Figure 10. Duration of Oxygen Desaturation vs. Visit, by Patient - Percentage of 4-Hour Period with SaO_2 < 90%: First Half of Night

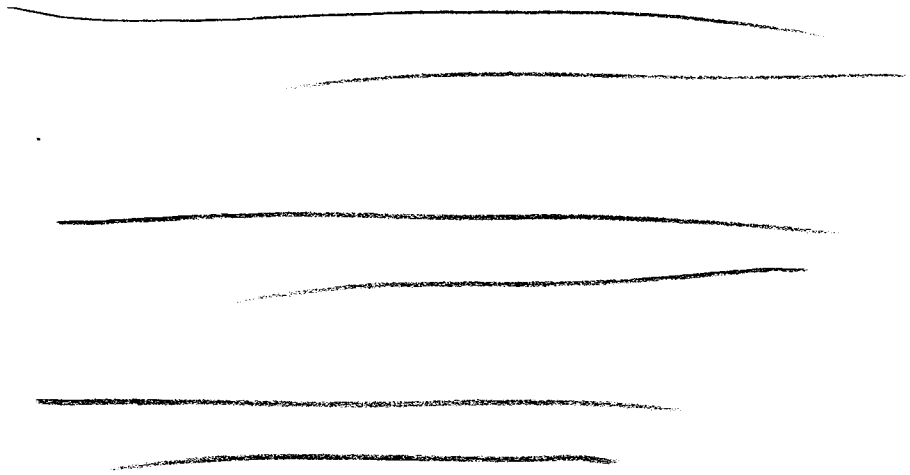
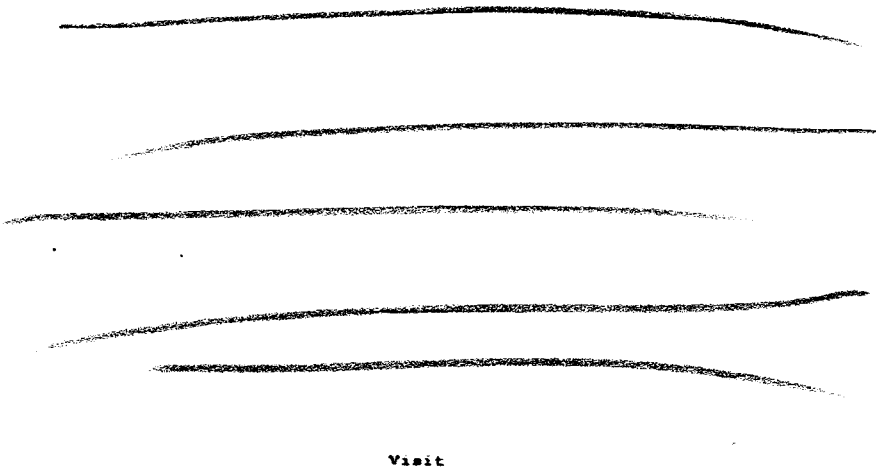


Figure 11. Duration of Oxygen Desaturation vs. Visit, by Patient - Percentage of 4-Hour Period with SaO_2 < 90%: Second Half of Night



The lowest SaO_2 recorded in this patient at each visit is summarized in the following table which I have created from the data listings

Visit	Lowest oxygen saturation (%)	
	First half of night	Second half of night
1	Not available	Not available
2a	84	85
2b	82	83
3	82	88
4	86	86
5	79	84
6	84	82

9.2.2 Patient #17302

Clinical information is not available for this patient. Based on the RDI at Visit 2a, the baseline visit, the patient does appear to have had moderate pre-existing sleep apnea.

RDI data for this patients are in the following table taken from the original data listings

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	4.88	3.18
2a	27.52	13.95
2b	Not available	Not available
3	29.63	37.66
4	9.2	14.02
5	2.08	11.88
6	1.72	5.82

In a subsequent submission the sponsor has provided a comprehensive table of the patient's respiratory event and oxygen saturation data, which I have copied below. Data for Visit 2b which were not included in the original data listings are highlighted in yellow.

Output Variables for Patient 026300	Visit 1 (anti-cataplectic medication)	Visit 2a (BASELINE)	Visit 2b (First Night at 4.5g)	Visit 3 (4 wks@4.5g)	Visit 4 (2 wks@6g)	Visit 5 (2 wks@7.5g)	Visit 6 (2 wks@9g)
1st_Number_of_Central_Apneas_(REM)							
2nd_Number_of_Central_Apneas_(REM)							
1st_Number_of_Central_Apneas_(NREM)							
2nd_Number_of_Central_Apneas_(NREM)							
1st_Number_of_Hypopneas_(REM)							
2nd_Number_of_Hypopneas_(REM)							
1st_Number_of_Hypopneas_(NREM)							
2nd_Number_of_Hypopneas_(NREM)							
1st_No._of_Obstructive_and_Mixed_Apneas_(REM)							
2nd_No._of_Obstructive_and_Mixed_Apneas_(REM)							
1st_No._of_Obstructive_and_Mixed_Apneas_(NREM)							
2nd_No._of_Obstructive_and_Mixed_Apneas_(NREM)							
1st_Respiratory_Disturbance_Index							
2st_Respiratory_Disturbance_Index							
1st_Apnea/Hypopnea_Index_(REM)							
2nd_Apnea/Hypopnea_Index_(REM)							
1st_Apnea/Hypopnea_Index_(NREM)							
2nd_Apnea/Hypopnea_Index_(NREM)							
1st_Lowest_O_2_Saturation_(%)_(NREM)							
2nd_Lowest_O_2_Saturation_(%)_(NREM)							
1st_Lowest_O_2_Saturation_(%)_(REM)							
2nd_Lowest_O_2_Saturation_(%)_(REM)							

* In this table, the "n/a" for lowest O2 saturation% (REM) for the first half of the night refers to the fact that the saturated oxygen signal during REM sleep during the first half of the night for these visits was so noisy that the minimum level could not be established

Note that the Respiratory Disturbance Index (for both halves of the night) was highest for this patient at Visit 3 (after 4 weeks of treatment at 4.5 g/day)

9.2.3 Patient #17304

This patient who discontinued Xyrem® during this trial on account of an adverse event was a 67 year old woman with a known history of narcolepsy (for 25 years), tonsillectomy, breast cancer in remission (treated with lumpectomy and radiation) and obstructive sleep apnea-hypopnea syndrome (confirmed by polysomnogram done over 1 ½ years prior to her enrollment) . Concomitant medications included venlafaxine and modafinil.

At screening this patient had a reportedly false-positive urine test for benzodiazepines. After entering the OMC-SXB-20 trial she failed to attend Visit 3 (on trial date 29) and indicated a desire to discontinue medication. However she then changed her mind and attended Visit 3 on Day 36. On Day 51, a day after beginning Xyrem® in a dose of 7.5 g/day she reported being "really sensitive" and her husband noted worsening snoring, and frequent and more severe episodes of apnea. By that time she had been treated with the following doses of Xyrem®: 4.5 g/day for 35 days and 6.0 g/day for 14 days. Xyrem® was discontinued on Day 51 on account of a perceived worsening in her obstructive sleep apnea-hypopnea syndrome. The adverse event was reported to have resolved by Day 52.

Her last study visit was Visit 4.

Several objective parameters – AHI (NREM), OMAs and RDI – all measured during the second half of the night showed no worsening at Visits 3 and 4 as compared with Visits 1 and 2a. However the following were seen only at Visits 3 and 4

- Increased AHI (REM and NREM), central apneas, hypopneas, and RDI during the first half of the night
- Increased AHI (REM) and central apnea during the second half of the night

Changes in RDI over the course of the study are summarized in the following table which I have created from the data listings

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	54.36	87.09
2a	27.39	36.02
2b	Not available	Not available
3	99.42	100.87
4	57.92	47.77

Oxygen saturation data are further summarized below. Lowest SaO_2 data are summarized in the following table

Visit	Lowest oxygen saturation (%)	
	First half of night	Second half of night
1	89	87
2a	91	87
2b	Not available	Not available
3	89	87
4	84	86

Plots by visit for another oxygen saturation parameter, the percentage of the 4-hour period with an $SaO_2 < 90\%$ are below, copied from a submission provided by the sponsor

Figure 19. Duration of Oxygen Desaturation vs. Visit, for Patient 017304 - Percentage of 4-Hour Period with SaO_2 < 90%: First Half of Night

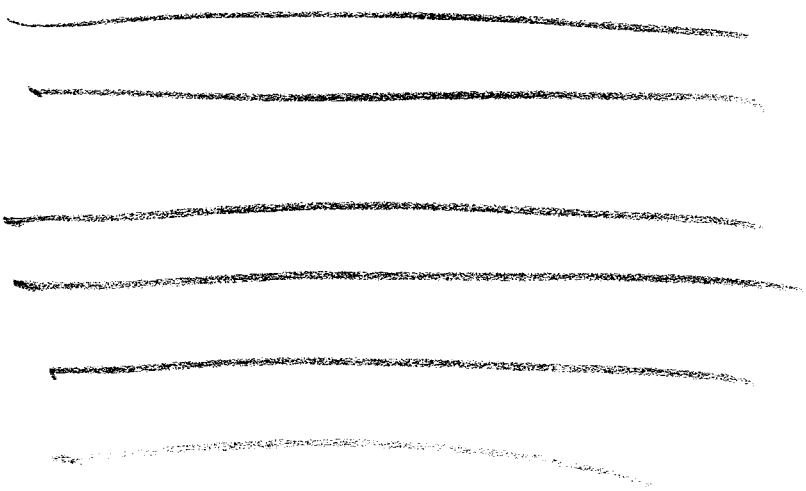


Figure 20. Duration of Oxygen Desaturation vs. Visit, for Patient 017304 - Percentage of 4-Hour Period with SaO_2 < 90%: Second Half of Night

9.2.4 Patient #41306

A clinical description is not available for this patient

Changes in this patient's RDI over the course of the study are summarized in the following table

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	21.73	19.43
2a	1.25	5.78
2b	5.53	5.6
3	1.19	7.54
4	2.99	0.7

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
5	8.36	9.79
6	2.14	2.7

The lowest SaO_2 recorded in this patient at each visit is summarized in the following table which I have created from the data listings

Visit	Lowest oxygen saturation (%)	
	First half of night	Second half of night
1	83	85
2a	87	90
2b	87	89
3	90	90
4	87	86
5	89	89
6	88	88

9.2.5 Patient #42303

A clinical description is not available for this patient

Changes in this patient's RDI over the course of the study are summarized in the following table

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	32.07	20.88
2a	24.07	45.24
2b	35.39	33.06
3	31.21	30.76
4	11.81	21.59
5	36.61	26.45
6	23.69	12.8

The lowest SaO_2 recorded in this patient at each visit is summarized in the following table which I have created from the data listings

Visit	Lowest oxygen saturation (%)	
	First half of night	Second half of night
1	85	92
2a	92	92
2b	91	91
3	89	92
4	90	92
5	89	84
6	91	92

9.3 Description Of A Single Patient With Mild Sleep Apnea At Baseline

9.3.1 Patient #02630

Patient #02630 completed the study but the data were not included in the 10/5/01 submission as they were unreadable for the following reason: the nocturnal polysomnogram data for this patient were not convertible by the Stanford laboratory (the central reading facility for this study) as Site #26 used an optical disk recording system instead of a CD-R based system. The data for this patient were instead submitted on 3/12/02, in response to a specific query from the Division seeking to fully account for all patients participating in the study.

The investigator for Site #26 was contacted and asked to score both the respiratory event and oxygen saturation data for this patient. The scoring of the overnight polysomnogram data was then carried out by the a single technician consistent with that site's clinical practice.

