

**Study Number:** R12103B

**Test Type:** Teratology

**Route:** Oral Gavage

**Species/Strain:** Rat/Harlan Sprague Dawley

**C Number:**

**Study Gender:**

**PWG Approval Date**

**R10: Fetal Defects**

**Test Compound:** Vinpocetine

**CAS Number:** 42971-09-5

R12103B

Female

See web page for date of PWG Approval

**Date Report Requested:** 11/13/2019

**Time Report Requested:** 15:10:45

**Lab:** Southern Research

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**F0 Female**

| Classification                       | Treatment Groups (mg/kg/day) |          |          |          |          |
|--------------------------------------|------------------------------|----------|----------|----------|----------|
|                                      | 0                            | 5        | 20       | 60       |          |
| Total number of fetuses examined     | 293                          | 239      | 261      | 51       |          |
| <b>External</b>                      |                              |          |          |          |          |
| No. Fetuses examined                 | 293                          | 239      | 261      | 51       |          |
| No. Litters examined                 | 21                           | 19       | 21       | 8        |          |
| <b>Body - General</b>                |                              |          |          |          |          |
| Body, Generalized subcutaneous edema | Malformation                 | 0 (0.00) | 1 (0.42) | 1 (0.38) | 0 (0.00) |
|                                      |                              | 0 (0.00) | 1 (5.26) | 1 (4.76) | 0 (0.00) |
| <b>Extremities</b>                   |                              |          |          |          |          |
| Tail, Bent                           | Malformation                 | 0 (0.00) | 0 (0.00) | 1 (0.38) | 0 (0.00) |
|                                      |                              | 0 (0.00) | 0 (0.00) | 1 (4.76) | 0 (0.00) |
| Tail, Short                          | Malformation                 | 0 (0.00) | 0 (0.00) | 1 (0.38) | 0 (0.00) |
|                                      |                              | 0 (0.00) | 0 (0.00) | 1 (4.76) | 0 (0.00) |
| <b>Trunk</b>                         |                              |          |          |          |          |
| General, Omphalocele                 | Malformation                 | 0 (0.00) | 0 (0.00) | 1 (0.38) | 0 (0.00) |
|                                      |                              | 0 (0.00) | 0 (0.00) | 1 (4.76) | 0 (0.00) |

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F0 Female

Treatment Groups (mg/kg/day)

| Classification                               | Treatment Groups (mg/kg/day) |                      |                      |                      |
|--|------------------------------|----------------------|----------------------|----------------------|
|  | 0                            | 5                    | 20                   | 60                   |
| <b>Visceral</b>                              |                              |                      |                      |                      |
| No. Fetuses examined                         | 293                          | 239                  | 261                  | 51                   |
| No. Litters examined                         | 21                           | 19                   | 21                   | 8                    |
| <b>Abdominal Viscera</b>                     |                              |                      |                      |                      |
| Diaphragm, Hernia                            | Malformation                 | 0 (0.00)<br>0 (0.00) | 1 (0.42)<br>1 (5.26) | 0 (0.00)<br>0 (0.00) |
| Diaphragm, Thin                              | Malformation                 | 0 (0.00)<br>0 (0.00) | 1 (0.42)<br>1 (5.26) | 0 (0.00)<br>0 (0.00) |
| Liver lobe, Additional fissure               | Variation                    | 1 (0.34)<br>1 (4.76) | 1 (0.42)<br>1 (5.26) | 3 (1.15)<br>2 (9.52) |
| Liver lobe, Supernumerary                    | Variation                    | 2 (0.68)<br>2 (9.52) | 1 (0.42)<br>1 (5.26) | 1 (0.38)<br>1 (4.76) |
| Liver lobe, left lateral, Additional fissure | Variation                    | 0 (0.00)<br>0 (0.00) | 1 (0.42)<br>1 (5.26) | 2 (0.77)<br>1 (4.76) |
| Liver lobe, left medial, Additional fissure  | Variation                    | 0 (0.00)<br>0 (0.00) | 0 (0.00)<br>0 (0.00) | 1 (0.38)<br>1 (4.76) |
| Liver lobe, left medial, Misshapen           | Variation                    | 0 (0.00)<br>0 (0.00) | 1 (0.42)<br>1 (5.26) | 0 (0.00)<br>0 (0.00) |
| Liver lobe, left medial, Supernumerary       | Variation                    | 2 (0.68)<br>2 (9.52) | 0 (0.00)<br>0 (0.00) | 1 (0.38)<br>1 (4.76) |
| Liver lobe, right medial, Additional fissure | Variation                    | 1 (0.34)<br>1 (4.76) | 0 (0.00)<br>0 (0.00) | 0 (0.00)<br>0 (0.00) |
| Liver lobe, right medial, Supernumerary      | Variation                    | 0 (0.00)<br>0 (0.00) | 1 (0.42)<br>1 (5.26) | 0 (0.00)<br>0 (0.00) |
| <b>General</b>                               |                              |                      |                      |                      |
| General, Fluid-filled abdomen                | Gross Finding                | 0 (0.00)<br>0 (0.00) | 1 (0.42)<br>1 (5.26) | 1 (0.38)<br>1 (4.76) |

