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Supplementary Material

Article Title: Population Pharmacokinetics and Dosing Simulations for Paliperidone Palmitate 351 mg as Alternative Maintenance Doses in Patients With Schizophrenia or Schizoaffective Disorders

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1. Pharmacokinetic sampling schedule in Study LY03010/CT-USA-102 and Study LY03010/CT-USA-103.

Study LY03010/CT-USA-102	Pharmacokinetic sampling time points for LY03010 and INVEGA SUSUTENNA Day 1 pre-dose and 8 hours after the dose, Days 2 and 4 (i.e., 24 and 72 hours after the dose); Days 6, 8, 10, 12, 15, 17, 19, 22, 29, 36, 43, 50 and 57 at the same time of day as the dose; and Days 64, 78, 92, 106 and 120.
Study LY03010/CT-USA-103	Pharmacokinetic sampling time points for LY03010 and INVEGA SUSTENNA LY03010 cohort: ***1st dose (Day 1):*** Pre-dose on Day 1; Day 2 ,4, 8 ,11, 15, 18 and 22 (1, 3, 7,10, 14 and 21 days after the 1st dose). ***2nd dose (Day 29):*** Pre-dose on Day 29, Days 32 and 36. ***3rd dose (Day 57):*** Pre-dose on Day 57. ***4th dose (Day 85):*** Pre-dose on Day 85. ***5th dose (Day 113):*** Pre-dose on Day 113. ***6th dose (Day 141):*** Pre-dose and 8 hours after the dose on Day 141; Days 142, 143, 144, 146, 148, 151, 154, 157, 161, 165, and 169 (1, 2, 3, 5, 7, 10, 13, 16, 20, 24 and 28 days after the 6th dose). INVEGA SUSTENNA cohort: ***1st dose (Day 1):*** Pre-dose on Day 1; Day 2 and 4 (1 and 3 days after the 1st dose). ***2nd dose (Day 8):*** Pre-dose on Day 8; Day 9, 11, 15, 18, 22, 25, 29, and 32 (1, 3, 7,10, 14 17, 21 and 24 days after the 2nd dose). ***3rd dose (Day 36):*** Pre-dose on Day 36. ***4th dose (Day 64):*** Pre-dose on Day 64. ***5th dose (Day 92):*** Pre-dose on Day 92. ***6th dose (Day 120):*** Pre-dose on Day 120. ***7th dose (Day 148):*** Pre-dose and 8 hours after the dose on Day 148; Days 149, 150, 151, 153, 155, 158, 161, 164, 168, 172, and 176 (1, 2, 3, 5, 7, 10, 13, 16, 20, 24 and 28 days after the 7th dose).

Supplementary Table 2. Pharmacokinetic parameters in the final population PK model

LY03010 + SUSTENNA Fit Simultaneously	**102+103 data** **Typical Value (%RSE, 95% CI)**
Summary of Data Used in Model Fitting	5731 concentrations in 276 patients
Objective Function Value	29606.214
Condition Number	399
CL/F (L/hr, for both LY03010 and SUSTENNA)	6.70 (2.45%; 6.37, 7.02)
CL/F~ CrCL Power (for both LY03010 and USTENNA)	0.325 (25.6%; 0.141, 0.491)
V/F （L, for both LY03010 and SUSTENNA）	2840 (7.82%; 2310, 3370)
Ka (1/hr) x 10^{-3} (for both LY03010 and SUSTENNA)	1.65 (7.65%; 1.40, 1.96)
F2 （Gluteal, LY03010）	0.179 (14.4%; 0.134, 0.234)
FINJS （Deltoid vs. Gluteal, LY03010）	1.47 (15.2%; 1.09, 1.95)
D2 (hr, LY03010）	97.8 (5.59%; 85.0, 111)
R_F2 (Gluteal, SUSTENNA vs. LY03010)	0.684 (20.6%; 0.442, 1.03)
R_FINJS (Deltoid vs. Gluteal, SUSTENNA vs. LY03010)	2.07 (20.7%; 1.42, 3.19)
R_D2 (SUSTENNA vs. LY03010)	1.05 (8.00%; 0.880, 1.27)
IIV （CL/F, LY03010)	33.4% (7.83%; 28.0%, 38.5%) *
IIV （V/F, LY03010)	50.6% (6.95%; 43.6%, 57.9%) *
IIV （Ka, LY03010)	63.0% (9.56%; 51.2%, 76.2%) *
IIV （CL/F, SUSTENNA)	38.7% (6.69%; 33.8%, 43.8%) *
IIV （V/F, SUSTENNA)	52.8% (6.63%; 45.9%, 60.0%) *
IIV （Ka, SUSTENNA)	85.9% (9.16%; 68.0%, 104%) *
Proportional Error	24.1% (3.13%; 22.8%, 25.6%)

