

Results:

51 patients were enrolled in the study. All patients contributed to safety data, and there were some isolated exclusions of efficacy data points described below. 34 patients contributed to the PK/PD analysis. There were no protocol amendments. As previously mentioned, a subgroup analysis was devised by agreement between the sponsor and the investigator based on the independent influence that plasma cholinesterase activity and clinical infusion dose requirement would have on the pharmacokinetic data. Patients were subcategorized as having normal or low plasma cholinesterase activity, with "low" defined as $\geq 20\%$ lower than the lower limit of normal range for plasma cholinesterase at the study institution. Patients were also subcategorized as constant or decreasing infusion rate requirement, where the latter were observed to not stabilize quickly at a constant infusion rate, and their infusion rates were $\geq 30\%$ less at the termination of the infusion than at 30-60 minutes after the initiation of the infusion. By these criteria, there were 11 patients who had decreasing infusion rate requirements over time. As a result, there were nine analytic subgroups for the major efficacy and safety parameters:

Normal pChE: Stable infusion rate: A-1, B1-1, B2-1
 Decreasing infusion rate: A-2, B1-2, B2-2
Low pChE: Stable infusion rate: A-3, B1-3, B2-3

There were no patients with both low pChE and decreasing infusion rate requirement.

The original protocol stated that 40 patients would be enrolled and that a replacement patient would be considered if a patient's primary endpoint (PK) data were not available. Following the enrollment of 40 patients, an additional 11 patients were enrolled to replace primary endpoint data not available due to loss or exclusion. No patients were excluded from efficacy, safety or PK data analysis on the basis of missing screening laboratory data. One patient was excluded from efficacy and PK analysis because of preoperative use of clonazepam. One patient who received gentamicin preoperatively had his T1 efficacy data excluded from analysis. Two patients who received gentamicin intraoperatively had their T1 data included in the efficacy analysis at time points before the gentamicin was administered, but excluded at all points after. Patients who briefly received isoflurane or phenylephrine were not excluded from any data analysis because of the brevity of their exposure.

Sixteen patients required pharmacologic reversal of neuromuscular blockade after the termination of their infusions. One patient received a total of three doses of neostigmine to achieve full recovery; the patient's data was excluded from the analysis of reversal data.

The eleven patients in the group who required decreasing doses of mivacurium to maintain paralysis were excluded from the average infusion rate analysis, and were analyzed separately. Eight patients who had lower than normal

plasma cholinesterase activity were also analyzed separately. There was no overlap between these two groups.

Pharmacokinetic data from 17 patients was excluded because of incorrect handling of the samples at the study site.

Demographics and initial vital signs are presented in Table 5.

Table 5. Summary of Demographics by Patient Groups. (Means \pm SD) (Summarized from Sponsor's Table 6)

	Group A	Group B1	Group B2
Total number	12	20	19
Age (yrs)	42.9 \pm 14.2	40.5 \pm 13.7	66.1 \pm 6.4
Weight (kg)	73.8 \pm 12.9	79.0 \pm 19.7	85.8 \pm 14.6
Height (cm)	169.0 \pm 10.9	175.8 \pm 9.9	177.6 \pm 8.0
Sex (M/F)	7/5	13/7	16/3
Systolic Pressure (mm Hg)	126.83 \pm 17.25	132.7 \pm 20.64	140.0 \pm 16.5
Diastolic Pressure (mm Hg)	79.66 \pm 11.59	76.9 \pm 12.63	80.15 \pm 10.41
Heart rate (beats/min)	73.8 \pm 9.43	79.15 \pm 11.08	78.9 \pm 10.5

All patients but one were Caucasian. There were no distinguishing demographic characteristics associated with stable vs decreasing rate of infusion, nor between subgroups with normal vs low plasma cholinesterase activity. The pChE and dibucaine numbers of patients with low values were characteristic of heterozygosity for the atypical pChE gene, except for one patient with extremely low values, consistent with homozygosity of the atypical gene.

The mean duration of infusion for patients in Group A was 151 minutes (range 74-221), in Group B1 was 311 minutes (range 219-1007), and in Group B2 was 272 minutes (range 148-1018 minutes).

Table 6.1 and 6.2 summarize median and range values for efficacy variables for subgroups with normal and low plasma cholinesterase activity respectively. Some subgroups have as few as 1-2 patients, limiting the significance of the data. The average infusion rate was not calculated for patients who required a decreasing rate of infusion. In the case of patients who demonstrated a stable infusion rate requirement, this required approximately 30 minutes from the start of the infusion to stabilize. In patients who demonstrated a decreasing infusion rate requirement, the infusion rate was decreased every 10-30 minutes throughout the infusion.

Table 6.1. T1 Suppression and Recovery Variables: Normal pChE. (Median and Ranges) (From Sponsor's Summary Report Table)

	Normal Plasma Cholinesterase											
	Stable Infusion Rate						Decreasing Infusion Rate					
	Young Short Infusion	n	Young Long Infusion	n	Elderly Long Infusion	n	Young Short Infusion	n	Young Long Infusion	n	Elderly Long Infusion	n
Max T1 suppression: %initial dose	100 (95-100)	8	100 (78-100)	11	100 (98-100)	9	100	1	98.5 (90-100)	6	99 (90-100)	4
Time to max T1 suppression (min)	3.1 (1.5-5.7)	7	4 (2-6.2)	11	3.5 (3.2-5)	9	4.1	1	5.6 (5.2-8.2)	6	7 (3.1- 9)	4
Time to 5% recovery (min)	12.2 (9-18)	5	12.4 (9-14.5)	6	14.2 (8-19.1)	7	8.5	1	7.9 (6.5-17)	5	14	1
Av infusion rate (µg/kg/min)	6.8 (5.1-9.4)	6	5.1 (3.6-11.4)	8	4.4 (4.0-6.1)	7	---	-	---	-	---	-
5-25% Recovery Index (min)	5 (4-12.9)	5	5.7 (4.5-13.3)	8	7.5 (5-13)	4	---	-	11.8 (11.2-12.3)	2	5.9 (4.3-7.5)	2
25-75% Recovery Index (min)	8.5 (5.9-19.5)	7	7.5 (6.1-10.3)	8	9 (6.7-9.7)	6	9	1	9 (6.2-21.5)	4	7.5 (5-13.7)	3

Table 6.2. T1 Suppression and Recovery Variables: Low pChE. (Median and Ranges) (From Sponsor's Summary Report Table)

	Low pChE Activity					
	Stable Infusion Rate					
	Young Short Infusion	n	Young Long Infusion	n	Elderly Long Infusion	n
Max T1 suppression: %initial dose	100	3	100	2	100	3
Time to max T1 suppression (min)	2 (1.7-3.5)	3	3.2 (3.2-3.2)	2	3.5 (3.5-4.7)	3

Time to 5% recovery (min)	21.5 (16-27)	3	26.2 (19.2-33.2)	2	24.4 (22.2-26.5)	2
Av infusion rate ($\mu\text{g}/\text{kg}/\text{min}$)	2.5 (2.4-4.2)	3	1.7 (1-2.5)	2	1.9	1
5-25% Recovery Index (min)	7.3 (7-7.5)	2	4.6	1	11.5	1
25-75% Recovery Index (min)	15.7 (12.2-19.2)	2	15.2 (9.2-21.2)	2	—	—

Patients with low plasma cholinesterase activity exhibited substantially longer recovery times compared to patients with normal plasma cholinesterase activity. This was true of both young and elderly patients. Median recovery times of young patients and elderly patients are similar; this was also true of patients who had decreasing infusion requirements compared to constant infusion requirements; however, the cohort numbers are too small in these groups to perform statistical comparisons.

