STN125034
California Department of Health Services
Botulism Immune Globulin (Human)(Intravenous)

Memorandum

TO: File of **STN: 125034/0**

From: Charles Maplethorpe, M.D., Ph.D., CBER/OBRR/DH/CRB HFM-392

Date: 23-Oct–2003

CC: Debbie Nadel, DBA, HFM-380; Dorothy Scott, M.D., DH, HFM-345; Toby Silverman, M.D., DH/CRB, HFM-392

Re: **125034/0** • Sponsor: **California Department of Public Health** • product: **Botulism Immune Globulin (Human)["Baby BIG"]** • Issue: Safety and Efficacy of BIG for treating infantile botulism

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Summary.

Botulism Immune Globulin (Human)(Intravenous)(BabyBIG®) for the treatment of infant botulism was studied in a randomized double-blinded placebo-controlled clinical trial (RCT) that enrolled 129 subjects, and in an open label study (OLS) that enrolled 292 subjects. The product has been shown to be safe and effective in significantly reducing the length of hospitalization of infants with infant botulism caused by botulinum toxins A or B.

BabyBIG® is indicated for the treatment of patients below one year of age with infant botulism caused by toxin type A or B.

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Background.

Infant botulism is a rare syndrome of flaccid paralysis that may develop in infants whose intestines become colonized with gram positive *Clostridia botulinum* producing toxins of several known serotypes (A-G). The predominant serotypes for infant botulism in the United States are type A or type B. The following two diagrams are from the CDC website (http://www.cdc.gov/ncidod/dbmd/diseaseinfo/botulism.pdf), showing the numbers of cases across the U.S. in recent years:

Figure 7. Outbreaks of infant botulism, type A, by state, 1976-1996

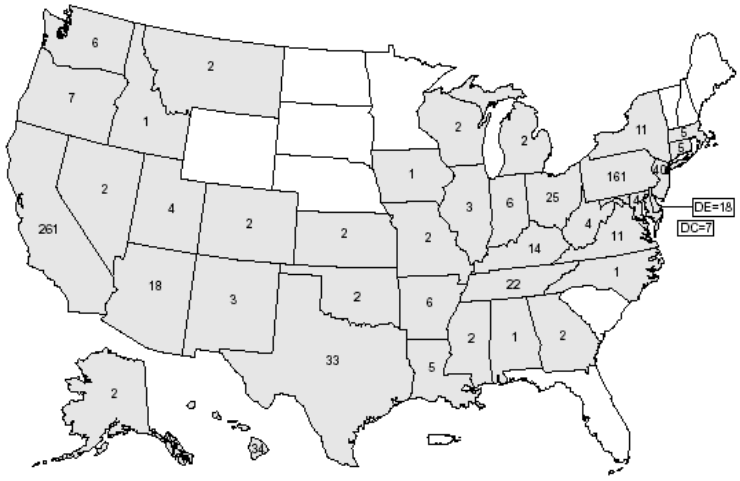


Figure 8. Outbreaks of infant botulism, type B, by state, 1976-1996

It can be seen that the largest number of cases of infant botulism occur in the state of California. For this reason, the state of California has established the Infant Botulism Treatment & Prevention Program (IBTPP), under the direction of Stephen S. Arnon, M.D., in the California Department of Health Services. The IBTPP and its website (http://www.dhs.ca.gov/ps/dcdc/html/ibtindex.htm) are important resources for persons wanting more information on this disease.

Botulism Immune Globulin (Human)(Intravenous)(BabyBIG®) was developed under IND ---- (sponsor Stephen S. Arnon), IND ---- (sponsor: California Dept. of Health Services), and several other ----------.

The product is made from pooled plasma collected from persons immunized with botulinum toxoid (see manufacturing review) and characterized for titers against botulinum toxin types A and B. Only a single product lot (Lot 1) was manufactured (in 1991) for the pivotal study, referred to here as the randomized controlled trial (RCT). The enrollment period for the RCT was from February 1992 to July 1998. Lot 1 was also used for some subjects in an open-label study (OLS). The enrollment period for the OLS was from March 1994 through December 1999.

FDA determined that the successful manufacture of a second product lot (Lot 2) would be a requirement for product licensure, and that a series of post-licensure commitments to ensure maintenance of product quality would be required.

Summary of the Randomzed Controlled Trial (RCT) Protocol.

This was a randomized double-blinded placebo-controlled clinical trial (RCT) of the use of BIG-IV (human) to treat infantile botulism. The clinical trial was conducted from February 1992 to July 1998. The primary endpoint was length of hospital stay; secondary endpoints included length of ICU stay, duration of mechanical ventilation, duration of tube feeding, cost of hospital stay, and incidence of adverse events.

Eligible subjects were all California infants suspected of having infantile botulism: previously healthy, usually constipated, afebrile unless infection apparent, acute to subacute onset of at least 3 bulbar palsies (ptosis, dilated sluggish pupils, disconjugate gaze, flaccid facial musculature, decreased ability to swallow/drooling, decrease corneal/gag/suck reflexes, loss of head control); generalized weakness to hypotonia, intact to depressed deep tendon reflexes. Electrolytes and CSF are normal. Toxin type (A or B) was determined after enrollment and treatment.

Following completion of the RCT, the sponsor filed IND ---- for open-label treatment of infant botulism; this study, including subjects enrolled in "compassionate use" and emergency IND studies, is referred to as the OLS. The RCT enrolled 129 subjects and the OLS enrolled 293 subjects. Dosing for both RCT and OLS is described below.

Dose

The sponsor justified the dose by reviewing several publications that attempted to measure botulinum toxin LD_{50} titers in sera from infant botulism patients and concluded that low (< 5 LD_{50} / mL) or unmeasurable levels circulated in these patients. The sponsor then reviewed pharmacokinetics data for other similar products and calculated the dose that would be expected to provide sufficient levels to neutralize 7 LD_{50} / mL of botulinum toxins A and B at 120 days (3 months).

Dosing the RCT:

BIG-IV Lot 1: 1 mL/kg i.v. (max rate 1 mL/kg/hr) (50 mg/kg) **Study arm T**
Placebo: Gammagard 1 mL/kg i.v. (max rate 1 mL/kg/hr) (50 mg/kg) **Study arm S**

Results.

Demographics.

For the RCT:

There were 129 subjects enrolled, with 122 subjects subsequently demonstrating C.botulinum toxin A or B strains in the feces.

The BIG-IV group (N = 59) was significantly older than the placebo group (N = 63)

Mean Age at Onset: BIG-IV 131 days Placebo 105 days

Racial distribution was as follows:

	Placebo	**BIG-IV**
White	41	37
Hispanic	14	20
Asian/Pac.Is.	6	7
Afr.-Amer.	1	0
Other	2	1

The lack of African-Americans in the study reflects the distorted distribution of the disease in the population at-large and the low occurrence of infant botulism in the California African-American population during the study time period. In response to a request to address this issue, the sponsor submitted the following graph showing the infant botulism event rate in the California African-American population for a time interval that included the study time period:

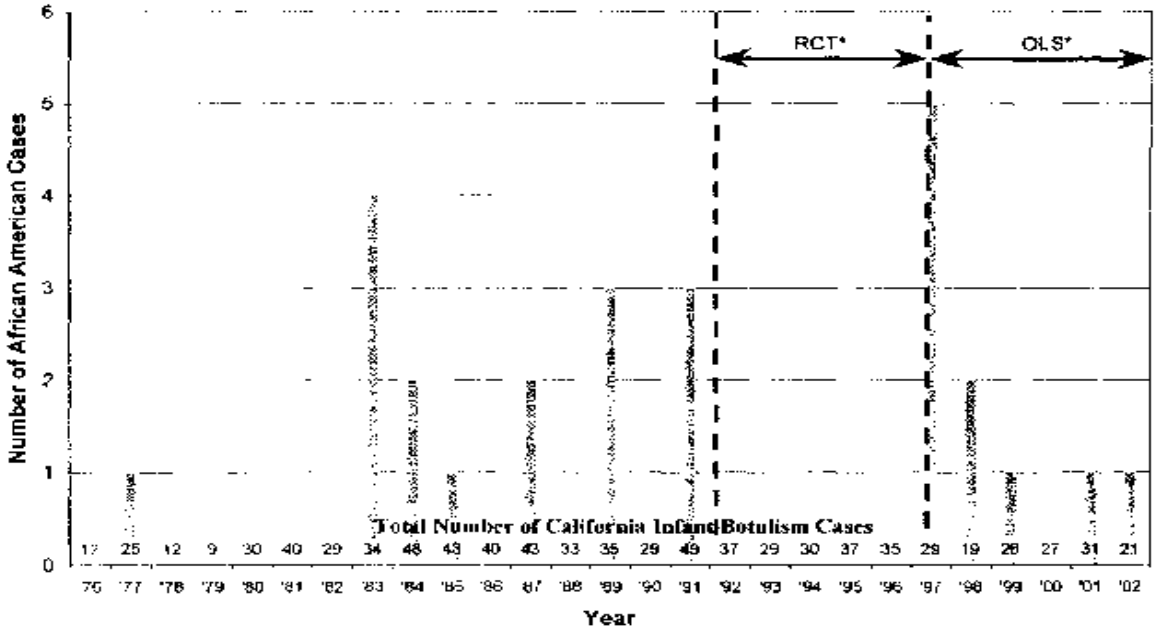


Figure 8.2-1. Incidence of African-American infant botulism cases in California.

