Designing and Implementing Studies in Patients with MDD at Imminent Risk for Suicide (MDSI): Insights from a Drug Development Program

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J&J Innovative Medicine

Disclosures

Full-time employee of Janssen Research & Development, LLC

Shareholder of Johnson & Johnson stock

Esketamine nasal spray is approved for rapid reduction in depressive symptoms in adults with MDSI

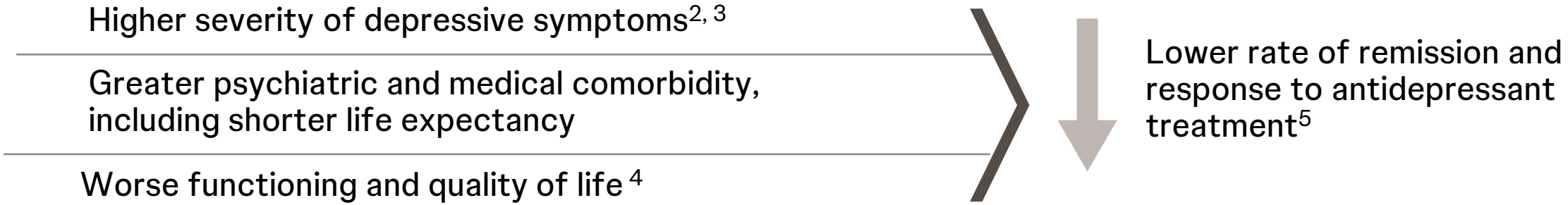
- *Esketamine is not approved for use in pediatric populations*
- *The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated*

Patients with MDSI Are A Particularly Ill Subpopulation

- **High Unmet Medical Need**

  MDD is the condition most frequently associated with suicide[1]

- **MDD patients with suicidal ideation and intent are a particularly ill subpopulation**



- **Challenges in treating this population**
  - Hospitalization , if accessible/ acceptable, is temporary. Post-discharge (ED/hospital) is a period of high vulnerability
  - Existing therapies may require several weeks to months
    - Delayed onset of antidepressant therapies; Electroconvulsive therapy; Psychotherapy
  - Little to no relevant clinical trial data as these patients are typically excluded from antidepressant clinical trials

1. Kessler, RC et al JAMA 2005; 2. Canuso, CM et al Am J Psychiatry 2018 2. Sokero TP et al 2005 Br J Psychiatry 186,:314; 3. Oquendo et al 2004 Am J Psychiatry 161: 1433-1441; 4. Salomon et al2015 Lancet Glob Health 3:e712; 5. Lopez-Castroman J et Al 2016 Depression & Anxiety 33(6): 483-494.

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Esketamine Global Clinical Development Program in MDSI

One Phase 2 and
two Phase 3 studies in adults
One Phase 2 in adolescents

Evaluated for safety in 671 patients with MDD who have active SI with intent

Three completed Phase 2/3 studies in adults

Completed Phase 2 & planned Phase 3 studies in adolescents

1

Short-term Phase 2
(n=68)[1]

2001

2

Short-term Phase 3
(n=456)[2,3]

3001

3002

3 **4**

Short-term Phase 2/3

2002 (n=147)[4]

3003 (n≥200)

Objectives:

- To provide urgent relief of depressive symptoms in this vulnerable and moderately to severely ill patient population
- To bridge the gap in efficacy created by the delayed onset of action of oral antidepressant treatments

2014 2017-2019 2023

1. Canuso CM, et al. *Am J Psychiatry* 2018; 175: 620–30; 2. Fu DJ, et al. *J Clin Psychiatry* 2020; 81: 19m13191; 3. Ionescu DF, et al. *Int J Neuropsychopharmacol* 2021; 24: 22–31; 4. Kosik-Gonzalez C, et al, APA 2023 poster presentation.

