Disclaimer

Deze nascholing wordt georganiseerd en ondersteund door Janssen, farmaceutische bedrijven van Johnsson & Johnsson.

De standpunten die in de slides worden gepresenteerd, zijn die van de individuele sprekers en weerspiegelen niet per se de standpunten van Janssen.

De presentaties kunnen discussies bevatten over off-label gebruik van geneesmiddelen.

Fase IIb RCT:
De effectiviteit en veiligheid van psilocybine bij patiënten met een behandelresistente depressieve stoornis

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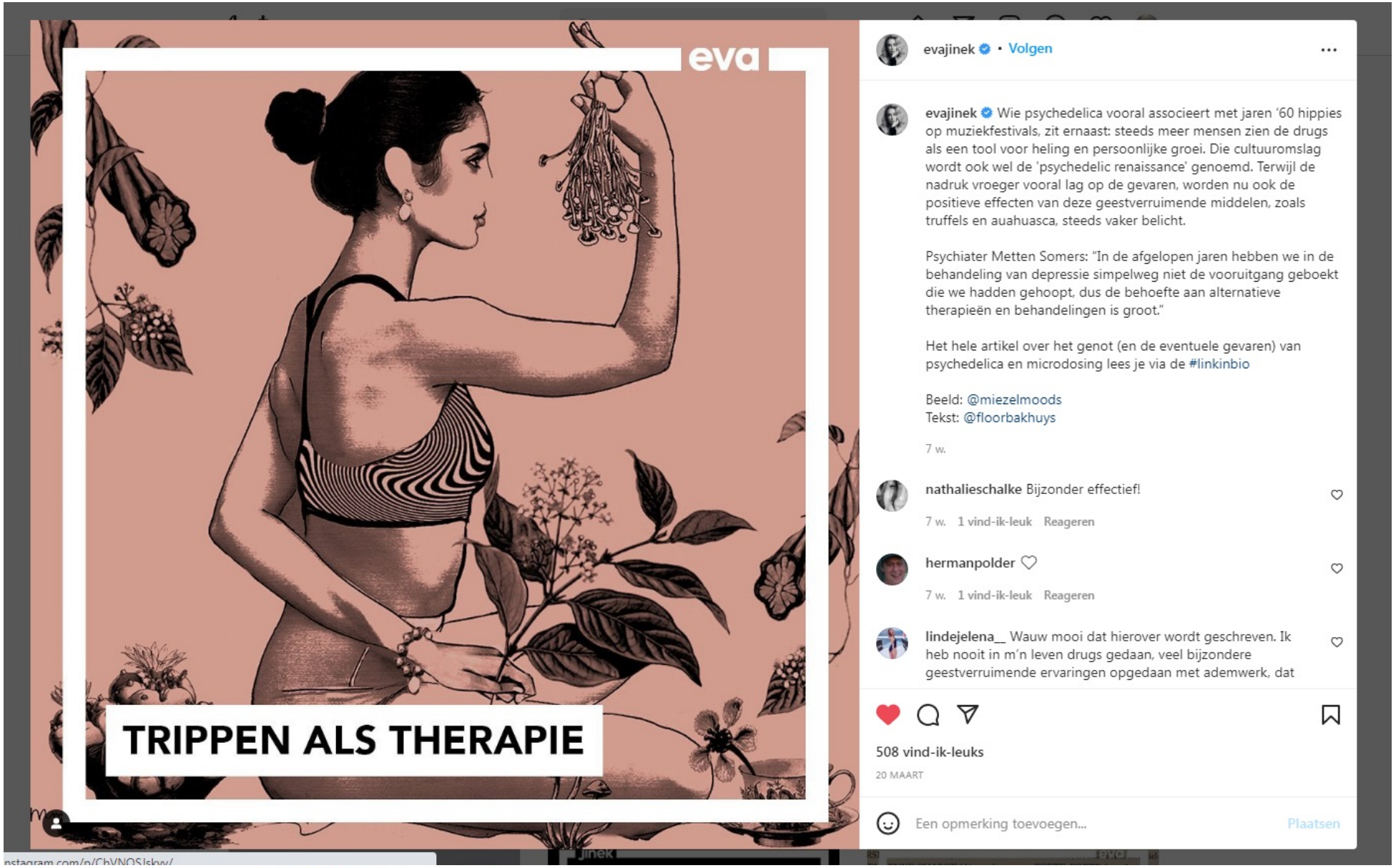
Disclosure dr. M. Somers, MBA

Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld	• UMC Utrecht ontvangt vergoeding van Compass voor aan uitvoering onderzoek besteedde tijd
• Honorarium of andere (financiële) vergoeding	• UMC Utrecht ontvangt vergoeding voor voorbereiding huidig Janssen-Cilag symposium
• Aandeelhouder	• Geen
• Andere relatie, namelijk …	• Geen



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Seije Slager 27 april 2022, 03:00

MDMA in PTSS

nature medicine

ARTICLES

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OPEN

MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

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Post-traumatic stress disorder (PTSD) presents a major public health problem for which currently available treatments are modestly effective. We report the findings of a randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial (NCT03537014) to test the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for the treatment of patients with severe PTSD, including those with common comorbidities such as dissociation, depression, a history of alcohol and substance use disorders, and childhood trauma. After psychiatric medication washout, participants ($n = 90$) were randomized 1:1 to receive manualized therapy with MDMA or with placebo, combined with three preparatory and nine integrative therapy sessions. PTSD symptoms, measured with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5, the primary endpoint), and functional impairment, measured with the Sheehan Disability Scale (SDS, the secondary endpoint) were assessed at baseline and at 2 months after the last experimental session. Adverse events and suicidality were tracked throughout the study. MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo ($P < 0.0001$, $d = 0.91$) and to significantly decrease the SDS total score ($P = 0.0116$, $d = 0.43$). The mean change in CAPS-5 scores in participants completing treatment was −24.4 (s.d. 11.6) in the MDMA group and −13.9 (s.d. 11.5) in the placebo group. MDMA did not induce adverse events of abuse potential, suicidality or QT prolongation. These data indicate that, compared with manualized therapy with inactive placebo, MDMA-assisted therapy is highly efficacious in individuals with severe PTSD, and treatment is safe and well-tolerated, even in those with comorbidities. We conclude that MDMA-assisted therapy represents a potential breakthrough treatment that merits expedited clinical evaluation.

Psilocybine in depressie

Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study

Robin L Carhart-Harris, Mark Bolstridge, James Rucker*, Camilla M J Day*, David Erritzoe, Mendel Kaelen, Michael Bloomfield, James A Rickard, Ben Forbes, Amanda Feilding, David Taylor, Steve Pilling, Valerie H Curran, David J Nutt

Summary

Background Psilocybin is a serotonin receptor agonist that occurs naturally in some mushroom species. Recent studies have assessed the therapeutic potential of psilocybin for various conditions, including end-of-life anxiety, obsessive-compulsive disorder, and smoking and alcohol dependence, with promising preliminary results. Here, we aimed to investigate the feasibility, safety, and efficacy of psilocybin in patients with unipolar treatment-resistant depression.

Methods In this open-label feasibility trial, 12 patients (six men, six women) with moderate-to-severe, unipolar, treatment-resistant major depression received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a supportive setting. There was no control group. Psychological support was provided before, during, and after each session. The primary outcome measure for feasibility was patient-reported intensity of psilocybin's effects. Patients were monitored for adverse reactions during the dosing sessions and subsequent clinic and remote follow-up. Depressive symptoms were assessed with standard assessments from 1 week to 3 months after treatment, with the 16-item Quick Inventory of Depressive Symptoms (QIDS) serving as the primary efficacy outcome. This trial is registered with ISRCTN, number ISRCTN14426797.

Findings Psilocybin's acute psychedelic effects typically became detectable 30–60 min after dosing, peaked 2–3 h after dosing, and subsided to negligible levels at least 6 h after dosing. Mean self-rated intensity (on a 0–1 scale) was 0·51 (SD 0·36) for the low-dose session and 0·75 (SD 0·27) for the high-dose session. Psilocybin was well tolerated by all of the patients, and no serious or unexpected adverse events occurred. The adverse reactions we noted were transient anxiety during drug onset (all patients), transient confusion or thought disorder (nine patients), mild and transient nausea (four patients), and transient headache (four patients). Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference −11·8, 95% CI −9·15 to −14·35, p=0·002, Hedges' g=3·1) and 3 months (−9·2, 95% CI −5·69 to −12·71, p=0·003, Hedges' g=2) after high-dose treatment. Marked and sustained improvements in anxiety and anhedonia were also noted.

