# Determination of Plasma Concentration Reference Ranges for Risperidone & Paliperidone

*Online Supplement 1:*

*Clinical Studies Included in the Analysis*

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**Table S1.1: Overview of Clinical Studies Included in the Analysis.**

| Study Name | Description | Usage |
|---|---|---|
| INDIGO-APS-1003 | Open-label pharmacokinetic study to evaluate the steady-state venous and capillary plasma concentrations of 5 antipsychotics: aripiprazole, olanzapine, paliperidone, quetiapine and risperidone | 8,9 |
| PAL-SCH-101 | A randomised, double-blind, placebo- and active-controlled, parallel-group, phase 1 study to compare the tolerability of OROS paliperidone (extended-release) with immediate-release (IR) risperidone in subjects with schizophrenia | 9 |
| PALIOROS-PSZ-1001 | A phase 1 PK and tolerability study in 25 subjects aged 10 to 17 years, inclusive, with schizophrenia, schizoaffective disorder, or schizophreniform disorder | 4 |
| PALIOROS-SCH-1011 | An open-label, single- and multiple-dose study to evaluate the pharmacokinetics of ER OROS paliperidone in healthy elderly and young subjects | 4 |
| PALM-JPN-3 | Clinical pharmacology study of JNS010 (paliperidone palmitate) in subjects with schizophrenia | 0,7,10 |
| PALM-JPN-4 | A randomised, double-blind, placebo-controlled, parallel-group, fixed-dose, multicentre study of JNS010 (paliperidone palmitate) in patients with schizophrenia | 0,7,10 |
| PALM-JPN-5 | A study of paliperidone palmitate in Japanese patients with schizophrenia: a long-term, open-label study of flexibly dosed paliperidone palmitate long-acting intramuscular injection in Japanese patients with schizophrenia | 0,7,10 |
| RIS-BEL-21 | A single dose open label study of risperidone in 6 children (4-8 years) who had a diagnosis of autistic disorder by DSM III R | 0,2,3 |
| RIS-BIM-301 | Research on the effectiveness of risperidone in bipolar disorder in adolescents and children (REACH): a double-blind, randomised, placebo-controlled study of the efficacy and safety of risperidone for the treatment of acute mania in bipolar I disorder | 0,3 |
| RIS-CAN-19 | Pharmacotherapy of disruptive behaviour and item changes on a standardised rating scale: Pooled analysis of risperidone effects in children with subaverage IQ | 0,3 |
| RIS-DEN-01 | Single and multiple dose study: 1 mg at Day 1 and then 1 mg once daily from Day 5 to Day 15 to evaluate the pharmacokinetics and safety of risperidone in psychogeriatric patients | 0,2,3 |

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**Table S1.1: Overview of Clinical Studies Included in the Analysis - cont.**

| Study Name | Description | Usage |
|---|---|---|
| RIS-FRA-4 | Investigation of the effect of carbamazepine as adjunctive treatment to risperidone. | 0,1,2 |
| RIS-FRA-12 | Double-blind, placebo- and reference- controlled, 4-way cross-over clinical pharmacology trial to assess the potential effects of two different single doses of risperidone (0.25 and 0.5 mg) compared to placebo and to a positive control, lorazepam 1 mg | 0,3 |
| RIS-GER-9 | Evaluation of the pharmacokinetics, tolerability and safety of risperidone when administered in addition to lithium therapy | 0,1,2 |
| RIS-IND-002 | Clinical efficacy trial: efficacy of risperidone as monotherapy in the treatment of the manic phase of Bipolar I Disorder; flexible QD dose, 1-6 mg | 1,2 |
| RIS-INT-02 | A randomized, double-blind, multicenter study compared five fixed doses of risperidone (1, 4, 8, 12 or 16 mg) and one dose of haloperidol (10mg) in schizophrenic patients. | 0 |
| RIS-INT-03 | A randomized, double-blind, placebo-controlled multicenter study compared four fixed doses of risperidone (2, 6, 10, or 16 mg) and one dose of haloperidol (20mg) in schizophrenic patients | 0 |
| RIS-INT-24 | International, multicentre Phase 3 trial with a double-blind, parallel-group design with three treatment groups: risperidone, haloperidol and placebo given at doses of 0.25 to 2 mg twice daily over 12 weeks to determine the efficacy and safety profile of risperidone compared to that of the placebo using haloperidol as internal reference | 0,3 |
| RIS-INT-28 | Randomised, double-blind, two-way cross over Phase 1 trial to assess the effect of 0.25 mg risperidone twice a day for 10 days on the steady-state concentrations of digoxin | 0,2,3 |
| RIS-INT-32 | An open, comparative pharmacokinetic trial in 86 subjects with schizophrenic disorder conducted to investigate the steady-state dose-proportionality of the risperidone microspheres formulation, and to compare the steady-state bioavailability between oral and depot treatment (2, 4 and 6 mg once daily versus 25, 50 and 75 mg biweekly) | 8,11 |
| RIS-INT-41 | The long-term safety and efficacy of Risperdal in conduct disorder in mild, moderate, and borderline mentally retarded children aged 5-14 years | 0,3 |