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Key Eligibility Criteria

- MDD without psychotic features confirmed by MINI/MINI-KID
- MADRS > 28 for adults or CDRS ≥ 58 for adolescents
- Borderline personality disorder excluded
- Moderate – severe substance use disorder excluded
- History of ketamine, PCP, MDMA, LSD use disorder excluded

Level of Suicidality Required -Imminent Risk for Suicide

- Active suicidal ideation with intent
  - Adult Phase 3: “Yes” response to MINI (DSM-5) Module B Questions
    - 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)
    - B10: Intend to act on thoughts of killing yourself in past 24 hours?
  - Adolescent Phase 2: “Yes” response to MINI-KID:
    - B3: Think about hurting yourself, with the possibility that you might die; Or did you think about killing yourself?
    - B10: Expect to go through with a plan to kill yourself in past 24 hours?
- Psychiatric hospitalization is clinically warranted

Study Design for a Vulnerable Population

- Conducted in the context of comprehensive standard of care treatment and consistent with local practice
  - Newly initiated or optimized standard antidepressant regimen per clinician judgment
  - Mandatory (but voluntary!) hospitalization
- No prohibition on newly initiated psychotherapy, including intensive out-patient programs
- Frequent study visits and sufficiently long duration of follow-up

Ethical Considerations

- Use of placebo/psychoactive Placebo sits on top of comprehensive standard of care
  - But signal dampening

- Are severely suicidal patients capable of making treatment decisions and consent to participate in research?

Additional Safety Monitoring

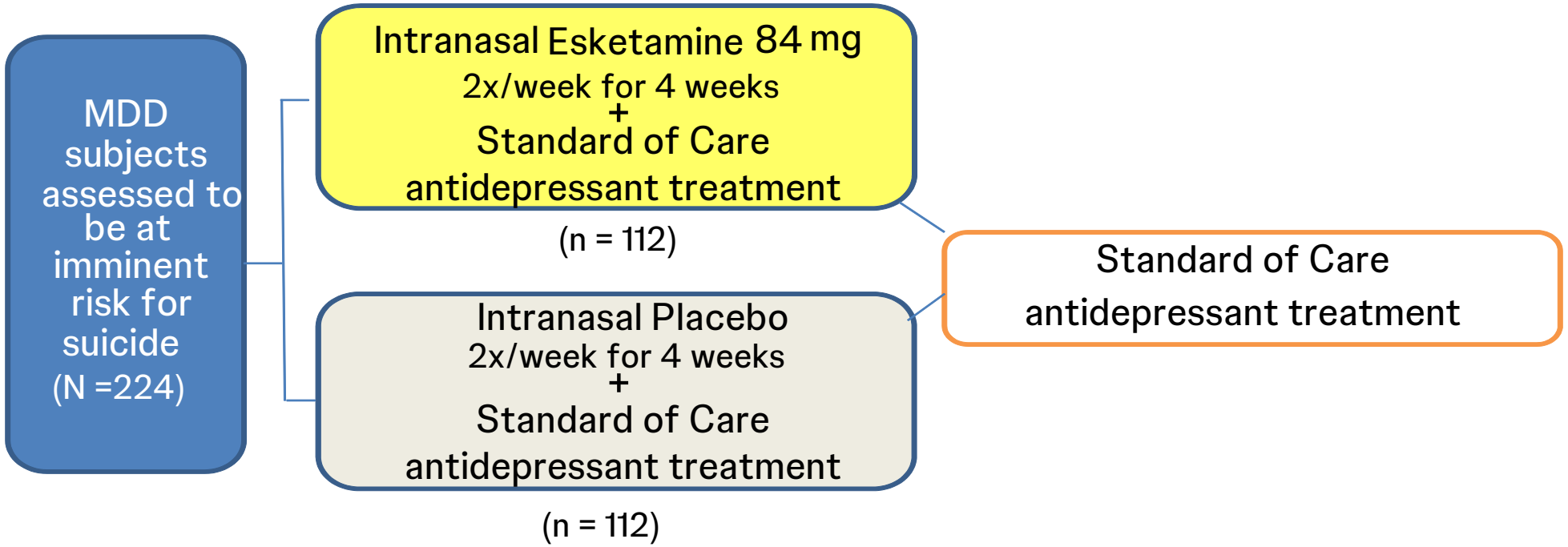
- Independent Data Review Committee
- AE monitoring and assessing SIB-related events (treatment emergent versus expression of underlying illness?)
- Follow up visits after completion of double-blind to assess for any AEs related to rebound or withdrawal