Interpretation This study provides preliminary support for the safety and efficacy of psilocybin for treatment-resistant depression and motivates further trials, with more rigorous designs, to better examine the therapeutic potential of this approach.

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See Comment page 592

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Psilocybine in depressie

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Psilocybin versus Escitalopram for Depression

Robin Carhart-Harris, Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy., Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc., Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc., David Erritzoe, M.D., and David J. Nutt, M.D.

ABSTRACT

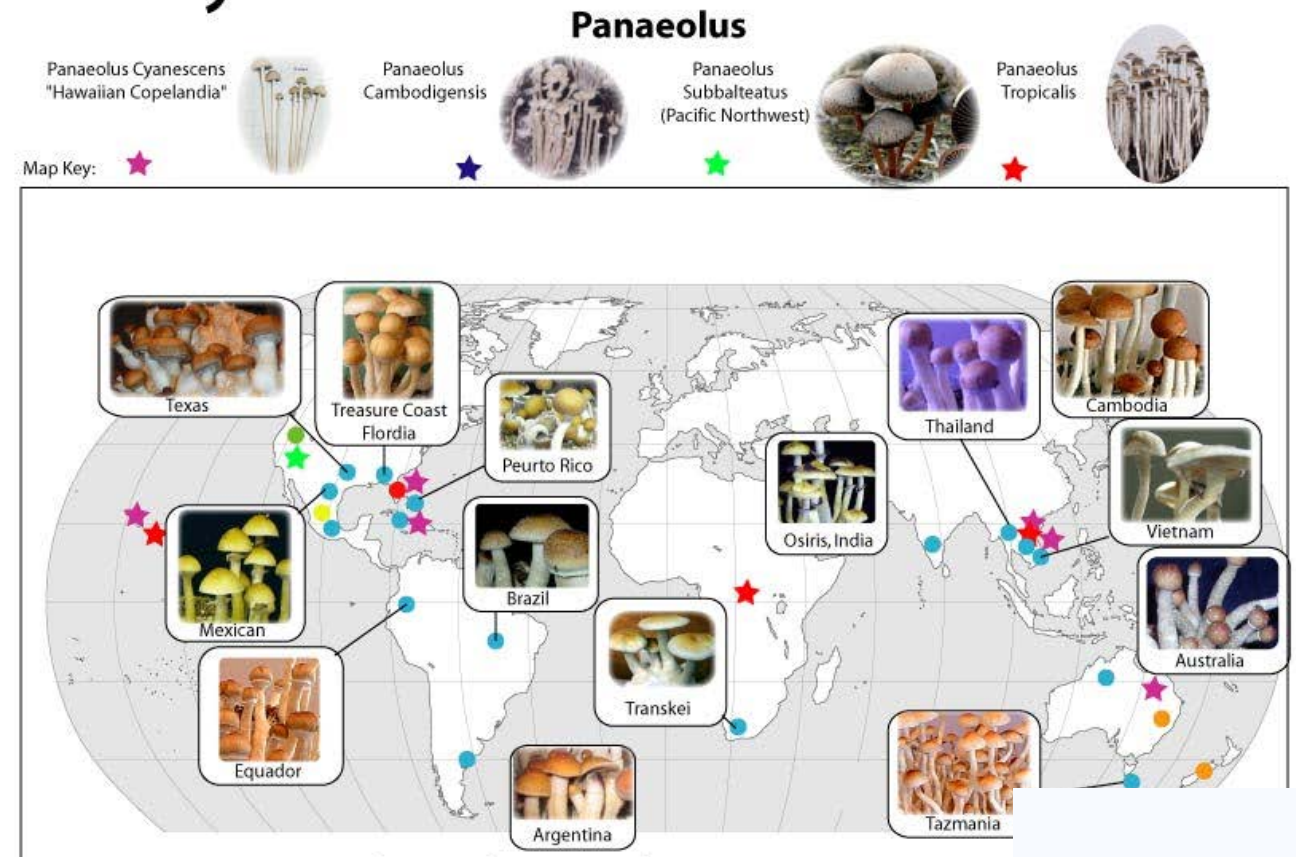
BACKGROUND

Psilocybin may have antidepressant properties, but direct comparisons between psilocybin and established treatments for depression are lacking.

