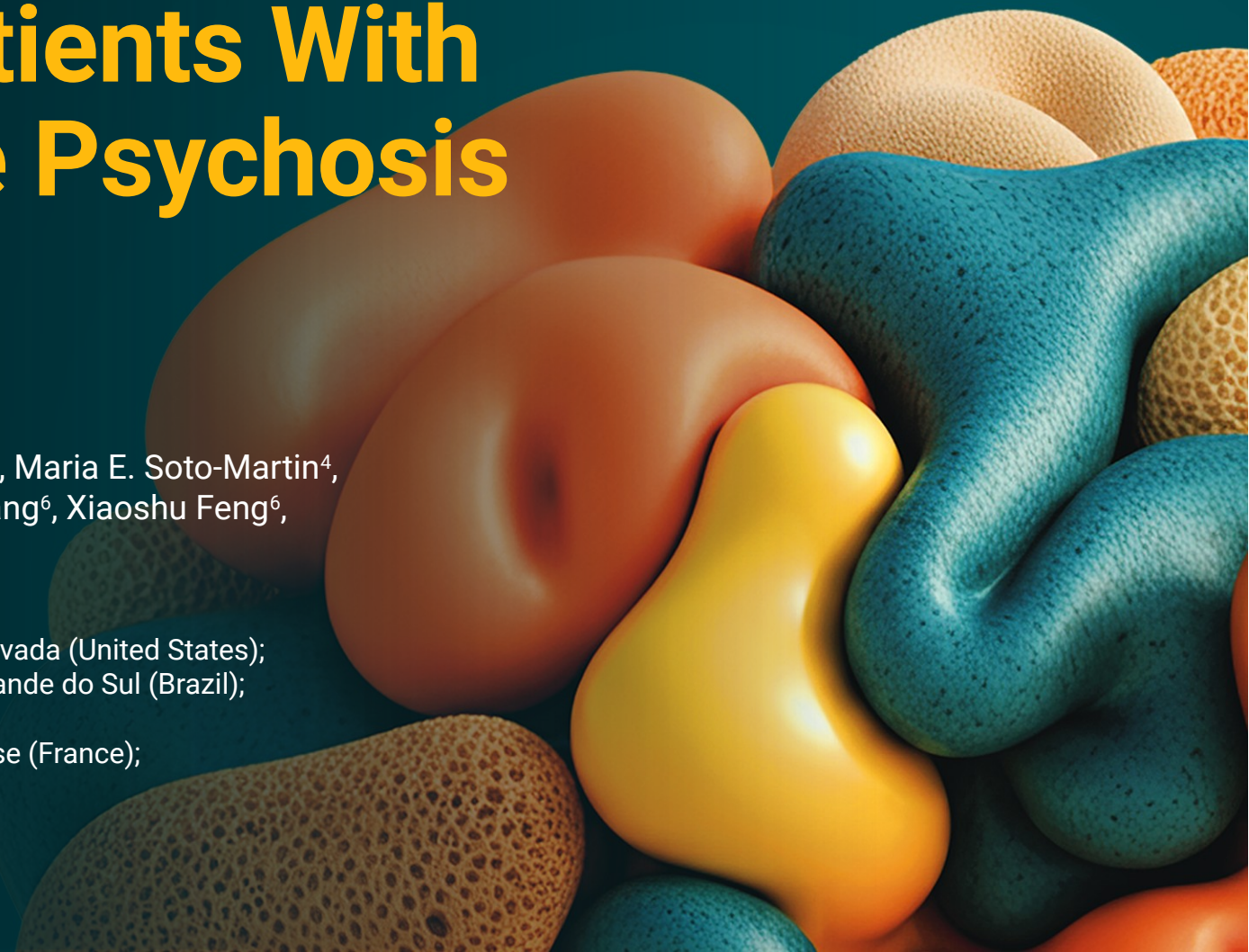
# Efficacy and Safety of Remlifanserin in Patients With Alzheimer's Disease Psychosis

## RADIANT Phase 2 Clinical Trial Results

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# Disclosures

**JC** reports consulting fees from Acadia, Alkermes, ALZpath, Artery, Axsome, Biogen, Biohaven, Bristol Myers Squibb, Eisai, Fosun, GAP Foundation, Hummingbird Diagnostics, Janssen, Karuna, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/EQT, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, Otsuka, Praxis, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, Sinaptica, and TrueBinding pharmaceutical, assessment, and investment companies; and stocks or stock options in Artery, Vaxxinity, Behrens, Alzheon, MedAvante-ProPhase, and Acumen.

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# Rationale for Advancing Remlifanserin in Alzheimer's Disease Psychosis

## Pimavanserin

Validated selective 5-HT$_{2A}$ targeting in Parkinson's disease psychosis

QTc considerations limited evaluation of higher doses

Evidence of efficacy in ADP: randomized study of 181 UK nursing home patients without biomarker confirmation of Alzheimer's disease[1]

## Remlifanserin

Built on the established 5-HT$_{2A}$ mechanism

No QTc signal in Phase 1

RADIANT Phase 2 evaluated remlifanserin for the treatment of psychosis in patients with biomarker-confirmed ADP

**Prior clinical experience provided the confidence to advance remlifanserin into the RADIANT Phase 2/3 program**

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5-HT$_{2A}$ = 5-hydroxytryptamine (serotonin) 2A receptor; ADP = Alzheimer's disease psychosis.

