CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-627/S-035

CLINICAL PHARMACOLOGY BIOPHARMACEUTICS REVIEW

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-627 **SUPPLEMENT NO.:** SE5-035
NAME: Diprivan® (Propofol) Injectable Emulsion
SPONSOR: Zeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19850
SUBMISSION TYPE: Labeling Supplement **SUMISSION DATE:** May 21, 1999
REVIEWER: Suresh Doddapaneni, Ph.D.

Filing Review

Diprivan® is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. In this submission, the sponsor is submitting pediatric study reports supporting the amended labeling regarding the use of Diprivan® in the pediatric population for general anesthesia _____ . The submitted study reports on two trials (trial 1 & trial 2) are stipulated in the pediatric written request and using these the sponsor is seeking pediatric exclusivity determination as permitted under the FDAMA regulations. A copy of the written request is appended to this review.

Regarding the Human Pharmacokinetics and Biopharmaceutics component of the submission, the written request stipulated that pharmacokinetic data in neonates, infants, and children be collected in trial 2 (birth to 3 years of age). Trial 0859US/0046 contains this data. Beyond this, the written request does not contain any other applicable specific language on the study design or analysis with respect to pharmacokinetics. In addition to conducting study 0859US/0046 for this pediatric exclusivity submission, the sponsor also conducted additional pharmacokinetic analysis by combining data from trial 0859US/0046 and trial 0859IL/0058 (previously conducted) in order to analyze clearance across a much wider age range of the pediatric population (birth to 16 years).

A cursory evaluation of the submission did not reveal any obvious deficiencies that would preclude its filing. Acceptable analytical methodology validation data was submitted. Labeling changes arising out of this submission were clearly annotated.

Recommendation

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics, supplement SE5-035 to NDA 19-627 can be filed.

(S) 7/15/99
Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist, DPE II/OCPB

FT initialed by Ramana Uppoor, Ph.D. (S) 7/16/99

CC:
NDA 19-627, HFD-170 (Division File, Fong), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), Barbara Murphy (CDR).

NDA: 19-627
Name: Diprivan ® (Propofol) Injectable Emulsion
Sponsor: Zeneca Pharmaceuticals, Wilmington, DE
Submission Type: Labeling Supplement
Reviewer: Paul L. Hepp, Pharm.D.

Supplement No.: SE5-035
Submission Date: May 21, 1999
June 11,1999

SYNOPSIS:

The purpose of the submission was to support proposed amended labeling regarding the use of Diprivan 1% emulsion in pediatric patients less than 3 years of age for induction and maintenance of general anesthesia during surgery. The submission was also intended to support proposed amended labeling regarding the use of Diprivan in pediatric patients [redacted] The results of two clinical trials in pediatric patients are reported in the submission. The two trials were stipulated in the Agency's April 22, 1999 Written Request for submission by Zeneca Pharmaceuticals of clinical studies for propofol in pediatric patients pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act .
The sponsor has submitted clinical studies to address safety and efficacy of diprivan 1% emulsion for the above pediatric age groups and indications, as well as to characterize diprivan clearance and diprivan clearance relationships in the subjects and subgroups within the studies.

None of the diprivan clearance information reported for the general anesthesia study (0859US/0046) is acceptable due to study design issues and analytical questions. No clearance information related to this general anesthesia study is acceptable for labeling purposes. In the Agency's April 22, 1999 Written Request to the sponsor, it was requested that for the general anesthesia study that data on plasma concentrations of propofol in neonates, infants, and children that can be correlated with effect and adverse effects be reported. No attempt to correlate these concentrations to effect and adverse effects were reported.

[redacted]

RECOMMENDATION:

[redacted]

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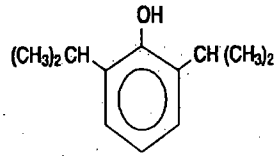
BACKGROUND

DIPRIVAN® Injectable Emulsion is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-diisopropylphenol and has a molecular weight of 178.27. The structural and molecular formulas are:



$C_{12}H_{18}O$

Due to limited solubility in aqueous systems, the product is formulated as an oil in water emulsion. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL), and disodium edetate (0.005%), with sodium hydroxide to adjust pH. The DIPRIVAN Injection emulsion is isotonic and has a pH of 7-8.5.

Diprivan is an intravenous sedative-hypnotic agent used for both induction and/or maintenance of anesthesia for inpatient and outpatient surgery as part of a balanced anesthetic technique in adults and children, 3 years of age or older. It is also approved for Monitored Anesthesia Care (MAC) sedation during diagnostic or surgical procedures involving local/regional anesthesia in

adult patients. Diprivan is also approved for continuous sedation and control of stress response in intubated , mechanically ventilated adult patients in the ICU setting.

The purpose of the submission is to support proposed amended labeling regarding the use of Diprivan in pediatric patients less than 3 years of age for induction and maintenance of general anesthesia during surgery. The submission is also intended to support proposed amended labeling regarding the use of Diprivan in pediatric patients (——————— ——————— The results of two clinical trials in pediatric patients are reported in the submission. The two trials were stipulated in the Agency's April 22, 1999 Written Request for submission by Zeneca Pharmaceuticals of clinical studies for propofol in pediatric patients pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act . According to the FDA Written Request, the two trials were to be as described below:

Type of Studies:

Trial A: A randomized, double blind, comparative dose-ranging trial of 1% versus 2% propofol versus standard anesthetic agents requested to evaluate the safety and efficacy in pediatric patients requiring ICU sedation. The Agency's written request indicated that dosages were to be individualized and titrated so that an appropriate range of safe and effective levels could be identified.

Trial B: A randomized, open –label, comparative, parallel group trial of 1% propofol versus standard anesthetic technique for induction and maintenance of general anesthesia for surgery or procedures lasting 15 minutes or more in patients from birth to 3 years of age. It was requested that this study provide data on the safety (and recovery) profile of propofol versus standard anesthetic technique, on propofol dosing for general anesthesia and on plasma concentrations of propofol in neonates, infants and children that could be correlated with effect and adverse effects. The Agency's written request also indicated that dosages were to be individualized and titrated so that an appropriate range of safe and effective levels could be identified.

The results of the above described studies have been submitted in this supplement as study trial 0859IL/0068 (Trial A above) and as study trial 0859US/0046 (Trial B above). Limited pharmacokinetic data was submitted as part of the trial 0859US/0046 and trial 0859IL/0068. Additionally, the sponsor submitted a pharmacokinetic analysis of clearance using combined data from trial 0859US/0046 and a previously conducted pediatric study (trial 0859IL/0058) which included patients aged 3 months to 16 years of age. It was indicated in the submission that combining study results for trial 0859IL/0058 with the results of trial 0859US/0046, would increase the number of pediatric patients to base clearance values on.

Finally, a June 11, 1999 submission was made by the sponsor and included assay validation information for trial 0859US/0046 and trial 0859IL/0058.

STUDY TRIAL 0859US/0046- SUMMARY

This study was conducted in pediatric patients aged from birth to 3 years of age who were administered standard sedative agents or propofol 1% emulsion for general anesthesia for surgery or procedures lasting 15 or more minutes. A summary of diprivan clearance by age group is presented below:

WEIGHT ADJUSTED PROPOFOL CLEARANCE IN PEDIATRIC SUBJECTS BY AGE GROUP

Age group	Clearance (ml/min/kg)				
	N	Mean	SD	Minimum	Maximum
Birth to <2 months	1	67.2	NA		
2 months to <2 years	25	110.2	69.6		
2 years to <3 years	7	90.0	15.7		

SD standard deviation.
NA not applicable.

Due to issues related to the establishment of steady-state and the appropriateness of sampling times, none of the calculated diprivan clearance information can be considered to be valid or dependable. Further, claims of no gender or ethnic based differences in diprivan clearance cannot be supported by study 0859US/0046. As a result, no diprivan clearance related descriptive or dosage related (starting, adjusting, etc) information based on this study should be allowed in the labeling. Although there are also analytical questions related to the study (Deficiencies 1,3), addressing them will not alter the above recommendation related to labeling.

PEDIATRIC TRIAL 0859US/0046- DETAILED METHODS AND RESULTS

The Safety of Diprivan TM (propofol) Anesthesia versus Standard Anesthetic Techniques in Pediatric Subjects less than 36 Months of Age

Principal investigator and location (center number): Raafat S Hannallah MD, Children's National Medical Center. Department of Anesthesiology, 111 Michigan Avenue NW, Washington, DC 20010-0002

Clinical phase: IIIb First subject recruited: 18 February 1999
Last subject completed: 25 March 1999

Study Medication: Diprivan Injectable Emulsion (Formulation number 11 309, Lot number 4787YA), an emulsion of 1% propofol containing 0.005% disodium edetate, in ready-to-use 50-ml vials. Diprivan Injectable Emulsion was stored between 4°C and 22°C

SPONSOR STATED OBJECTIVES

Primary: to compare the safety profile of Diprivan versus standard anesthetic technique
Secondary: to compare the recovery profile of Diprivan versus standard anesthetic technique; to determine Diprivan dosing information; and to assess the blood levels of propofol, where possible, in neonates, infants, and children.

METHODS

Design: multicenter, open-label, comparative, parallel-group, randomized trial in which subjects were allocated to receive general anesthesia for surgical or other procedures with either Diprivan or a standard anesthetic agent. Anesthesia was expected to last for at least 15 minutes.

Population: A maximum of 120 pediatric subjects whose parent or legal guardian gave written informed consent for trial participation were sought for enrollment to obtain 100 evaluable subjects.

KEY INCLUSION CRITERIA

Boys or girls in American Society of Anesthesiology (ASA) classes I to IV who were less than 36 months of age and who were admitted for surgical or other procedures expected to last for 15 minutes or more.

DOSAGE

For subjects randomized to Diprivan, induction of anesthesia (as opposed to maintenance of anesthesia) could occur with either inhalation medication or Diprivan. For Diprivan induction, a dose of 2.5 to 3.5 mg/kg was administered intravenously over 20 to 30 seconds. For maintenance of anesthesia, Diprivan was given by intravenous infusion at a recommended rate of 200 to 300ug/kg per minute for the first 30 minutes, with a subsequent reduction in rate to 125 to 150 ug/kg per minute.

PHARMACOKINETIC ASSESSMENTS

Collection and Analysis of Samples

Blood samples for analysis of propofol levels were to be collected when possible for subjects who were given Diprivan. Two samples were obtained during maintenance of anesthesia; these

Derivation Of Pharmacokinetic Parameters And Statistical Analysis

The pharmacokinetic analysis of propofol concentration and clearance was performed by the Drug Disposition and Metabolism group, Zeneca. Plasma concentrations of propofol were summarized, and clearance was calculated using the relationship $CL=R/C_{ss}$ (clearance = infusion rate/propofol concentration at steady state) when appropriate dose information and plasma propofol concentration data were available. The relationship between clearance and various covariates (e.g. age, weight. body surface area) was investigated.

ANALYSIS OF SAMPLES FOR PROPOFOL

Plasma sample analysis began on 01-Apr-1999 and was completed on 08-Apr-1999. Sample analysis was completed over 3 chromatographic assay runs. Single assays were carried out with samples repeated for cause, when sufficient plasma volume remained. Due to sample volume limitations, all samples, with the exception of baseline samples, were analyzed at an initial dilution. Samples assaying above the upper validated limit at this initial dilution were reanalyzed at a higher, appropriate dilution, to bring all final reported results within the validated assay range. The first analytical run had to be reinjected in its entirety due to chromatographic problems and was reinjected within the established stability period for samples in injection solvent.

The stability, precision and accuracy of the propofol plasma bioanalytical method were assessed over the course of the assays based on the results of the spiked plasma quality control samples which were assayed on each day of the clinical analysis. Spiked quality control pools

propofol before the start of the analysis. Frozen aliquots of these pools were analyzed on each day in duplicate. Additional quality control samples were analyzed on 05-Apr-1999 due to the length of the analytical run. Low controls averaged 115% of theory (6.0% RSD), middle controls averaged 106% of theory (9.5% RSD) and high controls averaged 104% of theory (13.2% RSD). At least four of the six quality control samples on each day, including one at each concentration, had to be within 20% of theory for the run to be accepted. No runs were rejected due to unacceptable quality control assay results

RESULTS

Demography

105 children from 3 centers were randomized (52 Diprivan, 53 standard anesthetic); 2 subjects (1 in each treatment group) were withdrawn before trial treatment; 103 subjects (69 boys, 34 girls) aged newborn through approximately 36 months (35.9 months) were given trial treatment (51 Diprivan 52 standard anesthetic) .

Of the 103 subjects treated, 5 were less than 2 months of age, 75 were 2 months to less than 2 years of age, and 23 were 2 to less than 3 years of age. All 53 subjects given Diprivan and 43 subjects given standard anesthetic agents were included in efficacy analyses; 9 subjects in the standard anesthetic group were excluded from analysis because of protocol deviations related to the disallowed anesthetic agents given. One subject given trial medication (standard anesthetic) was withdrawn from the trial, due to an adverse event.

Below is shown the study population data by age group:

POPULATION BY AGE GROUP

Category	Age and treatment group					
	Birth to <2 months		2 months to <2 years		2 years to <3 years	
	Diprivan	Standard	Diprivan	Standard	Diprivan	Standard
Number of subjects randomized[a]	1	4	41	34	9	14
Number of randomized subjects who never were given trial treatment[a]	0	0	0	0	0	0
Safety data set (all subjects who were given trial treatment)	1	4	41	34	9	14
Efficacy data set (evaluable subjects[b])	1	2	41	32	9	9
Not evaluable	0	2	0	2	0	5

[a] Age was not recorded for the 2 subjects who were not given trial treatment; thus, they are not included in this table.
[b] Subjects who completed the trial without any protocol deviations that had an impact on the assessment of efficacy.

Demographic characteristics are presented in Tables 1 and 2 (by age group).

Pharmacokinetics

[A comprehensive table (TABLE 1A) of relevant individual and average pharmacokinetic information related to study 0859US/0046- Other tables are also referred to in this section]

The blood sampling in this pediatric population was designed to accommodate the small subject size. Only 2 blood samples were taken during a time when the rate of infusion of propofol was held constant for a minimum of 15 minutes. Based on data available from a prior pediatric trial (0859IL/0058), 15 minutes was the interval assumed necessary to approach an apparent steady state plasma propofol concentration. Forty-two subjects had blood samples drawn for propofol analysis. Thirty-five of these 42 subjects had samples drawn within the time frame required by the protocol. The individual propofol total dose (mg and mg/kg), infusion rate, and infusion duration are shown in Tables 3A-3B. Average diprivan administration during maintenance of anesthesia for all subjects and by age group is shown in Table 4 and below:

Variable	Age group			All subjects
	Birth to <2 months N=1	2 months to <2 years N=41	2 years to <3 years N=9	N=51
Dose (mg)				
Mean	65.3	149.2	150.2	147.7
±SD	NA	123.3	82.3	115.7
Median	65.3	93.3	155.0	93.3
Range	65.3	27.6-606.7	49.0-291.9	27.6-606.7
Dose (mg/kg)				
Mean	21.8	18.5	11.9	17.4
±SD	NA	15.8	6.0	14.5
Median	21.8	11.1	9.7	11.1
Range	21.8	4.1-79.8	5.6-22.0	4.1-79.8
Rate (µg/kg/min)				
Mean	66.8	238.8	219.2	232.0
±SD	NA	61.2	40.6	62.2
Median	66.8	224.2	204.1	223.1
Range	66.8	119.1-394.1	170.7-293.6	66.8-394.1
Duration (min)				
Mean	326.0	82.5	55.3	82.5
±SD	NA	70.2	31.0	73.6
Median	326	50	40	50
Range	326	12-266	26-117	12-326

The propofol concentrations for the 1st sample time are shown in Figure 1 while baseline and the first and second maintenance concentrations are summarized in Tables 5A-5E. Twenty-nine subjects had infusion rates of 200 ug/kg/min; the balance had rates ranging from 90-300 ug/kg/min. Subjects 202 and 229 (200 ug/kg/min infusion rate) had extremely low concentrations of propofol (<100 ng/ml). It was reported that these low propofol concentrations were not consistent with the apparent anesthetic response observed in these subjects. The sponsor reports that the cause of these low concentrations was not known. The firm did not conduct pharmacokinetic analysis on data from these 2 subjects. Sixteen subjects had reported concentrations of propofol in baseline samples. For most of these subjects, the baseline concentrations were less than 1% of the concentrations obtained during maintenance of anesthesia. Three subjects (Subjects 123, 232, and 247) had baseline values that were more than 1% of concentrations obtained during maintenance. The firm indicated that the baseline concentrations represented some unknown contamination.

Comparison of the plasma concentrations of propofol from the 27 subjects receiving approximately 200 ug/kg/min infusion was performed to determine whether propofol concentrations had reached steady state in these children. Three subjects in this group had only 1 plasma propofol concentration. There was less than a 20% difference in propofol concentrations in the 2 samples obtained from 13 children (48%) in this group. Three subjects (11%) in this group had propofol concentrations differing by more than 40%. The remaining subjects' (41%) propofol concentrations were within 40% for the duplicate samples. These data are displayed graphically in Figure 2.

The sponsor states that the agreement between the Maintenance 1 and Maintenance 2 propofol concentrations indicates that an apparent steady state in propofol plasma concentration was likely to have been achieved in these subjects. However, when looking at all infusion rates, it appears that about half of the subjects with two maintenance samples had very large differences between M1 and M2 (16 of 32 subjects). About a third of the subjects (11 of 32 subjects) had large increases between M1 and M2, while about a fifth of the subjects (6 of 32 subjects) had large decreases from M1 to M2.

Weight-adjusted clearance was calculated for each individual propofol concentration. When duplicate samples were obtained, the 2 clearance values were averaged for each subject. Averaged clearance values for each infusion rate are graphically displayed in Figure 3.

