45 [20]. The number of procedures was calculated using the number of patients receiving ECT every year based on the Capital Region webpage for psychiatry of 1,800, which was multiplied by 12 sessions per patient [36].

Table 45. ECT material costs

	Acquisition cost (DKK)	Depreciation	Number of procedures	Cost per session (DKK)
ECT device	150,000	10 years	§21,600	0.69
Wires for ECT device	7,500	NA	*100	75.00
Total cost per session (DKK)				75.69

Abbreviations: *DKK = Danish krone*

Note: **Clinical expert estimated that wires should be replaced by new ones after 100 procedures with ECT. §estimated total number of sessions using the ECT device per year*

The average treatment and monitoring costs for a patient treated with ECT was estimated to be 2,718.71 DKK per session and was applied for both the MDSI population and the CGI-SS-r ≥4 subpopulation, see Table 46. In line with the previous unit cost catalogue, the cost of 2,510.00 DKK was multiplied by a factor of two to account for any overhead cost equal to a total of 5,228.69 DKK per ECT session, see Table 46 [30].

Table 46. Total cost per ECT session, micro-costing

	Estimated cost (DKK)	Estimated overhead cost (DKK)	Total cost per session (DKK)
ECT	2,718.69	2,510.00	5,228.69

Abbreviations: *ECT = Electroconvulsive Therapy; DKK = Danish krone*

Medicinrådet

Medicinrådets protokol for vurdering vedrørende esketamin til kortvarig behandling af voksne med moderat til svær depressiv episode med akut øget selvmordsrisiko

Version 1.0

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 protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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 den ansøgende virksomhed få besked.

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1. Begreber og forkortelser

CGI-SR-I:	*Clinical Global Impression of Imminent Suicide Risk*
CGI-SR-LT:	*Clinical Global Impression of Long Term Suicide Risk*
CGI-SS-R:	*Clinical Global Impression-Severity of Suicidality - Revised*
ECT:	Elektrokonvulsiv terapi
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
FoST:	*Frequency of Suicidal Thinking*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
ICD-10:	*International Classification of Diseases and Related Health Problems-10*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention-to-treat*
MADRS:	*Montgomery-Åsberg Depression Rating Scale*
MDD:	*Major Depressive Disorder*
MKRF:	Mindste klinisk relevante forskel
NICE:	*The National Institute for Health and Care Excellence*
NMDA:	N-methyl-D-aspartat
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PP:	*Per Protocol*
RR:	Relativ risiko
SIBAT:	*The Suicide Ideation and Behavior Assessment Tool*
SMD:	*Standardized Mean Difference*
SNRI:	Serotonin-/noradrenalingenoptagelseshæmmer
SSRI:	Serotoningenoptagshæmmer

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Janssen-Cilag, som ønsker, at Medicinrådet vurderer esketamin (Spravato®*) i tillæg til antidepressiva til hurtig reduktion af selvmordsrisiko hos voksne med moderat til svær depressionsepisode* (godkendt indikation). Medicinrådet modtog den foreløbige ansøgning den 18. december 2020. Janssen-Cilag fik forhåndsgodkendelse (*positive opinion*) i EMA den 10. december 2020.

2.1 Moderat til svær unipolar 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 65,3 % af disse, svarende til ca. 72.400 voksne individer, bliver diagnosticeret og kan komme i behandling [2]. En mindre andel vil have særskilt behov for akut behandling med hurtigindsættende virkning på depressive symptomer, fordi de udviser alvorlig selvmordsadfærd. Fagudvalget anslår, at dette omfatter 1.000-2.000 voksne individer om året, som vil være mulige kandidater til kortvarig behandling med esketamin. En mindre andel af disse vil dog i praksis ikke blive tilbudt behandlingen, fordi de er særligt sårbare (typisk ved høj alder i kombination med somatisk komorbiditet) eller pga. misbrug, psykiatrisk eller somatisk komorbiditet i øvrigt.

Depression præsenterer sig typisk med symptomer som nedtrykthed og nedsat energi over længere tid, manglende selvværd, isolationstendens, selvbebrejdelser, nedsat eller øget appetit, tab af livslyst og ofte ved svær og moderat depression som selvmordstanker eller -planer [3]. I alvorlige tilfælde kan der være psykotiske symptomer i form af hallucinationer og vrangforestillinger [3]. 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 [3].