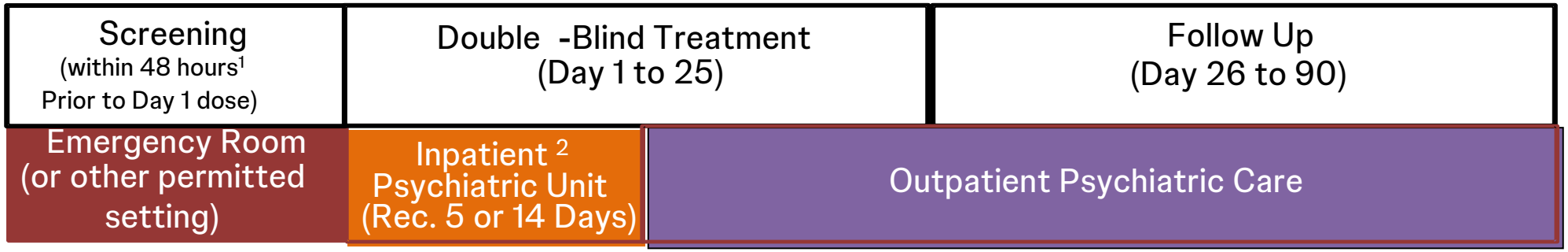
Regional Considerations

- Differences in local practice and Standard of Care
  - Duration of hospitalization
  - Alternatives to hospitalization
  - Access to psychological therapy

- Country/region-specific amendments

Study Design: Adult Phase 3 Studies





- [1]If possible, screening should be performed within 24 hours
- [2]Duration of hospitalization depends on subject's clinical status and local standard of care.

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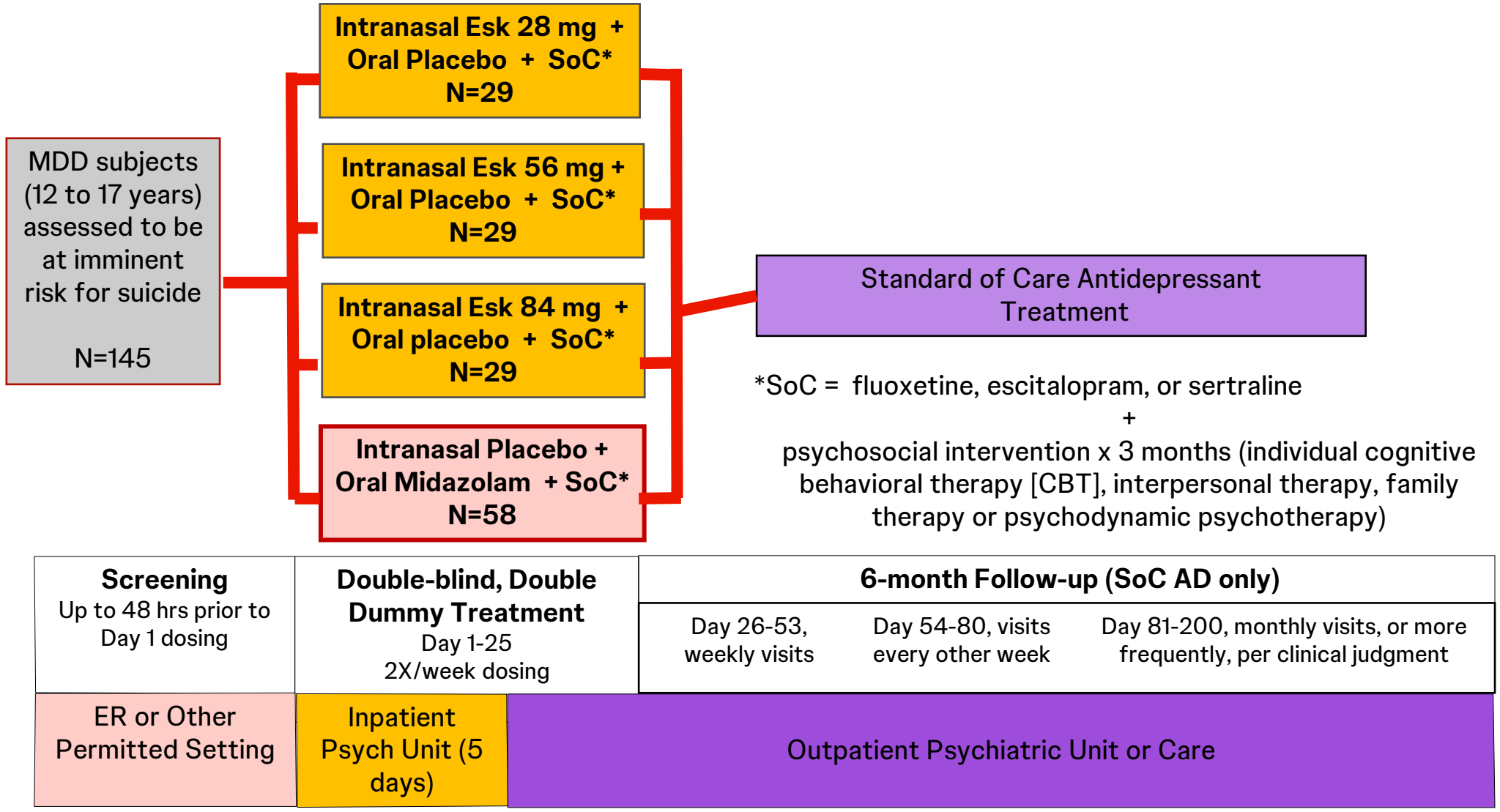
Study Design: Adolescent Phase 2 Study