9.3.1.1 Narrative

This 58 year old man had a medical history significant for narcolepsy, obesity, "mild apnea," plastic surgery for ptosis and on the ears, a submucous resection for a deviated septum and smoking. Concomitant medication included sertraline (withdrawn during the study as per protocol), a nicotine patch, nabumetone, methylprednisolone and cyclobenzaprine. While on treatment with GHB he experienced brief, intermittent anxiety, dizziness, nausea, and vomiting.

9.3.1.2 Table

The following table provides respiratory event and oxygen saturation data for patient #026300. Note that he had a total AHI/RDI of 6.5 at Visit 1 which is consistent with mild sleep apnea.

Output Variables for Patient 026300	Visit 1 (anti-cataplectic meds)	Visit 2a (BASELINE)	Visit 2b (1st nt@ 4.5g)	Visit 3 (4 wks@4.5g)	Visit 4 (2 wks@6g)	Visit 5 (2 wks@7.5g)	Visit 6 (2 wks@9g)
1st Half Number of Hypopneas and Apneas							
2nd Half Number of Hypopneas and Apneas							
1st Half Apnea/Hypopnea Index (NREM)							
2nd Half Apnea/Hypopnea Index (NREM)							
1st Half Apnea/Hypopnea Index (REM)							
2nd Half Apnea/Hypopnea Index (REM)							
1st Half Apnea/Hypopnea Index (Total) *							
2nd Half Apnea/Hypopnea Index (Total)							
Obstructive Apneas (NREM)							
Mixed Apneas (NREM)							
Central Apneas (NREM)							
Hypopneas (NREM)							
Obstructive Apneas (REM)							
Mixed Apneas (REM)							
Central Apneas (REM)							
Hypopneas (REM)							
Apnea/Hypopnea Index (REM)							
Apnea/Hypopnea Index (NREM)							
Apnea/Hypopnea Index (Total)							
Lowest O_2 Saturation (%) (NREM) **							
Lowest O_2 Saturation (%) (REM)							

The representation of "1st" and "2nd" in the labels for the output variables are as follows. "1st" refers to the first half of the night, which represents the 1st dosing. "2nd" refers to the second half of the night, which represents the 2nd dosing, taken four hours after the 1st dose.

* Terminology of "Apnea/Hypopnea Index" and "Respiratory Disturbance Index" are used interchangeably when combining REM and NREM indices.

** Lowest O_2 Saturation (%) represents the lowest measurement of O_2 Saturation (%) while the patient was having a respiratory event. This is unique for this site, in contrast to the centralized scoring from Stanford which recorded the lowest O_2 Saturation (%) value for the entire time period, whether the patient had a respiratory event or not.

9.3.1.3 Sponsor's interpretation of results

"In general, these data convey intra-patient variation across doses without a first night effect. This is consistent with the results demonstrated for the main OMC-SXB-20 respiratory events data obtained through centralized scoring."

9.4 Reviewer's Comments

- As noted earlier it is difficult to draw any firm conclusions from this study as a whole regarding the effect of sodium oxybate on respiratory parameters; the reasons for such a view are as follows
  - The study was open-label and uncontrolled
  - The number of patients enrolled was small
  - There was considerable inter-patient variability in changes from baseline in all parameters with standard deviations consistently exceeding means

- However when individual data listings for patients are reviewed concerns have been raised about the effects of Xyrem® on respiratory parameters in patients with pre-existing sleep apnea. Particularly noteworthy are 2 patients
  - Patient 17301 who had the following abnormalities:
    - An elevated RDI at baseline, falling in the 'moderate to severe sleep apnea' range increasing up to ~ 100 an extremely abnormal value, at Visit 3, after 4 weeks of treatment at 4.5 g/day
    - A steady increase over the course of the study (i.e., with increasing dose) in the period of time spent at an SaO_2 < 90%; by the end of the study almost 70% of a 4 hour period had been spent at an oxygen saturation in that range.
  - Patient 17304 who had the following abnormalities
    - An elevated RDI at baseline falling in the severe sleep apnea range increasing further to ~ 100 at Visit 3 , after 4 weeks of treatment at 4.5 g/day
    - A perception by her husband that the severity of her snoring as well as apneic episodes had increased over the course of the trial leading her to discontinue at Visit 4

  Admittedly,
  - No evidence of a dose response in the severity of sleep apnea were seen in either of these patients
  - Changes in oxygen saturation parameters in these patients did not correlate with changes in RDI
  - It cannot be proven that the changes in respiratory parameters in these 2 patients were due to Xyrem® as opposed to spontaneous variability in the severity of sleep apnea
- The study cannot therefore be considered to provide reassurance that Xyrem®, clearly a central nervous system depressant drug, does not have a respiratory depressant effect, especially in patients with pre-existing obstructive sleep apnea. In this regard, it is noteworthy that narcolepsy and obstructive sleep apnea are reported to co-exist frequently.
- In order to provide reassurance that Xyrem® does not have a respiratory depressant effect, a formal controlled trial evaluating the effects of Xyrem® on respiratory parameters and oxygen saturation in patients with already compromised pulmonary function, and especially in those with obstructive sleep apnea, appears warranted. An alternative approach, contraindicating use of the drug in patients with obstructive sleep apnea, appears less desirable without the availability of "hard" data to support restricting the use of the drug in what must be a significant proportion of those with narcolepsy.
- This concern is especially justified given that at least 2 subjects reviewed earlier in the NDA, one a healthy subject and the other a patient with narcolepsy, appear to have developed depressed respiration when given doses of Xyrem® within the recommended range. In addition, at least one further subject participating in earlier clinical trials of Xyrem® was reported to have developed breathing difficulty on 2 separate occasions, once at a dose of 9 g/day and later at a dose of 3 g/day, and needed to discontinue Xyrem® on each occasion; although a narrative supplied by the sponsor suggests that the cause of the patient's difficulty breathing may have been sleep paralysis that has not been substantiated (see additional details about this subject in Section 16.3.3.2 which tends to substantiate the assertion that the patient had sleep paralysis).

10. Response In Current Submission Regarding Respiratory Data In OMC-SXB-20

The sponsor's response is under 2 separate headings

- Variability in sleep-disordered breathing
- Variability in respiratory event parameters in OMC-SXB-20

10.1 Variability In Sleep-Disordered Breathing

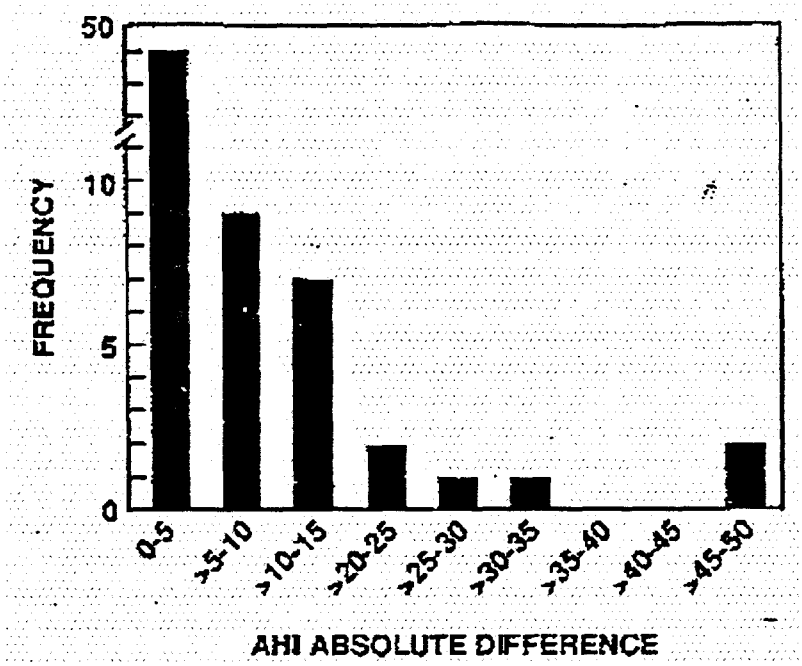
The sponsor cites a number of publications that indicate that the RDI varies considerably even in the absence of a drug effect. I have reviewed these publications in regard to their relevance to the current application, and have summarized them below.

10.1.1 Bliwise DL, Benkert RE, Ingham RH. Factors associated with nightly variability in sleep-disordered breathing in the elderly. Chest 1991; 100(4): 973-976.

The 71 subjects enrolled in this cohort study had a mean age of 74.6 years and were free from psychoactive medications and alcohol on both nights that they participated in the study, based on zero blood levels. On each night the subjects underwent polysomnographic monitoring. 13/71 subjects were determined to have high variability in sleep disordered breathing based on an absolute hypopnea-apnea index difference of ≥ 10 events/hour between the 2 nights. The remaining 58 subjects were determined to have low variability. The following were noteworthy about the results of the study

- In the high variability group the mean (± standard deviation) two-night absolute difference in apnea-hypopnea index was 19.4 ± 12.2 events per hour. In the low variability group the mean (± standard deviation) two-night absolute difference in apnea-hypopnea index was 2.5 ± 2.2 events per hour. The difference was considered statistically significant ($p < 0.001$)
- The higher variability group had a higher 2-night mean apnea hypopnea index (34.7 ± 19.3) than the lower variability group (7.4 ± 9.1). The difference was considered statistically significant ($p < 0.001$)

The frequency distribution for the absolute difference in AHI across the 2 laboratory nights is in the following figure which I have copied from the submission.



Since gross body position was constant for each subject in the higher variability group on both nights, the sponsor concluded that the variability in sleep disordered breathing in this might be related to upper airway anatomical factors that were inconstant from night to night.

10.1.2 Wittig RM, Romaker A, Zorick FJ, Roehrs TA, Conway WA, Roth T. Night-to-night consistency of apneas during sleep. Am Rev Resp Dis 1984; 129(2):244-246.

A case series of 22 patients was selected from a larger group of 50 adult male patients based on the following criteria

- At least polysomnographic studies performed within 90 days of each other (each recording lasted 8 hours).
- Not weight changes of > 10 lbs between the 2 studies
- No changes in medication in the interval between the 2 studies
- No treatments, surgical or otherwise, in the interval between the 2 studies

These 22 patients were divided into 2 groups

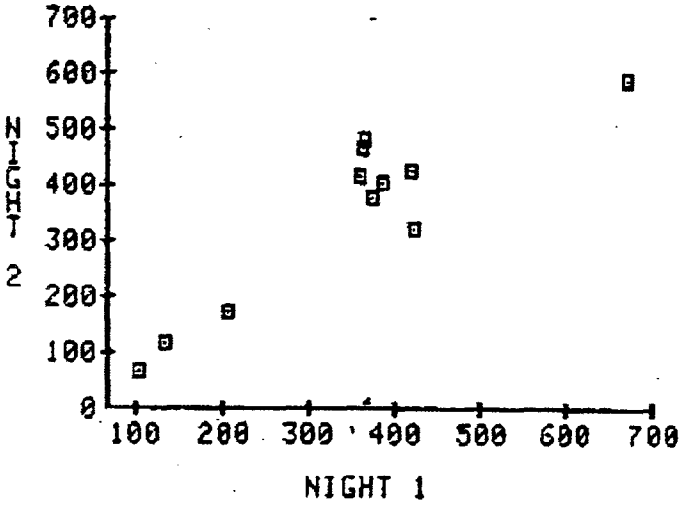
- Infrequent apnea (11 patients) with less than 100 apneic episodes during the first polysomnogram
- Frequent apnea (11 patients) with greater than 100 apneic episodes during the first polysomnogram

The consistency in the number of apneas between the 2 nights was examined.