Depression diagnosticeres, jf. klassifikationssystemet *International Classification of Diseases and Related Health Problems-10* (ICD-10), ud fra en række grundliggende kriterier. Varighed samt antal og sværhedsgrad af depressive kerne- og ledsagesymptomer afgør, om der er tale om depression, og hvorvidt denne er af let, moderat eller svær grad. Depression ses ofte sammen med andre psykiske lidelser som f.eks. angstlidelser og personlighedsforstyrrelser [3,4]. Herudover er alkohol og/eller stofmisbrug også almindeligt hos patienter med svær depression [3]. Især stofpåvirkede patienter kan optræde med akut opstået selvmordsadfærd. I sådanne tilfælde bør behandlingen tilrettelægges ud fra patientens psykiske tilstand efter afrusning.

Patienter med svær depression kan udvise selvmordstanker og -adfærd, der er så alvorlig, at det kan være nødvendigt med indlæggelse og akut behandling. Dette gælder også for et fåtal af patienter med moderat depression. Selvmordsrisikoen beror på et klinisk skøn af den behandlende speciallæge i psykiatri og kan afdækkes ved en klinisk vurdering og bl.a. følgende spørgsmål:

- Har patienten tidligere foretaget selvmordsforsøg? Er det for nyligt? Hvad var omstændighederne for selvmordsforsøget?
- Har patienten aktuelle selvmordstanker? Hvad omhandler selvmordstankerne?
- Har patienten aktuelle selvmordsplaner? Hvad omhandler selvmordsplanerne, og i hvilket omfang har patienten forberedt sig på at effektuere planerne?
- Kan patienten på troværdig vis tage afstand fra selvmordsimpulser? Hvilke modforestillinger har patienten? Kan der indgås en troværdighed sikkerhedsplan med patienten?

Et selvmordsforsøg beskrives som en handling, hvor en person intentionelt udviser en adfærd, der kan have dødelig udgang. Selvmordstanker strækker sig fra forbigående forestillinger og overvejelser om at dø til mere vedvarende og påtrængende overvejelser og i sidste ende en endelig beslutning om at begå selvmord. Selvmordsadfærd dækker over egentlige selvmordsforsøg eller forberedelser herpå. For patienter med moderat til svær depression med akut øget selvmordsrisiko er der ofte tale om en risiko, der er øget i en igangværende depressionsepisode eller som led i en nyligt påbegyndt depressionsepisode. Årsagerne kan være mange, men sociale forhold og misbrug spiller ofte en rolle.

Patienter med selvmordsadfærd henvises til psykiatrisk intensivbehandling for hurtig akut behandling, og patienter diagnosticeres ofte i akutmodtagelsen eller som en del af en akut indlæggelsesvurdering. Patienter med moderat til svær depression med akut øget selvmordsrisiko udgør en højrisikogruppe med behov for hurtig krisestyring eller akut indlæggelse for at føre opsyn med patienten og nedbringe selvmordsrisikoen.

2.2 Esketamin

Esketamin (handelsnavn Spravato®) eller s-ketamin er ét af to spejlmolekyler af ketamin (s- og r-ketamin), hvor s-formen har størst specificitet [5]. Esketamin påvirker N-methyl-D-aspartat (NMDA)-receptoren i hjernen til at frigive mere glutamat, der bl.a. har betydning for reguleringen af affektiv og emotionel adfærd [6–8]. Esketamin har imidlertid også andre effekter på hjernen.

Esketamin kan som ketamin have dissociative effekter, der typisk giver brugeren en følelse af at forlade kroppen [5]. Andre psykotomimetiske effekter er også beskrevet. Til behandling af depression hos voksne er esketamin udviklet som en nasal formulering [2]. Den intranasale administrationsvej tillader en hurtig absorption og virkning, hvor det modsat kan tage flere uger at opnå en ønsket effekt af andre traditionelt anvendte behandlinger som f.eks. orale antidepressiva [2].

Esketamin har været administreret i kliniske forsøg som monoterapi og som add-on-terapi med antidepressiva [9–11]. Esketamin i tillæg til eksisterende eller optimeret behandling med antidepressiva er godkendt som en indikationsudvidelse til hurtig reduktion af selvmordstanker eller -adfærd hos voksne med moderat til svær depressionsepisode. Den anbefalede behandling til denne patientpopulation består af en fast dosis intranasal esketamin 84 mg to gange om ugen i fire uger i kombination med antidepressiva. Behandlingen forventes seponeret senest efter 4 uger. Fagudvalget finder, at voksne patienter med moderat til svær depressionsepisode med akut øget selvmordsrisiko kan være relevante kandidater til kortvarig behandling med esketamin.