Principal pharmacokinetic variables for individual isomers and primary metabolites are summarized in Table 7. Clearance of *trans-trans* and *cis-trans* isomers was not calculated at 15 minutes for patients with low plasma cholinesterase because they would not be expected to reach steady state in that time. In general, CL of the *trans-trans* isomer was similar in young adults receiving either long-term or short-term infusion, and was higher than the CL seen in elderly patients. Measurements of CL of the *cis-trans* isomer were not consistent across patient subgroups. As in other studies, CL measurements of the *cis-cis* isomer were not done because at the measurement time point of 160 minutes into the infusion period, all patients except two were still having adjustments made to their rate of infusion, a non-steady state condition. Two patients in Group B1 were at steady state at 160 minutes, and their estimated CL for the *cis-cis* isomer were 5.51 and 3.24 ml/kg/min. C_{max} and T_{max} for the *cis-cis* isomer were made from AUC estimates, but probably not at steady state conditions. The median C_{max} for the *cis-cis* isomer was approximately 18% higher in young patients on long-term infusion than on short term infusions. C_{max} was similar for young and elderly patients on long-term infusions. T_{max} for the *cis-cis* isomer was approximately 1.5 hours in young patients on short-term infusion, 2 hours in young patients on long-term infusion, and 2.2 hours in elderly patients on long-term infusions. Patients with decreasing infusion rate requirements tended to have earlier T_{max} and higher C_{max} compared to patients with constant rate requirements.

There was a trend toward positive correlations between plasma cholinesterase activity and the clearances of the *trans-trans* and *cis-trans* isomers. There was an inverse correlation between increasing age and CL of the *trans-trans* isomer ($p=0.0173$, $r^2=0.1694$) and the *cis-trans* isomer ($p=0.0079$, $r^2=0.2063$).

Table 7. Pharmacokinetics of Isomers. (Means \pm SD) (From Sponsor's Summary table for PK Parameters)

	Normal Plasma Cholinesterase						Low Plasma Cholinesterase		
	Stable Infusion Rate			Decreasing Infusion Rate			Stable Infusion Rate		
	Group A	Group B1	Group B2	Group A	Group B1	Group B2	Group A	Group B1	Group B2
n	6	6	5	1	5	3	0	0	0
CL <i>trans-trans</i>	77.2 \pm 50.1	74.3 \pm 34.6	31.5 \pm 13.8	32.1*	55.7 \pm 17.1	44.2 \pm 12.4	--	--	--
CL <i>cis-trans</i>	117.0 \pm 68.4	233.2 \pm 294.2	50.9 \pm 27.5	73.6*	169.7 \pm 222.6	54.4 \pm 19.5	--	--	--
EC ₉₅	97 \pm 48	116 \pm 39	166 \pm 82	152*	53**	137 \pm 53	--	--	--
Cmax <i>cis-cis</i>	104 \pm 41	118 \pm 46	249 \pm 341	174**	222 \pm 149	117 \pm 13	51 \pm 13	428**	69**
Tmax ^f <i>cis-cis</i>	88	124	151	119	88	90	30	62	34

* n=1, single value reported; ** n=2, median value reported; ^f median values reported.

Plasma clearances for isomers, the alcohol metabolite (141U86), and the monoester metabolite (879U84) are summarized in Table 8.

Table 8. Clearances at the End of Infusion for Isomers and Metabolites. Median (Range) (From Sponsor's Summary Table for PK Parameters)

	Normal Plasma Cholinesterase						Low Plasma Cholinesterase		
	Stable Infusion Rate			Decreasing Infusion Rate			Stable Infusion Rate		
	Young /Short	Young /Long	Elderly /Long	Young/ Short	Young/ Long	Elderly/ Long	Young/ Short	Young/ Long	Elderly/ Long
n	5	6	5	1	4	3	3	2	2
Cp (ng/ml):									
<i>trans-trans</i>	75 (24-104)	51 (35-78)	48 (44-204)	63	84 (31-52)	75 (53-88)	23 (16-54)	164 (32-295)	44 (25-62)

<i>cis-trans</i>	32 (8-59)	22 (19-31)	18 (13-90)	13	34 (16-151)	36 (25-43)	8 (5-37)	91 (21-160)	6*
<i>cis-cis</i>	108 (30-134)	74 (48-166)	66 (49-133)	120	122 (25-407)	88 (80-105)	46 (12-46)	38 (23-52)	43 (38-47)
141U86	2034 (330-3984)	2033 (1159-3941)	1280 (635-2491)	2557	2254 (715-4013)	3015 (1374-3269)	1108 ^f (385-1831)	1255*	515 (476-553)
879U84	1735 (130-4867)	2280 (442-3785)	1874 (875-2699)	1163	2873 (916-3341)	2932 (2344-2935)	1255 ^f (1254-1256)	1773*	654 (628-679)

*n=1, ^fn=2

There are no consistent differences in metabolic clearances of the isomers and metabolites between young patients and elderly patients, or between young patients receiving short or long term infusions. Likewise, patients who had decreasing requirements for mivacurium did not demonstrate differences in plasma clearance from patients who had constant dose requirements. Patients with low plasma cholinesterase generally had lower clearances, compared to normal; however, the values were measured in small numbers of patients.

Safety:

There was one patient who experienced an adverse event. The patient was a 33 year old male who exhibited inverted T-waves in leads II and AVF at 206 minutes after the initiation of mivacurium by infusion. The patient was treated with nitroglycerine and had no sequelae. This event is unrelated to the use of mivacurium, having no temporal or physiologic relationship to the onset, duration or activity of the drug.

Conclusions:

The median average infusion rate was approximately 14% less in elderly patients than in young adult patients receiving long duration infusions. There were no consistent differences between pharmacodynamics to explain the lower dose requirement in the elderly. The pharmacokinetic data suggest lower clearances and higher C_{max} of the active and inactive isomers in the elderly; however, because of subcategories of abnormal cholinesterase and different patterns of dose requirement, each cohort contains a small number of patients, making definitive conclusions difficult. Spontaneous recovery from neuromuscular blockade was similar in young adults receiving infusions for 1-3 hours or 5-6 hours, indicating that the primary metabolic pathway of ester hydrolysis by plasma cholinesterase is not saturated in this duration, and that there is no depot accumulation of mivacurium. Recovery characteristics of elderly patients receiving 5-6 hours of

infusion were comparable to those of younger patients. As expected, patients with abnormal plasma cholinesterase activity had lower infusion dose requirements and longer durations of spontaneously recovery compared to normal patients.