**Reference: 1.** Ballard C, et al. *Lancet Neurol*. 2018;17(3):213–222.

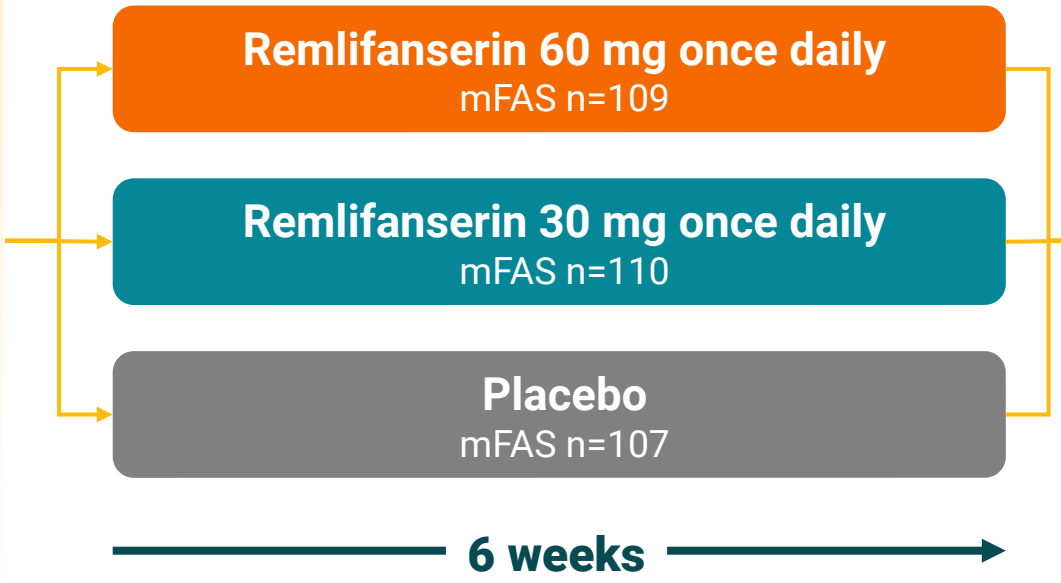
# RADIANT Phase 2: Study Design and Key Enrollment Criteria

## Key enrollment criteria

- Age 55–95 years
- Clinical criteria for AD
- Blood-based biomarker, PET, or CSF
- Psychosis meeting revised IPA criteria
- MMSE score 6–24
- NPI/NPI-NH hallucinations ≥6, delusions ≥6, or psychosis score ≥9
- CGI-S-ADP ≥4
- SAPS-H+D total score ≥10

## Randomized treatment design

N=363 | Double-blind | Randomized 1:1:1




## Efficacy endpoints

**Primary endpoint**

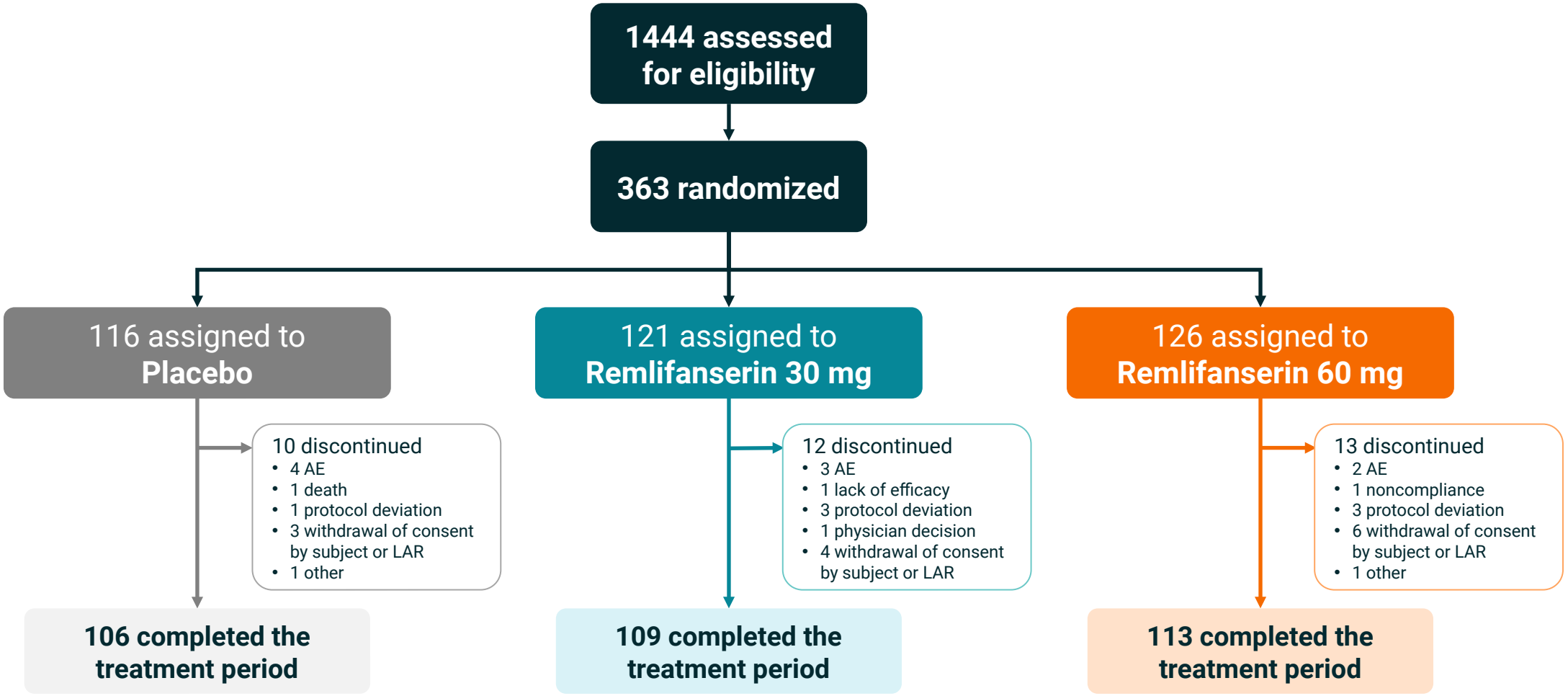
SAPS-H+D total score change from baseline to Week 6

