Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on Boehringer Ingelheim’s Policy on Transparency and Publication of Clinical Study Data.

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2. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor:</th>
<th>Individual Study Table</th>
<th>(For National Authority Use only)</th>
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</thead>
<tbody>
<tr>
<td>SSP Co., Ltd.</td>
<td>Referring to Part of the Dossier</td>
<td></td>
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<tr>
<td>Name of Finished Product:</td>
<td>Not decided</td>
<td></td>
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<tr>
<td>Name of Active Ingredient:</td>
<td>Dried extract of red vine leaves</td>
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<tr>
<td>Title of study:</td>
<td>Clinical Study of BNS003 on Swelling due to Disorder of Leg Venous Reflux</td>
<td></td>
</tr>
<tr>
<td>Investigators:</td>
<td>and others, 6 investigators in total (see page 14 in the text)</td>
<td></td>
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<tr>
<td>Study centers:</td>
<td>and others, 6 study centers in total (see page 14 in the text)</td>
<td></td>
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<tr>
<td>Publication (reference):</td>
<td>None</td>
<td></td>
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<tr>
<td>Study period:</td>
<td>July 5, 2004 (date of first subject consent)</td>
<td>January 22, 2005 (date of last follow-up completed)</td>
</tr>
<tr>
<td>Phase of development:</td>
<td>Phase III clinical study</td>
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<tr>
<td>Objectives:</td>
<td>To investigated the efficacy and safety of BNS003 on subjective symptoms such as &quot;sensation of heaviness/tiredness (dullness),&quot; &quot;tension,&quot; &quot;tingling,&quot; &quot;pain,&quot; &quot;fever&quot; or &quot;itching&quot; associated with swelling of calf and ankle due to disorder of leg venous reflux.</td>
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<tr>
<td>Methodology:</td>
<td>A multi-center cooperative open clinical study was conducted. Two capsules of BNS003 were taken orally once daily in the morning. Global improvement and adverse reactions were evaluated as primary variables.</td>
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<tr>
<td>Number of subjects (planned and analyzed):</td>
<td>Planned number of subjects eligible for efficacy analysis: 150 or more, number of subjects administered with the drug: 180, number of subjects analyzed: 179.</td>
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| Subjects and main criteria for inclusion: | (1) Inclusion criteria: 1) Persons with swelling of their calf and ankle due to the disorder of leg venous reflux, and with edematous impression by palpation who met the following conditions.  
   - Manifestation of swelling falling into Class 1 according to Porter's classification.  
   - With more than 2 symptoms of "sensation of heaviness/tiredness (dullness)," "tension," "tingling," "pain," "fever" or "itching" and a total score of ≥3 for severity by symptoms.  
   2) Persons aged 20 years or older at the time of obtaining their informed consent and available for hospital visits. Both genders are acceptable.  
   3) Persons who have consented to participating in the study in written form with good understanding of the objective of the study, the methods, and notices for the study period.  
   (2) Exclusion criteria: 1) Persons with edema not due to venous diseases of the legs (e.g., lymphedema, latent cardiac or renal insufficiency, etc.)  
   2) Persons with peripheral arterial diseases  
   3) Persons with acute phlebitis, venous ulcer, congenital vascular anomaly, or Behcet's Syndrome  
   4) Persons with "moderate" or "severe" renal, hepatic, cardiac or haematological disorder, or with a history of such disorder (Grade 3 or 4 in "Common Toxicity Criteria (CTC)," Annex 4)  
   5) Persons with diabetes mellitus (excluding those curable with dietary therapy), neuropathy, hyper- or hypocalcemia, or malignant tumors  
   6) Persons with drug or alcohol abuse  
   7) Persons with immobility  
   8) Persons with pulmonary embolism  
   9) Persons with hypersensitivity to drugs (particularly to the ingredients contained in the investigational drug)  
   10) Persons with clinical indication of requiring venous treatment such as physical application (use of elastic bandage and compression stockings) and phlebectomy (vein stripping surgery to remove vein affected with varicosis and valve insufficiency)  
   11) Persons who received venous sclerosing therapy within the last 4 weeks before starting this study  
   12) Persons who constantly use theophylline preparations, diuretics, cardiac glycosides  
   13) Persons who had changed to or initiated post-menopausal hormone replacement therapy within the last 2 months before starting this study  
   14) Persons unable to suspend the frequent use and exceeded dosage/administration of laxatives (more than 6 times) during the study period  
   15) Persons planned to undergo a surgery requiring systemic anesthesia during the study period  
   16) Women in pregnancy or nursing, or those who wish for a pregnancy during the study period  
   17) Persons who participated in another study within the last 3 months before starting this study, or who plan to participate in another study during the study period  
   18) Persons who were considered to be ineligible to be a subject for the trial by the investigator or sub-investigators |                                |
2. SYNOPSIS (continued)