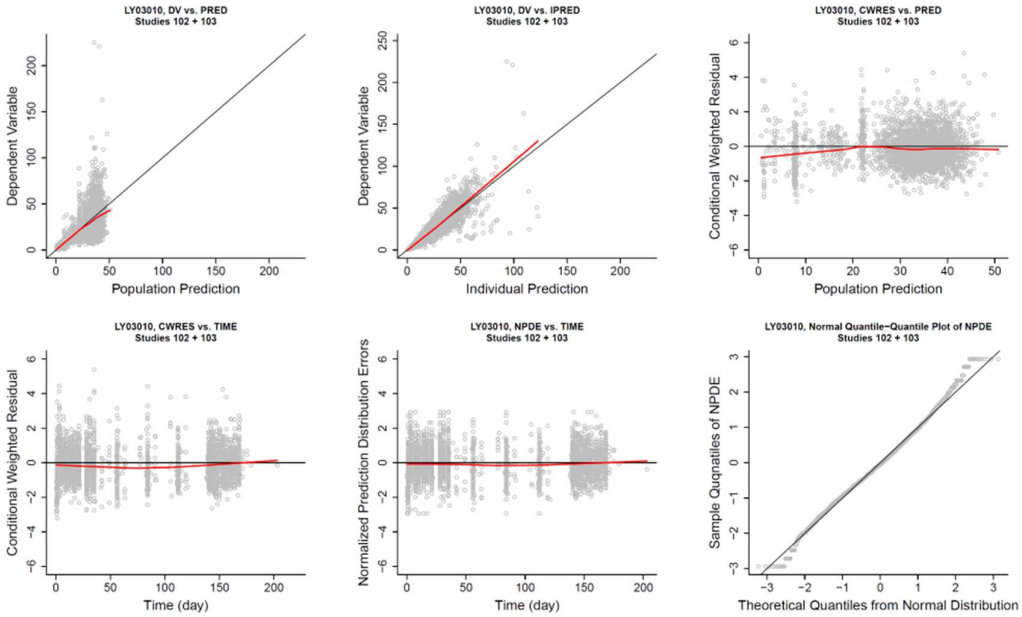
Abbreviations: CI = confidence interval; CL/F = apparent clearance; CrCL = creatinine clearance; D2 = duration of zero-order absorption or lag time for first-order absorption; F2 = fraction of the dose entering the systemic circulation via a zero-order process; FINJS = F2 ~ injection site relationship for LY03010; IIV= inter-individual variability; Ka = first-order absorption rate; R_D2 = ratio for D2 between SUSTENNA against LY03010; R_FINJS = ratio for F2 ~ injection site relationship between SUSTENNA against LY03010; %RSE = relative standard error of estimation; V/F = apparent volume of distribution.

*: Reported as %CV;

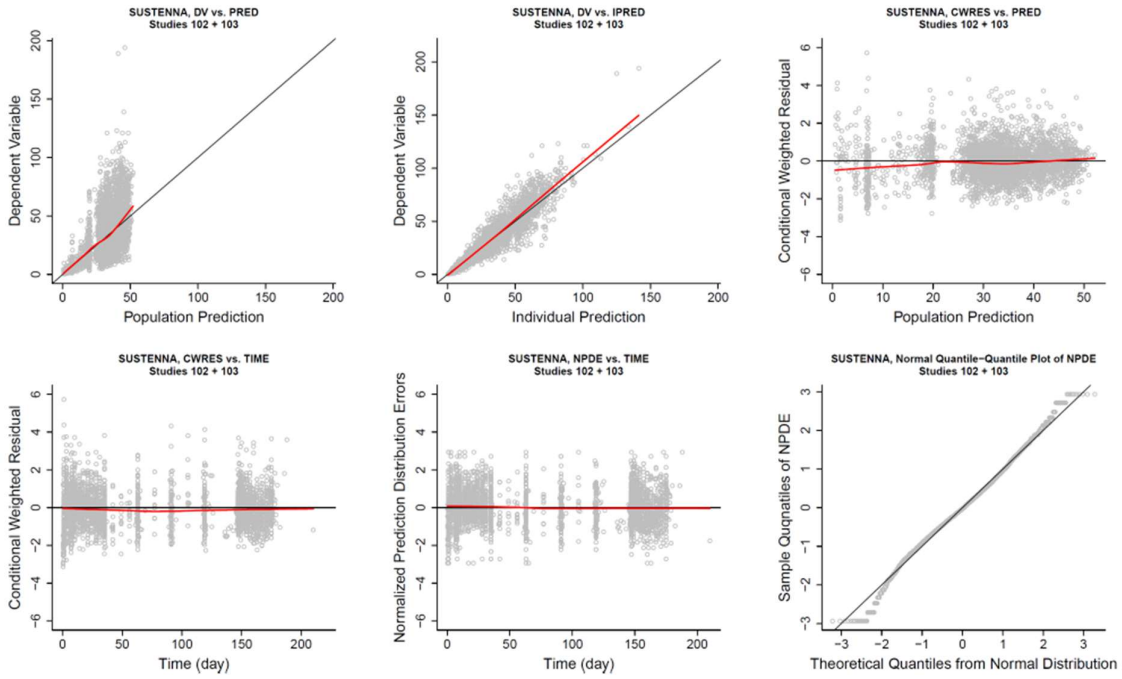
95% CI: obtained by bootstrap analysis (1500 bootstrap runs, of which 1272 successfully converged).