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**Table S1.1: Overview of Clinical Studies Included in the Analysis - cont.**

| Study Name | Description | Usage |
|---|---|---|
| RIS-INT-46 | Clinical efficacy trial: efficacy of risperidone as adjunctive therapy to mood stabilisers in the treatment of the manic phase of Bipolar I Disorder; flexible QD dose, 1-6 mg | 0,1,2 |
| RIS-INT-54 | A comparative single-dose bridging bioavailability trial using risperidone depot 56 microspheres (25, 50 and 75 mg) originating from two different manufacturing scales | 11 |
| RIS-INT-57 | An open-label, long-term safety trial in 725 subjects with schizophrenia or schizoaffective disorder administered biweekly i.m. injections of risperidone de- pot microspheres (25, 50 or 75 mg) over a period of 12 months | 8,12 |
| RIS-INT-61 | Risperidone depot (microspheres) versus risperidone tablets - a non-inferiority, efficacy trial in subjects with chronic schizophrenia | 0,3,8,12 |
| RIS-INT-62 | A randomised, open-label, active-controlled, repeated-dosing study to confirm non-inferiority of injectable risperidone depot microspheres (25 or 50 mg every 2 weeks) to oral olanzapine tablets (5, 10, 15, and 20 mg/day) and to document long-term safety and efficacy | 13 |
| RIS-NED-18 | Open, randomised, three-way crossover, Phase 1 trial to assess the bioequivalence (BE) of single oral doses of 1 mg risperidone given as two tablets of 0.5 mg, four tablets of 0.25 mg or one tablet of 1 mg | 0,2,3 |
| RIS-P01-103 | A bioequivalence study comparing a single oral Intake of a 4 mg orally-disintegrating tablet with a 4 mg conventional Risperdal tablet in patients with schizophrenia | 0,2,3 |
| RIS-RSA-005 | A bioequivalence trial comparing risperidone 4 mg tablets manufactured by a direct compression process and Risperdal marketed tablets in subjects with schizophrenia or schizoaffective disorder | 0,2,3 |

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**Table S1.1: Overview of Clinical Studies Included in the Analysis - cont.**

