INVEGA HAFYERA®
(paliperidone palmitate 6-month)

Clinical Overview

Disclaimers

- The information in this slide deck is presented in response to your specific request for this information and is based on published literature/data on this topic.
- The information provided is not intended to advocate the use of our product in any manner other than as described in the full Prescribing Information.
- Please note that the doses for paliperidone palmitate products have been presented according to the dosage strengths available in the US commercial market.
- See the full Prescribing Information accompanying this slide deck.

INVEGA SUSTENNA®, INVEGA TRINZA®, INVEGA HAFYERA® (paliperidone palmitate) Indication and Important Safety Information

INDICATION

INVEGA HAFYERA®, an every-six-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in adults after they have been adequately treated with:

- A once-a-month paliperidone palmitate extended release injectable suspension (e.g., INVEGA SUSTENNA®) for at least four months or
- An every-three-month paliperidone palmitate extended release injectable suspension (e.g., INVEGA TRINZA®) for at least one three-month cycle.

INVEGA TRINZA® is an atypical antipsychotic indicated for the treatment of schizophrenia in patients after they have been adequately treated with INVEGA SUSTENNA® for at least four months.

INVEGA SUSTENNA® is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.

IMPORTANT SAFETY INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.

See full prescribing information for complete Boxed Warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA HAFYERA®, INVEGA TRINZA® and INVEGA SUSTENNA® are not approved for use in patients with dementia-related psychosis.

Contraindications: INVEGA HAFYERA®, INVEGA TRINZA®, and INVEGA SUSTENNA®, are contraindicated in patients with a known hypersensitivity to either paliperidone, risperidone, or to any excipients of their formulation.

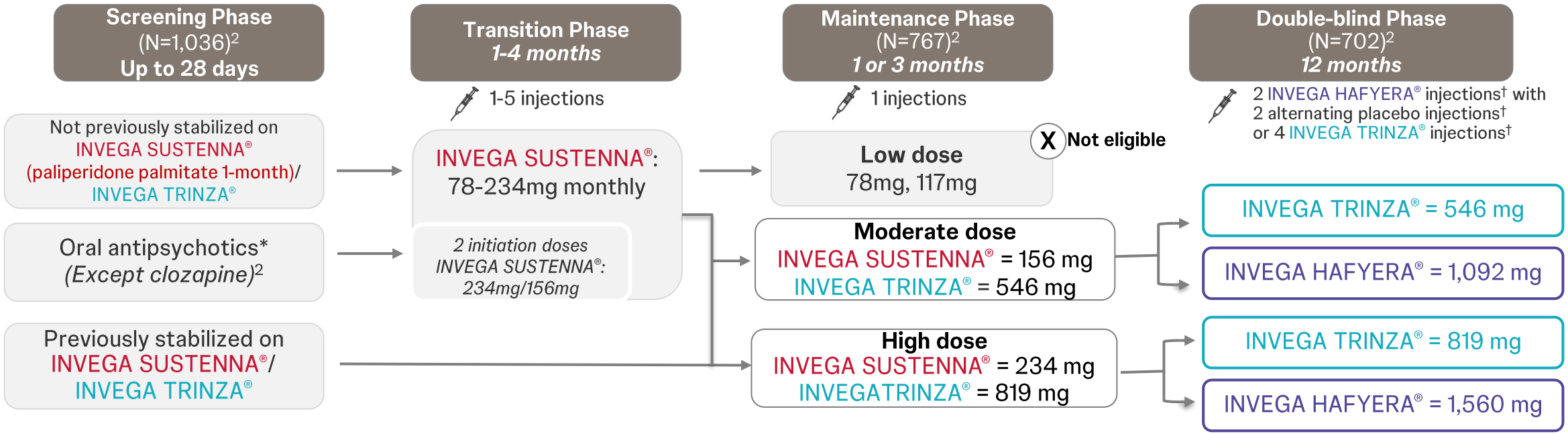
J&J **1.** INVEGA SUSTENNA® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** INVEGA TRINZA® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **3.** INVEGA HAFYERA® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.

Pivotal Noninferiority Trial

Najarian D, et al. *Int J Neuropsychopharmacol.* 2022;25(3):238-251

Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing INVEGA HAFYERA® (paliperidone palmitate 6-month) vs INVEGA TRINZA® (paliperidone palmitate 3-month) in Patients with Schizophrenia

Of the 1036 Patients Who Entered the Initial Screening Phase, 702 Continued on to the 12-month, Randomized, Double-blind Phase of the Noninferiority Trial[1,2]



A total of 702 stabilized patients were randomized in a 2:1 ratio to receive INVEGA HAFYERA® (n=478) or INVEGA TRINZA® (n=224) over the 12-month, double-blind phase.[1]

*Patients without documented tolerability to any oral or injectable risperidone or paliperidone formulations received paliperidone extended-release/prolonged-release 6-mg tablets or risperidone 3 mg/d for 4–6 consecutive days during screening.
†Administered by gluteal injection only.

J&J 1. INVEGA HAFYERA® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2. Najarian D, et al. *Int J Neuropsychopharmacol.* 2022;25(3):238-251.

Key Study Criteria

Key Inclusion Criteria[1]

- Age: 18 to 70 years
- Diagnosed with schizophrenia (per DSM-5) for at least 6 months before screening
- Receiving treatment with INVEGA SUSTENNA® (paliperidone palmitate 1-month), INVEGA HAFYERA® (paliperidone palmitate 6-month), injectable risperidone, or any oral antipsychotic (except clozapine)
- Total PANSS score of <70 points at screening and at randomization

Key Exclusion Criteria[1]

- Receiving any form of involuntary treatment
- Suicide attempt within 12 months before screening or imminent risk of suicide or violent behavior
- DSM-5 diagnosis of moderate or severe substance use disorder (except for nicotine and caffeine) within 6 months of screening
- History of NMS or TD
- Unstable medical conditions
- History of unresponsiveness or intolerance to paliperidone/risperidone

Relapse Criteria[1,2]

- Relapse was defined as any of the following:
  - Psychiatric hospitalization
  - Increase of ≥25% in total PANSS score from randomization for 2 consecutive assessments (if baseline score was >40)
  - 10-point increase in total PANSS score for 2 consecutive assessments (if baseline score was ≤40)
  - Deliberate self-injury, violent behavior, suicidal/homicidal ideation
  - Score of ≥5 (if the maximum baseline score was ≤3) or ≥6 (if the maximum baseline score was 4) on 2 consecutive assessments of the specific PANSS items

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; **NMS**, neuroleptic malignant syndrome; **PANSS**, Positive and Negative Syndrome Scale;; **TD**, tardive dyskinesia.

J&J **1.** Najarian D, et al. *Int J Neuropsychopharmacol.* 2022;25(3):238-251. **2.** INVEGA HAFYERA®[Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.

Patient Demographics and Baseline Characteristics*

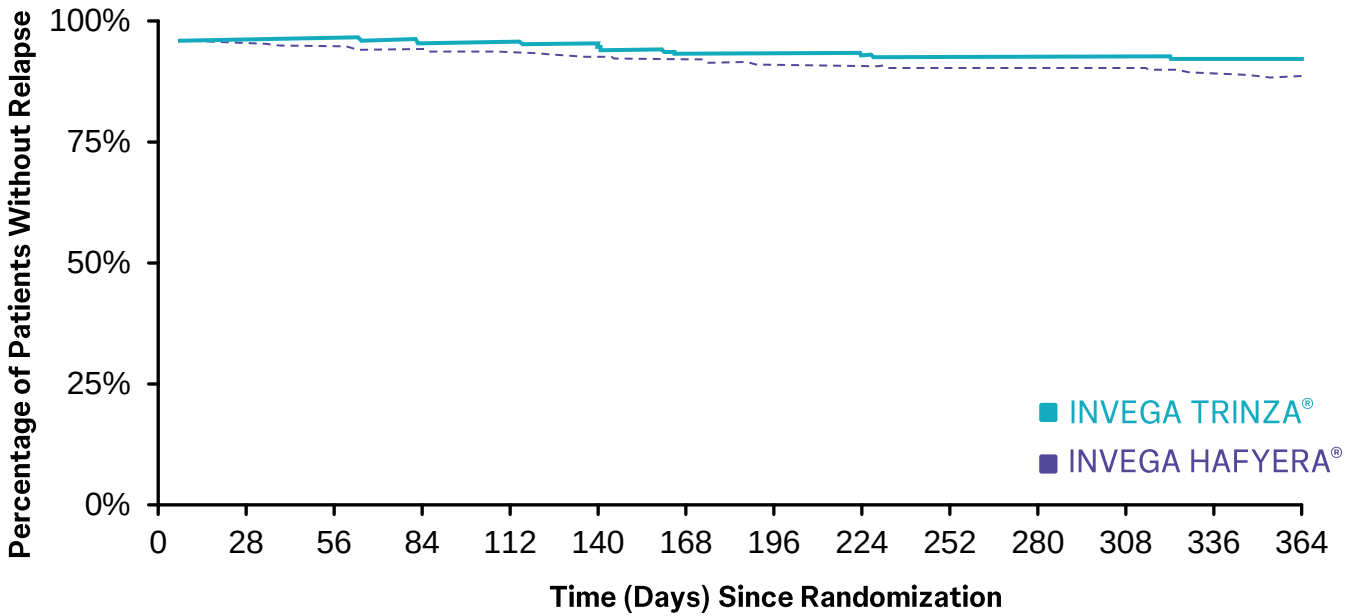
	INVEGA TRINZA® (paliperidone palmitate 3-month) (N=224)	INVEGA HAFYERA® (paliperidone palmitate 6-month) (N=478)
Mean age, years	40.0	41.2
Male, %	68.8	68.2
Race, %		
White	75.0	73.8
Asian	13.4	13.8
Black or African American	10.3	10.3
Other	1.3	1.4
Mean weight at OL baseline, kg	80.8	81.9
Mean BMI, kg/m^2	27.5	27.9
Mean age at schizophrenia diagnosis, years	27.5	27.7
Number of prior hospitalizations in the prior 24 months, n (%)		
N	168	356
None	98 (58.3)	205 (57.6)
Once	47 (28.0)	97 (27.2)
Twice or more	23 (13.7)	54 (15.2)
Mean PANSS score at DB baseline	51.4	51.9
Mean CGI-S at DB baseline	3.0	3.0
Mean PSP scale at DB baseline	66.5	66.3

*For DB ITT analysis

BMI, body mass index; **CGI-S**, Clinical Global Impressions Scale; **DB**, double-blind; **ITT**, intent to treat; **OL**, open-label; **PANSS**, Positive and Negative Syndrome Scale; **PSP**, Personal and Social Performance.