The sponsor reports that clearance was independent of infusion rate and that clearance values obtained for all infusion rates were pooled and summarized by pediatric age group. There was very large variation in the clearance values obtained, which ranged from 9.0 to 364 ml/min/kg. The average overall Cl was 104.6 ml/min/kg (59%CV). Data for the pediatric age groups are summarized below:

WEIGHT ADJUSTED PROPOFOL CLEARANCE IN PEDIATRIC SUBJECTS BY AGE GROUP

Age group	Clearance (ml/min/kg)				
	N	Mean	SD	Minimum	Maximum
Birth to <2 months	1	67.2	NA		
2 months to <2 years	25	110.2	69.6		
2 years to <3 years	7	90.0	15.7		

SD standard deviation.
NA not applicable.

The sponsor reported that there was no correlation between clearance values and age, weight, and body surface area. This is displayed graphically in Figures 4, 5, and 6, respectively. The sponsor also reported that there was no effect of gender on clearance (Figure 7). Figure 7A shows that there appeared to be no difference between the black and white subjects in the study in terms of clearance.

It was reported that the clearance values obtained in this trial are higher than those reported in the literature. Mean propofol clearance values obtained during pediatric anesthesia range from 30.6 to 52.7 ml/min/kg (Aun et al 1996, Cohen et al 1997, Kataria et al 1994, Marsh et al 1991, Murat et al 1995, Raoof et al 1995, Saint-Maurice et al 1989, Valtonen et al 1989). The clearance values obtained in these earlier studies are based on more fully characterized plasma concentration-time profiles and compartmental analysis and modeling of the data. Cockshott (1985) reported that steady-state propofol concentrations may not be reached for several hours after constant rate infusion in adults; propofol concentrations at less than 1 hour may be only 65% of those finally reached at steady state. The sponsor indicates that this was not apparent from the concentration-time profiles from the prior Zeneca-sponsored Trial 0859IL/0058, where 15 to 30 minutes appeared to be an adequate time to reach steady-state propofol plasma concentrations. The sponsor states that the plasma concentrations observed in this trial may have been at "pseudo" steady state and, thus an underestimation of the true C_{ss}. This would then result in the higher calculated clearance values found in this trial.

The sponsor also states that the small sample sizes (<100 ul) used in this trial may be more sensitive to the effects of propofol loss due to volatility or dilution (from atmospheric water during frozen storage) than plasma samples in prior trials where large sample volumes could be obtained.

Integrated Summary Of Pharmacokinetics From Trials 0859IL/0058 And 0859US/0046

In a prior Zeneca pediatric trial (0859IL/0058), population pharmacokinetic analysis using data from 26 patients (ages 3 months to 16 years) found a mean (SD) propofol clearance of 52.7 (16.0) ml/min/kg (Cohen et al 1997). The sponsor reports that since the patients in Trial 0859US/0046 were so small, it was felt only 2 samples could be obtained safely from each subject, and therefore it was not possible to analyze the data in the same manner as was done in Trial 0859IL/0058 where multiple samples had been taken. The sponsor reports that in order to compare data from both pediatric trials (0859IL/0058 and 0859US/0046), propofol concentrations measured 15 and 30 minutes after the start of infusion from all 0859IL/0058 subjects (N=60) were considered to represent an apparent steady-state propofol concentration. From this data set, average weight-adjusted clearance values were determined using the relationship: $Cl = R/C_{ss}$, where Cl is weight-adjusted clearance, R is infusion rate, and C_{ss} is the propofol concentration at steady state. The clearance values obtained from this reanalysis of Trial 0859IL/0058 data are shown below:

CLEARANCE OF PROPOFOL IN CHILDREN 3 MONTHS TO 16 YEARS (TRIAL 0859IL/0058)

Age	Clearance (ml/min/kg)				
	N	Mean	SD	Minimum	Maximum
3 months to <2 years	14	79.3	20.8		
2 to <12 years	41	67.3[a]	18.1		
>12 years	19	55.3[b]	34.3		
	(18)[c]	(48.1)	(14.9)		

[a] Statistically significantly different from 3 months to <2 years age group (p=0.042, Student's t-test).
[b] Not statistically significantly different from 2 to <12 years age group (p=0.087, Student's t-test).
[c] Recalculated values without outlier value of 185 ml/min/kg in >12 years age group. Statistically significantly different from 2 to <12 years age group (p=0.00024, Student's t-test).
SD standard deviation.

It is reported that the clearance values calculated using the above limited data set are higher in the 3 month to <2 years and 2 to <12 years pediatric subpopulations than the single value reported for the overall study population, whereas the clearance calculated for the >12 years age group was similar to that reported as a single value for Trial 0859IL/0058. The sponsor indicates that Cockshott reports that steady-state propofol concentration may not be reached for several hours after constant rate infusion in adults; propofol concentrations at less than 1 hour may be only 65% of those finally reached at steady state (Cockshott 1985). The sponsor states that this was not apparent from the Trial 0859IL/0058 concentration-time profiles where 15 to 30 minutes appeared to be an adequate time to reach steady-state propofol plasma concentrations. The sponsor states that therefore, the plasma concentrations observed in this study may have been at "pseudo" steady state and thus, an underestimation of the true C_{ss}, and this would then result in the higher calculated clearance values. The sponsor indicates that nevertheless, this reanalysis of

the 0859IL/0058 data set allows for direct comparison between Trials 0859IL/0058 and 0859US/0046 clearance data. The data from Trial 0859IL/0058 for the younger age pediatric subpopulation was limited; consequently Trial 0859US/0046 was required. A comparison of the results obtained from the 2 trials for the younger pediatric patients is shown below:

PROPOFOL CLEARANCE VALUES OBTAINED IN 2 SEPARATE PEDIATRIC TRIALS IN CHILDREN UNDER 3 YEARS OF AGE

Age	Trial	Clearance (ml/min/kg)				
		N	Mean	SD	Minimum	Maximum
2 months to <2 years[a]	0859US/0046	25	110	70		
	0859IL/0058	14	79.3	20.7		
2 to <3 years[b]	0859US/0046	7	90.0	15.7		
	0859IL/0058	9	78.8	15.0		

[a] Clearance not statistically significantly different between the 2 trials (p=0.116, Student's t-test).
[b] Clearance not statistically significantly different between the 2 trials (p=0.168, Student's t-test).
SD standard deviation.

The sponsor reports that there was no difference in clearance values obtained for the 2 pediatric populations from the 2 trials, and that therefore the data from both trials were combined in order to analyze clearance across the full pediatric population. The sponsor reports that there was an inverse relationship between clearance and the covariates of age, weight, and body surface area as indicated by the negative slopes obtained for the plotted data sets (Figures 8-10). It is reported that the observation that clearance is inversely related to age and weight have been reported by other investigators (Aun et al 1996, Cohen et al 1997, Kataria et al 1994, Raoof et al 1995).

OVERALL CONCLUSIONS- STUDY 0859US/0046

There was no correlation between propofol clearance values and age, weight, and body surface area in children less than 36 months of age. Further, it appears that there is no effect of gender on clearance in this population. The sponsor reported that pooled results from this trial and the previous trial in children 3 months to 16 years of age, show an inverse relationship between propofol clearance and age, weight, and body surface area. However, it is important to note that this relationship in the birth to <3 years group is not supported by the data (Figure 4).

STUDY TRIAL 0859IL/0068- SUMMARY

This study was conducted in pediatric patients aged from birth to < 17 years who were administered propofol 1% or 2% emulsion (with or without concurrent adjunct medication) or standard sedative agents for sedation of critically ill patients, or post trauma or surgical patients.

A number of pharmacokinetic and pharmacodynamic conclusions can be drawn from the study, provided assay validation and specific assay performance information for this study is provided and found to be acceptable (Deficiencies 1,2,3). These conclusions are listed below:

- There appears to be no dependency of diprivan clearance (ml/min/kg) on the number of days of diprivan sedative administration in children

-There appears to be no relationship between diprivan clearance (ml/min/kg) and diprivan sedative administration rate in children

-When diprivan is administered to children for sedation, there appears to be no difference in clearance (ml/min/kg) when given with or without fentanyl

-Diprivan clearance (ml/min/kg) appears to be independent of diprivan sedative dose in children

-There appears to be no difference in diprivan clearance (ml/min/kg) between black and white children being administered diprivan for sedation

-There appears to be no difference in the clearance between the 1% and 2% concentration diprivan formulations administered for sedation

-When diprivan was administered for sedation, diprivan clearance in neonates (birth to < 2 months) was 26% higher than in children 2 to < 12 years, but this was not statistically significant

-Diprivan clearance on a ml/min basis appears to be proportional to weight when diprivan is administered for sedation in children

-Diprivan clearance on a ml/min/kg basis appears not to be proportional to weight when diprivan is administered for sedation in children

-Diprivan clearance (ml/min/kg) may be higher in male than in female children

A summary of diprivan clearance (ml/min/kg) values resultant from the sedation study is presented in the table below:

CLEARANCE (ML/MIN/KG) OBTAINED IN PEDIATRIC POPULATION DURING ICU SEDATION

		Clearance (ml/min/kg)			
Age range	Number	Mean	S.D.	Minimum	Maximum
birth to < 2mo.	4	92.8	40.0		
2mo. To < 2y.	16	78.2	55.3		
2y. to < 12y.	9	73.5	40.3		
> 12y.	1	68.2			

PEDIATRIC TRIAL 0859IL/0068- DETAILED METHODS AND RESULTS

A Multicenter, Comparative, Randomized Trial to Determine the Overall Safety and Efficacy of 1 % Diprivan vs 2% Diprivan vs Standard Agents Without Disodium Edetate for Sedation of Trauma, Postsurgical, or Critically Ill Pediatric Subjects

Clinical phase: IIIb

First patient recruited: 12 December 1996
Last patient completed: 26 July 1998

Finished Product: Diprivan Aqueous Emulsion (Diprivan contains 0.005% disodium edetate (Na_2EDTA))

Principal investigators and location: Michael D Reed Pharm.D. and Jeffrey Blumer Ph.D., M.D.; Rainbow Babies and Children's Hospital, 11100 Euclid Avenue, Cleveland, OH

SPONSOR STATED OBJECTIVES

Primary: to compare the safety and efficacy of Diprivan 2% versus Diprivan 1% versus standard sedative agents without disodium edetate (SSA) in trauma, postsurgical, and critically ill pediatric patients.

Secondary: to evaluate the change in urinary zinc, cobalt, copper, iron, and calcium excretion to estimate the amount of trace metal and calcium supplementation required during continuous sedation with Diprivan compared with SSA in a subset of patients with urinary catheters; to examine significant differences in the overall safety profiles of intensive care unit sedation with

Diprivan 2% versus Diprivan 1% versus SSA; to evaluate the safety and efficacy of Diprivan 2% and Diprivan 1 % monotherapy versus Diprivan 2% and Diprivan 1% with continuous analgesia (at Center 1 only).

The pharmacokinetics of diprivan were also to be studied at Center 1.

METHODS

This was a multicenter comparative, randomized Phase IIIb trial. Patients were stratified by age as follows:

newborn through 1 year

2 through 11 years

12 through 16 years

The age stratification was to ensure a balance between treatment groups without limiting the number of patients required for each age group. The total number of patients enrolled was not expected to be equally stratified across the 3 age groups. Within each completely stratified group, patients were allocated to be given Diprivan 1%, Diprivan 2%, or a standard sedative agent without disodium edetate.

At Center 1, patients who were given Diprivan 1% or Diprivan 2% were further allocated, in a double-blind design, to be given either a continuous infusion of fentanyl or a continuous infusion of normal saline for analgesia.

The trial consisted of the following periods:

(1) Baseline: the 12 hour period before the start of the sedative infusion

(2) Sedation: the period beginning with the initiation of the sedative infusion and ending with the discontinuation of the infusion. Day 1 started at the initiation of the infusion and ended at 2400. Day 2 began at 0001 and ended at either 2400 or the end of sedation.

(3) Post-sedation: the 24-hour period following the discontinuation of the sedative infusion; monitored 72 hours for adverse events

(4) Follow-up for survival: the 28-day period after the end of sedation

Table 6 presents the schedule of assessments. During the trial, blood was drawn only if it did not compromise the safety of the patients.

Trial population

The total numbers of randomized and treated patients are summarized below:

TRIAL POPULATION

Treatment group	Age group[a] Number of patients		
	Newborn through 1 year	2 through 11 years	12 through 16 years
Total randomized	189	122	37
Randomized to			
Diprivan 2%	64	43	12
Diprivan 1%	65	37	13
SSA	60	42	12
Total treated	182	109	36
Treated with			
Diprivan 2%	62	39	12
Diprivan 1%	62	34	13
SSA	58	36	11

[a] Protocol-defined age groups. See Section 2.7.1 for the FDA-defined age groups that are reported in this clinical trial report.
SSA Standard sedative agents without disodium edetate.

Patients were trauma, postsurgical, or critically ill mechanically ventilated patients aged newborn through 16 years who were expected to require sedation for at least 24 hours.

Trial treatment

Diprivan 1% (F11309, lot numbers: 5048W, 5052W, 3766Y,4033Y, and 4122Y) and Diprivan 2% (F11356, lot numbers: 06COO 1 /A and 37923K97) in ready to use 50-ml infusion vials.

Diprivan 1% (F12288, lot number: 5383W) in prefilled 50-ml syringes.

Dosage and administration of trial treatment

Sedative regimen

Patients were randomized to be given either Diprivan 1%, Diprivan 2%, or SSA. SSA was given according to a normal dosing regimen to maintain a comfort scale score between 17 and 26 points. Trial medication was administered continuously using volumetric infusion pumps or as a bolus dose when appropriate.

Initiation and maintenance of Diprivan

Suggested continuous infusion rates for Diprivan started at 5.5 mg/kg per hour (at 0.0 to 0.5 hours) through 9 mg/kg per hour (at 3 to 4 hours), and patients were titrated to clinical response. If the patient needed a dosage increase over 9 mg/kg per hour, a bolus of 2 mg/kg over 15 minutes (using infusion pump) was given before titrated increases of 1 mg/kg per hour. Dosages were individualized and titrated to clinical response in an attempt to maintain a comfort scale score between 17 and 26 points.

Decreases of sedative dosage and change in the level of sedation of the patient were permitted for short periods of time (less than 30 minutes) when clinically indicated as follows: for acute evaluations of respiratory, cognitive, or neurological function or for family visits.

If a patient reached a dose of 12 mg/kg per hour for 8 hours the sponsor was to be consulted regarding further increases in the rate or duration of treatment. If the patient exhibited clinically significant elevated triglyceride levels (as defined by the investigator), the trial medication was discontinued for a maximum of 48 hours after the sponsor was notified.

Adjunctive analgesic agents during sedation

Only at Center 1, patients who were randomized to be given Diprivan were also randomized to be given either fentanyl or normal saline solution simultaneously. A fentanyl bolus was generally given to patients who required noxious procedures.

Concomitant treatment

Only Diprivan or SSA was to be used for sedation. Only patients at Center 1 were randomized to be given either fentanyl or normal saline solution for analgesia. A bolus of fentanyl was given to patients requiring special procedures.

The following concomitant medications were recorded: lipids (not including trial medication), neuromuscular blocking agents, sedative agents, diuretics, and analgesic agents. During the baseline and post-sedation periods and drug holidays, any sedative or analgesic agents other than the trial regimen could be used.

Reporting age stratification

The sponsor indicates that, at the request of the FDA, data presented in this report are stratified into 4 age groups instead of the 3 protocol-designated age groups. The following age stratifications were used:

Birth-<2 months
2 months-<2 years
2-<12 years
12-<17 years

PRIMARY ASSESSMENTS

Maintenance dosage requirements were summarized for each age group for Diprivan 2% and Diprivan 1%.

PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic Parameters Analyzed

Blood samples were analyzed for propofol levels at baseline, Days 2 through 7, every 7 days thereafter, and at the end of sedation for patients only at Center 1.

Collection and analysis of samples

Propofol assay (Center 1 only)

Derivation Of Pharmacokinetic Parameters And Statistical Analysis

The pharmacokinetic analysis of propofol concentrations were performed by the Drug Disposition and Metabolism group, Zeneca. If appropriate, the propofol plasma concentration-time data were used to evaluate the effect of various covariates (e.g., age, weight, body surface area) on the pharmacokinetics of propofol.

RESULTS

Demography

A total of 348 boys and girls entered the trial; 21 of these patients were withdrawn before they were given trial treatment. All 327 patients who were given trial treatment were included in the safety analyses. The safety patient population consisted of the following FDA-defined age classifications:

neonate (birth-<2 months): 36
infant (2 months-<2 years): 146
child (2-<12 years): 109
adolescent (12-<17 years): 36

Population data for all patients by FDA defined age groups are presented below:

POPULATION DATA FOR ALL PATIENTS BY FDA DEFINED AGE GROUPS

Category	Age group / Treatment group											
	Birth-<2 months			2 months-<2 years			2-<12 years			12-<17 years		
	Dip 2%	Dip 1%	SSA	Dip 2%	Dip 1%	SSA	Dip 2%	Dip 1%	SSA	Dip 2%	Dip 1%	SSA
Number of patients randomized	17	11	11	47	54	49	43	37	42	12	13	12
Number of patients randomized who never were given trial treatment	1	0	2	1	3	0	4	3	6	0	0	1
Safety data set (all patients who were given trial treatment)	16	11	9	46	51	49	39	34	36	12	13	11

[a] Pa

[b] Patients who had a protocol deviation but were evaluable at the time of the deviation.

Dip Diprivan.

SSA Standard sedative agents without disodium edetate.

Population data for Center 1 (Monotherapy and combination therapy) are presented below:

POPULATION DATA FOR CENTER 1 (MONOTHERAPY AND COMBINATION THERAPY)

Category	Treatment groups				
	Diprivan 2%		Diprivan 1%		SSA
	Monotherapy	Combination	Monotherapy	Combination	
Number of patients randomized	9	9	9	9	19
Number of patients randomized who never were given trial treatment	0	1	1	1	2
Safety data set (all patients who were given trial treatment)	10	8	8	8	17

[b] Patients who had a protocol deviation but were evaluable at the time of the deviation.

SSA Standard sedative agents without disodium edetate.

Tables 7A and 7B present a summary of demographic characteristics by age group for all patients who were given trial treatment. No statistically significant differences were noted among treatment groups for demographic characteristics, except for the height parameter for patients aged 2 months to less than 2 years between Diprivan 1% and SSA ($p<0.0$ 1).