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Test product, dose, and mode of administration, batch number:
- **Dose:** Each capsule contains 180 mg of dried extract of red vine leaves as an active ingredient
- **Mode of administration:** 2 capsules of the investigational drug were taken with water once daily in the morning. If the subject failed to take the drug in the morning, the missed dose was skipped. Only 2 capsules were taken in the morning of the following day without doubling the dose (not 4 capsules).
- **Batch No.:** 0331260P1

Duration of treatment: Screening period: 1 week, dosing period: 12 weeks

**Criteria for evaluation:**

(1) **Efficacy**
- **[Primary efficacy variables]**
  1) **Global improvement**
     The degree of improvement was evaluated according to the evaluation criteria for improvement by symptoms based on severity of each symptom at the time of enrollment (baseline) and in Week 12 after initiation of dosing (or at discontinuation).
- **[Secondary efficacy variables]**
  1) **Improvement rate by symptoms**
     Severity of each subjective symptom (sensation of heaviness/tiredness (dullness), tension, tingling, fever, pain or itching) associated with swelling was evaluated at visits at the time of enrollment (baseline) and in Weeks 3, 6, and 12 (or at discontinuation) of dosing.
  2) **Change of circumference measurements of calf and ankle**
     Descriptive statistics (mean, standard error, maximum, minimum, median, 25 percentile, 75 percentile) were calculated on each evaluation day. In addition, descriptive statistics were calculated for the differences between the values obtained at baseline and on each evaluation day.
  3) **Subject’s impression**
     Changes in subjective symptoms (sensation of heaviness/tiredness (dullness), tension, tingling, fever, pain or itching) associated with swelling were investigated at the visit in Week 12 of dosing (or at discontinuation) from the baseline.

(2) **Safety**
- **[Primary variables]**
  1) **Adverse reactions**
- **[Secondary variables]**
  1) **Adverse events**
  2) **Vital signs**
  3) **Laboratory tests**
2. SYNOPSIS (continued)

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**Statistical methods:**
Following statistical analyses were performed on analysis sets. Secondary variables were used as supplementary information to confirm the validity of primary variables.

**1) Demographic and other baseline characteristics**
Descriptive statistics (number of subjects, mean, standard error, minimum, median, and maximum) were calculated for continuous data in the efficacy and safety analysis sets. Also, contingency tables were prepared for discrete values.

**2) Efficacy variables**
1) **Analysis of the primary variables**
The primary analysis for efficacy was performed on the FAS (Full Analysis Set) and referential analysis on the PPS (Per Protocol Set).
   ① **Global improvement**
   Contingency tables were prepared, and frequency and percentage were totaled and calculated by category. The rate of global improvement ("moderate improvement" or better) and two-sided 95% confidence interval were also calculated.

   2) **Analysis of the secondary variables**
   ① **Improvement rate by symptoms**
   Contingency tables were prepared for each symptom evaluated for global improvement (sensation of heaviness/tiredness (dullness), tension, tingling, pain, fever or itching), and frequency and percentage were totaled and calculated by category. Improvement rate of each symptom is the ratio of "moderate improvement" or better.

   ② **Change of circumference measurements of calf and ankle**
   Descriptive statistics (mean, standard error, maximum, minimum, median, 25 percentile, 75 percentile) were calculated on each evaluation day. In addition, descriptive statistics were calculated for the differences between the values obtained at baseline and on each evaluation day.

   ③ **Subject's impression**
   Contingency tables were prepared, and frequency and percentage were totaled and calculated by category. The improvement rate ("improved" or better) and two-sided 95% confidence interval for subject's impression were also calculated.

**3) Safety variables**
1) **Analysis of the primary safety variables**
   ① **Adverse drug reactions**
   Incidence rates were calculated for adverse events of subjective symptoms and objective findings and adverse events in vital signs, ECG or laboratory test values, which are rated as being causally related to the investigational drug.

   2) **Analysis of the secondary safety variables**
   ① **Adverse events**
   Incidence rate of each adverse event was tabulated and listed, and adverse events were tabulated by severity, onset time, and causal relationship. A list of adverse events was also prepared. Serious and significant adverse events were tabulated by subject.

   ② **Vital signs**
   Incidence rates of abnormal changes in vital signs were tabulated and listed. The distribution of values before and after dosing was plotted for each measurement parameter. Descriptive statistics were calculated for vital signs at one week before initiation of dosing and in Weeks 3, 6, 9, and 12 (or at discontinuation) of dosing.