**Key secondary endpoint**

CGI-S-ADP change from baseline to Week 6

FAS includes randomized subjects who received ≥1 dose and had baseline and ≥1 post-baseline SAPS-H+D total score, analyzed by planned randomized treatment; mFAS includes FAS subjects with baseline SAPS-H+D total score ≥10. AD = Alzheimer's disease; ADP = Alzheimer's disease psychosis; CGI-S-ADP = Clinical Global Impression–Severity in ADP; CSF = cerebrospinal fluid; FAS = Full Analysis Set; IPA = International Psychogeriatric Association; mFAS = modified Full Analysis Set; mg = milligrams; MMSE = Mini-Mental State Examination; N/n = number of subjects; NPI = Neuropsychiatric Inventory; NPI-NH = Neuropsychiatric Inventory–Nursing Home version; PET = positron emission tomography; SAPS-H+D = Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions.

# RADIANT Phase 2: Subject Disposition




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AE = adverse event; LAR = legally authorized representative; mg = milligrams.

# Demographics and Baseline Disease Characteristics (mFAS)

| | Placebo (N=107) | Remlifanserin 30 mg (N=110) | Remlifanserin 60 mg (N=109) | Remlifanserin Overall (N=219) |
|---|---|---|---|---|
| **Sex, n (%)** | | | | |
| Female | 68 (64) | 69 (63) | 75 (69) | 144 (66) |
| Male | 39 (36) | 41 (37) | 34 (31) | 75 (34) |
| **Age (years)** | | | | |
| Mean (SD) | 76.3 (6.26) | 76.9 (5.51) | 75.7 (6.25) | 76.3 (5.91) |
| Median (Min, Max) | 76.0 (60, 88) | 77.0 (61, 89) | 76.0 (60, 95) | 76.0 (60, 95) |
| **Primary race, n (%)** | | | | |
| White | 96 (89.7) | 89 (80.9) | 93 (85.3) | 182 (83.1) |
| Black or African American | 4 (3.7) | 3 (2.7) | 2 (1.8) | 5 (2.3) |
| Asian | 4 (3.7) | 11 (10.0) | 5 (4.6) | 16 (7.3) |
| American Indian or Alaska Native | 1 (0.9) | 3 (2.7) | 4 (3.7) | 7 (3.2) |
| Other (includes unknown, not reported, multiple) | 2 (1.9) | 4 (3.6) | 5 (4.6) | 9 (4.1) |
| **SAPS-H+D total score** | | | | |
| Mean (SD) | 24.5 (10.25) | 24.6 (10.39) | 25.5 (12.81) | 25.1 (11.64) |
| Median (Min, Max) | 24.0 (10, 80) | 23.0 (10, 68) | 22.0 (10, 87) | 23.0 (10, 87) |
| **CGI-S-ADP score** | | | | |
| Mean (SD) | 4.8 (0.70) | 4.8 (0.65) | 4.7 (0.69) | 4.7 (0.67) |
| Median (Min, Max) | 5.0 (4, 6) | 5.0 (4, 6) | 5.0 (4, 7) | 5.0 (4, 7) |