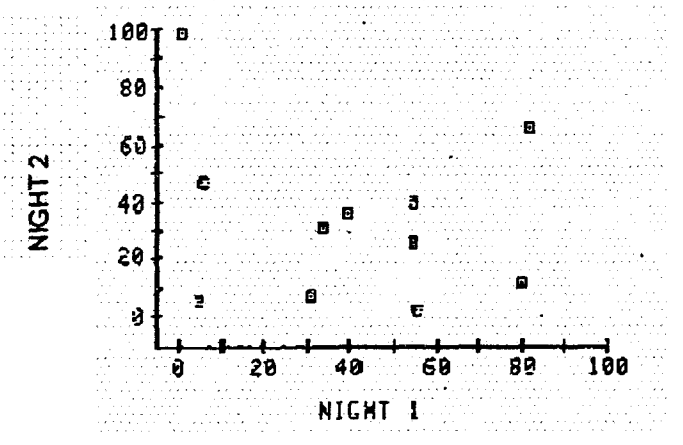
The key results of the study were as follows

- The frequent apnea group showed a consistent number of apneas on the 2 nights ($r = 0.92$; $p < 0.01$). This group had a mean (± standard deviation) number of apneas on Nights 1 and 2 of 349.6 ± 156.3 and 349.6 ± 166.8, respectively. This correlation is also

displayed graphically in the following figure which I have copied from the submission



- The infrequent apnea group showed a highly variable number of apneas between the 2 nights ($r = 0.35$; $p > 0.10$). This group had a mean (± standard deviation) number of apneas on Nights 1 and 2 of 40.4 ± 28.4 and 33.2 ± 29.8, respectively. This lack of correlation is also displayed graphically in the following figure which I have copied from the submission



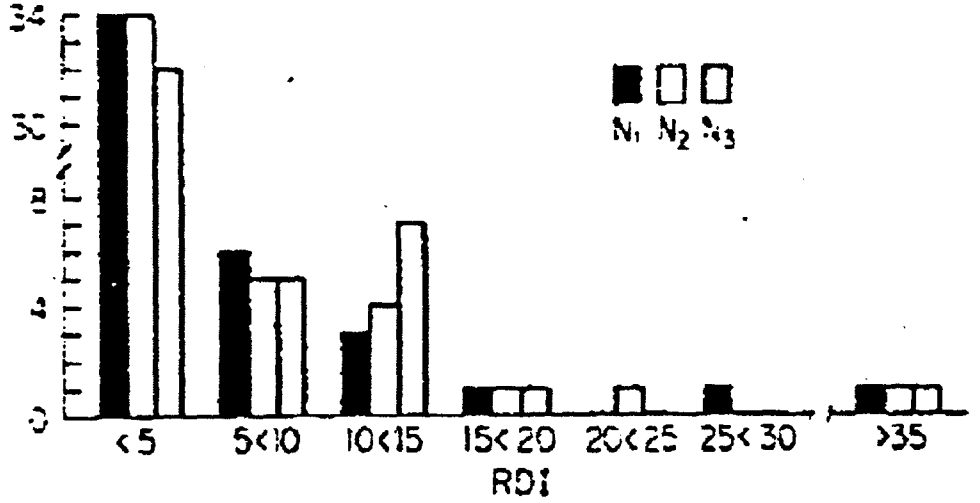
- Similar correlations were seen in the apnea index (apneas per hours of sleep)
  - The frequent apnea group had mean (± standard deviation) apnea indices of 54.1 ± 20.6 and 56.0 ± 26.8 on Nights 1 and 2, respectively
  - The infrequent apnea group had mean (± standard deviation) apnea indices of 6.5 ± 4.6 and 5.2 ± 4.6, on Nights 1 and 2, respectively
- Apnea duration and type were consistent between the 2 groups

10.1.3 Mosko SS, Dickel MJ, Ashurst J. Night-to-night variability in sleep apnea and sleep-related periodic leg movements in the elderly. Sleep 1988; 11(4):340-348.

In this prospective study, 46 community-dwelling subjects (30 women and 16 men) with a mean age of 68.7 years underwent 3 consecutive nights of polysomnography; only 6 of these subjects were taking medications for sleep which they were asked to continue.

Key study results, pertinent to the current submission, were as follows

- A prominent first-night effect was seen in the pattern of sleep as evidenced by greater total sleep time, shorter sleep latency, less waking after sleep onset, better sleep efficiency, more REM sleep, shorter REM latency, and a greater number of REM periods on Nights 2 and 3, as compared with Night 1.
- The frequency histogram for RDI on each night is shown in the following figure which I have copied from the submission. Pairwise comparisons of the nightly distributions failed to show significant night-to-night differences. Note that in the figure below the number of subjects is displayed on the y-axis



- Means and standard deviations for RDI for each night are in the following table, which I have copied from the submission. No statistically significant trends across nights were seen

	RDI (/h)
Night 1	4.7 ± 7.2 (0–35.4)
Night 2	4.3 ± 7.4 (0.1–40.3)
Night 3	5.3 ± 8.3 (0–50.3)
All nights	4.8 ± 7.6 (0.2–42.0)

- Several individual subjects had "substantial" night-to-night variations in RDI large enough to influence diagnosis or treatment plan. Although the publication does not provide data for each subject or state how many subjects had "substantial" night-to-night variations in RDI, the text states that a subject had an RDI of < 5 on one night and 25.3 on another night.
- If subjects were grouped into 2 categories based on a cut-off score of 5 RDI episodes per night, 20/46 (43%) subjects were classified differently on Nights 2 and 3 as compared with Night 1. The cut-off RDI score of 5 is stated to be used to group patients according to severity of sleep apnea.

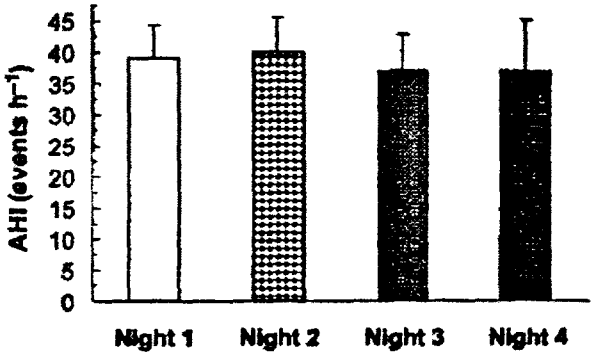
The authors of the article have concluded that "caution should be taken drawing conclusions from single-night studies, especially in individuals with relatively mild forms of sleep apnea where nightly variations could easily place them above or below an arbitrary cut-off score."

10.1.4 Bittencourt L, Suchecki D, Tufik S, et al. The variability of the apnoea-hypopnoea index. J Sleep Res 2001; 10(3):245-251.

In this prospective study 20 patients with obstructive sleep apnea-hypopnea syndrome of both sexes and selected based on an age range of 30 –60 years underwent polysomnography on 4 consecutive nights.

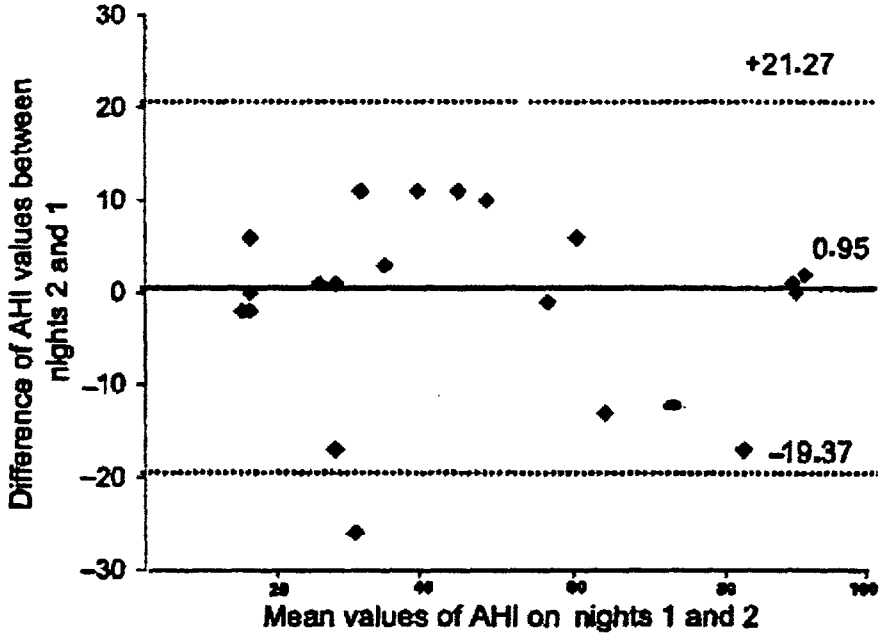
Key results of the study, pertinent to the current application, were as follows:

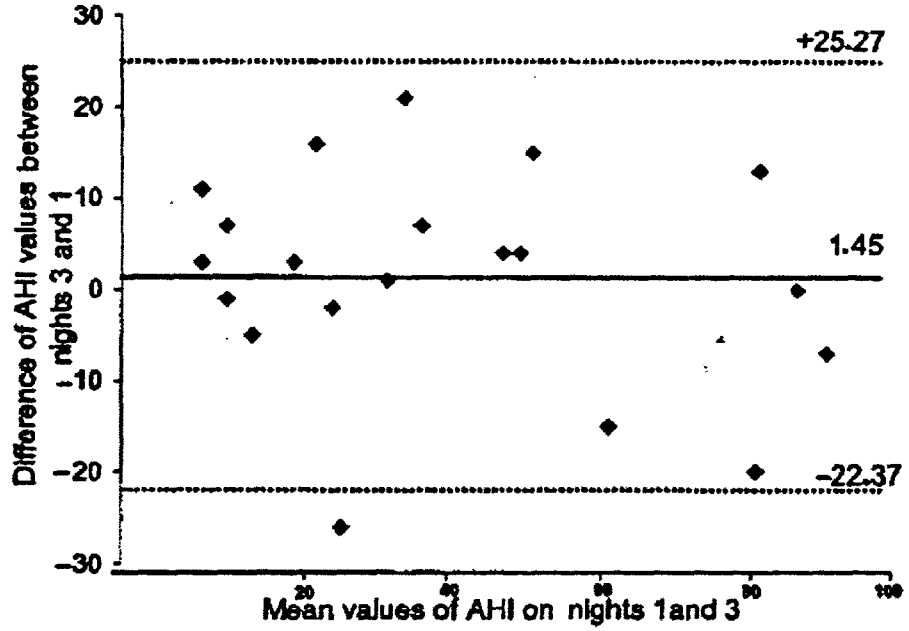
- Mean apnea-hypopnea index (AHI) values were not significantly altered during the four nights of recording ($p = 0.67$). The intra-class correlation coefficient on the 4 nights was 0.92 ± 0.01 (SEM) with a 95% confidence interval ranging from 0.90 to 0.95. The following figure, copied from the submission, shows mean (± SEM) for each of the nights for all 20 patients enrolled in the study

