# Summary Result of Lodopin® Aggression Study

## I.  Overall Summary

This is a multi-centre comparative study to evaluate the anti-aggression effect and safety of Zotepine versus Risperidone in aggressive schizophrenic patients of acute ward.   The study protocol was approved by IRB and was disclosed in the www.clinicaltrial.gov as well. This study was conducted at ███████████████████ since 2007.   The fist patient was enrolled in March 2007 and the last patient was enrolled in November 2009.   A total of 43 patients with aggressive schizophrenia were screen, and 39 patients were enrolled into the study.   There were 32 patients completed the 6 weeks treatment, and 7 patients withdrawn from the study due to various reasons.   Patients who met the inclusion/exclusion criteria of the study, took the study medication and had at least one efficacy assessment were included in the efficacy analysis set.   For safety analysis, patients took at least one dose of study medication were included in the safety analysis set. According to the study protocol, the last observation carried forward (LOCF) technique will be applied for missing variable.

## II.  Result：

(1)  Patient disposition at each study site：

| Study Site | No. of Patient Enrolled | No. of Patient Completed | Withdrawal |
|---|---|---|---|
| ███████(02) | 19 (LP: 9; RIS: 10) | 14 (LP: 7; RIS; 7) | 5 (LP: 2; RIS: 3) |
| ████(01) | 7 (LP: 3; RIS: 4) | 6 (LP: 3; RIS: 3) | 1 (LP: 0; RIS: 1) |
| ████(03) | 12 (LP: 7; RIS:P 5) | 11 (LP: 6; RIS: 5) | 1 (LP: 1; RIS: 0) |
| ████(04) | 1 (LP: 0; RIS: 1) | 1 (LP: 0; RIS: 1) | 0 |
| **Total** | **39 (LP: 19; RIS: 20)** | **32 (LP: 16; RIS: 16)** | **7 (LP: 3; RIS: 4)** |

The reasons of withdrawn including:

(1) Patient's willing: 4 (LP; 3; RIS: 1)

(2) Lack of efficacy: 2 (LP: 0; RIS: 2)

(3) Protocol violation (use of long-acting antipsychotics): 1 (LP: 0; RIS; 1)

(2) Demographics：

| | Lodopin (n=19) | Risperidone (n=20) | p-value* |
|---|---|---|---|
| Gender | Male: 8<br>Female: 11 | Male: 12<br>Female: 8 | 0.343 |
| Age (y/o) | 37.1±9.9<br>(25 ~ 59) | 38.8±9.0<br>(23 ~ 50) | 0.509 |
| History (year) | 15.8±7.7<br>(0.1 ~ 29.0) | 13.6±8.4<br>(0.3 ~ 26.0) | 0.456 |
| Height (cm) | 161.5±10.7<br>(139 ~ 179) | 164.3±9.0<br>(146 ~ 180) | 0.406 |
| Weight (Kg) | 65.1±16.1<br>(46.2 ~ 111.5) | 64.1±13.0<br>(42.0 ~ 97.0) | 0.855 |
| BMI | 24.91±5.02<br>(18.83 ~ 36.41) | 23.66±3.73<br>(17.26 ~ 29.94) | 0.565 |
| Waist (cm) | 80.3±12.5<br>(64.5 ~ 107.5) | 81.5±11.9<br>(63.5 ~ 101.0) | 0.704 |
| Hip (cm) | 94.6±10.5<br>(80.0 ~ 117.0) | 94.2±7.8<br>(79.5 ~ 106.0) | 0.653 |
| Waist-Hip Ratio | 0.871±0.083<br>(0.76 ~ 1.00) | 0.838±0.054<br>(0.74 ~ 0.95) | 0.310 |
| Pulse (beat/min) | 81.8±15.2<br>(62 ~ 124) | 79.6±10.8<br>(54 ~ 96) | 0.899 |
| SBP (mmHg) | 114.5±14.8<br>(92 ~ 140) | 117.8±12.4<br>(93 ~ 136) | 0.456 |
| DBP (mmHg) | 74.2±10.8<br>(55 ~ 99) | 76.3±12.2<br>(56 ~ 95) | 0.603 |

There was no significant difference between the 2 treatment groups on the above variables at baseline.

(3) The majority of patients (34/39) use of one or more antipsychotics within 2 months prior the study.  All the antipsychotics were stopped prior enrollment.  Doses of Lodopin and Risperidone were shown in the following table.

| | Dose at D0 (mg) | Dose at D42 (mg) | Minimum Dose (mg) | Maximum Dose (mg) |
|---|---|---|---|---|
| Lodopin (n=19) | 127.6±62.3<br>(25 ~ 250) | 236.8±74.2<br>(100 ~ 350) | 127.6±62.3<br>(25 ~ 250) | 236.8±74.2<br>(100 ~ 350) |
| Risperidone (n=20) | 3.3±1.6<br>(2 ~ 7) | 4.8±1.7<br>(2 ~ 8) | 3.2±1.6<br>(2 ~ 7) | 5.1±1.9<br>(2 ~ 10) |

Data file: ██████████████
Date: April 06, 2010

Efficacy Parameters

All 39 patients were included into the efficacy analysis set, although there was one case in the Risperidone group using long-acting antipsychotics and was withdrawn from the study thereafter.

