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: Viseral®				
Name of active ingredient: 160 mg bilberry extract standardised to a content of 25% anthocyanidines		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 15th January 2001	**Number:**	**Study period (years):** December 1999 to July 2000		

Title of study:	Efficacy of a bilberry extract standardised to a content of 25% anthocyanosides in improving the night vision of healthy volunteers: a double-blind, randomised, placebo-controlled, crossover trial over 2 x 28 days.
Investigator:	[redacted]
Study centre:	1 Centre in [redacted] Germany
Publication (reference):	none
Clinical phase:	II
Objectives:	To determine the efficacy of standardised bilberry extract in improving night vision and to evaluate its tolerability and safety.
Methodology:	Randomised, double-blind, placebo-controlled, crossover study over 28 days; 28 days washout between treatment periods. Assessments at Day 1 and 28, at Day 57 and 84
No. of subjects entered:	
total:	119
each treatment:	119
Diagnosis and main criteria for inclusion:	Healthy, young and collaborative subjects
Test product:	Bilberry extract capsules, 160 mg (25% anthocyanosides)
dose:	1 capsule once daily in the morning
mode of admin.:	p.o.
batch no.:	M 401/3, 01PV/010100
Duration of treatment:	2 x 28 days
Reference therapy:	Placebo capsules, visually matching the verum
dose:	1 capsule once daily in the morning
mode of admin.:	p.o.
batch no.:	M 401/1, 01PP/010100

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Criteria for evaluation:

Efficacy:

Primary

Change of dark adaptation of the pupil from Day 1 (baseline) to Day 28 during Period 1 and from Day 57 (baseline) to Day 84 during Period 2 using the method of the Dark Adaptation Goggles. At least 0.3 log difference to prove efficacy of the product.

Secondary

Pupillography (dark adaptation using dark flashes) on Day 1 (baseline) and 28 during Period 1 and Day 57 and 84 during Period 2

Mesoptometry on Day 1 (baseline) and 28 during Period 1 and Day 57 and 84 during Period 2

Subjective Efficacy Rating Questionnaire (VAS) on Day 1 (baseline) and 28 during Period 1 and Day 57 and 84 during Period 2

Clinical Global Impression (CGI) scale Day 1 (baseline) and 28 during Period 1 and Day 57 and 84 during Period 2

Safety: Adverse events, overall tolerability, clinical Global Impression

Statistical methods: The primary efficacy variable and all continuous variables were evaluated by analysis of covariance. The clinical global improvement was summarised by treatment group and analysed by descriptive methods.. Baseline characteristics, adverse events and tolerability were also summarised by treatment group.

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SUMMARY - CONCLUSIONS:

Efficacy results:

For the primary efficacy endpoint of this study, the lower asymptote of the dark adaptation curve after green light stimuli for the ITT population, no significant difference was observed between the patients' responses when receiving Bilberry extract and when receiving Placebo (p=0.3119). The effects of sequence and patient within sequence were not statistically significant, with p-values of 0.5018 and 0.1515, respectively. Both period and individual baseline were statistically significant with p-values of 0.0036 and 0.0002, respectively. The 95% confidence intervals of the adjusted mean changes ranged from -0.191 to -0.069 (Bilberry) and from -0.146 to -0.025 (Placebo).

A significant treatment effect was seen for the secondary parameters initial pupil diameter (p=0.0243; 95%-CI of the mean changes –0.100 to 0.036 for Bilberry, -0.212 to –0.075 Placebo) and subject's efficacy rating for visual contrast (p=0.0472; 95%-CI of the mean changes 46.5 to 49.1 for Bilberry, 48.4 to 50.9 Placebo).

Safety results:

No serious adverse events or deaths occurred. From the 58 adverse events reported by the 49 patients, 91% were of mild or moderate intensity, and mainly concerning the gastro-intestinal system (abdominal pain, constipation) or skin and appendages (skin disorder, photosensitivity). A relationship with the test product was suspected in 19 (Bilberry) and 15 adverse events (Placebo), respectively. The tolerability of Bilberry and Placebo was rated very good by 82.8% and 85.3% of the subjects of the safety population, respectively. No subject reported poor tolerability for Bilberry, whereas two subjects did so for Placebo.

Conclusions:

There were improvements of contrast vision as well as of visual acuity with both treatments and both treatments were well tolerated. However, the results of the study failed to show a significant effect of bilberry extract on night vision. The two significant treatment effects observed probably occurred by chance. This finding is in contrast to previous studies reporting significant effects of bilberry extract on night vision and other ophthalmologic parameters. The inconclusive results may be explained by a dose regimen based on too low a dose, or by the fact that the subjects did not suffer from deficient night vision.