Study #	Frequency of vital sign testing
OMC-GHB-3	Baseline, 2 weeks and Months 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 18, 21 and 24
OMC-SXB-6	Screening, Week 2 and Months 2 and 6
OMC-SXB-7	Baseline and Months 6, 12, 18 and 24
Scrima	No provision for checking vital signs

8.7.1.2 Lammers Trial

There was no provision for recording vital signs during this trial

8.7.1.3 Integrated Pharmacokinetic Trials

Vital signs recorded and analyzed, when specified, included sitting and standing blood pressure, heart rate, respiration, body temperature and body weight.

Vital signs were to be checked in each of the single-dose pharmacokinetic trials as follows.

Study #	Frequency of Vital Sign Checks
OMC-GHB-4	Baseline and 60 hours after dosing
OMC-SXB-8	Baseline and 2, 4 and 8 hours after dosing
OMC-SXB-9	Baseline and 2, 6 and 10 hours after dosing
OMC-SXB-10	Baseline and 1, 3, and 8 hours after dosing
OMC-SXB-11	Baseline and 2, 6 and 10 hours after dosing
OMC-SXB-12	Baseline and 1, 2, 6 and 10 hours after dosing
OMC-SXB-14	Baseline and 2, 6, 10 and 24 hours after dosing
OMC-SXB-17	Baseline and 1, 2, 6 and 10 hours after dosing

8.7.1.4 Scharf Trial

There was no provision for checking vital signs in the protocol or Case Report Form.

8.7.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled Clinical trial: OMC-GHB-2 (this was the only controlled clinical trial in which vital signs were checked after administration of study drug)
- Integrated Clinical Trials
- Integrated Pharmacokinetic Trials

8.7.3 Standard Analyses and Explorations of Vital Sign Data

8.7.3.1 Controlled Clinical Trial OMC-GHB-2

The sponsor has provided a table that displays descriptive statistics for changes in vital signs across dose groups from baseline to Visit 6 (end of period of double-blind treatment). The mean changes seen were not clinically significant. The data suggested a dose-related decrease in weight and sitting diastolic blood pressure. An abbreviated form of the sponsor's main table, including only mean changes is reproduced below

Changes from baseline to Visit 6 in vital signs

Changes in vital signs	Placebo	GHB dose (g) 3	6	9
Weight (kg) - mean	0.69	-0.09	-0.34	-0.8
Sitting systolic blood pressure (mm Hg) - mean	1.41	3.56	-1.10	-0.31
Sitting diastolic blood pressure (mm Hg) - mean	2.09	0.53	0.77	-1.83
Standing systolic blood pressure (mm Hg) - mean	4.26	5.47	-1.55	0.00
Standing diastolic blood pressure (mm Hg) - mean	1.74	0.63	-0.55	-2.79
Pulse rate (bpm) - mean	-0.94	1.0	3.16	-1.76
Respiration (breaths per minute) - mean	-0.24	-0.87	-0.2	-0.19

The sponsor's main table also indicates that there were no clinically significant differences between the placebo group and the individual GHB dose groups in minimum and maximum changes for the above adverse events.

8.7.3.2 Integrated Clinical Trials

The sponsor has presented a table containing descriptive statistics for the change from baseline to last observation in vital signs. The tables indicate that mean changes for all parameters were very small and similar across all treatment groups. I have not reproduced these vital signs.

8.7.3.3 Integrated Pharmacokinetic Trials

Individual data listings have been made available for all pharmacokinetic trials except OMC-GHB-4; for the latter trial descriptive statistics have been made available for vital signs.

These data do not reveal any changes that could be considered clinically significant.

8.8 ECG

8.8.1 Extent of Electrocardiogram Testing During Development

The data below refer only to post-treatment electrocardiograms

8.8.1.1 Integrated Clinical Trials

Standard 12-lead resting electrocardiograms were performed.

The frequency at which electrocardiogram testing were intended to be checked (as per protocol) in these studies is indicated in the following table

Study #	Frequency of electrocardiogram testing
OMC-GHB-2	Screening and end of period of study drug administration
OMC-GHB-3	Baseline and Months 6, 12 and 18
OMC-SXB-6	Screening, and Month 6 (if medically indicated)
OMC-SXB-7	No provision for checking electrocardiograms
Scrima	No provision for checking electrocardiograms

8.8.1.2 Lammers Trial

There was no provision for checking electrocardiograms during this trial

8.8.1.3 Integrated Pharmacokinetic Trials

No post-treatment electrocardiograms were checked during these trials

8.8.1.4 Scharf Trial

A standard 12-lead electrocardiogram was to be checked at or prior to study entry, and annually thereafter

8.8.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled clinical trial: OMC-GHB-2
- Integrated Clinical Trials
- Scharf trial