PANSS-EC Score

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 18.7±3.0 (14 ~ 24) | 14.2±3.3 (6 ~ 19) | 11.8±4.1 (6 ~ 24) | 10.8±3.5 (5 ~ 19) | 8.7±3.3 (5 ~18) |
| **Risperidone (n=20)** | 17.1±2.1 (14 ~ 22) | 12.4±4.6 (5 ~ 26) | 10.9±5.4 (5 ~ 26) | 9.6±5.4 (5 ~ 26) | 9.1±5.6 (5 ~ 26) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** | | -4.5±4.3 (-18 ~ +1) -22.6% | -6.9±5.3 (-18 ~ 5) -35.2% | -8.0±4.9 (-17 ~ +1) -40.7% | -10.1±4.7 (-18 ~+1) -52.2% |
| **Risperidone (n=20)** | | -4.7±4.0 (-13 ~ +4) -27.6% | -6.2±4.8 (-15 ~ +4) -37.1% | -7.5±4.8 (-15 ~ +4) -44.5% | -8.0±5.3 (-15 ~ +4) -47.1% |
| *p-value* | | 0.745 | 0.592 | 0.966 | 0.265 |

There was no significant difference between the 2 treatment groups on the PANSS EC score at baseline (p=0.072).   No significance differences between the 2 treatment groups on the change from baseline PANSS EC score at each visit.

PANSS Total Score

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 96.8±14.4 (72 ~ 123) | 86.0±15.2 (64 ~ 112) | 76.2±13.0 (58 ~ 101) | 70.7±13.8 (49 ~ 101) | 62.1±12.8 (43 ~83) |
| **Risperidone (n=20)** | 95.3±20.5 (71 ~ 137) | 83.4±22.5 (50 ~ 139) | 76.6±19.5 (44 ~ 124) | 72.7±19.0 (42 ~ 120) | 66.8±17.3 (42 ~ 101) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** | | -10.8±12.3 (-46 ~ +5) -10.7% | -20.7±12.2 (-41 ~ +4) -20.7% | -26.1±14.6 (-52 ~ +4) -26.3% | -34.7±15.8 (-61 ~+4) -35.0% |
| **Risperidone (n=20)** | | -12.0±12.3 (-31 ~ +11) -12.7% | -18.7±13.3 (-40 ~ +9) -19.3% | -22.7±12.8 (-45 ~ +5) -23.6% | -28.6±14.3 (-64 ~ +5) -29.6% |
| *p-value* | | 0.602 | 0.683 | 0.439 | 0.125 |

There was no significant difference between the 2 treatment groups on the PANSS total score at baseline (p=0.593).   No significance differences between the 2 treatment groups on the change from baseline PANSS total score at each visit.

PANSS -General Score

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 47.5±5.3 (40 ~ 56) | 42.0±7.0 (30 ~ 56) | 37.1±6.5 (27 ~ 48) | 34.4±6.8 (25 ~ 50) | 30.0±6.7 (21 ~45) |
| **Risperidone (n=20)** | 46.1±9.9 (33 ~ 64) | 40.0±10.6 (24 ~ 65) | 36.0±10.3 (19 ~ 58) | 34.0±9.9 (18 ~ 56) | 31.2±9.5 (18 ~ 54) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** |  | -5.5±7.3 (-26 ~ +4) -11.0% | -10.4±6.7 (-24 ~ +4) -21.6% | -13.1±7.4 (-23 ~ +4) -27.0% | -17.5±8.7 (-30 ~+4) -36.0% |
| **Risperidone (n=20)** |  | -6.1±6.3 (-15 ~ +4) -13.2% | -10.1±6.9 (-21 ~ +2) -21.8% | -12.1±6.1 (-21 ~ +1) -26.3% | -14.9±7.3 (-30 ~ +1) -32.2% |
| ***p-value*** |  | 0.526 | 0.833 | 0.583 | 0.196 |

There was no significant difference between the 2 treatment groups on the PANSS general score at baseline (p=0.331). No significance differences between the 2 treatment groups on the change from baseline PANSS general score at each visit.