   ③ **Laboratory tests**
   Incidence rates of abnormal changes in laboratory tests were tabulated and listed. Distribution of values before and after dosing was plotted for each measurement parameter. Descriptive statistics were calculated for laboratory test values at one week before initiation of dosing and in Week 12 (or at discontinuation) of dosing.
2. SYNOPSIS (continued)

**SUMMARY - CONCLUSIONS:**

(1) **Efficacy results**
- Global improvement was rated as "remarkable improvement" by 38.5% and "moderate improvement" by 42.5% in 179 subjects of FAS. The improvement rate was evaluated as "moderate improvement" or better was 81.0% (two-sided 95% CI: 75.3 to 86.8%).
- Improvement by symptom for each swelling-associated subjective symptom was analyzed in 179 subjects with improvement of heaviness/tiredness (dullness), 156 subjects of tension, 53 subjects of tingling, 100 subjects of pain, 107 subjects of fever, and 43 subjects of itching among the FAS. The improvement of symptoms was evaluated as "moderate improvement" or better by 59.8% in heaviness/tiredness, 69.9% in tension, 79.2% in tingling, 74.0% in pain, 61.7% in fever, and 74.4% in itching.
- In 179 subjects in the FAS, the mean circumference (mean±SD) of the calf was 33.5±2.99 (cm) on the day of enrollment (the day before initiation of dosing) and was 21.9±1.82 (cm) in Week 12 of dosing, indicating a statistically significant decrease (p<0.05) in the circumference of the calf in comparison to the baseline. The mean circumference (mean±SD) of the ankle was 22.3±1.84 (cm) on the day of enrollment (the day before initiation of dosing) and was 14.8±1.84 (cm) in Week 12 of dosing, indicating a statistically significant decrease (p<0.05) in the circumference of the ankle in comparison to the baseline.
- Subject's impression was evaluated as "improved" or better by 46.4% (two-sided 95% CI: 39.1 to 53.7%) in 179 subjects of the efficacy analysis set.

(2) **Safety results**
- A total of 13 adverse drug reactions were reported in 12 out of 180 subjects of safety analysis set for subjective symptoms and objective findings. The incidence rate was 6.7% and two-sided 95% confidence interval was 3.0 to 10.3%. Individual adverse drug reactions were one case of "ear and labyrinth disorders" such as vertigo (1 case), 6 cases of "gastrointestinal disorders" such as constipation (4 cases), abdominal pain upper (1 case), and enterocolitis (1 case), 3 cases of "skin and subcutaneous tissue disorders" such as urticaria (1 case), dermatitis (1 case), and haemorrhage subcutaneous (1 case), 3 cases of "reproductive system and breast disorders" such as hypomenorrhoea (1 case), genital haemorrhage (1 case), and menometrorrhagia (1 case).
- A total of 15 adverse drug reactions were reported in 11 out of 179 subjects of the analysis set for vital signs, ECGs, and laboratory test values, and the incidence rate was 6.1% and two-sided 95% confidence interval was 2.6 to 9.7%. The individual adverse drug reactions were blood pressure systolic increased (1 case), blood pressure diastolic increased (1 case), pulse rate increased (1 case), white blood cell count decreased (1 case), white blood cell count increased (1 case), aspartate aminotransferase increased (1 case), alanine aminotransferase increased (2 cases), gamma-glutamyltransferase increased (1 case), blood lactate dehydrogenase increased (1 case), blood creatine phosphokinase increased (1 case), and protein urine positive (4 cases).
- A total of 157 adverse events (55.6%) were reported in 100 out of 180 subjects for analysis of subjective symptoms and objective findings. A total of 144 adverse events (48.9%) in 88 subjects were not related to the investigational drug. Individual adverse events were "infections and infestations" (54 cases), "metabolism and nutrition disorders" (1 case), "nervous system disorders" (16 cases), "eye disorders" (10 cases), "cardiac disorders" (1 case), "respiratory, thoracic, and mediastinal disorders" (22 cases), "gastrointestinal disorders" (14 cases), "skin and subcutaneous tissue disorders" (6 cases), "musculoskeletal and connective tissue disorders" (5 cases), "general disorders and administration site conditions" (4 cases), and "injury, poisoning, and procedural complications" (11 cases). In one out of 11 cases of "injury, poisoning, and procedural complication," the patient was hospitalized for treatment, and the event was reported as a serious adverse event, but the causal relationship to the investigational drug was evaluated as "not related."
- A total of 28 adverse events were reported in 23 out of 179 subjects (12.8%) for analysis of vital signs, ECGs, and laboratory test values. Of those, 13 adverse events (laboratory test values) (6.7%) in 12 subjects were not related to the investigational drug; they were blood pressure diastolic increased (1 case), body temperature increased (4 cases), white blood cell count decreased (1 case), red blood cell count increased (1 case), alanine aminotransferase increased (2 cases), gamma-glutamyltransferase increased (1 case), blood potassium decreased (1 case), protein urine positive (1 case), and urinary occult blood positive (1 case). No serious adverse event was observed in the vital signs, ECGs, or laboratory test values.
- One serious adverse event (joint sprain) observed in this study was judged as "not related" to the investigational drug.

Date of the report: April 21, 2005