FINAL REPORT

STALDREN®

ACUTE DERMAL TOXICITY STUDY
IN RATS

Date of Final Report: 06 October 2010
STUDY CODE: 10/072-002P
STATEMENT OF THE STUDY DIRECTOR

This study has been performed in accordance with the study plan, OECD Guidelines for Testing of Chemicals (No.: 402, 24th Feb. 1987), Commission Regulation (EC) No 440/2008, B.3 (L142, 30 May 2008), OPPTS 870.1200 (EPA 712-C-98-192, August 1998) and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 9/2001. (III. 30.) EÜM-FVM joint decree of the Minister of Health and the Minister of Agriculture and Regional Development which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

The acute dermal median lethal dose (LD₅₀) of the test item Staldren® was found to be higher than 2000 mg/kg body weight in male and female CRL:(WI)BR rats.

Signature: Viktória Zelenáč, M.Sc.
Study Director

Date: 04 October 2010
STATEMENT OF THE MANAGEMENT

According to the conditions of the research and development agreement between J. N. Jorenku (as Sponsor) and LAB Research Ltd., the study titled "Staldren® Acute Dermal Toxicity Study in Rats" was performed in compliance with the Principles of Good Laboratory Practice.

Signature: [Signature]  Date: 06 Oct. 2010
Christopher Banks, DABT  Managing Director
QUALITY ASSURANCE STATEMENT

Study Code: 10/072-002P
Study title: Staldren® Acute Dermal Toxicity Study in Rats
Test item: Staldren®

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

<table>
<thead>
<tr>
<th>Date of Inspection</th>
<th>Phase(s) Inspected/Audited</th>
<th>Date of report to Management</th>
<th>Date of report to Study Director</th>
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<tr>
<td>22 April 2010</td>
<td>Study Plan</td>
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<tr>
<td>27 April 2010</td>
<td>Treatment</td>
<td>27 April 2010</td>
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<td>06 October 2010</td>
<td>Final Report</td>
<td>06 October 2010</td>
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Signature: [Signature]
Istvánne Kiss, M.Sc.
On behalf of QA

Date: 06 October 2010
GENERAL INFORMATION

STUDY TITLE: Staldren® Acute Dermal Toxicity Study in Rats

SPONSOR: J. N. Jorenku
Teglvaerksej 11-13
4733 Tappernoje-Danmark
Phone: +45 56 21 40 70
Fax: +45 57 82 11 92

MANUFACTURER: J. N. Jorenku

STUDY PERFORMED BY: LAB Research Ltd.
Address: H-8200 Veszprem, Szabadságpuszta
Phone: +36 (88) 545-300
Fax: +36 (88) 545-301

STUDY DIRECTOR: Viktoria Zelenak, M.Sc.

QUALITY ASSURANCE: Istvanne Kiss, M.Sc.
On behalf of QAU

RESPONSIBLE PERSONS: Judit Tavaszi, M.Sc. - assistant scientist
Istvan Pasztor DVM - veterinary control
Peter Maslej, DVM, PhD – Head of Pathology Unit
Tamás Mészáros, PhD – Technical Team Leader of Central Dispensary
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<td>1-15</td>
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1. **SUMMARY**

An acute dermal toxicity study was performed with test item Staldren® in CRL:(WI)BR rats, in compliance with OECD Guideline No.: 402.

A limit test was carried out at 2000 mg/kg body weight (bw) in both sexes (5 rats/sex). The test item was applied as supplied as a single dermal 24-hour exposure followed by a 14-day observation period.

Clinical observations were performed on all animals at 1 and 5 hours after dosing and daily for 14 days thereafter. Body weight was measured prior to dosing on Day 0 and on Days 7 and 14. Rats were euthanized and a gross macroscopic examination performed at the end of the 2-week observation period (Day 14).

The results of the study were summarized as follows:

**Mortality**

No mortality occurred.

**Systemic clinical signs**

No clinical signs were observed after the treatment with the test item or during the 14-day observation period.

**Local dermal signs**

No local dermal signs were observed during the entire study period.

**Body weight**

The body weight and body weight gain of Staldren® treated animals did not show any test item-related effect.

**Necropsy**

There were no test item-related macroscopic findings observed at necropsy.
Conclusions

The acute dermal median lethal dose (LD₅₀) of the test item Staldren® was found to be higher than 2000 mg/kg bw in male and female CRL:(WI)BR rats.
2. **OBJECTIVE OF STUDY**

The objective of the study was to assess the acute dermal toxicity of the test item Staldren® when administered as a single 24-hour dermal treatment in rats at one or more defined dose levels followed by a 14-day observation period.