PANSS -Positive Score

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 27.6±5.2 (18 ~ 36) | 22.8±4.4 (15 ~ 30) | 20.6±4.7 (15 ~ 31) | 18.4±4.8 (12 ~ 29) | 15.7±4.0 (10 ~23) |
| **Risperidone (n=20)** | 25.7±5.1 (17 ~ 34) | 20.5±7.3 (9 ~ 35) | 18.6±6.7 (8 ~ 33) | 17.5±6.3 (8 ~ 33) | 15.7±6.3 (3 ~ 33) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** |  | -4.8±4.6 (-20 ~ +1) -16.1% | -7.0±5.3 (-17 ~ +4) -23.8% | -9.2±5.7 (-23 ~ +1) -32.0% | -11.8±5.4 (-22 ~+1) -41.7% |
| **Risperidone (n=20)** |  | -5.2±4.0 (-12 ~ +2) -21.7% | -7.1±4.6 (-17 ~ +2) -28.3% | -8.2±5.1 (-17 ~ +2) -31.9% | -10.0±4.9 (-17 ~ +2) -39.6% |
| ***p-value*** |  | 0.437 | 0.843 | 0.746 | 0.331 |

There was no significant difference between the 2 treatment groups on the PANSS positive score at baseline (p=0.254). No significance differences between the 2 treatment groups on the change from baseline PANSS positive score at each visit.

PANSS -Negative Score

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 21.8±7.2 (12 ~ 39) | 21.2±7.7 (11 ~ 37) | 18.5±6.1 (11 ~ 29) | 18.0±6.0 (10 ~ 28) | 16.4±5.4 (10 ~26) |
| **Risperidone (n=20)** | 23.6±8.9 (9 ~ 40) | 22.9±7.6 (11 ~ 39) | 22.1±6.3 (11 ~ 36) | 21.2±6.7 (11 ~ 35) | 20.0±6.1 (11 ~ 31) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** | | -0.6±3.3 (-7 ~ +5) -2.7% | -3.3±4.4 (-12 ~ +4) -13.6% | -3.8±5.1 (-16 ~ +4) -15.9% | -5.4±4.8 (-16 ~+4) -23.1% |
| **Risperidone (n=20)** | | -0.7±4.1 (-9 ~ +6) 1.1% | -1.6±4.6 (-15 ~ +6) -1.4% | -2.5±4.8 (-16 ~ +5) -5.9% | -3.7±5.3 (-17 ~ +7) -9.9% |
| *p-value* | | 0.977 | 0.189 | 0.397 | 0.248 |

There was no significant difference between the 2 treatment groups on the PANSS negative score at baseline (p=0.399).    No significance differences between the 2 treatment groups on the change from baseline PANSS negative score at each visit.

CGI - Severity of Illness

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 5.4±0.7 (4 ~ 6) | 4.9±0.7 (3 ~ 6) | 4.6±0.7 (4 ~ 6) | 4.2±1.0 (2 ~ 6) | 3.4±1.1 (1 ~5) |
| **Risperidone (n=20)** | 4.9±0.8 (4 ~ 6) | 4.5±0.9 (3 ~ 6) | 4.2±0.8 (3 ~ 6) | 3.8±0.9 (3 ~ 6) | 3.6±0.9 (2 ~ 6) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** | | -0.5±0.8 (-3 ~ 0) | -0.7±0.7 (-2 ~ 0) | -1.2±1.1 (-4 ~ 0) | -2.0±1.1 (-5 ~0) |
| **Risperidone (n=20)** | | -0.4±0.5 (-1 ~ 0) | -0.7±0.6 (-2 ~ 0) | -1.1±0.6 (-2 ~ 0) | -1.3±0.7 (-3 ~ 0) |
| *p-value* | | 0.814 | 0.704 | 0.988 | 0.029 |

There was a significant difference between the 2 treatment groups on the CGI severity of illness score at baseline (p=0.043).    No significance differences between the 2 treatment groups on the change from baseline PANSS negative score at each visit until D28.    A significant difference between the 2 treatment groups and in favor of Lodopin was observed at D42 visit.

CGI – Global Improvement

| | D7 | D14 | D28 | D42 |
|---|---|---|---|---|
| **Lodopin (n=19)** | 3.1±0.9 (1 ~ 5) | 2.7±1.2 (1 ~ 5) | 2.3±1.2 (1 ~ 5) | 2.0±1.0 (1 ~5) |
| **Risperidone (n=20)** | 3.2±1.0 (1 ~ 6) | 2.6±1.1 (1 ~ 6) | 2.5±1.1 (1 ~ 6) | 2.3±1.3 (1 ~ 6) |
| *p-value* | 0.831 | 0.561 | 0.390 | 0.426 |

No significance differences between the 2 treatment groups on CGI – global impression at each visit.

(4) Safety Parameters

All 39 patients were included into the safety analysis set, except for the analysis of 12-Lead ECG and Hematology, Biochemistry and Lipid Profiles.   For the analysis of hematology, biochemistry and lipid profiles, only patients with both baseline and D42 data were analyzed.

