SYNOPSIS

Name of Company: Zambon S.p.A., Bresso, Italy	**TABULAR FORMAT**		**(For National Authority Use only)**
Name of Finished Product: Prefolic®, 15 mg tablets	**REFERRING TO PART OF THE DOSSIER**	5.3	
Name of active substance(s):	**Volume:**		
5-methyltetrahydrofolate (5-MTHF)	**Page:**		

Title of the study:
A multicentre, open-label study to evaluate the efficacy and safety of 5-MTHF administration, added on to the individual established therapy, on plasma homocysteine levels in patients with congenital homocystinuria

Investigator(s):
Principal Investigator: Prof. Olaf Bodamer, Division of Biochemical and Paediatric Genetics, Vienna University Medical School, AKH, Währinger Gürtel 18-20, A-1090 Vienna, Austria

Study centres:
Five clinical centres (Austria, Slovakia, UK, Hungary, Italy)

Publication (reference):

Studied period (years): **2006 – 2007**	**Date of first enrolment:** **Date last patient completed:**	22NOV06 07JUN07	**Phase of development:** **II**

Objectives:
To investigate the efficacy and safety of a 3 month 5-MTHF treatment in terms of decreasing total plasma homocysteine (tHcy) in homocystinuric patients, while co-administered with an individual established therapy as a folic acid substitute

Methodology:
multi-centre, open label, efficacy and safety study of a 3-month treatment with 5-MTHF 15 mg administered once a day to patients with homocystinuria

Number of subjects (planned and analysed):
Twenty-two (22) patients were planned. Four patients were enrolled and completed the study. The study was interrupted upon Sponsor decision and no further patients were enrolled.

Main Selection Criteria:
Patients with congenital homocystinuria were enrolled in the study if they met the following criteria:

Inclusion criteria:

1. signed informed consent (signed by patient and countersigned by legal representative in case of patients below age of consent);
2. ≥16 years of age
3. classical (non-pyridoxine responsive) homocystinuria (CBS deficiency)
4. stable clinical condition
5. willing to complete all phases and all procedures of the study
6. on B6, B12, betaine and folic acid treatment
7. ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study

Exclusion criteria

1. multivitamin supplements, folic acid or creatine treatment which could interfere with or create difficulties in efficacy or safety assessment of the study drug
2. episodes of thrombosis and/or embolism one year before inclusion in the study
3. history of drug and/or alcohol abuse during the 6 months before the beginning of the study
4. patients with serious illness(es) or diseases (e.g., haematological, renal, hepatic, respiratory, endocrine, psychiatric) that could interfere with, or put patients at additional risk for their ability to receive the treatment outlined in the protocol
5. donation or receipt of blood or blood products (within 2 months before baseline)
6. pregnant or lactating female
7. participation in the evaluation of any drug for 3 months prior to the start of the study
8. substantial changes in eating habits within the past 4 weeks.

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Test product, dose, mode of administration, batch N°:
Prefolic®, 5-Methyltetrahydrofolate (5-MTHF), 15 mg tablets, Zambon Italia S.r.l., Italy.
Batch N. 336318E02, expiry date SEP08.
5-MTHF (15 mg tablets) was administered once a day during a period of 3 months

Reference therapy, dose, mode of administration, batch N°:
Not applicable

Criteria for evaluation (efficacy):
Primary efficacy criterion: levels of tHcy in plasma at 3 months vs. baseline
Secondary endpoint criteria: levels of plasma tHcy, SAH, SAM, methionine, t-PA, PAI-1, PT, PTT, fibrinogen and coagulation factor V and urine homocystine and 8-iso-PGF2α
Compliance variable: Plasma levels of folate as total folate and folate/5-MTHF ratio and their change from baseline

Criteria for evaluation (safety):
Laboratory parameters at screening, day 1, and 90 (final visit); ECG: at screening and final visit; vital signs (BP, HR, BW): at screening, baseline, day 14, 30 and 90 (final visit); AEs including Treatment Emerged AE (TEAE) during the entire study.