CONCLUSIONS

On the basis of the change in depression scores on the QIDS-SR-16 at week 6, this trial did not show a significant difference in antidepressant effects between psilocybin and escitalopram in a selected group of patients. Secondary outcomes generally favored psilocybin over escitalopram, but the analyses of these outcomes lacked correction for multiple comparisons. Larger and longer trials are required to compare psilocybin with established antidepressants. (Funded by the Alexander Mosley Charitable Trust and Imperial College London's Centre for Psychedelic Research; ClinicalTrials.gov number, NCT03429075.)

Psilocybin Mushrooms of the World



Waarom psilocybine?

Psilocybine: Psychedelicum

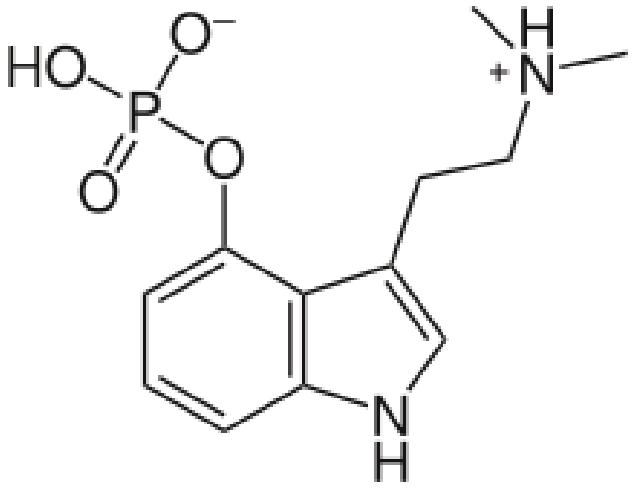
- Psychedelica:
  - Psilocybine, LSD, DMT (ayahuasca), mescaline
- MDMA

Psychedelisch: ‘geest-openbarend’, neemt werkelijkheid anders waar: **‘trip’**

- Euforie, hallucinaties, ego dissolutie ≈ non-dualiteit
- toename introspectie, faciliteren zelf-reflectie en persoonlijke groei

Psilocybine

- Psilocybine / psilocine (= tryptamine).
- Effecten veroorzaakt door agonisme 5-HT2A/C en 5-HT1A receptor
- Vergelijkbaar met LSD, iets meer sederend / relaxerend
  - Alle ‘klassieke’ psychedelica hebben dit werkingsmechanisme



Werkingsmechanisme

- Mystieke ervaring?
- ‘Ego dissolutie’?
- Inzicht?
- Doorbreken ruminatie / gedachtenloops?
- Default Mode network activiteit?
- Effect van 5HT2A stimulatie?
- Receptor downregulatie?
- Glutamaat release

De trial..

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Fase IIb RCT: effectiviteit en veiligheid van psilocybine bij therapieresistente depressie

- #216 deelnemers in UK, EU, VS en Canada
- In NL: UMCU, UMCG, LUMC
- Antidepressiva worden geheel afgebouwd
- Tijdens de psilocybine-sessie begeleid door twee getrainde therapeuten
- Primaire uitkomst: reductie depressieve symptomen (MADRS) week 3 en 12 post-sessie