INVEGA HAFYERA® (paliperidone palmitate 6-month) Was Noninferior to INVEGA TRINZA® (paliperidone palmitate 3-month) After the 12-Month DB Phase[1,2]

After 12 Months, 92.5% of Patients Taking INVEGA HAFYERA® vs 95% of Patients Taking INVEGA TRINZA® Were Relapse-Free*



A total of 702 stabilized patients were randomized in a 2:1 ratio to receive INVEGA HAFYERA® (n=478) or INVEGA TRINZA® (n=224) over the 12-month, double-blind phase.[1]

92.5% of patients in the **INVEGA HAFYERA®** group

VS

95% of patients in the **INVEGA TRINZA®** group

were relapse-free at 12 months

Results of a 12-month, randomized, DB, noninferiority trial.

- **The primary efficacy variable was time to first relapse in the double-blind phase. The prespecified noninferiority margin was -10%.**
- **The study determined that the efficacy of INVEGA HAFYERA® was noninferior to the efficacy of INVEGA TRINZA® in adults with a DSM-5 diagnosis of schizophrenia.**

*Relapse was pre-defined as emergence of 1 or more of the following: psychiatric hospitalization, ≥25% increase (if the baseline score was >40) or a 10-point increase (if the baseline score was ≤40) in total PANSS score on 2 consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, a score of ≥5 (if the maximum baseline score was ≤3) or ≥6 (if the maximum baseline score was 4) on 2 consecutive assessments of the specific PANSS items.
DB, double-blind; **DSM-5**, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; **PANSS**, Positive and Negative Syndrome Scale.

1. INVEGA HAFYERA® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** Najarian D, et al. *Int J Neuropsychopharmacol.* 2022;25(3):238-251.

INVEGA TRINZA® (paliperidone palmitate 3-month) and INVEGA HAFYERA® (paliperidone palmitate 6-month) Demonstrated Similar Changes in PANSS total score, CGI-S, and PSP scores

Secondary Efficacy Measures

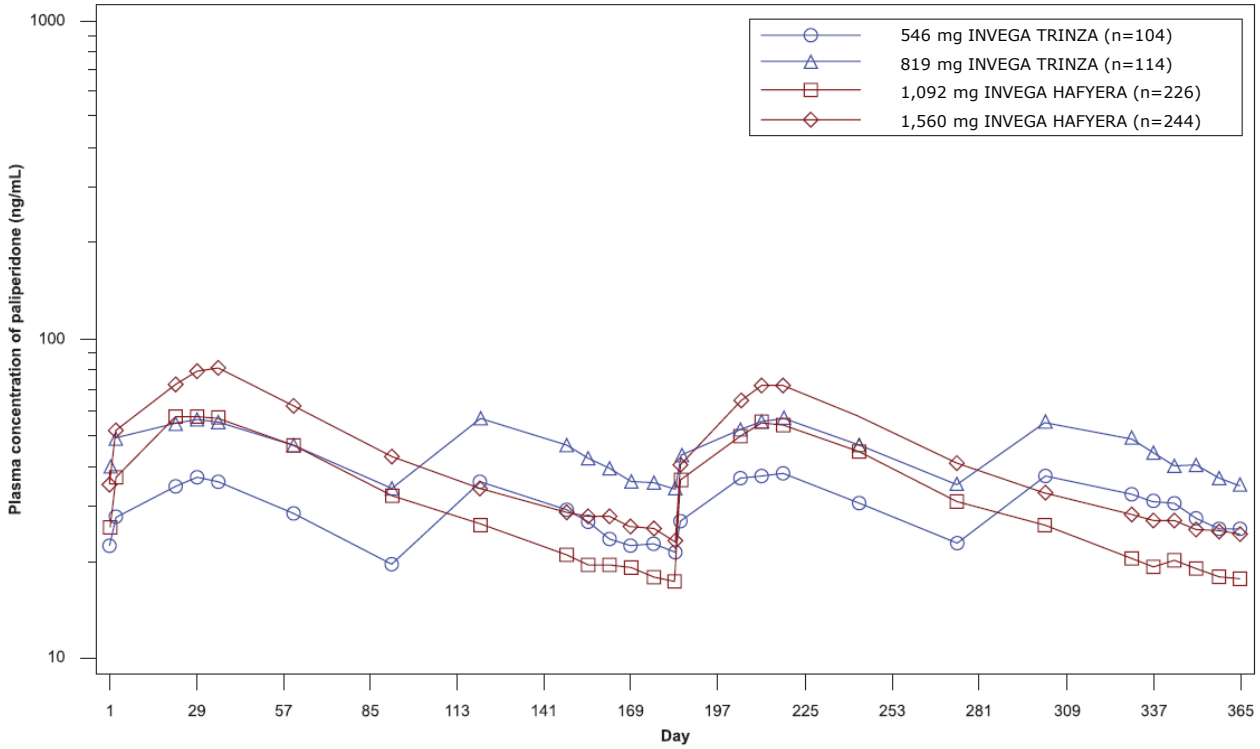
	INVEGA TRINZA® (n=224)	INVEGA HAFYERA® (n=478)	Between Group Difference-LS mean (SE) (95% CI)
PANSS total score Baseline, mean (SD) Change from baseline, mean (SD)	 51.4 (9.77) -1.6 (7.40)	 51.9 (9.60) -1.8 (8.92)	-0.1 (0.67) (-1.44 to 1.19)
CGI-S score[a], n Baseline, mean (SD) Change from baseline, mean (SD)	224 3.0 (0.77) 0.0 (0.63)	477 3.0 (0.78) 0.0 (0.70)	-0.0 (0.05) (-0.11 to 0.09)
PSP score[a], n Baseline, mean (SD) Change from baseline, mean (SD)	224 66.5 (11.82) 1.1 (8.11)	478 66.3 (12.50) 1.0 (7.12)	-0.2 (0.57) (-1.27 to 0.97)

	INVEGA TRINZA® (n=224)	INVEGA HAFYERA® (n=478)	Relative Risk (95% CI)[b]
Improvement in PANSS total score (≥20%), n (%)	70 (32.1)	183 (38.9)	1.12 (1.00 to 1.25)
DB 6-month remission status[c], n (%) Achieved remission	224 157 (70.1)	478 317 (66.3)	0.89 (0.71 to 1.13)

[a]Based on analysis of covariance (ANCOVA) model with treatment (INVEGA HAFYERA® vs INVEGA TRINZA®) and country as factors, and baseline value as a covariate. [b]Point estimate (95% CI) of relative risk is based on Cochran-Mantel-Haenszel test controlling for country. [c]Remission is defined as having a score of ≤3 on all of the following 8 PANSS items: P1, P2, P3, N1, N4, N6, G5, and G9 for the last 6 months of DB treatment, with 1 excursion allowed. [b]Point estimate 95% CI of relative risk is based on Cochran-Mantel-Haenszel test controlling for country. [c]Remission is defined as having a score of ≤3 on all of the following 8 PANSS items: P1, P2, P3, N1, N4, N6, G5, and G9 for the last 6 months of DB treatment, with 1 excursion allowed.

CGI-S, Clinical Global Impression-Severity; **CI**, confidence interval; **DB**, double-blind; **LS**, least squares; **PANSS**, Positive and Negative Syndrome Scale; **PSP**, Personal and Social Performance; **SE**, standard error

Pharmacokinetic Profile of INVEGA HAFYERA® (paliperidone palmitate 6-month) and INVEGA TRINZA® (paliperidone palmitate 3-month) in the DB Phase



Reproduced from *International Journal of Neuropsychopharmacology*, Najarian D, et al., A Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing Paliperidone Palmitate 6-Month Versus the 3-Month Long-Acting Injectable in Patients With Schizophrenia, page 1-14, 2021, with permission from copyright holder.

- Mean C_{max} was achieved around 1 month after each dose for all treatments and administered dosages.
- Compared with patients who received INVEGA TRINZA®, patients who received INVEGA HAFYERA® had approximately 20%–25% lower trough concentrations (dose normalized C_{trough}).
- Mean peak paliperidone concentrations (dose normalized C_{max}) after INVEGA HAFYERA® dosing compared to after INVEGA TRINZA® dosing was slightly higher (1.4- to 1.5-fold) and mean total paliperidone exposure (dose normalized AUC_{6month}) after INVEGA TRINZA® and INVEGA HAFYERA® dosing was comparable.
- Relapses did not appear to be clustered near the end of dosing cycle and were observed throughout dosing cycle for both treatments, this could imply that the comparably lower INVEGA HAFYERA® C_{trough} is likely not the key determinant of relapse.

AUC, area under the curve; **DB**, double-blind.

The Safety Profile of INVEGA HAFYERA® (paliperidone palmitate 6-month) Was Similar to That Seen With INVEGA TRINZA® (paliperidone palmitate 3-month) in the Double-blind Phase of the Study[1]

Treatment-emergent Adverse Events (≥2%) During the Noninferiority Study*

	INVEGA TRINZA® (n=224)	INVEGA HAFYERA® (n=478)
Upper respiratory tract infection	13%	12%
Injection site reaction	5%	11%
Weight increased	8%	9%
Extrapyramidal symptoms†	5%	7%
Headache	5%	7%
Akathisia	4%	4%
Psychosis	3%	3%
Insomnia	2%	3%
Back pain	1%	3%
Musculoskeletal pain	1%	3%
Urinary tract infection	1%	3%
Anxiety	0%	3%
Diarrhea	1%	2%

- The mean duration of exposure was 329.8 ± 86.97 days in the INVEGA HAFYERA® group and 336.4 ± 80.89 days in the INVEGA TRINZA® group during the double-blind phase
- The most common treatment-emergent adverse reactions (incidence at least 5% in the double-blind phase) of the INVEGA HAFYERA® clinical trial were upper respiratory tract infection, injection site reaction, weight increased, headache and parkinsonism
- In the double-blind phase of the INVEGA HAFYERA® clinical trial, 1.3% of patients in the INVEGA HAFYERA® group and 0.4% of patients in the INVEGA TRINZA® group discontinued due to adverse reactions
- An examination of population subgroups in the INVEGA HAFYERA® trial did not reveal any evidence of differences in safety on the basis of age, gender, or race alone
- In the double-blind study, investigators were blinded to prolactin laboratory results to prevent the risk of unblinding study treatment.[2]

*At least 2% in the double-blind INVEGA HAFYERA® treatment group.
†Extrapyramidal symptoms includes: blepharospasms, bradykinesia, drooling, dyskinesia, dystonia, hypokinesia, musculoskeletal stiffness, muscle rigidity, muscle spasms, oculogyric crisis, Parkinsonism, Parkinsonism rest tremor, reduced facial expression, tardive dyskinesia

J&J 1. INVEGA HAFYERA® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2. Data on file. Janssen Pharmaceuticals, Inc. Titusville, NJ. 2021.