Pharmacokinetics

Propofol maintenance dosage requirements

A summary of the required daily propofol dose by age group is presented below:

DAILY PROPOFOL DOSE BY AGE GROUP

Dose (mg/kg)	Age group / Treatment group							
	Birth-<2 months		2 months-<2 years		2-<12 years		12-<17 years	
	Diprivan 2% (N=16)	Diprivan 1% (N=11)	Diprivan 2% (N=46)	Diprivan 1% (N=51)	Diprivan 2% (N=39)	Diprivan 1% (N=34)	Diprivan 2% (N=12)	Diprivan 1% (N=13)
Day 1								
Number	15	10	46	48	38	32	11	13
Mean	44.38	45.91	48.98	40.17	61.87	46.41	27.86	25.36
±SD	45.34	29.14	34.25	36.19	44.57	38.72	27.71	16.64
Range	4.0-172.1	11.2-93.8	5.1-144.8	3.8-199.9	1.4-207.4	1.4-169.6	5.5-104.9	3.6-66.7
Day 2								
Number	14	10	36	35	30	25	8	9
Mean	113.52	124.29	142.84	134.50	162.83	115.25	78.40	95.58
±SD	56.03	77.47	77.68	63.82	85.74	46.35	40.34	46.68
Range	27.4-228.3	41.9-312.6	26.1-384.0	25.5-272.4	34.7-488.0	33.0-239.3	31.8-132.0	7.2-139.2
End of sedation								
Number	16	11	45	50	39	34	12	13
Mean	63.37	57.96	102.91	89.98	97.94	59.79	52.90	43.77
±SD	49.93	57.60	70.63	69.96	93.24	37.55	49.02	49.65
Range	3.8-176.5	1.8-210.5	5.0-338.0	2.5-296.0	5.9-517.5	3.0-135.3	2.7-152.5	0.1-174.2

Dose requirements for Diprivan monotherapy and combined therapy

Although variability was large for all groups, patients given Diprivan 2% combination therapy generally had higher values for mean daily propofol dose (mg/kg) than did patients given

Diprivan 2% monotherapy and mean daily propofol doses were generally lower for patients given Diprivan 1% combination therapy compared with patients given Diprivan 1% monotherapy. Below is summarized the dose requirements for Diprivan monotherapy and combined therapy at Center 1:

DOSE REQUIREMENTS FOR DIPRIVAN MONOTHERAPY AND COMBINED THERAPY AT CENTER 1

Dose (mg/kg)	Treatment group			
	Diprivan 2%[a]		Diprivan 1%[a]	
	Monotherapy	Combination	Monotherapy	Combination
Day 1				
Number of patients	8	6	9	7
Mean	101.15	57.91	46.62	48.93
±SD	63.38	64.76	43.47	59.55
Range	10.9-207.4	7.9-172.1	4.1-117.2	5.2-169.6
Day 2				
Number of patients	5	4	6	5
Mean	175.86	192.49	186.79	142.57
±SD	44.03	84.09	95.57	28.19
Range	130.1-228.3	112.4-311.0	56.4-312.6	103.9-182.8
End of sedation				
Number of patients	8	8	10	8
Mean	121.13	96.59	140.05	87.54
±SD	42.29	65.25	84.90	42.67
Range	61.5-183.8	6.9-198.7	37.7-296.0	33.1-159.5

[a] Data for 2 patients was recorded only at end of sedation, because trial drug was started and stopped on the same day.

Propofol Administration

At Center 1, mean duration of sedation was 4 days for patients given Diprivan 2% or Diprivan 1% monotherapy, and mean duration of sedation was 3 days for patients given either Diprivan 2% or Diprivan 1% combination therapy. Table 8 summarizes the overall propofol administration by age group. Below is summarized the overall propofol administration for patients at Center 1:

OVERALL PROPOFOL ADMINISTRATION FOR PATIENTS AT CENTER 1

Propofol administration	Treatment group			
	Diprivan 2%[a]		Diprivan 1%[a]	
	Monotherapy	Combination	Monotherapy	Combination
Number of patients	8	8	10	8
Mean total dose±SD (mg) (range)	10721±19480 (1164-58509)	6892±8033 (24-21716)	5508±4705 (1111-15830)	6354±8472 (182-26230)
Mean total dose±SD (mg/kg) (range)	526±462 (202-1581)	632±839 (7-2405)	857±1269 (42-3769)	494±431 (33-1248)
Mean rate±SD (µg/kg/min) (range)	139±43 (68-208)	122±56 (70-243)	141±42 (77-202)	107±13 (91-123)
Mean duration of sedation±SD (h) (range)	85±123 (22-387)	69±72 (1-165)	86±118 (9-376)	75±59 (5-172)

[a] Data for patients for whom trial drug was started and stopped on the same day were recorded at the end of sedation.

The sponsor reports that the mean rate of propofol administration in this trial is consistent with the mean or highest rate of propofol administration reported in the literature (Figure 11).

Tables 11A-11J present individual and mean daily and overall dose, dose rate, and infusion durations for patients in this study.

Plasma Propofol Concentration: Center 1

The sponsor reports that for patients at Center 1 given Diprivan 2%, mean plasma propofol concentrations were higher on Day 2 for patients given Diprivan 2% combination therapy when compared with patients given Diprivan 2% monotherapy; however, at the end of sedation, mean plasma propofol concentrations for patients given Diprivan 2% combination therapy or Diprivan 2% monotherapy were comparable. For patients given Diprivan 1 %, mean plasma propofol concentrations were higher on Day 2 and at the end of sedation for patients given Diprivan 1% monotherapy when compared with patients given Diprivan 1% combination therapy. Below is summarized the plasma propofol concentrations for patients at Center 1 (plasma propofol concentrations for patients at Center 1 are further summarized in Tables 9A-C):

PLASMA PROPOFOL CONCENTRATIONS: CENTER 1

Time	Plasma propofol concentration (µg/ml) Treatment group							
	Diprivan 2%				Diprivan 1%			
	n	Monotherapy	n	Combination	n	Monotherapy	n	Combination
		Mean±SD (range)		Mean±SD (range)		Mean±SD (range)		Mean±SD (range)
Baseline	8	NQ	7	NC	9	NC	4	NQ
Day 2	5	2±1 (1-4)	3	8±9 (1-18)	3	5±6 (1-12)	5	2±1 (1-3)
End of sedation	8	2±1 (1-4)	5	2±0.3 (1-2)	9	5±6 (1-22)	6	1±1 (0.4-3)

NC If more than half of the values were not quantifiable, then no mean was calculated, and NC was reported.
NQ If all values were not quantifiable, then NQ was reported.

Individual propofol concentration values for Center 1 subjects for are presented in Tables 10A-D.

Tables 11A-11I present individual and mean daily propofol concentrations for patients in this study.

Propofol Clearance: Center 1

Propofol clearance values were calculated using the daily propofol concentrations obtained. Possible relationships between clearance and the covariates of days of sedation, rate of infusion, formulation, age, weight, and gender were examined.

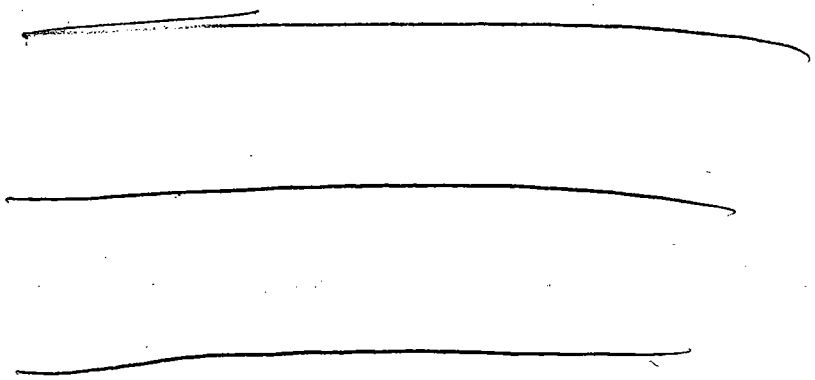
Single plasma samples were obtained daily from days 2 through 7, on day 14 (where appropriate) and at the end of sedation from 30 patients ages 0.7 months to 12.5 years. Weight adjusted clearance was calculated using the relationship: $Cl = R/C_{ss}$ where Cl is weight adjusted clearance, R is infusion rate, and C_{ss} is the propofol concentration at steady state.

Tables 11A-11J present individual and mean daily and overall clearance information for patients in this study.

The relationship between DIPRIVAN plasma clearance and a series of covariates is shown in the figures below. These covariates are duration of infusion, rate of infusion, Diprivan formulation, age, weight, and gender.

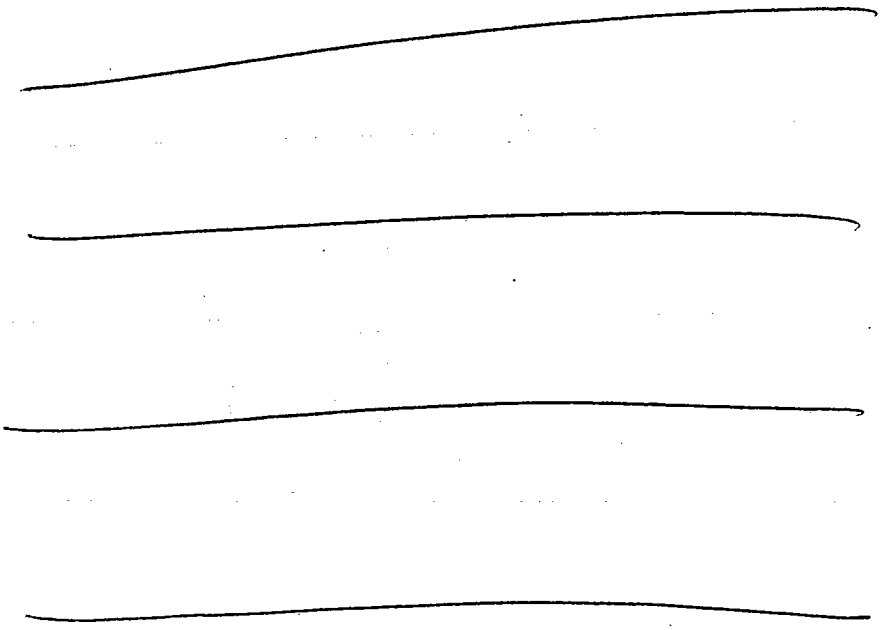
The sponsor reports that there was no dependency of clearance on the number of days of sedation as seen below:

CLEARANCE AS A FUNCTION OF DAYS OF SEDATION IN PEDIATRIC POPULATION



In addition, it was reported that there appeared to be no relationship between clearance and diprivan infusion rate as shown below:

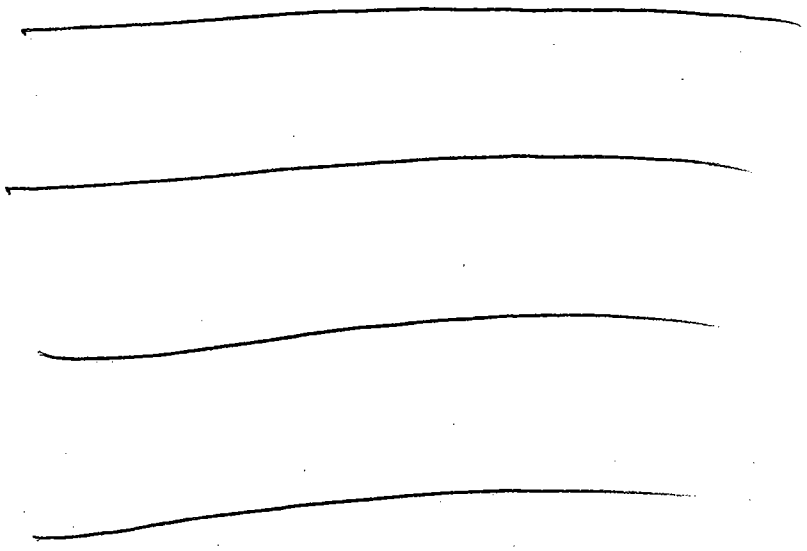
CLEARANCE AS FUNCTION OF RATE OF INFUSION IN PEDIATRIC POPULATION



Therefore, the sponsor averaged individual clearance values to obtain a single clearance value for each patient.

The sponsor reports that there was no difference in the clearance values using 1 or 2% DIPRIVAN formulations as seen below:

CLEARANCE IN PEDIATRIC POPULATION DURING ADMINISTRATION OF 1 % OR 2 % DIPRIVAN FOR ICU SEDATION



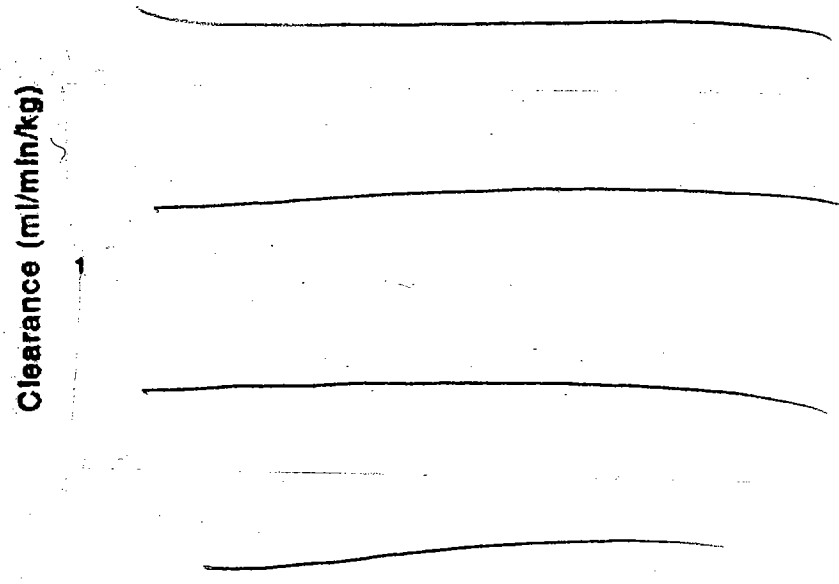
There was a wide range in clearance values obtained in this study. These data are shown for the pediatric age groups below:

CLEARANCE OBTAINED IN PEDIATRIC POPULATION DURING ICU SEDATION

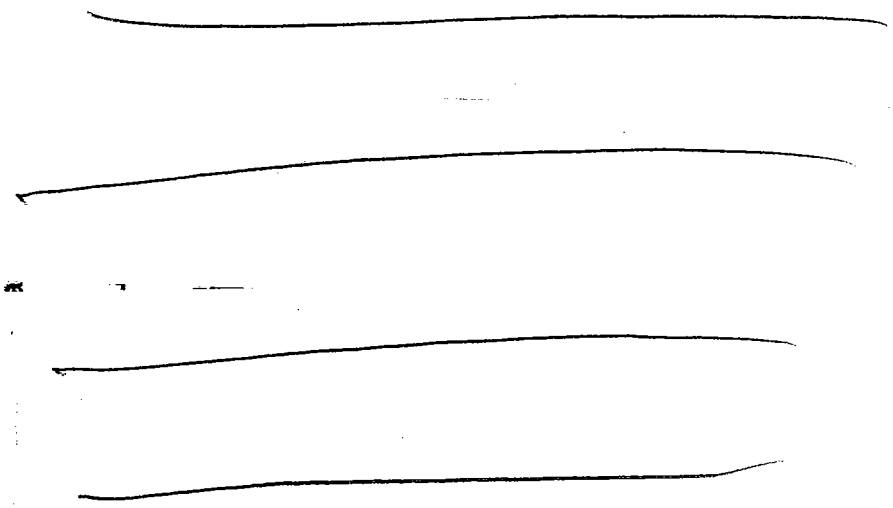
		Clearance (ml/min/kg)			
Age range	Number	Mean	S.D.	Minimum	Maximum
birth to < 2mo.	4	92.8	40.0		
2mo. To < 2y.	16	78.2	55.3		
2y. to < 12y.	9	73.5	40.3		
> 12y.	1	68.2			

Clearance in neonates (0 to < 2mo.) was 26% higher than clearance in children 2yr to < 12yr. This difference did not reach statistical significance (p=0.44), most likely due to the high variability of the data and the limited sample size. Clearance as a function of age is shown graphically below:

CLEARANCE AS A FUNCTION OF AGE IN PEDIATRIC POPULATION



The sponsor reported that there was no dependency of clearance on weight as shown below [It should be noted that clearance reported in the graph below has already been adjusted for weight. If it had not been so adjusted, a clear dependency of clearance on weight would have been seen]:

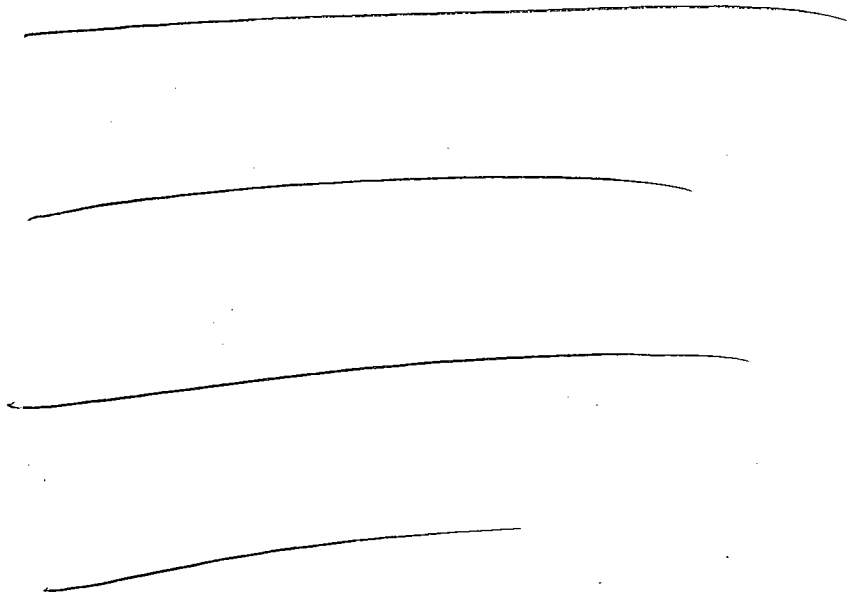


In this study, the sponsor reports that higher clearance values were obtained in males than females as seen in the table and figure below:

CLEARANCE OF PROPOFOL IN MALE AND FEMALE CHILDREN DURING ICU SEDATION

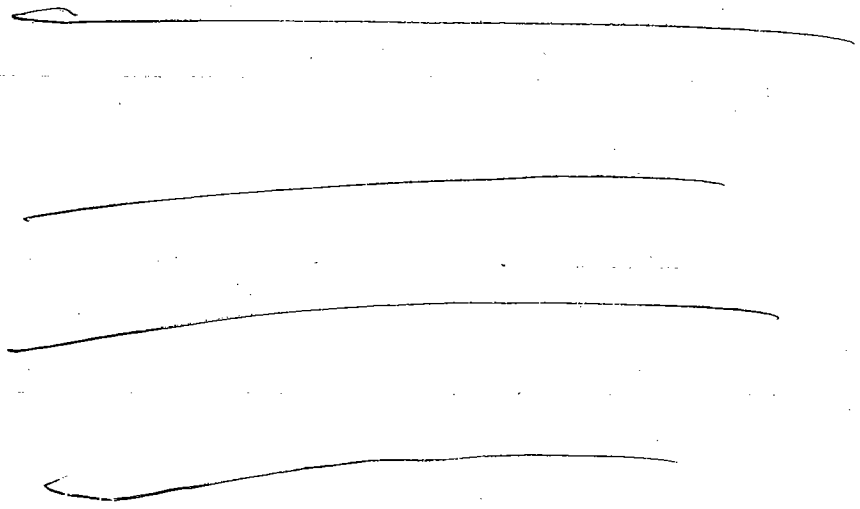
		Clearance (ml/min/kg)			
Gender	Number	Mean	S.D.	Minimum	Maximum
Male	18	96.7	52.1		
Female	12	50.9	18.2		

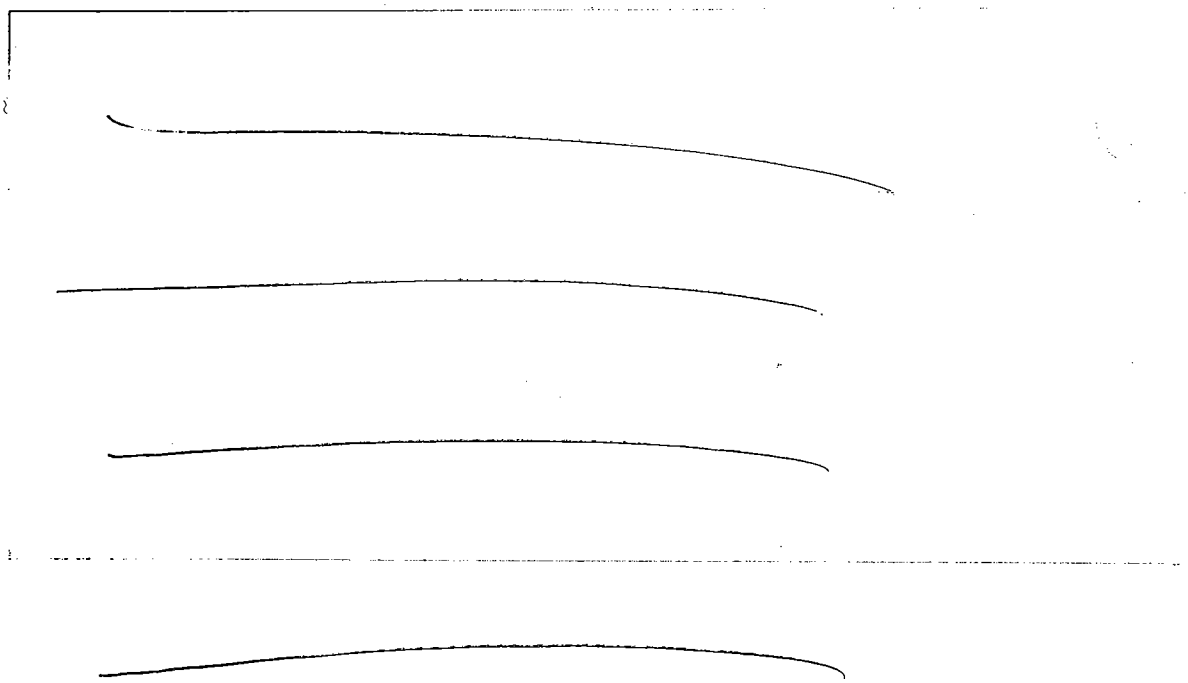
CLEARANCE IN MALE AND FEMALE PEDIATRIC PATIENTS DURING ICU SEDATION



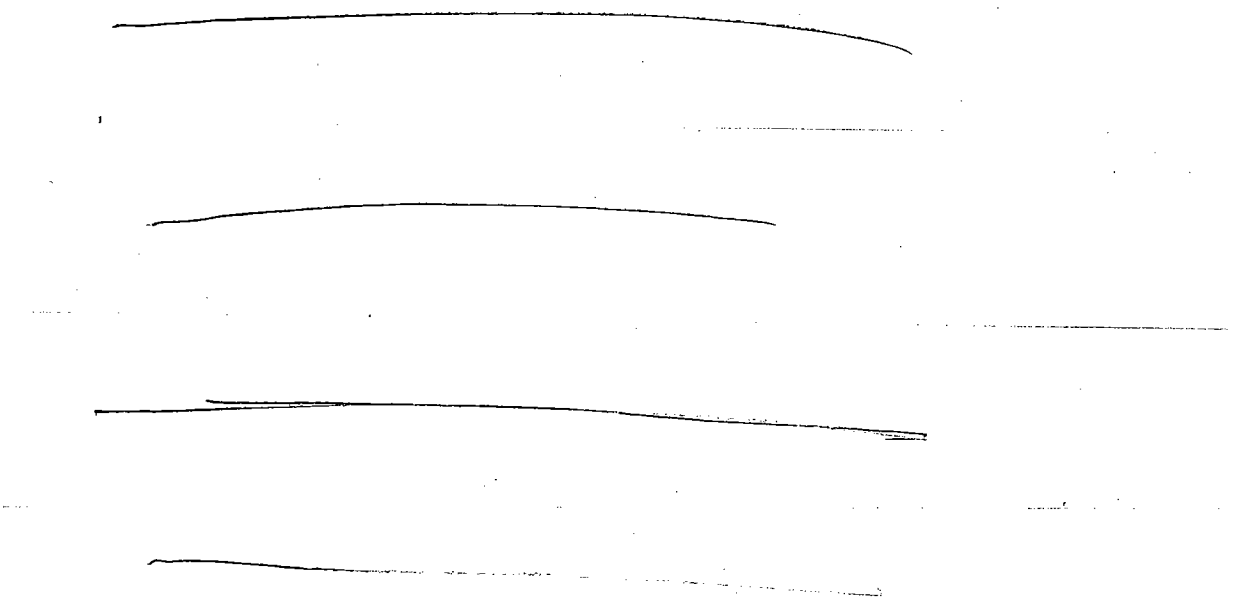
The sponsor reported that gender differences in propofol clearance are generally not observed, and speculated that the difference observed in this study may be due to the high variability of the data and the limited number of patients.

As shown below, clearance did not seem to differ greatly between patients on monotherapy or combination therapy and clearance did not appear to be dependent on dose:





As shown below, there did not seem to be any marked difference in clearance between the black and white patients in the study:



Again, as in study 0859US/0046, the sponsor reports that the clearance values obtained in this study are [redacted]. Reported systemic propofol clearance values obtained during pediatric anesthesia range from 30.6 to 52.7 ml/min/kg in the literature. Reed et al. (Canadian Journal of Physiology and Pharmacology, 72 Suppl 1, 205, Abs 3.1.18, 1994) have reported propofol clearance as 57.5 (s.d 21.9) ml/min/kg during ICU sedation in children. The clearance values obtained in these earlier studies are based on more fully characterized plasma concentration-time profiles and compartmental analysis and modeling of the data. Cockshot (Postgraduate Medicine J., 61, Suppl 3, 45-60 , 1985) reports that steady state propofol concentration may not be reached for several hours after constant rate infusion in adults. Prior investigators have indicated that 5 h is adequate time to reach steady state propofol concentrations in adult ICU sedation (Bailie, Br. J. Anaeshesia, 68, 486-491, 1992). The sponsor reports that [redacted] would be found as described in this study. This argument is not particularly convincing as infusion times were long (days) and blood sampling occurred at times when steady state should have been reached. Also, clearance for this study was lower than for study 0859US/0046 and was closer to previously reported values. The sponsor also speculates that the extremely small sample volume (<100ul) used in this study may be more sensitive to the effects of propofol loss (due to volatility) or dilution (from atmospheric water during frozen storage) than plasma samples of prior studies where large sample volumes could be obtained.

Overall, the sponsor claims [redacted]

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

COMMENTS

8. The sponsor's proposed labeling should be modified as follows based on the unacceptability of reported diprivan clearance reported in study 0859US/0046 (See Dificiencies 1,3,4,5,6,7,8 and Comments 1,2,4):

   The proposed labeling under the **Pharmacokinetics/Pediatrics** section with the following text should not be in the labeling

   s

   The proposed labeling under the **Individualization of Dosage/ Induction of General Anesthesia/Pediatrics** section with the following text should only be allowed if it is based on clinical information and not the reported clearance information from study 0859US/0046 – **"Within this dosage range, younger pediatric patients may require higher induction doses than older pediatric patients"**

   The proposed labeling under the **Maintenance of General Anesthesia / Pediatric Patients** section with the following text should only be allowed if it is based on clinical information and not the reported clearance information from study 0859US/0046 – **"However, younger pediatric patients may require higher maintenance infusion rates than older pediatric patients."**

/S/ 5/9/00

Hepp, Pharm.D.

RD Initialed by (S) Uppoor, Ph.D.
FT Initialed by (S) Uppoor, Ph.D.

5/9/00

cc: NDA-19-627, HFD-170 (Governale,Hartwell), HFD-850 (Hepp,Lesko), HFD-870 (Uppoor, Huang), HFD-344 (Viswanathan), CDR (for scanning)

APPENDIX I- TABLES

TABLE 1A STUDY 0859US/0046-- Subjects 202/229 Removed- 046x.xls

Av

SD

%RSD

TABLE 1A CONT.- STUDY 0859US/0046-Subjects 202/229 Removed- 046x.xls

TABLE 1 DEMOGRAPHIC CHARACTERISTICS

Category	Age and treatment group					
	Birth to <2 months		2 months to <2 years		2 years to <3 years	
	Diprivan N=1	Standard N=4	Diprivan N=41	Standard N=34	Diprivan N=9	Standard N=14
Age (mo)						
n	1	4	41	34	9	14
Mean	0.2	1.0	11.4	11.9	28.8	29.0
±SD	NA	0.7	6.3	6.2	3.7	4.2
Range	0.2	0.1-1.8	2.1-23.7	2.3-23.0	24.5-35.8	24.9-35.9
Sex						
Boys (%)	1 (100)	4 (100)	26 (63)	24 (71)	4 (44)	10 (71)
Girls (%)	0	0	15 (37)	10 (29)	5 (56)	4 (29)
Weight (kg)						
n	1	4	41	34	9	14
Mean	3.0	3.4	8.5	8.8	12.4	12.7
±SD	NA	1.5	2.4	2.2	2.2	3.7
Range	3.0	1.4-4.7	4.1-13.5	5.0-13.2	8.7-16.0	2.7-16.8
Height (cm)						
n	1	3	35	29	7	10
Mean	52	50	69.5	69.8	87.7	87.7
±SD	NA	6.5	11.8	10.4	6.3	8.6
Range	52	43-56	38-90	51-89	79-96	71-98
Race						
White (%)	1 (100)	3 (75)	28 (68)	22 (65)	5 (56)	11 (79)
Black (%)	0	1 (25)	10 (24)	7 (21)	3 (33)	3 (21)
Hispanic (%)	0	0	3 (7)	4 (12)	1 (11)	0
East Indian (%)	0	0	0	1 (3)	0	0
Type of surgery						
Bypass (%)	1 (100)	0	3 (7)	1 (3)	1 (11)	0
Nonbypass (%)	0	4 (100)	38 (93)	33 (97)	8 (89)	14 (100)
ASA class						
I (%)	0	1 (25)	26 (63)	19 (56)	5 (56)	7 (50)
II (%)	0	2 (50)	12 (29)	10 (29)	3 (33)	6 (43)
III (%)	0	0	2 (5)	4 (12)	1 (11)	0
IV (%)	1 (100)	1 (25)	1 (2)	1 (3)	0	1 (7)

NA not applicable.

TABLE 2 DEMOGRAPHIC CHARACTERISTICS BY AGE GROUP

Category	Age and treatment group					
	Birth to <2 months		2 months to <2 years		2 years to <3 years	
	Diprivan N=1	Standard N=4	Diprivan N=41	Standard N=34	Diprivan N=9	Standard N=14
Age (mo)						
n	1	4	41	34	9	14
Mean	0.2	1.0	11.4	11.9	28.8	29.0
±SD	NA	0.7	6.3	6.2	3.7	4.2
Range	0.2	0.1-1.8	2.1-23.7	2.3-23.0	24.5-35.8	24.9-35.9
Sex						
Boys (%)	1 (100)	4 (100)	26 (63)	24 (71)	4 (44)	10 (71)
Girls (%)	0	0	15 (37)	10 (29)	5 (56)	4 (29)
Weight (kg)						
n	1	4	41	34	9	14
Mean	3.0	3.4	8.5	8.8	12.4	12.7
±SD	NA	1.5	2.4	2.2	2.2	3.7
Range	3.0	1.4-4.7	4.1-13.5	5.0-13.2	8.7-16.0	2.7-16.8
Height (cm)						
n	1	3	35	29	7	10
Mean	52	50	69.5	69.8	87.7	87.7
±SD	NA	6.5	11.8	10.4	6.3	8.6
Range	52	43-56	38-90	51-89	79-96	71-98
Race						
White (%)	1 (100)	3 (75)	28 (68)	22 (65)	5 (56)	11 (79)
Black (%)	0	1 (25)	10 (24)	7 (21)	3 (33)	3 (21)
Hispanic (%)	0	0	3 (7)	4 (12)	1 (11)	0
East Indian (%)	0	0	0	1 (3)	0	0
Type of surgery						
Bypass (%)	1 (100)	0	3 (7)	1 (3)	1 (11)	0
Nonbypass (%)	0	4 (100)	38 (93)	33 (97)	8 (89)	14 (100)
ASA class						
I (%)	0	1 (25)	26 (63)	19 (56)	5 (56)	7 (50)
II (%)	0	2 (50)	12 (29)	10 (29)	3 (33)	6 (43)
III (%)	0	0	2 (5)	4 (12)	1 (11)	0
IV (%)	1 (100)	1 (25)	1 (2)	1 (3)	0	1 (7)

NA not applicable.

TABLE 3A

(B59US/0046
TABLE G5.1
DIPRIVAN ADMINISTRATION AND DOSE OF NA2 EDTA DURING MAINTENANCE

AGE GROUP	TREATMENT	CENTER NUMBER	SUBJECT NUMBER	DOSE (MG)	DOSE (MG/KG)	RATE (MCG/KG/MIN)	DURATION (MIN)	NA2 EDTA DOSE (MCG)	NA2 EDTA DOSE (MCG/KG)	NA2 EDTA RATE (MCG/KG/MIN)
BIRTH - < 2 M	DIPRIVAN									
2 M - < 2 Y	DIPRIVAN	1								

0859US/0046

TABLE G5.1

DIPRIVAN ADMINISTRATION AND DOSE OF NA2 EDTA DURING MAINTENANCE

AGE GROUP	TREATMENT	CENTER NUMBER	SUBJECT NUMBER	DOSE (MG)	DOSE (MG/KG)	RATE (MCG/KG/MIN)	DURATION (MIN)	NA2 EDTA DOSE (MCG)	NA2 EDTA DOSE (MCG/KG)	NA2 EDTA RATE (MCG/KG/MIN)
2 M - < 2 Y	DIPRIVAN									
2 - < 3 Y	DIPRIVAN									

TABLE 4

DIPRIVAN ADMONISTRATION DURING MAINTENANCE OF ANESTHESIA FOR ALL SUBJECTS AND BY AGE GROUP

Variable	Age group			All subjects
	Birth to <2 months N=1	2 months to <2 years N=41	2 years to <3 years N=9	N=51
Dose (mg)				
Mean	65.3	149.2	150.2	147.7
±SD	NA	123.3	82.3	115.7
Median	65.3	93.3	155.0	93.3
Range	65.3	27.6-606.7	49.0-291.9	27.6-606.7
Dose (mg/kg)				
Mean	21.8	18.5	11.9	17.4
±SD	NA	15.8	6.0	14.5
Median	21.8	11.1	9.7	11.1
Range	21.8	4.1-79.8	5.6-22.0	4.1-79.8
Rate (µg/kg/min)				
Mean	66.8	238.8	219.2	232.0
±SD	NA	61.2	40.6	62.2
Median	66.8	224.2	204.1	223.1
Range	66.8	119.1-394.1	170.7-293.6	66.8-394.1
Duration (min)				
Mean	326.0	82.5	55.3	82.5
±SD	NA	70.2	31.0	73.6
Median	326	50	40	50
Range	326	12-266	26-117	12-326

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TABLE G10.1

PLASMA PROPOFOL CONCENTRATION (NG/ML)

AGE GROUP	TREATMENT	CENTER NUMBER	SUBJECT	PROTOCOL TIME	TIME	PROPOFOL CONCENTRATION
BIRTH – < 2 M						
2 M – < 2 Y	L					

NOTE: ASSAY DATA FROM SUBJECTS 202 AND 229 WERE EXCLUDED FROM THE TABLES AND ANALYSES BECAUSE VALUES WERE NOT CONSISTENT WITH ANESTHETIC RESPONSE.
A: NO SAMPLES RECEIVED FOR ANALYSIS.
K: INSUFFICIENT SAMPLE REMAINING FOR REASSAY.
Q: NONQUANTIFIABLE.