It can be seen that the racial distribution in the RCT reflected the disease distribution in the California population.

Gender distribution was as follows:

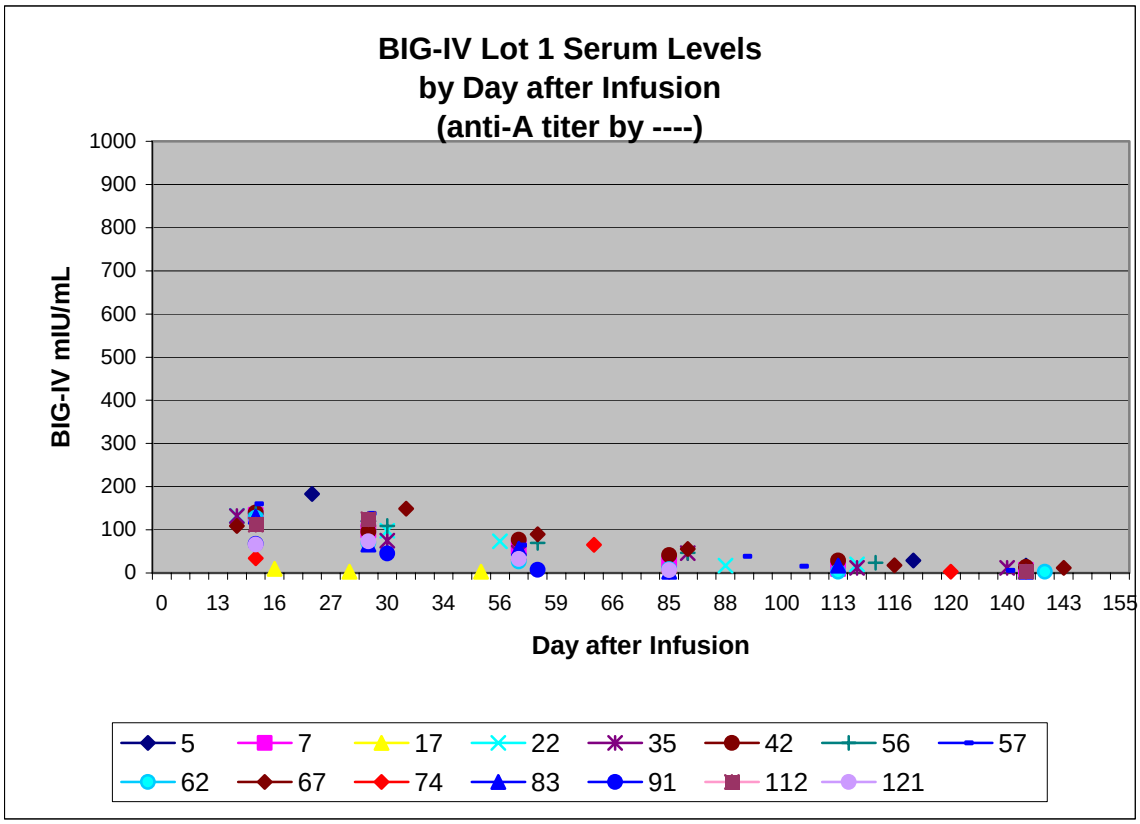
	Placebo	**BIG-IV**
Male	21	31
Female	43	34

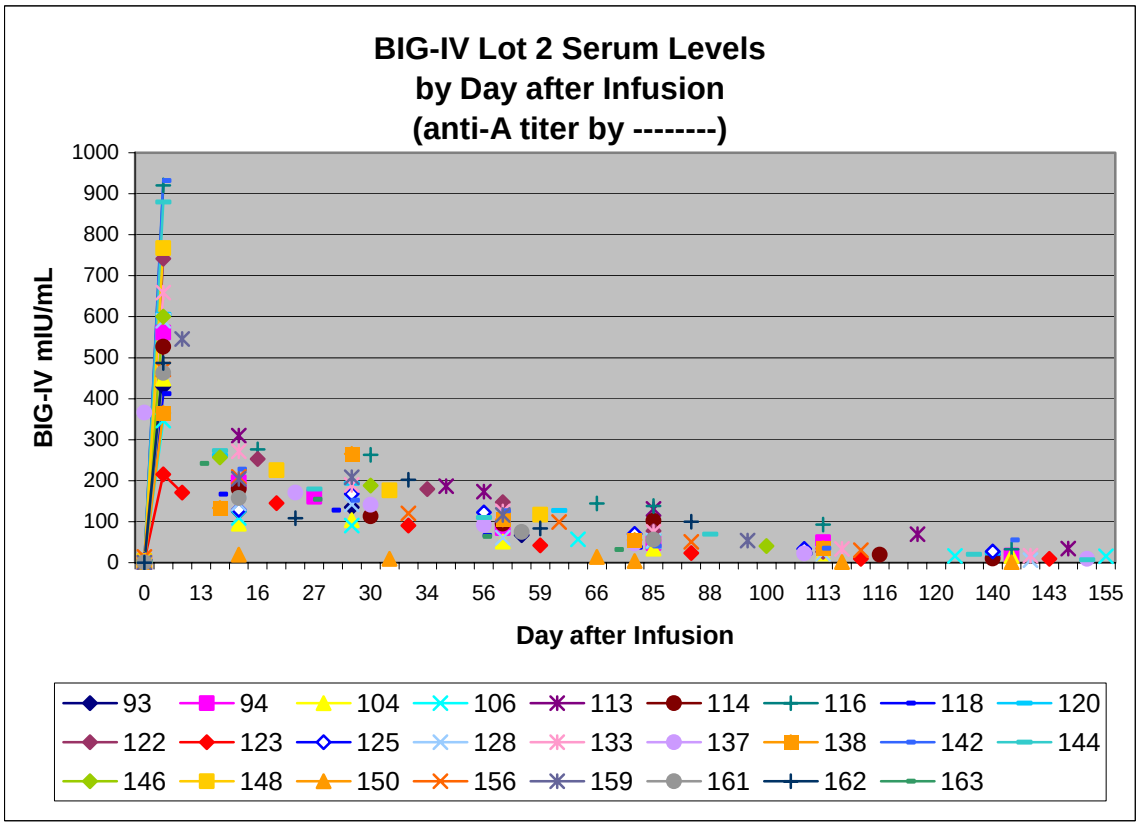
Pharmacokinetics.

The RCT was conducted using only one product lot (Lot 1). Therefore, FDA set a requirement to manufacture a second product lot (Lot 2) prior to licensure, and to demonstrate that Lot 1 and Lot 2 are equivalent. The sponsor elected to do this through a pharmacokinetic comparison of Lot 1 and Lot 2 for circulating anti-A and Anti-B toxin titers in patient sera. This attempt was frustrated by administrative and methodological delays, as well as by incomplete sample collection during the clinical studies. In addition, the submitted pharmacokinetics database is stated to be selected data, in the sense that some time points for some subjects have been censored. In particular, data from samples with titers below the limit-of-detection have not been submitted. As a result, no valid comparison of Lots 1 and 2 for the traditional pharmacokinetic parameters can be performed.

Section 20.3 of the sponsor's December 2001 submission to this BLA of pharmacokinetics information is attached as Appendix 1, below.

The following two charts present data requested in a CR letter, and received in an October 10, 2003, e-mail:


BIG-IV Lot 1 Serum Levels
by Day after Infusion
(anti-A titer by ----)
BIG-IV mIU/mL
1000
900
800
700
600
500
400
300
200
100
0
0 13 16 27 30 34 56 59 66 85 88 100 113 116 120 140 143 155
Day after Infusion
5 7 17 22 35 42 56 57
62 67 74 83 91 112 121


BIG-IV Lot 2 Serum Levels
by Day after Infusion
(anti-A titer by --------)
BIG-IV mIU/mL
1000
900
800
700
600
500
400
300
200
100
0
0 13 16 27 30 34 56 59 66 85 88 100 113 116 120 140 143 155
Day after Infusion
93 94 104 106 113 114 116 118 120
122 123 125 128 133 137 138 142 144
146 148 150 156 159 161 162 163

The sponsor makes the following statements regarding the pharmacokinetics data for Lots 1 and 2:

- As reported in Items 6 and 8.3, Lot 1 patients with less than three measurements from Day 14 through Week 20 assessment were excluded from the PK analysis. Also, Lot 1 patients whose first usable data point was below the detectable limit of the ----- were excluded from the analysis. For an individual patient, all measurements that were either (a) before Day 14, (b) after Week 20, or (c) after two below-the-detectable-limit data points, were not used in the analysis.