Oprindeligt blev esketamin i kombination med SSRI/SNRI godkendt af EMA i 2019 til voksne med behandlingsresistent moderat til svær depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva under den igangværende moderate til svære depressionsepisode. I 2020 afviste Medicinrådet esketamin som mulig standardbehandling til denne indikation, bl.a. pga. manglende evidens for langtidseffekterne.

2.3 Nuværende behandling

Ifølge den gældende behandlingsvejledning udarbejdet af Rådet for Anvendelse af Dyr Sygehusmedicin for medicinsk behandling af unipolær depression, behandles moderat depression (score på despressionsskala *Montgomery-Åsberg Depression Rating Scale* (MADRS) 22-29) med antidepressiva eller psykoterapi, mens svær depression (MADRS 30-60) bør behandles med antidepressiva og samtaler tilpasset patientens tilstand [12]. En patient med moderat til svær depression, der er i overhængende fare for at begå selvmord, vil typisk allerede være i behandling med et eller flere antidepressiva og evt. andre psykofarmaka. For nogle patienter er der tale om en ny episode, hvor patienten skal påbegynde antidepressiv behandling. For begge situationer gælder, at patienten som udgangspunkt bliver indlagt til psykiatrisk intensivbehandling, hvor det primære mål vil være at afværge selvmordsfaren og derefter at sikre nattesøvnen, som ofte vil være svært forstyrret, og reducere agitation med f.eks. antidepressiva med sederende virkning, antipsykotika eller benzodiazepiner. Desuden skal de øvrige symptomer behandles.

Ved moderat til svær depression med akut øget selvmordsrisiko er der indikation for elektrokonvulsiv terapi (ECT) [13]. Efter 1-3 ECT-behandlinger inden for en uge forventes en bedring i tilstanden, og typisk gives 8-12 behandlinger i alt, men behandlingsvarigheden varierer fra patient til patient. Patienter vil blive kontinuerligt observeret af personalet, indtil der er bedring i tilstanden. Det vil ikke altid være muligt at tilbyde ECT, og en andel af patienterne ønsker ikke behandlingen. Alternativt kan der som led i krisestyringen forsøges optimering eller ændring af patientens antidepressive behandling. I sjældne tilfælde lykkes det patienter at begå selvmord under indlæggelsen på trods af akut behandling og forebyggende tiltag.

I Danmark er den gennemsnitlige indlæggelsesvarighed 19-20 dage, hvorefter patienterne udskrives til opfølgende ambulant behandling. Ca. 20-25 % genindlægges akut inden for 30 dage efter udskrivelsen.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparatorer), og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med placebo i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko?

Population
Indlagte patienter over 18 år med moderat til svær depression, hvor lægen vurderer, at der er behov for akut behandling til reduktion af selvmordsrisiko, og som ikke kan behandles med ECT, f.eks. fordi ECT er kontraindiceret, eller fordi patienten ikke har ønsket behandling med ECT.

Fagudvalget ønsker desuden behandlingseffekten belyst i en subpopulation med en *Clinical Global Impression-Severity of Suicidality - Revised* (CGI-SS-R)-score på 4 eller højere ved baseline.

Intervention
Intranasal esketamin (84 mg to gange om ugen i fire uger) i tillæg til antidepressiva.

Komparator
Intranasal placebo (to gange om ugen i fire uger) i tillæg til antidepressiva.

Effektmål
De valgte effektmål fremgår af tabel 2.

3.2 Klinisk spørgsmål 2

Hvilken værdi har esketamin i tillæg til antidepressiva sammenlignet med ECT i tillæg til antidepressiva for voksne patienter i den aktuelle moderate til svære depressive episode med akut øget selvmordsrisiko?

Population
Indlagte patienter over 18 år med moderat til svær depression, hvor lægen vurderer, at der er behov for akut behandling til reduktion af selvmordsrisiko.

Fagudvalget ønsker desuden behandlingseffekten belyst i en subpopulation med en CGI-SS-R-score på 4 eller højere ved baseline.

Intervention
Intranasal esketamin (84 mg to gange om ugen i fire uger) i tillæg til antidepressiva.

Komparator
ECT i tillæg til antidepressiva.

