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Memorandum

DATE: 8 May 1998

TO: NDA 20-895

SUBJECT: Amendment to clinical review of 22 January 1998: Effects of sildenafil on the electroretinogram in Study 148-232.

Because of some public concern about the NDA clinical review's description (22 January 1998) of changes in the ERG in Study 148-232, the sponsor has asked this reviewer to re-examine this aspect of this study. The review is based upon the final study report dated 22 August 1997, for Study 148-232, entitled "A randomised, double-blind, placebo-controlled, crossover pilot study to investigate the effects of a single oral tablet dose of sildenafil (200mg) on visual function (electroretinogram, photostress, visual field and colour discrimination tests) in healthy male volunteers and patients with diabetic retinopathy", although the results presented were only those for the 8 normal volunteers.

Briefly, 8 normal volunteers received, in random order, sildenafil 200 mg and placebo on different study days, and then had pharmacokinetic sampling and visual function testing performed. A detailed description of the ERG procedures is taken from pages 14 and 21 of the study report:

> *"Flash Ganzfeld full-field ERGs were to be recorded using a Metrovision apparatus (Villeneuve d'Ascq, France). Electrode impedance was to be maintained below 5KΩ. All the electrophysiological examinations of vision were to be recorded by the same technician and analysed by the same ophthalmologist throughout the study.*
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> *"The ERG test was designed to separate the contribution from the rods and the cones cells of the retina. A contact lens electrode was to be placed on the cornea when the subject was fully dark adapted (10 minutes). Skin electrodes were to be placed near each orbital rim and the reference ground skin electrode placed on the forehead. A local anaesthetic (oxybuprocaine) was to be used to place the corneal contact lens electrode. As recommended by the International Society of Clinical Electroretinography (ISCERG, Marmor et al, 1989), the pupils were to be fully dilated for ERG recordings. Tropicamide was to be used to dilate the pupil (1 drop every five minutes until complete pupil dilation (15-25 minutes). Subjects were to be instructed to look at a fixation point in front of each eye within a full-field Ganzfeld dome from which the flashes were to be emitted. The light stimulus was to consist of white flashes with an intensity of 10,000lux and with a duration of ten milliseconds. Coloured filters were to be used to enhance the separation of the rod (blue light) and cone (red light) responses. In addition, 30Hz white flashes (flicker) that isolate cone function were to be performed.*
>
> *"Static ERG to flash stimuli of white, red, orange and blue light followed by a flicker stimulus of 30Hz white flashes was to be performed after 15 minutes of dim light adaptation followed by a dynamic ERG which was recorded every two minutes for 16 minutes using an orange light flash stimulus during dark adaptation and preceded by a dazzle. The ERG was to be recorded for both eyes with amplifiers set at 0.3-500Hz and 25 epochs of 100 milliseconds were to be averaged for each light stimulation.*
>
> *"Both amplitude and implicit time or latency for selected signals were measured for white (a and b waves), red (cone or photopic response with a1 and b1 waves), blue (rod or scotopic responses with essentially b2 waves) and orange light (scotopic and photopic responses with a, b1 and b2 waves). Peak and trough amplitude were also recorded after the flicker stimuli to assess cone function.*
>
> *"Baseline ERGs were taken at screening or at a separate pre-study visit. ERGs were taken at two time points commencing 1.25 and 5 hours post-dose.*
>
> *...*
>
> *"For photopic and scotopic ERGs, the average of the two eyes was calculated and subjected to an ANOVA. The model allowed for variation due to pre-treatment value, sequence, subject, period, treatment and time post-dose with all time points and relevant interactions (period*time, treatment*time) used for each parameter. Pre-treatment values were included in the model to assess any between subject sequence effects."*

The earlier time point was probably picked to catch the peak plasma concentration, but the actual peak plasma concentrations of sildenafil and UK-103,320 occurred at about 2 hours. Plasma levels of sildenafil and UK-103,320 were about 40% higher at 1.25 hours than they were at 5 hours; plasma levels at the earlier time point were about 80% of the

peak levels.

Results for photopic vision (obtained from the statistical appendix to the study report) are shown in Table 1 below.

Table 1. Amplitudes and latencies for photopic ERGs.

	Time (h)	White		Red		Blue	Orange	
		A	B	A1	B1	B2	A	B
Amplitude (μV±SD)								
Placebo	1.25	-40±9	108±16	-17±5	53±18	8±10	-32±7	90±18
	5	-45±16	126±16	-21±7	51±9	8±8	-33±8	93±18
Sildenafil	1.25	-44±17	125±29	-17±5	37±16	14±10	-32±13	85±23
	5	-42±14	140±31	-19±9	44±16	18±14	-29±3	92±19
Latency (ms±SD)								
Placebo	1.25	29±3	53±1	32±1	53±2	66±7	28±2	52±1
	5	29±3	52±2	33±1	54±1	69±4	29±2	52±1
Sildenafil	1.25	29±3	54±1	35±2	56±3	71±5	30±1	53±1
	5	30±3	54±1	35±1	58±2	72±2	30±2	55±1
30 Hz flicker amplitude								
Placebo	1.25	19±25		—				
	5	28±27						
Sildenafil	1.25	38±18						
	5	44±15						

Results for scotopic vision are shown in Figure 1 below (amplitudes) and Figure 2 below (latencies).