Statistical methods:
The statistical analyses were performed using SAS® version 9.1.2. Individual data were listed and summarised by descriptive statistic or frequencies, when applicable.
No statistical analysis as planned in the protocol and statistical analysis plan was carried out because the study was interrupted prematurely.

Results:
This multicentre, open-label study had been planned to evaluate the efficacy and safety of Prefolic® (5-MTHF) administration, added on to the individual established therapy, on plasma homocysteine levels in patients with congenital homocystinuria. Because of the difficulties to find naïve/never treated patients, 5-MTHF activity was tested after withdrawal of folic acid/folate from the individual standard treatment, while the other components of the individual standard therapy (betaine, B6 and B12) were maintained. During the folic acid wash-out a significant/marked increase of the plasma tHcy levels was expected. This study design was considered correct in ethical terms because did not require the patients to entirely withdraw the individual therapy, and the tHcy level monitoring during wash-out assured the safety of the patients.

However, since homocystinuria is a very rare inborn genetic defect, it had been impracticable to enrol the patient sample size necessary to assess the primary clinical end-point. Only 4 out of the 22 planned patients have been recruited. In addition, preliminary results obtained in the 4 enrolled patients (see Table 1 and Table 2 below) showed that the wash-out period did not modify the plasma tHcy levels, the primary clinical end-point.

The difficulty in recruiting patients and the unexpected preliminary results on homocysteine plasma levels during the wash-out period, led to the decision to discontinue the clinical study, which was interrupted in all countries concerned. The concerned Ethical Committees and Competent Authorities were informed.

The 4 patients enrolled completed the study per protocol. One patient belonged to clinical centre N. 1 (Vienna, Austria) and 3 to clinical centre N. 2 (Bratislava, Slovakia). No patient was enrolled in any of the other clinical sites.

SYNOPSIS (cont.)

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Results, cont.:
Total plasma homocysteine data for the 4 enrolled patients determined locally at each clinical laboratory centre were collected and are presented in the tables below for descriptive purposes only.

Table 1 Total homocysteine (tHcy) plasma levels (µmol/L) during the study: Centre N. 1

Subject N.	Screening	Visit 2 a day -10	Visit 2 b day -7	Visit 2 c day -5	Visit 2 d day -3	Visit 2 e day 0	Visit 3 day 1*	Visit 4 day 14	Visit 5 day 30	Visit 6 day 90
101	184.0	212.0	191.0	175.0	196.0	174.0	211.0	188.0	166.0	221.0

Normal range: 0.0 - 16.0 µmol/L
*Visit 3/day 1: baseline

Table 2 Total homocysteine (tHcy) plasma levels (µmol/L) during the study: Centre N. 2

Subject N.	Screening	Visit 2 a day -10	Visit 2 b day -7	Visit 2 c day -5	Visit 2 d day -3	Visit 2 e day 0	Visit 3 day 1*	Visit 4 day 14	Visit 5 day 30	Visit 6 day 90
201	20.6	19.2	14.4	11.7	12.2	20.8	22.2	16.7	16.2	17.9
202	101.5	95.4	79.7	101.3	106.4	60.2	31.0	9.9	6.5	12.5
203	149.9	40.6	82.6	95.6	91.2	65.3	25.7	141.0	143.0	96.0

Normal range: 5.0 - 15.0 µmol/L
*Visit 3/day 1: baseline

Results of other measurements, i.e. plasma PT, PTT, factor V, fibrinogen, methionine and urinary homocysteine and creatinine, are also listed in this report. For some parameters only partial data have been collected.

Safety data have been collected during the study for the 4 enrolled patients. No AEs associated to study treatment were reported. No SAEs occurred. In addition no relevant effects of study treatment on vital signs, body weight, ECG recordings or laboratory parameters were observed.

Conclusions:
The study was interrupted prematurely upon mutual decision of the study Principal Investigator and Sponsor. The primary efficacy endpoint of the study could not be assessed and as a consequence no conclusion on the efficacy of the study treatment could be drawn.

Safety data obtained in this study for the 4 patients enrolled confirm a favourable tolerability profile for Prefolic® (5-MTHF) when administered at doses of 15 mg per day for 3 months.

Date of the report: Final version, 15SEP08