MAINT (MAINTENANCE) #1: DRAWN AFTER THE RATE HAS BEEN HELD CONSTANT FOR A MINIMUM OF 15 MINUTES.
MAINT (MAINTENANCE) #2: DRAWN AT A MINIMUM OF 10 MINUTES AFTER THE PREVIOUS SAMPLE, BUT NOT LONGER THAN 30 MINUTES.

0859US/0046
TABLE G10.1
PLASMA PROPOFOL CONCENTRATION (NG/ML)

AGE GROUP	TREATMENT	CENTER NUMBER	SUBJECT	PROTOCOL TIME	TIME	PROPOFOL CONCENTRATION
2 M - < 2 Y						

NOTE: ASSAY DATA FROM SUBJECTS 202 AND 229 WERE EXCLUDED FROM THE TABLES AND ANALYSES BECAUSE VALUES WERE NOT CONSISTENT WITH ANESTHETIC RESPONSE.
A: NO SAMPLES RECEIVED FOR ANALYSIS.
K: INSUFFICIENT SAMPLE REMAINING FOR REASSAY.
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MAINT (MAINTENANCE) #2: DRAWN AT A MINIMUM OF 10 MINUTES AFTER THE PREVIOUS SAMPLE, BUT NOT LONGER THAN 30 MINUTES.

0859US/0046
TABLE G10.1
PLASMA PROPOFOL CONCENTRATION (NG/ML)

AGE GROUP	TREATMENT	CENTER NUMBER	SUBJECT	PROTOCOL TIME	TIME	PROPOFOL CONCENTRATION
2 M - < 2 Y	L					

NOTE: ASSAY DATA FROM SUBJECTS 202 AND 229 WERE EXCLUDED FROM THE TABLES AND ANALYSES BECAUSE VALUES WERE NOT CONSISTENT WITH ANESTHETIC RESPONSE.
A: NO SAMPLES RECEIVED FOR ANALYSIS.
K: INSUFFICIENT SAMPLE REMAINING FOR REASSAY.
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MAINT (MAINTENANCE) #2: DRAWN AT A MINIMUM OF 10 MINUTES AFTER THE PREVIOUS SAMPLE, BUT NOT LONGER THAN 30 MINUTES.

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TABLE G10.1

PLASMA PROPOFOL CONCENTRATION (NG/ML)

AGE GROUP	TREATMENT	CENTER NUMBER	SUBJECT	PROTOCOL TIME	TIME	PROPOFOL CONCENTRATION
2 M - < 2 Y						
2 - < 3 Y						

NOTE: ASSAY DATA FROM SUBJECTS 202 AND 229 WERE EXCLUDED FROM THE TABLES AND ANALYSES BECAUSE VALUES WERE NOT CONSISTENT WITH ANESTHETIC RESPONSE.
A: NO SAMPLES RECEIVED FOR ANALYSIS.
K: INSUFFICIENT SAMPLE REMAINING FOR REASSAY.
Q: NONQUANTIFIABLE.

MAINT (MAINTENANCE) #1: DRAWN AFTER THE RATE HAS BEEN HELD CONSTANT FOR A MINIMUM OF 15 MINUTES.
MAINT (MAINTENANCE) #2: DRAWN AT A MINIMUM OF 10 MINUTES AFTER THE PREVIOUS SAMPLE, BUT NOT LONGER THAN 30 MINUTES.

0859US/0046

TABLE G10.1

PLASMA PROPOFOL CONCENTRATION (NG/ML)

AGE GROUP	TREATMENT	CENTER NUMBER	SUBJECT	PROTOCOL TIME	TIME	PROPOFOL CONCENTRATION
2 – < 3 Y						

NOTE: ASSAY DATA FROM SUBJECTS 202 AND 229 WERE EXCLUDED FROM THE TABLES AND ANALYSES BECAUSE VALUES WERE NOT CONSISTENT WITH ANESTHETIC RESPONSE.
A: NO SAMPLES RECEIVED FOR ANALYSIS.
K: INSUFFICIENT SAMPLE REMAINING FOR REASSAY.
Q: NONQUANTIFIABLE.

MAINT (MAINTENANCE) #1: DRAWN AFTER THE RATE HAS BEEN HELD CONSTANT FOR A MINIMUM OF 15 MINUTES.
MAINT (MAINTENANCE) #2: DRAWN AT A MINIMUM OF 10 MINUTES AFTER THE PREVIOUS SAMPLE, BUT NOT LONGER THAN 30 MINUTES.

TABLE 6 SCHEDULE OF ASSESSMENTS STUDY 0859IL/0068

Event	Pretreatment	Treatment					Post-treatment		
	Baseline	Day 1	Day 2	Day 3	Days 4-6	Day 7 and every 7 days thereafter	End of trial sedation	24 hours after sedation	28 days after sedation
Admitting diagnosis and PRISM score	√								
Blood gases	√		√	√	√	√	√	√[a]	
Comfort scale[b]	√	√	√	√	√	√	√		
Total dose trial medication, analgesic		√	√	√	√	√	√		
Medications 12-hour period pretrial	√								
Concurrent medications		√	√	√		√	√	√	
Vital signs	√		√	√		√	√	√	
Sepsis	√		√	√		√	√		
Hematology	√		√	√		√	√	√[a]	
Serum chemistry[c]	√		√	√		√	√	√[a]	
Lactic acid and free fatty acid	√		√	√		√	√	√[a]	
Serum trace metals[d]	√		√	√		√			
Urine assessments[d,e]			√	√		√			
Date and time of intubation, extubation, or criteria met	√						√	√	√
Adverse events		√	√	√	√	√	√	√[f]	
Follow-up for survival									√
Center 1 propofol and disodium edetate assay	√		√	√	√	√	√		

[a] Only if access lines were still available.
[b] Before each titration for the first 4 hours.
[c] Triglyceride levels were assessed before and after trial treatment was temporarily discontinued.
[d] Only catheterized patients.
[e] Urine assessments included osmolality, albumin, sediment, and glucose levels; 24-hour urine samples for measurement of trace metal excretion and calculated creatinine clearance.
[f] Patients monitored for adverse events through 72 hours.
PRISM Pediatric Risk of Mortality Score.

TABLE 7A DEMOGRAPHIC CHARACTERISTICS FOR ALL PATIENTS BY AGE GROUP

Demographic characteristic	Age group Treatment group											
	Birth-<2 months N=36			2 months-<2 years N=146			2-<12 years N=109			12-<17 years N=36		
	Diprivan 2%	Diprivan 1%	SSA	Diprivan 2%	Diprivan 1%	SSA	Diprivan 2%	Diprivan 1%	SSA	Diprivan 2%	Diprivan 1%	SSA
Age (y)[a]												
n	16	11	9	46	51	49	39	34	36	12	13	11
Mean	0.9	1.0	0.8	9.6	11.2	8.7	5.3	6.1	5.5	13.9	14.2	14.2
±SD	0.50	0.59	0.59	5.73	6.58	5.13	2.75	3.18	2.87	1.50	1.47	1.41
Range	0.2-1.9	0.1-1.9	0.1-1.5	2.1-20.0	2.1-23.4	2.1-23.5	2.1-11.9	2.1-11.6	2.1-11.0	12.2-17.0	12.3-16.1	12.5-16.8
Sex												
n	16	11	9	46	51	49	39	34	36	12	13	11
Boys (%)	9 (56)	7 (64)	4 (44)	26 (57)	36 (71)	35 (71)	28 (72)	21 (62)	17 (47)	5 (42)	10 (77)	7 (64)
Girls (%)	7 (44)	4 (36)	5 (56)	20 (43)	15 (29)	14 (29)	11 (28)	13 (38)	19 (53)	7 (58)	3 (23)	4 (36)
Weight (kg)												
n	16	11	9	46	51	49	39	34	36	12	13	11
Mean	3.8	3.7	3.7	7.4	7.9	6.6	21.0	23.3	22.0	72.5	66.5	55.4
±SD	0.67	0.81	0.45	2.77	2.94	1.95	12.98	12.39	11.12	27.17	23.09	17.72
Range	2.9-5.1	2.3-5.3	3.2-4.3	3.4-13.6	3.6-16.5	2.5-10.5	9.0-80.0	5.6-58.0	10.0-50.0	37.0-112.5	43.0-120.0	27.0-85.0
Height (cm)												
n	16	11	8	45	47	44	34	28	32	11	13	11
Mean	53	52	52	67	71	64	108	113	106	162	163	161
±SD	4.2	4.7	2.0	11.0	11.5	3.7	22.2	25.6	20.2	15.1	12.8	17.3
Range	44-62	43-59	49-55	51-90	51-102	43-83	76-150	73-155	74-150	132-183	142-185	124-178

TABLE 7B DEMOGRAPHIC CHARACTERISTICS FOR ALL PATIENTS BY AGE GROUP

Demographic characteristic	Age group / Treatment group											
	Birth-<2 months N=36			2 months-<2 years N=146			2-<12 years N=109			12-<17 years N=36		
	Diprivan 2%	Diprivan 1%	SSA	Diprivan 2%	Diprivan 1%	SSA	Diprivan 2%	Diprivan 1%	SSA	Diprivan 2%	Diprivan 1%	SSA
Race[b]												
n	16	11	9	46	51	49	39	34	36	12	13	11
White (%)	12 (75)	9 (82)	7 (78)	30 (65)	31 (61)	27 (55)	22 (56)	18 (53)	17 (47)	5 (42)	10 (77)	9 (82)
Black (%)	1 (6)	2 (18)	1 (11)	9 (20)	13 (25)	9 (18)	7 (18)	14 (41)	12 (33)	2 (17)	2 (15)	1 (9)
Asian (%)	0	0	0	0	0	0	0	0	3 (8)	0	0	0
Hispanic (%)	2 (13)	0	1 (11)	6 (13)	6 (12)	13 (27)	8 (21)	2 (6)	3 (8)	4 (33)	1 (8)	1 (9)
Other (%)[c]	1 (6)	0	0	1 (2)	1 (2)	0	2 (5)	0	1 (3)	1 (8)	0	0
CSS[d]												
n	16	11	9	44	51	48	38	34	35	12	13	11
Mean	29	30	30	29	28	29	27	27	28	25	26	29
±SD	2.7	2.9	1.8	3.5	5.4	3.5	6	7	6	8	6	6
Range	26-36	26-36	26-32	21-38	9-37	24-38	12-36	8-40	10-40	10-37	11-32	17-40

[a] Age for birth through 2 years presented in months.
[b] Because of rounding some percentages do not add up to 100%.
[c] Other includes bi-racial, unknown, Armenian, Pakistani, American Indian, Indian (Guyanese).
[d] Patients with comfort scale scores <8 or >40 were excluded from analysis.
SSA Standard sedative agents without disodium edetate.
CSS Comfort score scale.

TABLE 8

Propofol administration

	Age group							
	Birth-<2 months		2 months-<2 years		2-<12 years		12-<17 years	
	Diprivan 2%[a] (N=16)	Diprivan 1%[a,b] (N=11)	Diprivan 2%[a] (N=46)	Diprivan 1%[a,b] (N=51)	Diprivan 2%[a] (N=39)	Diprivan 1%[a,c] (N=34)	Diprivan 2%[a] (N=12)	Diprivan 1% (N=13)
Mean total dose±SD (mg) (range)	4133±5697 (24-23524)	6434±11580 (50-40200)	8642±10860 (378-52989)	5634±7673 (181-38944)	15925±16884 (470-78291)	12315±15007 (790-73464)	32998±63019 (152-226676)	21690±26945 (1804-95567)
Mean total dose±SD (mg/kg) (range)	1089±1519 (7-6190)	1932±3870 (22-13400)	1195±1411 (56-6882)	798±1197 (26-6753)	1055±1562 (32-8699)	771±1404 (42-7595)	426±696 (4-2180)	339±354 (40-985)
Mean rate±SD (µg/kg per min) (range)	87±42 (12-168)	89±52 (26-202)	124±60 (26-265)	109±54 (16-235)	121±54 (35-242)	91±37 (26-167)	59± 36 (23-156)	61±34 (11-120)
Mean duration of sedation ±SD (h) (range)	242±385 (1-1562)	270±370 (5-1349)	160±177 (13-927)	115±135 (5-656)	115±118 (7-604)	123±169 (8-847)	98±115 (1-387)	84±74 (11-262)

[a] Data for patients for whom trial drug was started and stopped on the same day were recorded at the end of sedation.
[b] Trial drug start and stop times, and dosage information for patient 13204 on Day 1 was unknown.
[c] Dosage information for Patient 10119 were unavailable.

TABLE 9A

PLASMA PROPOFOL CONCENTRATION (MCG/ML) - CENTER 1 ONLY

PROTOCOL TIME		TREATMENT			
		DIPRIVAN 2%		DIPRIVAN 1%	
		MONOTHERAPY	COMBINATION	MONOTHERAPY	COMBINATION
BASELINE	N	8	7	9	4
	MEAN	NQ	NC	NC	NQ
	MIN				
	MAX				
	STD	NQ	NC	NC	NQ
DAY 2	N	5	3	3	5
	MEAN	2.208	7.500	5.441	2.100
	MIN				
	MAX				
	STD	1.241	9.403	6.025	0.619
DAY 3	N	3	3	4	2
	MEAN	2.240	2.205	4.123	3.345
	MIN				
	MAX				
	STD	0.972	1.436	2.941	2.199
DAY 4	N	2	3	3	-
	MEAN	0.966	2.507	2.940	-

(CONTINUED)

NOTE: 1. IF MORE THAN HALF THE VALUES WERE NOT QUANTIFIABLE (NQ), THEN NO MEAN WAS CALCULATED AND NOT CALCULATED (NC) WAS REPORTED.
2. IF ALL VALUES WERE NQ THEN NQ WAS REPORTED.

TABLE 9B

PLASMA PROPOFOL CONCENTRATION (MCG/ML) - CENTER 1 ONLY

PROTOCOL TIME		TREATMENT			
		DIPRIVAN 2%		DIPRIVAN 1%	
		MONOTHERAPY	COMBINATION	MONOTHERAPY	COMBINATION
DAY 4	MIN				-
	MAX	-----	-----	-----	-
	STD	0.162	1.433	1.971	-
DAY 5	N	1	3	2	1
	MEAN	0.744	10.112	3.570	31.800
	MIN				
	MAX	-----	-----	-----	-----
	STD	-	14.410	1.527	-
DAY 6	N	-	3	2	1
	MEAN	-	6.567	2.355	1.010
	MIN				
	MAX	-----	-----	-----	-----
	STD	-	8.265	1.478	-
DAY 7	N	1	2	2	-
	MEAN	0.630	5.106	2.915	-
	MIN				-
	MAX	-----	-----	-----	-

(CONTINUED)

NOTE: 1. IF MORE THAN HALF THE VALUES WERE NOT QUANTIFIABLE (NQ), THEN NO MEAN WAS CALCULATED AND NOT CALCULATED (NC) WAS REPORTED.
2. IF ALL VALUES WERE NQ THEN NQ WAS REPORTED.

TABLE 9C

PLASMA PROPOFOL CONCENTRATION (MCG/ML) - CENTER 1 ONLY

PROTOCOL TIME		TREATMENT			
		DIPRIVAN 2%		DIPRIVAN 1%	
		MONOTHERAPY	COMBINATION	MONOTHERAPY	COMBINATION
DAY 7	STD	-	5.424	0.898	-
DAY 14	N	1	-	1	-
	MEAN	1.460	-	4.120	-
	MIN				-
	MAX				-
	STD	-	-	-	-
END OF SEDATION	N	8	5	9	6
	MEAN	2.198	1.630	4.773	1.353
	MIN				
	MAX				
	STD	1.131	0.326	6.474	0.949

NOTE: 1. IF MORE THAN HALF THE VALUES WERE NOT QUANTIFIABLE (NQ), THEN NO MEAN WAS CALCULATED AND NOT CALCULATED (NC) WAS REPORTED.
2. IF ALL VALUES WERE NQ THEN NQ WAS REPORTED.