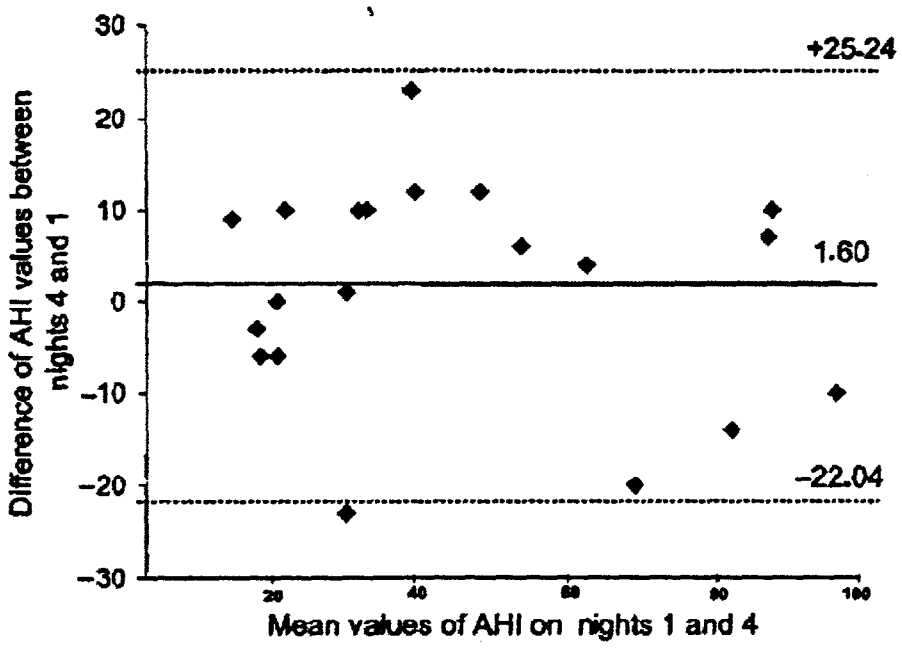


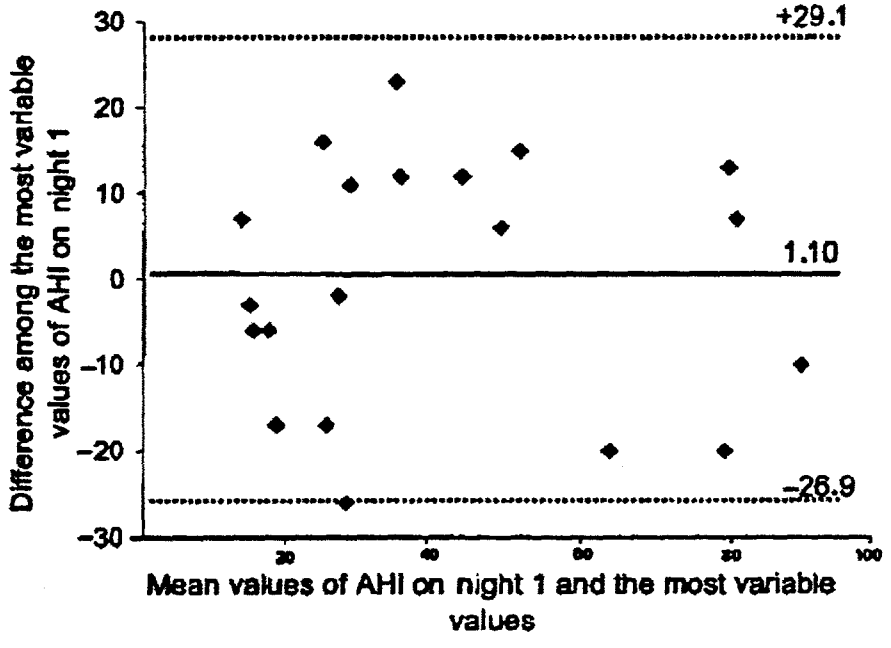
- Bland and Altman plots (see below) were used to analyze individual variability between the AHI values on the first versus each of the subsequent nights, and between the first night and the most deviating values. These indicated substantial variability unrelated to the initial value. The plots are below copied from the submission.

APPEARS THIS WAY
ON ORIGINAL


30
20
10
0
-10
-20
-30
+21.27
0.95
-19.37
Difference of AHI values between nights 2 and 1
Mean values of AHI on nights 1 and 2


30
20
10
0
-10
-20
-30
+25.27
1.45
-22.37
Difference of AHI values between nights 3 and 1
Mean values of AHI on nights 1and 3





10.1.5 Mendelson WB. Use of the sleep laboratory in suspected sleep apnea syndrome: is one night enough? Cleveland Clinic Journal of Medicine 1994b; 61(4):299-303

This prospective study was on 50 patients with a mean age of 50.2 years who presented to a sleep center and were clinically suspected of having obstructive sleep apnea; patients taking long-acting hypnotics or "major" analgesics were excluded from the study. They underwent 2 consecutive nights of polysomnography.

Patients who had an AHI ≥ 5 on at least of the nights, and in whom obstructive disordered breathing events (apneic and hypopneic) constituted > 50% of disordered breathing time were included in the analysis.

Gross body position was not systematically recorded between nights

Key results of the study that are pertinent to the current submission are below

- Sleep and respiratory variables that showed a nominally statistically significant difference between the 2 nights based on group means are in the following table which I have copied from the submission. Note that the AHI, total number of disordered breathing events and minimum arterial oxygen saturation did not change significantly between nights (the author did not state precisely what these values were). The AHI was highly correlated between nights ($r = 0.86$; $p < 0.0001$) for the 49 patients who had an AHI of 5 or more on one of the 2 nights.

SLEEP AND RESPIRATORY VARIABLES
THAT SIGNIFICANTLY DIFFERED BETWEEN THE TWO NIGHTS (N=50)

Variable	First night (mean ± SEM)	Second night (mean ± SEM)	P value*
Total sleep time, minutes	356.6 ± 11.1	375.3 ± 8.6	.06
Sleep latency, minutes	16.8 ± 6.7	8.6 ± 2.5	.06
Rapid-eye-movement (REM) latency, minutes	132.5 ± 10.6	101.1 ± 10.5	.04
Sleep efficiency, %	69.1 ± 4.5	84.9 ± 1.6	.001
Stage 1, minutes	33.4 ± 4.4	21.7 ± 2.0	.01
Stage 2, minutes	249.4 ± 9.1	271.8 ± 8.1	.01
Obstructive apnea time in REM sleep, %	71.2 ± 4.8	55.5 ± 5.7	.01
Baseline oxygen saturation in nonREM sleep, %	93.6 ± 0.2	94.2 ± 0.2	.04
Subjective sleep latency, minutes	29.4 ± 5.3	21.1 ± 3.4	.001
Subjective total sleep, minutes	332.0 ± 19.2	374.4 ± 13.4	.02

*By paired t test

- The next table indicates the number of patients who had AHIs ≥ 5 and ≥ 10 on the first and second nights

AHI	Night 1 Number of patients	Night 2 Number of patients
≥ 5	46	49
≥ 10	42	46

- 57% of patients had a difference in AHI of at least 10 or more between Night 1 and Night 2
- In the current submission, the sponsor has drawn attention to the following table which summarizes mean (± SE) in sleep and respiratory measures in 46 patients who had an AHI of 5 or more on the first night . The parameters that the sponsor wants to draw particular attention to are highlighted in red borders. The sponsor states that there was significant oxygen desaturation based on absolute minimum means of 78.9% and 68.9% during NREM and REM sleep, respectively.

Variable	Mean ± SEM
Total recording period, minutes	438.9 ± 4.5
Total sleep time minutes	364.8 ± 8.8
Sleep latency, minutes	10.0 ± 1.3
Rapid-eye-movement (REM) sleep latency, minutes	131.0 ± 10.7
Sleep efficiency, %	73.2 ± 4.1
Number of REM periods	3.0 ± 0.2
Number of REM episodes	8.0 ± 0.9
Stage 1, minutes	35.6 ± 4.6
Stage 2, minutes	253.2 ± 7.8
Stage 3, minutes	8.2 ± 1.5
Stage 4, minutes	10.6 ± 3.9
Total REM sleep, minutes	61.3 ± 5.7
Wake after sleep onset, minutes	63.2 ± 7.3
Period-leg-movement index, no. per hour	1.2 ± 0.5
Number of disordered breathing events in nonREM sleep	264.7 ± 28.0
Number of disordered breathing events in REM sleep	50.4 ± 7.0
Apnea-hypopnea index (AHI) in nonREM sleep, no. per hour	51.4 ± 5.2
AHI in REM sleep, no. per hour	51.1 ± 4.5
AHI for all sleep, no. per hour	51.7 ± 5.0
Average duration of disordered breathing events (apneic and hypopneic) in nonREM sleep, seconds	24.4 ± 0.9
Average duration of disordered breathing events (apneic and hypopneic) in REM sleep, seconds	31.0 ± 1.5
Obstructive apnea in nonREM sleep, %	56.8 ± 4.3
Obstructive apnea in REM sleep, %	71.2 ± 4.8
Obstructive hypopnea in nonREM sleep, %	29.0 ± 4.3
Obstructive hypopnea in REM sleep, %	22.9 ± 4.9
Central apnea in nonREM sleep, %	10.4 ± 3.2
Central apnea in REM sleep, %	6.0 ± 2.1
Central hypopnea in nonREM sleep, %	4.6 ± 1.6
Central hypopnea in REM sleep, %	0.4 ± 0.4
Baseline oxygen saturation in nonREM sleep, %	93.8 ± 0.2
Baseline oxygen saturation in REM sleep, %	92.8 ± 0.5
Mean minimum saturation in nonREM sleep, %	85.7 ± 0.6
Mean minimum saturation in REM sleep, %	79.0 ± 1.4
Absolute minimum saturation in nonREM sleep, %	78.9 ± 1.2
Absolute minimum saturation in REM sleep, %	68.9 ± 2.4

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10.1.6 Punjabi NM, Bandeen-Roche K, Marx JJ, Neubauer DN, Smith PL, Schwartz AR. The association between daytime sleepiness and sleep-disordered breathing in NREM and REM sleep. Sleep 2002; 25(3):307-314.

This was a retrospective study carried out on a series of 2736 patients consisting all those who underwent an overnight polysomnogram in a specific sleep laboratory between January 1996 and September 1999. Based on specific criteria, the polysomnograms of 1821 patients (who also underwent Multiple Sleep Latency Tests) was selected from this group for further analysis.

The only result of the study that appears pertinent to the current submission, and to which the sponsor has drawn attention, is the wide-range of sleep disordered breathing seen. This variability is seen in the scatter plot for the AHI (NREM) and AHI (REM) in the figure below which I have copied from the submission. The red line inserted by the sponsor into the figure is to demonstrate the potential for the RDI to be greatly in excess of the highest levels seen in the OMC-SXB-20 study without an attributable relationship to a drug.

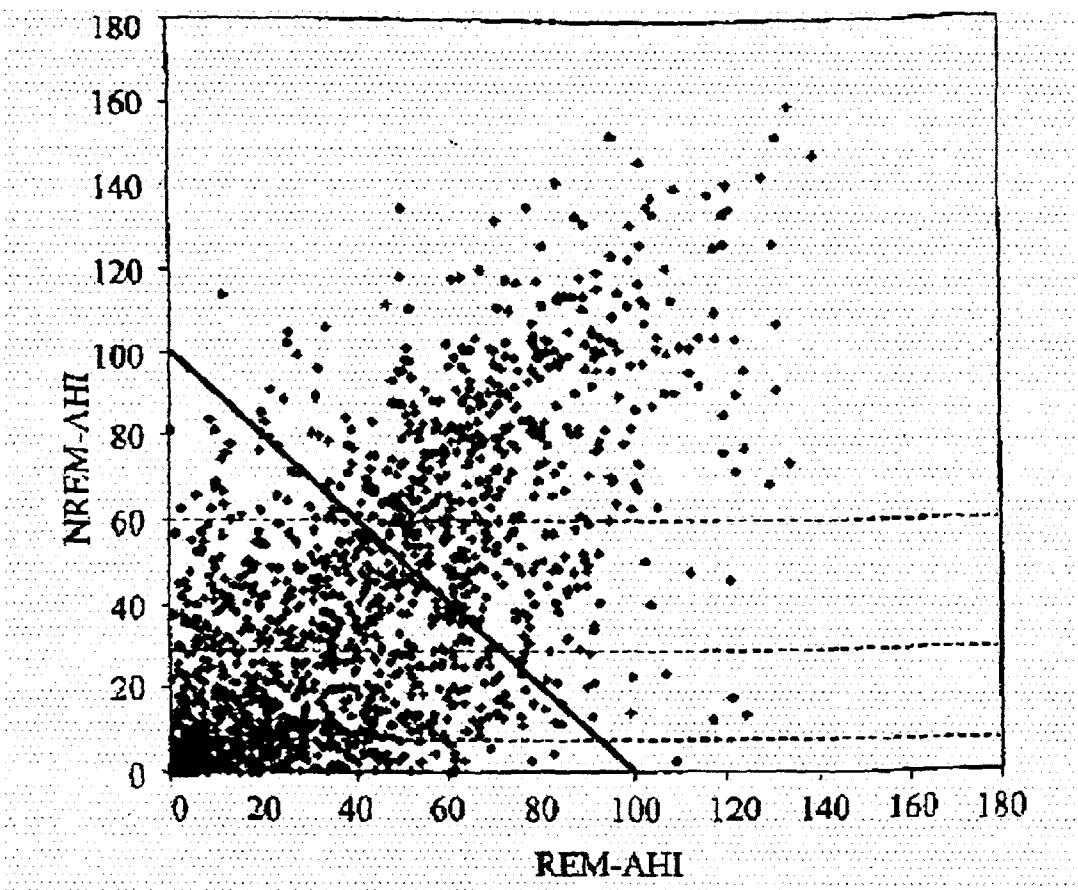


FIGURE 5: Scatter plot of NREM-AHI and REM-AHI (dashed lines represent cut-points for NREM-AHI quartiles). Punjabi 2002.