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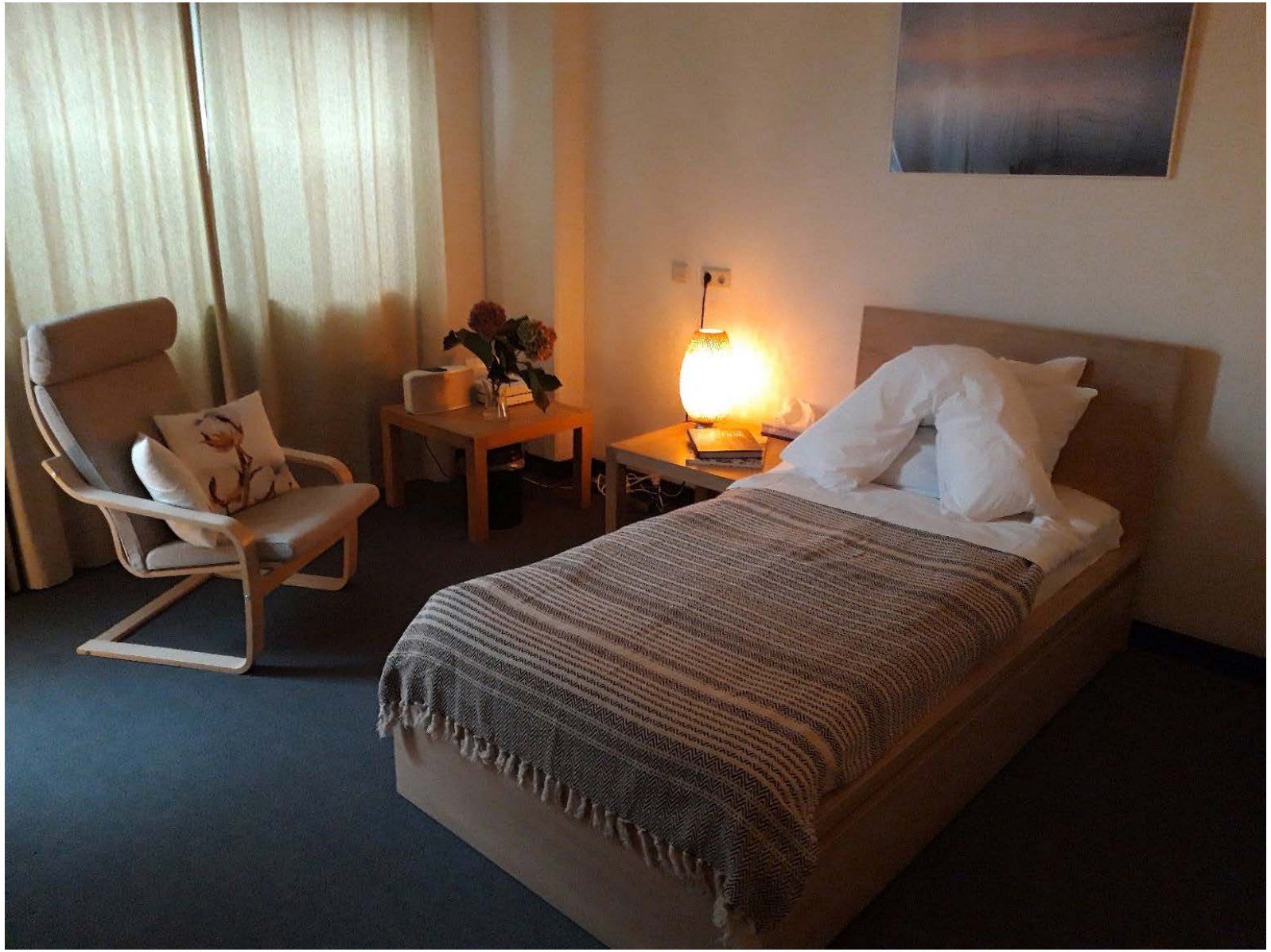