Heart

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R10: Fetal Defects

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Lab: Southern Research

F0 Female

|   | Classification | Treatment Groups (mg/kg/day) |                         |                             |                           |
|---|----------------|------------------------------|-------------------------|-----------------------------|---------------------------|
|   |                | 0                            | 5                       | 20                          | 60                        |
| Aortic valve, Misshapen                         | Malformation   | 19 (6.48)<br>12 (57.14) **   | 14 (5.86)<br>11 (57.89) | 17 (6.51)<br>10 (47.62)     | 0 (0.00) *<br>0 (0.00) ** |
| Atrium, right, Large                            | Malformation   | 0 (0.00)<br>0 (0.00)         | 0 (0.00)<br>0 (0.00)    | 1 (0.38)<br>1 (4.76)        | 0 (0.00)<br>0 (0.00)      |
| Ventricle, bilateral, Ventricular septum defect | Malformation   | 0 (0.00) **<br>0 (0.00)      | 3 (1.26)<br>3 (15.79)   | 8 (3.07) **<br>7 (33.33) ** | 2 (3.92) *<br>2 (25.00)   |
| Ventricle, left, Thick Wall                     | Malformation   | 0 (0.00)<br>0 (0.00)         | 0 (0.00)<br>0 (0.00)    | 1 (0.38)<br>1 (4.76)        | 0 (0.00)<br>0 (0.00)      |
| <b>Major Vessels</b>                            |                |                              |                         |                             |                           |
| Carotid artery, right, Supernumerary            | Malformation   | 0 (0.00)<br>0 (0.00)         | 0 (0.00)<br>0 (0.00)    | 0 (0.00)<br>0 (0.00)        | 1 (1.96)<br>1 (12.50)     |
| Ductus arteriosus, Patent                       | Variation      | 0 (0.00)<br>0 (0.00)         | 0 (0.00)<br>0 (0.00)    | 1 (0.38)<br>1 (4.76)        | 0 (0.00)<br>0 (0.00)      |
| Innominate artery, Absent                       | Variation      | 4 (1.37)<br>4 (19.05)        | 7 (2.93)<br>6 (31.58)   | 8 (3.07)<br>5 (23.81)       | 1 (1.96)<br>1 (12.50)     |
| Innominate artery, Short                        | Variation      | 3 (1.02)<br>3 (14.29)        | 4 (1.67)<br>4 (21.05)   | 2 (0.77)<br>2 (9.52)        | 1 (1.96)<br>1 (12.50)     |
| <b>Thoracic Viscera</b>                         |                |                              |                         |                             |                           |
| Lung lobe, accessory, Absent                    | Malformation   | 0 (0.00)<br>0 (0.00)         | 1 (0.42)<br>1 (5.26)    | 0 (0.00)<br>0 (0.00)        | 0 (0.00)<br>0 (0.00)      |
| Lung lobe, right cranial, Fused                 | Variation      | 0 (0.00)<br>0 (0.00)         | 1 (0.42)<br>1 (5.26)    | 0 (0.00)<br>0 (0.00)        | 0 (0.00)<br>0 (0.00)      |
| Thymus, Split                                   | Variation      | 0 (0.00)<br>0 (0.00)         | 0 (0.00)<br>0 (0.00)    | 1 (0.38)<br>1 (4.76)        | 0 (0.00)<br>0 (0.00)      |