2.1. **STUDY SCHEDULE**

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Absolute Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

**PRE-EXPERIMENTAL PERIOD**

- Animal receipt: Day [-5] 22 April 2010
- Veterinary control: Day [-5] 22 April 2010
- Animal identification: Day [-1] 26 April 2010

**TREATMENT PERIOD**

- The day of treatment: Day 0 27 April 2010
- Body weight measurement: Day 0, 7, 14 27 April, 04, 11 May 2010
- Clinical observation: 1 and 5 hours after treatment, then daily for 14 days
- Necropsy: Day 14 11 May 2010
3. MATERIALS AND METHODS

3.1. TEST ITEM

Substance Name: Staldren®
Batch Number: 1603201000
Description: Granulate powder/ pale red
Expire Date: 16 March 2012
Storage conditions: Room temperature (15-25°C)
Safety Precautions: Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials were applied to assure personnel health and safety.

3.1.1. Identification, Receipt

The test item of a suitable chemical purity together with all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of test item was made by its appearance, pH, labelling and colour in the Central Dispensary Unit of LAB Research Ltd. on the basis of the information provided by Sponsor.

3.1.2. Formulation

The test item was administered as a single dose without using any vehicle. The test item was placed onto a gauze pad which was fixed with a hypoallergenic plaster on the shaved skin of the animals. The entire trunk of the animal was then wrapped with semi occlusive plastic wrap for 24 hours.

At the end of the exposure period, the area of skin treated with the test item was washed with water of body temperature.
3.1.3. Other Materials

For treatment:

Sterile gauze pad  
Lot No.: 0920329  
Expiry Date: May 2014  
Supplier: bella Hungária Kft.  
3394, Egerszalók, Külsősor u.2., Hungary

Leukosilk (hypoallergenic plaster)  
Lot No: 90440351  
Expiry Date: December 2013  
Supplier: Beiersdorf Kft.,  
1126, Budapest, Tartsay V.u. 3., Hungary

For euthanasia:

Euthasol® 40 %  
Lot No.: 07K05 7  
Expiry Date: October 2010  
Produced by: AST Beheer B.V. Oudewater Netherlands

3.2. EXPERIMENTAL ANIMALS

Species and strain: CRL:(WI)BR Wistar rats  
Source: CHARLES RIVER (EUROPE) LABORATORIES INC.  
Hygienic level at arrival: SPF  
Hygienic level during the study: Standard housing conditions  
Justification of strain: The Wistar rat is one of the standard rodent species used in acute toxicity studies  
Number of animals: 5 animals/sex  
Sex: Male and female, female rats were nulliparous and non-pregnant.  
Age of animals at study start: Young adult rats  
Body weight range at dosing: Between 200 g and 238 g  
Acclimatization time: 5 days
3.2.1. Husbandry

Animal health: Only healthy animals were used for the study. The veterinarian certified health status.
Room-Box: 245/2
Housing: Individual caging
Cage type: Type II. polypropylene/polycarbonate
Bedding: Laboratory bedding:
Lignocel® Hygienic Animal Bedding produced by J. Rettenmaier & Söhne GmbH+Co.KG (Holzmühle 1, 73494 Rosenberger, Germany;
A copy of the relevant Certificate of Analysis is maintained in LAB Research Ltd.’s archive

Light: 12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature: 22 ± 3 °C
Relative humidity: 30 - 70 %
Ventilation: 15-20 air exchanges/hour
Enrichment: Rodents were housed with deep wood sawdust bedding to allow digging and other normal rodent activities.

The temperature and relative humidity was recorded twice daily during the study.

3.2.2. Food and Water Supply

Animals received ssniff® SM R/M-Z+H "Autoclavable complete feed for rats and mice – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494 Soest Germany ad libitum, and tap water from the municipal supply, as for human consumption from 500 ml bottle ad libitum. The food is not considered to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

For contents of the standard diet see Appendix 1. The supplier provided an analytical certificate for the batch used.

Water quality control analysis is performed once every three months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József A.u.36., Hungary). The quality control results are retained in the archives at LAB Research Ltd.
3.2.3. Identification

The individual identification was performed using numbers written on the tail with a marker pen. The numbers were given on the basis of LAB Research Ltd.'s Master File for each animal allocated to the treatment groups. The cages were identified by cards containing information about study code, sex, dose group, cage number and individual animal numbers.

3.3. ADMINISTRATION OF THE TEST ITEM

3.3.1. Dosages

Justification of the doses:
The test item was not expected to be lethal at 2000 mg/kg bw. A limit test was therefore performed.

3.3.2. Experimental design

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Number of cages</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male group 2000 mg/kg bw</td>
<td>Cages 1-5</td>
<td>5</td>
</tr>
<tr>
<td>Female group 2000 mg/kg bw</td>
<td>Cages 6-10</td>
<td>5</td>
</tr>
</tbody>
</table>

A single administration was performed by the dermal route and was followed by a fourteen-day observation period. The test item was applied as supplied.