Supplementary Figure 1. Goodness-of-fit plots for the final population pharmacokinetic model.

A.



B.

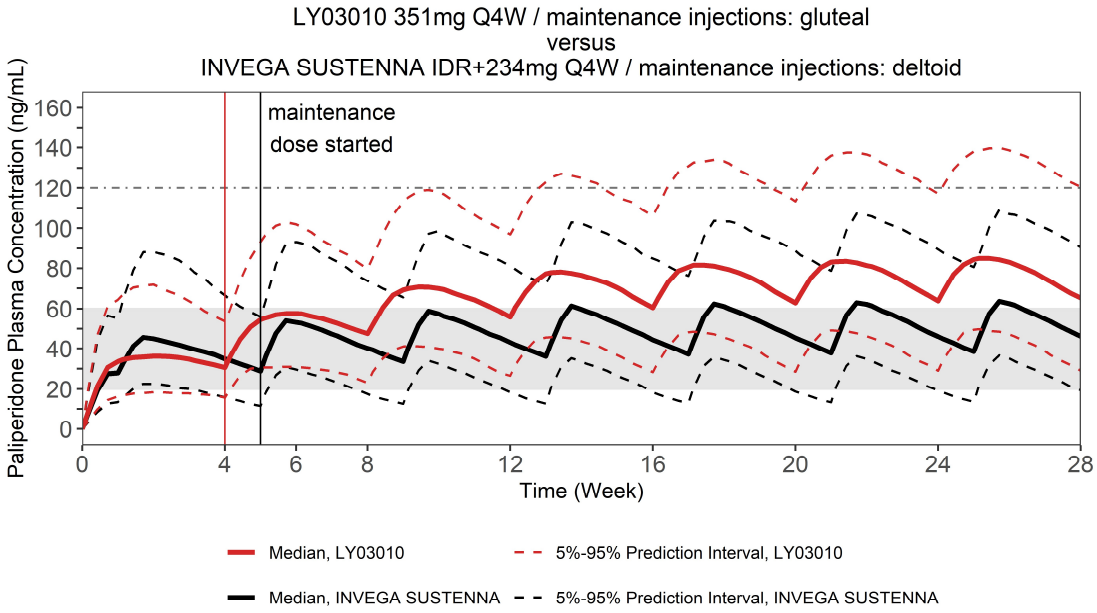


Abbreviations:

CWRES = conditional weighted residuals; DV = observed concentrations; IPRED = individual predicted concentration; NPDE = normalized prediction distribution error; PRED = predicted concentration.

Supplementary Figure 2. Simulated Paliperidone Concentration-Time Profile of LY03010 351mg Administered Q4W in the Gluteal Muscle Compared with PP1M 234 mg Q4W or Q3W Regimens. (Note: The horizontal dash-dotted line represents the laboratory alert level of 120 ng/mL; the shaded area represents the therapeutic reference range of 20-60 ng/mL.)

A.