A small subset of patients in both age categories was observed to have a higher initial infusion requirement which did not stabilize in the first 30 minutes of infusion, and whose final infusion rate could be tapered over time. However, the recovery profile was not different from patients with constant rate requirements. Because of the small number of patients of this kind studied, the significance of this observation is unclear.

BLVS/93/0013: The Disposition of a Single Intravenous Bolus Dose of ¹⁴C-MIVACRON (¹⁴C-mivacurium chloride) in Healthy Male Patients Undergoing Scheduled General Anesthesia

This was an open study of six male patients undergoing elective extraction of third molars under N₂O/O₂/isoflurane anesthesia after induction with thiopental. The pharmacokinetics of mivacron were studied for 48 hours in the blood and 120-168 hours in the urine and feces by means of radioactive tracing after a single intravenous bolus of ¹⁴C-mivacurium chloride 0.15 mg/kg.

Patients were healthy male patients, ASA 1, age 18-50 years and weighing between 60-100 kg, who required short-term intubation for extraction of third molars under general anesthesia. Patients received a screening history and physical examination, screening blood tests, including plasma cholinesterase and Hbs antigen, and consented to participate. After induction of general anesthesia with thiopental 3.8 mg/kg, the intravenous bolus of ¹⁴C-mivacurium chloride was administered over 10-15 seconds for nasotracheal intubation. Anesthesia was maintained with N₂O/O₂/isoflurane. After surgery, patients were allowed to recover spontaneously from neuromuscular blockade. Patients received standard non-invasive intraoperative monitoring (BP, ECG, SpO₂, capnography), and during recovery and adverse experiences were observed up to the end of the sampling phase.

Venous blood samples were collected from the arm opposite to the administration site at baseline (prior to injection), and 1, 2, 4, 6, 9, 12, 15, 20, 30, 45, 60 and 90 minutes. All urine was collected as separate samples up to +24 hours, and as pooled 24 hour samples up to +120 hours. All fecal samples were collected up to 168 hours. The soda lime in the circle absorber system was collected and the radiolabel content was also determined.

For the purposes of reporting, the concentrations of mivacurium isomers and metabolites were converted from ng/ml or µg/ml to nM or µM respectively. The concentration of total mivacurium + 879U84 + 141U86 was defined as "total cold." The concentration of ¹⁴C was compared to "total cold," so that if ¹⁴C concentration was the greater of the two, this would indicate that another metabolite was present.

Because of the small number of subjects, no tests of statistical significance were performed.

Results:

The mean age of the 6 subjects was 28 years, mean height was 176 cm, mean weight was 71.3 kg; 4 subjects were Caucasian and two were black. All subjects completed the protocol and no data was excluded. One urine sample, the first postoperative collection, was inadvertently discarded in one case, and an incomplete collection was suspected in another case. Pharmacokinetic data for mivacurium are summarized in Table 9.1-9.4.

Table 9.1. Pharmacokinetic Parameters for Total Mivacurium (Sponsor's Table 2)

	Dose (mg/kg)	AUC (min. μ g/ ml)	t $\frac{1}{2}$ (min)	CL (ml/min/kg)	Vz (L/kg)	Cmax (ng/ml)
n	6	6	6	6	6	6
mean	0.154	2.978	33.7	55.9	2.400	1118.6
sd	0.006	0.908	19.9	17.1	0.811	330.9
CV (%)	3.8	30.5	58.9	30.7	33.8	29.6

Table 9.2. Pharmacokinetic Parameters for *Trans-trans* Mivacurium (Sponsor's Table 2)

	Dose (mg/kg)	AUC (min. μ g/ml)	t $\frac{1}{2}$ (min)	CL (ml/min/kg)	Vz (L/kg)	Cmax (ng/ml)
n	6	3	3	3	3	6
mean	0.089	1.067	3.0	86.0	0.379	716.8
sd	0.003	0.156	0.9	11.1	0.141	208.1
CV (%)	3.8	14.6	30.0	12.9	37.1	29.0

Table 9.3. Pharmacokinetic Parameters for *Cis-trans* Mivacurium (Sponsor's Table 2)

	Dose (mg/kg)	AUC (min.µg/ml)	t _{1/2} (min)	CL (ml/min/kg)	V _z (L/kg)	C _{max} (ng/ml)
n	6	4	4	4	4	6
mean	0.064	0.545	4.9	129.0	0.906	285.7
sd	0.002	0.194	1.6	34.6	0.388	94.1
CV (%)	3.8	35.6	32.6	26.8	42.8	32.9

Table 9.4. Pharmacokinetic Parameters for *Cis-cis* Mivacurium (Sponsor's Table 2)

	Dose (mg/kg)	AUC (min.µg/ml)	t _{1/2} (min)	CL (ml/min/kg)	V _z (L/kg)	C _{max} (ng/ml)
n	6	6	6	6	6	6
mean	0.0069	1.087	34.8	7.3	0.323	116.1
sd	0.0003	0.436	13.4	3.0	0.059	42.4
CV (%)	3.8	40.1	38.4	41.1	18.2	36.5

Table 10 below summarizes the pharmacokinetic parameters for the metabolites of mivacurium. Recovery of ¹⁴C from ¹⁴C-mivacurium was complete. Comparison of ¹⁴C from plasma and urine was completely accounted for by the measured metabolites, indicating no evidence of other metabolic products. The fraction of mivacurium and metabolites cleared renally was complete by 24 hours. Of the total dose of mivacurium administered, 5% was excreted as unchanged mivacurium (4.2% as *cis-trans* and *trans-trans* mivacurium), 36% was 879U84, and 20% was 141U86.

Table 10. Pharmacokinetic Parameters for Metabolites (n = 6). Mean ± SD (Sponsor's Tables 3-4)

	AUC (min.µg/ml)	C _{max} (ng/ml)	t _{1/2} (min)
Total 879U84	37.7 ± 8.7	1216 ± 337.7	62.9 ± 10.8

Cis-879U84	16.3 ± 4.1	496 ± 143.6	71.0 ± 11.7
Trans-879U84	21.5 ± 4.9	720 ± 195.7	60.4 ± 12.4
Total 141U86	13.8 ± 4.1	751.6 ± 158.9	37.1 ± 18.8
Cis-141U86	---	12.2 ± 3.4	---
Trans-141U86	13.7 ± 4.0	739 ± 158.3	37.3 ± 19.0

CL_R data was calculated from four patients who had complete urine collections. Table 11 contains renal clearance data for mivacurium and metabolites. Compared to total body clearance for mivacurium and isomers, 4-5% of total plasma clearance for the *cis-trans* and *trans-trans* isomers can be accounted for by renal clearance, while 19% of plasma CL for the *cis-cis* isomer could be accounted for by renal clearance.