| Study Name | Description | Usage |
|---|---|---|
| RIS-USA-19 | Open, single-centre, 2-way cross-over trial to explore a potential interaction at steady state when galantamine and risperidone were co-administered/RIS: risperidone 0.5 mg BID for 6 days then QD for 1 day/RIS+GAL: galantamine 4 mg BID for 7 days, followed by 8 mg BID for 7 days, then 12 mg BID for 7 days, then 12 mg BID for 6 days and QD for 1 day co-administered with risperidone, and risperidone 0.5 mg BID for 6 days and QD for 1 day co-administered with galantamine 12 mg BID during Days 22 to 27 (or 44 to 49) and QD on Days 28 or 50 | 0,2,3 |
| RIS-USA-63 | Randomized, double-blind, parallel-group, multicentre Phase 3 trial to evaluate the efficacy and safety profile of QD risperidone (0.5, 1.0, and 2.0 mg/day) compared with placebo over 12 weeks | 0,3 |
| RIS-USA-93 | Disruptive Behaviour Study Group. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviours in children with subaverage intelligence | 0,3 |
| RIS-USA-121 | A multicenter, randomized, double-blind, parallel-group trial comparing the efficacy and safety of intramuscular injections of 25, 50 and 75 mg of risperidone depot and placebo in the treatment of subjects with schizophrenia or schizoaffective disorder | 0,12 |
| RIS-USA-122 | Open, 3-way cross-over, 14-day treatment/interaction between donepezil and risperidone/risperidone 0.5 mg BID + placebo, donepezil 5 mg QD + placebo, and risperidone 0.5 mg BID + donepezil 5 mg QD to compare the pharmacokinetic profiles of risperidone and donepezil when taken alone and together at steady state | 0,2,3 |
| RIS-USA-160 | Determination of the pharmacokinetics and safety of risperidone at steady state in children and adolescents 5 to less than 18 years of age | 0,2,3 |
| RIS-USA-231 | The efficacy and safety of risperidone in the treatment of adolescents with schizophrenia | 0,3 |
| RIS-USA-239 | Clinical efficacy trial: efficacy of risperidone as monotherapy in the treatment of the manic phase of Bipolar I Disorder; flexible QD dose, 1-6 mg | 1,2 |

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**Table S1.1: Overview of Clinical Studies Included in the Analysis - cont.**

| Study Name | Description | Usage |
|---|---|---|
| R064766/RIS-JRD0001 | A randomised, open, 2-way cross-over, bioequivalence trial comparing the 4 mg market tablet (91E12/F31) with the 4 mg research tablet (90E11/269) | 0,1,2 |
| R064766/RIS-JRD0002 | A randomised, open, 3-way cross-over, bioequivalence trial comparing the 1 mg market tablet (91I04/F23) and the 4 mg market tablet (91I11/F31) with the 1 mg research tablet (88F17/F5) | 0,1,2 |
| R076477-SCH-102 | Comparison of steady-state pharmacokinetics of paliperidone after extended-release OROS immediate-release oral risperidone 8 mg BID | 0,2,3,9 |
| R076477-SCH-1014 | A randomised, double-blind, placebo-controlled, parallel-group study evaluating QT/QTc intervals following administration of extended-release paliperidone and quetiapine in subjects with schizophrenia or schizoaffective disorder | 11 |
| R076477-PSZ-3001 | A 6-week, randomised, double-blind, weight-based fixed dose, parallel-group, placebo-controlled, multicentre study in approximately 200 adolescents aged 12 to 17 years, inclusive, with schizophrenia | 4 |
| R076477-PSZ-3003 | Randomised, double-blind, active-controlled, parallel-group, multicentre Phase 3 study designed to evaluate the efficacy and safety of flexibly-dosed paliperidone ER in adolescent subjects (12-17 years of age, inclusive) with schizophrenia | 0,5,9 |
| R076477-P01-1010 | Dose-proportionality study of the five ER OROS paliperidone to-be-marketed tablet strengths (3, 6,9,12 and 15mg) in healthy male subjects | 4 |
| R076477-REI-1001 | The pharmacokinetics of ER OROS paliperidone in subjects with varying degrees of impaired renal function (mild, moderate, and severe) as compared to subjects with normal renal function | 4 |
| R076477-SCH-302 | A randomised, 6-week double-blind, placebo-controlled study with an optional 24-week open-label extension to evaluate the safety and tolerability of flexible doses of paliperidone extended release in the treatment of geriatric patients with schizophrenia | 9 |
| R076477-SCH-303 | A randomised, double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of extended release paliperidone (6, 9, and 12 mg/day) and olanzapine (10 mg/day), with open-label extension, in the treatment of subjects with schizophrenia | 0,5,9 |