- Separate institutions performed the Lot 1 and Lot 2 pharmacokinetic analyses (Lot 1; ----------, Lot 2; --------). ---- assigned a value of 2.8 mIU/mL to samples below the detectable limit of the assay, and -------- assigned a value of 0 mIU/mL to samples below the detectable limit.

- The derivation of Study Day has been made consistent between the Lot 1 and Lot 2 data.

These data are the basis for the following table from the package insert that presents the pharmacokinetics data:

Time	BabyBIG Lot 1 Anti-A Titer (mean ± S.D.)	BabyBIG Lot 2 Anti-A Titer (mean ± S.D.)
	mIU/mL	
Day 1	Not done	537.1 ± 213.4
Week 2	106.7 ± 44.6	192.2 ± 71.2
Week 4	90.0 ± 39.2	155.5 ± 56.7
Week 8	54.9 ± 22.8	96.0 ± 33.2
Week 12	26.0 ± 20.5	61.4 ± 32.3
Week 16	15.6 ± 10.4	33.0 ± 22.3
Week 20	7.6 ± 6.6	19.3 ± 14.1

Efficacy.

The following three charts give the results for total duration of hospitalization (primary endpoint), length of time in the intensive care unit (ICU), and the length of time while intubated:

Average Duration of Hospitalization

		Female Weeks (N)					Male Weeks (N)						
Treatment	**Type of Insurance**	**W**	**H**	**A**	**Other**	**Female Total**	**W**	**H**	**A**	**B**	**Other**	**Male Total**	**Grand Total**
IGIV	Private	6.0 (23)	8.6 (4)	3.1 (2)	2.5 (1)	6.0 (30)	9.1 (10)	3.4 (1)	5.0 (2)		3.2 (1)	7.6 (14)	6.5 (44)
	MediCal	2.2 (6)	3.0 (6)			2.6 (12)	13. (1)	3.1 (3)	6.7 (2)	4.4 (1)		5.8 (7)	3.8 (19)
	None	4.5 (1)				4.5 (1)							4.5 (1)
IGIV Total		5.2 (30)	5.3 (10)	3.1 (2)	2.5 (1)	5.0 (43)	9.5 (11)	3.2 (4)	5.9 (4)	4.4 (1)	3.2 (1)	7.0 (21)	**5.7** (64)
BIG-IV	Private	4.3 (13)	2.4 (3)	2.4 (3)		3.7 (19)	2.1 (15)	1.6 (5)	4.3 (3)		3.4 (1)	2.3 (24)	2.9 (43)
	MediCal	2.2 (3)	2.4 (8)			2.3 (11)		2.5 (3)	1.8 (1)			2.2 (4)	2.3 (15)
	None	1.5 (1)	1.4 (1)			1.5 (2)							1.5 (2)
	CHAMPUS	1.3 (2)				1.3 (2)	1.4 (3)					1.4 (3)	1.4 (5)
BIG-IV Total		3.5 (19)	2.3 (12)	2.4 (3)		3.0 (34)	2.0 (18)	1.8 (8)	3.7 (4)		3.4 (1)	2.2 (31)	**2.6** (65)
Grand Total		4.5 (49)	3.7 (22)	2.7 (5)	2.5 (1)	4.2 (77)	4.8 (29)	2.3 (12)	4.8 (8)	4.4 (1)	3.3 (2)	4.2 (52)	4.2 (129)

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Total Time in ICU

Treatment	Type of Insurance	Female Weeks (N) W	H	A	Other	Female Total	Male Weeks (N) W	H	A	B	Other	Male Total	Grand Total
IGIV	Private	3.8 (23)	3.8 (4)	1.1 (2)	0 (1)	3.5 (30)	8.1 (10)	3.3 (1)	3.6 (2)		0 (1)	6.6 (14)	4.4 (44)
	MediCal	0.7 (6)	0.5 (6)			0.6 (12)	11.7 (1)	1.6 (3)	4.6 (2)	3.0 (1)		4.1 (7)	1.9 (19)
	None	0 (1)				0 (1)							0 (1)
IGIV Total		3.0 (30)	1.8 (10)	1.1 (2)	0 (1)	2.6 (43)	8.5 (11)	2.0 (4)	4.1 (4)	3.0 (1)	0 (1)	5.6 (21)	**3.6** (64)
BIG-IV	Private	2.4 (13)	0.6 (3)	0.7 (3)		1.9 (19)	1.4 (15)	0.8 (5)	2.4 (3)		3.0 (1)	1.5 (24)	1.6 (43)
	MediCal	0.6 (3)	0.8 (8)			0.7 (11)		0.9 (3)	1.6 (1)			1.1 (4)	0.8 (15)
	None	0 (1)	0.6 (1)			0.3 (2)							0.3 (2)
	CHAMPUS	0.8 (2)				0.8 (2)	0.8 (3)					0.8 (3)	0.8 (5)
BIG-IV Total		1.8 (19)	0.7 (12)	0.7 (3)		1.3 (34)	1.3 (18)	0.8 (8)	2.2 (4)		3.0 (1)	1.4 (31)	**1.3** (65)
Grand Total		2.6 (49)	1.3 (22)	0.9 (5)	0 (1)	2.1 (77)	3.9 (29)	1.3 (12)	3.2 (8)	3.0 (1)	1.5 (2)	3.1 (52)	2.5 (129)

Total Time Intubated

Treatment	Type of Insurance	Female Weeks (N) W	H	A	Other	Female Total	Male Weeks (N) W	H	A	B	Other	Male Total	Grand Total
IGIV	Private	2.3 (23)	3.4 (4)	0.6 (2)	0 (1)	2.3 (30)	5.6 (10)	2.3 (1)	3.0 (2)		0 (1)	4.5 (14)	2.9 (44)
	MediCal	0.3 (6)	0.4 (6)			0.3 (12)	10.3 (1)	1.4 (3)	3.1 (2)	2.1 (1)		3.3 (7)	1.4 (19)
	None	0 (1)				0 (1)							0 (1)
IGIV Total		1.8 (30)	1.6 (10)	0.6 (2)	0 (1)	1.7 (43)	6.0 (11)	1.6 (4)	3.1 (4)	2.1 (1)	0 (1)	4.1 (21)	**2.4** (64)
BIG-IV	Private	1.3 (13)	0 (3)	0 (3)		0.9 (19)	0.8 (15)	0.5 (5)	1.9 (3)		2.6 (1)	1.0 (24)	0.9 (43)
	MediCal	0 (3)	0.3 (8)			0.2 (11)		0.4 (3)	1.3 (1)			0.7 (4)	0.3 (15)
	None	0 (1)	0 (1)			0 (2)							0 (2)
	CHAMPUS	0 (2)				0 (2)	0.7 (3)					0.7 (3)	0.4 (5)
BIG-IV Total		0.8 (19)	0.2 (12)	0 (3)		0.6 (34)	0.8 (18)	0.5 (8)	1.7 (4)		2.6 (1)	1.0 (31)	**0.7** (65)
Grand Total		1.5 (49)	0.9 (22)	0.3 (5)	0 (1)	1.2 (77)	2.7 (29)	0.9 (12)	2.4 (8)	2.1 (1)	1.3 (2)	2.2 (52)	1.6 (129)

W = White. A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

H =Hispanic or Latino. A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

A = Asian. A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

B = Black or African American. A person having origins in any of the black racial groups of Africa.

The sponsor submitted the following requested analyses of the primary endpoint outcomes by subject age categories:

Mean Length of Hospital Stay for Infant Botulism Patients in the RCT Treated with Placebo

Age at Onset (Days)	All Patients	Toxin Type A Patients	Toxin Type B Patients
	Mean Length of Hospital Stay in Weeks (n)		
0-60	3.8(10)	29(1)	4.0(9)
61-120	5.6(29)	6.0(21)	4.4(8)
> 120	6.6(24)	7.9(16)	4.0(8)
Total	5.7 (63)	6.7(38)	4.1 (25)
P-value*	0.36	0.55	0.91

RCT = randomized, double-blind, placebo-controlled trial.
*ANOVA of length of hospital stay between each age group.