TABLE 10A

PLASMA PROPOFOL CONCENTRATION (MCG/ML) - CENTER 1

TREATMENT RECEIVED=DIPRIVAN 2%

CENTER NUMBER	SUBJECT NUMBER	THERAPY	PROTOCOL TIME	PLASMA PROPOFOL CONCENTRATION (MCG/ML)

TABLE 10B

PLASMA PROPOFOL CONCENTRATION (MCG/ML) - CENTER 1

TREATMENT RECEIVED=DIPRIVAN 2%

CENTER NUMBER	SUBJECT NUMBER	THERAPY	PROTOCOL TIME	PLASMA PROPOFOL CONCENTRATION (MCG/ML)
[redacted]				

NOTE: CENTER 1 ONLY BLINDED TO ANALGESIC: MONOTHERAPY=SALINE; COMBINATION=FENTANYL

TABLE 10C

PLASMA PROPOFOL CONCENTRATION (MCG/ML) - CENTER 1

TREATMENT RECEIVED=DIPRIVAN 1%

CENTER NUMBER	SUBJECT NUMBER	THERAPY	PROTOCOL TIME	PLASMA PROPOFOL CONCENTRATION (MCG/ML)

TABLE 10D

PLASMA PROPOFOL CONCENTRATION (MCG/ML) - CENTER 1

TREATMENT RECEIVED=DIPRIVAN 1%

CENTER NUMBER	SUBJECT NUMBER	THERAPY	PROTOCOL TIME	PLASMA PROPOFOL CONCENTRATION (MCG/ML)

NOTE: CENTER 1 ONLY BLINDED TO ANALGESIC: MONOTHERAPY=SALINE; COMBINATION=FENTANYL

TABLE 11A MONOTHERAPY DAY 1 AND 2- STUDY 0859IL/0068

TABLE 11B MONOTHERAPY DAY 3 AND 4- STUDY 0859IL/0068

Weight	Gender (M/F) Ethnicity (W/B/H	Subject Number /Formulation	Monotherapy Plasma Propofol Concentration	Monotherapy Dose (mg)	Monotherapy Dose (mg/Kg)	Monotherapy Dose Rate (ug/kg/min)	Monotherapy Infusion Duration (Hr)	Cl- Mono	Monotherapy Plasma Propofol Concentration	Monotherapy Dose (mg)	Monotherapy Dose (mg/Kg)	Monotherapy Dose Rate (ug/kg/min)	Monotherapy Infusion Duration (Hr)	Cl- Mono

TABLE 11C MONOTHERAPY DAY 5 AND 6- STUDY 0859IL/0068

ge	Weight	Gender (M/F) Ethnicity (W/B/H)	Subject Number /Formulation	Monotherapy Plasma Propofol Concentration	Monotherapy Dose (mg)	Monotherapy Dose (mg/Kg)	Monotherapy Dose Rate (ug/kg/min)	Monotherapy Infusion Duration (Hr)	Cl- Mono	Monotherapy Plasma Propofol Concentration	Monotherapy Dose (mg)	Monotherapy Dose (mg/Kg)	Monotherapy Dose Rate (ug/kg/min)	Monotherapy Infusion Duration (Hr)	Cl- Mono

TABLE 11D MONOTHERAPY DAY 7 AND 14- STUDY 0859IL/0068

Age	Weight	Gender (M/F) Ethnicity (W/B/H	Subject Number /Formulation	Monotherapy Plasma Propofol Concentration	Monotherapy Dose (mg)	Monotherapy Dose (mg/Kg)	Monotherapy Dose Rate (ug/kg/min)	Monotherapy Infusion Duration (Hr)	Cl- Mono -	Monotherapy Plasma Propofol Concentration	Monotherapy Dose (mg)	Monotherapy Dose (mg/Kg)	Monotherapy Dose Rate (ug/kg/min)	Monotherapy Infusion Duration (Hr)	Cl- Mono

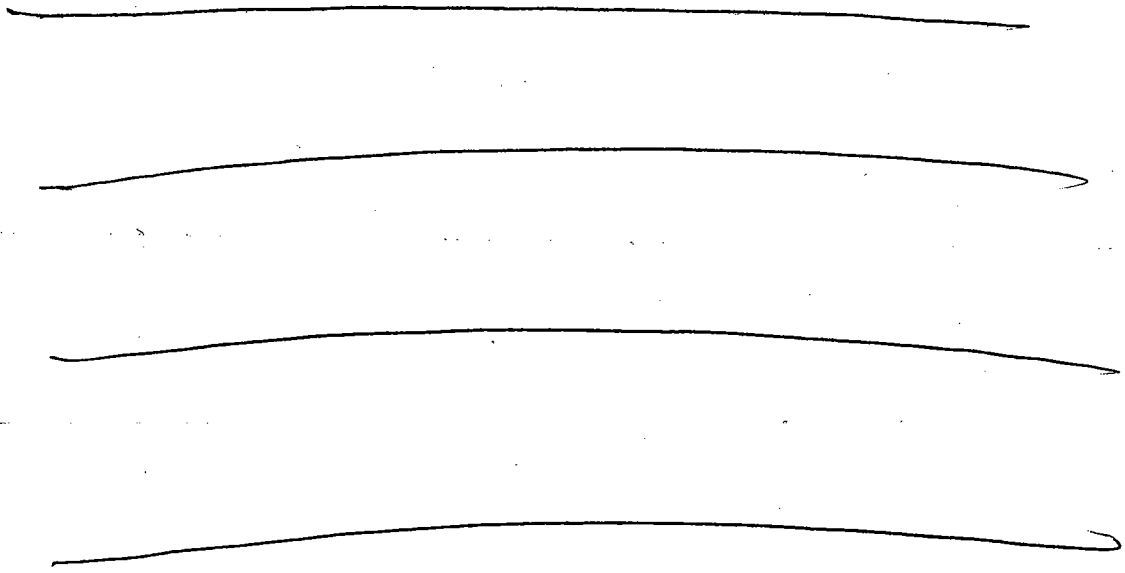


TABLE 11E MONOTHERAPY DAY 17 AND MONOTHERAPY SUMMARY- STUDY 0859IL/0068

Age (years)	Weight (kg)	Gender (M/F) Ethnicity (W/B/H	Subject Number /Formulation	Monotherapy Plasma Propofol Concentration Day 17 (ug/ml)	Monotherapy Dose (mg) Day 17	Monotherapy Dose (mg/Kg) Day 17	Monotherapy Dose Rate (ug/kg/min) Day 17	Monotherapy Infusion Duration (Hr) Day 17	Cl- Mono D17 (ml/kg/min)	Mono Average Individual Subject Clearance (ml/kg/min)	Mono Average Individual Subject Clearance %RSD	Monotherapy Plasma (ug/ml) Propofol Concentration End of Sedation	Monotherapy Dose (mg) Overall	Monotherapy Dose (mg/Kg) Overall	Monotherapy Dose Rate (ug/kg/min) Overall	Monotherapy Infusion Duration (Hr) Overall
[redacted]																

TABLE 11F COMBOTHERAPY DAY 1 AND 2- STUDY 0859IL/0068

Age	Weight	Gender (M/F) Ethnicity (W/B/H	Subject Number /Formulation	Combotherapy Plasma Propofol Concentration	Combotherapy Plasma Propofol Concentration	Combotherapy Dose (mg)	Combotherapy Dose (mg/Kg)	Combotherapy Dose Rate (ug/kg/min)	Combotherapy Infusion Duration (Hr)	Cl- Combo	Combotherapy Plasma Propofol Concentration	Combotherapy Dose (mg)	Combotherapy Dose (mg/Kg)	Combotherapy Dose Rate (ug/kg/min)	Combotherapy Infusion Duration (Hr)	Cl- Combo
[redacted]																

TABLE 11G COMBOTHERAPY DAY 3 AND 4- STUDY 0859IL/0068

Age	Weight	Gender (M/F) Ethnicity (W/B/H	Subject Number /Formulation	Combotherapy Plasma Propofol Concentration	Combotherapy Dose (mg)	Combotherapy Dose (mg/Kg)	Combotherapy Dose Rate (ug/kg/min)	Combotherapy Infusion Duration (Hr)	Cl- Combo	Combotherapy Plasma Propofol Concentration	Combotherapy Dose (mg)	Combotherapy Dose (mg/Kg)	Combotherapy Dose Rate (ug/kg/min)	Combotherapy Infusion Duration (Hr)	Cl- Combo
				Day 3	Day 3	Day 3	Day 3	Day 3	D3 (ml/kg/min)	Day 4	Day 4	Day 4	Day 4	Day 4	D4 (ml/kg/min)
															86.0

TABLE 11H COMBOTHERAPY DAY 5 AND 6- STUDY 0859IL/0068

Age	Weight	Gender (M/F) Ethnicity (W/B/H	Subject Number /Formulation	Combotherapy Plasma Propofol Concentration	Combotherapy Dose (mg)	Combotherapy Dose (mg/Kg)	Combotherapy Dose Rate (ug/kg/min)	Combotherapy Infusion Duration (Hr)	CL Combo	Combotherapy Plasma Propofol Concentration	Combotherapy Dose (mg)	Combotherapy Dose (mg/Kg)	Combotherapy Dose Rate (ug/kg/min)	Combotherapy Infusion Duration (Hr)	CL Combo
(years)	(kg)			Day 5	Day 5	Day 5	Day 5	Day 5	D5 (ml/kg/min)	Day 6	Day 6	Day 6	Day 6	Day 6	D6 (ml/kg/min)

TABLE 11-I COMBOTHERAPY DAY 7 AND 8- STUDY 0859IL/0068

e	Weight	Gender (M/F) Ethnicity (W/B/H	Subject Number /Formulation	Combotherapy Plasma Propofol Concentration Day 7	Combotherapy Dose (mg) Day 7	Combotherapy Dose (mg/Kg) Day 7	Combotherapy Dose Rate (ug/kg/min) Day 7	Combotherapy Infusion Duration (Hr) Day 7	Cl- Combo D7 (ml/kg/min)	Combotherapy Plasma Propofol Concentration Day 8	Combotherapy Dose (mg) Day 8	Combotherapy Dose (mg/Kg) Day 8	Combotherapy Dose Rate (ug/kg/min) Day 8	Combotherapy Infusion Duration (Hr) Day 8	Cl- Combo D8 (ml/kg/min)
arc\	(kg)														

TABLE 11J COMBOTHERAPY SUMMARY AND OVERALL SUMMARY- STUDY 0859IL/0068

Weight	Gender (M/F) Ethnicity	Subject Number /Formulation	Combo Average Individual Subject	Combo Average Individual Subject	Combotherapy Plasma Propofol	Combotherapy Dose (mg)	Combotherapy Dose (mg/Kg)	Combotherapy Dose Rate (ug/kg/min)	Combotherapy Infusion Duration	Monotherapy Individual Subject Average	Monotherapy Individual Subject Average	Combotherapy Individual Subject Average	Clearance (M+C) Individual Subject Average	Overall (M+C) Individual Subject Average

APPENDIX II FIGURES

FIGURE 1 AGE VS PLASMA PROPOFOL CONCENTRATION (ALL AGES)