Effektmål
De valgte effektmål fremgår af tabel 2.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Selvmordsrisiko	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig forbedring i selvmordssymptomer på CGI-SS-R	3 point
			Andel med resolution af selvmordstankerne (score på ≤ 2) på CGI-SS-R	30 %-point
			Andel med forværring (*deterioration* defineret som forværring på ≥ 1 point) af selvmordssymptomer på CGI-SS-R	5 %-point
Uønskede hændelser	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Kvalitativ gennemgang af specifikke hændelser relevante for behandling og sygdom	Ikke relevant
Respons	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der reducerer score fra baseline med 50 % på MADRS	20 %-point
Remission	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der opnår remission på MADRS	15 %-point
Depressive symptomer	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på MADRS	3 point

*For effektmålet uønskede hændelser ønsker Medicinrådet data med længst mulig opfølgningstid. For effektmålene selvmordssymptomer, remission og respons er der flere relevante måletidspunkter, se afsnit 3.3.1
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

3.3.1 Måletidspunkter

Fagudvalget ønsker effektmålene selvmordssymptomer, remission, respons og depressive symptomer opgjort efter to måletidspunkter:

- 24 timer efter første dosisadministration ud fra rationalet om, at effekten er hurtigtindsættende
- 4 uger efter første dosisadministration ud fra et klinisk rationale om, at effekten af antidepressiva kan vurderes efter fire uger.

Begge måletidspunkter vægtes lige højt, da en gavnlig effekt af behandling fordrer en akut indsættende effekt, som holder ved hos patienter, hvor den psykiske tilstand kan ændres på kort tid.

3.3.2 Kritiske effektmål

Selvmordsrisiko
Patienter med akut øget selvmordsrisiko udgør en højrisikogruppe med behov for at nedbringe den overhængende risiko for, at patienten tager sit eget liv. Selvmordsrisiko udgør derfor et kritisk effektmål. Der er i Danmark ikke en landsdækkende standardiseret metode for måling af overhængende selvmordsrisiko blandt patienter med moderat til svær depression. Fagudvalget vurderer, at det er relevant at inddrage specifikke værktøjer, som bruges i forskningsøjemed, for at kunne vurdere resultaterne af de kliniske forsøg. Fagudvalget ønsker at vurdere effekten på selvmordsrisikoen ved *Clinical Global Impression-Severity of Suicidality - Revised* (CGI-SS-R) *Scale*. CGI-SS-R er et værktøj udviklet til at måle en klinikers indtryk af sværhedsgraden af suicidalitet. CGI-SS-R-scoren vurderes ud fra en syvpunktskala fra 0 (ingen selvmordstanker/normal) til 6 (alvorlig påhængende fare for selvmord) og bygger på den samlede information, der er tilgængelig for klinikeren. I esketamin-studierne indgår CGI-SS-R som en integreret del af modul 7 i *The Suicide Ideation and Behavior Assessment Tool* (SIBAT). Foruden CGI-SS-R indeholder dette modul også tre andre delelementer: *Clinical Global Impression of Imminent Suicide Risk* (CGI-SR-I), *Clinical Global Impression of Long Term Suicide Risk* (CGI-SR-LT) og *Frequency of Suicidal Thinking (FoST)*. I selve kategoriseringen vil fagudvalget lægge CGI-SS-R til grund for vurderingen som anført nedenfor. Fordi værktøjer til vurdering af selvmordsrisiko er ringe valideret, vil resultatet fra CGI-SS-R blive sammenholdt med de øvrige elementer fra SIBAT modul 7 samt MADRS-subskala for *Suicidal Thoughts* (se under effektmålsbeskrivelsen for 'remission' i afsnit 3.3.3). Resultaterne fra de forskellige selvmordsskalaer vil blive inddraget i en diskussion af resultaterne og kategoriseringen baseret på CGI-SS-R.

Fagudvalget ønsker effektmålet selvmordssymptomer opgjort som:

- En forskel på den gennemsnitlige ændring fra baseline på CGI-SS-R. Den mindste klinisk relevante forskel er sat til 3 point ud fra rationalet om, at patienter, der er i overhængende risiko for selvmord (score på 5 eller 6), først oplever klinisk bedring, når deres score nedbringes med mere end 2 point.