(A) Rating Scales

AIMS Total Score

| | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 1.1±1.9 (0 ~ 6) | 1.1±2.1 (0 ~ 8) | 1.1±2.0 (0 ~ 8) | 0.9±1.9 (0 ~ 8) | 1.0±2.1 (0 ~8) |
| **Risperidone (n=20)** | 0.7±2.1 (0 ~ 9) | 0.8±2.3 (0 ~ 10) | 0.8±2.1 (0 ~ 9) | 0.8±2.1 (0 ~ 9) | 0.9±2.1 (0 ~ 9) |
| *p-value* | 0.099 | 0.437 | 0.267 | 0.649 | 0.973 |

SAS Total Score

| | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 1.6±2.1 (0 ~ 7) | 1.1±1.5 (0 ~ 6) | 1.2±1.6 (0 ~ 6) | 1.1±1.8 (0 ~ 6) | 1.2±1.8 (0 ~6) |
| **Risperidone (n=20)** | 3.1±5.6 (0 ~ 23) | 2.7±4.8 (0 ~ 19) | 2.5±5.0 (0 ~ 20) | 2.9±5.3 (0 ~ 20) | 2.3±4.9 (0 ~ 20) |
| *p-value* | 0.881 | 0.551 | 0.710 | 0.253 | 0.638 |

Barnes Akathisia Scale Total Score

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 0.6±1.2 (0 ~ 4) | 0.3±0.8 (0 ~ 2) | 0.3±0.7 (0 ~ 2) | 0.3±0.6 (0 ~ 2) | 0.3±0.6 (0 ~ 2) |
| **Risperidone (n=20)** | 0.8±1.3 (0 ~ 4) | 0.4±0.9 (0 ~ 3) | 0.3±0.7 (0 ~ 2) | 0.5±0.9 (0 ~ 3) | 0.5±0.8 (0 ~ 2) |
| ***p-value*** | 0.776 | 0.736 | 0.768 | 0.451 | 0.462 |

UKU Total Score

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 4.2±5.2 (0 ~ 21) | 4.0±2.9 (0 ~ 10) | 3.9±3.2 (0 ~ 10) | 3.8±3.1 (0 ~ 9) | 3.7±2.7 (0 ~ 8) |
| **Risperidone (n=20)** | 4.5±4.5 (0 ~ 14) | 4.6±3.2 (0 ~ 10) | 3.9±2.6 (0 ~ 9) | 3.9±2.3 (0 ~ 7) | 3.1±2.1 (0 ~ 7) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** |  | -0.16±4.59 (-17 ~ 5) | -0.26±5.81 (-21 ~ 7) | -0.32±5.64 (-21 ~ 6) | -0.47±5.94 (-21 ~8) |
| **Risperidone (n=20)** |  | 0.05±2.82 (-6 ~ 4) | -0.65±4.23 (-12 ~ 4) | -0.60±3.87 (-9 ~ 4) | -1.35±4.02 (-12 ~ 3) |
| ***p-value*** |  | 0.875 | 0.876 | 0.876 | 0.591 |

There was no significant difference between the 2 treatment groups on the UKU total score at baseline (p=0.776). No significance differences between the 2 treatment groups on the change from baseline UKU total score at each visit.

(B) Body Weight, BMI, Waist Hip Ratio

Body Weight

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 65.1±16.1 (46.2 ~ 111.5) | 65.1±15.5 (47.5 ~ 109) | 65.6±15.3 (47.5 ~ 109) | 66.3±14.6 (50 ~ 106) | 66.3±14.4 (51 ~ 107) |
| **Risperidone (n=20)** | 64.1±13.0 (42 ~ 97) | 64.1±12.9 (42 ~ 97.2) | 64.2±13.0 (41 ~ 99) | 64.6±13.1 (42 ~ 100) | 64.4±12.7 (40 ~ 98) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** |  | -0.03±1.44 (-3 ~ 2) | 0.43±1.34 (-2.5 ~ 3) | 1.15±2.62 (-5.5 ~ 6.5) | 1.20±3.07 (-4.5 ~ 6.1) |
| **Risperidone (n=20)** |  | -0.03±1.41 (-3.5 ~ 2) | 0.11±1.45 (-4 ~ 2) | 0.5±2.0 (-2 ~ 5.5) | 0.3±2.4 (-4 ~ 5.5) |
| ***p-value*** |  | 0.777 | 0.453 | 0.165 | 0.339 |

There was no significant difference between the 2 treatment groups on the body weight at baseline (p=0.855).   No significance differences between the 2 treatment groups on the change from baseline body weight at each visit.   No significant increase on body weight was observed in both Lodopin and Risperidone treated groups.