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| Study Name | Description | Usage |
|---|---|---|
| R076477-SCH-304 | A randomised, double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 2 fixed dosages of extended release paliperidone (6 and 12 mg/day) and olanzapine (10 mg/day), with open-label extension, in the treatment of subjects with schizophrenia | 0,5,9 |
| R076477-SCH-305 | A randomised, double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of extended release paliperidone (3, 9, and 15 mg/day) and olanzapine (10 mg/day), with open-label extension, in the treatment of subjects with schizophrenia | 0,5,9 |
| R092670-INT-11 | Multiple-dose, randomised, double-blind, crossover study of two monthly injections to investigate comparative PK, tolerability and safety of two formulations (F004 and F011) of paliperidone palmitate originating from two different production methods at two dose levels (paliperidone 50 and 150 mg eq.) with two injections of one formulation followed by two injections of the other formulation | 0,6 |
| R092670-INT-12 | To document the PK profile of paliperidone enantiomer disposition and its palmitate ester after a single IM injection of paliperidone palmitate at paliperidone 25, 50, 100 and 150 mg eq. | 0,6 |
| R092670-PSY-1001 | To compare the PK of paliperidone at steady state following multiple IM injections of paliperidone palmitate (paliperidone 100 mg eq.) on days 1, 8, 36 and 64 in the deltoid and gluteal muscle | 0,6,7 |
| R092670-PSY-1002 | Randomised, open-label, parallel-group study (paliperidone 50 mg eq.) to explore the *in vitro/in vivo* correlation of paliperidone palmitate long-acting formulations and the comparability of the F011 and F013 formulations after a single IM injection | 0,6 |
| R092670-PSY-1004 | Randomised, open-label, parallel-group, dose-proportionality PK study of paliperidone after a single IM injection of paliperidone palmitate in the deltoid or gluteal muscle (paliperidone 25, 50, 100 and 150 mg eq.) | 0,6 |
| R092670-PSY-1008 | An open-label, long-term, multiple-dose, safety and tolerability, pharmacokinetic study of 150 mg eq. paliperidone palmitate in the treatment of subjects with schizophrenia | 0,7,10 |

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**Table S1.1: Overview of Clinical Studies Included in the Analysis - cont.**

| Study Name | Description | Usage |
|---|---|---|
| R092670-PSY-3002 | A randomised, double-blind, parallel-group, comparative study of flexibly administered paliperidone palmitate (paliperidone 50, 75 or 100 mg eq.) injected every month (every 4 weeks) | 0,6,7 |
| R092670-PSY-3003 | A randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of three fixed doses (paliperidone 50, 100 and 150 mg eq.) on days 1, 8, 36 and 64 | 0,6,7 |
| R092670-PSY-3004 | A randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of three fixed doses (paliperidone 25, 50 and 100 mg eq.) on days 1, 8, 36 and 64 | 0,6,7 |
| R092670-PSY-3005 | A randomised, double-blind, crossover study (paliperidone 50, 75 or 100 mg eq.) designed to answer two basic questions: (i) is it safe and well tolerated to initiate treatment in the deltoid muscle; and (ii) is it safe and well tolerated to switch injection sites after three injection cycles (13 weeks)? Treatment sequence: Gluteal group received four IM injections into the gluteal muscle (days 1, 8, 36 and 64) followed by three IM injections into the deltoid muscle (days 92, 120 and 148); Deltoid group received four IM injections into the deltoid muscle (days 1, 8, 36 and 64) followed by three IM injections into the gluteal muscle (days 92, 120 and 148) | 0,6,7 |
| R092670-PSY-3006 | A randomized, double-blind, parallel-group, comparative study of flexible doses of paliperidone palmitate and flexible doses of risperidone long-acting intramuscular injection in subjects with schizophrenia | 0,7,10 |
| R092670-PSY-3007 | A randomised, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia | 0,7,10 |
| R092670-SCH-201 | To evaluate the efficacy and safety of repeated long-acting injections of two fixed doses of paliperidone palmitate (paliperidone 50 and 100 mg eq.) compared with placebo. The study involved a 7-day oral paliperidone ER run-in period followed by IM injections on days 1, 8 and 36 | 0,6,7 |

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**Table S1.1: Overview of Clinical Studies Included in the Analysis - cont.**

| Study Name | Description | Usage |
|---|---|---|
| R092670-USA-3 | To compare the PK of paliperidone and its palmitate ester after repeated IM injection of paliperidone palmitate (25 and 150 mg eq.) in two different injection sites, the deltoid and gluteal muscle, after injections on days 1 and 8 | 0,6 |

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