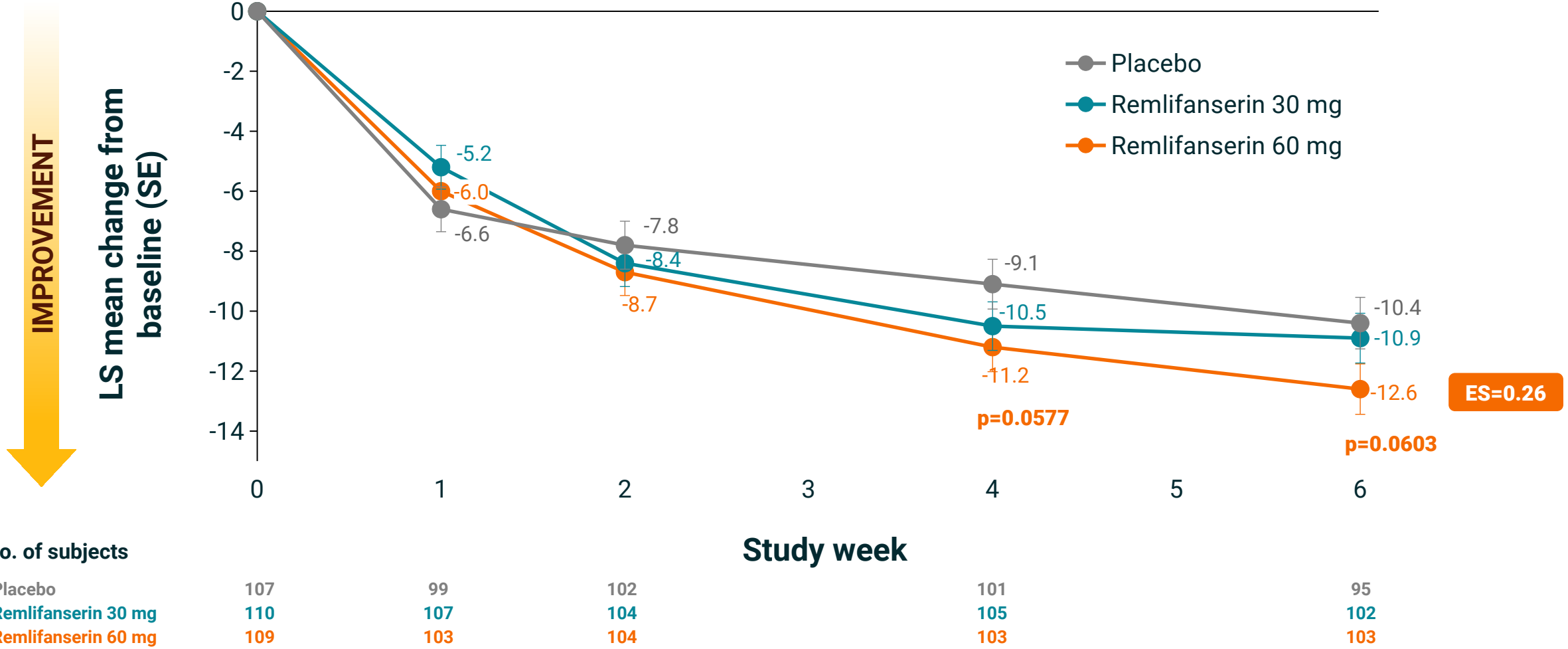
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mFAS population. CGI-S-ADP = Clinical Global Impression–Severity in Alzheimer's disease psychosis; Max = maximum; mFAS = modified Full Analysis Set; mg = milligrams; Min = minimum; SAPS-H+D = Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions; SD = standard deviation.

# SAPS-H+D Total Score Over Time

## Primary Endpoint Not Met

### SAPS-H+D




**No. of subjects**

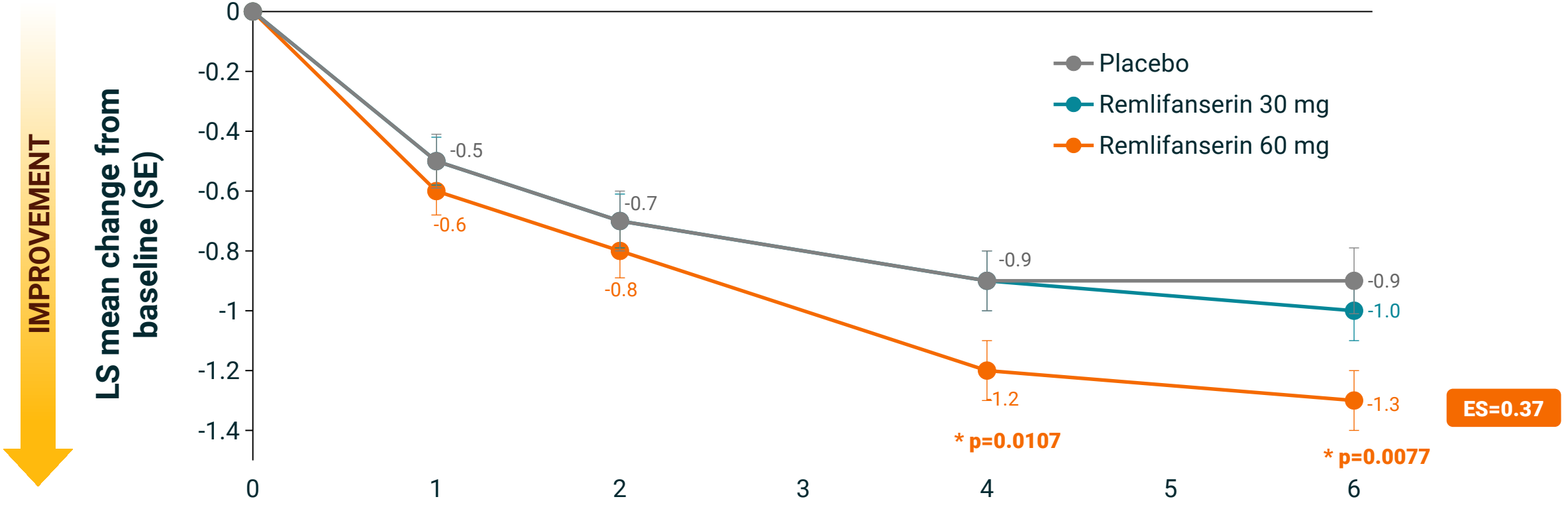
| | | | | | |
|---|---|---|---|---|---|
| Placebo | 107 | 99 | 102 | 101 | 95 |
| Remlifanserin 30 mg | 110 | 107 | 104 | 105 | 102 |
| Remlifanserin 60 mg | 109 | 103 | 104 | 103 | 103 |