3.3.3. Procedure

The back of each animal was shaved (approximately 10% area of the total body surface) approximately 24 hours prior to treatment. The test item was applied as a single dose as supplied to the shaved skin and remained in contact with the skin for the 24-hour exposure period. Sterile gauze pads were placed on the skin of rats to cover the test item. These gauze pads were kept in contact with the skin by a patch with adhesive hypoallergenic plaster. The entire trunk of the animal was then wrapped with semi occlusive plastic wrap for 24 hours.

At the end of the exposure period, the area of skin treated with the test item was washed with water of body temperature.
3.4. OBSERVATIONS

3.4.1. Clinical Observations

Clinical observations were performed on the day of treatment at 1 and 5 hours after application of the test item and once each day for 14 days thereafter. Observations included the skin and fur, eyes and mucous membranes, the respiratory, circulatory, autonomic and central nervous system, somatomotor activity and behaviour pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

3.4.2. Measurement of Body Weight

The body weights were recorded on Day 0 (before test item administration) and on Days 7 and 14.

3.5. NECROPSY

All animals were anaesthetised with Euthasol®40% (details in 3.1.3.) and exsanguinated. After examination of the external appearance, the cranial, thoracic and abdominal cavities were opened and the appearance of the tissues and organs was observed. All macroscopic changes were recorded.

3.6. EVALUATION

Body weight and body weight gain are summarized in tabular form. Clinical signs and necropsy findings are described and summarized in tabular form.
4. ARCHIVES

The study documents and samples:
- study plan,
- all raw data,
- sample of test item,
- one original of Final Report,
- correspondence

are stored according to the Hungarian GLP and to the applicable SOP’s in the archives
of LAB Research Ltd. 8200 Veszprém, Szabadságpuszta Hungary.
After the retention time agreed with the Sponsor has elapsed, all the archived
materials listed above will be offered to the Sponsor or retained for a further period if
agreed by a contract. Otherwise the materials will be discarded.

5. DEVIATIONS TO THE STUDY PLAN

There was no deviation from the Study Plan.

6. THE PERMISSION OF THE IACUC

The Institutional Animal Care and Use Committee (IACUC) of LAB Research Ltd.
reviewed the study plan and authorised the conduct of the study.

7. DISTRIBUTION OF THE FINAL REPORT

Sponsor: A PDF document sent by email, and 1 bound certified copy,
1 unbound certified copy sent by courier.
Archive: 1 original
8. RESULTS AND CONCLUSION

8.1. MORTALITY

No mortality occurred after a 24-hour dermal exposure of Staldren® administered at 2000 mg/kg bw to CRL:(WI)BR rats followed by a 14-day observation period.

8.2. SYSTEMIC CLINICAL SIGNS

Tables for individual clinical observations are listed in Appendix 2, page 20

No clinical signs were observed after the treatment with the test item or during the 14-day observation period.

8.3. LOCAL DERMAL SIGNS

Tables for individual clinical observations are listed in Appendix 2, page 20

No local dermal signs were observed during the entire study period.

8.4. BODY WEIGHT

Tables for individual body weight and body weight gain are listed in Appendix 3, page 21

The body weight and body weight gain of Staldren® treated animals did not show any test item-related effect.

8.5. MACROSCOPIC FINDINGS

Tables for macroscopic findings are listed in Appendix 4, page 22

A single 24-hour dermal administration Staldren® to the CRL: (WI) BR rat at a dose level of 2000 mg/kg bw, followed by a 14 day observation period, was not associated with any macroscopic findings.
CONCLUSIONS

The acute dermal median lethal dose (LD₅₀) of the test item Staldren® was found to be higher than 2000 mg/kg body weight in male and female CRL:(WI)BR rats.
APPENDICES
APPENDIX 1:

CONTENTS OF THE DIET

SSNIFF® SM R/M-Z+H, AUTOCLAVABLE
Complete feed for rats and mice – breeding and maintenance"

Batch number: 928 3711
Expiry date: September 2010

NUTRIENTS

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<thead>
<tr>
<th>Nutrient</th>
<th>Value</th>
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<tbody>
<tr>
<td>Crude protein</td>
<td>19.00%</td>
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<tr>
<td>Crude fat</td>
<td>3.50%</td>
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<tr>
<td>Crude fibre</td>
<td>3.60%</td>
</tr>
<tr>
<td>Ash</td>
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<tr>
<td>Lysine</td>
<td>1.10%</td>
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<tr>
<td>Methionine</td>
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<td>Calcium</td>
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<tr>
<td>Sodium</td>
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<td>Magnesium</td>
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<td>Phosphorus</td>
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VITAMINS