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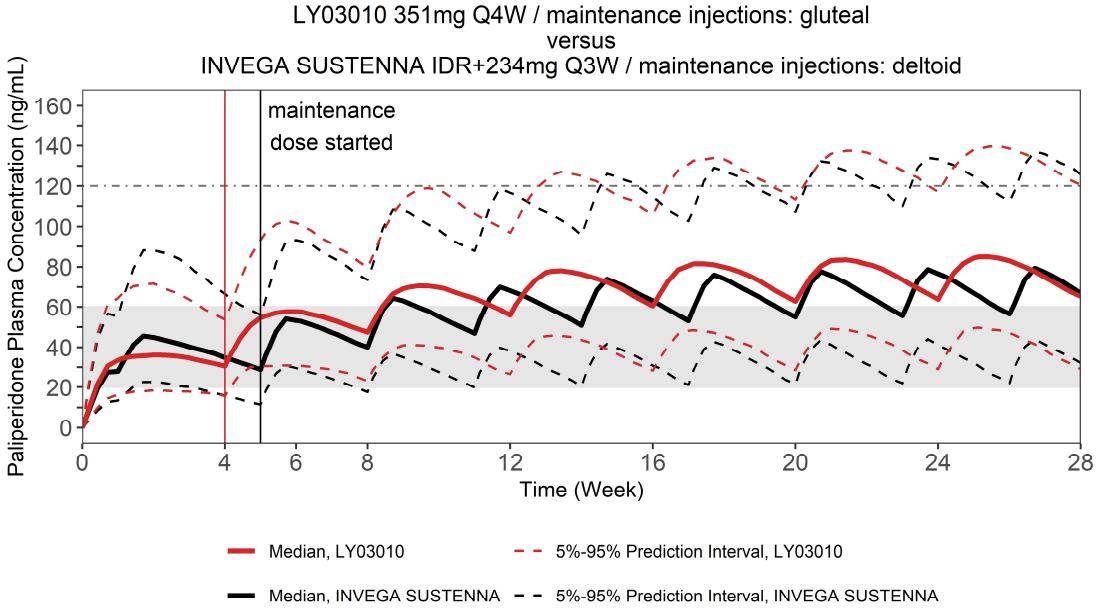
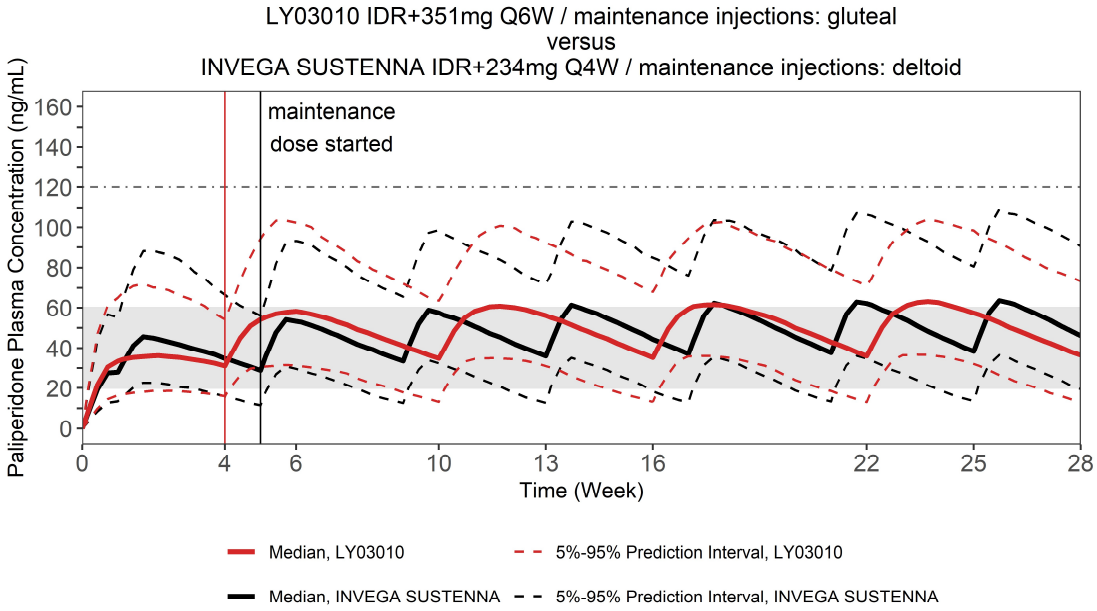


Supplementary Figure 3. Simulated Paliperidone Concentration-Time Profile of LY03010 351mg Administered Q6W Compared with PP1M 234 mg Q4W Dosing Regimen. (Note: The horizontal dash-dotted line represents the laboratory alert level of 120 ng/mL; the shaded area represents the therapeutic reference range of 20-60 ng/mL.)

A.