Treatment-emergent Adverse Events of Special Interest Were Similar in the Double-blind Phase[1]

Treatment-emergent Adverse Events of Special Interest*

	INVEGA TRINZA® (paliperidone palmitate 3-month) (n=224)	INVEGA HAFYERA® (paliperidone palmitate 6-month) (n=478)
EPS*	19 (8.5)	46 (9.6)
Suicidality	6 (2.7)	5 (1.0)
Agitation and aggression	0	3 (0.6)
Somnolence	3 (1.3)	9 (1.9)
Tachycardia	1 (0.4)	7 (1.5)
Orthostatic hypotension	2 (0.9)	2 (0.4)
QT Prolongation	2 (0.9)	2 (0.4)
Diabetes and hyperglycemia	6 (2.7)	15 (3.1)

- The occurrence of TEAEs of special interest were **generally similar** between INVEGA TRINZA® and INVEGA HAFYERA®
- There were **no reported TEAEs** for neuroleptic malignant syndrome (NMS) or post-injection delirium/sedation syndrome (PDSS) during the study

*Extrapyramidal symptoms includes: blepharospasms, bradykinesia, drooling, dyskinesia, dystonia, hypokinesia, musculoskeletal stiffness, muscle rigidity, muscle spasms, oculogyric crisis, Parkinsonism, Parkinsonism rest tremor, reduced facial expression, tardive dyskinesia.

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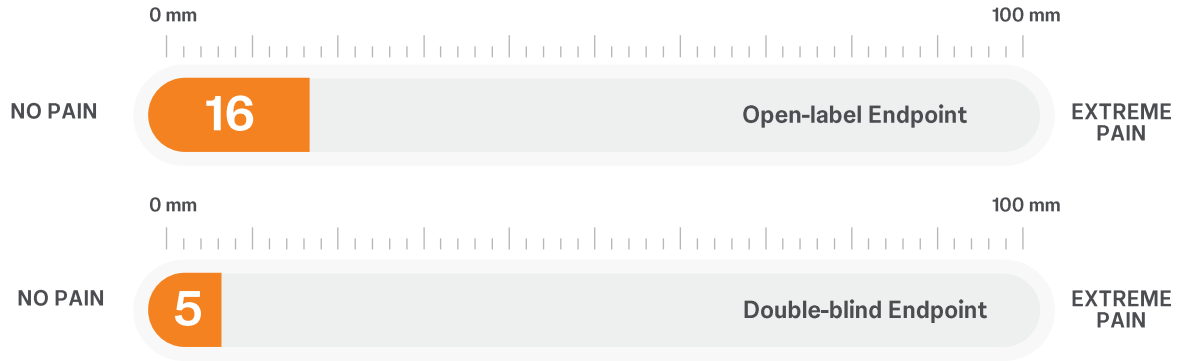
Patient Ratings of Injection-Site Pain

In the noninferiority trial comparing INVEGA HAFYERA® (paliperidone palmitate 6-month) to INVEGA TRINZA® (paliperidone palmitate 3-month)

No Patients Discontinued Treatment Because of Injection-site Pain[1]

Patient Ratings of Injection-site Pain Were Mild, According to Visual Analog Scale[2]

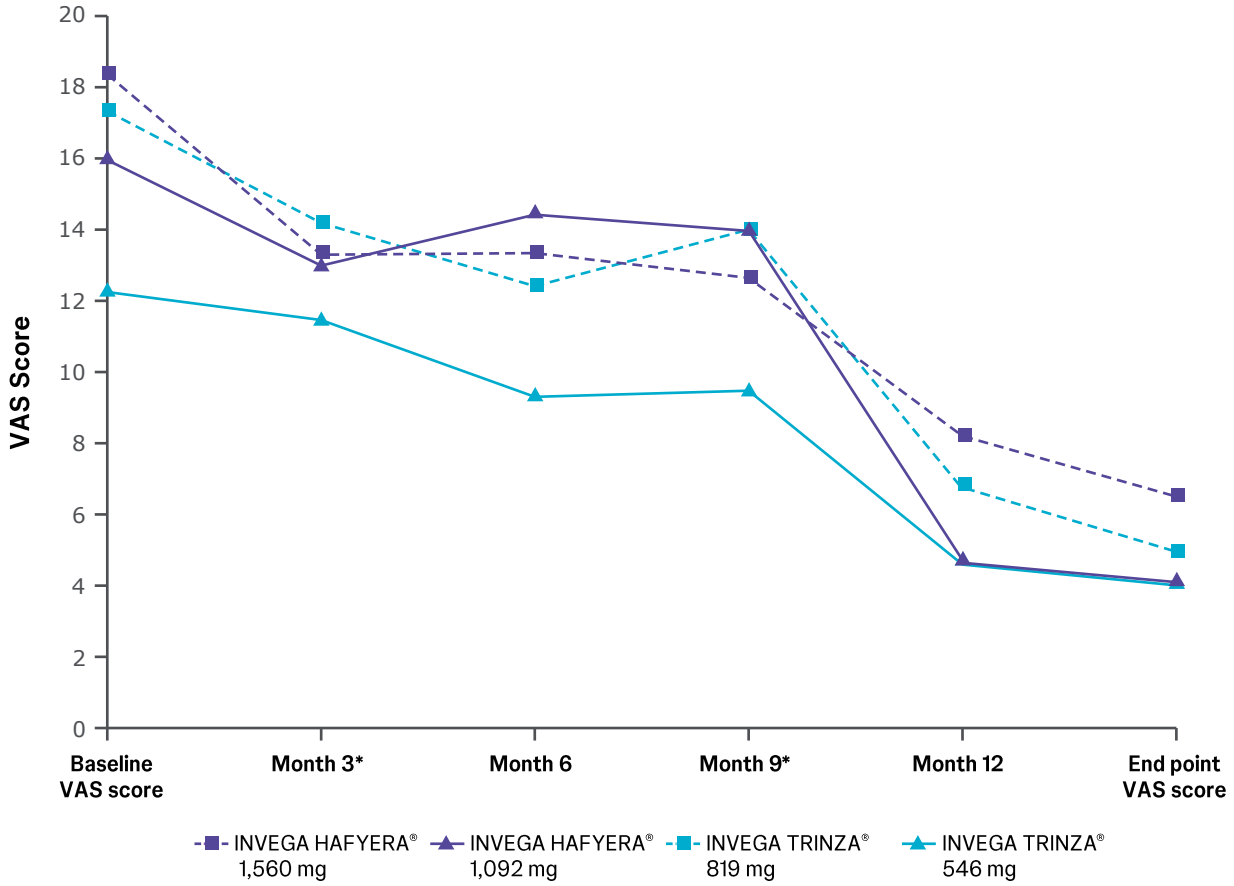


Open-label phase of the trial also included INVEGA SUSTENNA®
(paliperidone palmitate 1-month)

- 30 minutes after injection, patients marked a Visual Analog Scale 100 millimeters in length, with 0 mm indicating no pain and 100 mm indicating EXTREME pain. Investigators measured each mark's distance from 0 mm to quantify injection-site pain[1]
- The average score for the patient's evaluation of injection-site pain on a scale of 0 to 100 was approximately 16 at the open-label-phase endpoint and approximately 5 in both groups at the double-blind-phase endpoint[2]
- Investigators' assessments of injection sites: Induration, redness and swelling were observed in 13% of the INVEGA HAFYERA® group and in 9% of the INVEGA TRINZA® group during the double-blind phase[2]

1. Najarian D, et al. *Int J Neuropsychopharmacol.* 2022;25(3):238-251. **2.** INVEGA HAFYERA® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.