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<td>Vitamin A</td>
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</tr>
<tr>
<td>Vitamin D₃</td>
<td>1000 IU</td>
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<tr>
<td>Vitamin E</td>
<td>125 mg/kg</td>
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These data are standard and guaranteed values which were provided by the supplier.
APPENDIX 2:

CLINICAL OBSERVATIONS

INDIVIDUAL CLINICAL OBSERVATIONS

STUDY CODE: 10/072-002P
TEST SYSTEM: CRL:(WI)BR RAT
TEST ITEM: Staldren®

<table>
<thead>
<tr>
<th>Cage No.</th>
<th>Sex</th>
<th>Dose Level (mg/kg)</th>
<th>Animal Number</th>
<th>Observations</th>
<th>Observation days</th>
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<td>2000</td>
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<td>2</td>
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<td>9499</td>
<td>Symptom Free</td>
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</table>

Remarks:
Severities: 1=Slight/Small/Few; 2=Moderate/Medium; 3=Marked/Large/Many
+: increased, or present; -: decreased, or absent
Treatment day = Day 0
## APPENDIX 3:

### BODY WEIGHT DATA

**INDIVIDUAL BODY WEIGHT AND BODY WEIGHT GAIN**

**STUDY CODE:** 10/072-002P  
**TEST SYSTEM:** CRL:(WI)BR RAT  
**TEST ITEM:** Staldren®

<table>
<thead>
<tr>
<th>Cage No.</th>
<th>Dose Level (mg/kg)</th>
<th>Sex</th>
<th>Animal No.</th>
<th>Body weight (g) Days</th>
<th>Body Weight Gain (g) 0-7</th>
<th>7-14</th>
<th>0-14</th>
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<td>28 341</td>
<td>55</td>
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</table>

Mean: (Body Weight (g)) | 228.0 | 279.6 | 331.0 | 51.6 | 51.4 | 103.0 |

Standard deviation: | 8.3   | 7.0   | 13.2  | 3.4  | 7.8  | 9.9   |

<table>
<thead>
<tr>
<th>Cage No.</th>
<th>Dose Level (mg/kg)</th>
<th>Sex</th>
<th>Animal No.</th>
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<td>9</td>
<td></td>
<td>Female</td>
<td>9498</td>
<td>21 231</td>
<td>20</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Female</td>
<td>9499</td>
<td>28 239</td>
<td>20</td>
<td>18</td>
<td>38</td>
</tr>
</tbody>
</table>

Mean: (Body Weight (g)) | 209.6 | 233.8 | 255.0 | 24.2 | 21.2 | 45.4  |

Standard deviation: | 11.4  | 19.8  | 24.7  | 11.9 | 8.4  | 14.2  |
# APPENDIX 4:

## MACROSCOPIC FINDINGS

**STUDY CODE: 10/072-002P**  
**TEST ITEM: Staldren®**  
**TEST SYSTEM: CRL:(WI)BR RAT**

<table>
<thead>
<tr>
<th>Cage No.</th>
<th>Dose (mg/kg)</th>
<th>Animal ID</th>
<th>Sex</th>
<th>Necropsy Date</th>
<th>External Observations</th>
<th>Internal Observations</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2000</td>
<td>9490</td>
<td>Male</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>2</td>
<td>2000</td>
<td>9491</td>
<td>Male</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>3</td>
<td>2000</td>
<td>9492</td>
<td>Male</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>4</td>
<td>2000</td>
<td>9493</td>
<td>Male</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>5</td>
<td>2000</td>
<td>9494</td>
<td>Male</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>6</td>
<td>2000</td>
<td>9495</td>
<td>Female</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>7</td>
<td>2000</td>
<td>9496</td>
<td>Female</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>8</td>
<td>2000</td>
<td>9497</td>
<td>Female</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>9</td>
<td>2000</td>
<td>9498</td>
<td>Female</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
<tr>
<td>10</td>
<td>2000</td>
<td>9499</td>
<td>Female</td>
<td>11 May 2010</td>
<td>No external observations</td>
<td>No internal observations</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
APPENDIX 5:
PATHOLOGY REPORT

INTRODUCTION

The objective of the study was to assess the acute dermal toxicity of Staldren when administered as a single 24-hour dermal treatment in rats at one or more defined dose levels.

RESULTS AND DISCUSSION

All rats survived until the scheduled termination of the study.

All animals were euthanized upon completion of the treatment period on Day 14. Rats were anesthetized with pentobarbital, followed by exsanguination. Gross pathology consisted of an external examination, including identification of all clinically-recorded lesions, as well as a detailed internal examination. Histopathological examination was not performed.

TERMINAL (DAY 14)

Macroscopic Findings

No observations were recorded at necropsy.

CONCLUSION

A single 24-hour dermal administration Staldren to the CRL: (WI) BR rat at a dose level of 2000 mg/kg bw, followed by a 14 day observation period, was not associated with any macroscopic findings.