Table 11. Mean Renal Clearances for Mivacurium Isomers and Metabolites (n = 4) (Sponsor's Table 7)

	Mivacurium Isomers			Metabolites		
	Cis-cis	Cis-Trans	Trans-trans	Cis-879U84	Trans-879U84	Total 141U86
CL _R (ml/kg/min)	1.73	6.70	3.96	1.50	2.13	1.04

The mean total ¹⁴C recovered in the urine and feces was 101%, of which 40% was in the urine and 60% was in the feces. ¹⁴C did not begin to appear in the feces until 48 hours, by which time urinary recovery of ¹⁴C was complete.

Safety:

The six patients experienced no serious adverse events. Four patients had a transient wheal and flare along the site of injection of mivacurium, which resolved spontaneously. One patient had a vaso-vagal reaction, and one patient experienced nausea, both of which are unrelated to the use of mivacurium.

Conclusions:

The major metabolite of mivacurium is the monoester, 879U84, detected in both the plasma and the urine. The radioactive labeling indicates that the known monoester and quaternary alcohol metabolites of all isomers completely account for all metabolic disposition of mivacurium. Renal clearances of the isomers of mivacurium account for a small fraction of their total clearance; however, the *cis-cis* isomer has the largest of these fractions appearing in the urine, 19%.

Four subjects experienced minor adverse reactions representative of the

histaminergic effects of mivacurium.

BQRT/94/0023: A Pharmacokinetic and Pharmacodynamic Study of Mivacurium and its Metabolites in Surgical Patients with Normal Hepatic Function or Hepatic Dysfunction Receiving Mivacurium During N₂O/O₂/Isoflurane Anesthesia

This was an open-label study of 22 patients, age 18-70 years, undergoing short surgical procedures under general endotracheal anesthesia. Patients were selected based on preoperative liver function, using the Child's classification, as follows:

	<u>A</u>	<u>B</u>	<u>C</u>
Serum bilirubin (μ M/l)	< 34	34-50	> 50
Serum albumin (g/l)	> 35	30-35	< 30
Ascites	None	Easily controlled	Poorly controlled
Neurologic disorder	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor

10 patients were recruited with normal hepatic function as controls (Group D), 5 patients were Child's Group A, 6 patients were in Child's Group B, and 1 patient was in Child's Group C.

Anesthesia was induced with midazolam 0.05 mg/kg, fentanyl 1.0-2.0 mg/kg, and thiopental 3-5 mg/kg iv. Mivacurium was administered as an infusion over 10 minutes at 0.015 mg/kg/min to a total dose of 0.15 mg/kg. Patients were intubated when clinically appropriate. Anesthesia was maintained with 70% N₂O/ oxygen + midazolam and/or fentanyl. Onset, depth, and duration of neuromuscular blockade was monitored and reported using standard mechanomyographic monitoring of the adductor pollicis. All patients were allowed to recover spontaneously from neuromuscular blockade and standard monitoring and clinical criteria were used for extubation.

Pharmacokinetics of mivacurium isomers and isomeric metabolites were measured from venous samples measured pre-dose and at +1, 2, 4, 6, 8, 10, 11, 12, 14, 16, 19, 22, 25, 30, 40, 70, 100, 130, and 190 minutes after initiation of infusion, and at 240 and 300 minutes after termination of the infusion. Venous samples were drawn from an intravenous catheter placed for that purpose in the arm opposite to the medication administration infusion.

Safety was monitored by pre- and post-procedure physical exam, by

intraoperative noninvasive monitoring of physiologic variables, and by observation for adverse events.

Sample size was clinically rather than statistically based. It was agreed to terminate recruitment of Child's C patients after 1 patient because of the difficulty of recruiting patients with this severity of illness undergoing non-emergency surgery.

There were four amendments to the protocol. Amendment #1 allowed for the recruitment of a minimum of 5 and a maximum of 8 into each study group, instead of a maximum of 5. The dilution of the mivacurium infusion with sterile water to a final concentration of 0.5 mg/ml was specified. The inclusion criterion for body weight was changed to within 30% of ideal body weight, from 20%. The terminal venous samples were added. Amendment #2 removed the necessity to record systemic pressure at 5 minutes after the start of the infusion. Detailed instructions for collection and handling of blood samples were specified, and collection of urine samples was added. Amendment #3 substituted serum creatinine for creatinine clearance to assess renal function. Amendment #4 increased the upper age limit to 70, from 65 years.

One patient's data (Child's B) was excluded from efficacy analysis because serum creatinine exceeded 150 $\mu\text{M/l}$, an exclusion criterion. There were no other exclusions on the basis of inclusion or exclusion criteria violations.

Other efficacy data that was not available: 1) time to 90% and 95% T1 suppression and time to 5% and 10% recovery for patients #3 and #5 because the maximal T1 suppression achieved was less than these criteria, 2) time to 95% T1 suppression was not available for patients #19 and #22 because the maximal T1 suppression observed was less than 95%, 3) times to recovery to 90% T1 for patients #6 and #12, and times to recovery to 95% T1 for patients #6, 7, 9, 10, 12, 13, 14, 15, 16, 18, 21, and 22 were not available because monitoring was discontinued prematurely. Missing safety data consisted of vital signs measurements at 10 minutes after the initiation of infusion in 5 patients, isolated screening laboratory data in 5 patients, and recovery room assessment in one patient.

Results:

Table 12 summarizes demographics. All patients were Caucasian. There was only one patient recruited to Group C.

Table 12. Demographic Characteristics of Patients, Grouped by Hepatic Function. (Sponsor's Table 5)

Variable (means)	Group A	Group B	Group C	Group D (normal)
number	5	6	1	10
age (yr)	53.4	56.1	57.1	46.9

weight (kg)	66.8	76.3	50.0	74.5
height (cm)	173.4	176.3	168.0	170.5
sex (F/M)	3/2	5/1	0/1	5/5

There were eight patients with plasma cholinesterase levels below normal; one in Group A, one in Group C, and the remaining six in Group B. There were four patients with mildly to moderately low dibucaine numbers, and four with low fluoride number; one patient was in Group A, and the remainder were in Group D. These findings are not unexpected, since the production of plasma cholinesterase is dependent on hepatic function, while heterozygosity for the abnormal forms is independent of hepatic function.

Mean depth and onset time to maximal suppression of T1 was not different between the Groups A, B, and D, by multiple comparisons of the 95% confidence intervals. All parameters for spontaneous recovery were longer in Group B patients compared to Groups A and D. This would be expected in patients with deficient plasma cholinesterase activity. There was a significant negative correlation between plasma cholinesterase activity and recovery indices. Table 13 summarizes representative data.