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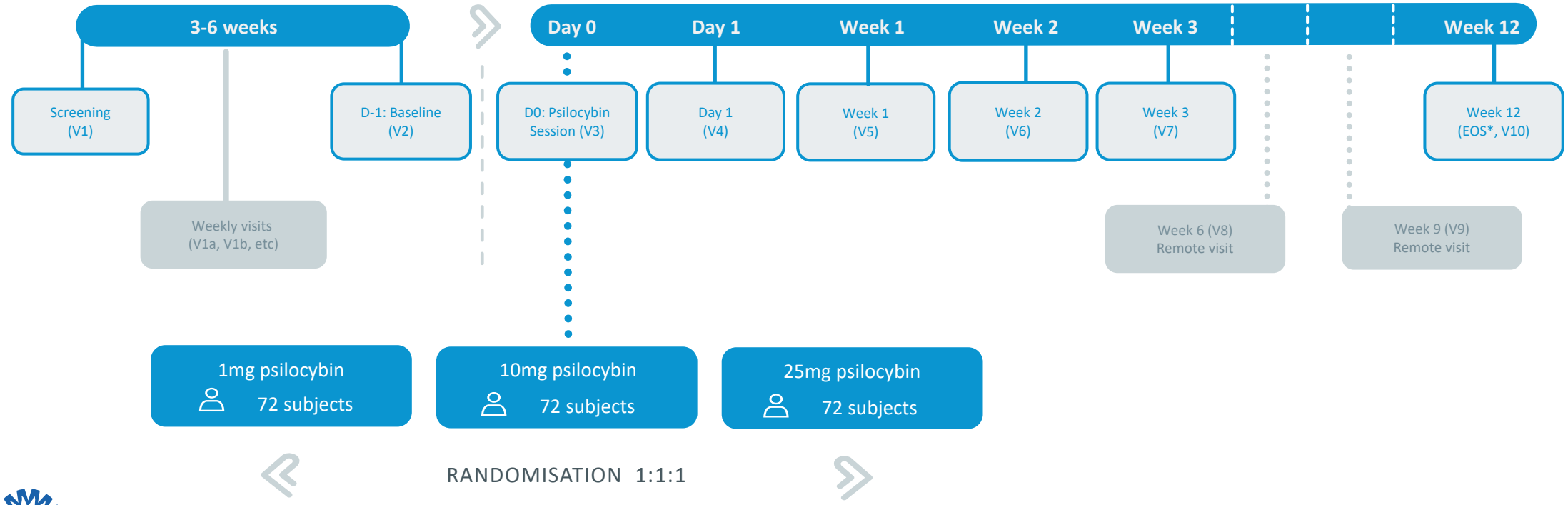
Trial design

Primary endpoint

- Reduction of symptoms of depression as measured by MADRS* from baseline to 3 weeks

Secondary endpoint

- Proportion of responders who maintained ≥ 50% improvement in MADRS up to week 12



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Note: *MADRS = Montgomery-Åsberg depression rating scale; EOS = end of study; TRD = treatment-resistant depression

Voor wie?

Inclusiecriteria

- Volwassenen >18 jaar, met een minstens matig ernstige depressieve stoornis, Hamilton > 18
- Duur: bij een eerste episode: minstens 3 maanden tot maximaal 2 jaar
- Behandeling: onvoldoende respons, of onvoldoende verdragen van 2 antidepressiva
  NB lithiumadditie of antipsychoticum-additie is ook een antidepressieve behandeling, maximaal 4 antidepressiva in de huidige episode.