[Signature]

Peter Maslen, D.V.M., Ph.D.
Head, Pathology Department

[Date]
APPENDIX 6:
COPY OF THE CERTIFICATE OF ANALYSIS

J.N. Jorenku

CERTIFICATE OF ANALYSIS

<table>
<thead>
<tr>
<th>Test performed:</th>
<th>Results</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>RED</td>
<td>RED</td>
</tr>
<tr>
<td>Theoretical volume</td>
<td>1.3</td>
<td>Min. 1.3  Max. 1.5</td>
</tr>
<tr>
<td>Average volume %</td>
<td>1.4</td>
<td>Min. 1.2  Max. 1.5</td>
</tr>
<tr>
<td>pH</td>
<td>6.44</td>
<td>Min. 6     Max. 8</td>
</tr>
<tr>
<td>Specific gravity (s.g.)</td>
<td>1.45</td>
<td>Min. 1.300 Max. 1.500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identity:</th>
<th>Results</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Fe</td>
<td>0.75% 0.80%</td>
</tr>
<tr>
<td>Magnesium Silicate</td>
<td>Mg</td>
<td>5.93% 5.98%</td>
</tr>
<tr>
<td>Oil</td>
<td>Oil</td>
<td>0.03% 0.05%</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>Ca</td>
<td>91.80% 91.87%</td>
</tr>
</tbody>
</table>

Test Result:

<table>
<thead>
<tr>
<th>Test Result:</th>
<th>Results</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Fe</td>
<td>2.00%</td>
</tr>
<tr>
<td>Magnesium Silicate</td>
<td>Mg</td>
<td>5.98%</td>
</tr>
<tr>
<td>Oil</td>
<td>Oil</td>
<td>0.05%</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>Ca</td>
<td>91.87%</td>
</tr>
</tbody>
</table>

We certify that the above product has been tested in accordance with J.N. Jorenku Quality standards, and found to be in order.

Test date 16/03/2010

Johani Pedersen
Biologisk Lab. Tec
APPENDIX 7:

COPY OF THE GLP CERTIFICATE

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

Based on the Inspection report and the discussion of follow up activities it is hereby certified that the test facility

LAB Research Ltd.
H-8201 Veszprém, Szabadságpuszta, Hungary

is able to carry out Physical-chemical testing, Toxicity studies, Mutagenicity studies, Environmental toxicity studies on aquatic and terrestrial organisms, Studies on behaviour in water, soil and air; bioaccumulation, Bioanalytical, Analytical and clinical chemistry testing compliance with the Principles of GLP (Good Laboratory Practice).

Date of the inspection: 13-22 October 2008.

This GLP Certificate is valid for 2 years.

Zsuzsanna Szepesi, Ph. D.
Director-General
APPENDIX 8:
COPY OF THE STUDY PLAN

LAB Research Ltd.
Address: 8200 Veszprém, Szabadságpuszta
Phone: +36 88 545 300
Fax: +36 88 545 301

STUDY PLAN
STALDREN®
ACUTE DERMAL TOXICITY STUDY
IN RATS

Date of Study Plan: 22 April 2010
STUDY CODE: 10/072-002P
## CONTENTS

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<th>Page</th>
</tr>
</thead>
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<td>5</td>
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<td>2. MATERIALS AND METHODS</td>
<td>5</td>
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<td>2.3. ADMINISTRATION OF THE TEST ITEM</td>
<td>7</td>
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<tr>
<td>2.4. OBSERVATIONS</td>
<td>8</td>
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<td>2.5. NECROPSY</td>
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<tr>
<td>2.6. EVALUATION</td>
<td>9</td>
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<td>3. GOOD LABORATORY PRACTICE (GLP) AND QUALITY ASSURANCE</td>
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</tr>
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<td>4. AMENDMENT AND DEVIATION PROCEDURES</td>
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<td>5. STUDY REPORT</td>
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<tr>
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<td>11</td>
</tr>
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<td>8. SIGNATURES</td>
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</tr>
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<td>APPENDICES</td>
<td>13</td>
</tr>
<tr>
<td>APPENDIX 1: CONTENTS OF THE DIET</td>
<td>14</td>
</tr>
<tr>
<td>APPENDIX 2: PROPOSED STUDY SCHEDULE</td>
<td>15</td>
</tr>
</tbody>
</table>
GENERAL INFORMATION

SPONSOR : J. N. Jorenku
Teglværksvej 11-13
4733 Tappernoje-Danmark
Phone: +45 56 21 40 70
Fax: +45 57 82 11 92

TEST ITEM : Staldren®

MANUFACTURER : J. N. Jorenku

STUDY PERFORMED BY : LAB Research Ltd.
Address: H-8200 Veszprém, Szabadságpuszta
HUNGARY
Phone: +36 88 545 -300
Fax: +36 88 545 -301

APPROVED BY ON BEHALF OF SPONSOR :

APPROVED BY ON BEHALF OF LAB :
Christopher Banks, DABT
Managing Director

STUDY DIRECTOR : Viktória Zelenák, M.Sc.