Table 13. Mean Onset and Recovery Indices By Patient Group.(Summary from Sponsor's Tables 8, 15, 19, 24)

	Group A	Group B	Group C	Group D
Max T1 suppression	98.6 (%)	97.6 (%)	94.1 (%)	96.0 (%)
Time to max T1 suppression	12.4 min	13.1 min	12.2 min	12.1 min
Time to 5% recovery	21.5 min	27.0 min	—	18.7 min
Time to 75% recovery	37.3 min	49.0 min	30.7 min	30.3 min
25-75% Recovery Index	9.5 min	16.4 min	10.2 min	7.3 min

Pharmacokinetics of mivacurium isomers were not different between Groups A and D, but the geometric mean for C_{max} in group B was significantly higher than for Group D. There were trends for increasing $AUC_{0-\infty}$, $t_{1/2}$, $V\beta$, and decreased CL with increasing hepatic dysfunction, with significance between values for Groups B vs D. Pharmacokinetic variables for the isomers are summarized by Group in Table

14. As in previous studies, the *cis-cis* isomer did not reach steady-state conditions within the measurement interval.

Table 14. Pharmacokinetics of Isomers of Mivacurium by Groups (Means \pm SD)
(Sponsor's Summary Table of PK Parameters)

	Group	N	<i>cis-cis</i> isomer	<i>cis-trans</i> isomer	<i>trans-trans</i> isomer
C _{max} (ng/ml)	D	10	57.7 \pm 15.1	70.2 \pm 30.1	175.7 \pm 59.2
	A	5	68.8 \pm 15.8	106.7 \pm 42.4	239.8 \pm 81.0
	B	6	84.9 \pm 25.7	184.9 \pm 98.8*	420.8 \pm 252.8*
AUC _{0-∞} (ng.h/ml)	D	9	20.9 \pm 7.8	9.3 \pm 4.3	26.3 \pm 10.2
	A	5	22.3 \pm 9.6	15.7 \pm 8.0	40.4 \pm 17.9
	B	6	32.7 \pm 12.7	26.8 \pm 16.4*	69.3 \pm 42.6*
t _{1/2β} (min)	D	9	14.7 \pm 7.6	1.2 \pm 0.5	2.4 \pm 1.0
	A	5	15.0 \pm 11.8	1.6 \pm 0.5	3.7 \pm 1.6
	B	6	23.1 \pm 7.8	1.9 \pm 0.8	5.3 \pm 2.4*
CL (ml/min/kg)	D	9	8.6 \pm 3.1	123.6 \pm 55.7	66.2 \pm 25.0
	A	5	8.6 \pm 4.8	73.0 \pm 31.5	43.1 \pm 16.2
	B	6	5.6 \pm 2.5	52.1 \pm 39.9*	30.7 \pm 20.0*
V β (ml/kg)	D	9	158.7 \pm 44.1	200.8 \pm 95.0	203.6 \pm 50.2
	A	5	147.4 \pm 56.6	151.8 \pm 60.1	221.2 \pm 138.9
	B	6	164.3 \pm 17.0	110.7 \pm 36.8*	190.5 \pm 70.2

* significant difference B vs D at 95% confidence interval

For metabolites of mivacurium, 879U84, and 141U86, the effect of reduced metabolic clearance of the parent compounds, due to hepatic disease, was to reduce C_{max} and increase AUC by a factor of 2-2.5.

Safety:

There were no changes in pre- and postoperative vital signs in any patients. Intraoperatively, no episodes of fall of mean arterial pressure \geq 30% and no significant changes in heart rate occurred. One patient experienced a transient flush that resolved spontaneously in the arm infused with mivacurium 2 minutes following infusion.

Conclusions:

Hepatic disease of increasing severity does not affect the onset and depth of neuromuscular blockade induced by intravenous infusion of mivacurium 15 μ g/kg/min. Patients with mild liver dysfunction demonstrated a recovery profile from neuromuscular blockade no different from that of patients with normal liver function. A greater degree of liver dysfunction, as defined by Child's B

classification, had a direct impact on the pharmacokinetics of mivacurium and metabolites, due to insufficient production of plasma cholinesterase. The recovery indices in these patients were 1.4-1.6 times longer than those in normal patients.

Because there was only one patient with severe hepatic disease, there is insufficient information in this study to assess the pharmacokinetics of mivacurium and its metabolites in the presence of severe hepatic disease.

BQRT/94/0025: A Pharmacokinetic and Pharmacodynamic Study of Mivacurium and its Metabolites in Surgical Patients with Normal Renal Function or Renal Dysfunction Receiving Mivacurium During N2O/O2/Narcotic Anesthesia.

This was an open-label, single center study in 27 adult patients (ages 18-65 years) undergoing elective surgery of at least one hour duration. Patients were selected on the basis of preoperative serum creatinine and divided into three groups:

- Group 1: normal renal function; $S_{CR} \leq 110$ mmol/l (n=11)
- Group 2: mild-moderate dysfunction; S_{CR} 150-300 mmol/l (n=8)
- Group 3: severe renal dysfunction; $S_{CR} > 700$ mmol/l (n=8)

Anesthesia was induced with midazolam 0.05 mg/kg iv, fentanyl 1.0-2.0 mg/kg iv, and thiopental 3-5 mg/kg iv. Following induction, mivacurium 0.15 mg/kg was administered as an iv infusion at 15 μ g/kg/min for 10 minutes. After 10 minutes the infusion rate of mivacurium was reduced to 7.5 μ g/kg/min and maintained for 10 minutes; subsequent adjustments could be made at the discretion of the investigator to maintain T1 suppression at $95 \pm 4\%$. Anesthesia was maintained with fentanyl and midazolam + N2O/O2 inhalation. Intubation and intraoperative management were carried out according to standard clinical practice. Electromyographic monitoring, recording of variables, and venous blood sampling for pharmacokinetic data was carried out as in previously described studies. All patients were allowed to recover spontaneously from neuromuscular block. Safety monitoring was carried out by: 1) comparing pre- and postoperative physical exam and vital signs, by monitoring intraoperative ECG and vital signs, 2) by recording heart rate and blood pressure just prior to and at 5 and 10 minutes after the start of the mivacurium infusion, and 3) by compilation of adverse event reports. Postoperatively, patients were evaluated clinically for recovery from neuromuscular blockade by bedside clinical assessment prior to discharge.

There were three amendments to the original protocol that were instituted: 1) changed final venous sample to 5 ml and sampling time from 240 min to 300 min, 2) allowed adjustment of infusion rate, after first two specified rates, at the discretion of the managing anesthesiologist, 3) change of the definition of renal function as based on serum creatinine rather than calculated creatinine clearance.

Results:

All patients completed the study and contributed data to the efficacy and safety analysis. Protocol violations included: ages of two patients, 16 and 66 years old; four patients who were defined as mild-to-moderate renal dysfunction by creatinine clearance had serum creatinine > 110 but less than 150 mmol/l, and therefore violated the terms of amendment #3. However, these patients' data were included because their serum creatinines were still higher than normal. All patients received 50% N2O rather than 70% N2O as originally specified in the protocol; five patients did not receive premedication; screening urinalysis was not obtained in 12 patients. These events were not felt, appropriately, to influence the quality of the data. Isolated measurements of electromyographics are missing from some patients' data. The pharmacokinetics were calculated based on real time measurements in those instances where the scheduled sampling time was missed.

Demographics of the groups are summarized in Table 15.