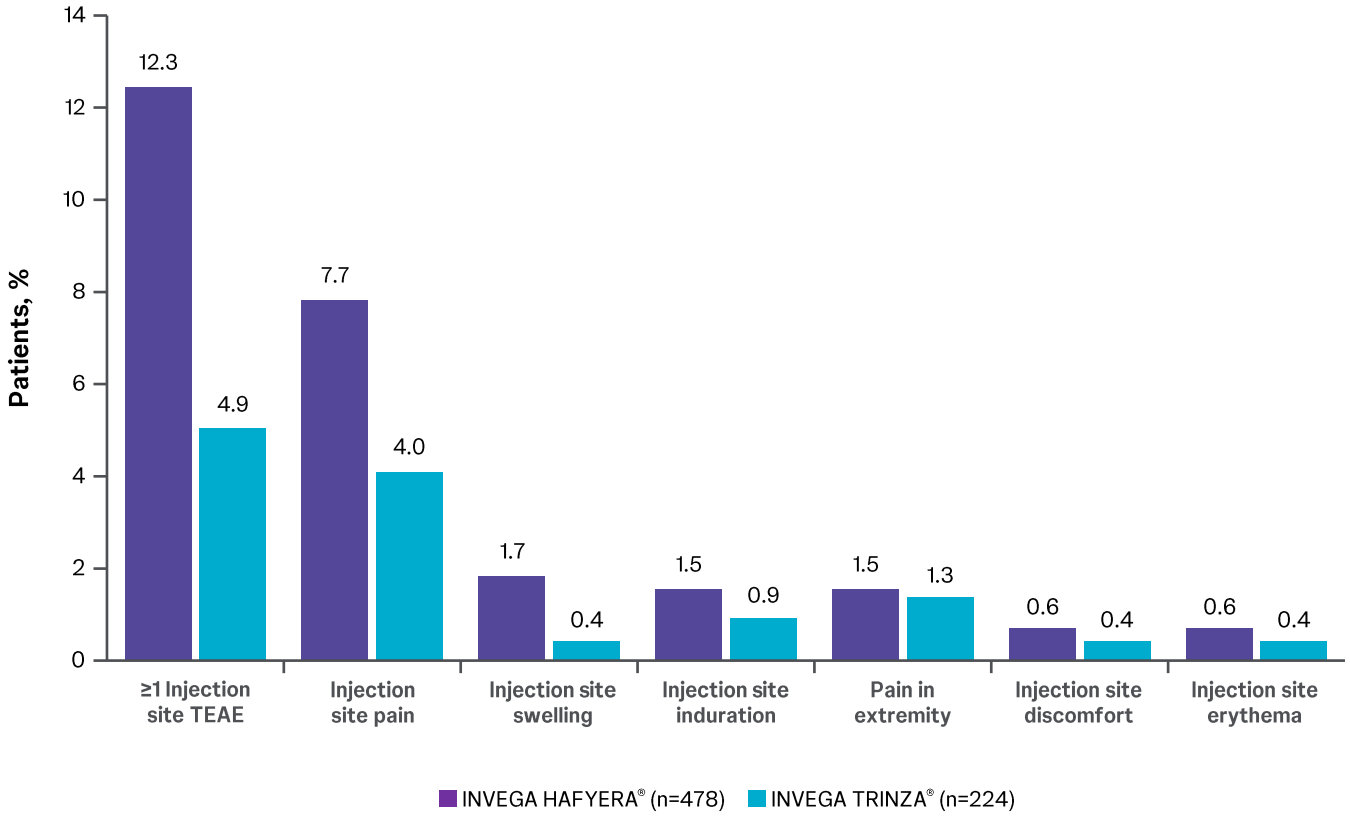
Visual Analog Scale Scores for Injection Site Pain



- The VAS scale ranged from 0 (no pain at all) to 100 (unbearably painful).
- Mean [SD] patient-rated VAS scores for injection site pain decreased from DB baseline to end point for patients in both groups (INVEGA HAFYERA® paliperidone palmitate 6-month): 17.22 [20.86] to 5.41 [10.76]; INVEGA TRINZA® (paliperidone palmitate 3-month): 14.98 [18.98] to 4.54 [8.93])
- Changes from baseline were generally consistent across treatment groups and moderate and high doses

*For INVEGA HAFYERA® doses, placebo injections were given at months 3 and 9 to maintain double-blinding.
VAS, visual analog scale.

Injection Site–related TEAEs



- In the DB phase, injection site–related TEAEs were reported in 59 of 478 patients (12.3%) in the INVEGA HAFYERA® (paliperidone palmitate 6-month) group and 11 of 224 patients (4.9%) in the INVEGA TRINZA® (paliperidone palmitate 3-month) group, with injection site pain being the most commonly reported (37 patients [7.7%] and 9 patients [4.0%], respectively)
- All other injection site–related TEAEs, including induration, redness, and swelling, occurred in <2% of patients in both treatment groups
- None of the injection site–related TEAEs were reported as serious, resulted in treatment discontinuation, or required dermatological consultation

Injection sites were evaluated by investigators for erythema/redness, induration/swelling, and tenderness. Symptoms were primarily absent in both treatment groups (88.9-99.8%) at DB baseline and endpoint; no patients had severe reactions

DB, double-blind; **TEAEs**, treatment-emergent adverse events.

Changes in Fasting Glucose Levels for INVEGA HAFYERA® (paliperidone palmitate 6-month) and INVEGA TRINZA® (paliperidone palmitate 3-month)

Change in Fasting Glucose From the Randomized, Double-blind Phase

	INVEGA TRINZA® (n=195)	INVEGA HAFYERA® (n=423)
Normal to High	3%	4%
Impaired glucose tolerance to high	4%	5%
Normal / impaired glucose tolerance to high	7%	9%
<126 mg/dL to ≥140 mg/dL	4%	5%
<126 mg/dL to ≥200 mg/dL	0%	1%
<126 mg/dL to ≥300 mg/dL	0%	<1%

Hyperglycemia and Diabetes Mellitus

- Monitor for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness
- Monitor glucose regularly in patients with diabetes or at risk for diabetes

Table reflects subjects with paired fasting data (baseline and any post-baseline assessment). Using the conversion factor (1 mg/dL=0.05551 mmol/L), the limits specified by the American Diabetes Association are as follows:
Normal: <100 mg/dL (<5.551 mmol/L)
Impaired: ≥100 mg/dL (≥5.551 mmol/L) to <126 mg/dL (<6.994 mmol/L)
High: ≥126 mg/dL (≥6.994 mmol/L)
126 mg/dL=6.994 mmol/L; 140 mg/dL=7.771 mmol/L; 200 mg/dL=11.102 mmol/L; 300 mg/dL=16.653 mmol/L.

Changes in Fasting Lipids for INVEGA HAFYERA® (paliperidone palmitate 6-month) and INVEGA TRINZA® (paliperidone palmitate 3-month)

Shifts in Fasting Lipids in the DB Phase From the Randomized, Active-controlled Study

	INVEGA TRINZA® (n=194)	INVEGA HAFYERA® (n=423)
Fasting Cholesterol (mg/dL): <200 mg/dL to ≥240 mg/dL	2 (1%)	3 (0.7%)
Fasting HDL Cholesterol (mg/dL): ≥40 mg/dL to <40 mg/dL	28 (14%)	55 (13%)
Fasting LDL Cholesterol (mg/dL): <100 mg/dL to ≥160 mg/dL	1 (0.5%)	2 (0.5%)
Fasting Triglycerides (mg/dL): <150 mg/dL to ≥200 mg/dL	22 (11%)	22 (5%)

For each fasting parameter, subjects with both baseline (DB) record and any post-baseline (DB) record during the DB phase are included in the denominator.

Dyslipidemia:

- Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

DB, double-blind.

Incidence of EPS for INVEGA HAFYERA® (paliperidone palmitate 6-month) and INVEGA TRINZA® (paliperidone palmitate 3-month)

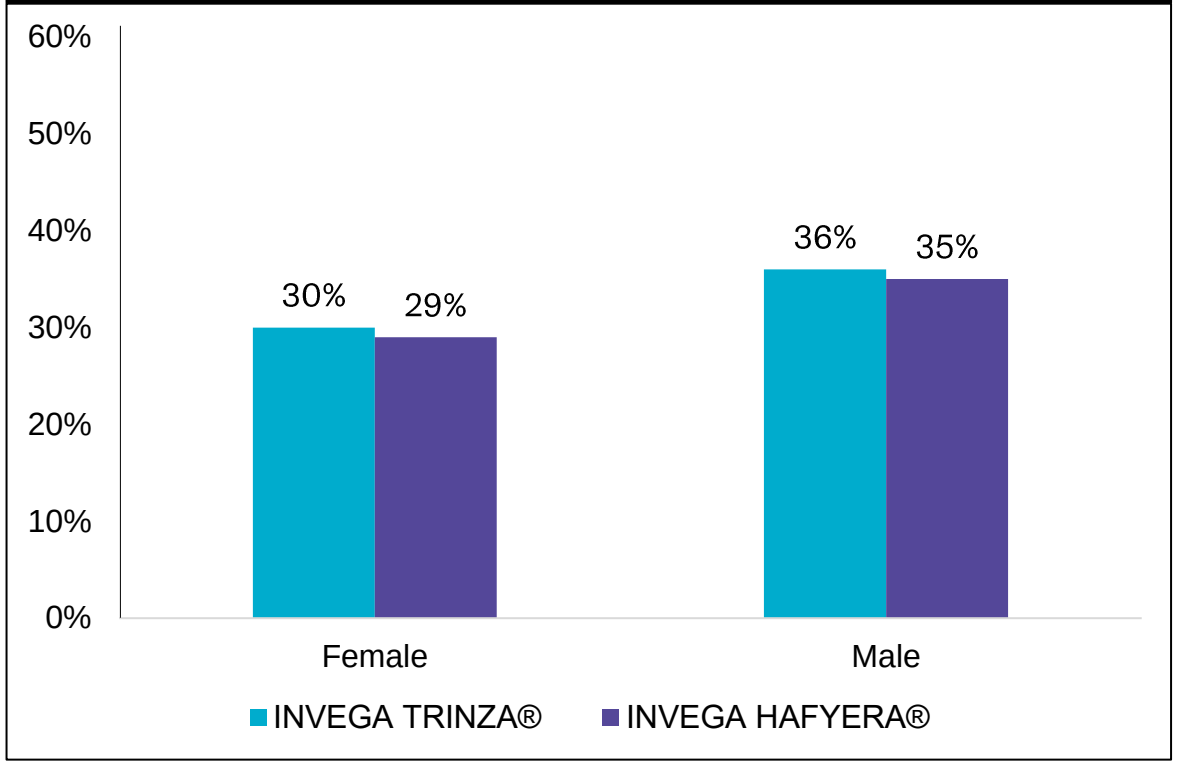
EPS Assessed by Rating Scales Incidence and Use of Anticholinergic Medication During the DB Phase

	INVEGA TRINZA® (n=224)	INVEGA HAFYERA® (n=478)
Use of Anticholinergic Medication*	13%	15%
Parkinsonism†	6%	7%
Akathisia‡	3%	3%
Dyskinesia§	1%	1%