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**F0 Female**

| Classification           | Treatment Groups (mg/kg/day) |          |          |          |          |
|--------------------------|------------------------------|----------|----------|----------|----------|
|                          | 0                            | 5        | 20       | 60       |          |
| <b>Head</b>              |                              |          |          |          |          |
| No. Fetuses examined     | 150                          | 125      | 134      | 29       |          |
| No. Litters examined     | 21                           | 19       | 20       | 8        |          |
| <b>Brain</b>             |                              |          |          |          |          |
| Ventricles, Hydrocephaly | Malformation                 | 0 (0.00) | 1 (0.80) | 0 (0.00) | 0 (0.00) |
|                          |                              | 0 (0.00) | 1 (5.26) | 0 (0.00) | 0 (0.00) |
| Ventricles, Dilated      | Variation                    | 0 (0.00) | 0 (0.00) | 1 (0.75) | 0 (0.00) |
|                          |                              | 0 (0.00) | 0 (0.00) | 1 (5.00) | 0 (0.00) |

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Lab: Southern Research

F0 Female

| Classification                                    | Treatment Groups (mg/kg/day) |                              |                             |                                  |                                 |
|---|------------------------------|------------------------------|-----------------------------|----------------------------------|---------------------------------|
|   | 0                            | 5                            | 20                          | 60                               |                                 |
| <b>Skeletal - Body</b>                            |                              |                              |                             |                                  |                                 |
| No. Fetuses examined                              | 293                          | 239                          | 261                         | 47                               |                                 |
| No. Litters examined                              | 21                           | 19                           | 21                          | 7                                |                                 |
| <b>Ribs</b>                                       |                              |                              |                             |                                  |                                 |
| Costal cartilage, 7th right, Not fused to sternum | Malformation                 | 1 (0.34)<br>1 (4.76)         | 0 (0.00)<br>0 (0.00)        | 0 (0.00)<br>0 (0.00)             | 0 (0.00)<br>0 (0.00)            |
| <b>Sternebrae</b>                                 |                              |                              |                             |                                  |                                 |
| Sternebra, 4th, Misaligned                        | Variation                    | 1 (0.34)<br>1 (4.76)         | 0 (0.00)<br>0 (0.00)        | 0 (0.00)<br>0 (0.00)             | 0 (0.00)<br>0 (0.00)            |
| <b>Supernumerary Rib</b>                          |                              |                              |                             |                                  |                                 |
| Thoracolumbar, Full                               | Malformation                 | 1 (0.34) ** ##<br>1 (4.76) * | 5 (2.09)<br>3 (15.79)       | 12 (4.60) **<br>4 (19.05)        | 12 (25.53) ** ##<br>3 (42.86) * |
| Thoracolumbar, Short                              | Variation                    | 29 (9.90) ** #<br>14 (66.67) | 30 (12.55)<br>10 (52.63)    | 55 (21.07) ** #<br>17 (80.95)    | 10 (21.28) * #<br>5 (71.43)     |
| Thoracolumbar, bilateral, Full                    | Malformation                 | 0 (0.00) **<br>0 (0.00)      | 2 (0.84)<br>2 (10.53)       | 9 (3.45) **<br>1 (4.76)          | 8 (17.02) **<br>2 (28.57)       |
| Thoracolumbar, bilateral, Short                   | Variation                    | 6 (2.05)<br>4 (19.05)        | 9 (3.77)<br>5 (26.32)       | 17 (6.51) ** #<br>11 (52.38) *   | 1 (2.13)<br>1 (14.29)           |
| Thoracolumbar, left, Full                         | Malformation                 | 0 (0.00) **<br>0 (0.00)      | 1 (0.42)<br>1 (5.26)        | 2 (0.77)<br>2 (9.52)             | 3 (6.38) **<br>1 (14.29)        |
| Thoracolumbar, left, Short                        | Variation                    | 21 (7.17) * #<br>13 (61.90)  | 10 (4.18)<br>6 (31.58)      | 22 (8.43)<br>13 (61.90)          | 7 (14.89)<br>5 (71.43)          |
| Thoracolumbar, right, Full                        | Malformation                 | 1 (0.34)<br>1 (4.76)         | 2 (0.84)<br>2 (10.53)       | 1 (0.38)<br>1 (4.76)             | 1 (2.13)<br>1 (14.29)           |
| Thoracolumbar, right, Short                       | Variation                    | 2 (0.68) *<br>2 (9.52)       | 11 (4.60) ** #<br>6 (31.58) | 16 (6.13) ** ##<br>12 (57.14) ** | 2 (4.26) #<br>2 (28.57)         |
| <b>Vertebrae</b>                                  |                              |                              |                             |                                  |                                 |
| Cervical arch, multiple sites, Misshapen          | Malformation                 | 0 (0.00)                     | 1 (0.42)                    | 0 (0.00)                         | 0 (0.00)                        |