Table 15. Demographics and Baseline Characteristics by Group, Based on Renal Dysfunction (Means \pm SD) (Summary from Sponsor's Tables 4-6)

	Group 1 (normal)	Group 2 (mild- moderate)	Group 3 (severe)
Age (yrs)	44.2 \pm 15.5	30.2 \pm 12.3	46.0 \pm 14.5
Weight (kg)	69.6 \pm 10.4	62.0 \pm 10.8	66.8 \pm 13.2
Height (cm)	170.3 \pm 10	171.7 \pm 8.9	168.6 \pm 7.5
Sex (M/F)	6/6	2/5	5/3
Race (white/other)	12/0	7/0	7/1
BP systolic (mmHg)	120.8 \pm 11.8	133.0 \pm 9.8	143.8 \pm 32.8
diastolic	71.7 \pm 8.3	82.9 \pm 11.5	82.5 \pm 16.5
HR (beats/min)	73.3 \pm 8.5	75.3 \pm 4.1	72.5 \pm 5.9

Five patients were found to have plasma cholinesterase activity below the normal lower limit: 2 were in Group 1, two were in Group 2, and 1 in Group 3. Two patients in Group 2 and two patients in Group 3 had lower than normal dibucaine numbers; three patients in Group 2 and one patient in Group 3 had lower than normal fluoride numbers.

Table 16 summarizes the pharmacodynamic data. Based on confidence intervals, there were no differences between groups for maximum T1 suppression and onset time to maximum suppression. Recovery indices also failed to reveal a difference between patient groups. The only significant difference demonstrated was that Group 2 had a higher mean infusion rate requirement to maintain the standard criterion of paralysis (91-99% suppression of T1); 95% confidence

intervals indicated the mean infusion rate in Group 2 could be 0.8-5.4 $\mu\text{g}/\text{kg}/\text{min}$ higher compared to Group 3. However, recovery times were unaffected. A direct relationship between plasma cholinesterase activity and mean infusion rate requirement was demonstrated in all patients.

Table 16. Mechanomyographic Variables (Means \pm SD) (From Sponsor's Summary Table of Pharmacodynamic Data Following Infusion)

	Group 1	Group 2	Group 3
Maximum block (%)	98.8 \pm 0.9	97.0 \pm 2.9	98.6 \pm 1.7
Time to maximum block (min)	14.3 \pm 7.4	16.2 \pm 13.7	13.8 \pm 4.8
Time to 25% T1 recovery (min)	11.7 \pm 4.6	10.7 \pm 6.4	11.2 \pm 3.6
Time to 95% T1 recovery (min)	28.6 \pm 6.2	31.3 \pm 19.6	30.0 \pm 12.1
Time to T4: T1 > 70% (min)	26.7 \pm 8.8	24.1 \pm 11.0	25.9 \pm 8.9
25-75% Recovery Index (min)	10.8 \pm 3.5	9.2 \pm 3.3	10.3 \pm 3.2
Mean infusion rate to maintain 91-99% T1 suppression ($\mu\text{g}/\text{kg}/\text{min}$)	7.4 \pm 2.1	9.4 \pm 2.0	6.3 \pm 2.6

For *cis-trans* and *trans-trans* isomers, there were no significantly different between groups for C_{max} , CL, CL_{ss} , $t_{1/2\beta}$, V_{β} . For the *cis-cis* isomer, mean C_{max} was not significantly different between groups; CL and $t_{1/2\beta}$ were significantly different between Group 2 and Group 1, and between Group 3 and Group 1. Plasma concentration of *cis*879U84 and *trans*879U84 increased during the infusion period, as expected and then declined in a biexponential manner. C_{max} for these metabolites were not significantly different between groups. The quantities of *cis*141U86 measured were too small to characterize its pharmacokinetics. Table 17 summarizes the salient pharmacokinetics of the isomers.

Table 17. Summary of Pharmacokinetic Parameters for Mivacurium Isomers, by Patient Groups (Mean \pm SD) (From Sponsor's Summary Table of PK Parameters)

	Groups	cis-cis isomer	cis-trans isomer	trans-trans isomer
Cmax (ng/ml)	1	102.5 \pm 36.0	87.7 \pm 43.4	216.2 \pm 81.6
	2	140.6 \pm 70.2	66.4 \pm 6.3	187.0 \pm 20.0
	3	115.8 \pm 57.9	93.1 \pm 66.0	217.9 \pm 102.8
Ratio (tmax)*	1	0.70 \pm 0.40	0.10 \pm 0.04	0.12 \pm 0.06
	2	1.02 \pm 0.01	0.13 \pm 0.05	0.14 \pm 0.05
	3	0.75 \pm 0.44	0.09 \pm 0.04	0.09 \pm 0.04
CL (ml/min/kg)	1	4.04 \pm 0.84	97.1 \pm 54.3	53.5 \pm 21.5
	2	2.52 \pm 0.61	93.3 \pm 14.9	49.3 \pm 5.9
	3	2.81 \pm 0.90	109.6 \pm 61.0	52.6 \pm 22.0
CLss (ml/min/kg)	1	-----	105.4 \pm 51.3	65.0 \pm 36.0
	2	-----	105.4 \pm 26.9	53.1 \pm 11.2
	3	-----	96.2 \pm 46.4	53.6 \pm 20.9
t $\frac{1}{2}$ β (min)	1	51.9 \pm 19.5	2.3 \pm 1.4	2.5 \pm 1.9
	2	89.9 \pm 12.1	3.6 \pm 1.9	3.5 \pm 3.1
	3	72.9 \pm 23.3	2.6 \pm 1.3	3.2 \pm 0.8
V β (ml/kg)	1	286.6 \pm 73.9	303.4 \pm 241.5	178.5 \pm 134.4
	2	323.2 \pm 74.1	473.8 \pm 212.9	243.3 \pm 197.2
	3	276.2 \pm 59.9	415.7 \pm 296.9	238.0 \pm 114.5

*Ratio (tmax): time for Cmax as a fraction of the infusion period.

Safety:

One episode of mild erythema was attributed to the administration of mivacurium. There was one case of mild phlebitis, which was not attributable to the use of mivacurium. Vital signs, and physical examination were unaffected by the use of mivacurium. No vasopressors, inotropes or bronchodilators were used intraoperatively in this series. One patient received two 20 mg doses of hydralazine intravenously for intraoperative hypertension. This patient was taking medication (metoprolol) for hypertension pre-operatively, and the occurrence of intraoperative hypertension is related to underlying disease and not the use of a particular NMB agent.

Conclusions:

In a previous study, pharmacokinetic and pharmacodynamic parameters were studied in 9 patients with end-stage renal failure prior to renal transplantation, after 0.15 mg/kg mivacurium was administered as a bolus. In that study, the onset and depth of NMB was the same as in normal patients, but recovery indices were approximately 1.5-2.0 times longer than in control patients. These clinical findings were not supported by pharmacokinetic parameters, which were the same in renal failure and control patients; however, the individual isomers could not be

characterized at that time.