mFAS population; Observed data; LS means from MMRM method with model terms: treatment, study site, visit, treatment by visit interaction, baseline score, and baseline score by visit interaction. ES = effect size; LS = least squares; mFAS = modified Full Analysis Set; mg = milligrams; MMRM = mixed model repeated measures; SAPS-H+D = Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions Subscales; SE = standard error.

# Clinical Global Impression of Severity (CGI-S-ADP) Score

## Key Secondary Endpoint

### CGI-S-ADP



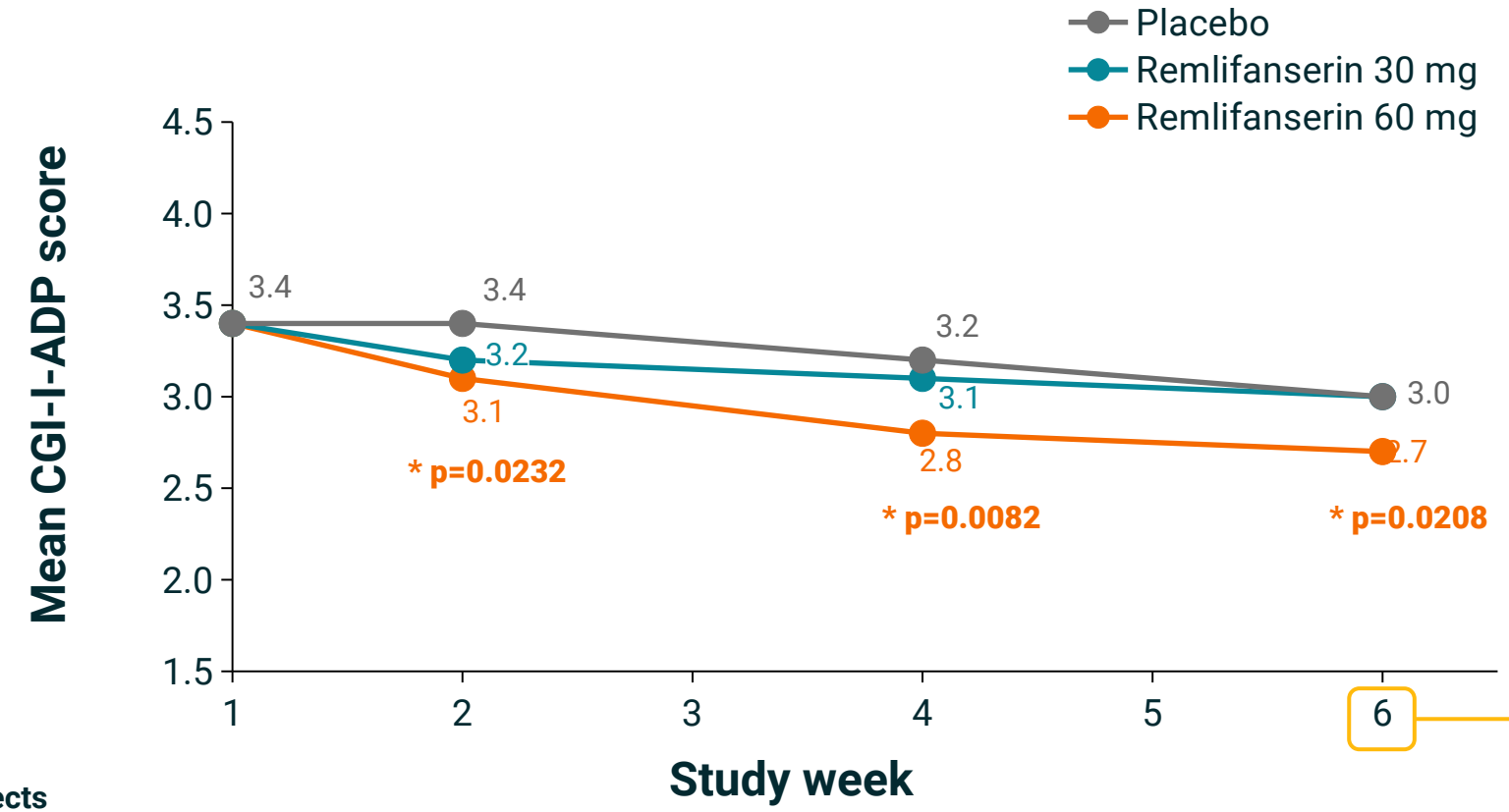

**No. of subjects**

| | | | | | |
|---|---|---|---|---|---|
| Placebo | 107 | 99 | 103 | 101 | 95 |
| Remlifanserin 30 mg | 110 | 107 | 103 | 105 | 102 |
| Remlifanserin 60 mg | 109 | 103 | 104 | 103 | 103 |