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F0 Female

| Classification                                  | Treatment Groups (mg/kg/day) |          |           |             |
|---|------------------------------|----------|-----------|-------------|
|   | 0                            | 5        | 20        | 60          |
| Lumbar arch, 5th left, Fused                    | 0 (0.00)                     | 1 (5.26) | 0 (0.00)  | 0 (0.00)    |
|   | 0 (0.00)                     | 0 (0.00) | 0 (0.00)  | 1 (2.13)    |
|   | 0 (0.00)                     | 0 (0.00) | 0 (0.00)  | 1 (14.29)   |
| Lumbar centrum, 1st, Incomplete ossification    | 0 (0.00)                     | 1 (0.42) | 0 (0.00)  | 0 (0.00)    |
|   | 0 (0.00)                     | 1 (5.26) | 0 (0.00)  | 0 (0.00)    |
| Lumbar centrum, 3rd, Incomplete ossification    | 0 (0.00)                     | 0 (0.00) | 1 (0.38)  | 0 (0.00)    |
|   | 0 (0.00)                     | 0 (0.00) | 1 (4.76)  | 0 (0.00)    |
| Lumbar centrum, 5th, Fused                      | 0 (0.00)                     | 0 (0.00) | 0 (0.00)  | 1 (2.13)    |
|   | 0 (0.00)                     | 0 (0.00) | 0 (0.00)  | 1 (14.29)   |
| Presacral vertebrae, Greater than 26            | 0 (0.00) **                  | 0 (0.00) | 0 (0.00)  | 4 (8.51) ** |
|   | 0 (0.00) **                  | 0 (0.00) | 0 (0.00)  | 2 (28.57)   |
| Sacral centrum, multiple sites, Misshapen       | 0 (0.00)                     | 1 (0.42) | 0 (0.00)  | 0 (0.00)    |
|   | 0 (0.00)                     | 1 (5.26) | 0 (0.00)  | 0 (0.00)    |
| Thoracic arch, 6th right, Misshapen             | 0 (0.00)                     | 0 (0.00) | 0 (0.00)  | 1 (2.13)    |
|   | 0 (0.00)                     | 0 (0.00) | 0 (0.00)  | 1 (14.29)   |
| Thoracic arch, multiple sites, Misshapen        | 0 (0.00)                     | 1 (0.42) | 0 (0.00)  | 0 (0.00)    |
|   | 0 (0.00)                     | 1 (5.26) | 0 (0.00)  | 0 (0.00)    |
| Thoracic centrum, 10th, Incomplete ossification | 1 (0.34)                     | 0 (0.00) | 0 (0.00)  | 1 (2.13)    |
|   | 1 (4.76)                     | 0 (0.00) | 0 (0.00)  | 1 (14.29)   |
| Thoracic centrum, 11th, Incomplete ossification | 0 (0.00) **                  | 0 (0.00) | 3 (1.15)  | 2 (4.26) *  |
|   | 0 (0.00) **                  | 0 (0.00) | 3 (14.29) | 2 (28.57)   |
| Thoracic centrum, 12th, Hemicentric             | 0 (0.00)                     | 1 (0.42) | 0 (0.00)  | 0 (0.00)    |
|   | 0 (0.00)                     | 1 (5.26) | 0 (0.00)  | 0 (0.00)    |
| Thoracic centrum, 12th, Incomplete ossification | 0 (0.00) **                  | 0 (0.00) | 1 (0.38)  | 3 (6.38) ** |
|   | 0 (0.00) **                  | 0 (0.00) | 1 (4.76)  | 2 (28.57)   |
| Thoracic centrum, 13th, Incomplete ossification | 0 (0.00) **                  | 0 (0.00) | 0 (0.00)  | 2 (4.26) *  |
|   | 0 (0.00) **                  | 0 (0.00) | 0 (0.00)  | 2 (28.57)   |
| Thoracic centrum, 1st, Hemicentric              | 0 (0.00)                     | 1 (0.42) | 0 (0.00)  | 0 (0.00)    |
|   | 0 (0.00)                     | 1 (5.26) | 0 (0.00)  | 0 (0.00)    |