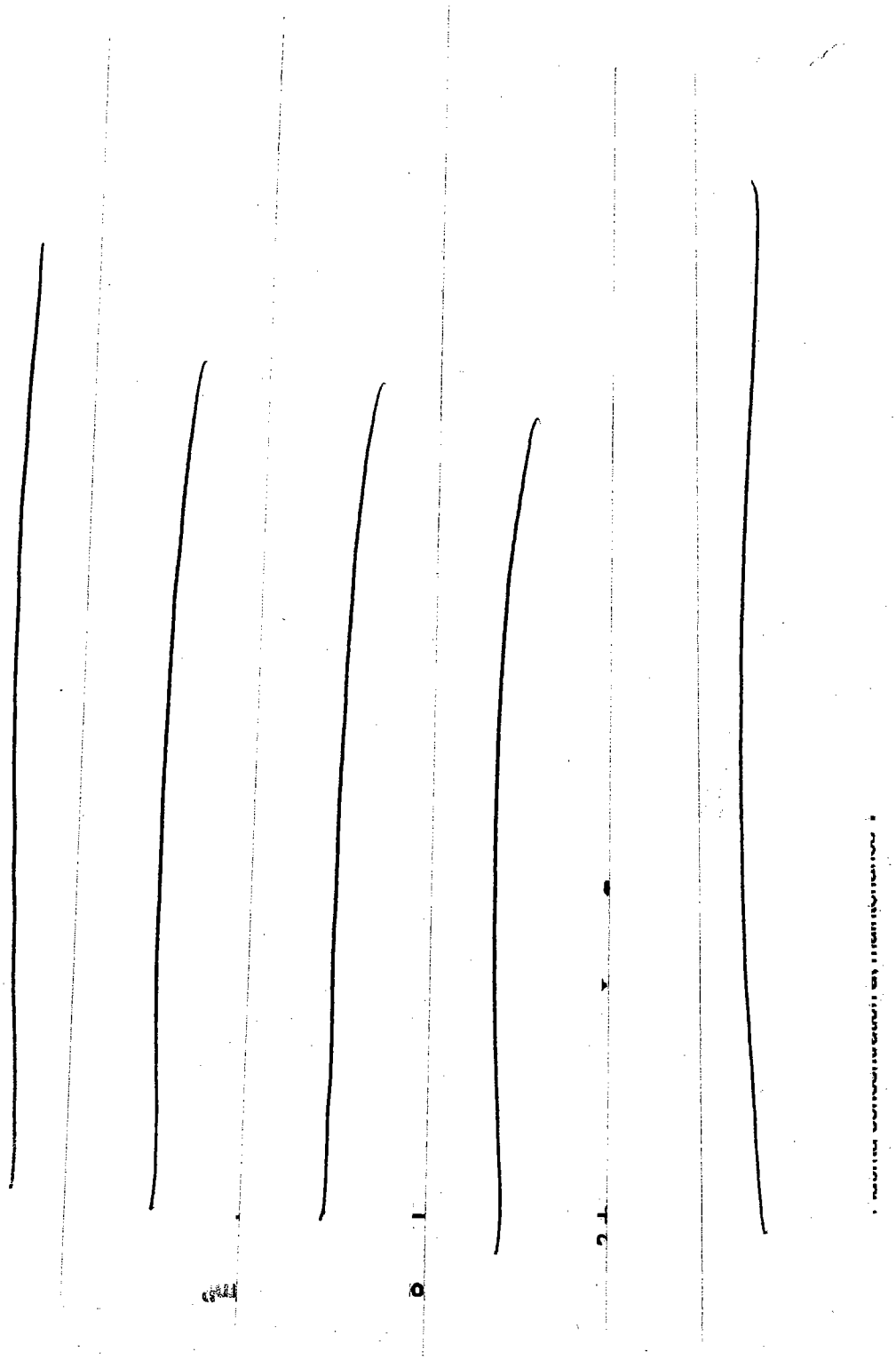


FIGURE 2 PROPOFOL CONCENTRATIONS AT ~200 UG/KG/MIN INFUSION RATE

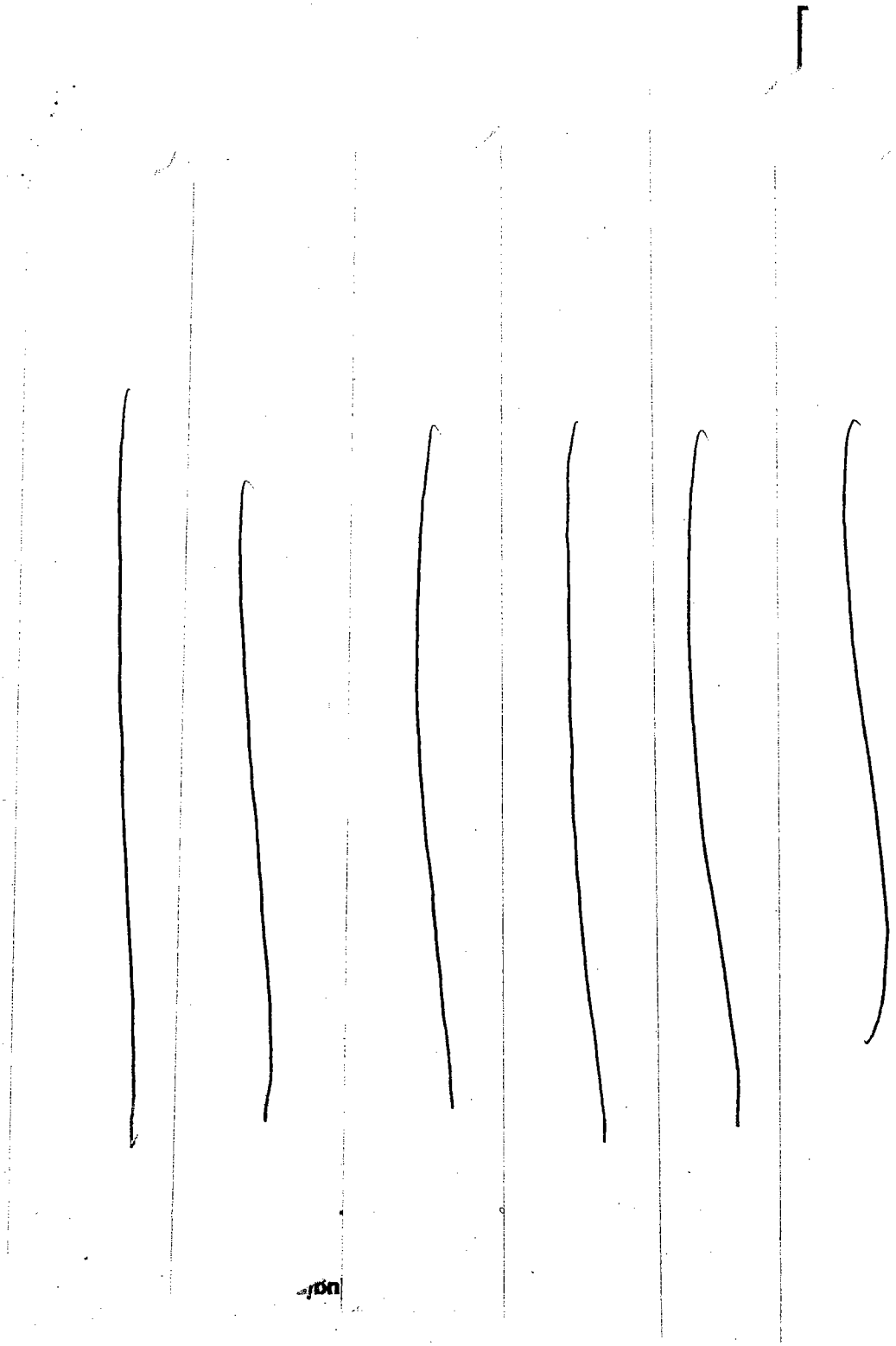


FIGURE 3

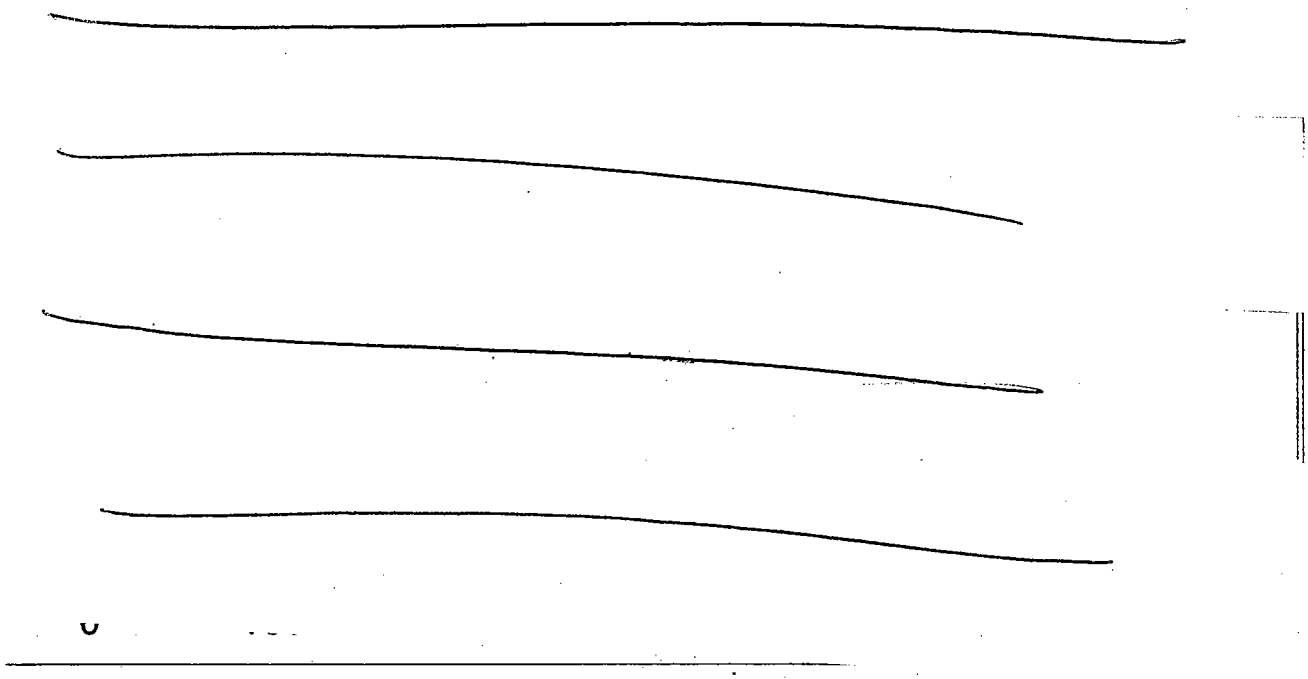


FIGURE 4 AGE VS PLASMA PROPOFOL CLEARANCE (ALL AGES)
STUDY 0859US/0046

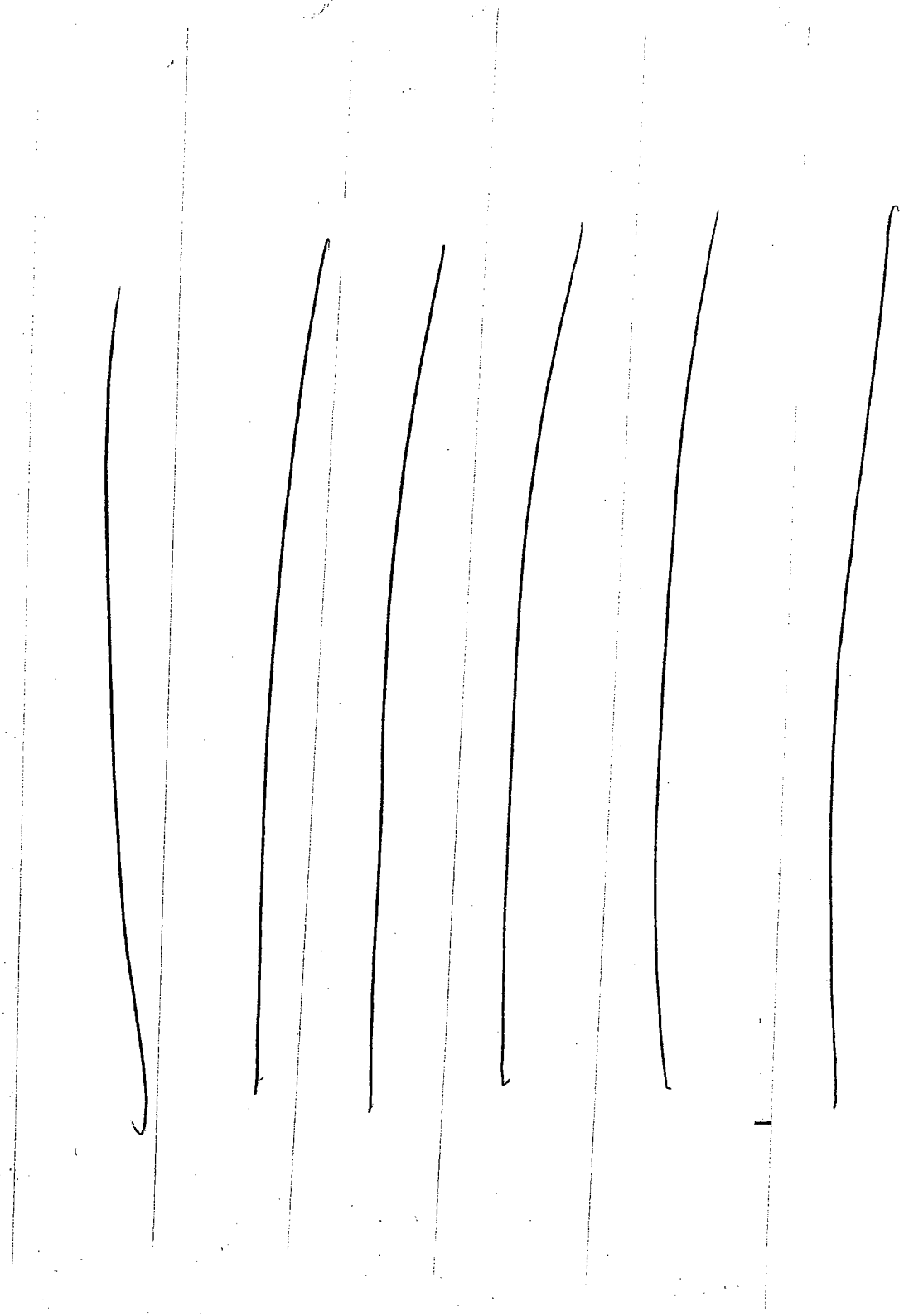


FIGURE 5 WEIGHT VS PLASMA PROPOFOL CLEARANCE (ALL AGES)
STUDY 0859US/0046

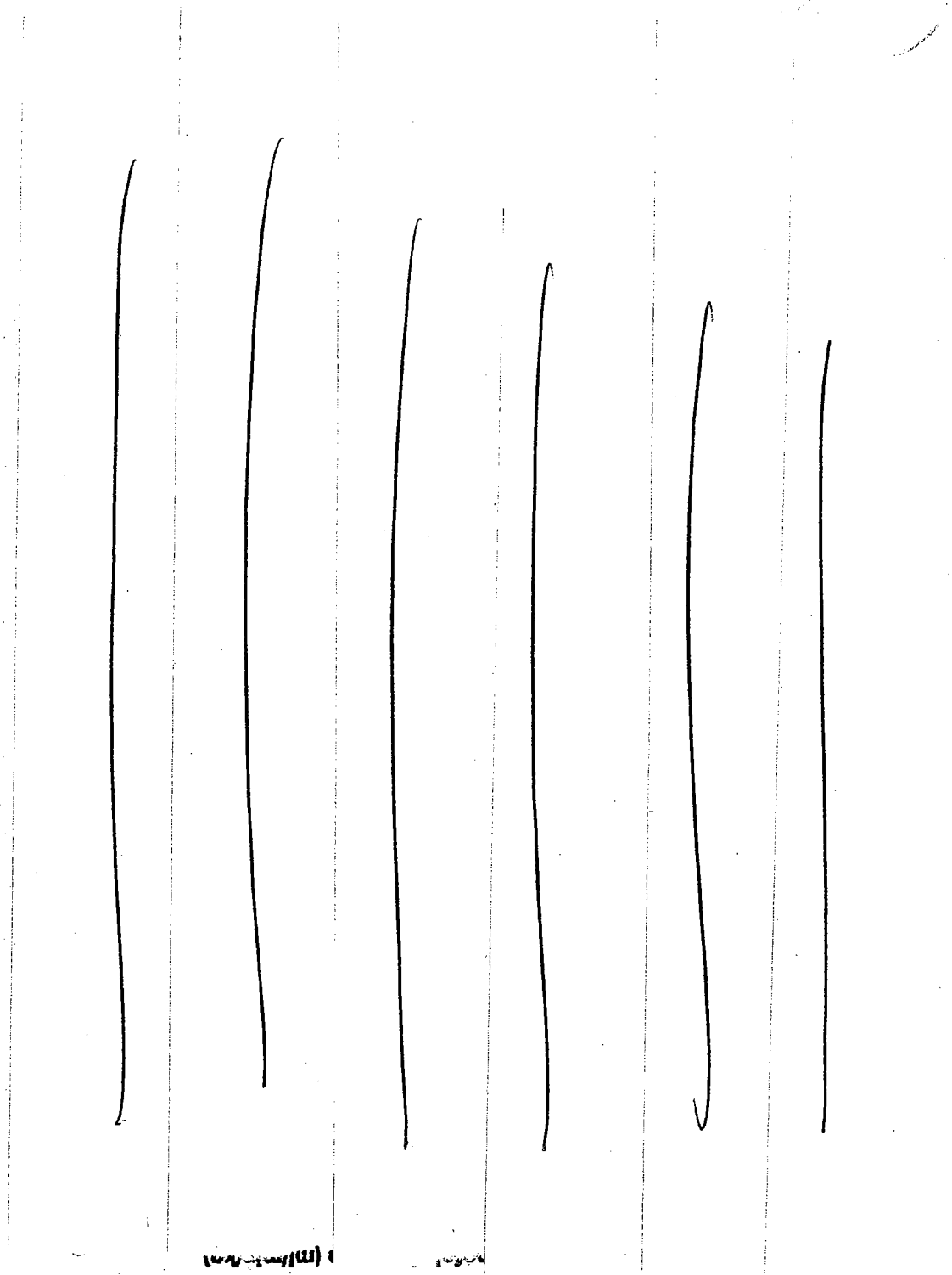


FIGURE 6 BODY SURFACE AREA VS PLASMA PROPOFOL CLEARANCE (ALL AGES)

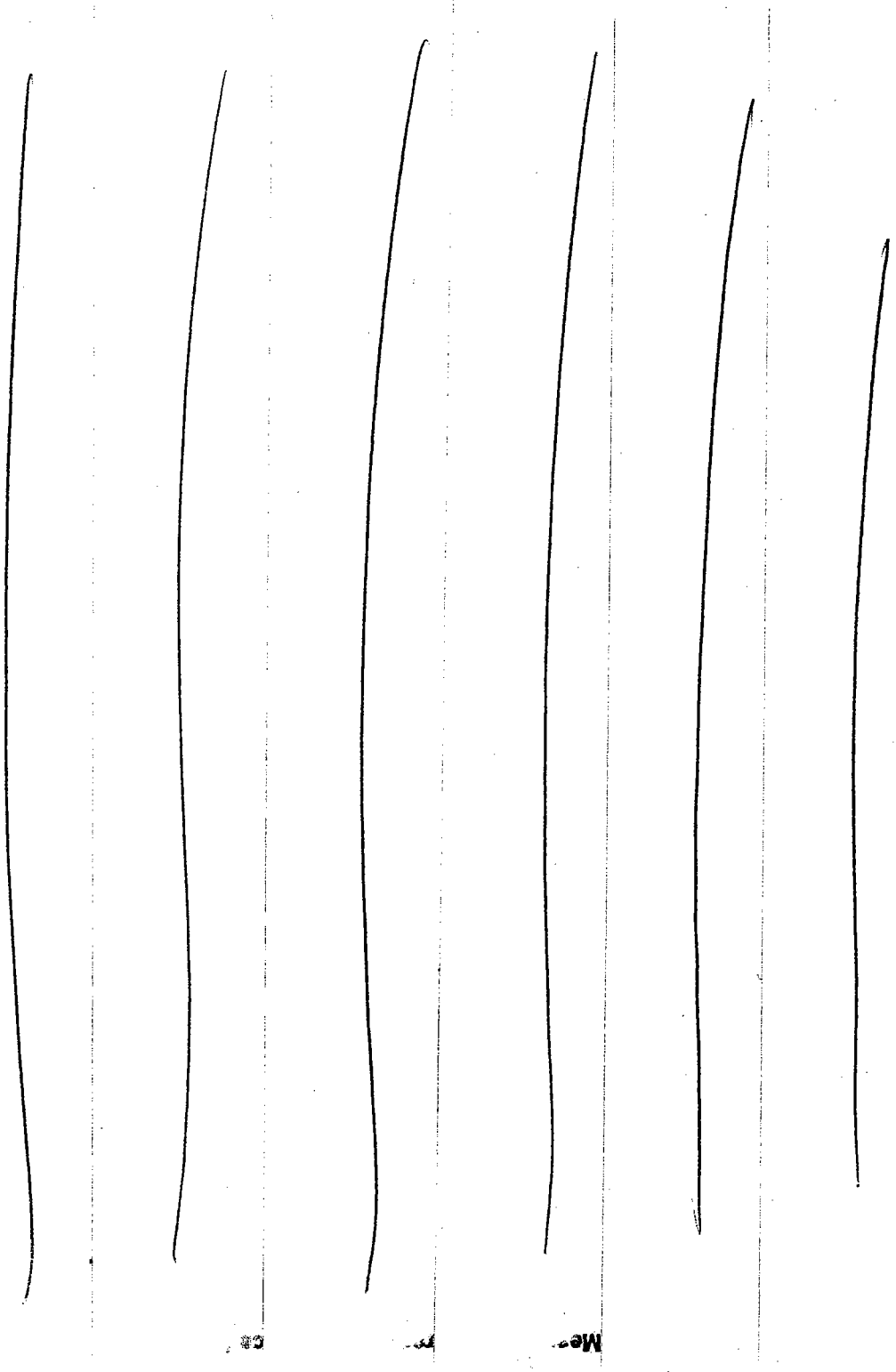


FIGURE 7 GENDER VS PLASMA PROPOFOL CLEARANCE (ALL AGES)

