1. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Solvay Pharmaceuticals</th>
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<tbody>
<tr>
<td>Name of Finished Product:</td>
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<tr>
<td>Name of Active Ingredient:</td>
<td>Lactulose crystalline</td>
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<tr>
<td>Title of Study:</td>
<td>An open, randomized group comparative study with lactulose syrup (Duphalac®) versus lactulose crystalline in constipated children.</td>
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<td>Investigators:</td>
<td>Removed for privacy reasons</td>
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<td>Study center(s):</td>
<td>Removed for privacy reasons</td>
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<tr>
<td>Publication (reference):</td>
<td>Not applicable</td>
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<tr>
<td>Studied period (years):</td>
<td>1993-1995</td>
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<td>Phase of development:</td>
<td>III</td>
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<td>Objectives:</td>
<td>To evaluate and compare the efficacy, tolerance, flavor and compliance of lactulose powder with lactulose syrup in the treatment of chronic constipation in children.</td>
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<td>Methodology:</td>
<td>Open, randomized, parallel group comparative study.</td>
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<td>Number of patients (planned and analyzed):</td>
<td>Planned: 60 patients totally (30 in each treatment group)</td>
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<td>Analyzed: 31 in the lactulose syrup group, 28 in the lactulose powder group. CRF of the remaining one patient was missing.</td>
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<td>Diagnosis and main criteria for inclusion:</td>
<td>Chronically constipated children between 7 and 14 years old.</td>
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<td>Test product, dose and mode of administration, batch number:</td>
<td>Lactulose powder, 10 g, administered orally once daily. In case of non-response after 48 hours, the dose was to be doubled to 20 g daily. Batch numbers used for lactulose powder were FPP92A009 and FPP95A270.</td>
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<td>Duration of treatment:</td>
<td>Four weeks</td>
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<tr>
<td>Reference therapy, dose and mode of administration, batch number:</td>
<td>Lactulose syrup, 10 g, administered orally once daily. In case of non-response after 48 hours, the dose was to be doubled to 20 g daily. The lactulose syrup was provided as trade medication (Duphalac®).</td>
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<td>Criteria for evaluation:</td>
<td>Efficacy: Efficacy was to be assessed from the number of stools and the consistence of stools. Additional criteria were patient's assessment of flavor (taste, sweetness) and convenience of use as essential items for compliance, investigator's assessment of treatment efficacy, and the percentage of non-responders after 48 and 96 hours.</td>
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SAFETY: Safety was to be assessed from the occurrence of adverse events as recorded on the signs and symptoms checklist.

Statistical methods: Wilcoxon Rank Sum Test, Signed Ranks Test and Fisher's Exact Test

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:
Both drugs were similarly effective in the therapy of constipation in children concerning stool frequency (no statistically significant difference). Stool frequency (number of stools per week) increased statistically significantly when using lactulose powder or lactulose syrup compared to baseline. Stool consistency improved to a higher percentage of normal and thin stools compared to baseline (more hard stools); similar in both treatment groups.

The efficacy of both formulations was rated very effective and effective by the investigator in more than 90%.

Patients’ assessment of flavor and convenience did not differ between treatment groups, although lactulose powder was rated as somewhat less sweet than lactulose syrup.

The responder rate after 48 hours could not be evaluated due to inconsistent data. A high number of protocol deviations and data inconsistencies that have not been clarified occurred during the trial. The trial was not completely performed according to GCP.

SAFETY RESULTS:
Adverse events were reported in 42 (71.2%) patients. In the lactulose powder group 20 (71.4%) patients and 22 (71.0%) in the lactulose syrup group reported adverse events. Most often reported adverse events (mild to moderate) were flatulence, meteorism and diarrhea. No difference between the treatment groups could be detected. No serious adverse event was reported. One patient in the lactulose powder group discontinued the drug due to meteorism.

CONCLUSION:
- Lactulose powder and syrup were similarly effective concerning stool frequency.
- Both drugs statistically significantly increased the stool frequency compared to baseline.
- Stool consistency also improved when using either the powder or lactulose syrup compared to baseline.
- Both drugs were well tolerated and safe.

Date of the report: May 1997