## 2.0 Synopsis

<table>
<thead>
<tr>
<th>The Boots Company PLC</th>
<th>Individual Study Table Referring to Part of Dossier:</th>
<th>(For National Authority Use Only)</th>
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<tbody>
<tr>
<td><strong>Name of Study Drug:</strong> Ibuprofen</td>
<td><strong>Volume:</strong></td>
<td></td>
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<td><strong>Name of Active Ingredient:</strong> Ibuprofen</td>
<td><strong>Page:</strong></td>
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<tr>
<td><strong>Title of Study:</strong> A Multicentre, Open Dose-Response Evaluation of the Safety and Efficacy of Ibuprofen Syrup in Children with Juvenile Chronic Arthritis (XXM85101)</td>
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<td><strong>Investigator:</strong> On file</td>
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<td><strong>Study Sites:</strong> 9 sites in Australia</td>
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<td><strong>Studied Period (Years):</strong> November 1986 to September 1988</td>
<td><strong>Phase of Development:</strong> NA</td>
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</table>

**Objective:** The objective of this study was to assess the efficacy, safety, and tolerability of ibuprofen syrup in a dose range of 10 to 40 mg/kg body weight in children with juvenile chronic arthritis (JCA) for a minimum period of 8 weeks.

**Methodology:** This was an open-label, dose-response study of ibuprofen in children with JCA. Once a patient was identified as suitable for study entry, all current nonsteroidal anti-inflammatory agent (NSAID) therapy (including salicylates) was discontinued, and patients underwent a 2 to 10 day washout period during which paracetamol was allowed for pain relief. Ibuprofen syrup was commenced at 10 mg/kg of body weight per day. Patients returned at least every 4 weeks for assessments at which time dosage was increased until a maximum of 40 mg/kg/day or until a satisfactory response was achieved. Once dosage was stabilized, subsequent assessments were at the discretion of the physician. Paracetamol was permitted as escape analgesia.

Periodic blood samples were taken for a full blood count (including erythrocyte sedimentation rate) and routine biochemical screening plus liver function tests, and antinuclear and rheumatoid factors. Active joint assessment recorded all limbs and whether swelling and/or tenderness was present.

**Number of Subjects (Planned and Analyzed):** 44 enrolled; 42 analyzed

**Diagnosis and Main Criteria for Inclusion:** Children aged 2 to 14 years who were clinically diagnosed as suffering from any category of JCA, with active synovitis of at least 1 peripheral joint, and who were considered suitable for treatment with NSAIDs.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**
Ibuprofen, 10, 20, 30, or 40 mg/kg/day administered orally divided into 3 daily doses, usually taken at breakfast time, after school, and at bedtime. The dosage started at 10 mg/kg/day and increased by 10 mg/kg at each visit to a maximum of 40 mg/kg or until a satisfactory response was obtained.

**Duration of Treatment:** 8 weeks minimum

**Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:** None
Criteria for Evaluation:
Response was determined by the physician regarding overall disease severity using a visual analog scale; concomitant therapy required; number of active joints (including whether swelling and/or tenderness was present) compared with previous visit; discussion with both parent and child about the child's general well-being; and morning stiffness.
Safety assessments included adverse event monitoring and clinical laboratory assessments.

Statistical Methods:
The comparison of joint count at the initial visit and Months 1, 2, and 3 were analyzed using a paired student's t-test. Comparison of disease severity at the initial visit versus Months 1, 2, and 3 and for each month compared to the others was also analyzed using a paired student's t-test.

Summary/Conclusions:
The 44 children (32 girls, 12 boys) enrolled ranged from 18 months to 13 years of age (mean: 6.8 years), with a duration of illness ranging from 2 weeks to 7.5 years. The subcategories of JCA included 24 patients with pauciarticular, 17 patients with polyarticular, 2 patients with systemic, and 1 patient with spondyloarthritis. Thirty-seven children completed the minimum 8-week treatment period (mean duration: 8 months) and 7 failed to complete the minimum 8-week treatment period (2 with suspected adverse reactions, 1 with a taste complaint, 2 who did not return after the first visit, 1 for noncompliance, and 1 who changed to ibuprofen tablets after 8 weeks but only had assessments at Week 4). Twenty-one children continued on ibuprofen syrup or tablets after the end of assessments.

Efficacy Results:
The mean responding dose was 26.89 mg/kg, and the average duration for which assessments were made was 8 months (range: 8 weeks to 2+ years), with more than 60% of children having at least 5 months of treatment. The mean joint count at Month 1 (mean: 7.0) was not statistically significantly different from baseline (mean: 9.5), but it was statistically significantly improved at Month 2 and Month 3 (mean: 4.8; P < 0.05). A significant reduction in disease severity compared with baseline (mean: 4.9) was observed at Month 1 (mean: 3.7), Month 2 (mean: 2.8), and Month 3 (mean: 2.6) (P < 0.001). There was also a significant reduction in disease severity at Month 2 and Month 3 compared with Month 1 (P < 0.001).
Long term efficacy follow-up indicated that 17 children were continuing ibuprofen syrup, 4 changed to ibuprofen tablets, 7 were lost to follow-up, 8 were in remission, and only 2 required a change to other medication because of limited benefit.
Safety Results:
Two patients were withdrawn from treatment because of suspected adverse reactions, which in the investigator's opinion, may have been related to drug therapy. The first patient (male, 11 years of age) had abdominal pains and nausea after 6 weeks (30 mg/kg/day) and was admitted to the hospital for further tests because of the severity of his arthritic disease. An endoscopy revealed a reddened area, and mild gastritis was diagnosed. The patient was withdrawn from the study and started on other nonsteroidal medication. The second patient (female, 2 years of age) developed feverish diarrhea after 6 weeks of treatment (30 mg/kg/day). The investigator attributed this event to a viral illness and not ibuprofen; however, the patient's mother attributed it to ibuprofen and discontinued the medication. The patient was discontinued from the study, re-entered after a 2-year interval, and continued on treatment for more than 4 months without recurrence. One additional patient discontinued study medication after 4 days because of "unpleasant taste."

Other adverse events reported during the study were listed as follows: viral rash for 2 patients, headache for 2 patients, abdominal discomfort for 1 patient, and mouth ulcer for 1 patient. All of these events were considered not related to study drug by the investigator.

Several children had slight abnormalities in some biochemical parameters (mainly alkaline phosphatase, serum creatinine, and erythrocyte sedimentation rate); however, these were considered common in JCA disease states.

Long-term safety follow-up (beyond the minimum 8-week treatment period) reports of adverse events included 4 children with concurrent eye problems: iritis diagnosed after 14 weeks of treatment for 1 patient (female, 4.5 years of age), chronic iridocyclitis for the previous 7 years for 1 patient (female, 10 years of age), uveitis for past 2 years for 1 patient (female, 9 years of age), and iritis that developed after 31 weeks of treatment (female, 3 years of age).

Conclusions:
Although this study was an open controlled study, it confirmed the safety of ibuprofen administered over long periods of time in children. The study also confirmed the efficacy of ibuprofen in controlling clinical symptoms of pain and inflammation in most children at an average daily dose of 25 mg/kg. The availability of ibuprofen in a liquid form that enables easy titration of dosage, particularly in young children, should ensure better patient compliance and control of symptoms.

Ibuprofen syrup in a dose range of 10 to 40 mg/kg/day proved to be a safety alternative to aspirin in children with JVA, providing a palatable, easily titrated, appropriate form of nonsteroidal anti-inflammatory therapy for children.