Mean Length of Hospital Stay for Infant Botulism Patients in the RCT Treated with BIG-IV

Age at Onset (Days)	All Patients	Toxin Type A Patients	Toxin Type B Patients
	Mean Length of Hospital Stay in Weeks (n)		
0-60	2.8(10)	3.4(6)	1.9(4)
61-120	1.9(17)	2.3 (9)	1.4(8)
> 120	3.0(32)	3.0(22)	2.9(10)
Total	2.6(59)	2.9(37)	2.2(22)
P-value*	0.35	0.59	0.59

BIG-IV = Botulism Immune Globulin Intravenous (Human);
RCT = randomized, double-blind, placebo-controlled trial.
*ANOVA of length of hospital stay between each age group.

Mean Length of Hospital Stay for Infant Botulism Patients in the Open-Label Studies

Age at Onset (Days)	All Patients	Toxin Type A Patients	Toxin Type B Patients
	Mean Length of Hospital Stay in Weeks (n)		
0-60	2.0(46)	2.5(14)	1.8(32)
61-120	2.0(68)	2.3 (29)	1.9(39)
> 120	1.8(92)	2.0(47)	1.7(45)
Total	2.0 (206)	2.2(90)	8(116)
P-value*	0.35	0.32	0.53

*ANOVA of length of hospital stay between each age group.

Safety.

Analysis of the adverse events database is complicated by the following factors:

1. Only one product lot (Lot 1) was used for the RCT. The OLS used both Lot 1 and Lot 2. Therefore, adverse event rates are not averages of rates obtained over several product lots, as would be desirable.
2. The adverse event database for the RCT was constructed from data collected on case report forms. The adverse event database for the OLS was largely constructed retrospectively by chart review. Therefore, there may be differences in adverse event rates between the two databases that are due to procedural differences in monitoring.
3. Due to a) infrequent and sporadic subject enrollment, b) the lack of a phase 2 study to establish study procedures, and 3) differences between study arms in hospitalization rates (and hence, observation rates), there is the possibility of some degree of systematic bias in the monitoring of safety outcomes.

The adverse events database in the original submission did not contain a field giving the date of the adverse event. After resubmission of the adverse events database, it could be seen that 27% of the entries occurred prior to infusion of the study agent and should more appropriately be considered baseline medical conditions for listing in a demographics database.

A listing of adverse events recorded on or after the date of study agent infusion is given in Appendix 3.

Adverse events that occurred in more than 5% of subjects are listed below:

	Number of AEs (Number of Subjects with the AE)			
MedDra Preferred Name	**RCT BIG-IV**	**RCT IGIV**	**OLS**	**Grand Total**
Blood pressure increased		1 (1)	1691 (216)	1692 (217)
Dysphagia			1106 (183)	1106 (183)
Irritability			466 (123)	466 (123)
Atelectasis			357 (107)	357 (107)
Rhonchi			662 (104)	662 (104)
Rash erythematous	35 (16)	25 (13)	152 (68)	212 (97)
Pallor			388 (88)	388 (88)
Loose stools			198 (73)	198 (73)
Dermatitis contact			180 (67)	180 (67)
Oxygen saturation decreased			121 (61)	121 (61)
Vomiting NOS			124 (58)	124 (58)
Nasal congestion			164 (56)	164 (56)
Pyrexia			96 (54)	96 (54)
Oedema NOS			201 (53)	201 (53)
Cardiac murmur NOS			122 (49)	122 (49)

Blood pressure decreased		1 (1)	150 (46)	151 (47)
Body temperature decreased			125 (46)	125 (46)
Rales			145 (41)	145 (41)
Dehydration			96 (40)	96 (40)
Intubation NOS			52 (40)	52 (40)
Cough			121 (39)	121 (39)
Abdominal distension			85 (38)	85 (38)
Anaemia NOS	2 (2)	12 (11)	73 (18)	87 (31)
Hyponatraemia	4 (3)	14 (9)	36 (19)	54 (31)
Breath sounds decreased			50 (30)	50 (30)
Haemoglobin decreased			92 (29)	92 (29)
Peripheral coldness			56 (28)	56 (28)
Agitation			116 (27)	116 (27)
Oral candidiasis			73 (25)	73 (25)
Lower respiratory tract infection NOS			49 (24)	49 (24)
Stridor			46 (24)	46 (24)
Tachycardia NOS			68 (22)	68 (22)
Dyspnoea NOS			47 (21)	47 (21)
Metabolic acidosis NOS			31 (21)	31 (21)
Hypokalaemia			23 (20)	23 (20)
Injection site reaction NOS			41 (20)	41 (20)
Otitis media NOS	7 (6)	8 (6)	11 (8)	26 (20)
Pneumonia NOS	8 (7)	11 (10)		19 (17)
Neurogenic bladder			101 (16)	101 (16)
Urinary tract infection NOS		12 (8)	13 (8)	25 (16)
Hypoventilation			23 (15)	23 (15)
Leucocytosis NOS			25 (15)	25 (15)
Feeding disorder NOS			36 (14)	36 (14)
Faecal occult blood positive			22 (13)	22 (13)
Mottled skin			19 (13)	19 (13)
Apnoea			19 (12)	19 (12)
Eye discharge			20 (12)	20 (12)
Injection site erythema			14 (12)	14 (12)

Adverse events that occurred in fewer than 5% of subjects receiving BIG-IV included the following:

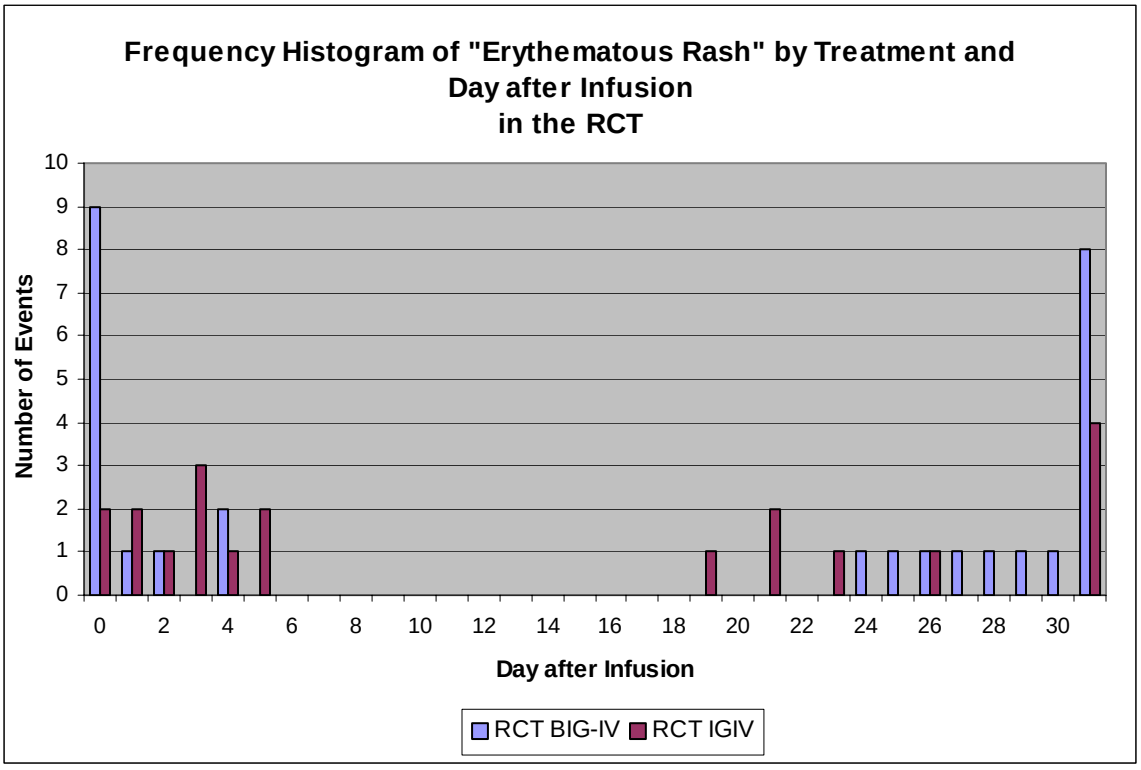
Blood albumin decreased, Bradycardia NOS, Conjunctivitis NEC, Hyperkalaemia, Injection site oedema, Rhinorrhoea, Tachypnoea, Dermatitis allergic, Hypothermia, Respiratory arrest (exc neonatal), Heart rate increased, Hypertension NOS, Mucosal dryness NOS, Oliguria, Aspartate aminotransferase increased, Blood phosphorus increased, Colitis pseudomembranous, Flatulence, Grunting, Protein total decreased, Rash papular, Blood calcium increased, Cyanosis NOS, Lip dry, Viral infection NOS, Alanine aminotransferase increased, Band neutrophil count increased, Convulsions NOS, Blood alkaline phosphatase NOS increased, Blood magnesium decreased, Calcium ionized increased, Faecal abnormality NOS, Frequent bowel movements, Gastro-oesophageal reflux disease, Hoarseness, Lacrimation increased, Metabolic alkalosis, Physical examination NOS abnormal, Pressure sore, Respiratory acidosis, Blood bilirubin increased, Body temperature increased, Hypotension NOS, Jaundice NOS, Blood in stool, Blood lactate dehydrogenase increased, Blood magnesium increased, C-reactive protein increased, Dry skin, Erythema NEC, Fontanelle bulging, Haematuria present, Heart rate decreased, Hiccups, Leukopenia NOS, Respiratory alkalosis, Subglottic stenosis, Sweating increased, Tongue coated,