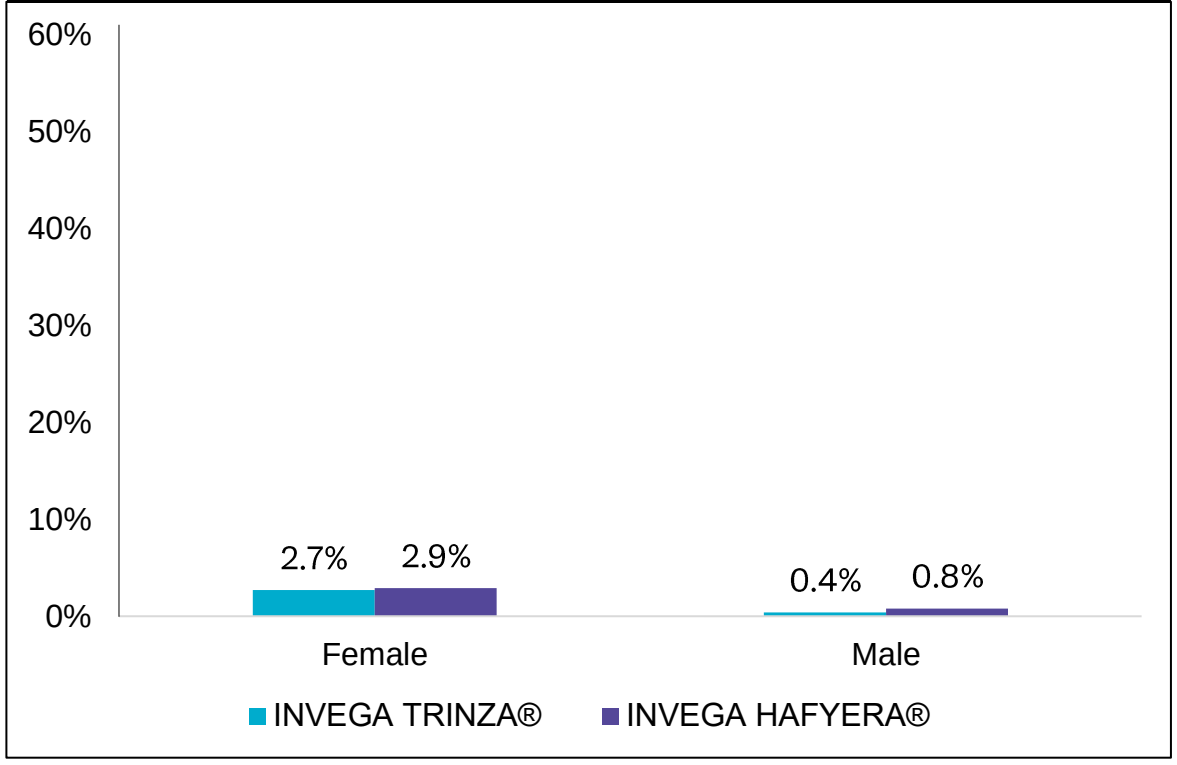
*Use of anti-EPS medication during the DB phase.
†Percent of subjects with Simpson-Angus Scale Global Score > 0.3 (Global Score defined as the total sum of items score divided by the number of items).
‡Percent of subjects with Barnes Akathisia Rating Scale Global Clinical Rating Score ≥2.
§Percent of subjects with a score ≥3 on any of the first 7 items or a score ≥2 on 2 or more of any of the first 7 items of the Abnormal Involuntary Movement Scale.
Note: Percentages are calculated based on the number of subjects in the DB safety analysis set per treatment group.
DB, double-blind; **EPS**, extrapyramidal symptoms.

Elevated Prolactin Levels and Potentially Prolactin-related Adverse Events Observed for INVEGA HAFYERA® (paliperidone palmitate 6-month) and INVEGA TRINZA® (paliperidone palmitate 3-month)

Percentage of Patients With Increased Prolactin Levels Relative to Maintenance Baseline



Percentage of Patients With Potentially Prolactin-related Adverse Events



Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels, and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Limitations

- Patients met the criteria of clinical stability prior to entry in the DB phase and therefore, the results may not reflect true efficacy for prevention of relapses in the overall population
- The absence of a placebo group limits the interpretation of the results; therefore, it is unknown how INVEGA HAFYERA® (paliperidone palmitate 6-month) may compare with oral antipsychotics
- The fixed doses evaluated during the DB phase may not reflect responses to change in dose of INVEGA HAFYERA® that may occur during long-term treatment in clinical practice
- Patients in the INVEGA HAFYERA® group received injections every 3 months which may impact results related to the difference in dosing intervals between INVEGA HAFYERA® and INVEGA TRINZA® (paliperidone palmitate 3-month) including injection site ratings, patient preference, and caregiver burden
- Placebo injections may also introduce a potential placebo effect in the INVEGA HAFYERA® group, which is an inherent limitation of most randomized controlled trials

DB, double blind.

Pivotal Noninferiority Trial Summary

- After 12-months, 92.5% of patients taking INVEGA HAFYERA® (paliperidone palmitate 6-month) vs 95% of patients taking INVEGA TRINZA® (paliperidone palmitate 3-month) were relapse-free
- Patients who received INVEGA HAFYERA® experienced similar changes in PANSS, CGI-S, and PSP to those who received INVEGA TRINZA®
- The most common treatment-emergent adverse reactions (incidence at least 5% in the DB phase) of the INVEGA HAFYERA® clinical trial were upper respiratory tract infection, injection site reaction, weight increased, headache and parkinsonism
  - TEAEs were reported in comparable percentages of patients in the INVEGA HAFYERA® (297/478 [62.1%]) and INVEGA TRINZA® (131/224 [58.5%]) groups, most TEAEs were mild or moderate in severity
  - In the DB phase, 1.3% of patients in the INVEGA HAFYERA® group and 0.4% of patients in the INVEGA TRINZA® group discontinued due to adverse reactions
    - No patients discontinued treatment because of injection-site pain

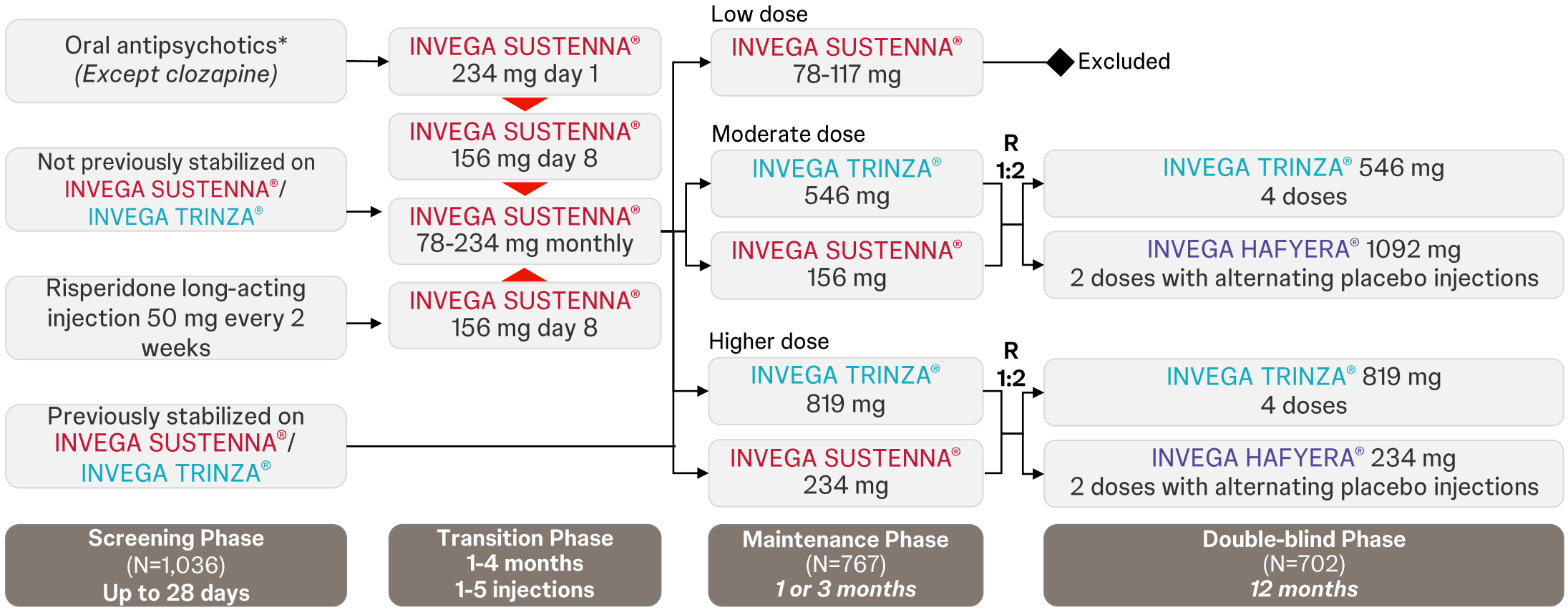
CGI-S, Clinical Global Impression-Severity; **DB**, double blind; **PANSS**, Positive and Negative Symptom Scale; **PSP**, Personal and Social Performance; **TEAEs**, treatment-emergent adverse events.

Post-hoc Analysis of Transitions From INVEGA SUSTENNA® (paliperidone palmitate 1-month) or INVEGA TRINZA® (paliperidone palmitate 3-month) to INVEGA HAFYERA® (paliperidone palmitate 6-month)

Correll CU, et al. *CNS Spectr*. 2024:1-7.