BMI

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 24.91±5.02 (18.83 ~ 36.41) | 23.89±4.77 (19.32 ~ 35.59) | 25.08±4.73 (19.32 ~ 35.59) | 25.40±4.53 (20.15 ~ 34.84) | 25.40±4.42 (20.31 ~ 34.97) |
| **Risperidone (n=20)** | 23.66±3.73 (17.26 ~ 29.94) | 23.63±3.58 (17.26 ~ 30.00) | 23.68±3.54 (16.85 ~ 30.56) | 23.76±3.51 (17.26 ~ 30.86) | 23.76±3.47 (16.44 ~ 30.25) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** |  | -0.01±0.57 (-1.37 ~ 0.78) | 0.18±0.50 (-0.82 ~ 1.17) | 0.49±1.03 (-1,80 ~ 2.48) | 0.49±1.20 (-1.47 ~ 2.48) |
| **Risperidone (n=20)** |  | -0.02±0.55 (-1.4 ~ 0.73) | 0.02±0.57 (-1.6 ~ 0.85) | 0.10±0.72 (-0.92 ~ 1.86) | 0.10±0.86 (-1.60 ~ 1.86) |
| *p-value* |  | 0.713 | 0.322 | 0.134 | 0.292 |

There was no significant difference between the 2 treatment groups on the BMI at baseline (p=0.565).   No significance differences between the 2 treatment groups on the change from baseline BMI at each visit.   No significant increase on BMI was observed in both Lodopin and Risperidone treated groups.

Waist Hip Ratio

|  | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 0.85±0.08 (0.74 ~ 1.00) | 0.86±0.07 (0.75 ~ 1.01) | 0.86±0.08 (0.74 ~ 1.02) | 0.86±0.07 (0.74 ~ 0.97) | 0.87±0.08 (0.74 ~ 1.00) |
| **Risperidone (n=20)** | 0.86±0.07 (0.75 ~ 0.96) | 0.87±0.07 (0.72 ~ 0.98) | 0.87±0.08 (0.71 ~ 0.99) | 0.87±0.08 (0.71 ~ 1.00) | 0.87±0.08 (0.71 ~ 0.98) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** |  | 0.02±0.04 (-0.07 ~ 0.11) | 0.02±0.04 (-0.05 ~ 0.11) | 0.02±0.05 (-0.05 ~ 0.14) | 0.02±0.07 (-0.06 ~ 0.17) |
| **Risperidone (n=20)** |  | 0.003±0.04 (-0.15 ~ 0.07) | 0.006±0.05 (-0.08 ~ 0.13) | 0.007±0.06 (-0.15 ~ 0.11) | 0.003±0.05 (-0.14 ~ 0.11) |
| *p-value* |  | 0.442 | 0.515 | 0.977 | 0.622 |

There was no significant difference between the 2 treatment groups on the BMI at baseline (p=0.390).   No significance differences between the 2 treatment groups on the change from baseline waist hip ratio at each visit.   No significant increase on waist hip ratio was observed in both Lodopin and Risperidone treated groups.

## (C) PR, BP, ECG

### Pulse Rate

| | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 81.8±15.2 (62 ~ 124) | 87.3±13.1 (65 ~ 109) | 88.3±10.5 (60 ~ 111) | 90.3±13.3 (65 ~ 112) | 91.9±12.6 (71 ~ 115) |
| **Risperidone (n=20)** | 79.6±10.8 (54 ~ 96) | 83.8±11.8 (55 ~ 100) | 85.5±16.3 (59 ~ 123) | 87.4±16.5 (70 ~ 135) | 80.5±13.7 (52 ~ 114) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** | | 5.5±11.5 (-24 ~ 22) | 7.0±15.0 (-25 ~ 46) | 7.9±17.1 (-24 ~ 42) | 9.4±15.3 (-14 ~ 42) |
| **Risperidone (n=20)** | | 4.3±11.7 (-24 ~ 26) | 6.0±16.4 (-16 ~ 46) | 8.7±15.6 (-16 ~ 40) | 1.0±12.5 (-17 ~ 29) |
| ***p-value*** | | 0.456 | 0.447 | 0.763 | 0.097 |

There was no significant difference between the 2 treatment groups on the pulse rate at baseline (p=0.899).   No significance differences between the 2 treatment groups on the change from baseline pulse rate at each visit.   No significant change on pulse rate was observed in both Lodopin and Risperidone treated groups.

### Systolic Blood Pressure

| | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 114.5±14.8 (92 ~ 140) | 109.0±13.9 (86 ~ 139) | 116.7±15.3 (90 ~ 143) | 114.3±15.3 (98 ~ 149) | 115.4±13.5 (98 ~ 153) |
| **Risperidone (n=20)** | 117.8±12.4 (93 ~ 136) | 113.9±11.6 (97 ~ 140) | 112.4±11.7 (100 ~ 137) | 114.7±10.4 (100 ~ 136) | 111.1±11.6 (92 ~ 131) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** | | -5.5±12.0 (-24 ~ 12) | 0.94±17.8 (-34 ~ 32) | 0.81±10.3 (-24 ~ 14) | 1.9±12.5 (-16 ~ 24) |
| **Risperidone (n=20)** | | -3.0±10.6 (-28 ~ 17) | -4.5±11.6 (-26 ~ 15) | -1.2±7.2 (-8 ~ 16) | -4.7±11.2 (-21 ~ 13) |
| ***p-value*** | | 0.693 | 0.338 | 0.395 | 0.146 |

There was no significant difference between the 2 treatment groups on the systolic blood pressure at baseline (p=0.456).   No significance differences between the 2 treatment groups on the change from baseline systolic blood pressure at each visit.   No significant change on systolic blood pressure was observed in both Lodopin and Risperidone treated groups.