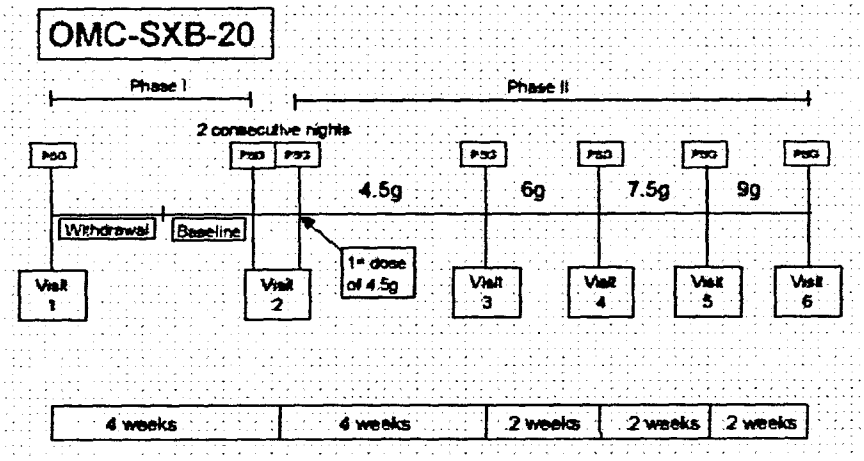
There is no data available in the paper regarding clinical symptoms, medication use, or oxygen saturation, in this sample, and especially in those with a REM/NREM AHI greater than 100. The authors concluded that sleep-disordered breathing during NREM sleep but not REM sleep, is associated with an increased risk of daytime sleepiness as daytime sleepiness as measured by the Multiple Sleep Latency Test.

10.2 Variability In Respiratory Event Parameters In OMC-SXB-20

The sponsor has first provided the study schematic and has highlighted the following aspects of the study and analysis

- Intrasubject variability in measures of sleep-disordered breathing in this study were interpreted in the context of the following
  - The spontaneous variability in these measures as described in the medical literature
  - The presence or absence of a dose-response relationship in regard to these measures
- Although the study was deficient in that it was not randomized and controlled
  - All study measures were objective and used the standard recording methods of a sleep laboratory.
  - The Xyrem® dosing regime was controlled and accurate
  - Each patient had 2 sets of measures recorded under conditions where he/she was not taking Xyrem®: Visit 1 (while still receiving anti-cataplectic medications other than Xyrem®) and Visit 2a (baseline, after washout of anti-cataplectic medications). Changes in measures of sleep-disordered breathing while taking Xyrem® could be compared against these baseline measurements

For convenience I have again copied the study schematic below



The rest of the sponsor's response is under the following headings (the headings have been modified somewhat by me)

10.2.1 Criteria Applied To Diagnose Sleep-Disordered Breathing Events

The sponsor states that while the well-documented variability in sleep-disordered breathing events is not well understood, this variability may be contributed to by sleep position, upper airway morphological features, sleep stage composition, and pulmonary status

The classification of sleep-disordered breathing events in this study was based on the following publication.

American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999; 22(5):667-689.

These criteria, according to the sponsor, are more rigorous than those used in clinical practice, and are as follows

A reduction in breathing occurring during sleep is defined as an apnea only if airflow

1. Ceases for at least 10 seconds AND
2. Is associated with an oxygen desaturation of ≥ 3% or is associated with arousal

A reduction in breathing occurring during sleep was defined as a hypopnea only if Criterion 1 or 2 plus Criterion 3 is satisfied).

1. A clear decrease (>50%) from baseline in a valid measure of breathing during sleep (baseline is defined as the measured amplitude of stable breathing over the 2 minutes preceding the onset of the event if breathing is stable, or in the amplitude of the 3 largest breaths)
2. Is associated with either an oxygen desaturation of ≥ 3% or arousal
3. The event lasted ≥ 10 seconds

The sponsor further states that, for both the above definitions, an oxygen desaturation ≥ 4% has now replaced the ≥ 3% figure. By the more liberal current criteria, there would have been a significant reduction in the incidence of RDI in the OMC-SXB-20 study

The sponsor also cites the above American Academy of Sleep Medicine Task Force article as listing the following factors as predisposing to sleep-disordered breathing events

- Obesity
- Male gender
- Craniofacial abnormalities (including mandibular/maxillary hypoplasia)
- Increased pharyngeal soft or lymphoid tissue
- Nasal obstruction
- Endocrine abnormalities (hypothyroidism and acromegaly)
- Family history

10.2.2 Relationship Between Respiratory Disturbance Index And Oxygen Desaturation

The sponsor states that

- There is generally a dissociation between the RDI score and its "seriousness" once the RDI extends into the "severe" (> 30) range; the sponsor believes that the "seriousness" of obstructive sleep apnea is dependent on the degree of oxygen desaturation that occurs, which, in turn, is directly related to a combination of decreased gas exchange and the duration of episodes of apnea and hypopnea.
- Apneas are typically 10 to 50 seconds in duration, although hypopneas lasting several minutes may occur in REM sleep (the American Academy of

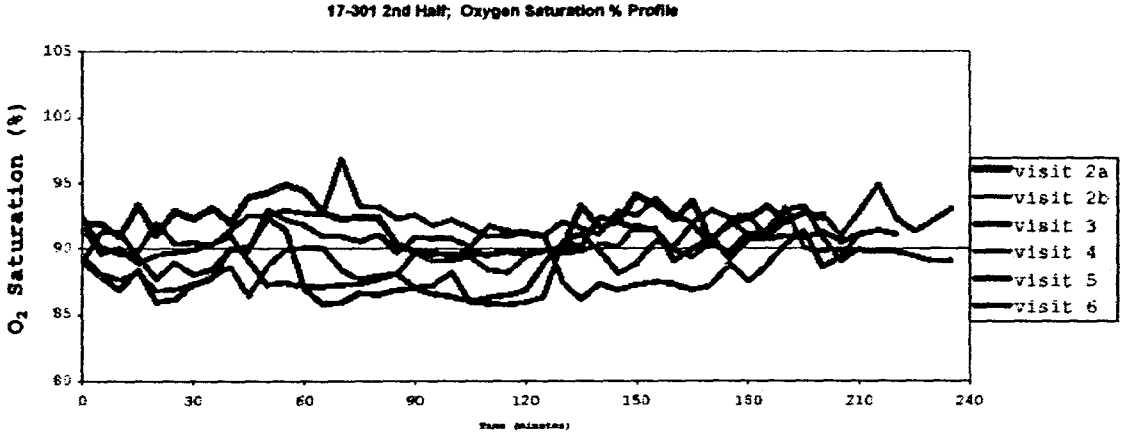
Sleep Medicine Task Force report referred to above is cited in support of this contention)

The sponsor further states that since desaturation did not occur in accompaniment of the sleep-disordered breathing changes recorded in OMC-SXB-20, "when increases in RDI occurred in that study they represented brief cyclical events without compromising gas exchange". As an example, the sponsor has compared the oxygen saturation and nasal airflow traces for Patient #17301 at Visit 2a (baseline, not being treated with Xyrem® or with other medications for cataplexy), and at Visit 3 (after 4 weeks of treatment with Xyrem® in a dose of 4.5 g/day, and while receiving that dose. These traces are stated to indicate the following

- At Visit 2a, episodes of apnea and hypopnea were less frequent but longer and were associated with desaturation
- At Visit 3, the frequency of apnea and hypopnea events was higher during many recording epochs, but the events were shorter and they had a minimal effect on gas exchange

In further support of the above contention, the sponsor also points out that for Patient #17301, for the 4-hour period constituting the second half of the night

- The RDI at Visit 3 was 76 (vs 32 at Visit 2a)
- The average oxygen saturation at Visit 3 was 93% (vs 92% at Visit 2a)
- The oxygen saturation trace at Visit 3 was "for the most part" above that for Visit 2, as demonstrated by the following figure which I have copied from the submission



The sponsor has cited a further publication [Aber WR, Block AJ, Hellard DW, Webb WB. Consistency of respiratory measurements from night to night during the sleep of elderly men. Chest 1989; 96(4):747-751] as stating that the nightly profile of desaturation is "very highly reliable across nights and the apnea index is relatively less reliable." The sponsor cites this publication as being consistent with the results of the OMC-SXB-20 study during which the RDI was variable, whereas oxygen saturation levels remained consistent. I have read the

publication which described the results of a two-night polysomnographic study in 14 healthy elderly men which was intended to determine the consistency of measures of sleep and breathing across the 2 nights. The two-night reliability of the AHI in this study was 0.655, whereas the reliability of measures of saturation/desaturation ranged from 0.625 to 0.862 as shown in the following table, which I have copied from the submission.

Table 2—*Respiratory Variables for Nights 1 and 2 in 14 Older Men**

Respiratory Variable	Night 1	Night 2	Two-Night Reliability
Apnea index†	3.6 ± 3.7	4.2 ± 4.7	0.607§
Hypopnea index†	3.0 ± 4.7	3.5 ± 5.7	0.755‖
AHI†	6.6 ± 6.6	7.7 ± 9.4	0.655¶
Mean saturation change:			
apneas/hypopneas‡	6.1 ± 3.5	6.4 ± 4.7	0.356‖
Mean low saturation, percent	92.7 ± 2.2	92.2 ± 3.7	0.625¶
No. of desaturations			
≥4 percent†	11.2 ± 11.6	11.7 ± 11.6	0.787‖
≥10 percent†	2.5 ± 3.7	4.2 ± 9.1	0.862‖
Length of period, s			
Desaturations ≥4 percent†	330.5 ± 321.1	354.3 ± 384.9	0.765‖
Desaturations ≥10 percent†	90.7 ± 137.9	154.9 ± 334.5	0.840‖

*Table values are means ± SD. All paired comparisons between nights 1 and night 2 were not statistically significant.
†Not normally distributed variable; Wilcoxon signed-rank test was used for paired comparison.
‡Normally distributed variable; paired *t* test was used for paired comparison.
§$p<0.05$.
‖$p<0.005$.
¶$p<0.01$.

