Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Memfit®				
Name of active ingredient: Standardised Ginkgo biloba extract (GK501) containing 24% ginkgoflavone glycosides and 6% terpene lactones		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 14 May 2003	**Number:** U03-1523	**Study period (years):** 2002		

Title of study:	Efficacy and safety of *Ginkgo biloba* film-coated tablets (2 x 60 mg daily p.o.) in improving cognitive functions and neuropsychological functioning of middle-aged cognitively intact adults: a double-blind, placebo-controlled, parallel group, randomised trial.
Investigator: / Study centre:	[redacted] USA
Publication (reference):	To date, there have been no publications based on this study.
Clinical phase:	III
Indication:	To improve cognitive functions, particularly those related to memory and mental performance, e.g., improved mental capacity and endurance, prevention of mental fatigue, improved retention of information, and reduction of forgetfulness.
Objectives:	To assess the efficacy and safety of *Ginkgo biloba* film-coated tablets in improving cognitive function and neuropsychological functioning of middle-aged, cognitively intact adults
Methodology:	This was a randomised, double-blind, placebo-controlled, parallel group trial designed according to international GCP.
No. of subjects entered:	120
total:	120
each treatment:	60
Diagnosis and main criteria for inclusion:	Male and female healthy, middle-aged (40-60 years old) subjects, with no known clinically significant pathology. Subjects had to show they were cognitively intact by scoring ≥ 28 on the Mini-Mental State Examination (MMSE) questionnaire.
Test product:	Memfit® (GK501)
dose:	2 x 60 mg tablet daily (morning and lunchtime)
mode of admin.:	p.o.
batch no.:	130202
Duration of treatment:	56 days

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Reference therapy: placebo (without active ingredients)

dose: 1 tablet twice daily (morning and lunchtime)

mode of admin.: p.o.

batch no.: 130202

Criteria for evaluation:

Efficacy:

- The baseline-adjusted change in the measurement of the cognitive test/ Cognitive Drug Research (CDR) factor Power of Attention at day 56 averaged from values at pre-dosing (-1:30) and at 2, 4 and 6 hours post-dosing (primary endpoint).
- The baseline-adjusted changes in CDR factors at days 28 and 56 (including the Power of Attention factor at day 28) as measured by the CDR tasks, averaged from values pre-dosing (-1:30) and at 2, 4 and 6 hours post-dosing.
- The baseline-adjusted changes in Stroop Color and Word Test at day 56.
- The baseline-adjusted changes in the Selective Reminding Test and Trail Making Test (Parts A and B) at day 56.

Safety:

- Adverse event reporting, general clinical assessment at the start and the end of the study and at all visits; laboratory data (hematology, blood chemistry) at the start and at the end of the study.
- Tolerability assessment by the subject and the Investigator at days 28 and 56.

Statistical methods: An intent-to-treat (ITT) analysis was performed, which included data from all subjects who received study medication and on whom reported efficacy data is available. A per protocol (PP) analysis was completed in which subjects were excluded for non-compliance and/or significant violations of the protocol. Baseline comparability of treatment groups was assessed by analysis of variance (ANOVA). Univariate repeated measures ANOVA for CDR factors were analysed, followed by the calculation of contrasts for each time point, two-sample t-tests for endpoints from the neuropsychological tests, the Wilcoxon test for tolerability assessment; descriptive statistics; and tabulation of incidence, severity and causal relationship of adverse events.

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SUMMARY - CONCLUSIONS:

Efficacy results:

In the primary endpoint, there was no significant difference between treatment groups in the CDR factor Power of Attention at day 56 ($p = 0.864$), and in fact, completion time increased when a decrease in speed was expected. The *Ginkgo biloba* group increased speed by 1.75% ($p = 0.010$) and the placebo group increased by 1.57% ($p = 0.020$). No significant within or between group differences occurred at day 28, a secondary endpoint, at which the *Ginkgo biloba* group increased 0.49% and the placebo group increased 0.21% as compared to baseline values.