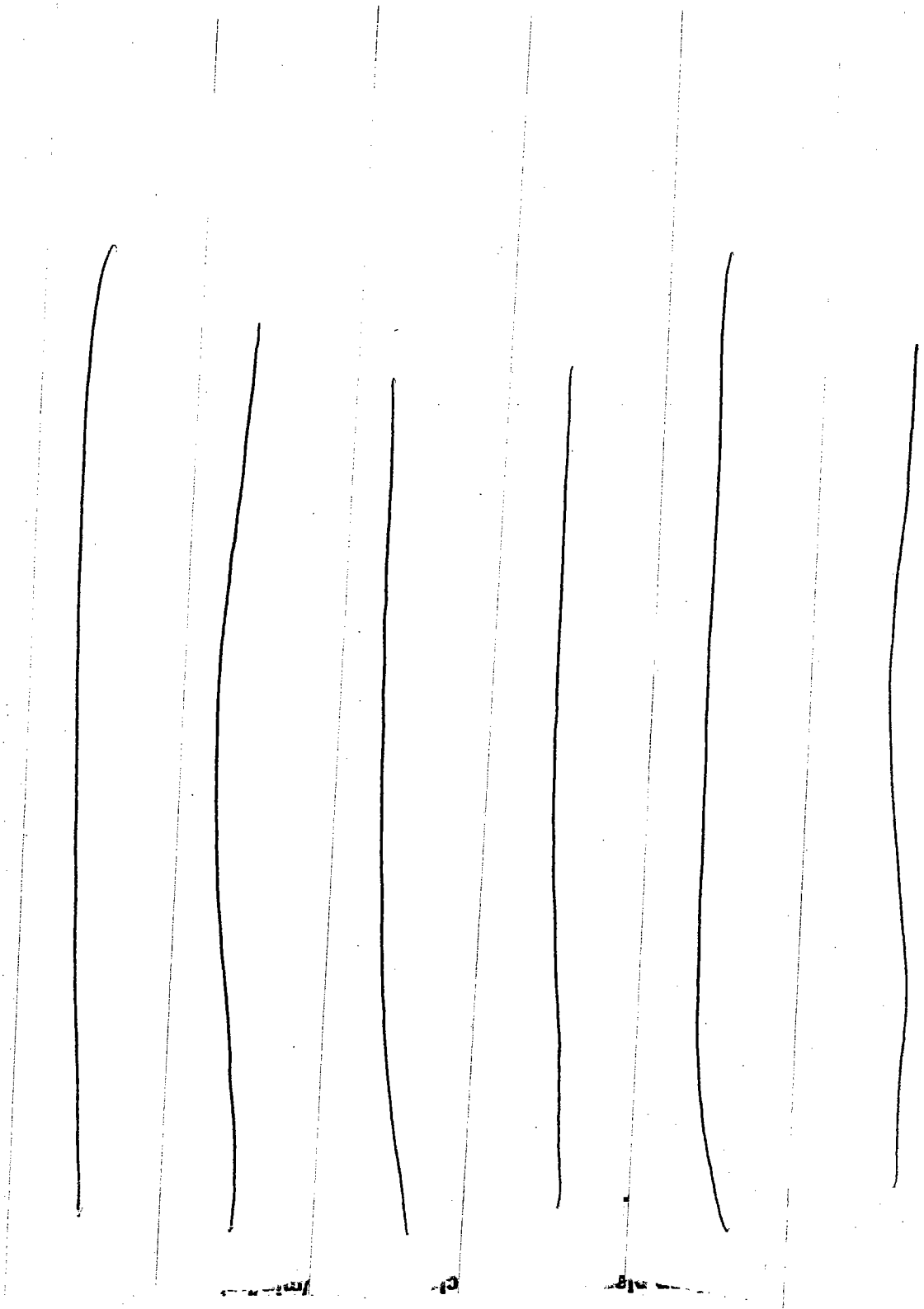


FIGURE 7A ETHNICITY VS CLEARANCE (ml/kg/min) STUDY 0859US/4600

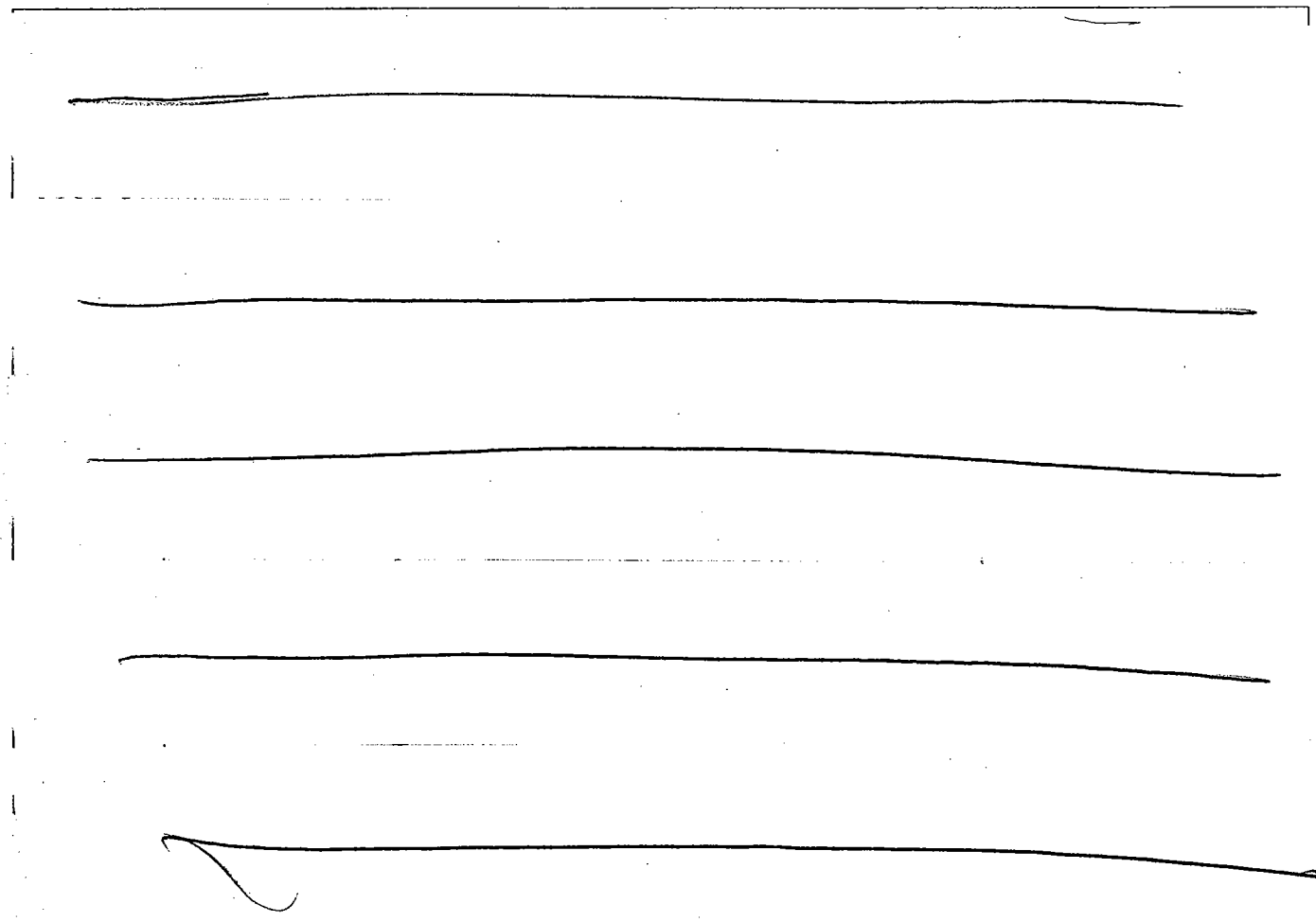


FIGURE 8 CLEARANCE AS A FUNCTION OF AGE IN CHILDREN 0-16 YEARS

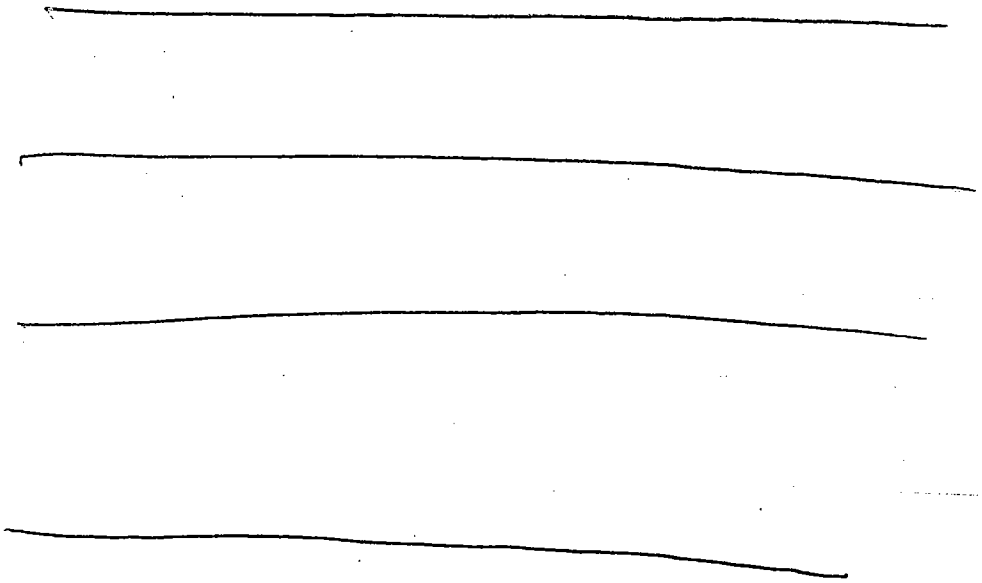


FIGURE 9 CLEARANCE AS A FUNCTION OF WEIGHT IN CHILDREN 0-16 YEARS

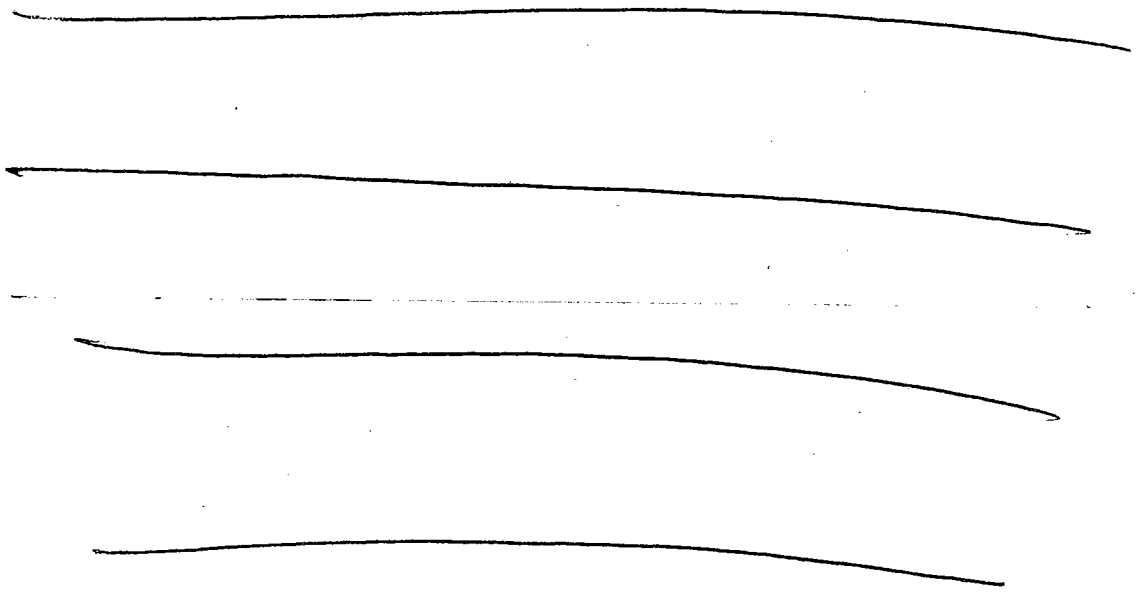


FIGURE 10 CLEARANCE AS A FUNCTION OF BODY SURFACE AREA IN CHILDREN 0-16 YEARS

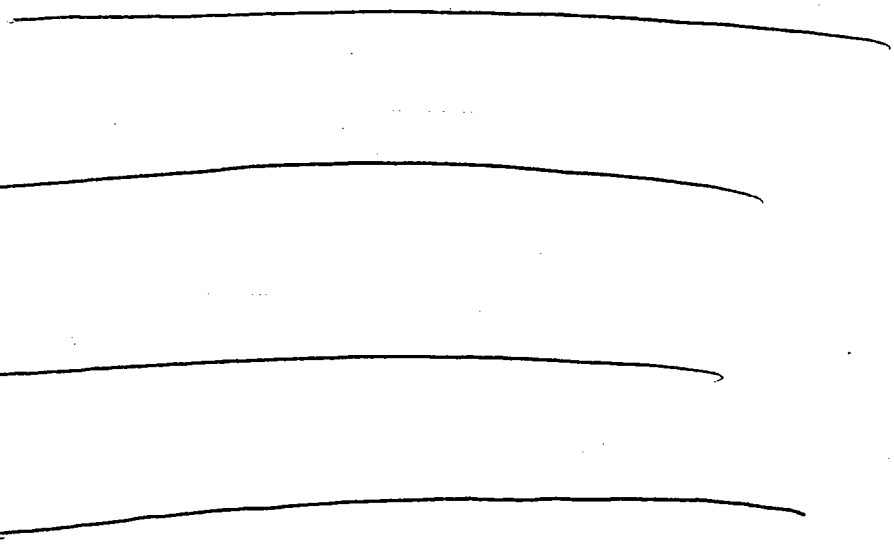
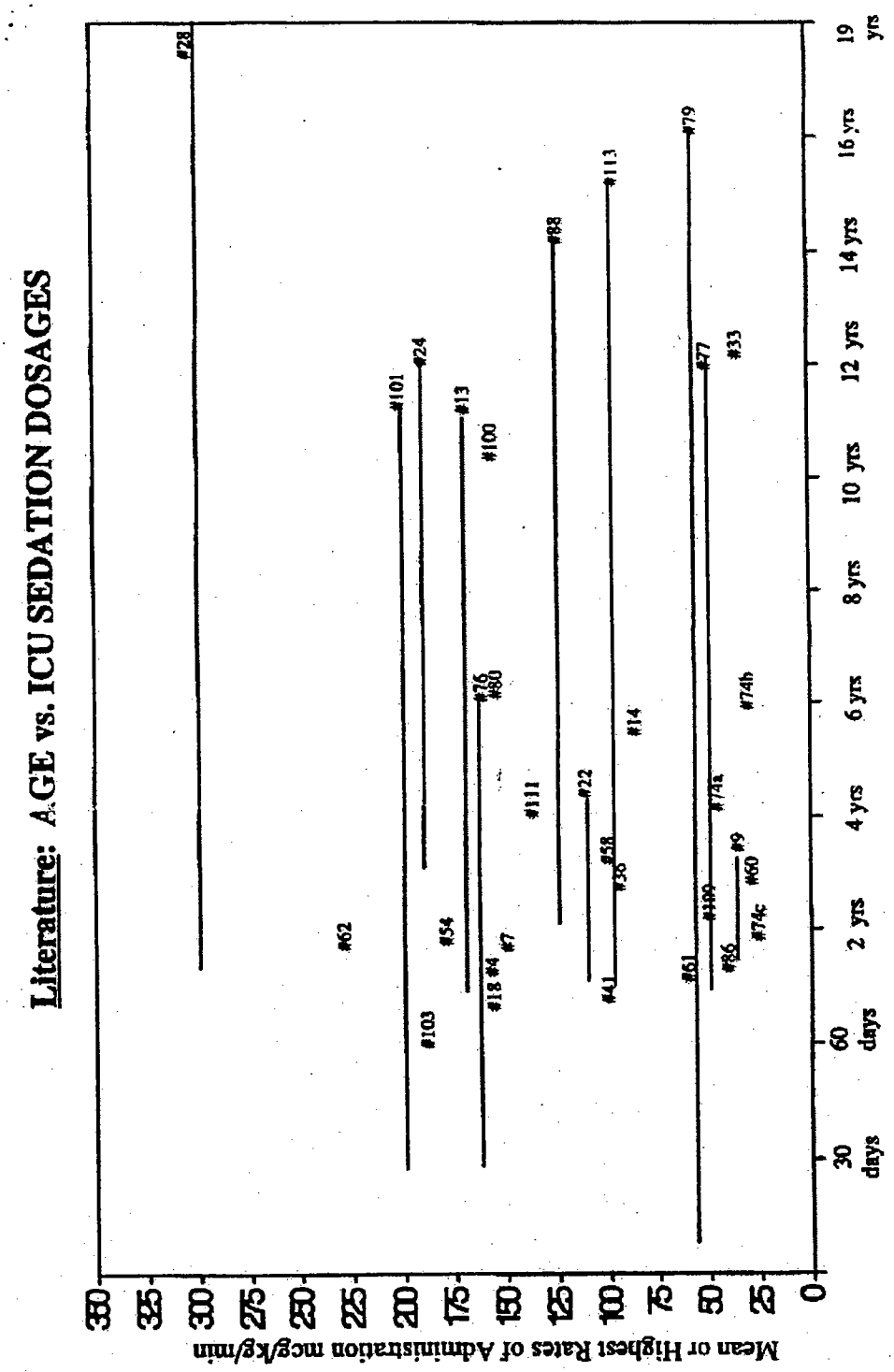


FIGURE 11



The NUMBERS within the graph represent the AGE, MEAN AGE or RANGE OF AGES for the corresponding numbered literature reference. Total Number of Patients = 469.

FIGURE 12

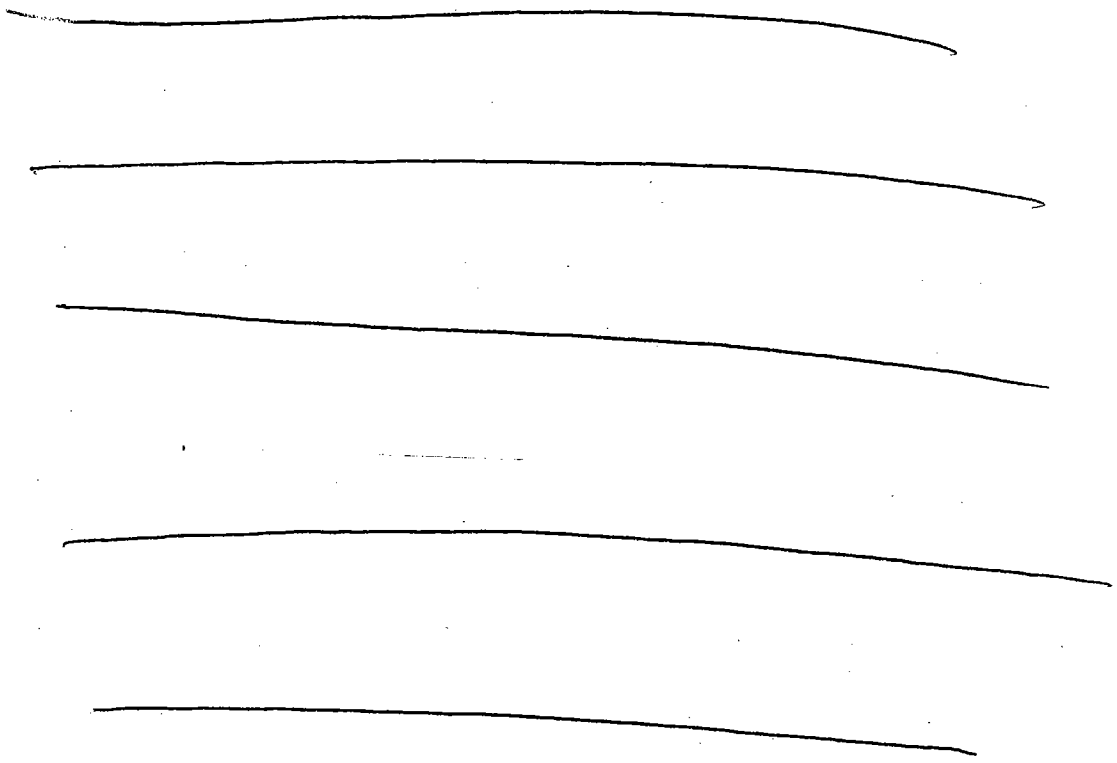


FIGURE 13 PLASMA PROPOFOL CLEARANCE VS WEIGHT (ALL AGES)
STUDY 0859IL/0068

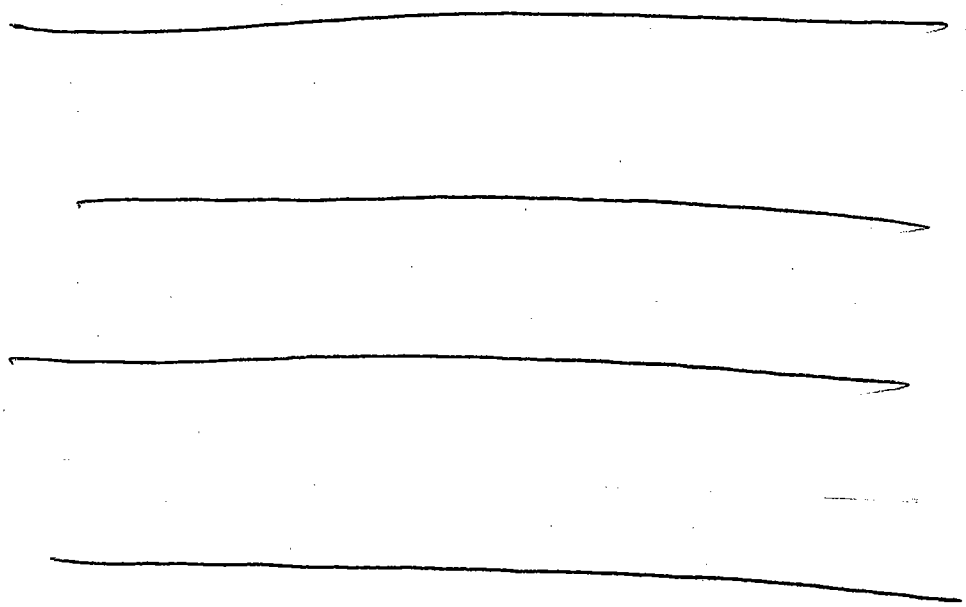


FIGURE 14