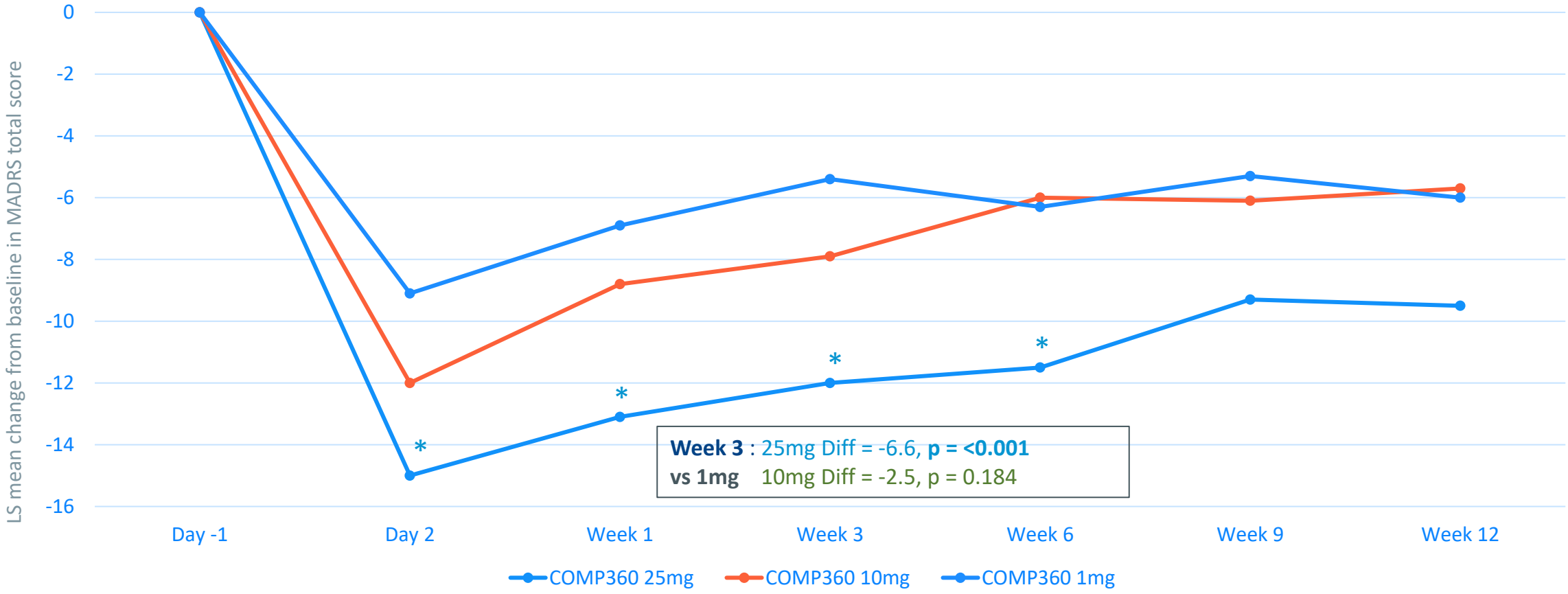
Exclusiecriteria

- Schizofrenie, bipolaire stoornis, psychotische depressie of een waanstoornis,
- Ernstige paranoïde- of borderline persoonlijkheidsstoornis
- Mensen met een sterk verhoogd risico op suïcide
- De huidige episode is behandeld met ECT of ketamine.
- Zwangerschap
- Alcohol- of drugsverslaving in het afgelopen jaar

Resultaten

Primary endpoint – change in MADRS total score

Statistically significant primary endpoint (p<0.001) at week 3 (25mg vs 1mg). There was a rapid onset of action and durable effects with treatment differences between the 25mg vs 1mg group apparent from the day after COMP360 psilocybin administration



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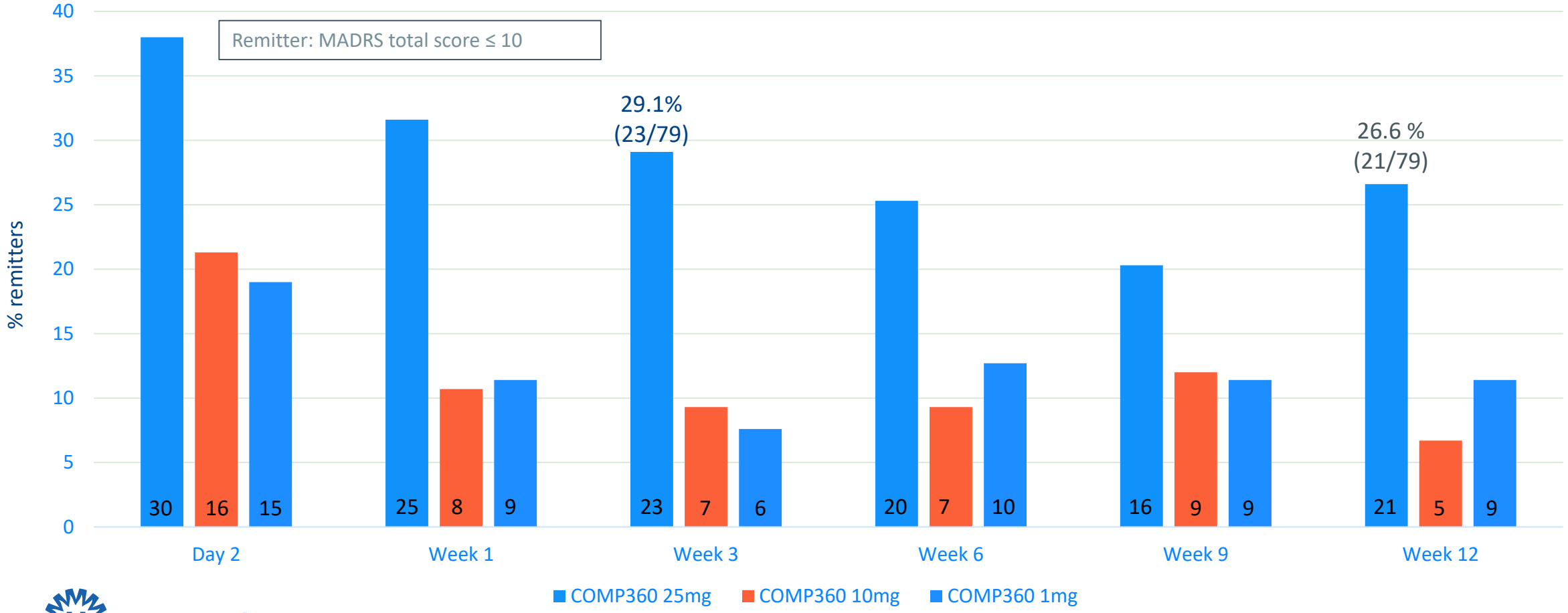
Baseline mean (SD): 25mg (n=79) = 31.9 (5.41); 10mg (n=75) = 33.0 (6.31); 1mg (n=79) = 32.7 (6.24)