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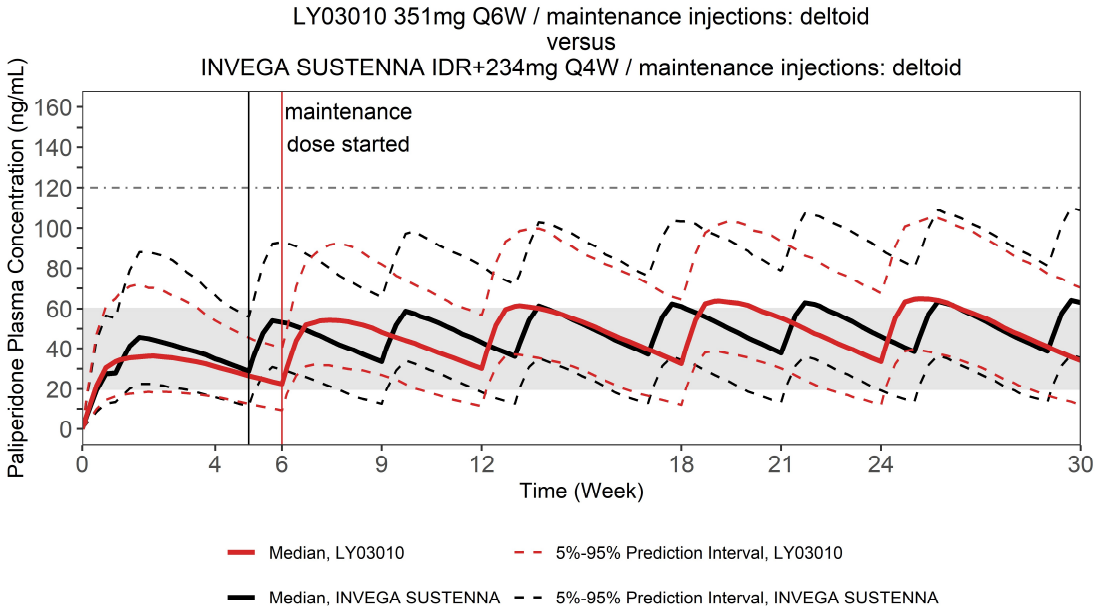

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