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Key Baseline Demographic And Clinical Features

Parameter	Phase 3 Adult[1] (N=451)	Phase 2 Adolescent[2] (N=145)
Age, mean (SD), years	40.1 (13.00)	14.9 (1.45)
Female, %	60.8	77.9
Race, % • White • Black • Other	 73.2 5.8 21.1	 80.7 10.3 9.0
MADRS, mean (SD)	40.4 (5.82)	39.8 (6.19)
CDRS-R, mean (SD)	N/A	76.3 (10.00)
Mod-Extreme CGI-SS-r, %	90	92.5
Prior Suicide Attempt, % • Lifetime • Past month	 63.1 27.3	 80.0 53.8

1. Canuso, CM et al J *Clin Psychopharmacol* 2021;41: 516–524; 2. Kosik-Gonzalez C et al, APA '23 Poster

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Primary Outcomes: MADRS* and CDRS-R**

Adult Pooled Phase 3 MADRS Total Score Change From BL to 24 Hours Post First Dose

Adolescent Phase 2 CDRS-R Total Score Change From BL to 24 Hours Post First Dose

Parameter	PBO + SOC	ESK 84 mg + SOC	MDZ 0.125mg/kg + SOC	ESK 28 mg + SOC	ESK 56 mg + SOC	ESK 84 mg + SOC	ESK 56/84 mg + SOC
N	227	229	63	28	31	23	54
Mean (SD) Change from Baseline	−12.6 (10.56)	−16.1 (11.73)	-26.2 (16.72)	-29.6 (18.15)	-31.8 (12.92)	-30.3 (17.48)	-31.2 (14.90)
Diff. of LS Means (SE) (minus PBO or MDZ)		−3.8 (0.98)		-2.4 (3.35)	-5.9 (3.23)	-5.7 (3.65)	-5.8 (2.74)
2-sided p-value		N/A***		N/A	0.072	0.123	0.037
95% Confidence Interval		−5.75, −1.89		-9.01, 4.26	-12.25, 0.53	-12.89, 1.57	-11.18, -0.34