Data file: ████████████████████
Date: April 06, 2010

Diastolic Blood Pressure

| | D0 | D7 | D14 | D28 | D42 |
|---|---|---|---|---|---|
| **Lodopin (n=19)** | 74.2±10.8 (55 ~ 99) | 74.7±8.8 (60 ~ 91) | 80.6±9.6 (62 ~ 97) | 76.8±10.8 (65 ~ 98) | 75.5±7.7 (62 ~ 90) |
| **Risperidone (n=20)** | 76.3±12.2 (56 ~ 95) | 75.6±11.3 (62 ~ 106) | 73.4±10.4 (60 ~ 97) | 73.3±7.8 (60 ~ 90) | 73.4±12.3 (60 ~ 95) |
| change from baseline to each visit | | | | | |
| **Lodopin (n=19)** | | 0.5±11.2 (-18 ~ 29) | 5.6±12.5 (-17 ~ 27) | 3.8±8.5 (-16 ~ 18) | 2.5±8.6 (-14 ~ 22) |
| **Risperidone (n=20)** | | 0.2±11.0 (-27 ~ 15) | -2.1±12.2 (-24 ~ 19) | 0.0±9.6 (-14 ~ 20) | -0.3±11.1 (-19 ~ 22) |
| *p-value* | | 0.826 | 0.068 | 0.146 | 0.427 |

There was no significant difference between the 2 treatment groups on the diastolic blood pressure at baseline (p=0.603).   No significance differences between the 2 treatment groups on the change from baseline diastolic blood pressure at each visit.   No significant change on diastolic blood pressure was observed in both Lodopin and Risperidone treated groups.

12-Lead ECG – QTc (some patient did not have ECG performed)

| | D0 | D42 |
|---|---|---|
| **Lodopin** | N=18 401.6±26.4 (360 ~ 458) | N=13 408.0±39.7 (343 ~ 480) |
| **Risperidone** | N=18 401.8±24.6 (374 ~ 474) | N=14 401.3±25.0 (370 ~ 448) |

No significant change on QTc was observed in both Lodopin and Risperidone treated groups.   However, there was one QTc prolonged case (430msec → 480msec) and one case of borderline sinus tachycardia reported in the Lodopin treated grout at D42.

(D) Hematology, Biochemistry and Lipid Profiles
1. No significant change on hematology test results (Hb, Hct, RBC, and WBC) was observed in both Lodopin and Risperidone treated groups.

2. No significant change on biochemistry test results was observed in both Lodopin and Risperidone treated groups, except T-bilirubin, uric acid, and prolactin.
   – A significant uric acid lowering effect was observed in Lodopin treated group only

– A significant prolactin level increased was observed in Risperidone treated group
3. No significant change on lipid profile test results was observed in both Lodopin and Risperidone treated groups

## Hemaglobin

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 13.0±2.0 (9.8 ~ 15.6) | 12.6±2.2 (8.0 ~ 15.6) | -0.4±0.9 (-2.0 ~ 1.5) | 0.854 |
| Risperidone (n=14) | 13.7±2.4 (8.5 ~ 16.6) | 13.2±2.1 (8.5 ~ 15.8) | -0.6±1.1 (-3.1 ~ 0.8) |  |

## Hematocrit

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 38.7±5.7 (29.3 ~ 48.0) | 37.3±7.0 (23.2 ~ 48.4) | -1.4±3.3 (-6.7 ~ 4.4) | 0.748 |
| Risperidone (n=14) | 39.9±6.1 (26.3 ~ 48.6) | 37.9±4.9 (25.5 ~ 43.7) | -2.0±3.3 (-9.6 ~ 2.3) |  |

## RBC

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 4.49±0.44 (3.77 ~ 5.16) | 4.36±0.46 (3.47 ~ 5.13) | -0.14±0.32 (-0.75 ~ 0.49) | 0.930 |
| Risperidone (n=15) | 4.52±0.57 (3.22 ~ 5.31) | 4.34±0.44 (3.23 ~ 5.01) | -0.18±0.36 (-1.04 ~ 0.22) |  |

## WBC

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 7.6±2.4 (4.7 ~ 12.0) | 6.4±2.4 (4.1 ~ 12.6) | -1.3±1.7 (-4.4 ~ 1.8) | 0.896 |
| Risperidone (n=15) | 6.9±2.8 (3.7 ~ 14.9) | 5.4±1.5 (3.8 ~ 8.6) | -1.5±2.4 (-9.4 ~ 0.9) |  |