- En forskel i andelen af patienter med resolution af selvmordssymptomer, hvor resolution defineres som patienter med en score på ≤ 2 på CGI-SS-R. *Cut-off* er sat til 2 eller lavere, da dette stemmer bedst overens med den klinisk relevante skildring mellem en passiv (score på ≤ 2) eller en aktiv (score på ≥ 3) intention om at begå selvmord. Den mindste klinisk relevante forskel er sat til 30 %-point.
- En forskel i andelen af patienter med forværring (*deterioration*) af selvmordssymptomer, defineret som patienter med forværring på ≥ 1 point på CGI-SS-R. Rationalet bag denne opgørelse er at sikre, at behandling med intranasal esketamin ikke i sig selv medfører en forværring af patientens symptomer. Det er velkendt, at behandling med visse antidepressiva i sjældne tilfælde kan være forbundet med en forværring i patientens selvmordstanker, så dette vil også til en vis grad kunne frygtes med intranasal esketamin. Da der er tale om patienter med en akut øget risiko, bør enhver forværring så vidt muligt undgås. Den mindste klinisk relevante forskel er på den baggrund sat til 5 %-point.

Fagudvalget betragter de tre opgørelser som komplementære – forstået på den måde, at enhver forværring altid skal holdes op imod de gavnlige effekter. Samlet set vil de tre opgørelser give et billede af intranasal esketamins effekt på selvmordsrisiko. Fagudvalget ønsker herudover ændringer i CGI-SS-R-scoren præsenteret grafisk for hver forsøgsdeltager over perioden fra baseline til endt opfølgning (se under afsnit *7 Andre overvejelser*) for at vurdere, om der er bemærkelsesværdige ændringer i effekt-scorerne over tid (såkaldt spaghetti-plot).

Uønskede hændelser
Alvorlige uønskede hændelser kan have stor betydning for den enkelte patients livskvalitet. Fagudvalget lægger vægt på, at der er tale om en patientgruppe med alvorlig øget selvmordsrisiko og en behandling med et lægemiddel kendt for sine dissociative effekter, der potentielt kan forværre patienternes psykiske tilstand. Herudover omfatter de kendte effekter af esketamin eufori, som fagudvalget vurderer kan have betydning for patienter med underliggende bipolar lidelse. Fagudvalget vil foretage en kvalitativ gennemgang af specifikke hændelser, som kan forværre patientens psykiatriske tilstand, herunder dissociation, selvmordstanker og eufori, og af alvorlige uønskede hændelser som død og selvmordsforsøg. Gennemgangen vil tage udgangspunkt i publicerede studier, produktresuméer og EPAR for at vurdere, om der er forskel mellem grupperne mht. alvorlighed, håndterbarhed og hyppighed.

3.3.3 Vigtige effektmål

Remission
Remission betyder, at patienten ikke længere har betydende symptomer på depression. Potentiel selvmordsadfærd er ofte afhængig af sværhedsgraden af depressionssymptomer, og derfor vurderes remission at være et vigtigt effektmål. Remission af depression måles i studierne ved, at antallet og sværhedsgraden af depressive symptomer er under et vist antal point på en given depressionsskala. F.eks. < 10 eller 12 point på MADRS. MADRS er en klinikervurderet skala med en pointscore fra 0-60 point udviklet med det formål at være mere følsom over for de ændringer, der er forårsaget af antidepressiva, men der er en høj korrelation mellem de scorer, der opnås

med hhv. MADRS og den i Danmark mere almindeligt anvendte depressionsskala *Hamilton Depression Rating Scale* (HDRS) [14]. Værktøjet består af 10 delelementer, der hver er scoret fra 0 (symptom er ikke til stede/normal) til 6 (alvorlig eller fortsat tilstedeværelse af symptom). En højere score angiver mere alvorlig sværhedsgrad. MADRS måler observeret tristhed, rapporteret tristhed, indre spænding og angst, søvnbesvær, appetitnedsættelse, koncentrationsbesvær, initiativløshed, svækket følelsesmæssigt engagement, depressivt tankeindhold og selvmordstanker. Værktøjet udviser høj inter-rater-pålidelighed. Den typiske '*recall*'-periode (tidsperiode, som symptomerne afdækkes for) for MADRS er 7 dage. Fagudvalget vurderer, at det for patienter med akut øget selvmordsrisiko er nødvendigt at måle symptomerne kortere tid efter dosisadministration og evt. med kortere intervaller. Som minimum forventes MADRS-score opgjort ved en '*recall*'-periode på 24 timer efter første dosisadministration (se afsnit 3.3.3).