*Montgomery Asberg Depression Rating Scale

**Children's Depression Rating Scale – Revised

***Individual studies: p=0.006

1. Canuso, CM et al J *Clin Psychopharmacol* 2021;41: 516–524; 2. Kosik-Gonzalez C et al, APA '23 Poster

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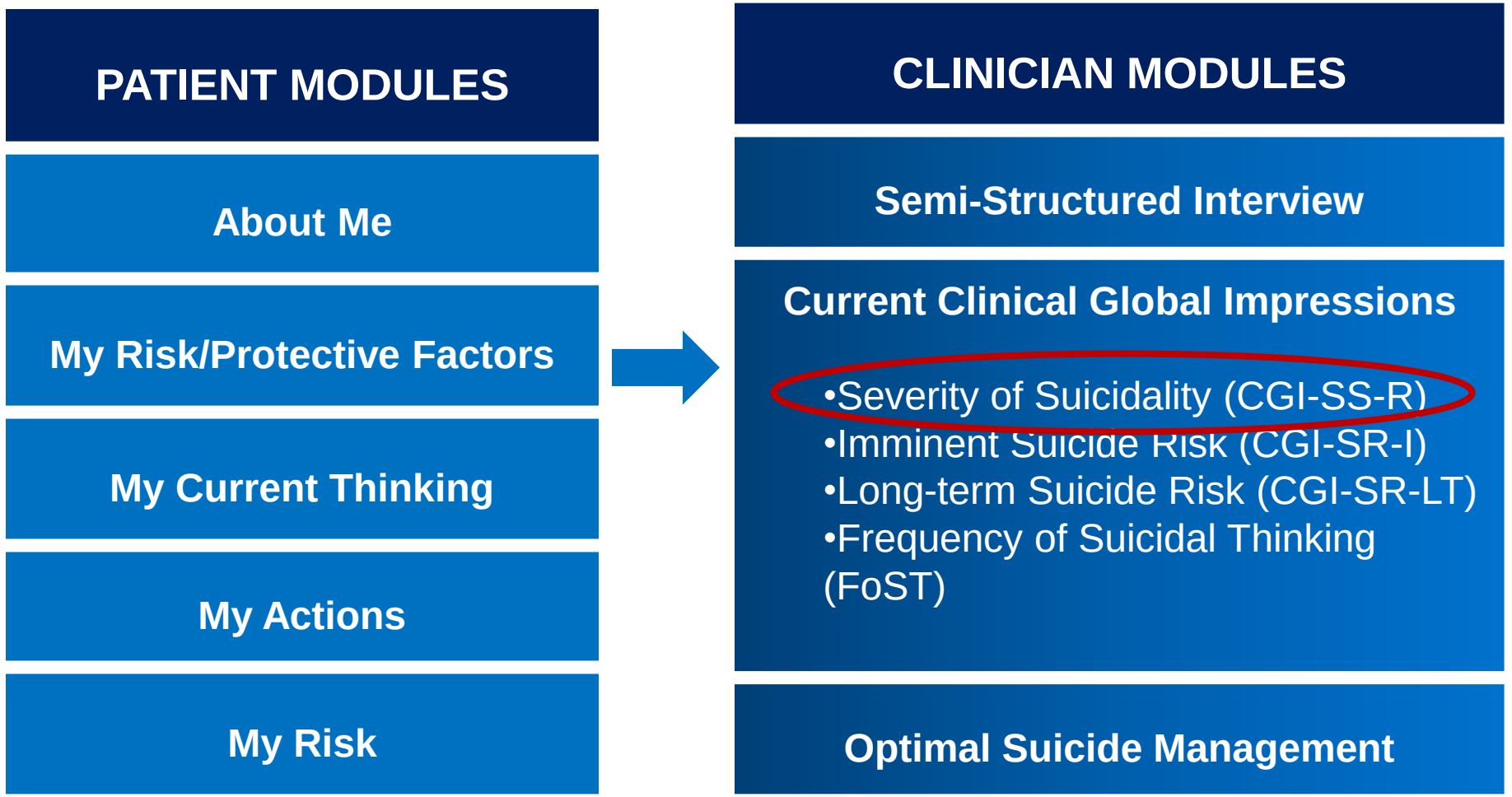
Suicide Ideation and Behaviour Assessment Tool (SIBAT)



SIBAT has a separate T&E table. Not all modules are assessed at all visits. 20-40 minutes to complete

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CGI-Severity of Suicidality – Revised