mFAS population; *Nominal p-value; LS means from MMRM method with model terms: treatment, study site, visit, treatment by visit interaction, baseline score, and baseline score by visit interaction. CGI-S-ADP = Clinical Global Impression–Severity in Alzheimer's disease psychosis; ES = effect size; LS = least squares; mFAS = modified Full Analysis Set; mg = milligrams; MMRM = mixed model repeated measures; SE = standard error.

# Clinical Global Impression of Improvement (CGI-I-ADP) Over Time

## CGI-I-ADP




At Week 6, % **improved** or **very much improved** (CGI-I-ADP score of **1** or **2**):

**44.0% Remlifanserin 60 mg**

**31.8% Placebo**

**No. of subjects**

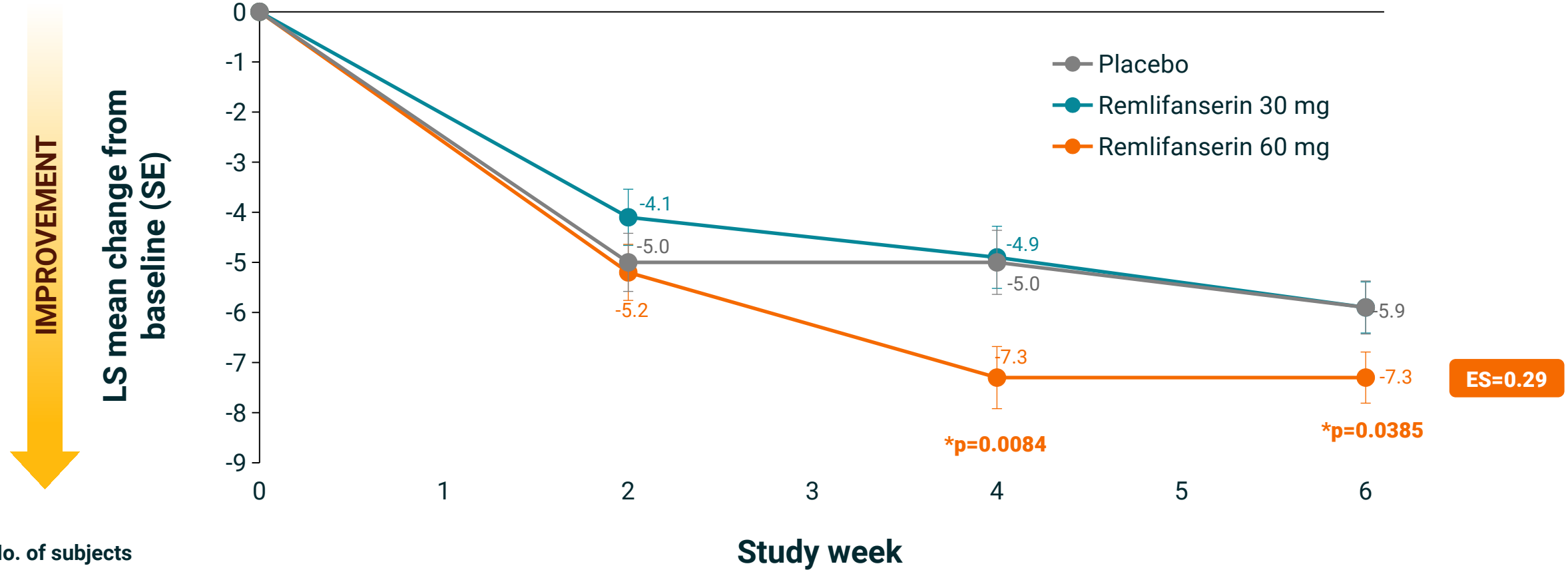
| | | | | |
|---|---|---|---|---|
| Placebo | 98 | 107 | 107 | 107 |
| Remlifanserin 30 mg | 107 | 110 | 110 | 110 |
| Remlifanserin 60 mg | 103 | 109 | 109 | 109 |

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mFAS population; *Nominal p-value; p-value and treatment difference derived using CMH. ADP = Alzheimer's disease psychosis; CGI-I-ADP = Clinical Global Impression –Improvement in ADP; CMH = Cochran–Mantel–Haenszel; LOCF = last observation carried forward; mFAS = modified Full Analysis Set; mg = milligrams.