The authors of the publication actually concluded the following

- Older individuals maintain their level of sleep-disordered breathing across the first 2 nights in the laboratory
- Measurements of desaturation are very highly reliable across nights, and the apnea index is relatively less reliable

10.2.3 Profiles Of Sleep-Disordered Breathing And Oxygen Saturation For Patients In OMC-SXB-20

The sponsor has provided graphical profiles of measures of sleep disordered breathing [AHI (REM), AHI (NREM), and RDI) and oxygen saturation (average SaO_2 and continuous SaO_2 at each visit) for every patient who participated in OMC-SXB-20.

Eight selected patients are discussed in greater detail. These patients were selected based on having an RDI in the moderate (15-30) or severe (> 30) at any timepoint during the study. These patients are listed and described further below. I have looked at the graphical profiles for each of these patients closely. As noted earlier Patient 17301 and, to a lesser extent, Patient 17304 were of particular concern to the Division.

10.2.3.1 Patient #17301

For convenience I have first copied this patient's graphical profiles, as contained in the text of the submission, below. Please also refer to the earlier narrative describing this patient in Section 9.2.1

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

lower mean SaO_2 at baseline (91.7% and 91.9% for the first and second halves of the night, respectively) than for any other patient in the study

- Although he had considerable "numerical variability" in RDI over the course of the study
  - There was no direct dose-response relationship
  - There was even variability within a single night as demonstrated by the RDI at baseline (14.12 for the first half of the night; 32.42 for the second half of the night)
  - At the timepoint when the patient's RDI was highest (Visit 3), average SaO_2 (91.4% and 92% for the first and second halves of the night, respectively) was similar to that at baseline, and the time spent under 90% saturation was the same as at baseline (the sponsor felt that this confirmed the dissociation between RDI and gas exchange at high RDIs, gas exchange being the primary determinant of respiratory function)
- The Division had been concerned that the patient spent an increasing proportion of time at an SaO_2 of < 90% over the course of the study as indicated by the figure below, which is for the first half of the night. The sponsor addresses that concern by stating the following
  - The baseline average SaO_2 in this patient was about 91%, close to the reference value of 90%
  - All patients participating in the study showed within variations of about 5% or higher for average SaO_2 over the course of the study.
  - A patient with a baseline average SaO_2 of 91% would thus have greater potential for spending time at an SaO_2 below 90%. This variability was not associated with a greater overall degree of desaturation, as demonstrated by the graphical displays included in this submission which included lowest oxygen saturation percentage (see figure below)
  - The variability in SaO_2 seen in these patients may be contributed to by multiple factors including body position, upper airway turbulent flow, varying degrees of arousal, and sleep architecture (presumably meaning REM vs NREM)

Reviewer's note: The sponsor's explanation does not address the <u>increase in time spent at an SaO_2 of < 90%</u> with <u>increasing dose of Xyrem®</u>, that was observed in this patient. This apparent dose-response is what was of special concern to the Division.

- The results of a polysomnogram done on this patient 2 weeks prior to entry into the OMC-SXB-20 study, and at a time when he was not receiving Xyrem®, have been provided. During this recording, the patient had an RDI of 18.8, whereas the time that he spent at a SaO_2 of < 90% was 54% of the recording. This percentage of time was higher than at the highest RDI of 100, when he spent about 35% of the recording at an SaO_2 of < 90%.
- Sleep-disordered breathing has its impact on patient safety through the duration of such events and the resulting effect on gas exchange and, primarily, on SaO_2.
- The safety of Xyrem® in this patient is supported by his continuing treatment with the drug at a stable dose of 6 g/day in Study OMC-SXB-7 without any respiratory adverse events. He failed to win approval from his insurance company for continuous positive airway pressure treatment of his sleep apnea.
- The lowest oxygen saturation readings (on continuous tracings recorded during the study) occurred in Patients 17305, 41300 and 41310 at visits during which Xyrem® was not being administered and "represent the multifactorial changes occurring during sleep in any population." These recordings were in the 75% to 85% range

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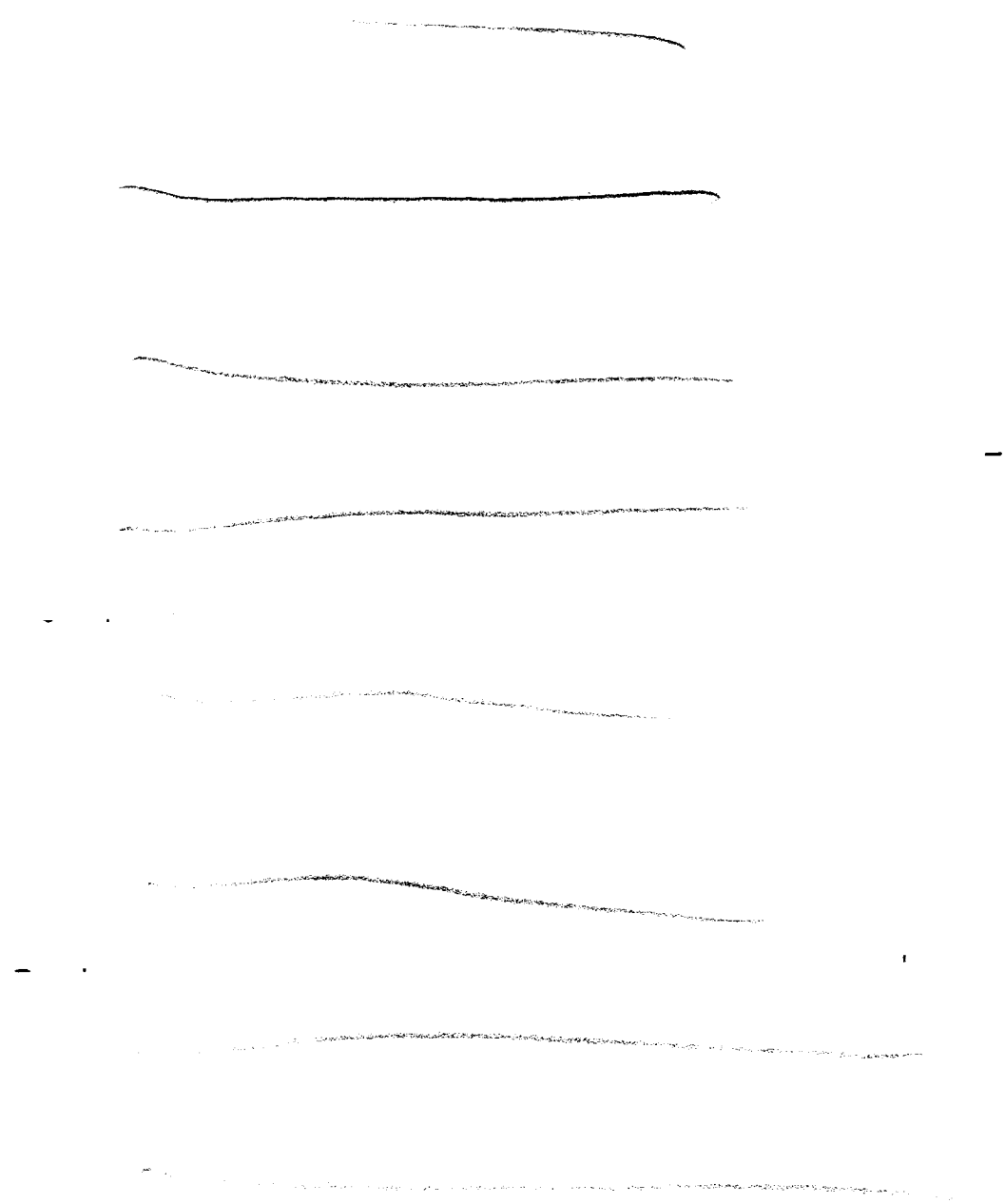
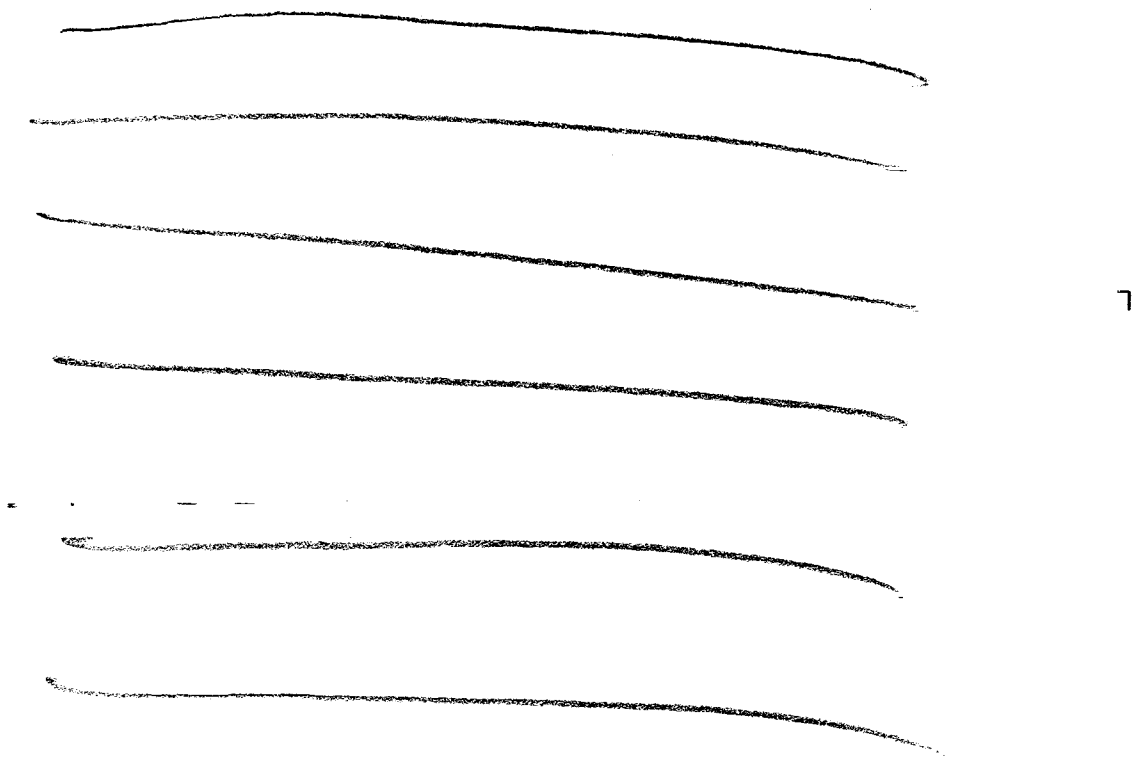


The sponsor has drawn attention to the following

- This woman had sleep apnea prior to study entry which was treated with continuous positive airway pressure during sleep. She did not however disclose this information at the time of her entry into the OMC-SXB-20 study
- At Visit 1, while still taking medication for cataplexy, her RDI was 54 for the first half of the night, and 87 for the second half of the night
- At Visit 2a (baseline; after withdrawal of medications for cataplexy) her RDI was 27 for the first half of the night, and 36 for the second half of the night.

- Her RDI increased further after 4 weeks of treatment with Xyrem® at 4.5 g/day but returned to starting levels after 4 weeks of treatment at 6 g/day
- Changes in RDI did not correlate with changes in average SaO_2; "minor" changes occurred in lowest SaO_2 with "negligible" time spent below 90% SaO_2
- The changes in RDI did not impinge upon the patient's safety, and these changes did not show a dose-relationship to Xyrem®, or a relationship to the drug itself
- The patient discontinued from the study after her husband became stated that she had been snoring more; the investigator believed that her husband became more aware of her snoring as a result of being treated with continuous positive airway pressure himself.

Reviewer's note: her lowest SaO_2 did fall below 90% for the first time (for both halves of the night) at Visit 6 as indicated by the figures below which I have copied from the submission.