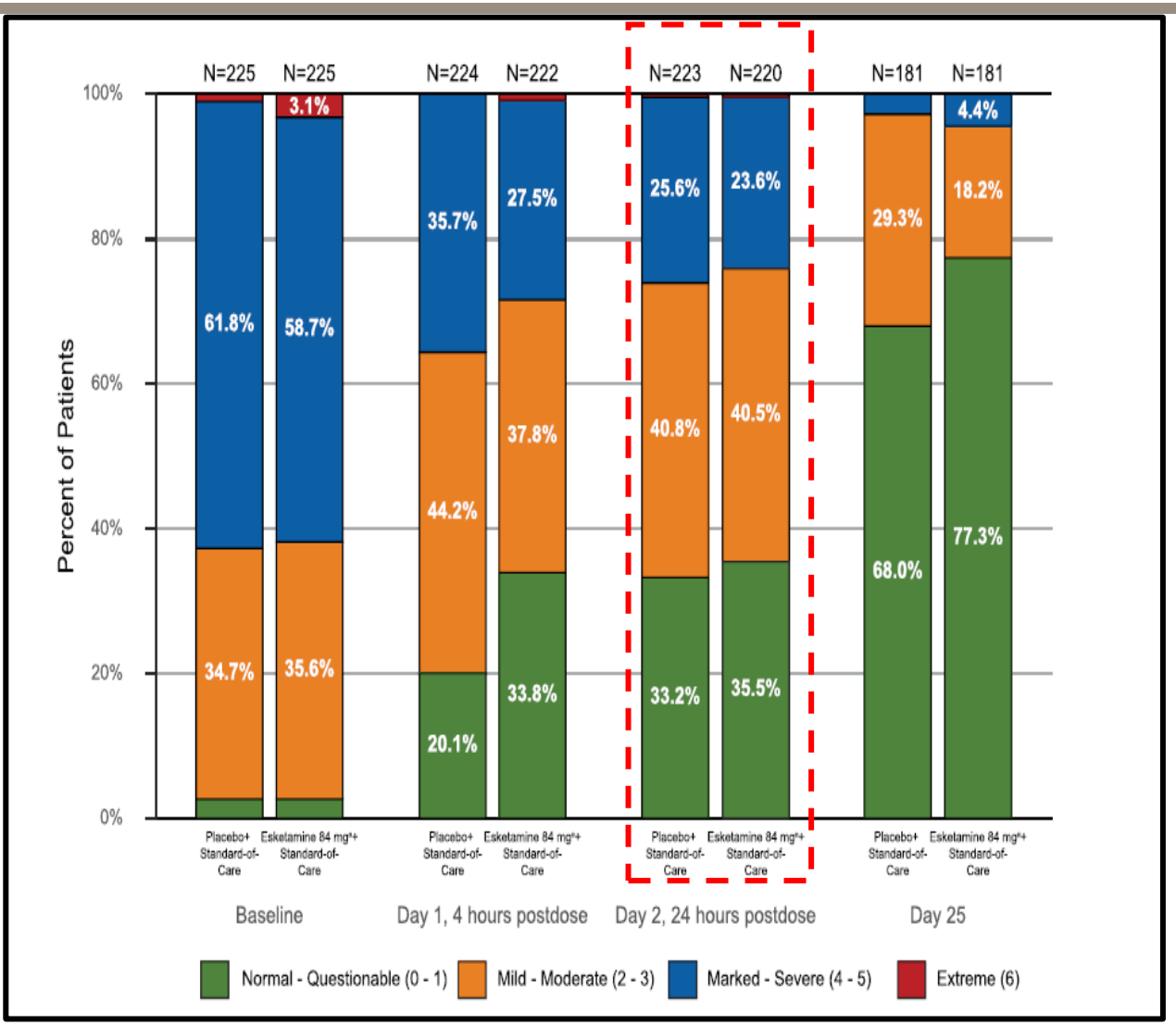
Considering your total clinical experience with suicidal patients and all information now available to you, how suicidal is this patient at this time?

RATING	GUIDE TO RATING
0 Normal, not at all suicidal	• Not suicidal
1 Questionably suicidal	• Minimal ideations; little if any impulsivity for suicide, few risk factors and many protective factors ; and no impact on function.
2 Mildly suicidal	• Occasional ideations; little if any impulsivity for suicide; few risk factors; adequate protective factors and no or minimal impact on function
3 Moderately suicidal	• Intermittent ideations; with possible impulsivity for suicide; may or may not have plan or recent attempt*; several risk factors; protective factors may outweigh risk factors and some impact on function.
4 Markedly suicidal	• Regular ideations with intent or potential for impulsive actions for suicide; may or may not have plan or recent attempt*; multiple risk factors out weigh protective factors; and marked impact on function.
5 Severely suicidal	• Frequent ideations with intent; well worked out suicide plan; may or may not have recent attempt*; multiple risk factors out-weigh protective factors; and major impact on function.
6 Among the most extremely suicidal patients	• Nearly constant suicidal ideations and intent; well worked out plan and preparations underway or recent attempt*; and severe impact on function.