This study was designed to further characterize the pharmacokinetics of the isomers and metabolites of mivacurium, as well as to compare varying degrees of renal impairment. No difference in onset and depth of NMB was observed in normal or renally-impaired patients. In patients with mild-to-moderate renal impairment, a higher mean infusion rate was used to maintain 91-99% T1 suppression; however, this finding is of little clinical significance, as the total dose and duration of mivacurium infusion does not influence the rate of recovery, provided that plasma cholinesterase activity is normal. In support of this, confidence intervals did not reveal a significant difference in measurements of neuromuscular recovery between patients with normal, mild-to-moderately impaired, or severely impaired renal function. The pharmacokinetics of the active isomers were not influenced by differences in renal function. As expected, the *cis-cis* isomer, which is more dependent on renal function for elimination, demonstrated prolonged clearance compared to normal.

BQRT/94/0024: Evaluation of the Safety and Efficacy of Mivacurium Chloride in Patients with Ranging Degrees of Renal Dysfunction Under N2O/O2/Propofol Anesthesia.

This was an open-label, parallel design, single center study to identify possible differences in efficacy or safety of mivacurium in patients with normal or abnormal renal function. 60 consenting adult patients, ages 18-65 years, and undergoing elective surgery of at least one hour duration were entered into the study, selected on the basis of preoperative estimated creatinine clearance and divided into three groups:

- Group 1: normal renal function, ASA 1 or 2 (n=21)
- Group 2: mild-to-moderate renal dysfunction; creatinine clearance 21-50 ml/min (n = 19)
- Group 3: severe renal dysfunction; creatinine clearance \leq 20 ml/min (n=20)

Group 2 was further subdivided to acquire an equal number of patients with mild renal impairment, Ccr = 36-50 ml/min, and moderate renal impairment, Ccr = 21-35 ml/min. For each patient aged 65-70 years with mild-to-moderate renal dysfunction, an age-matched healthy adult and an age-matched patient with severe renal failure were entered into their respective groups.

General anesthesia was induced with propofol 1.5 mg/kg iv, fentanyl 1-3 μ g/kg iv, and maintained with N2O/O2 by inhalation, supplemented with continuous infusion of propofol or fentanyl as required. Mivacurium was administered as an intravenous bolus, 0.15 mg/kg over 20-30 seconds. Intubation was attempted at 2.5 minutes after the completion of the bolus injection, but intubating conditions were not recorded as a variable in this study. Paralysis was maintained with a

continuous infusion of mivacurium, starting with an infusion rate of 10 $\mu\text{g}/\text{kg}/\text{min}$, and was commenced at the time of spontaneous recovery of T1 to 5% of baseline. The infusion was adjusted at no less than 3 minute intervals, if necessary, to maintain 95% suppression of T1 ($5 \pm 4\%$ of baseline). If the procedure was too short to require a continuous infusion of mivacurium, maintenance doses could be administered by boluses between 0.013- 0.08 mg/kg. Monitoring of neuromuscular transmission used standard surface electromyographic stimulation of the ulnar nerve to elicit an evoked response of the adductor pollicis. Standard twitch height and train-of-four monitoring were recorded, as previously described.

An average infusion rate was determined for each patient with at least five evaluable epochs after the first five epochs, each epoch was defined as a 3-minute interval in which the infusion rate was known and the depth of neuromuscular blockade was stable at 91-95%. The average infusion rate was defined as the mean of the infusion rates for all evaluable epochs from the sixth to the last complete epoch, inclusive.

Pre- and post-operative safety assessments were: screening history and physical examination, chest x-ray and ECG for patients ≥ 55 years of age, routine hematology and chemistry tests and urinalysis, and plasma cholinesterase and dibucaine number. Intraoperative safety assessments were monitoring of vital signs and ECG according to standard-of-care anesthesia practice. In the post-treatment period recovery from neuromuscular blockade was assessed by standard clinical bedside assessments of head-lift and grip strength. All periods of the study were monitored for any adverse experiences.

Patients were included according to criteria of age 18-70 yrs, body weight 80-130% ideal body weight, and categories of renal function as specified above. Exclusions were made based on anatomic characteristics predictive of difficult intubation, allergy to neuromuscular blocking agents, history of reactive airway disease, alcohol or drug abuse, significant intercurrent medical disease, usage of medications known to effect neuromuscular transmission within 48 hours prior to baseline.

Summary statistics (mean, standard deviation, range, 95% confidence interval) were generated for each group.

Results:

There was one protocol amendment to the study, raising the age limit from 65 to 70 years of age. A total of 60 patients were recruited; no data was excluded on the basis of protocol violations. Some data was excluded from efficacy analysis for receiving additional boluses of mivacurium during the infusion (3 patients), loss of data (1 patient), and prolonged neuromuscular block after the initial dose (1 patient). Other protocol violations were judged to be minor and irrelevant to the validity of the data.

Demographic data and baseline vital signs are summarized in Table 18.

**Table 18. Demographics of Patients Grouped by Renal Function. (Mean \pm SD)
(Summarized From Sponsor's Tables 5-7)**

	Group 1 (n=21)	Group 2 (n= 19)	Group 3 (n=20)
Age (yrs)	53 \pm 13.3	61.3 \pm 7.4	52.6 \pm 13.1
Weight (kg)	67.9 \pm 8.9	65.9 \pm 11.6	68.0 \pm 8.3
Height (cm)	169.6 \pm 8.0	167.6 \pm 7.7	169.7 \pm 9.0
Sex (M/F)	14/7	6/13	5/15
Race (white/other)	21/0	19/0	19/1
Systolic (mmHg)	128.3 \pm 11.1	135.0 \pm 21.2	151.0 \pm 24.7
Diastolic (mmHg)	78.1 \pm 6.8	76.8 \pm 9.3	85.5 \pm 11.7
Heart Rate (beats/min)	74.9 \pm 9.6	72.6 \pm 11.4	82.0 \pm 12.5

Twenty-one patients had abnormal pseudocholinesterase levels (Group 1:3, Group 2: 9, Group 3: 9). Three patients had low dibucaine numbers, 2 in Group 1 and 1 in Group 3. There were no differences in onset of neuromuscular block between patient groups. Recovery after the initial mivacurium bolus was 9 minutes longer in patients with renal dysfunction compared to normal. While mean rates of infusion required to maintain 95% T1 suppression were not affected by renal function, recovery after the termination of infusion was prolonged in patients with renal dysfunction compared to normal. Efficacy variables are summarized in Table 19.

Table 19. Comparative Pharmacodynamic Data After Mivacurium by Bolus and Infusion. (Means \pm SD) (From Sponsor's Summary Table of PK Data)

	Group 1	Group 2	Group 3
Time to Maximum T1 suppression (min)	4.8 \pm 1.8	5.3 \pm 1.8	4.5 \pm 1.9
Maximum T1 Suppression (%)	96.1 \pm 5.9	96.5 \pm 7.4	97.1 \pm 6.3
Time to 5% Recovery (min)	11.0 \pm 3.9	18.0 \pm 10.7*	19.4 \pm 11.7
Infusion Rate (μ g/kg/min)	6.2 \pm 2.2	5.7 \pm 3.5	4.9 \pm 3.2
25-75% Recovery Index (min)	7.5 \pm 4.0	13.9 \pm 12.5*	11.7 \pm 9.7

Time to T4:T1 \geq 70% (min)	17.8 \pm 5.7	35.5 \pm 33.0*	29.2 \pm 20.9
Time to 95% T1 Recovery (min)	19.8 \pm 7.1	35.9 \pm 26.8*	32.0 \pm 20.4

* 95% confidence difference indicates a difference between the means of Groups 1 and 2.