Study Design

Post hoc analyses of DB, randomized, active-controlled, non-inferiority trial to assess efficacy and safety of transition to INVEGA HAFYERA® (paliperidone palmitate 6-month) from INVEGA SUSTENNA® (paliperidone palmitate 1-month) versus INVEGA TRINZA® (paliperidone palmitate 3-month) in clinically stable patients with schizophrenia



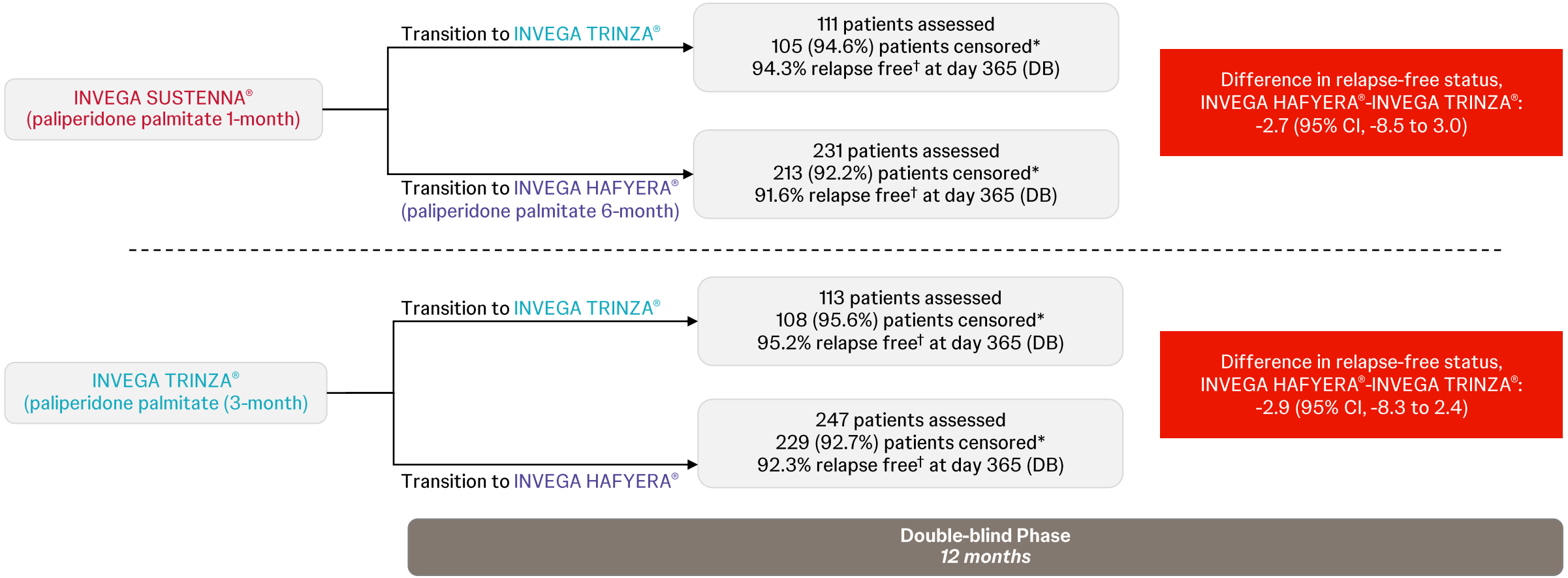
INVEGA TRINZA® and INVEGA HAFYERA® were administered dorsogluteally because of the larger volume of INVEGA HAFYERA®.
*Patients without documented tolerability to any oral or injectable risperidone or paliperidone formulations received paliperidone extended-release/prolonged-release 6-mg tablets or risperidone 3 mg/d for 4–6 consecutive days during screening.
DB, double-blind; **OAP**, oral antipsychotic; **R**, randomization.

Baseline Demographics and Disease Characteristics

	INVEGA SUSTENNA® (paliperidone palmitate 1-month) / INVEGA HAFYERA® (paliperidone palmitate 6-month) n=231	INVEGA TRINZA® (paliperidone palmitate 3-month)/ INVEGA HAFYERA® n=247	INVEGA TRINZA® n=224	Total N=702
Mean age (SD), years*	39.4 (11.91)	42.8 (11.42)	40.0 (10.98)	40.8 (11.53)
Male, n (%)	148 (64.1)	178 (72.1)	154 (68.8)	480 (68.4)
Race, n (%) White Asian† Black and/or African American	 174 (75.3) 43 (18.6) 13 (5.6)	 179 (72.5) 23 (9.3) 36 (14.6)	 168 (75.0) 30 (13.4) 23 (10.3)	 521 (74.2) 96 (13.7) 72 (10.3)
Ethnicity, n (%) Hispanic or Latino	 38 (16.5)	 37 (15.0)	 25 (11.2)	 100 (14.2)
Mean BMI (SD), kg/m^2	26.9 (4.79)	28.8 (4.96)	27.5 (4.96)	27.7 (4.96)
Mean age at first SCZ diagnosis (SD), years	28.0 (9.11)	27.4 (8.93)	27.5 (9.05)	27.6 (9.02)
Mean duration of illness (SD), years	11.4 (9.89)	15.5 (10.71)	12.5 (9.84)	13.2 (10.30)
Mean duration PH prior to study (SD), days‡	63.3 (72.13)	62.8 (67.76)	44.6 (53.09)	57.2 (65.75)

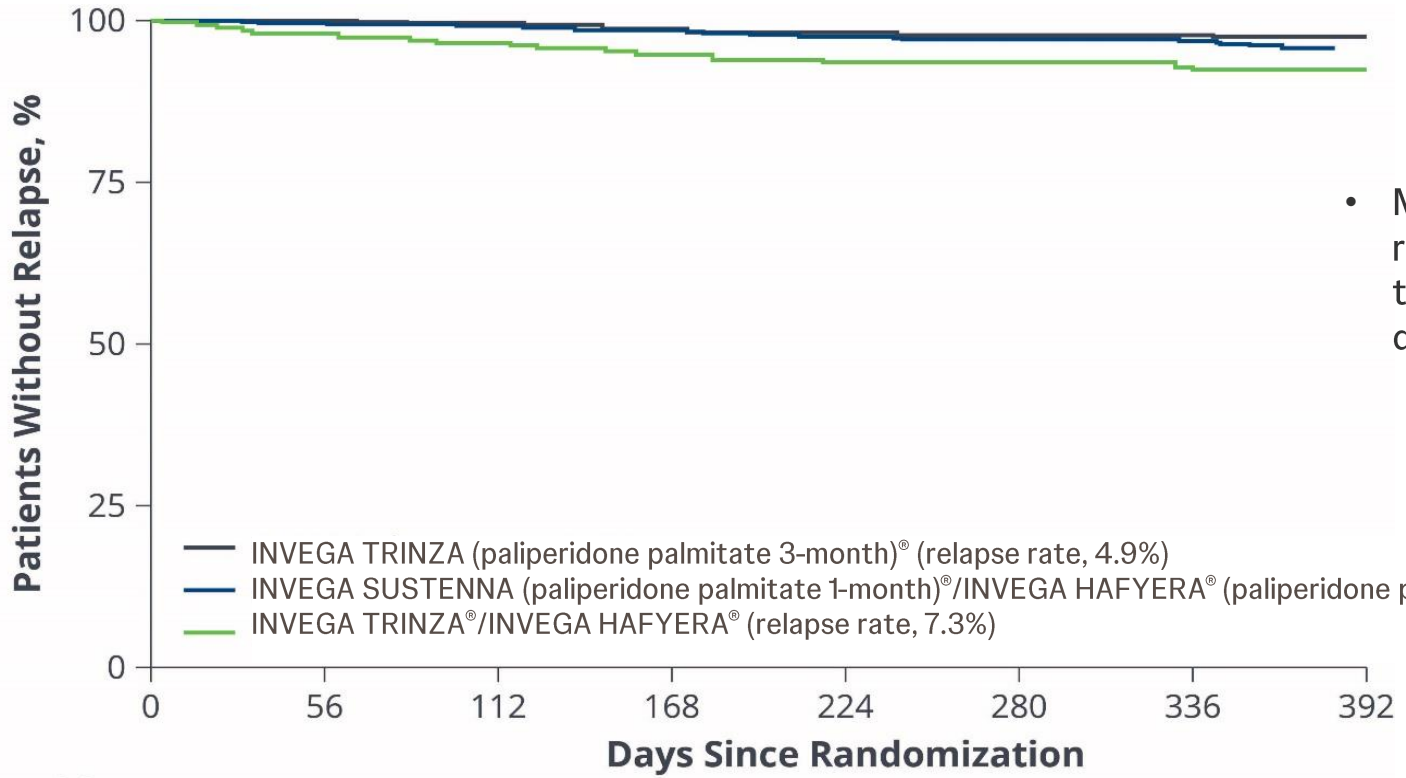
*Age at screening visit.
†Asian race subcategories include Chinese, Korean, Japanese, Filipino, Asian Indian, Thai, Malaysian, and other Asian races.
‡Duration of the most recent hospitalization for psychosis any time prior to study start (not restricted to 24 months prior to study start).
BMI, body mass index; **PH**, psychiatric hospitalization; **SCZ**, schizophrenia.

Kaplan-Meier Estimate of Transition Group Differences at Month 12



*Censored data included patients who completed the DB phase without relapses and patients who withdrew early during the DB phase.
†Based on Kaplan-Meier product limit estimates.
CI, confidence intervals; **DB**, double-blind.

Kaplan-Meier Plot of Patients Without Relapse During the DB Phase



- Median time to relapse was not reached for any group due to the low number of relapses during the DB phase

Patients at risk

INVEGA TRINZA®	224	223	221	219	215	211	205	200	196	193	193	193	193	160	1
INVEGA SUSTENNA®/INVEGA HAFYERA®	231	231	228	224	221	217	216	208	203	201	201	200	199	165	0
INVEGA TRINZA®/INVEGA HAFYERA®	247	240	237	233	226	223	220	209	205	203	202	199	194	163	1

DB, double blind.

Summary of Change From Baseline in PANSS, CGI-S, and PSP During the DB Phase

	INVEGA SUSTENNA® (paliperidone palmitate 1-month)/ INVEGA HAFYERA® (paliperidone palmitate 6-month) n=231	INVEGA TRINZA® (paliperidone palmitate 3-month)/ INVEGA HAFYERA® n=247	INVEGA TRINZA® n=224
PANSS total score			
Mean at DB baseline (SD)	53.3 (9.52)	50.6 (9.51)	51.4 (9.77)
Mean change from baseline (SD)	−1.8 (9.74)	−1.8 (8.11)	−1.6 (7.40)
Mean PANSS subscale scores (SD)			
Positive subscale			
Baseline (DB)	11.3 (3.36)	10.7 (3.05)	10.8 (2.98)
Change from baseline	−0.1 (3.54)	−0.2 (3.06)	−0.1 (2.82)
Negative subscale			
Baseline (DB)	16.3 (4.06)	15.8 (4.32)	15.9 (4.18)
Change from baseline	−0.8 (2.85)	−0.6 (2.54)	−0.6 (2.61)
CGI-S score*			
Mean at DB baseline (SD)	3.0 (0.76)	3.0 (0.80)	3.0 (0.77)
Mean change from baseline (SD)	0.0 (0.77)	0.0 (0.63)	0.0 (0.63)
PSP score†			
Mean at DB baseline (SD)	66.5 (11.15)	66.2 (13.67)	66.5 (11.82)
Mean change from baseline (SD)	1.1 (7.31)	0.9 (6.94)	1.1 (8.11)

*INVEGA SUSTENNA®/INVEGA HAFYERA®, n = 228; INVEGA TRINZA®/INVEGA HAFYERA®, n = 245; INVEGA TRINZA®, n = 220.
†INVEGA SUSTENNA®/INVEGA HAFYERA®, n = 229; INVEGA TRINZA®/INVEGA HAFYERA®, n = 246; INVEGA TRINZA®, n = 221.
CGI-S, Clinical Global Impression-Severity scale; **DB**, double-blind; **PANSS**, Positive and Negative Syndrome Scale; **PSP**, Personal and Social Performance scale.