8.8.3 Standard Analyses and Explorations of Electrocardiogram Data

8.8.3.1 Controlled Clinical Trial: OMC-GHB-2

The number and percentage of patients in each treatment group whose values went from normal to abnormal in each treatment group between the baseline and Week 6 (end of double-blind period) visits is summarized in the following table

Treatment Group	Number	Patient ID #s
Placebo	2 (6 %)	512, 818
GHB 3 g	2 (6 %)	407, 1610
GHB 6 g	1 (3.5 %)	105
GHB 9 g	3 (11.5 %)	206, 217, 1309

Details of all 8 patients are summarized in the following table

Abnormal ECGs at Visit 6

Patient number	Visit 1 Interpretation	Visit 6 Comments on abnormality	Follow-up (for ECGs not labeled NCS at V6)
105	Within normal limits	Sinus bradycardia – not clinically significant	
206	Within normal limits	Consider left atrial enlargement	Not clinically significant as determined by site
217	Within normal limits	Sinus arrythmia, vertical axis	Not clinically significant as determined by site
407	Within normal limits	Normal sinus rhythm, nonspecific T wave abnormality	Not clinically significant as determined by site No Change from baseline, CRF incorrectly reported
512	Within normal limits	QRS axis range 0 to 14 horizontal axis- not clinically significant	
818	Within normal limits	Sinus tachycardia - not clinically significant	
1309	Within normal limits	OCL unifocal ventricular extra beat (VPC), RR complex V1-V2 indicate primary right bundle branch block with QRS 0.10-0.11 seconds	ECG was repeated on 12/30/97 and read by It was interpreted as Borderline ECG Within normal limits
1610	Within normal limits	Nonspecific T-wave abnormality in anterior-lateral leads when compared with ECG 08/08/97 per — — - change possibly due to hypokalemia - not clinically significant	

None of the above electrocardiogram abnormalities was felt to be clinically significant.

8.8.3.2 Integrated Clinical Trials

The sponsor has presented shift tables for the categorical change from baseline to last observation in vital signs. The shift categories were:

Abnormal to abnormal	Within normal limits to abnormal
Abnormal to within normal limits	Within normal limits to within normal limits
Abnormal to not done	Within normal limits to not done

The tables indicate that no shifts of > 10% were seen for the entire population or for the "normal to abnormal" category in any single electrocardiogram parameter.

For the within normal limits to abnormal category the distribution was as follows

Dose Group	Placebo	3 g/day	4.5 g/day	6 g/day	7.5 g/day	9 g/day	Total
Number With Change	o	0	2	3	1	3	9
Total number in dose group	3	26	88	141	61	83	402

Note that all patients in each dose group did not have electrocardiograms done both at baseline and subsequently, the last row cannot therefore be used as a denominator to calculate percentages for the second row

8.8.3.3 Scharf Trial

All electrocardiograms in the study were categorized as being normal or abnormal and a shift table generated which demonstrates categorical change by dose group from baseline. This table is reproduced below.

ECG Shift	GHB dose (g) n (%) All Patients	3	4.5	6	7.5	9
Norm to Norm	9 (6.3)	0 (0.0)	3 (6.1)	4 (6.5)	2 (11.1)	0 (0.0)
Norm to Abn[1]	36 (25.2)	1 (20.0)	11 (22.4)	16 (25.8)	4 (22.2)	4 (44.4)
Abn to Norm[2]	5 (3.5)	0 (0.0)	3 (6.1)	2 (3.2)	0 (0.0)	0 (0.0)
Abn to Abn	39 (27.3)	0 (0.0)	13 (26.5)	19 (30.6)	5 (27.8)	2 (22.2)

[1]Patients included if they had a normal baseline ECG and had an abnormal ECG anytime while receiving GHB.
[2]Patients included if they had an abnormal baseline ECG and had a normal ECG anytime while receiving GHB.

Source: Section 15-Table 8

Note that of those patients who had baseline electrocardiograms, some had a single repeat recording whether others had multiple recordings done. The interval between recordings was highly variable.

Of the 36 patients who had electrocardiograms that were normal at baseline but abnormal later

- 28 patients had abnormalities that were considered "non-specific, benign and highly unlikely to be clinically significant"
- In the remaining 8 patients the abnormalities were considered to possibly be clinically significant, but probably not related to study medication. The sponsor has provided short descriptions of the conclusions(diagnoses) drawn for the electrocardiograms for these 8 patients. The diagnoses reached in these 8 patients were distributed in the following 4 categories: except for 1 patient each who were considered to have acute pericarditis and ischemic heart disease, the remainder had multiple electrocardiograms. No additional information is available for these patients and there is no evidence that an attempt was made to correlate electrocardiogram abnormalities with symptoms, physical signs or other cardiac tests in these patients.

Left ventricular hypertrophy	1 patient
Ischemic heart disease	3 patient
Conduction system disease	3 patient
Acute pericarditis	1 patient

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