Safety:

There were 16 adverse experiences reported in this patient series, listed below. The possible relationship of the adverse event to administration of mivacurium is ascribed to the reviewer only where there is divergence from the sponsor's report.

Pt# 1: age 60, Group 1; bradycardia; possibly related to mivacurium (*reviewer*); onset 9 minutes after initial bolus; duration 5 minutes, treated with atropine; rated mild intensity; no sequellae.

1: age 60; hypotension; possibly related to mivacurium (*reviewer*); onset 4 minutes after bolus; duration 13 minutes, treated with etilefrine; rated mild intensity; no sequellae.

28: age 54, Group 2; hypotension; possibly related to mivacurium (*reviewer*); onset 10 minutes after bolus; duration 1 minute, treated with norfenefrine; rated moderate intensity; no sequellae.

47: age 66, Group 2; hypotension; possibly related to mivacurium (*reviewer*); onset 11 minutes after bolus; duration 4 minutes; treated with etilefrine; rated mild intensity; no sequellae.

60: age 59, Group 2; hypotension; possibly related to mivacurium (*reviewer*); accompanied by flushing²; onset 77 minutes after bolus dose; duration 8 minutes; treated with colloid infusion, etilefrine, epinephrine; rated moderate intensity; no sequellae.

10: age 29, Group 3; hypotension; unrelated to mivacurium; onset before administration; duration 26 minutes; treated with colloid infusion; rated moderate intensity; no sequellae.

hypotension, second episode; unrelated to mivacurium; onset 8 minutes after dose; duration 35 minutes; rated moderate intensity; treated with norfenefrine; no sequellae.

² Reported as a separate adverse event by the sponsor.

- 40: age 40, Group 3; hypotension; possibly related to mivacurium (*reviewer*); onset 16 minutes after bolus; duration 5 minutes; rated moderate intensity; treated with volume infusion; no sequellae.
- 19: age 64, Group 1; hypertension; unrelated to mivacurium; onset 31 minutes after dose; duration 90 minutes; rated moderate intensity; treated with vasodilator; no sequellae.
- 1: age 60, Group 1; bradycardia; unrelated to mivacurium; onset 9 minutes after bolus; duration 5 minutes; rated mild intensity; treated with etilefrine; no sequellae.
- 50: age 70, Group 2; bigeminy; unrelated to mivacurium; onset prior to administration; duration 27 min; rated mild intensity; treated with lidocaine, atropine; no sequellae. (*Most likely due to surgery-reviewer*)
- 49: age 59, Group 1; anticholinergic syndrome; possibly related to mivacurium; occurred after termination of infusion; duration 40 minutes; rated moderate intensity; treated with physostigmine; recovered without sequellae.
- 56: age 69, Group 1; anticholinergic syndrome; possibly related to mivacurium; occurred after termination of infusion; duration 60 minutes; rated moderate intensity; treated with 0.4 mg naloxone; recovered without sequellae. (*More likely relationship to fentanyl- reviewer*).
- 4: age 45, Group 3; anticholinergic syndrome; possibly related to mivacurium; occurred after termination of infusion; duration 30 minutes; rated moderate intensity; treated with physostigmine; recovered without sequellae.
- 7: age 58, Group 3; prolonged neuromuscular block; related to mivacurium; occurred after initial bolus; duration 165 minutes; rated severe intensity; treated with appropriate support; recovered without sequellae.
- 60: age 59, Group 2; bleeding; unrelated to mivacurium; duration 40 minutes; rated severe intensity; treatment not specified; recovered without sequellae.

Except for one episode of hypotension which occurred before the administration of mivacurium, it is not possible to definitely identify a causal relationship between mivacurium and occurrence of hypotension. While other causes, including volume status, electrolyte imbalance, underlying disease, and other medications may also be implicated, it is impossible to definitively say that the vasodilatory effects of mivacurium, mediated by histamine, had no influence on

these episodes of hypotension. Patient #60, who experienced cutaneous flushing with hypotension, would exemplify an event with a likely relationship to mivacurium use, although typically such an event would occur immediately after a bolus dose rather than during or after an infusion. Other possible causes may have been intraoperative administration of ampicillin or blood products (not documented).

The case of prolonged neuromuscular block occurred after the administration of the initial bolus of mivacurium. The patient's plasma cholinesterase activity was mildly depressed, and the patient was also documented to have abnormal sensitivity to succinylcholine and atracurium. A neurologic diagnosis of polyneuropathy was subsequently made.

Conclusions:

In this study, the onset and intensity of neuromuscular block induced by mivacurium were unaffected by impairment of renal function. Patients with mild-to-severe renal dysfunction do not show an enhanced sensitivity to mivacurium, as evidenced by: 1) the same onset time and degree of T1 suppression after a bolus of 0.15 mg/kg, and 2) their requirement for the same rate of infusion as normal adults to maintain 95% T1 suppression. Recovery indices were prolonged in patients with mild-to-severe renal dysfunction, to approximately twice the time for spontaneous recovery seen in normal patients. This observation agrees with prior evidence in patients with end-stage renal disease in two studies, but not with a previously described pharmacokinetic study in this series (BQRT/94/0025).

Post-marketing Data

From 1992 to 1997 inclusive, there have been 43 cases of anaphylactic shock associated with the use of mivacurium. These cases have been reviewed in conjunction with the Division of Pharmacovigilance and Epidemiology. 37 of these have been serious, including six considered life-threatening and one death. Cases have occurred in pediatric and adult patients, including patients with no atopic or allergic history, and no prior exposure to benzylisoquinolinium muscle relaxants. Where reported, the doses of mivacurium administered were within the recommended doses provided in the label. In ten cases, allergen skin testing confirmed that mivacurium was the inducing agent. The current labeling for mivacurium de-emphasizes the allergic potential of mivacurium in some places, and lists the possible component symptoms of anaphylaxis separately rather than describing anaphylaxis by name. Recommendations for labeling changes to discuss anaphylaxis will be made together with the sponsor's proposed labeling amendment below.

Labeling Review

The sponsor's proposed labeling changes are based on the information contained in the completed Phase IV reviewed above. The sponsor's revisions of

content are listed by line and page of the annotated package insert submitted with this filing, with redactions ~~struck through~~ and additions underlined. These are followed by the reviewer's comments in *italics*. Minor stylistic revisions are acceptable without comment.

Redacted

4

pages of trade

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confidential

commercial

information

Conclusions and Recommendations

Based on the completed Phase IV commitments, the sponsor's proposed labeling changes are acceptable as noted above. Based on postmarketing surveillance data indicating the occurrence of 43 anaphylactic reactions to mivacurium, recommendations have been made to strengthen the wording of the package insert regarding this specific adverse event.