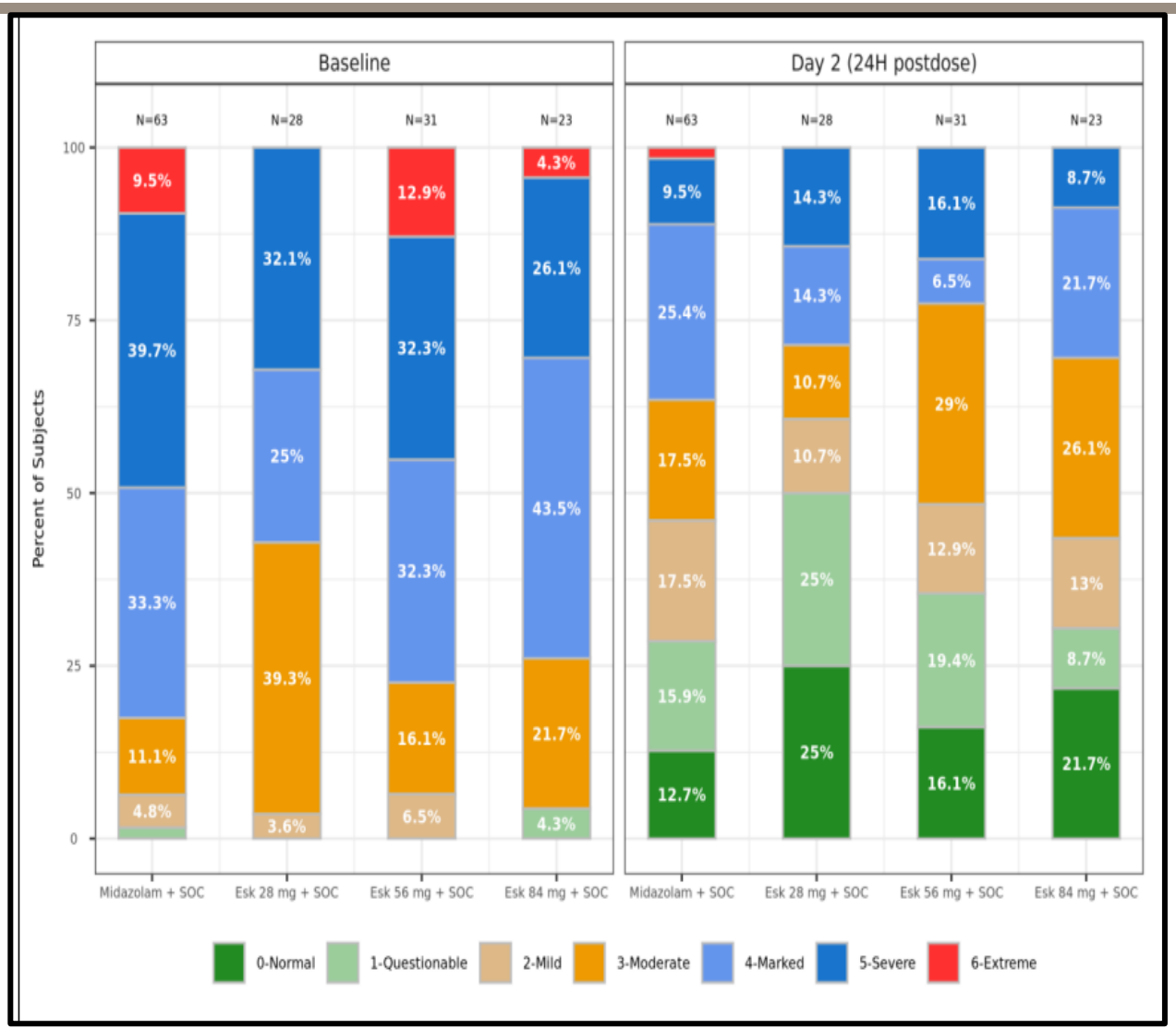
* Consider seriousness/lethality of any plan or suicide attempt in overall rating