QUALITY ASSURANCE : Istvánné Kiss, M.Sc.

ON BEHALF OF IACUC :
Member of IACUC

PATHOLOGY : Peter Maslej, DVM, PhD

DATE: 22 April 2010
RESPONSIBLE PERSONS:  
Judit Tavaszi, M.Sc. - assistant scientist  
István Pásztor DVM - veterinary control  
Peter Maslej, DVM, PhD – Head of Pathology Unit  
Tamás Mészáros, PhD – Technical Team Leader of Central Dispensary

START OF EXPERIMENT : 27 April 2010  
END OF EXPERIMENT : Not later than 11 May 2010  
DRAFT REPORT : Not later than 25 June 2010

BASIS OF STUDY : OECD GUIDELINES FOR TESTING OF CHEMICALS (No.: 402, 24th Feb. 1987)  
OPPTS 870.1200 (EPA 712-C-98-192, August 1998)
1. OBJECTIVE OF STUDY

The objective of the study is to assess the acute dermal toxicity of the test item Staldren® when administered as a single 24-hour dermal treatment in rats at one or more defined dose levels.

2. MATERIALS AND METHODS

2.1. TEST ITEM

<table>
<thead>
<tr>
<th>Substance Name:</th>
<th>Staldren®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch Number:</td>
<td>1603201000</td>
</tr>
<tr>
<td>Description:</td>
<td>Granulate powder/ pale red</td>
</tr>
<tr>
<td>Expire Date:</td>
<td>16 March 2012</td>
</tr>
<tr>
<td>Storage conditions:</td>
<td>Room temperature (15-25°C)</td>
</tr>
<tr>
<td>Safety Precautions:</td>
<td>Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials will be applied to assure personnel health and safety.</td>
</tr>
<tr>
<td>Manufacturer:</td>
<td>see Sponsor</td>
</tr>
</tbody>
</table>

2.1.1. Identification, Receipt

The test item of a suitable chemical purity was provided by the Sponsor. All precautions required in the handling and disposal of the test item were outlined by the Sponsor. Identification of the test item was performed on the basis of information provided by the Sponsor (labelling, colour and appearance) in the Central Dispensary of LAB Research Ltd.

2.1.2. Formulation

The test item will be administered as a single dose without using any vehicle.
2.1.3. Other Materials

For euthanasia:

Name: Euthasol® 40 %
Lot No.: 07K05 7*
Expiry Date: Oct 2010
Produced by: AST Beheer B.V. Oudewater Netherlands

* should any other Lot be employed, it will not be considered as a deviation but stated in the report

2.2. EXPERIMENTAL ANIMALS

Species and strain: CRL:(WI)BR Wistar rats
Source: CHARLES RIVER (EUROPE) LABORATORIES INC.
Hygienic level at arrival: SPF
Hygienic level during the study: Standard housing conditions
Justification of strain: The Wistar rat as a rodent is one of the standard species of acute toxicity studies
Number of animals: 5 animals/sex
Sex: Male and female, female rats will be nulliparous and non-pregnant.
Age of animals at dosing: Young adult rats
Planned body weight range at dosing: Between 200 g and 300 g
Acclimatization time: At least 5 days

2.2.1. Husbandry

Animal health: Only healthy animals will be used for the study. The veterinarian will certify health status.
Housing: Individual caging
Cage type: Type II. polypropylene/polycarbonate
Bedding: Laboratory bedding
Light: 12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature: 22 ± 3 °C
Relative humidity: 30 - 70 %
Ventilation: 15-20 air exchanges/hour
Enrichment: Rodents are housed with deep wood sawdust bedding to allow digging and other normal rodent activities.

The temperature and relative humidity will be recorded twice daily during the study.
2.2.2. Food and Water Supply

Animals will receive ssniff® SM R/M-Z+H "Autoclavable complete feed for rats and mice – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494 Soest Germany ad libitum, and tap water from the municipal supply, as for human consumption from 500 ml bottle ad libitum. The food is considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

For contents of the standard diet see Appendix 1. The supplier will provide an analytical certificate for the batch used.

Water quality control analysis is performed once every three months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József A.u.36., Hungary). The quality control results are retained in the archives of LAB Research Ltd.

2.2.3. Bedding

Lignocel® Hygienic Animal Bedding will be available to animals during the study.

2.2.4. Identification

Animals will be individually identified by numbers written on the tail with an indelible pen. The numbers will be given on the basis of LAB Research Ltd.'s master file, for each animal allocated to the study.