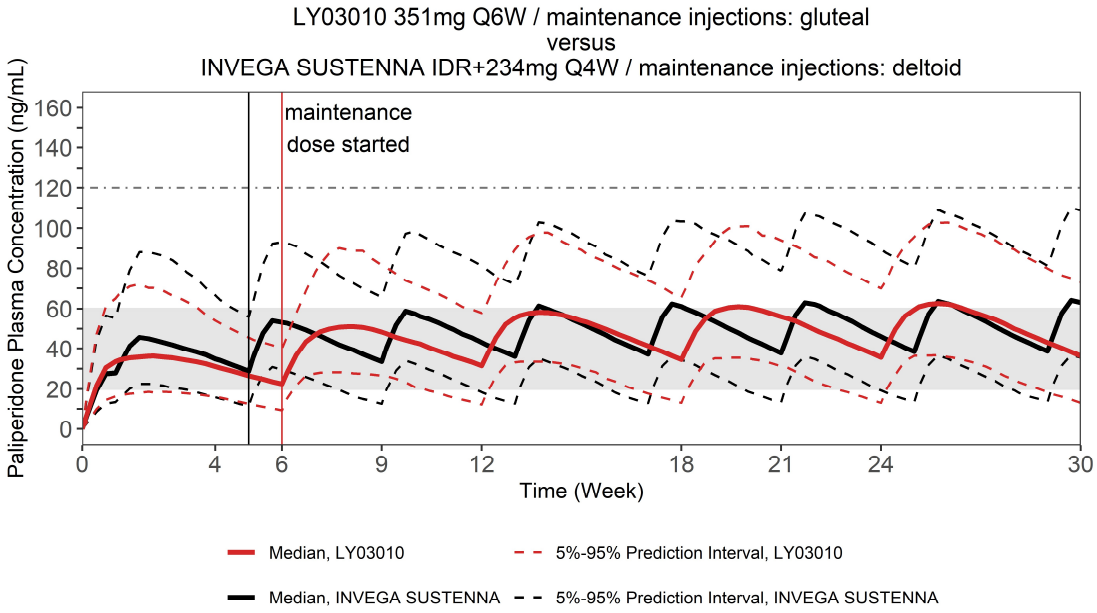
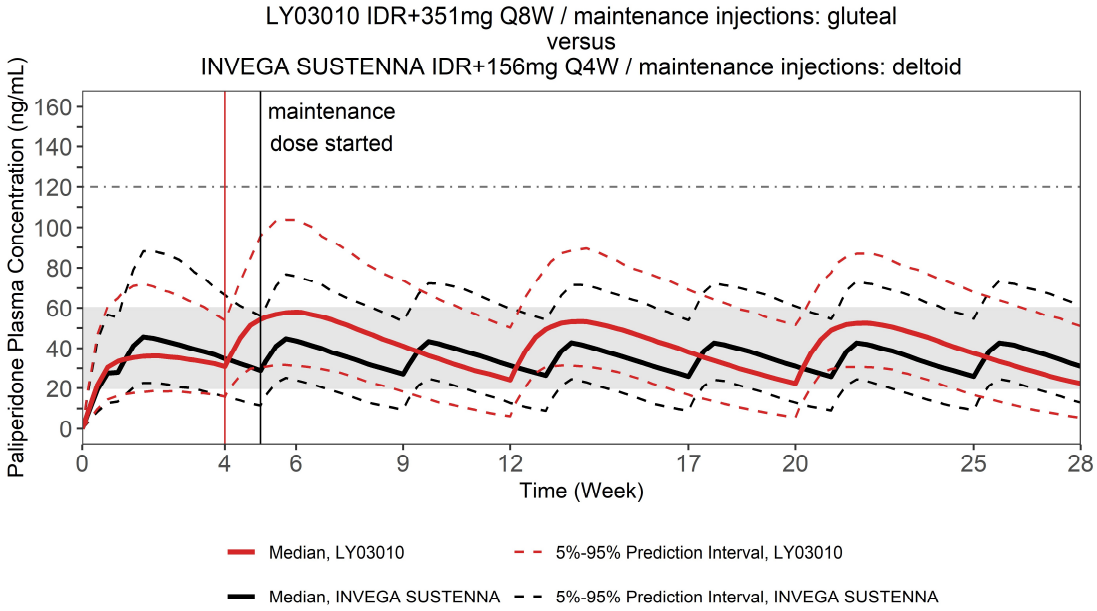
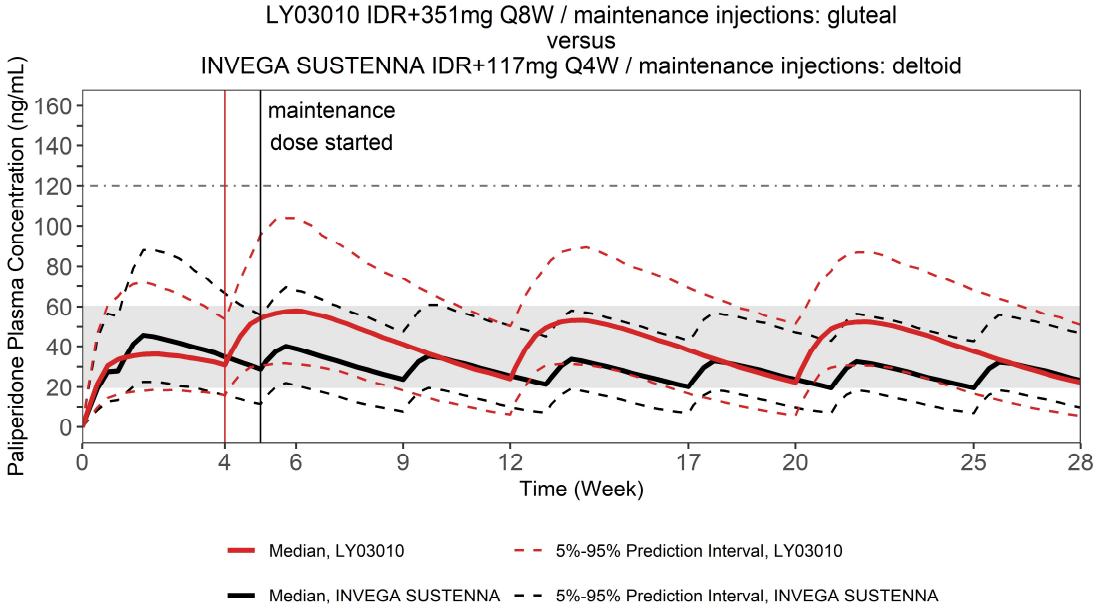