Note: MADRS = Montgomery-Åsberg Depression Rating Scale; n = number observed; SD = standard deviation; LS = least squares; * = statistically significant treatment difference vs 1mg at visit; p = p-value

https://compasspathways.com/further-positive-results-phase-iib-trial/

Key secondary endpoint - MADRS remitters

25mg group demonstrated rapid remission, with treatment differences from day 2 to week 3 compared with the 1mg group



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Note: MADRS = Montgomery-Åsberg Depression Rating Scale; number of remitters stated in bar. Participants who started new treatment for depression were assumed to be non-remitters, hence decreasing numbers reflecting antidepressant use over time

https://compasspathways.com/further-positive-results-phase-iib-trial/

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Most frequent TEAEs

MedDRA TEAE preferred term	COMP360 25mg	COMP360 10mg	COMP360 1mg	Overall
	N=79	N=75	N=79	N=233
	n (%)			
Headache	27 (34.2)	16 (21.3)	20 (25.3)	63 (27.0)
Nausea	18 (22.8)	7 (9.3)	4 (5.1)	29 (12.4)
Fatigue	12 (15.2)	5 (6.7)	7 (8.9)	24 (10.3)
Insomnia	8 (10.1)	11 (14.7)	14 (17.7)	33 (14.2)
Anxiety	7 (8.9)	13 (17.3)	3 (3.8)	23 (9.9)
Mood altered	7 (8.9)	3 (4.0)	1 (1.3)	11 (4.7)
Back pain	6 (7.6)	0	3 (3.8)	9 (3.9)
Dizziness	6 (7.6)	1 (1.3)	1 (1.3)	8 (3.4)
Suicidal ideation	5 (6.3)	5 (6.7)	4 (5.1)	14 (6.0)
Myalgia	5 (6.3)	2 (2.7)	1 (1.3)	8 (3.4)
Euphoric mood	4 (5.1)	5 (6.7)	4 (5.1)	13 (5.6)
Depression	4 (5.1)	6 (8.0)	5 (6.3)	15 (6.4)
Abdominal pain upper	4 (5.1)	2 (2.7)	1 (1.3)	7 (3.0)
Irritability	4 (5.1)	2 (2.7)	1 (1.3)	7 (3.0)
Panic reaction	4 (5.1)	1 (1.3)	1 (1.3)	6 (2.6)
Depressed mood	3 (3.8)	5 (6.7)	4 (5.1)	12 (5.2)
Paraesthesia	3 (3.8)	4 (5.3)	1 (1.3)	8 (3.4)
Thinking abnormal	0	4 (5.3)	0	4 (1.7)

TEAE incidence is higher in the 25mg group overall

Key mood-related TEAEs (euphoric mood, depression, depressed mood, suicidal ideation) do not have a higher incidence in the 25mg arm

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Note: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event; N = number of participants in the population; n = number observed
https://compasspathways.com/further-positive-results-phase-iib-trial/

Vervolgstappen

- 2022: fase III studie: beste dosis vs placebo
- Daarna: mogelijk geregistreerd als geneesmiddel
- Dan begint het pas..
  - Optimaliseren behandeling?
  - Andere indicaties?
  - Voor wie?

Conclusie

Er is een hernieuwde interesse voor toepassing van psychedelica

Deze eerste internationale RCT laat zien dat psilocybine therapie bij therapieresistente depressie werkzaam en veilig is

Hiermee kan een volgende stap gezet worden (fase III) , waarna mogelijk registratie als geneesmiddel kan volgen

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