Overall Safety Summary (DB phase)

Most common TEAEs (occurring in ≥5% of patients): weight increased, injection site pain, headache, nasopharyngitis and upper respiratory infection

	INVEGA SUSTENNA® (paliperidone palmitate 1-month)/ INVEGA HAFYERA® (paliperidone palmitate 6-month) n=231	INVEGA TRINZA® (paliperidone palmitate 3-month)/ INVEGA HAFYERA® n=247	INVEGA TRINZA® n=224	Total N=702
≥1 TEAE	141 (61.0)	156 (63.2)	131 (58.5)	428 (61.0)
≥1 possibly related TEAE	70 (30.3)	78 (31.6)	61 (27.2)	209 (29.8)
≥1 serious TEAEs	12 (5.2)	12 (4.9)	15 (6.7)	39 (5.6)
TEAEs leading to drug withdrawn	6 (2.6)	10 (4.0)	6 (2.7)	22 (3.1)
TEAEs leading to death	1 (0.4)	0 (0)	2 (0.9)	3 (0.4)
Most common (≥5%) TEAEs				
Weight increased	17 (7.4)	23 (9.3)	17 (7.6)	57 (8.1)
Injection site pain	11 (4.8)	26 (10.5)	9 (4.0)	46 (6.6)
Headache	19 (8.2)	13 (5.3)	12 (5.4)	44 (6.3)
Nasopharyngitis	10 (4.3)	12 (4.9)	13 (5.8)	35 (5.0)
Upper respiratory infection	7 (3.0)	17 (6.9)	9 (4.0)	33 (4.7)
Most common (≥1%) serious TEAEs				
Psychiatric disorders	8 (3.5)	6 (2.4)	7 (3.1)	21 (3.0)
Schizophrenia	4 (1.7)	4 (1.6)	1 (0.4)	9 (1.3)
Treatment-emergent abnormal plasma prolactin results by gender				
Female, n	83	68	69	220
High, n (%)*	11 (13.3)	13 (19.1)	14 (20.3)	38 (17.3)
Male, n	148	178	152	478
High, n (%)*	17 (11.5)	35 (19.7)	16 (10.5)	68 (14.2)

*High = baseline value ≤ normal range upper limit and postbaseline > normal range upper limit. For males, the reference range is 2.64-13.13 µg/L and for females the reference range is 2.74–26.72 µg/L.
DB, double-blind; **TEAE**, treatment-emergent adverse event.

Post-hoc Analysis Summary

- Adult patients with schizophrenia who transitioned to INVEGA HAFYERA® (paliperidone palmitate 6-month) from either INVEGA SUSTENNA® (paliperidone palmitate 1-month) or INVEGA TRINZA® (paliperidone palmitate 3-month) experienced similarly low relapse rates
- Assessments of schizophrenia symptoms, patient functioning, disease severity and safety were similar between transition groups
- Results support the generalizability of the noninferority findings whether patients transitioned from INVEGA SUSTENNA® to INVEGA HAFYERA® or INVEGA TRINZA® to INVEGA HAFYERA®

Limitations: This was a post hoc analysis of a double-blind, non-inferiority trial (NCT03345342) and initial INVEGA SUSTENNA® or INVEGA TRINZA® treatment prior to baseline of the DB phase was not randomized

DB, double blind.

Open-Label Extension

Najarian D, et al. *Int J Neuropsychopharmacol*. 2023;26(8):537-544.

Long-term Safety, Efficacy, and Tolerability

INVEGA HAFYERA® (paliperidone palmitate 6-month) demonstrated noninferiority to INVEGA TRINZA® (paliperidone palmitate 3-month) in adult patients with schizophrenia in a global, phase 3, DB, randomized study

- Eligible patients from 6 countries* who completed the DB noninferiority study on INVEGA TRINZA® or INVEGA HAFYERA® without relapse, and wished to continue treatment with INVEGA HAFYERA®, enrolled in the 2-year, open-label extension trial. A total of 178 patients opted into the trial.

- **Efficacy Endpoints:** Relapse rate†, PANSS total, PSP, and CGI-S scale change scores from baseline to endpoint

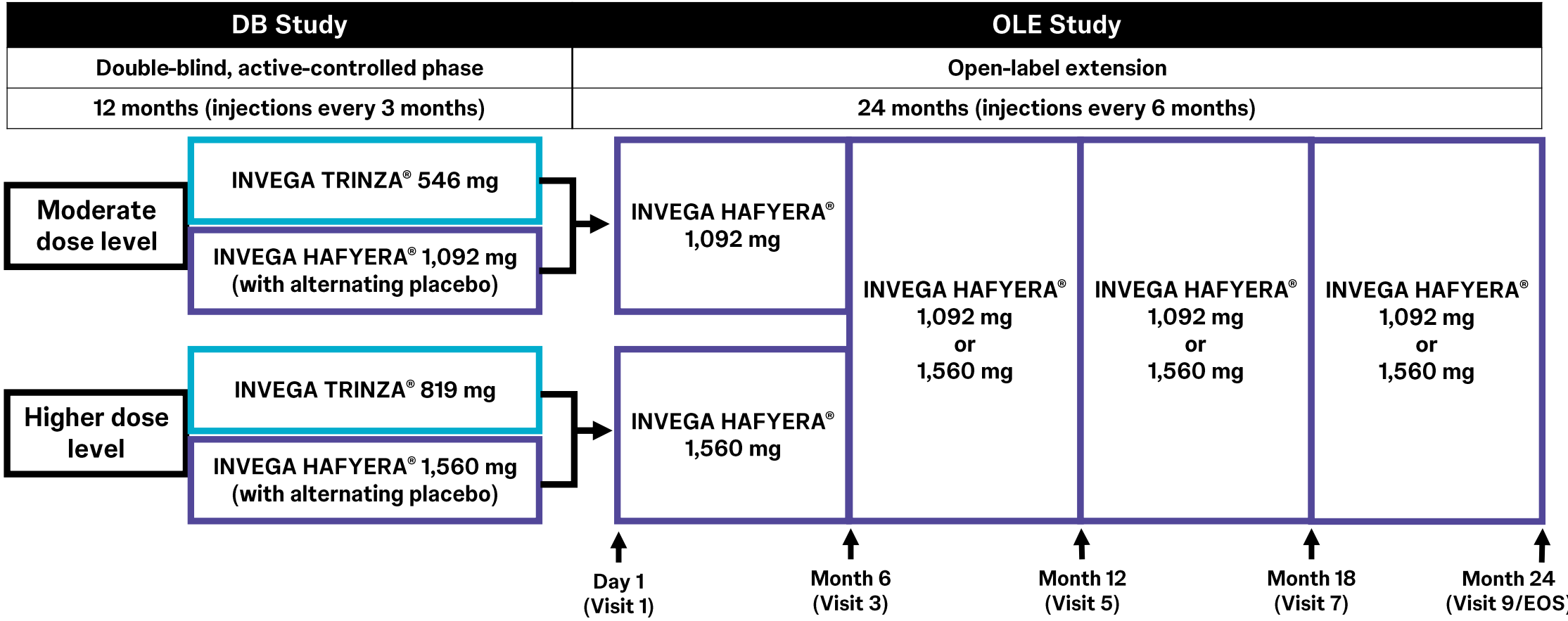
- **Safety Endpoints:** TEAEs, physical examinations, and laboratory tests

*Argentina, Hong Kong, Italy, Poland, Russian Federation, and Ukraine
†A relapse was defined as presence of one or more episodes of psychiatric hospitalization, emergency department treatment due to schizophrenia symptoms, participant behavior resulting in harm (self-injury, suicide, harm to another person, or property damage), or suicidal or homicidal ideation
CGI-S, Clinical Global Impression-Severity; **DB**, double-blind; **PANSS**, Positive and Negative Syndrome Scale; **PSP**, Personal and Social Performance; **TEAE**, treatment-emergent adverse event.

Study Objective & Design

Objective: To describe longer-term efficacy and safety of INVEGA HAFYERA® (paliperidone palmitate 6-month) in adults with schizophrenia

178 patients who were relapse-free on INVEGA HAFYERA® (n=121) or INVEGA TRINZA® (paliperidone palmitate 3-month) (n=57) in the DB phase chose to continue treatment with INVEGA HAFYERA in the OLE



DB, double blind; **EOS**, end of study; **OLE**, open label extension.

Long-term Efficacy

Efficacy (ITT Analysis*)

96.1%

of patients who entered the study remained relapse-free on INVEGA HAFYERA® (paliperidone palmitate 6-month)

- Overall, 7/178 (3.9%) participants relapsed during the study between days 20 and 703 of study enrollment.
- Mean (SD) change from open-label baseline to endpoint: PANSS total score, 0.7 (8.22); CGI-S, 0.0 (0.51); PSP Scale, 0.5 (7.47).

Disposition*

86.5%

of patients completed the study

- Of the 178 participants enrolled, 154 (86.5%) completed the study
- The mean (SD) duration of exposure was 682.1 (150.18) days
- Mean dose (SD)=1366 (218.63) mg

*ITT population=178
ITT, intent-to-treat; **PANSS**, Positive and Negative Syndrome Scale.