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F0 Female

Treatment Groups (mg/kg/day)

| Classification  | Treatment Groups (mg/kg/day) |                |          |              |                 |
|---|------------------------------|----------------|----------|--------------|-----------------|
|   | 0                            | 5              | 20       | 60           |                 |
| Thoracic centrum, 1st, Incomplete ossification            | Variation                    | 0 (0.00)       | 0 (0.00) | 1 (0.38)     | 0 (0.00)        |
|   |                              | 0 (0.00)       | 0 (0.00) | 1 (4.76)     | 0 (0.00)        |
| Thoracic centrum, 5th, Incomplete ossification            | Variation                    | 0 (0.00)       | 0 (0.00) | 1 (0.38)     | 0 (0.00)        |
|   |                              | 0 (0.00)       | 0 (0.00) | 1 (4.76)     | 0 (0.00)        |
| Thoracic centrum, 6th, Incomplete ossification            | Variation                    | 0 (0.00)       | 0 (0.00) | 0 (0.00)     | 1 (2.13)        |
|   |                              | 0 (0.00)       | 0 (0.00) | 0 (0.00)     | 1 (14.29)       |
| Thoracic centrum, 9th, Incomplete ossification            | Variation                    | 0 (0.00)       | 0 (0.00) | 0 (0.00)     | 1 (2.13)        |
|   |                              | 0 (0.00)       | 0 (0.00) | 0 (0.00)     | 1 (14.29)       |
| Thoracic centrum, Incomplete ossification                 | Variation                    | 1 (0.34) ** ## | 1 (0.42) | 6 (2.30) * # | 8 (17.02) ** ## |
|   |                              | 1 (4.76) **    | 1 (5.26) | 5 (23.81)    | 3 (42.86) *     |
| Thoracic centrum, multiple sites, Incomplete ossification | Variation                    | 0 (0.00)       | 1 (0.42) | 0 (0.00)     | 0 (0.00)        |
|   |                              | 0 (0.00)       | 1 (5.26) | 0 (0.00)     | 0 (0.00)        |
| <b>Skeletal - Skull</b>                                   |                              |                |          |              |                 |
| No. Fetuses examined                                      |                              | 143            | 114      | 124          | 20              |
| No. Litters examined                                      |                              | 21             | 19       | 21           | 5               |
| <b>Skull</b>  |                              |                |          |              |                 |
| General, Isolated ossification site                       | Variation                    | 0 (0.00)       | 1 (0.88) | 1 (0.81)     | 0 (0.00)        |
|   |                              | 0 (0.00)       | 1 (5.26) | 1 (4.76)     | 0 (0.00)        |
| General, Supernumerary site                               | Variation                    | 1 (0.70)       | 0 (0.00) | 1 (0.81)     | 0 (0.00)        |
|   |                              | 1 (4.76)       | 0 (0.00) | 1 (4.76)     | 0 (0.00)        |
| Interparietal, Incomplete ossification                    | Variation                    | 0 (0.00)       | 0 (0.00) | 1 (0.81)     | 0 (0.00)        |
|   |                              | 0 (0.00)       | 0 (0.00) | 1 (4.76)     | 0 (0.00)        |



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## LEGEND

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Upper row denotes number of affected fetuses (%) and lower row the number of affected litters (%)

Trend and pairwise significance levels are determined using one-sided tests.

Statistical analysis for litter data and for fetal data ignoring the litter effects were performed by Cochran-Armitage (trend) and Fisher Exact (pairwise) tests.

\* Statistically significant at  $P \leq 0.05$

\*\* Statistically significant at  $P \leq 0.01$

Statistical analysis for fetal data including litter effects was performed by using a Generalized Linear Mixed Model, where the Dam ID was the random effect for both trend and pairwise analysis.

# Statistically significant at  $P \leq 0.05$  (litter based analysis)

## Statistically significant at  $P \leq 0.01$  (litter based analysis)

Statistical significance for the control group indicates a significant trend test

Statistical significance for a treatment group indicates a significant pairwise test compared to the vehicle control group

**\*\* END OF REPORT \*\***