Effects on photopic vision were generally small compared with the intra-subject and inter-subject variability. Few of the observed differences achieved nominal statistical significance, in fact, no more than would be expected based upon the number of comparisons made. Plausibly treatment-related effects included the increase in 30-Hz flutter amplitude, decrease in B1-wave (red) amplitude, and increase in B2-wave (blue) amplitude. Similar interpretive difficulties pertain to the scotopic amplitudes and latencies.

The choice of sampling times after dosing was suboptimal; the time of the peak plasma levels was underestimated and the rate of decline in plasma levels was overestimated. However, plasma levels were near peak at the first sampling time for the ERG and 40% lower at the time of the second ERG. There was no clinically meaningful difference between ERGs obtained on placebo and on sildenafil. There was no difference in effect between the two assessments on sildenafil attributable to differences in plasma levels of sildenafil at the two sampling times. Even nominally statistically significant differences sporadically observed in this study are unlikely to prove reproducible.

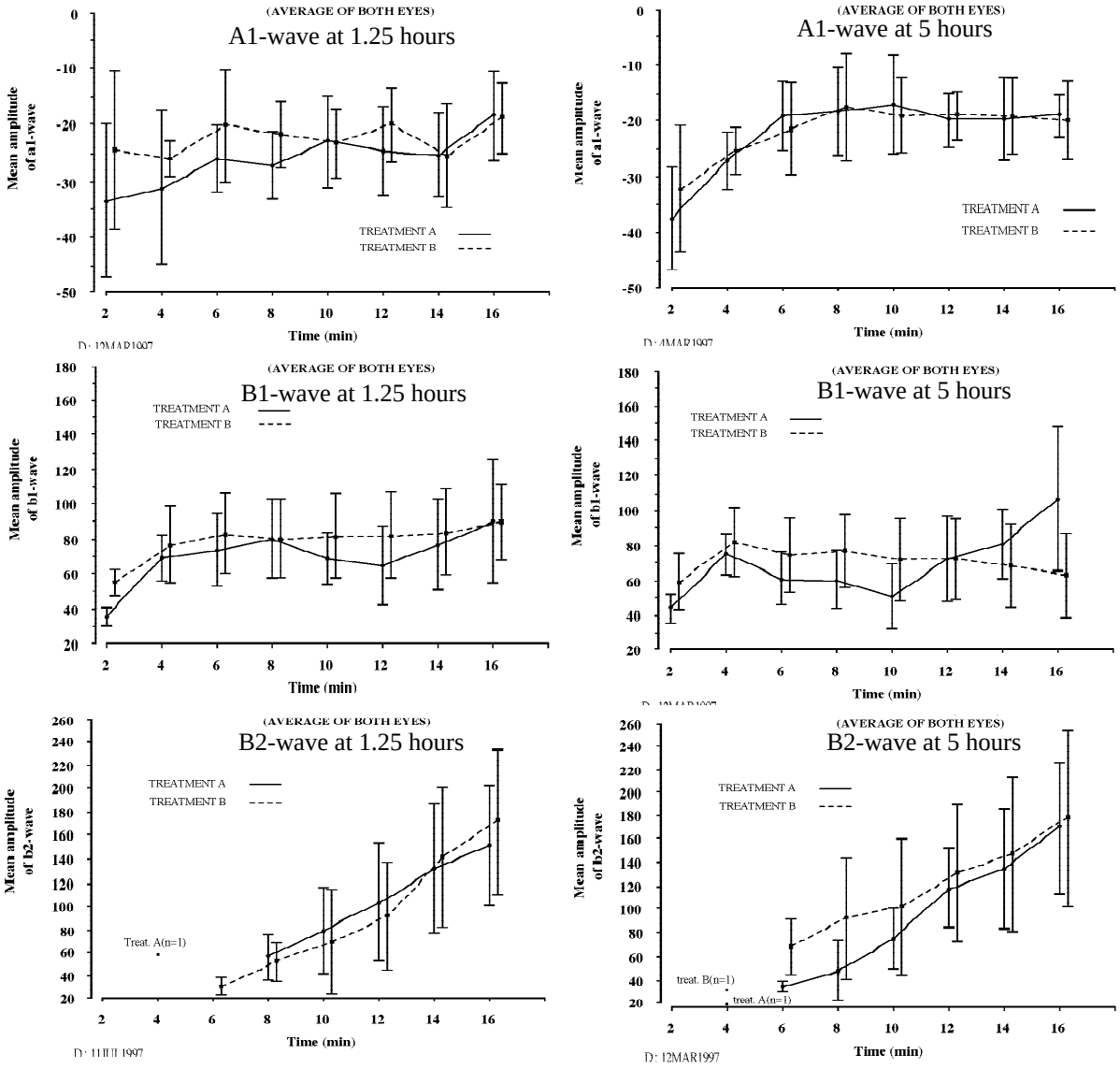

Figure 1. Scotopic vision amplitude (μV±SD) results.
Treatment group A is sildenafil and group B is placebo.

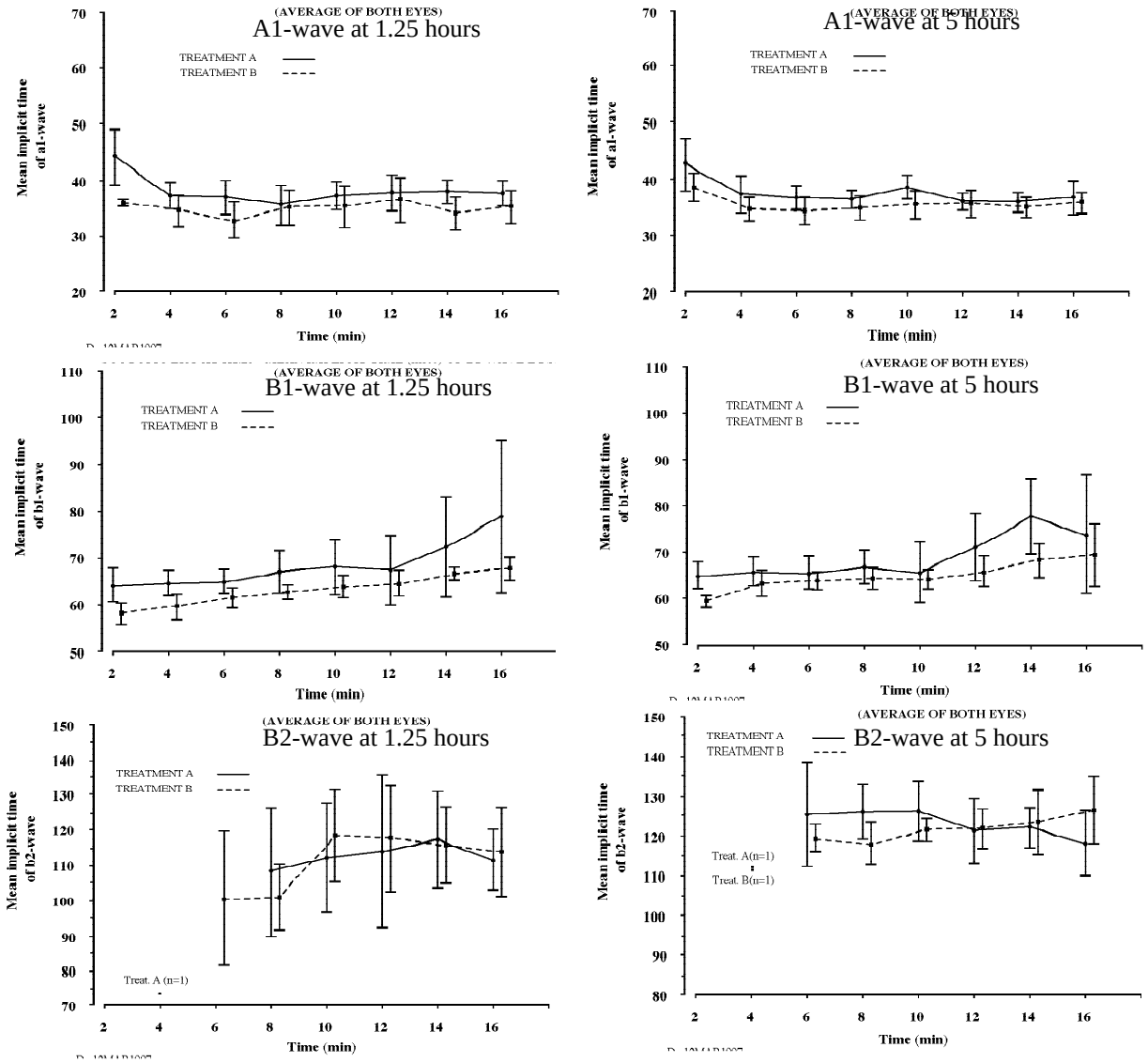

Figure 2. Scotopic vision latency (ms±SD) results.
Treatment group A is sildenafil and group B is placebo.