LY03010 351mg Q6W / maintenance injections: gluteal
versus
INVEGA SUSTENNA IDR+234mg Q4W / maintenance injections: deltoid
Paliperidone Plasma Concentration (ng/mL)
160
140
120
100
80
60
40
20
0
maintenance
dose started
0
4
6
9
12
18
21
24
30
Time (Week)
Median, LY03010
5%-95% Prediction Interval, LY03010
Median, INVEGA SUSTENNA
5%-95% Prediction Interval, INVEGA SUSTENNA

Supplementary Figure 4. Simulated Paliperidone Concentration-Time Profile of LY03010 351mg Administered Q8W in the Gluteal Muscle Compared with PP1M Q4W Dosing Regimen. (Note: The horizontal dash-dotted line represents the laboratory alert level of 120 ng/mL; the shaded area represents the therapeutic reference range of 20-60 ng/mL.)

A.

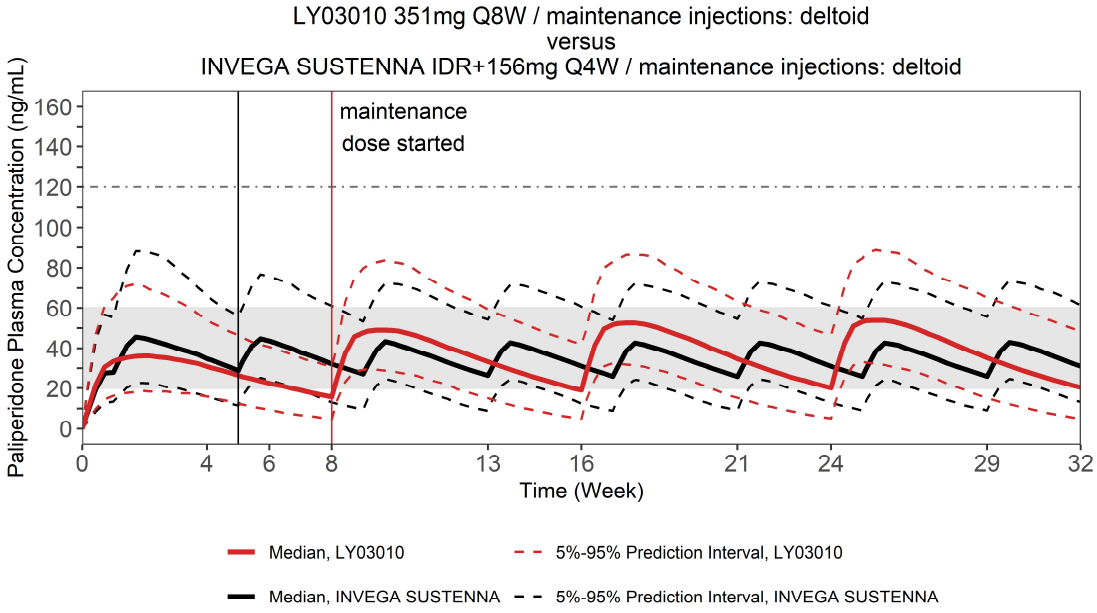


B.



Supplementary Figure 5. Simulated Paliperidone Concentration-Time Profile of Ongoing LY03010 351mg Administered Q8W Compared with PP1M Q4W Dosing Regimen. (Note: The horizontal dash-dotted line represents the laboratory alert level of 120 ng/mL; the shaded area represents the therapeutic reference range of 20-60 ng/mL.)

A.



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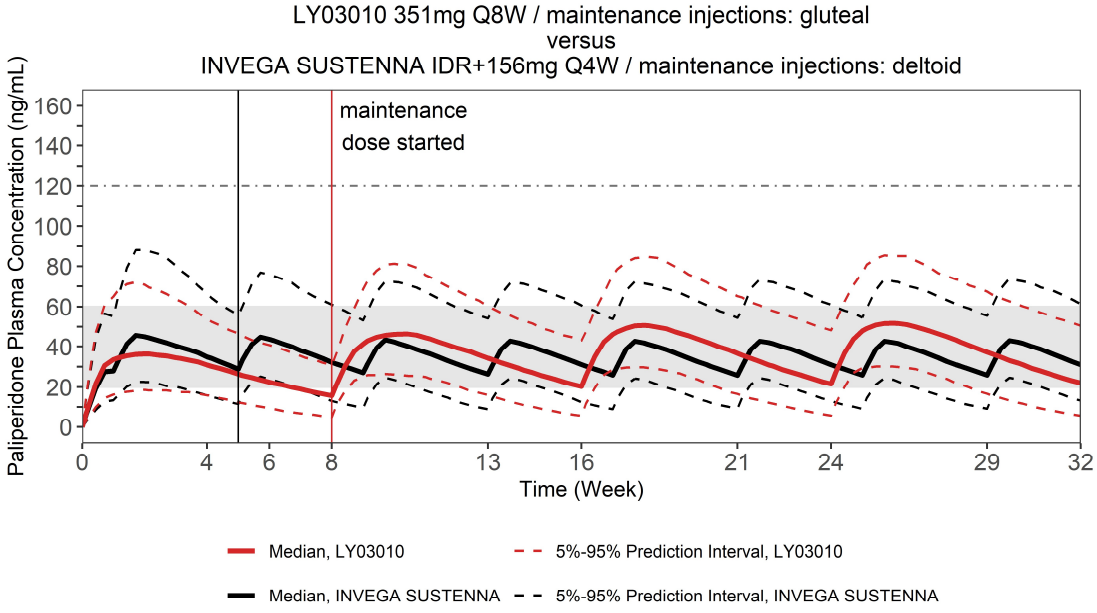