For the other CDR factors, the difference between treatment groups in the Quality of Episodic Secondary Memory was significant at day 28 ($p = 0.018$) and there was a trend towards significance at day 56 ($p = 0.093$). Within the *Ginkgo biloba* group, this factor increased significantly at days 28 and 56 (7.3% and 7.6%, respectively, both $p = 0.001$). In the placebo group, increases at days 28 and 56 were 2.3% ($p = 0.114$) and 3.4% ($p = 0.043$), respectively.

In addition, the Quality of Working Memory in the *Ginkgo biloba* group increased 1.65% at day 28 ($p = 0.037$) and 1.10% at day 56 ($p = 0.074$), as compared to baseline. Between group changes were not significant due to small increases in the placebo group. For the Speed of Memory Processes, significant within-group improvements were displayed in both groups at days 28 and 56 (all $p = 0.0001$), which cancelled out any between group differences.

Other secondary endpoints were the neuropsychological tests at Day 56 as compared to baseline (Day 0), including the Stroop Colour and Word Tests, the Trail Making Tests (parts A and B), and the Selective Reminding Tests. No statistically significant results were seen.

Safety results:

Treatment-emergent adverse events (AEs) were reported by 23 (38.5%) of subjects enrolled in the study [17 (28.3%) from the *Ginkgo biloba* group and 6 (10.2%) from the placebo group]. The most frequently observed adverse event (AE) was fatigue, which occurred in 3 (5.0%) subjects in the *Ginkgo biloba* treatment group alone (all rated as mild intensity). Secondary to this, dizziness (excluding vertigo) and headache not otherwise specified (NOS) each occurred in 2 (3.3%) of the *Ginkgo biloba* subjects (all rated as moderate intensity).

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SUMMARY - CONCLUSIONS:

Safety results (continued):

Only 6 types of AEs were graded as severe in intensity [4 (6.7%) *Ginkgo biloba* and 2 (3.4%) placebo subjects]. Those deemed not related to the study medication included one incidence each of retinal detachment and migraine NOS in the *Ginkgo biloba* group and one case of nasal septum perforation in the placebo group. Of those that were considered related to the study medication, there was one instance of upper abdominal pain and two instances (in one subject) of urticaria NOS in the *Ginkgo biloba* group and two cases of headache NOS in the placebo group. Only one subject discontinued due to an AE, that being a cluster of dizziness, headache, and nausea (all of moderate intensity).

No serious AEs occurred during this study. There were no significant differences between groups in vital signs, ECG parameters, or laboratory values.

Conclusions:

In summary, no improvement was seen in the primary endpoint, the difference between *Ginkgo biloba* and placebo groups in the CDR factor Power of Attention, in middle-aged, cognitively intact adults after 56 days of Memfit® (GK501) 60 mg (*Ginkgo biloba* extract) administered twice daily. Curiously, completion time increased when a decrease in speed was expected, and this increase was significant within each group at day 56 as compared to baseline.

The Quality of Episodic Secondary Memory exhibited significant differences between treatment group responses at day 28 and significant changes within the *Ginkgo biloba* group on both days (~7.5% increases), as compared to baseline. As the placebo group also improved significantly at day 56 (3.4% increase), this allowed for only a trend towards significance between groups at day 56. In addition, the Quality of Working Memory significantly improved in the *Ginkgo biloba* group at day 28 and a trend towards improvement was seen at day 56 (increases of 1.65% and 1.10%, respectively), as compared to baseline. Between group changes were not significant due to small increases in the placebo group. For the Speed of Memory Processes, significant within-group improvements were displayed in both groups at days 28 and 56, which cancelled out any between group differences.

No statistically significant differences between treatment groups were observed from baseline to end-of-treatment for the neuropsychological tests, including: the Stroop Colour and Word Tests, Trail Making Tests (parts A and B), and the Selective Reminding Tests.

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SUMMARY - CONCLUSIONS: Conclusions: (continued):	This study is to our knowledge the first to be done utilising a chronic regimen of *Ginkgo biloba* extract alone in a cognitively healthy, middle-aged population. Therefore, the significant results seen in the Quality of Episodic Secondary Memory and the within group improvements in the Quality of Working Memory are noteworthy for this new combination of variables.			