Upper respiratory tract infection NOS, Urine analysis abnormal NOS, Abdominal pain NOS, Acne infantile, Birth mark NOS, Blood calcium decreased, Blood creatine phosphokinase increased, Blood culture positive, Blood triglycerides increased, Bone mass decreased, Bronchiolitis, Coagulation disorder NOS, Colitis NOS, Ear infection NOS, Electroencephalogram abnormal, Eosinophilia (exc pulmonary), Faeces discoloured, Femur fracture NOS, Haematemesis, Hyperammonaemia, Hyperbilirubinaemia, Injection site bruising, Injection site haemorrhage, Lung infiltration NOS, Nasal passage irritation, Nasogastric tube insertion, Pneumothorax NOS, Prealbumin decreased, Sneezing, Ultrasound kidney abnormal, Accident NOS, Activated partial thromboplastin time prolonged, Acute respiratory distress syndrome, Anuria, Aspiration, Atrial septal defect NOS, Bacteraemia, Bacterial infection NOS, Balanitis NOS, Biliary tract disorder NOS, Blister, Blood alkaline phosphatase NOS decreased, Blood bilirubin decreased, Blood cholinesterase decreased, Blood creatine kinase low, Blood glucose increased, Blood iron decreased, Blood lactic acid decreased, Blood lactic acid increased, Blood phosphate decreased, Blood phosphorus decreased, Blood pyruvic acid decreased, Blood sodium increased, Bradypnoea, Cachexia, Calcium ionized decreased, Carnitine decreased, Carnitine increased, Central line management, Cephalhaematoma, Cerumen impaction, Cholelithiasis, Constipation, CSF glucose decreased, CSF glucose increased, CSF pressure increased, CSF protein increased, Ecchymosis, Echocardiogram abnormal NOS, Eczema NOS, Electrocardiogram abnormal NOS, Enterovirus infection, Extubation, Fluid retention, Fungus urine test positive, Gasping, Gastrostomy, Hepatomegaly, Humerus fracture, Hypervolaemia, Hypogammaglobulinaemia NOS, Hypoglycaemia NOS, Hypoproteinaemia, Intertrigo, Iron binding capacity total decreased, Lymphadenopathy, Mouth haemorrhage, Neutropenia, Neutrophilia, Packed red blood cell transfusion, Parotitis, Periorbital oedema, Petechiae, Pigmentation disorder NOS, Pigmented naevus, Pneumonia aspiration, Posturing, Procedural site reaction, Prothrombin time abnormal NOS, Pulmonary congestion, Pulse pressure decreased, Rash pustular, Rash vesicular, Respiratory distress, Scratch, Seborrhoea, Serology abnormal, Sinusitis NOS, Skin candida NOS, Skin infection NOS, Spinal muscular atrophy, Staphylococcal infection NOS, Subcutaneous emphysema, Teething, Throat irritation, Thrombocythaemia, Thrombocytopenia, Transfusion reaction, Tricuspid valve incompetence, Tympanic membrane disorder NOS, Upper respiratory tract infection viral NOS, Urine delta aminolevulinate increased, Urine osmolarity decreased, Vaginal discharge, White blood cell count abnormal NOS, X-ray NOS chest abnormal, and X-ray NOS gastrointestinal tract abnormal,

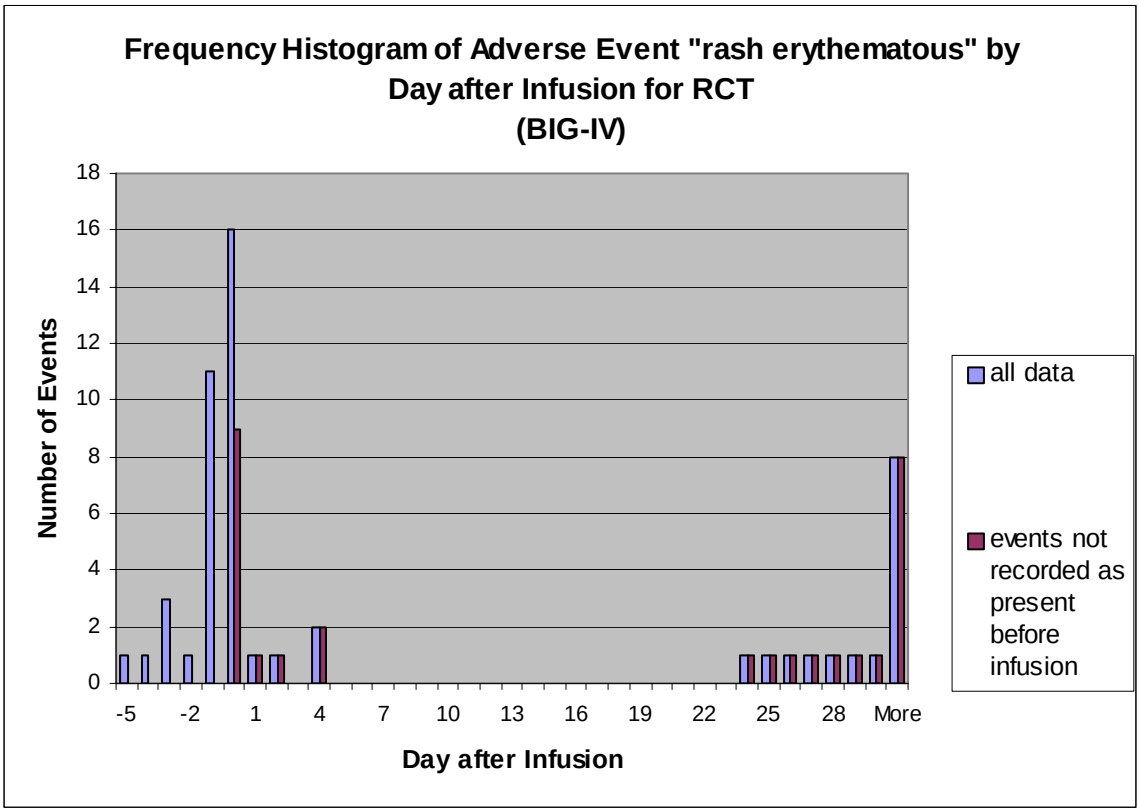
"Rash." There appears to be a higher incidence of "rash" (listed as Rash erythematous, Rash papular, Rash pustular, or Rash vesicular in the database) in the BIG-IV treated subjects [(14 botulism + 4 non-botulism)/(59 botulism +6 non-botulism) RCT subjects and (69 botulism +3 non-botulism)/(293 botulism +8 non-botulism) OLS subjects, or **25%**] than in the IGIV treated subjects [12 botulism/(63 botulism +1 non-botulism) RCT subjects, or **19%**]. The preceding calculation includes the 15 non-botulism subjects according to treatment. The following table contains the data for the "rash" adverse event category:

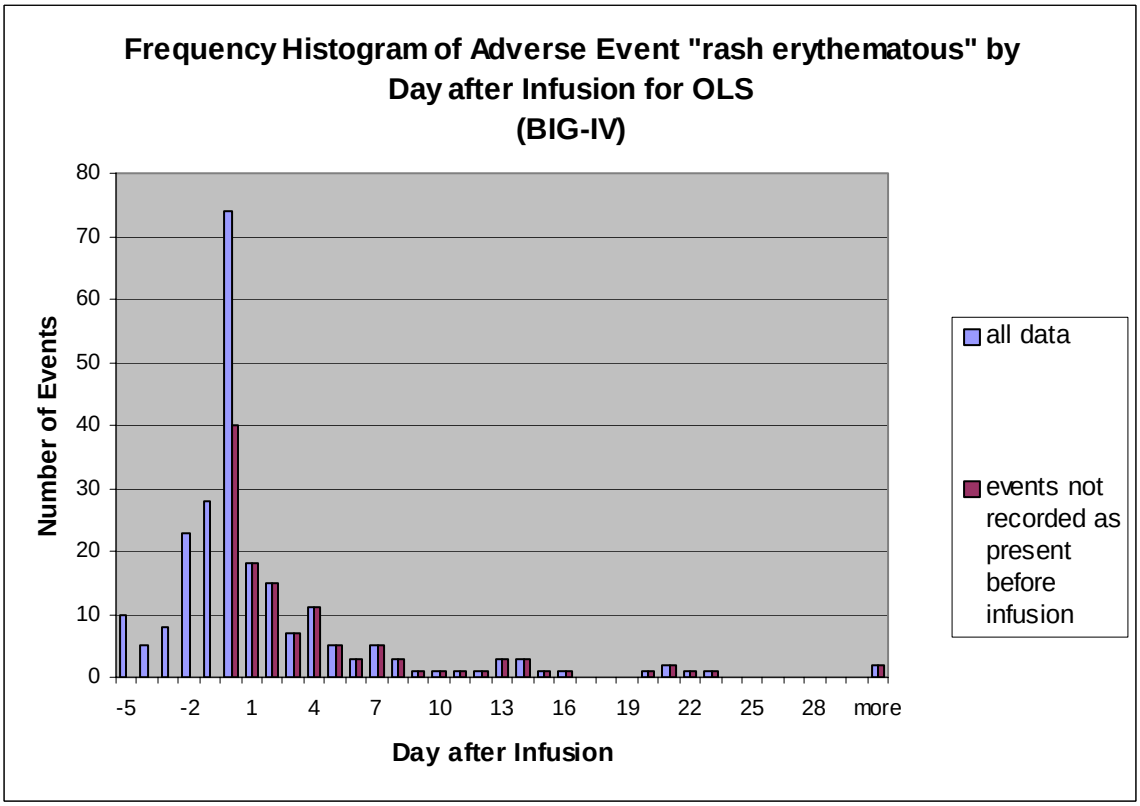
	Non-Botulism				Botulism			Grand Total All Studies
					OLS	RCT		
	RCT BIG-IV	RCT IGIV	OLS	Total	BIG-IV	BIG-IV	IGIV	
Rash erythematous	4	0	3	7	61	14	12	92
Rash papular					6			6
Rash pustular					1			1
Rash vesicular					1			1
Grand Total	4/6	0/1	3/8	7/15	69/293	14/59	12/63	100

However, the above analysis may not be appropriate for detecting product-related events because the "rash" adverse event database includes events occurring long after product infusion. The following frequency histogram of the number of "rash" adverse events by the day after infusion may provide a better comparison of the test agent and placebo for evaluating product tolerability:



The following two frequency histograms for the adverse event "rash erythematous" in the BIG-IV treated groups present a) all events irrespective of time of event, and b) events not recorded as being present at the time of infusion:


Frequency Histogram of Adverse Event "rash erythematous" by Day after Infusion for RCT (BIG-IV)
Number of Events
0
2
4
6
8
10
12
14
16
18
-5
-2
1
4
7
10
13
16
19
22
25
28
More
Day after Infusion
all data
events not recorded as present before infusion

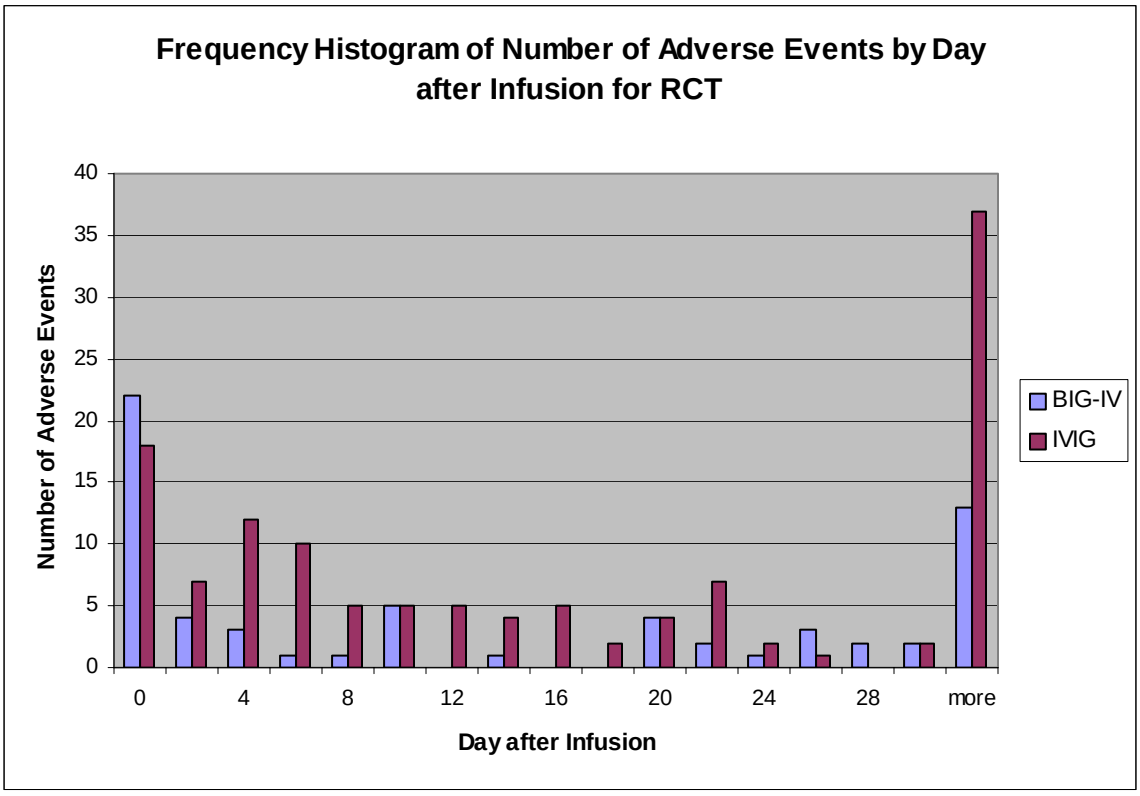

Frequency Histogram of Adverse Event "rash erythematous" by Day after Infusion for OLS (BIG-IV)
Number of Events
0
10
20
30
40
50
60
70
80
-5
-2
1
4
7
10
13
16
19
22
25
28
more
Day after Infusion
all data
events not recorded as present before infusion

From the above two histograms, it can be seen that even if "rash erythematous" adverse events existing prior to infusion are removed from the database there is still an elevated event rate at day 0 that may be attributable to the BIG-IV product.

Blood Pressure. Increased blood pressure (listed as "blood pressure increased" or as "hypertension NOS") occurred in 222 of 293 OLS subjects (76%); however in the RCT, this event is recorded for only 1 of 63 IGIV subjects (6%), and for none of the RCT BIG-IV subjects. The entry "hypertension NOS" is recorded for only 6 OLS subjects, and 3 RCT IGIV subjects.

Decreased blood pressure (listed as "blood pressure decreased" or as "hypotension NOS") occurred in 50 of 293 OLS subjects (17%); however in the RCT, this event is recorded for only 4 of 63 IGIV subjects (6.3%), and for none of the RCT BIG-IV subjects. The entry "hypotension NOS" is recorded for only 4 OLS subjects, and for none of the RCT subjects.

Timing of Adverse Events. The following chart shows the time sequence of all adverse events for the RCT:



The adverse events in the RCT for the period day 2 through day 6 are given in the following table:

MedDra Preferred Term	BIG-IV	IGIV	Grand Total
Rash erythematous	35	25	60
Hyponatraemia	4	14	18
Pneumonia NOS	8	10	18
Otitis media NOS	7	8	15
Anaemia NOS	2	11	13
Convulsions NOS		12	12
Urinary tract infection NOS		12	12
Respiratory arrest (exc neonatal)	2	7	9
Hypertension NOS		4	4
Gastro-oesophageal reflux disease	1	2	3
Acute respiratory distress syndrome		2	2
Colitis pseudomembranous	1	1	2
Constipation		2	2
Femur fracture NOS		2	2
Subglottic stenosis	2		2
Blood culture positive		1	1
Blood pressure decreased		1	1
Blood pressure increased		1	1
Bronchiolitis		1	1
Fungus urine test positive		1	1
Humerus fracture		1	1
Pneumonia aspiration		1	1
Pneumothorax NOS		1	1
Toxic dilatation of colon	1		1
Transfusion reaction		1	1
Grand Total	63	121	184

Deaths.

In the RCT, there was 1 death of a non-botulism subject, occurring 5 months after dosing and not attributed to the product.