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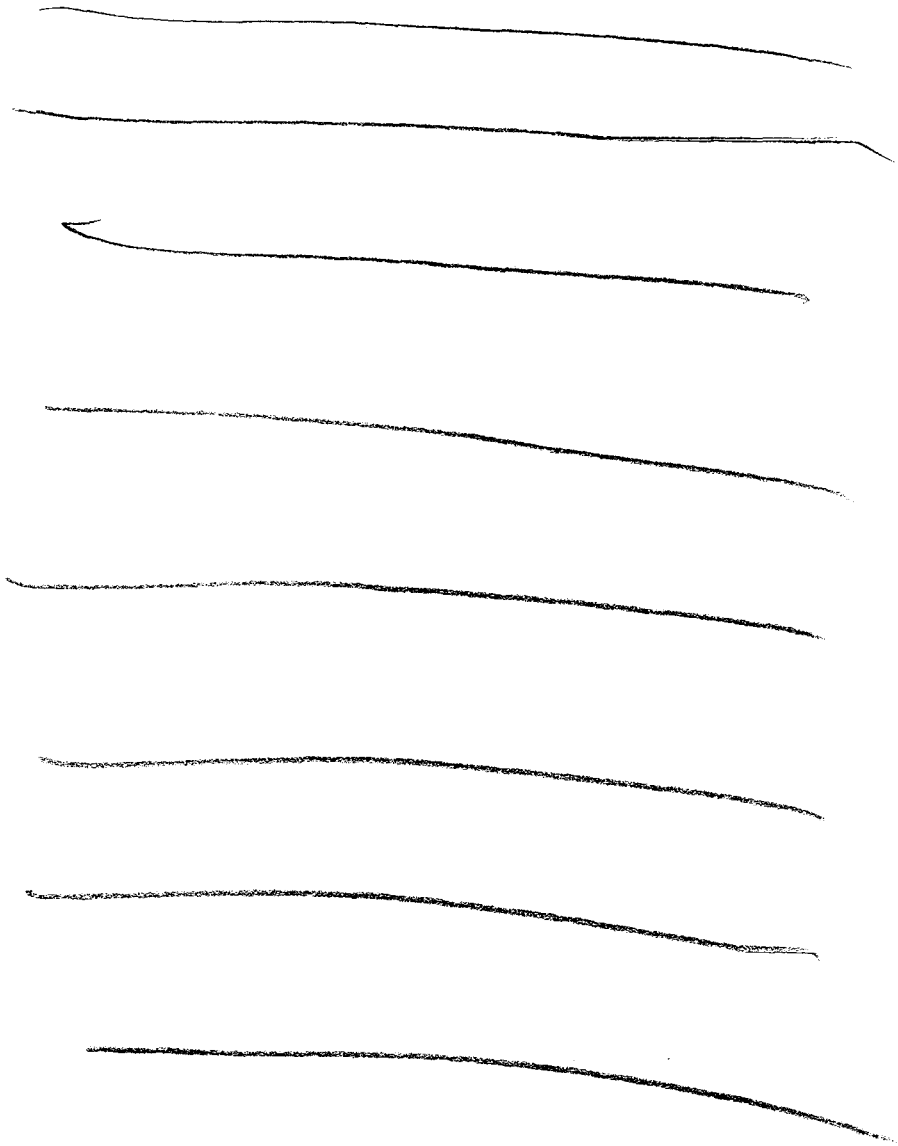

The sponsor has drawn attention to the following

- This patient had an elevated RDI at baseline (Visit 2a) which fell into the "moderate" range, and which increased at Visit 3. At neither visit was gas exchange compromised (the recordings did not suggest hemoglobin desaturation) as represented by average SaO_2, continuous oxygen tracing, and time under 90% saturation (zero in both halves of the night)
- At Xyrem® doses higher than 4.5 g/day, this patient's RDI was lower than at baseline.

The sponsor believes that this patient's RDI fluctuations during the study represented spontaneous variability and not a pharmacological effect of Xyrem®

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The sponsor considers this patient to have shown episodic numerical increases in RDI, mainly during the second half of the night. The increases in RDI did not suggest a dose-response with Xyrem® and were not associated with oxygen desaturation, as pointed out by the sponsor.

I have not copied the continuous oxygen tracings, but the readings were consistently above 90%.

10.2.3.5 Patient #41304

This patient's respiratory event tracings are reproduced below

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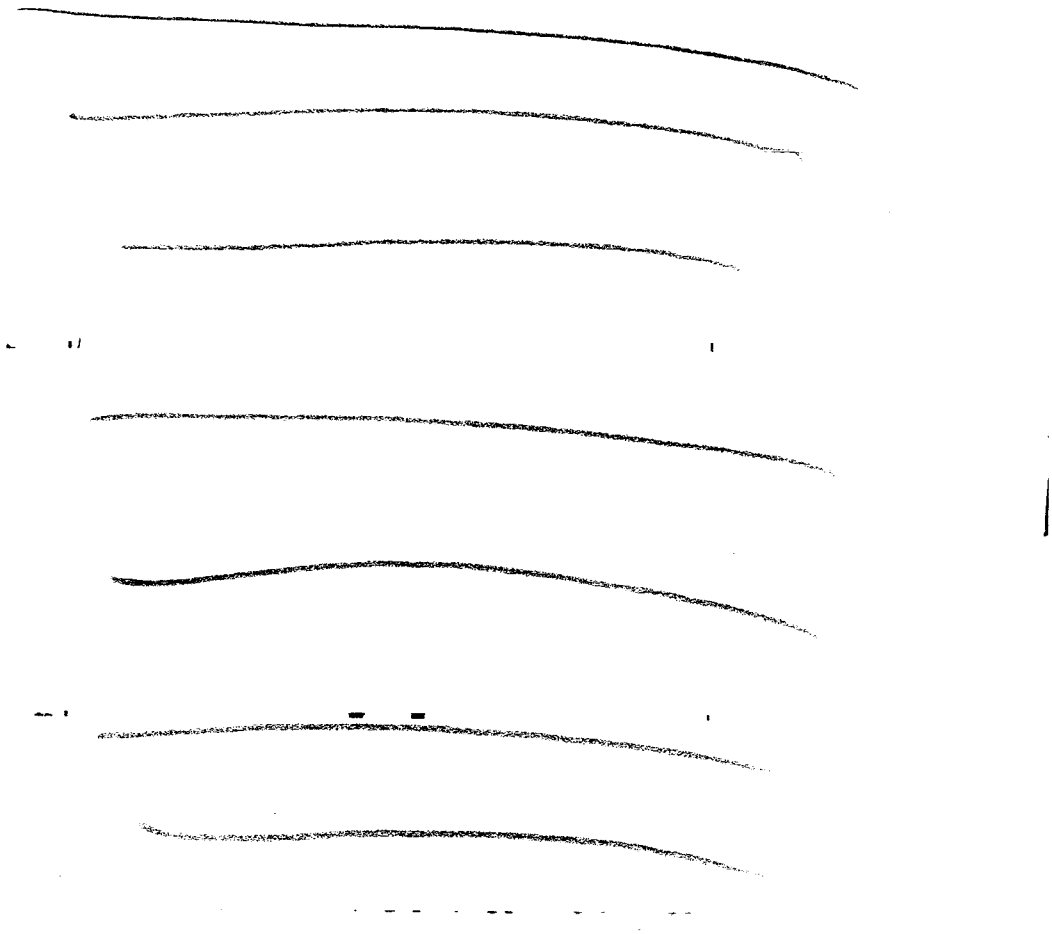

The sponsor considers this patient to have shown episodic numerical increases in RDI, mainly during the second half of the night. Again, the sponsor points out that the increases in RDI did not suggest a dose-response with Xyrem® and were not associated with oxygen desaturation

I have not copied the continuous oxygen tracings for this patient, but the readings were consistently above 90%.

10.2.3.6 Patient #41306

Please also see Section 9.2.4.

This patient's respiratory event profiles are reproduced below

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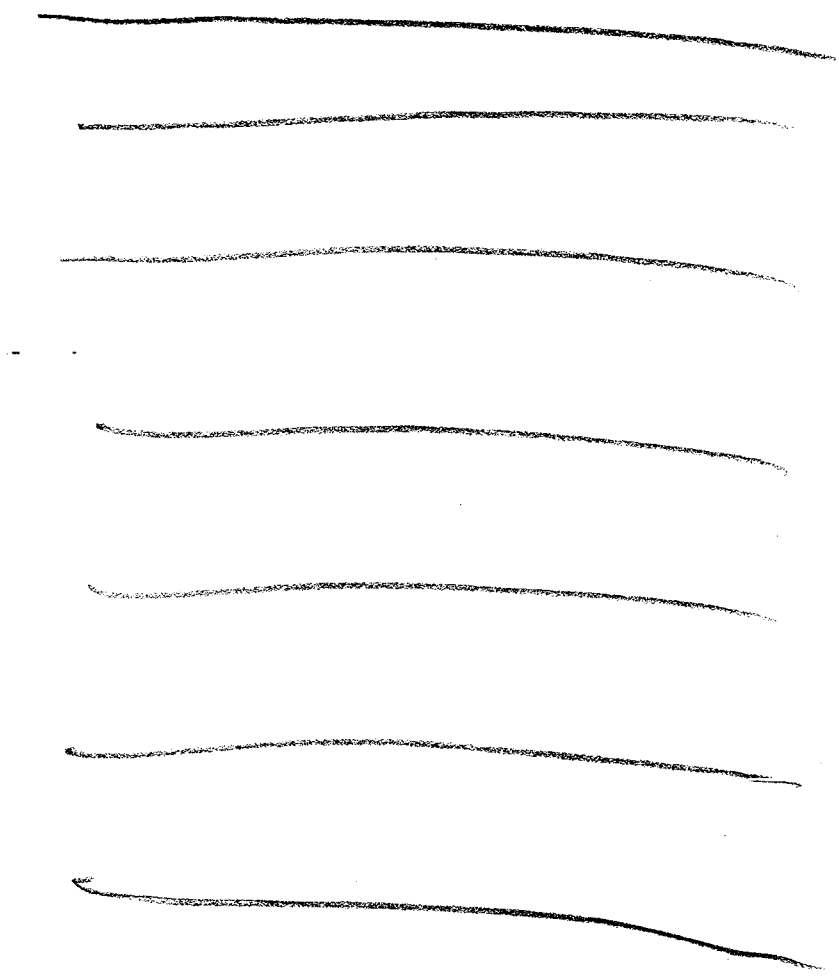

The sponsor points out that this patient's RDI was "moderately" elevated at Visit 1, but failed to be as high at any Xyrem® dose. Spontaneous variability is likely to have been the cause of these fluctuations, according to the sponsor.

I have not copied the continuous oxygen tracings for this patient, but the readings were consistently above 90%.