Long-term Safety

Treatment-emergent Adverse Events in ≥5% of Participants in any Group in the OLE (Intent-to-Treat)

n (%)	INVEGA TRINZA® (paliperidone palmitate 3-month)/ INVEGA HAFYERA® (paliperidone palmitate 6-month) n=57	INVEGA HAFYERA®/ INVEGA HAFYERA® n=121	Total (N=178)
≥ 1 TEAEs	35 (61.4)	76 (62.8)	111 (62.4)
Headache	8 (14.0)	16 (13.2)	24 (13.5)
Blood prolactin increased*	5 (8.8)	14 (11.6)	19 (10.7)
Hyperprolactinemia*	4 (7.0)	9 (7.4)	13 (7.3)
Diarrhea	4 (7.0)	7 (5.8)	11 (6.2)
Weight increased	4 (7.0)	5 (4.1)	9 (5.1)
Nasopharyngitis	2 (3.5)	7 (5.8)	9 (5.1)
Blood creatinine phosphokinase increased	3 (5.3)	2 (1.7)	5 (2.8)
Insomnia	3 (5.3)	2 (1.7)	5 (2.8)

Overall, 111/178 patients (62.4%) reported ≥1 TEAE

- The most common (≥5%) treatment-emergent adverse reactions were headache (13.5%), blood prolactin increased (10.7%), hyperprolactinemia (7.3%), diarrhea (6.2%), weight increased (5.1%), and nasopharyngitis (5.1%)
- A total of 6/178 (3.4%) patients withdrew due to TEAEs, and 8/178 (4.5%) patients experienced serious TEAEs
- No deaths were reported

*Note: In the OLE design, investigators were not blinded to laboratory results. Comparisons between double-blind and OLE studies should not be made. Both 'blood prolactin increased' and 'hyperprolactinemia' are MedDRA terms, hence listed separately.
OLE, open label extension.

Open-Label Extension Study Summary

- Eligible patients who completed the DB noninferiority study on INVEGA TRINZA® (paliperidone palmitate 3-month) or INVEGA HAFYERA® (paliperidone palmitate 6-month) without relapse, and wished to continue treatment with INVEGA HAFYERA®, enrolled in the 2-year, open-label extension trial
- 96.1% of patients who entered the study remained relapse-free on INVEGA HAFYERA®
- The most common (≥5%) treatment-emergent adverse reactions were headache (13.5%), blood prolactin increased (10.7%), hyperprolactinemia (7.3%), diarrhea (6.2%), weight increased (5.1%), and nasopharyngitis (5.1%)

DB, double blind.

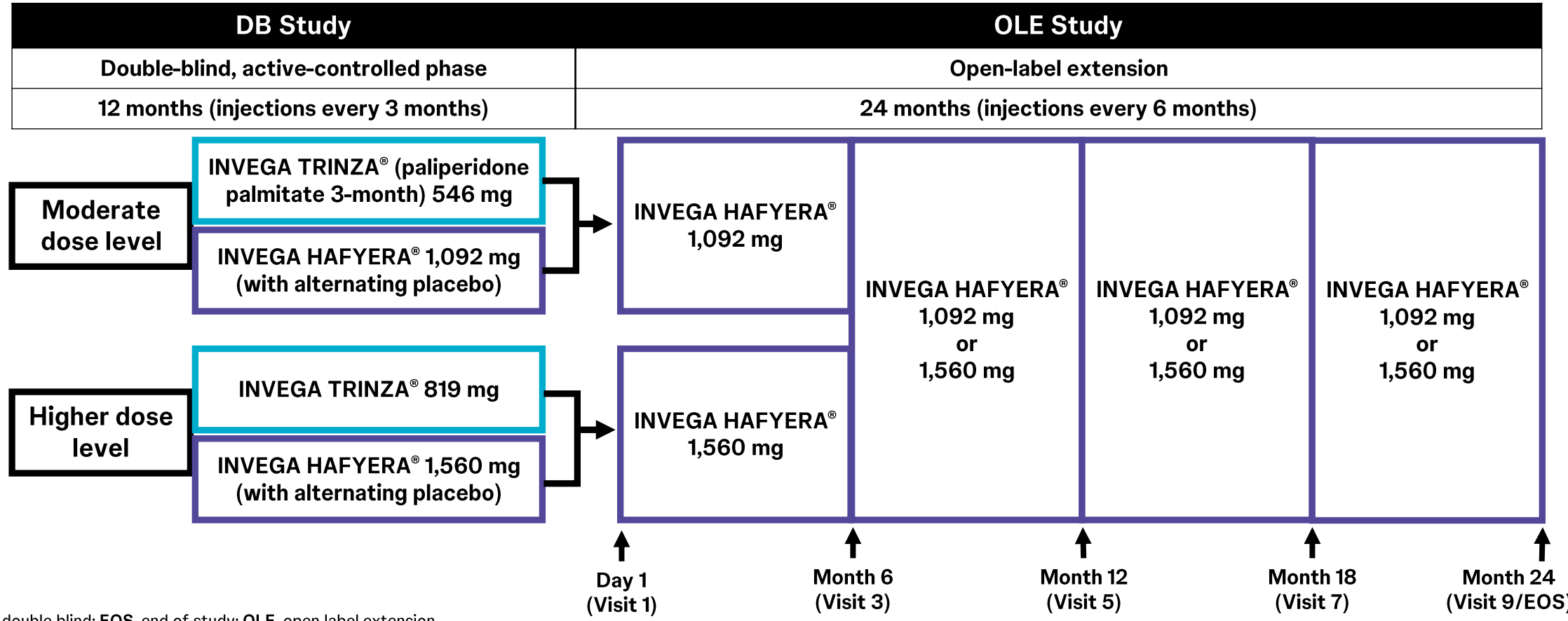
Post-hoc 3-Year Analysis

Correll CU, et al. *JAMA Netw Open*. 2024;7(7):e2421495.

Study Objective & Design

Objective: To describe longer-term efficacy and safety of INVEGA HAFYERA® (paliperidone palmitate 6-month) in adults with schizophrenia

121 patients who were relapse-free on INVEGA HAFYERA® in the double-blind phase chose to continue treatment in the OLE[1,2]



DB, double blind; **EOS**, end of study; **OLE**, open label extension.

J&J 1. Najarian D, et al. *Int J Neuropsychopharmacol.* 2023;26(8):537-544. 2. Correll CU, et al. *JAMA Netw Open.* 2024;7(7):e2421495.

Demographics and Disease Characteristics

Double-blind Baseline Characteristics	INVEGA HAFYERA® (paliperidone palmitate 6-month) n=121
Mean age* (SD), years	38.6 (11.24)
Male, n (%)	83 (68.6)
Mean baseline BMI (SD), kg/m^2	27.9 (4.84)
Mean duration of illness (SD), years	11.0 (9.45)
Mean PANSS baseline score (SD)†	53.4 (9.72)
Mean PSP baseline score (SD)‡	68.7 (12.10)
Mean CGI-S baseline score (SD)§	3.0 (0.77)

*Age at screening visit.
†Score range, 30 to 210, with higher scores indicating greater symptom severity.
‡Score range, 1 to 100, with higher scores indicating better personal and social functioning.
§Score range, 1 to 7 and baseline range 1 to 5, with higher scores indicating more severe illness.
BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); **CGI-S**, Clinical Global Impression–Severity scale; **PANSS**, Positive and Negative Syndrome Scale; **PSP**, Personal and Social Performance scale.

Efficacy

Relapse rate was 4.1% (5 of 121 patients)

- Reasons for relapse were:
  - Psychiatric hospitalization (n=2)
  - Suicidal or homicidal ideation (n=2)
  - Deliberate self-injury (n=1)

Relapse was defined as ≥1 of the following:

- Psychiatric hospitalization
- Emergency visit due to schizophrenia symptoms
- Participant behavior resulting in harm (self-injury, suicide, harm to another person or property damage)
- Suicidal or homicidal ideation and aggressive behavior

Patients treated with INVEGA HAFYERA® (paliperidone palmitate 6-month) were clinically stable and well maintained, as evidenced by stable scores on the PANSS, CGI-S, and PSP scales over the 3-year period

- Mean change (SD) from DB baseline to OLE endpoint:
  - PANSS total score: −2.6 (9.96)
  - CGI-S total score: −0.2 (0.57)
  - PSP total score: 3.1 (9.14)

CGI-S, Clinical Global Impression-Severity Scale; **DB**, double-blind; **OLE**, open-label extension; **PANSS**, Positive and Negative Syndrome Scale; **PSP**, Personal and Social Performance Scale; **SD**, standard deviation.

TEAEs Occurring in ≥5% of Patients

- Overall, 97 of 121 patients (80.2%) reported ≥1 TEAE

n (%)	INVEGA HAFYERA® (paliperidone palmitate 6-month)/ INVEGA HAFYERA® (n=121)
≥1 TEAEs	97 (80.2)
Headache	22 (18.2)
Weight increased	15 (12.4)
Blood prolactin increased*	14 (11.6)
Nasopharyngitis	13 (10.7)
Injection site pain	13 (10.7)
Diarrhea	10 (8.3)
Hyperprolactinemia*	9 (7.4)
Back pain	6 (5.0)
Blood thyroid stimulating hormone increased	6 (5.0)

- Most common TEAEs (occurring in ≥ 10% of patients) were headache, weight increased, blood prolactin increased/hyperprolactinemia, nasopharyngitis and injection site pain

*Blood prolactin increased and hyperprolactinemia represent the same condition; the distinction was based on the investigator selection of MedDRA term
TEAE, treatment-emergent adverse event.

Post-hoc 3-Year Analysis Summary

Findings:

- Results supported the long-term efficacy and safety of INVEGA HAFYERA® (paliperidone palmitate 6-month) up to 3 years in adults with schizophrenia
- Based on a 3-year intent-to-treat analysis of 121 patients on INVEGA HAFYERA® who completed the 1-year DB phase without relapse and continued into the 2-year OLE phase, **95.9%** remained relapse-free
- Patients on INVEGA HAFYERA® were clinically stable and well-maintained, as evidenced by stable scores on PANSS, CGI and PSP scales over the 3-year period
- No new safety signals were identified, and no deaths were reported in this cohort. Three-year safety data of INVEGA HAFYERA® was consistent with the known profile of paliperidone palmitate

Limitations:

- No comparator group was included in this subgroup analysis
- Patients who started INVEGA HAFYERA® and relapsed or discontinued during DB phase (year 1) or opted out of the OLE study (years 2-3) were excluded from the analysis
- OLE study was limited to 6 participating countries and data may have been affected by confounding demographic factors

Countries where study was conducted: Argentina, Hong Kong, Italy, Poland, Russian Federation, Ukraine

CGI-S, Clinical Global Impression-Severity Scale; **DB**, double-blind; **OLE**, open-label extension; **PANSS**, Positive and Negative Syndrome Scale; **PSP**, Personal and Social Performance Scale.