Remissionsraten med den nuværende standardbehandling til patienter med akut øget selvmordsrisiko afhænger af en række faktorer, f.eks. behandling (medicin vs. ECT), type af depression, antal depressive episoder og komorbiditet. Fagudvalget ønsker effektmålet opgjort som andel, der opnår remission, og vurderer, at en forskel i andel, der reducerer scoren til, hvad der er beskrevet som et relativt nulpunkt svarende til ≤ 11 på MADRS [15,16] uanset udgangspunkt og opgjort ved efter 24 timer og efter fire uger, skal udgøre mindst 15 %-point for at være klinisk relevant.

Respons

For patienter med akut behov for behandling pga. selvmordtanker eller tanker om selvskade har en bedring i behandlingsrespons (kortsigtet effekt) afgørende betydning for, at den akutte depressive tilstand bedres, indtil andre mere langsomt indsættende lægemidler eller behandlinger kan udøve effekt. Respons vurderes derfor at være et vigtigt effektmål. Respons kan ligesom effektmålet remission måles vha. MADRS-skalaen. Respons i forhold til den generelle sygdom opgøres som en halvering af symptomer målt som en reduktion i MADRS-score på mindst 50 % fra baseline. Ifølge fagudvalget ses der typisk effekt på responsraten uger efter påbegyndt behandling, da indlæggelse eller påbegyndt behandling er en meget virksom psykosocial intervention (antidepressiva inden for 4-8 uger; ECT efter 1-3 behandlinger givet inden for en uge). En positiv effekt blandt indlagte patienter behandlet med intranasal esketamin bør ifølge fagudvalget optimalt set måles op imod en placebokontrol og en aktiv kontrol. Fagudvalget ønsker effektmålet opgjort som andel, der opnår respons. Responsraten med antidepressiva efter 4-8 ugers behandling er 20 % ift. placebo [12,17]. Fagudvalget vurderer, at en forskel i andel, der opnår respons opgjort efter 24 timer og efter fire uger til begge måletidspunkter, skal udgøre mindst 20 %-point for at være klinisk relevant.

Depressive symptomer

En reduktion i depressive symptomer er i tillæg til remission (ingen betydende symptomer) og respons (halvering af MADRS-score) relevant at opgøre for at vurdere, om der er en generel bedring i den psykiatriske tilstand for hele populationen. Effektmålet depressive symptomer vurderes at være et vigtigt effektmål. Fagudvalget ønsker effektmålet depressive symptomer opgjort som en gennemsnitlig ændring fra

baseline på MADRS. En klinisk relevant gennemsnitlig ændring fra baseline på MADRS er i litteraturen beskrevet som en forskel på 2-3 point [18,19]. Fagudvalget finder, at en forskel i MADRS skal udgøre minimum 3 point for at være klinisk relevant.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Klinisk spørgsmål 1
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes tre studier, hvor intranasal esketamin i kombination med antidepressiva er sammenlignet direkte med placebo i kombination med antidepressiva. Der er tale om følgende studier:

- Aspire I/54135419SUI3001: NCT03039192
- Aspire II/54135419SUI3002: NCT03097133
- CR103162/ESKETINSUI2001: NCT02133001

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere.

Klinisk spørgsmål 2
Medicinrådet er ikke bekendt med studier, hvor intranasal esketamin i kombination med antidepressiva er sammenlignet direkte med ECT i kombination med antidepressiva. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

[1] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål og kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.

- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, f.eks. behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Fagudvalget ønsker ændringer i CGI-SS-R-scoren præsenteret grafisk over perioden fra baseline til endt opfølgning som spaghetti-plots for patienter med en score på 4 eller derover og for patienter med en score på 3 eller derunder for at vurdere, om der er en sammenhæng mellem behandling og ændring i selvmordssymptomer over kortere tidsintervaller og/eller på individniveau.

Ansøger bedes redegøre for, om der er specifikke uønskede hændelser, som optræder med en anden frekvens i de pivotale studier, der lægger til grund for den aktuelle population, sammenlignet med de studier, der undersøger effekten af intranasal esketamin hos patienter med behandlingsresistent depression. Særligt ønskes en vurdering af, hvilken betydning det kan have for sikkerheden, at doseringen er den højest mulige (84 mg) for den aktuelle population sammenlignet med doseringen ved behandling af behandlingsresistent depression (hhv. 28 mg, 56 mg og 84 mg), hvorfra data indikerer, at omfanget eller frekvensen af uønskede hændelser er dosisafhængig. Herudover ønskes en vurdering af mulige implikationer af høj alder.