# NPI/NPI-NH Psychosis Score Over Time

## NPI/NPI-NH Psychosis




**No. of subjects**

| | | | | |
|---|---|---|---|---|
| Placebo | 99 | 62 | 63 | 93 |
| Remlifanserin 30 mg | 107 | 63 | 65 | 102 |
| Remlifanserin 60 mg | 108 | 62 | 63 | 101 |

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mFAS population; *Nominal p-value; LS means from MMRM with model terms: treatment, study site, visit, treatment by visit interaction, baseline score, and baseline score by visit interaction. ES = effect size; LS = least squares; mFAS = modified Full Analysis Set; mg = milligrams; MMRM = mixed model repeated measures; NPI = Neuropsychiatric Inventory; NPI-NH = Neuropsychiatric Inventory–Nursing Home version; SE = standard error.

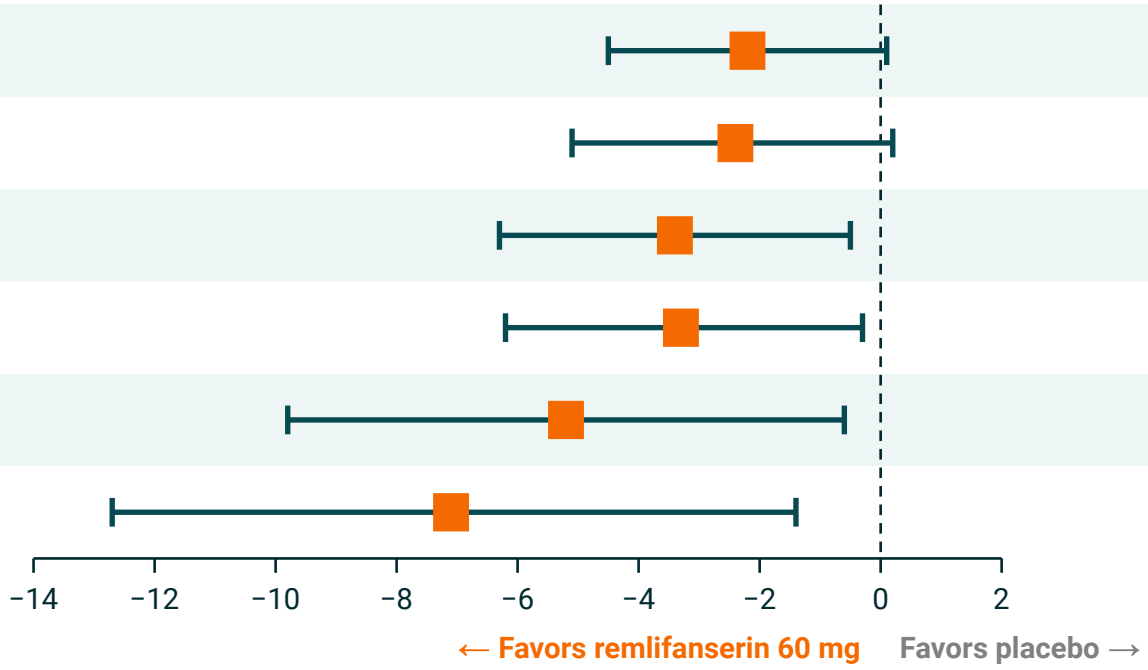
# SAPS-H+D Treatment Effect Across Baseline Psychosis Severity Subgroups

Treatment estimates favored remlifanserin 60 mg across severity subgroups, with larger estimated effects in populations with higher baseline psychosis severity

SAPS-H+D

## Week 6 SAPS-H+D treatment difference for remlifanserin 60 mg versus placebo

| Baseline NPI/NPI-NH psychosis severity subgroup | Placebo, n | Remlifanserin 60 mg, n | Cohen's d |
|---|---|---|---|
| NPI Psychosis ≥ 6 | 107 | 109 | 0.26 |
| NPI Psychosis ≥ 8 | 95 | 98 | 0.26 |
| NPI Psychosis ≥ 10 | 83 | 84 | 0.36 |
| NPI Psychosis ≥ 12 | 83 | 78 | 0.34 |
| NPI Psychosis ≥ 14 | 43 | 42 | 0.48 |
| NPI Psychosis ≥ 16 | 32 | 31 | 0.63 |




*Exploratory analysis of ordered, overlapping subgroups defined by baseline NPI/NPI-NH psychosis score. Subgroups are not independent, and estimates become less precise as subgroup size decreases.*

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mFAS population; n = subjects at baseline; LS mean difference in change from baseline to Week 6 in SAPS-H+D total score (MMRM); negative values favor 60 mg; subgroups defined by baseline NPI/NPI-NH psychosis score ≥ threshold. LS = least squares; mg = milligrams; MMRM = mixed model repeated measures; NPI = Neuropsychiatric Inventory; NPI-NH = NPI–Nursing Home version; SAPS-H+D = Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions.