## AST

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 29.7±18.7 (14 ~ 80) | 35.8±37.0 (14 ~ 154) | 6.1±38.6 (-28 ~ 137) | 0.743 |
| Risperidone (n=15) | 23.7±9.4 (12 ~ 49) | 21.9±11.4 (12 ~ 50) | -1.8±9.0 (-16 ~ 18) |  |

## ALT

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 24.3±13.1 (13 ~ 66) | 63.0±111.7 (11 ~ 447) | 38.7±113.0 (-17 ~ 427) | 0.232 |
| Risperidone (n=14) | 24.9±11.8 (10 ~ 46) | 29.5±23.1 (11 ~ 99) | 4.6±19.1 (-14 ~ 56) | |

## ALP

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 75.5±15.8 (51 ~ 99) | 71.0±16.2 (32 ~ 91) | -4.5±18.5 (-57 ~ 13) | 0.490 |
| Risperidone (n=14) | 74.9±17.2 (47 ~ 112) | 71.4±19.3 (45 ~ 108) | -3.4±9.4 (-20 ~ 16) | |

## Total Bilirubin

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 0.49±0.27 (0.1 ~ 1.2) | 0.40±0.23 (0.1 ~ 1.0) | -0.09±0.25 (-0.7 ~ 0.4) | 0.043 |
| Risperidone (n=14) | 0.49±0.29 (0.1 ~ 1.3) | 0.57±0.23 (0.3 ~ 0.9) | 0.08±0.22 (-0.4 ~ 0.5) | |

## BUN

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 10.1±2.8 (5.0 ~ 15.0) | 11.2±1.6 (9.0 ~ 14.0) | 1.1±3.0 (-5.0 ~ 0.4) | 0.140 |
| Risperidone (n=15) | 11.9±3.3 (9.0 ~ 22.0) | 11.3±2.6 (7.0 ~ 16.0) | -0.6±3.3 (-9.0 ~ 3.0) | |

## Creatinine

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 0.74±0.11 (0.6 ~ 1.0) | 0.77±0.14 (0.6 ~ 1.0) | 0.04±0.16 (-0.2 ~ 0.3) | 0.875 |
| Risperidone (n=15) | 0.85±0.16 (0.6 ~ 1.2) | 0.86±0.16 (0.5 ~ 1.1) | 0.01±0.11 (-0.2 ~ 0.2) | |

## Uric Acid

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 4.6±1.6 (1.4 ~ 6.5) | 2.1±1.0 (0.9 ~ 4.0) | -2.5±1.7 (-5.6 ~ 0) | <0.001 |
| Risperidone (n=14) | 5.2±1.5 (2.2 ~ 8.2) | 5.2±1.4 (2.6 ~ 8.1) | 0.02±0.59 (-1.0 ~ 1.1) | |

## Prolactin

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=12) | 55.5±72.1 (5.7 ~ 195.6) | 40.9±39.3 (6.1 ~ 146.8) | -14.6±60.7 (-161.0 ~ 75.8) | 0.018 |
| Risperidone (n=12) | 31.9±15.6 (2.8 ~ 60.5) | 75.5±57.6 (8.5 ~ 206.5) | 43.7±59.3 (-27.2 ~ 185.1) | |

## Glucose AC

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 96.4±17.9 (77 ~ 135) | 96.3±21.3 (77 ~ 164) | -0.14±28.9 (-46 ~ 87) | 0.308 |
| Risperidone (n=13) | 31.9±15.6 (2.8 ~ 60.5) | 75.5±57.6 (8.5 ~ 206.5) | 2.1±8.8 (-12 ~ 20) | |

## HDL

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 52.3±15.8 (32.4 ~ 91.0) | 53.0±14.7 (30.7 ~ 82.0) | 0.7±8.8 (-16.2 ~ 16.5) | 0.854 |
| Risperidone (n=13) | 41.4±11.7 (28.3 ~ 60.9) | 42.0±11.5 (25.7 ~ 61.2) | 0.7±6.4 (-14 ~ 12.2) | |

## LDL

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 100.1±36.0 (60.0 ~ 189.0) | 105.4±31.5 (58.0 ~ 169.0) | 5.2±19.8 (-20.0 ~ 53.6) | 0.748 |
| Risperidone (n=14) | 117.0±51.3 (68.0 ~ 264.0) | 122.8±45.0 (48.9 ~ 201) | 5.9±34.3 (-63.0 ~ 71.0) | |

## Cholesterol

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 170.6±31.5 (115 ~ 235) | 187.7±38.3 (125 ~ 260) | 17.1±24.0 (-16 ~ 56) | 0.765 |
| Risperidone (n=14) | 181.0±49.6 (123 ~ 323) | 192.0±50.7 (95 ~ 285) | 11.0±35.7 (-46 ~ 78) | |

## Triglyceride

|  | Baseline | D42 | Change from baseline | p-value |
|---|---|---|---|---|
| Lodopin (n=14) | 105.2±62.0 (39 ~ 245) | 127.2±79.8 (39 ~ 288) | 22.0±48.1 (-53 ~ 159) | 0.241 |
| Risperidone (n=14) | 128.0±92.9 (33 ~ 398) | 123.1±85.6 (37 ~ 333) | -4.9±81.2 (-137 ~ 162) | |

## (E) Adverse Event

A total of 61 adverse events in 29 patients (LP: 15; RIS: 14) were reported in this study. No subject was withdrawn from the study due to adverse event.   Most of the adverse events were mild to moderate and transit.