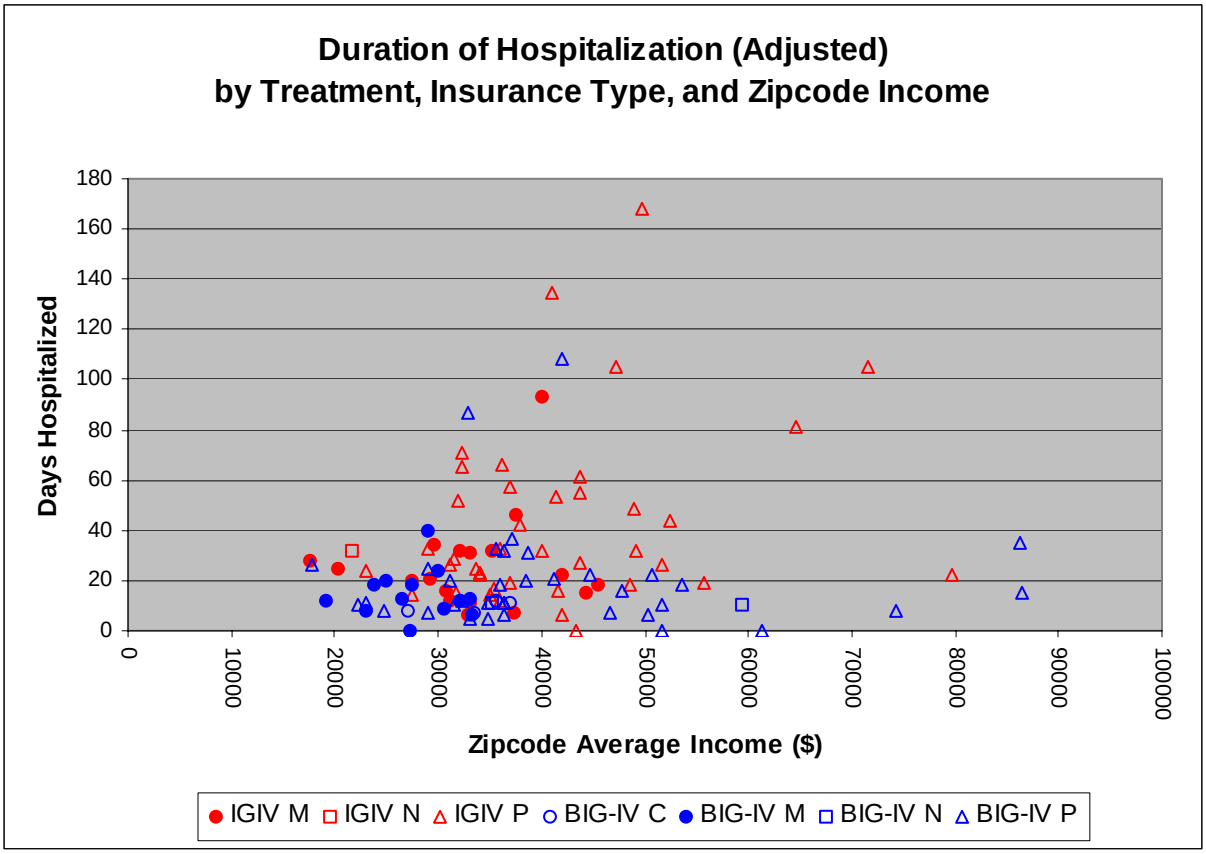
From the summary basis of approval: "Seven deaths occurred in the OLS: 5 of the 7 patients who died were later found not to be infant botulism patients. Two infant botulism patients who received BabyBIG® died. The first received BabyBIG® only after irreversible brain damage had occurred from a prior cardiopulmonary arrest. The second received BabyBIG® and recovered from infant botulism, but died subsequently from underlying neuroblastoma. None of the deaths was considered related to BabyBIG® administration.

STN125034
California Department of Health Services
Botulism Immune Globulin (Human)(Intravenous)
Comment on the Use of Length of Hospitalization as the Primary Endpoint.

The event "hospitalization" can be a useful endpoint for clinical studies of prophylactic treatments, which are conducted in previously healthy subjects. However, the use of the endpoint "length of hospitalization" for subjects who are invariably hospitalized can be biased by factors that do not relate to product efficacy. One such factor may be the ability of the subject to pay for extended hospitalization.

In the RCT, there were many demographic attributes collected, including "type of insurance" (see above in the efficacy section) and also the subject's zipcode. Average income by zipcode is publicly available from the website of the Internal Revenue Service. Although assigning subject attributes, such as income, by zipcode may be drastically incorrect in individual cases, this procedure may enable a useful exploratory analysis that may be statistically valid for large cohorts.

The following chart shows outcomes (length of hospitalization) by treatment, type of insurance, and zipcode average income:



From the above chart it appears that there is a trend for longer periods of hospitalization for subjects who have private insurance and who reside in more affluent zipcodes. The disease infant botulism is known to have a highly skewed epidemiologic distribution that

could account for this apparent trend [e.g., there are studies claiming mothers of infant botulism patients have a higher percentage of college graduates than random population samples (*Am. J. Public Health* **73**(12):1385-1388(1983))]; however, it may also be true that affluence may directly affect the endpoint "length of hospitalization".

The above criticism of the choice of the primary endpoint was discussed with the sponsor in regard to another issue. The following is the position submitted by the sponsor on the use of "length of hospitalization as the primary endpoint:

"CDHS has reanalyzed the length of stay data from the controlled clinical trial by type of insurance. Patients in the controlled clinical trial were classified as having 1 of 3 insurance types: private, MediCal, and CHAMPUS. Because CHAMPUS is the military equivalent of private insurance (*i.e.*, the military pays the full costs of private hospitalization), the analyses were conducted by grouping private insurance and CHAMPUS patients together. The length of hospital stay data for patients with private insurance and CHAMPUS were then compared to length of stay data for patients with MediCal. These analyses also considered the toxin type of illness (Type A or Type B) because toxin type of illness is an important predictor of length of hospital stay. Tables 1 and 2 summarize the results of these analyses.

Table 1. Length of Hospital Stay for Type A Patients by Type of Disease and Insurance Type

Treatment Group	Private or CHAMPUS		MediCal		p-value*
	n	LOS (weeks)	n	LOS (weeks)	
BIG-IV	30	2.9	7	2.9	$p = 1.0$
Placebo	27	7.8	11	4.0	$p < 0.03$

* t-test comparing the LOS between insurance groups
LOS= length of hospital stay

Table 2. Length of Hospital Stay for Type B Patients by Type of Disease and Insurance Type

Treatment Group	Private or CHAMPUS		MediCal		p-value*
	n	LOS (weeks)	n	LOS (weeks)	
BIG-IV	14	2.6	8	1.6	$p = 0.34$
Placebo	16	4.4	9	3.7	$p > 0.17$

* t-test comparing the LOS between insurance groups
LOS= length of hospital stay

There was a significant difference in mean length of hospital stay when placebo-treated Type A Private and CHAMPUS insured patients were compared with MediCal insured patients ($p < 0.03$) (Table 1). The reason for this difference is unknown. Analysis by type of insurance did not indicate significant differences in length of hospital stay for Type B placebo-treated patients or for Type A or Type B BIG-IV-treated patients (Tables 1 and 2).

Hospital discharge criteria for infant botulism patients are relatively uniform, which is consistent with the premise behind its choice as the primary endpoint of the controlled trial. In planning the controlled trial, CDHS recognized that various physician and institutional factors might extend the stay of an infant who would otherwise have been ready for discharge.

Thus, as part of the controlled study design, the CDHS established *a priori* standardized discharge criteria to be applied before the study was unblinded in order to minimize the institutional variability in discharging study patients. These standardized criteria were applied to the controlled study data *before* the code was broken and the data were analyzed. Adjustment of data to the standardized criteria resulted in 18 fewer days of hospital stay (out of 3603 total days; 0.5%) cumulatively for the 122 efficacy-evaluable patients (12 days placebo, 6 days BIG-IV). The fact that application of the standard discharge criteria resulted in such a small magnitude of adjustment indicates that discharge of infant botulism patients was quite uniform across all 41 hospitals that enrolled patients in the controlled trial.
The finding that discharge criteria were applied uniformly was consistent with the premises that led to the choice of length of hospital stay as an endpoint: (1) unlike some adult patients who are awaiting nursing home care or other post-discharge arrangements, patients with infant botulism have parents or guardians who wish for discharge to occur as soon as possible, (2) because of their fragile physiological state, infant botulism patients are not discharged prematurely to make room for other patients, (3) infant botulism patients are otherwise healthy children who have just the one disease (unlike many adult patients with several illnesses in several organ systems, only one of which is under study), (4) the disease is caused by just one molecule that affects just one anatomic site, the neuromuscular junction, (5) stopping the toxemia by administering antitoxin stops the disease process and enables regeneration of the injured nerve endings to begin immediately.