# Overall Summary of Safety

Both remlifanserin 60 mg and 30 mg were well tolerated, with low rates of TEAEs, serious TEAEs, and discontinuations due to TEAEs

No deaths occurred in either remlifanserin treatment arm

Serious TEAEs in remlifanserin-treated patients included acute kidney injury (n=1), COVID-19 (n=1), and leukopenia and neutropenia (n=1; drug-related)

Somnolence (3.2%) and nausea (2.4%) were the only TEAEs occurring in >2% of patients receiving remlifanserin 60 mg and at a numerically higher incidence than placebo

| Subjects, n (%) | Placebo (N=115) | Remlifanserin 30 mg (N=120) | Remlifanserin 60 mg (N=125) | Remlifanserin Overall (N=245) |
|---|---|---|---|---|
| **Any TEAE** | 48 (41.7) | 46 (38.3) | 46 (36.8) | 92 (37.6) |
| **Any serious TEAE** | 3 (2.6) | 1 (0.8) | 2 (1.6) | 3 (1.2) |
| **Any non-serious TEAE** | 48 (41.7) | 45 (37.5) | 46 (36.8) | 91 (37.1) |
| **Any common non-serious TEAE[a]** | 0 | 0 | 0 | 0 |
| **Any drug-related TEAE** | 9 (7.8) | 8 (6.7) | 7 (5.6) | 15 (6.1) |
| **Any drug-related serious TEAE** | 0 | 0 | 1 (0.8) | 1 (0.4) |
| **Any drug-related non-serious TEAE** | 9 (7.8) | 8 (6.7) | 7 (5.6) | 15 (6.1) |
| **Any TEAE leading to discontinuation from study drug** | 3 (2.6) | 1 (0.8) | 3 (2.4) | 4 (1.6) |
| **Any drug-related TEAE leading to discontinuation from study drug** | 3 (2.6) | 0 | 1 (0.8) | 1 (0.4) |
| **Any TEAE with an outcome of death[b]** | 2 (1.7) | 0 | 0 | 0 |
| **Any TEAE of special interest** | 2 (1.7) | 0 | 4 (3.2) | 4 (1.6) |

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[a]Common TEAE is an AE with an incidence of ≥ 5% of either remlifanserin treatment group and ≥ 2x the incidence of placebo; [b]Two subjects in the placebo group had TEAEs with an outcome of death: one subject experienced cardiac failure; one subject experienced cardiac arrest and a fall. TEAE = treatment-emergent adverse event.

# No Negative Impact on Motor Symptoms, Cognition, or QTcF in Phase 2

| Safety measure | Placebo | Remlifanserin 30 mg | Remlifanserin 60 mg |
|---|---|---|---|
| **Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A): Parkinsonism subscale total score[a]** | **N=113** | **N=117** | **N=119** |
| Week 6 ***(decrease = improvement)*** | | | |
| Change from baseline: LS mean[b] (SE[b]) | -0.1 (0.09) | -0.1 (0.09) | -0.1 (0.09) |
| Difference[b] [95% CI: lower[b], upper[b]] | | **-0.0 [-0.3, 0.2]** | **-0.1 [-0.3, 0.2]** |
| **Total Mini-Mental State Examination (MMSE) score[a]** | **N=113** | **N=118** | **N=119** |
| Week 6 ***(increase = improvement)*** | | | |
| Change from baseline: LS mean[b] (SE[b]) | 1.0 (0.27) | 1.3 (0.26) | 1.6 (0.26) |
| Difference[b] [95% CI: lower[b], upper[b]] | | **0.3 [-0.4, 1.0]** | **0.6 [-0.1, 1.3]** |
| **QTcF (msec) – categorical changes** | **N=113** | **N=120** | **N=120** |
| Overall post-baseline, n (%) | | | |
| New onset (> 480 msec) | 0 | 0 | 0 |
| Increase > 30 to ≤ 60 msec | 11 (9.7) | 15 (12.5) | 10 (8.3) |
| Increase > 60 msec | 0 | 0 | 0 |

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[a]Analyses using LOCF; [b]Estimates derived from ANCOVA. ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; msec = milliseconds; QTcF = QT interval corrected using Fridericia's formula; SD = standard deviation; SE = standard error.

# RADIANT Phase 2: Key Conclusions

## Primary endpoint not met

Efficacy signal observed with 60 mg on SAPS-H+D, with a −2.2-point difference vs placebo (p=0.0603)

## Consistent efficacy across psychosis scales supports advancement to Phase 3

60 mg showed an effect on other endpoints at Week 6 (nominal p-values):

- CGI-S-ADP: p=0.0077
- CGI-I-ADP: p=0.0208
- NPI/NPI-NH Psychosis: p=0.0385

Trend for increasing effect size with increase in baseline psychosis severity

Dose response observed, with minimal efficacy at 30 mg

## Safety was favorable and consistent with expectations

TEAE rates similar to placebo

No evidence of motor dysfunction, cognitive impairment, or QTc prolongation versus placebo

**Study results support continued evaluation of remlifanserin 60 mg in ongoing Phase 3**

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CGI-I-ADP = Clinical Global Impression–Improvement in Alzheimer's disease psychosis; CGI-S-ADP = Clinical Global Impression–Severity in Alzheimer's disease psychosis; NPI = Neuropsychiatric Inventory; NPI-NH = Neuropsychiatric Inventory–Nursing Home version; SAPS-H+D = Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions; TEAE = treatment-emergent adverse events.