Ansøger bedes estimere, hvor stor en andel patienter fra den aktuelle population der forventes genbehandlet, når patienter f.eks. er i en akut øget selvmordsrisiko opstået fire uger efter påbegyndt behandling med intranasal esketamin.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning udarbejdet af Medicinrådet på området.

9. Referencer

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende behandlingsresistent depression hos voksne

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Poul Videbech *Professor, overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Ny udpegning igangsat	Region Nordjylland
Simon Hjerrild *Afdelingslæge*	Region Midtjylland
Claus Havregaard Sørensen *Overlæge*	Region Syddanmark
Dénes Langyel *Overlæge*	Region Sjælland
Lars Vedel Kessing *Professor, overlæge*	Region Hovedstaden
Sidsel Arnsbang Pedersen *Hoveduddannelseslæge*	Dansk Selskab for Klinisk Farmakologi
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
Leni Grundtvig Nielsen *Patient/patientrepræsentant*	Danske Patienter
Louise Dahl Wulff *Patient/patientrepræsentant*	Danske Patienter

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

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	17. marts 2021	Godkendt af Medicinrådet.

12. Bilag

Bilag 1: Søgestreng

Søgestreng til PubMed:

#	Søgestreng	Kommentar
#1	"Depressive Disorder, Major/therapy"[Mesh] OR "Depressive Disorder, Treatment-Resistant"[Mesh	Samlet søgning for populationen
#2	(major[tiab] OR treatment-resistant[tiab]) AND depressi*[tiab]	
#3	#1 OR #2	
#4	"Suicidal Ideation"[Mesh]	
#5	suicid*[tiab]	
#6	#4 OR #5	
#7	#3 AND #6	
#8	"Esketamine" [Supplementary Concept] OR "Ketamine/therapeutic use"[Mesh]	Søgetermer for interventionen
#9	esketamine[tiab] OR s-ketamine[tiab] OR spravato*[tiab] OR ketamine[tiab]	
#10	#8 OR #9	
#11	Administration, Intranasal[Mesh] OR nasal[tiab] OR intranasal[tiab]	
#12	#10 AND #11	
#13	"Electroconvulsive Therapy"[Mesh] OR "Electroshock"[MeSH]	Søgetermer for komparator
#14	(electroshock[tiab] OR electroconvulsive[tiab] OR electric shock[tiab] OR electric convulsive[tiab]) AND Therap*[tiab]	
#15	ECT[tiab]	
#16	#13 OR #14 OR #15	
#17	#12 OR #16	Intervention + komparator
#18	#7 AND #17	
#19	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	Eksklusion af ikke relevante publikationstyper
#20	#18 NOT #19	Endelig søgning

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	[mh "Depressive Disorder, Major"/TH]	Søgetermer til populationen
#2	[mh “Depressive Disorder, Treatment-Resistant”]	
#3	((major or treatment-resistant) and depressi*):ti,ab,kw	
#4	#1 or #2 or #3	
#5	[mh “Suicidal Ideation”]	
#6	suicid*:ti,ab,kw	
#7	#5 or #6	
#8	#4 and #7	Samlet søgning for populationen
#9	(esketamine or s-ketamine or spravato* or ketamine):ti,ab,kw	Søgetermer for interventionen
#10	[mh Ketamine/TU]	
#11	#9 or #10	
#12	[mh "Administration, Intranasal"] or (nasal or intranasal):ti,ab,kw	
#13	#11 and #12	
#14	[mh "Electroconvulsive Therapy"] or [mh "Electroshock"]	Søgetermer for komparator
#15	((electroshock or electroconvulsive or electric shock or electric convulsive) and Therap*):ti,ab,kw	
#16	ect:ti,ab,kw	
#17	#14 or #15 or #16	
#18	#13 or #17	Intervention + komparator
#19	#8 and #18	
#20	NCT*:au	Eksklusion af ikke relevante publikationstyper
#21	("conference abstract" or review):pt	
#22	(clinicaltrials.gov or trialsearch):so	
#23	(abstract or conference or meeting or proceeding*):so	
#24	#20 or #21 or #22 or #23	
#25	#19 not #24	Endelig søgning