The most commonly seen adverse events including: constipation (n=9; LP: 6, RIS: 3), Diarrhoea (n=4; LP: 1, RIS: 3), Insomnia (n=3, LP: 2, RIS: 1), Influenza-like symptom (n=3; LP: 2, RIS: 1), headache (n=3, LP: 1, RIS: 2).

Detail of adverse event reported in the study is presented below.

| Adverse Event | Lodopin (n=19) | Risperidone (n=20) |
|---|---|---|
| Abdominal Pain | 0 | 1 |
| Abrasion NOS | 1 | 0 |
| Agitation | 1 | 1 |
| Anaemia | 1 | 0 |
| Anxiety | 1 | 0 |
| Arthritis | 1 | 0 |
| Back Pain | 0 | 1 |
| Bradykinesia | 0 | 1 |
| Chest Pain | 0 | 1 |
| Conjunctivitis | 0 | 1 |
| Constipation | 6 | 3 |
| Delirium | 1 | 0 |
| Diarrhoea | 1 | 3 |
| Dizziness | 1 | 0 |
| Extrapyramidal Disorder | 0 | 2 |
| Flatulence | 1 | 0 |
| Headache | 1 | 2 |
| Hepatic Function Abnormal | 0 | 1 |
| Hyperkinesia | 0 | 1 |
| Hypertension | 1 | 0 |
| Influenza-like symptoms | 2 | 1 |
| Insomnia | 2 | 1 |
| Myalgia | 1 | 0 |
| Nail Disorder | 1 | 0 |
| Nervousness | 2 | 1 |
| Neurosis | 1 | 0 |
| Oculogyric Crisis | 1 | 0 |
| Pharyngitis | 11 | 1 |
| QT Prolonged | 1 | 0 |
| Rash | 1 | 0 |
| Skin Exfoliation | 0 | 1 |
| Somnolence | 2 | 0 |
| Tachycardia | 2 | 0 |
| Upper Respiratory Tract Infection | 1 | 1 |
| Vision Abnormal | 0 | 1 |

## (E) Concomitant Medication

The use of anticholinergics (biperiden), beta-blocker (propranolol), and antimuscarinic agent (trihexyphenidyl), mainly for symptom relief of EPS, are summarized below.

|  | Lodopin (n=19) | Risperidone (n=20) |
|---|---|---|
| Anticholinergics | 9<br><br>New concomitant: 2<br>Increased dose: 1<br>Given at same day: 1<br>Previous concomitant: 5 | 11<br><br>New concomitant: 5<br>Increased dose: 0<br>Given at same day: 2<br>Previous concomitant: 4 |
| Beta blocker | 7<br><br>New concomitant: 3<br>Increased dose: 0<br>Given at same day: 2<br>Previous concomitant: 2 | 6<br><br>New concomitant: 3<br>Increased dose: 0<br>Given at same day: 1<br>Previous concomitant: 2 |
| Antimuscarinic agent | 4<br><br>New concomitant: 3<br>Increased dose: 0<br>Given at same day: 1<br>Previous concomitant: 0 | 3<br><br>New concomitant: 1<br>Increased dose: 0<br>Given at same day: 1<br>Previous concomitant: 1 |

| Group |  |  | Class |  |  | Total |
|---|---|---|---|---|---|---|
|  |  |  | Anticholinergics | Beta blocker | Antimuscarinic |  |
| LP | Use | No | 5 | 2 | 0 | 7 |
|  |  | Yes | 2 | 3 | 3 | 8 |
|  |  | Same day | 1 | 2 | 1 | 4 |
|  |  | Increase | 1 | 0 | 0 | 1 |
|  | Total |  | 9 | 7 | 4 | 20 |
| RIS | Use | No | 4 | 2 | 1 | 7 |
|  |  | Yes | 5 | 3 | 1 | 9 |
|  |  | Same day | 2 | 1 | 1 | 4 |
|  | Total |  | 11 | 6 | 3 | 20 |

## Overall Summary

The anti-aggression effect of Zotepine is comparable with Risperidone in aggressive schizophrenic patients.   The safety profile of the 2 drugs is similar.   It was demonstrate that Zotepine was as effective and as safe as Risperidone in treating aggressive schizophrenic patients.

Data file: ████████████████████████
Date: April 06, 2010