SYNOPSIS

Name of Sponsor:
Solvay Healthcare Ltd.
Hamilton House, Gaters Hill
West End
Southampton SO18 3JD, UK

Name of Finished Product:
Duphalac® Powder

Name of Active Ingredient:
Lactulose

Study Title:
Pilot study of lactulose effects on the bacterial content of stools of children suffering from cystic fibrosis, both antibiotic-treated and untreated: comparison with healthy children.

Publications (Reference):
Not applicable

Study Period:
02 SEP 1998 (first subject first visit) to 22 MAR 1999 (last subject last visit)

Phase of Development:
Phase IIIb

Objectives:
The primary objectives of this study were to compare the bacterial species and counts in stools from cystic fibrosis children (antibiotic-treated and untreated) with healthy controls, both before and after treatment with lactulose.

The secondary objectives were to compare between groups the secondary variables of stool pattern (frequency and consistency), antibiotic use in the preceding year, and height, weight and body mass index (BMI) (current, last year’s from medical notes and derived growth velocity).

Safety and tolerability were to be evaluated over the treatment period of 3 weeks.

Methodology:
This was a pilot parallel group, open study including three groups of patients and one group
of healthy children, recruited in 1 center specialized in cystic fibrosis:

There was an initial visit at the specialized department of the hospital for checking of inclusion/exclusion criteria, stool characteristics and collection of stool sample.

After the 3 weeks of regular treatment with lactulose dry at home, the children came back for the final visit, stool characteristics, review of possible clinical adverse events (AEs) and collection of stool sample.

The stool samples were taken during the visit and were conditioned as soon as possible (diluted and stored at -70°C), for microbacteriological identification and quantification of bacteria, in the department of microbiology of the hospital.

**Number of Subjects (Planned, Consented, Randomized and Analyzed):**

It was planned to include 40 subjects.

All subjects consented sample: 20 subjects (six in group A, three in group B, eight in group C and two in group D). There were no available data regarding the treatment group of one subject.

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion criteria for cystic fibrosis**

1. Signed ICF
2. Males and females
3. Children aged between four and seventeen (inclusive)
4. All ethnic groups
5. Adequate symptom control
6. The three groups were:
   - **Group B:** 11 cystic fibrosis children who are not taking oral or inhaled antibiotics and who have not received antibiotics for at least one month prior to the study.
   - **Group C:** 11 cystic fibrosis children who are not taking oral antibiotics and have not received antibiotics for 1 month prior to the study but who are being treated with regular inhaled Colomycin® (at usual dosages).
   - **Group D:** 11 cystic fibrosis children who are taking Ciprofloxacin® and who have been treated with for at least 10 days.

**Inclusion criteria for healthy siblings**

Same criteria except n°5 and 6. The group was:

**Group A:** 11 healthy non-cystic fibrosis siblings of children known to have cystic fibrosis, who have no history of gastrointestinal disorders and have not received antibiotics for one month prior to the study; control group.
Test Product, Dose and Mode of Administration, Batch Number:
The substance was supplied as powder in pots of 350 g, with a measure spoon for 3, 5, 6, 10 g.
The daily dosage was 6 g (1 x 6 g or 2 x 3 g) for children from 4 to 9 years and 10 g (1 x 10 g or 2x 5 g) for children from 10 to 17 years old.
The batch number of the supplies was 97F152.

Duration of Treatment:
The planned treatment period was three weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable

Criteria for Evaluation

Efficacy:
The primary variables were the fecal bacterial counts as follows:

1. total bacteria count
2. total obligate anaerobes (Bacteroides, Bifidobacteria, Clostridia, Lactobacilli)
3. total facultative anaerobes (Enterobacteria, Enterococci, Pseudomonas)

The secondary variables, stool pattern (frequency and nature), height/weight/BMI velocity in preceding year and antibiotic use in preceding year were to be summarized and compared descriptively.

Safety:
Adverse events (AEs) were to be reported

Statistical Methods:
Statistical analyses described in the protocol were not performed. The available study data were presented by listings only. No efficacy data were presented.

The study data were entered in MS Excel Office 2003 and transferred in statistical analysis system (SAS). The datasets were archived in Solvay Clinical Data Platform (SCALA). As the study was performed more than 10 years ago, no data validation and cleaning was done and no data review was performed.

Analysis data sets and statistical output were produced by the Global Biometrics department Abbott Healthcare Products B.V., Weesp, using the SAS® system Version 9.2.

The All Subjects Consented sample consisted of all subjects who gave their informed consent. This sample was to serve as Safety sample for the safety presentation.

Listings were created displaying drug exposure and treatment duration, the incidence of AEs and demographic data of the subjects.

Summary - Conclusions

Efficacy Results:
No analysis regarding efficacy data were performed and therefore no efficacy data are
presented in this report.

Safety Results:
The only one reported AE “respiratory exacerbation” led to discontinuation of study drug and was considered by the investigator as mild in severity and with no relationship with study drug. The subject recovered completely.

Conclusion:

• The study was stopped prematurely because of a very low subject recruitment rate. Due to the small number of subjects and the absence of data validation no analyses of efficacy were performed.

• The available safety data in this study did not show any safety concerns of lactulose.