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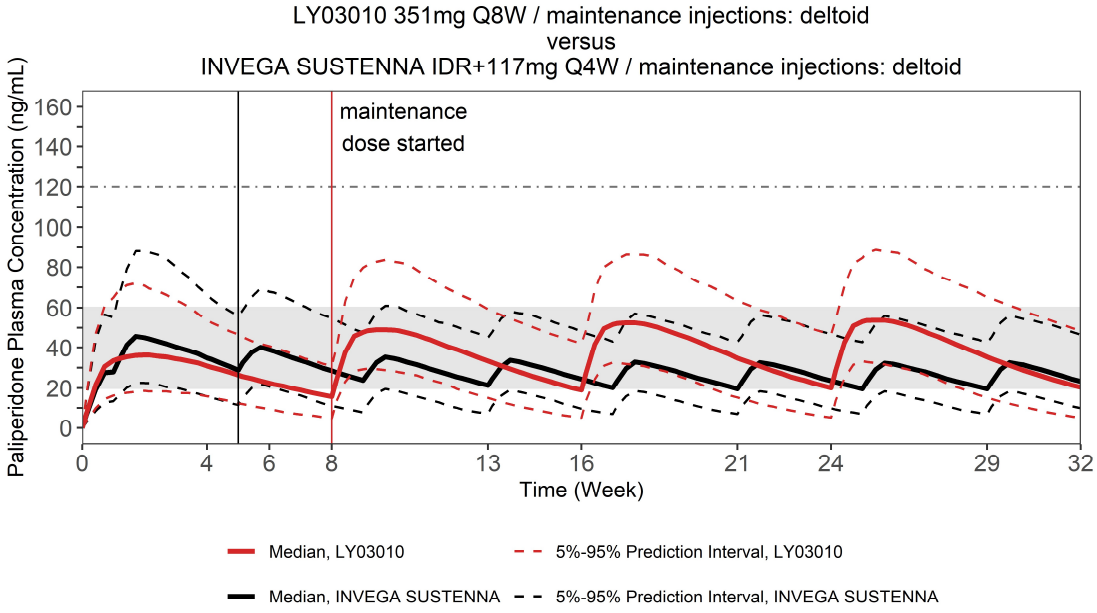
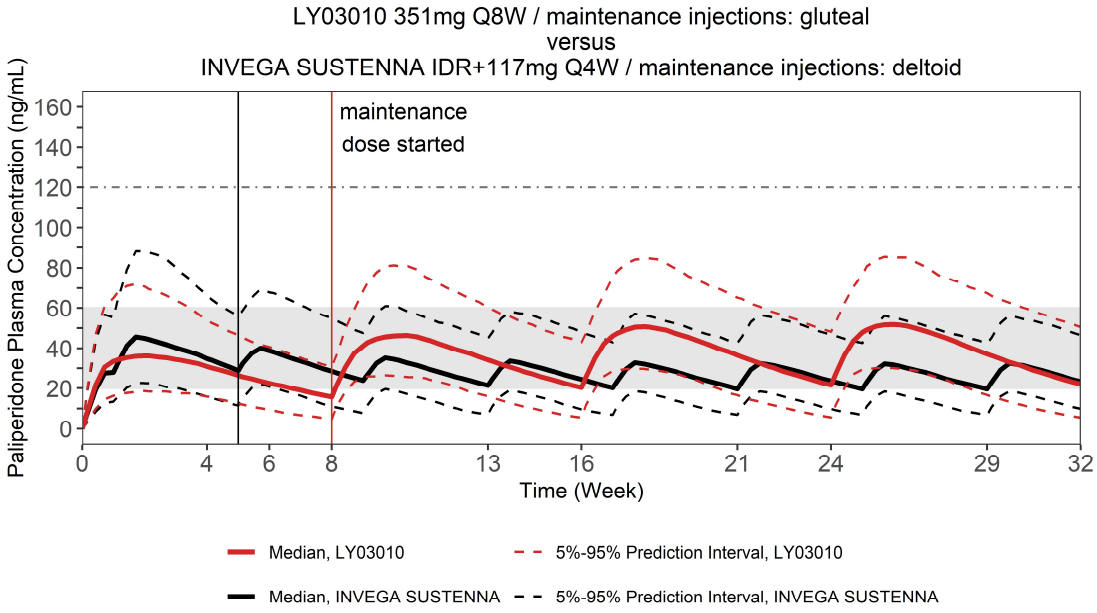

LY03010 351mg Q8W / maintenance injections: deltoid
versus
INVEGA SUSTENNA IDR+117mg Q4W / maintenance injections: deltoid
maintenance
dose started
Paliperidone Plasma Concentration (ng/mL)
Time (Week)
Median, LY03010
5%-95% Prediction Interval, LY03010
Median, INVEGA SUSTENNA
5%-95% Prediction Interval, INVEGA SUSTENNA

D.


LY03010 351mg Q8W / maintenance injections: gluteal
versus
INVEGA SUSTENNA IDR+117mg Q4W / maintenance injections: deltoid
maintenance
dose started
Paliperidone Plasma Concentration (ng/mL)
Time (Week)
Median, LY03010
5%-95% Prediction Interval, LY03010
Median, INVEGA SUSTENNA
5%-95% Prediction Interval, INVEGA SUSTENNA