10.2.3.7 Patient #41307

This patient's respiratory event profiles are reproduced below

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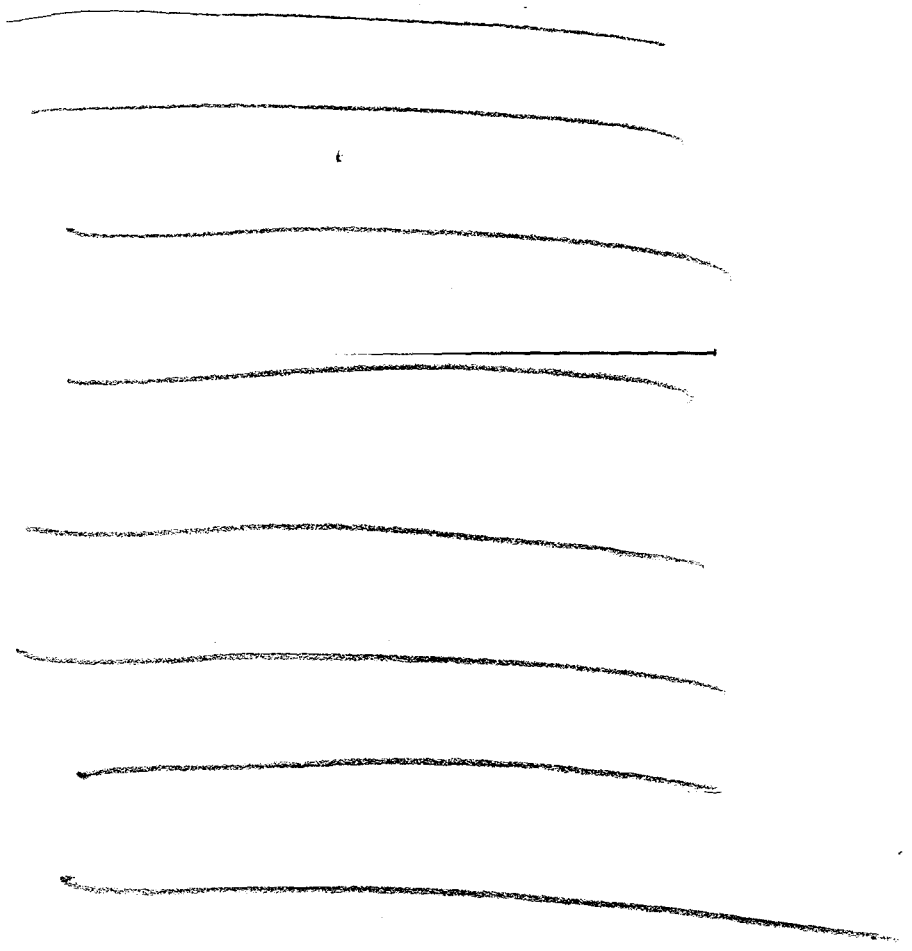

The sponsor has drawn attention to the following: This patient had an elevation in RDI in the "moderate" range when undergoing a polysomnogram at 7.5 g/day, but there was no accompanying oxygen desaturation, and the changes in RDI did not show a dose-response.

I have copied this patient's continuous oxygen tracings below. Note that at Visit 3, the patient's SaO_2 did show a tendency to troughs that reached or were below 90% during the second half of the night.

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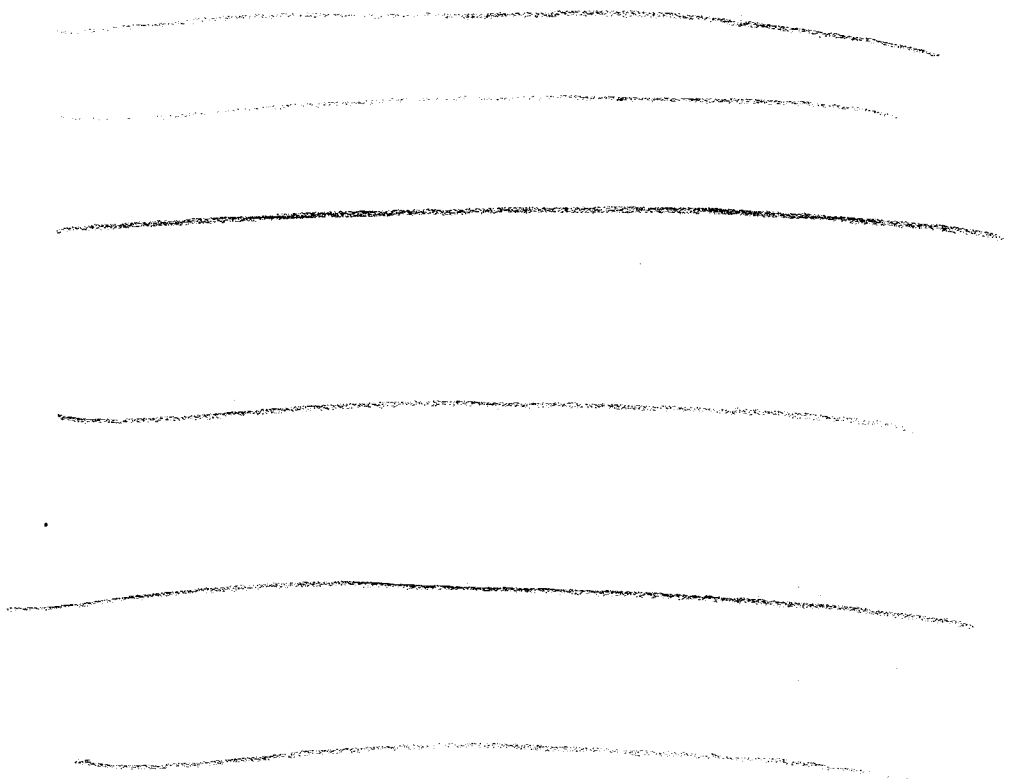
The sponsor has pointed out that (for the second half of the night) this patient had a "moderately" elevated RDI at Visit 1, which entered the "severe" category at Visit 2, and then fluctuated across the course of the study, never entering the "severe" range again. No "significant" oxygen desaturation was noted.

I have copied this patient's continuous oxygen tracings below. Note that at Visit 3, the patient's SaO_2 did show a tendency to troughs that reached or were below 90% during the second half of the night.



10.3 Sponsor's Conclusions

- The preceding discussion confirms variability in sleep disordered-breathing that is characteristic of the disease (i.e., obstructive sleep apnea), as supported by the literature. Since there was no association between numerical changes in Respiratory Disturbance Index and oxygen desaturation in any patient in this study, these changes do not represent a safety concern.

- Although study OMC-SXB-20 was not designed as a randomized, blinded, controlled study, it does present objective measures of respiratory events, sleep architecture and oxygen saturation data. Each patient provides their own control as represented by baseline measures. Confirmation of non-oxybate effect is available from initial polysomnogram recordings (prior to cessation of anti-cataplectic medications). Interpretation of intra-patient variability is limited by lack of randomization in this study, but is strongly supported in the literature.

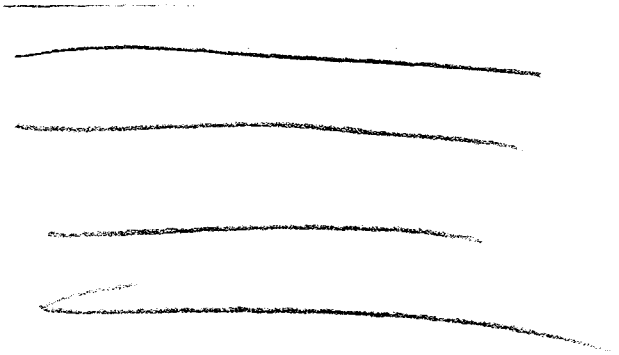
- There is no dose-related effect demonstrated in the incidence of sleep-disordered breathing events that could support a pharmacologic response attributable to sodium oxybate in the dose range studied from 4.5-9g/night. There is disassociation between the numerical representations of Respiratory

Disturbance Index and the effects on oxygen saturation in this study, indicating such events are brief in duration and have not led to prolonged decreases in ventilation with consequent hypoxia. Since the primary measure of respiratory function is gas exchange, the absence of desaturation does not represent a decline in respiratory function.

10.4 Reviewer's Comments

- The literature review of variability in sleep-disordered breathing provided by the sponsor does appear to indicate the following
  - There is spontaneous intrasubject variability in measures of sleep-disordered breathing in some individuals
  - However, spontaneous intrasubject variability in measures of sleep-disordered breathing, of the magnitude seen in Patient #17301 in OMC-SXB-20 between Visits 2a and 3, does not appear to be common.
  - Sleep-disordered breathing that is severe (as measured by the AHI/RDI), and even more prominent than that seen in the OMC-SXB-20 study, may not be uncommon among those presenting to a sleep center
- Individual patient profiles do continue to raise concern about the effects of Xyrem® on respiratory parameters in patients with pre-existing sleep apnea based on the following 2 patients
  - Patient 17301 who had the following abnormalities:
    - An elevated RDI at baseline, in the ~ 14 to 32 range, increasing up to ~ 100, an extremely abnormal value, at Visit 3, after 4 weeks of treatment at 4.5 g/day. The RDI decreased with further increases in dose, but not to baseline levels
    - A steady increase over the course of the study (i.e., with increasing dose) in the period of time spent at an SaO_2 < 90%; by the end of the study, almost 70% of a 4-hour period had been spent at an oxygen saturation in that range. Admittedly, this increase did not occur in parallel with changes in RDI after Visit 3.

      Note that an oxygen saturation of 90% represents a particularly critical segment of the oxyhemoglobin dissociation curve; at this stage, the curve changes from flat to steep with small decreases in pO2 resulting in steep decreases in SaO_2, as indicated by the following figure. Also note that, in the figure below, the pO2 and SaO_2, are represented on the x- and y-axis, respectively



  - Patient 17304 who is of less concern and had the following abnormalities
    - An elevated RDI at baseline falling in the ~ 14 to 32 range, and increasing further to ~ 100 at Visit 3 , after 4 weeks of treatment at 4.5 g/day
    - A perception by her husband that the severity of her snoring as well as apneic episodes had increased over the course of the trial leading her to discontinue at Visit 4

It is also equally noteworthy, however, that

- No evidence of a dose response in the severity of sleep apnea was seen in either of these patients
- Changes in oxygen saturation parameters in these patients did not correlate with changes in RDI
- It cannot be proven that the changes in respiratory parameters in these 2 patients were due to Xyrem®, as opposed to spontaneous variability in the severity of sleep apnea

- In the initial Approvable action letter, dated 7/2/01, the following was stated

"As a CNS depressant, sodium oxybate is capable of producing respiratory depression. However, your application contains no formal assessment of this potential. Such assessments are routinely required in the evaluation of sedative-hypnotic drug products. For this reason, you should perform such a study. The study should examine the effects of the recommended dosing regimen (2 doses nightly, including the highest recommended dose-9 gms divided), with both doses given in the fasted state. The study should include patients who are and who are not receiving concomitant stimulant treatment, a positive control, and patients with concomitant illnesses that might increase their risk of respiratory depression (e.g., patients with COPD, sleep apnea, etc.). In addition, plasma level data should be obtained at appropriate times. We would be happy to discuss the design of such a study with you. We believe there is sufficient suggestion of occasional respiratory depression in the clinical studies to ask that these data be collected prior to marketing."

By agreement with this Division, the sponsor submitted respiratory data from Study OMC-SXB-20 (in the Amendment/Response to Approvable Letter submitted 10/5/01) in an effort to allay Divisional concerns about the potential respiratory depressant effects of Xyrem® sufficiently for approval to be granted, with a commitment from the sponsor to perform a definitive study post-approval.

- As has been noted several times earlier in this review, it is difficult to draw any firm conclusions from this study as a whole regarding the effect of sodium oxybate on respiratory parameters; the reasons for such a view are as follows
  - The study was open-label and uncontrolled
  - The number of patients enrolled was small
  - There was considerable inter-patient variability in changes from baseline in all parameters with standard deviations consistently exceeding means
- This study cannot therefore be stated to have allayed Divisional concerns about the respiratory depressant effects of Xyrem®. In fact, the study has raised at least some concern about the safety of Xyrem® in patients with moderate-severe obstructive sleep apnea, a condition that may not infrequently co-exist with cataplexy.

11. Risk Management Program Elements

9 separate documents have been submitted by the sponsor. Each has been submitted in 3 separate formats: Microsoft Word, PDF (annotated), if necessary, and PDF ("clean")