The boxes will be identified by cards holding information on the study code, the sex of animals, the dose group, the cage number and the individual animal number.

2.3. ADMINISTRATION OF THE TEST ITEM

2.3.1. Dosages

Justification of the doses:

The test item is not expected to be lethal at 2000 mg/kg bw. A limit test will be performed. If test item related mortality occurs, a full study will be conducted according to OECD 402, Commission Regulation (EC) No 440/2008 B.3 and OPPTS 870.1200.
EXPERIMENTAL DESIGN

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Number of cages</th>
<th>Number of animals</th>
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<tbody>
<tr>
<td>Male group 2000 mg/kg bw</td>
<td>Cages 1-5</td>
<td>5</td>
</tr>
<tr>
<td>Female group 2000 mg/kg bw</td>
<td>Cages 6-10</td>
<td>5</td>
</tr>
</tbody>
</table>

A single dermal administration will be followed by at least an observation period of at least fourteen-days. The test item will be applied as supplied.

2.3.2. Procedure

The back of each animal will be shaved (approximately 10% area of the total body surface) approximately 24 hours prior to treatment. The test item will be applied as supplied as a single dose to the shaved skin and will remain in contact with the skin for the 24-hour exposure period. Sterile gauze pads will be placed on the skin of the rats to cover the test item. The gauze will be kept in contact with the skin by a patch with adhesive hypoallergenic plaster. The entire trunk of the animal will then be wrapped with semi occlusive plastic wrap. At the end of the exposure period, residual test item will be removed, using body temperature water.

2.4. OBSERVATIONS

2.4.1. Clinical Observations

A clinical examination will be made on the day of treatment, at 1 and 5 hours after the application of the test item, and at least once each day during the 14 days observation period. Additional observations may be performed on the day of application (2, 4 and 6 hours after application) should any sign of severe toxicity be observed at one hour after administration. Observations will include the skin and fur, eyes and mucous membranes, and also respiratory, circulatory, autonomic and central nervous system, and somatomotor activity and behaviour pattern. Particular attention will be directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma. The time of death will be recorded as precisely as possible.
2.4.2. Measurement of Body Weight

The body weights will be recorded on Day 0 (just before the treatment) and on Days 7 and 14.

2.5. NECROPSY

All animals (including those that die during the test or are removed from the study for animal welfare reasons) will be subjected to a necropsy and a macroscopic examination. All surviving animals will be exsanguinated after verification of narcosis following an injection of Euthasol® 40%. After examination of the external appearance, the cranial, thoracic and abdominal cavities will be opened and the appearance of the tissues and organs will be observed. All gross macroscopic changes will be recorded for each animal on the post mortem record sheets.

2.6. EVALUATION

Toxic response data will be recorded. The type, severity and duration of clinical observations will be described. Body weight and body weight changes will be summarized in tabular form. Necropsy findings will be described and summarized in tabular form.

3. GOOD LABORATORY PRACTICE (GLP) AND QUALITY ASSURANCE

In order to enable the results of this study to meet legal requirements including regulatory submission and/or safety assessment, it will be performed in compliance with the principles of Good Laboratory Practice Regulations as requested by the Sponsor and specified in national Hungarian GLP Regulations: 9/2001. (III.30.) EüM-FVM joint decree of the Minister of Health and the Minister of Agriculture and Regional Development that corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.

The Quality Assurance Unit will conduct inspections of the study plan, various phases of the study, certain repetitive operations and the report will be audited according to applicable Standard Operating Procedures.
4. AMENDMENT AND DEVIATION PROCEDURES

Planned changes to the study plan can be made at the discretion of the study director and will be agreed with the Sponsor. Detailed descriptions of all study plan amendments will be effective at the time of Study Director's signature. All such amendments will be sent to the Sponsor. The study plan amendment will be distributed and added to all copies of the study plan.

Unplanned changes to the study plan will be documented in the raw data and communicated to the Sponsor. The final report will reflect every study plan deviation, the reason for the study plan deviation and its anticipated effect on the outcome of the study.

5. STUDY REPORT

The results of the study will be reported in a detailed Final Report in line with EPA 86-5 format requirements.