CGI-SS-R Distribution

Pooled Phase 3 Adult Data



Adolescent Phase 2 Data



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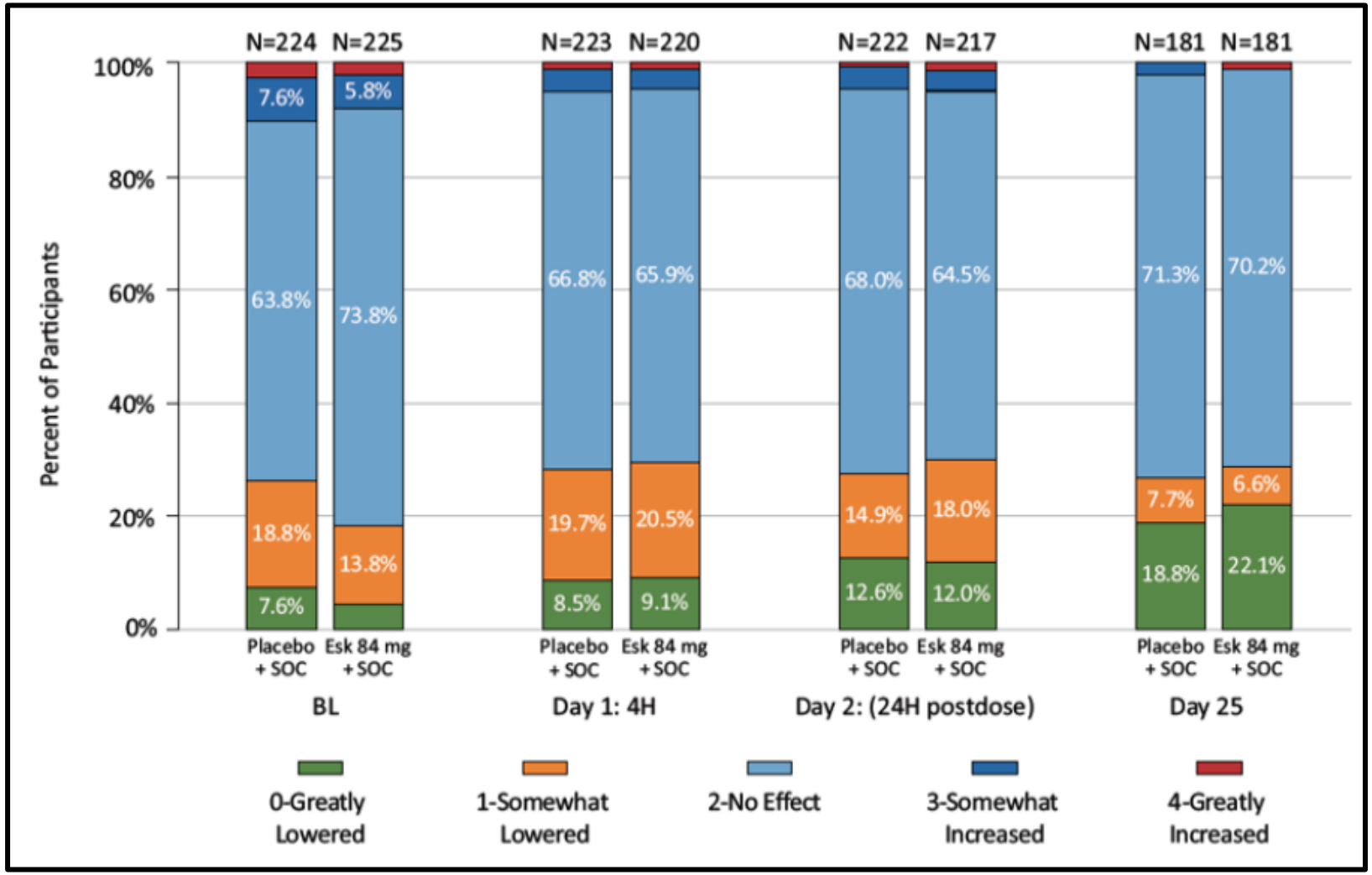
Effect of Completing SIBAT on Suicidality

- SIBAT comprises 5 digitally delivered patient-reported modules and 3 clinician-rated modules
- Patient modules with up to 121 questions
- Module 5 Question 5: Did completing this assessment affect your desire to take your life in any way?
- Adolescent results similar (responses of “greatly or somewhat lowered” ranged from ~ 4%-30%)



Kajs, BL et al. Poster ISCTM 2023

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Summary

- SIB is not uncommon in MDD and excluding these patients limits the generalizability but including them requires careful consideration for safe and ethical care
- Pharmacological trials can be designed to safely and ethically include adult and adolescent patients who are actively suicidal and considered at imminent risk for suicide
- Identification, recruitment and retention of such subjects is feasible but can be challenging
- Acute treatment trials require outcome measures that are sensitive to rapid change
- Drugs showing benefit on suicidality will need to have sufficiently large treatment effects to overcome the non-specific benefits of research participation and comprehensive standard of care

Future Considerations

- Can acutely suicidal patients be studied in less restrictive environments than in-patient hospitals?
  - What additional precautions should be taken?
- Should mild to moderately suicidal patients routinely be included in outpatient antidepressant trials?
- How can technology be applied in clinical trials to better monitor and assess suicidality?

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