The original English final report will be sent to the Sponsor and will include but will not be limited to:
- Name and address of the Sponsor, the test facility and the study schedule.
- The names of the Study Director and other scientists and supervisory personnel involved in the study.
- The signatures of the personnel of test facility, who signed the Study Plan.
- The signature of the Sponsor (if requested by the Sponsor).
- The statement of compliance, signed by the Study Director.
- The signature and statement of the management.
- The quality assurance statement, signed by the QAU.
- Characterisation of test item: The identification of the test item, either by name or code number. The concentration, purity, stability, composition and other appropriate characteristics of the test item, if the Sponsor provides data.
- A description of the animals: strain, health status, sex, source, identification, weight at commencement of the study, group size and animal husbandry.
- Details of food and water quality (including diet type/source, water source).
- Rationale for initial dose level selection.
- Details of the administration of the test item.
- Tabulation of individual and test group data, response data for each animal and dose level (i.e., number of animals exposed, number of animals showing signs of toxicity including nature, severity, duration of effects, and mortality, number of animals that were sacrificed in extremis). Time course of onset of signs of toxicity and whether these were reversible for each animal.
- Tabulation of body weight/body weight changes.
- Individual weights of animals at the day of dosing, in weekly intervals thereafter, and at the time of death or sacrifice.
- Necropsy findings for each animal, if available.
- Evaluation of results (description of computer routine used and spreadsheet tabulation of calculations).
- Discussion and interpretation of results.
- Conclusions.
- A copy of the GLP-Certificate of the test facility.
- A copy of the Certificate of Analysis if available
- Details of archiving - the storage location, list of archived data and samples.

The draft report will be sent to the Sponsor by e-mail for comment. Following receipt of comments, the final report will be issued as a PDF document sent to the Sponsor by e-mail, with one bound and one unbound hard copy sent by courier.

6. ARCHIVES

The study documents:
- study plan and any amendments,
- all raw data,
- sample of the test item,
- study report and any amendments,
- correspondence

will be archived according to the Hungarian GLP and to applicable SOP’s in the archives of LAB Research Ltd. 8200 Veszprém, Szabadságpuszta. After the retention time agreed with the Sponsor has elapsed, all the archived materials listed above will be offered to the Sponsor or retained for a further period if agreed by a contract. Otherwise the materials will be discarded.

7. DISTRIBUTION OF THE STUDY PLAN

Sponsor: 1 x PDF-file, 1x copy
Study Director: 1 copy
QAU: 1 copy
Archive: 1 original
Departments: 1 copy, each

1Central Dispensary, Scientific Documentation and Statistics, Pathology if required
8. SIGNATURES

The Study Director, LAB Research Ltd. management, QAU and IACUC will sign the Study Plan before the start of the study. The PDF version of the Study Plan will be sent to the Sponsor after the content of the Study Plan has been agreed. If the Sponsor does not sign the Study Plan within 5 working days (or as specified in the contract) then the study may be started with the signature of the Sponsor being made after study initiation.
APPENDICES
APPENDIX 1:
CONTENTS OF THE DIET

SSNIFF® SM R/M-Z+H, AUTOCLAVABLE
Complete feed for rats and mice – breeding and maintenance

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude protein</td>
<td>19.00 %</td>
</tr>
<tr>
<td>Crude fat</td>
<td>3.50 %</td>
</tr>
<tr>
<td>Crude fiber</td>
<td>4.00 %</td>
</tr>
<tr>
<td>Crude ash</td>
<td>6.60 %</td>
</tr>
<tr>
<td>Lysine</td>
<td>1.10 %</td>
</tr>
<tr>
<td>Methionine</td>
<td>0.60 %</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.00 %</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.20 %</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.20 %</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.80 %</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>25000 IU</td>
</tr>
<tr>
<td>Vitamin D₃</td>
<td>1000 IU</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>120 mg/kg</td>
</tr>
</tbody>
</table>

These data are standard and guaranteed values provided by the supplier.

These values can slightly differ in case of changing the Batch of the feed used under the duration of the study. Should any other Batch will be used, the details will be documented in draft report, but it will not be considered as a deviation to the Study Plan.
APPENDIX 2:

PROPOSED STUDY SCHEDULE

<table>
<thead>
<tr>
<th>Relative Date</th>
<th>Absolute Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE-EXPERIMENTAL PERIOD</td>
<td></td>
</tr>
<tr>
<td>Animal receipt:</td>
<td>Day [-5]</td>
</tr>
<tr>
<td>Veterinary control:</td>
<td>According to the applicable SOP.</td>
</tr>
<tr>
<td>Animal identification:</td>
<td>Day [-1]</td>
</tr>
<tr>
<td>TREATMENT PERIOD</td>
<td></td>
</tr>
<tr>
<td>The day of treatment:</td>
<td>Day 0</td>
</tr>
<tr>
<td>Body weight measurement:</td>
<td>Day 0, 7, 14</td>
</tr>
<tr>
<td>Clinical observation:</td>
<td>1 and 5 hours after treatment, then daily for at least 14 days, depending on signs of toxicity</td>
</tr>
<tr>
<td>Necropsy:</td>
<td>Just after death (if possible) or on Day 14 (surviving animals, if applicable)</td>
</tr>
<tr>
<td>Draft Report:</td>
<td>Not later than 25 June 2010</td>
</tr>
</tbody>
</table>