In addition, an Advisory Panel convened by CDHS to help design the controlled trial unanimously considered the length of hospital stay to be the best choice for the primary outcome variable because it embodied the "real world" circumstances under which physicians would use the product and assess its utility in positively impacting the course of the illness. The Advisory Panel included representatives of the ----------, hospitals, infectious disease specialists, the Maternal and Child Health Branch of CDHS, the Children's Medical Services Branch of CDHS and distinguished individuals such as ----------

Recommendation.

Based on the results of the RCT, and the supporting clinical data acquired in the OLS, this reviewer concludes that Botulism Immune Globulin (Human) (Intravenous) (BabyBIG®) is safe and effective for the treatment of patients below one year of age with infant botulism caused by toxin type A or B.

20.3 ----- VALIDATION AND PHARMACOKINETICS OF BIG-IV LOT 2

20.3.1 BACKGROUND

During the RCT, PK data were analyzed for 41 patients with laboratory confirmed infant botulism (Item 6 and Section 8.3 of the 29 June 2001 BLA Submission). Twenty-six of these patients had illness caused by type A toxin, and 15 patients had illness caused by type B toxin. Serum samples were collected for up to 28 weeks after treatment with BIG-IV Lot 1. The sera were used to determine the absence of anti-type A and anti-type B antibodies in pretreatment serum, to verify presence of the antibodies in post-treatment serum of BIG-IV treated patients, and to determine the half-life of anti-type A and anti-type B antibodies in infants treated with BIG-IV. The BIG-IV Lot 1 serum specimens were analyzed in the ---- botulism laboratory by means of separate ------ that used highly purified botulinum toxins type A or type B as the ----------. Analyses showed that the half-life of BIG-IV Lot 1 was approximately 2i.7 (±9.3) days (disregarding the toxin type of illness). The average half-life (t,,) of the BIG-IV antibodies against toxin type A was determined to be 27.3 (f8.3) days, and the average t.,, of the BIG-IV antibodies against type B toxin was determined to be 27.9 (t 9.9) days.

The anti-botulinum toxin ----- was originally developed at the --- for the purpose of measuring BIG-IV levels in serum samples from patients treated in the RCT. In response to an FDA request at the 13 September 2000 pre-BLA meeting, validation of the ----- was carried out at -------- using the reagents and methods originally developed by ---. The anti-type A ----- was validated from January through September 2001; data from the validation studies are presented in Section 20.3.2, and the validation report is provided in Appendix B. The anti-type B ----- could not be validated because the --- was unable to supply -------- with the necessary anti-type B ---------- antibody as a result of preparation for bioterrorism threat, supply depletion, and other commitments.

The validated assay was used to analyze serum samples from 26 patients treated with BIG-IV Lot 2. These serum samples were collected before

treatment with BIG-IV and for up to 20 weeks after treatment. The results of these analyses are discussed in Section 20.3.3 of this submission.

20.3.2 VALIDATION OF ANTI-TYPE A ------

The results of the validation demonstrate the performance of the anti-type A ----- and define the conditions of ----- use for analysis of BIG-IV Lot 1 and BIG-IV Lot 2 in patient sera. The results of the validation also demonstrate the limitations of the -----. Notably, the ----- estimated less anti-type A BIG-IV Lot 2 than was predicted based on the BIG-IV Lot I standard curve. It would therefore be difficult to determine an absolute concentration of anti-type A BIG-IV present in a BIG-IV Lot 2 sample with the -----. In addition, there was significant variability from dilution set to dilution set making it difficult to compare samples that are prepared independently of each other.

However, the analysis of each dilution series indicated that BIG-IV Lot 2 concentration was estimated at the same efficiency, regardless of its dilution, within each set. This indicates dilutional linearity of the BIG-IV Lot 2 samples, which is important in establishing relationships between serial samples. A series of samples prepared for one patient at the same time should be comparable to each other, and therefore cal be used to determine half-lives of BIG-IV Lot 2.

Because not all BIG-IV Lot 2 serum samples can be prepared and analyzed at the same time, relationships between sets of samples cannot be determined. For this reason, ---------- and ---------- cannot be accurately determined. Therefore, only the elimination rates of BIG-IV Lot 1 and BIG-IV Lot 2 are presented.

20.3.3.1 Pharmacokinetic Population

Serum samples from 26 patients with infant botulism caused by type B toxin were analyzed using the anti-type A -----. Estimates of anti-type A half-life were made only in type B patients because the concentration of antibody specific to

the toxin type causing disease in a patient may be influenced by the circulating toxin (mainly through endogenous antibody production[2]).

Demographic data for the 26 type B patients are shown in Table 20.3-1.

Table 20.3-1. Demographic Data for BIG-IV Lot 2 Pharmacokinetic Population

Demographic Data		All Patients (Type B) N=26
Mean (range) age at infusion (days)		115.0 (19-275)
Mean weight kg		6.28
Gender	Male (%)	15 (57)
	Female (%)	11 (42)
Race	White (%)	21 (80)
	African-American (%)	2(7)
	Hispanic (%)	1 (3)
	Asian/Pacific Islander (%)	2(7)
	Other (%)	0

20.3.3.2 Pharmacokinetic Results

The BIG-IV Lot 1 mean half-life data presented in Item 6 and Section 8.3 of the BLA were calculated by using a weighting function. In this report, half-life data are presented using the weighting function as well as in terms of harmonic means. Appendix C contains the BIG-IV Lot 1 and Lot 2 serum concentration data, and identifies the data points used in the half-life calculations for BIG-IV Lot 1 and BIG-IV Lot 2. Table 20.3-2 summarizes the half-life data for BIG-IV Lot 1 and Lot 2.

Table 20.3-2. Summary of BIG-IV Lot 1 and BIG-IV Lot 2 Half-Life Data

Method of Calculation	Half-Life of BIG-IV Lot 1 (days)	Half-Life of BIG-IV Lot 2 (days)
Weighted Mean	27.3	30.9
Harmonic Mean	24.7	31.0

Note: All values are for the anti-A component of BIG-IV only.
The harmonic mean of the half-life of the anti-type A component of BIG-IV Lot I was determined to be 24.7 days. The harmonic mean of the half-life of the antitype A component of BIG-IV Lot 2 was determined to be 31.0 days. The weighted mean of the anti-A component of BIG-IV Lot 1 was 27.3 days, and the weighted mean of the anti-type A component of BIG-IV Lot 2 was 30.9 days (Table 20.3-2).

No statistically significant difference existed in the elimination rate constants of the two BIG-IV lots (p=0.0685), although the BIG-IV Lot I elimination rate constant was slightly higher (0.028± 0.011 per day) than the BIG-IV Lot 2 elimination rate constant (0.022 t 0.008 per day). The approximate 90% confidence interval of the ratio of the mean of BIG-IV Lot 2 to Lot 1 is (0.613, 0.979), suggesting that the rate constants for BIG-IV Lot 2 are less than would be desired to conclude that the elimination rates are equivalent.

Comparable exposures based upon ---- and ---- could not be made due to incomplete data sets for individual patients that received either Lot 1 or Lot 2, and because of the variability from dilution set to dilution set observed in the ---------- validation.
A comparison of the elimination rate is appropriate given the pathophysiology of infant botulism and the mechanism of action of BIG-IV. The therapeutic task in treating infant botulism is to neutralize all circulating botulinum toxin and any additional toxin that may be absorbed from the intestine during the course of the illness. It is clinically appropriate and useful that BIG-IV is calibrated in toxin-

neutralizing units by means of the ----- bioassay. As long as the serum BIG-IV concentration exceeds 1 to 2 ----- LD50s of toxin while intestinal toxin remains present in the patient, the infant is protected. Knowing the elimination rate of BIG-IV enables the achievement of this therapeutic goal. Applying the elimination rate that was determined for either BIG-IV Lot 1 or BIG-IV Lot 2, it can be demonstrated that BIG-IV provides protection to the patient for more than 6 months. Length-of-hospital-stay data (Tables 20.1-3 and 20.1-4) indicate that months of protection is more than sufficient.

20.4 CONCLUSIONS

The comparability of BIG-IV Lot 1 and BIG-IV Lot 2 has been examined by comparing the efficacy and safety results of open-label studies similar in all design aspects except for the use of either BIG-IV Lot 1 or BIG-IV Lot 2. Where relevant, these results have also been compared to the results of the RCT. In addition, the elimination rates of the two lots of BIG-IV have been compared. The data from the safety, efficacy, and pharmacokinetic comparisons demonstrate that BIG-IV Lot I and BIG-IV Lot 2 are comparable.

The efficacy results (length of hospital stay) for the 96 infant botulism patients treated with BIG-IV Lot 2 (2.4 weeks) were consistent with the efficacy results obtained in OLS conducted with BIG-IV Lot 1 (2.3 weeks) and in the RCT (2 6 weeks) (Tables 20.1-3 and 20.1-4). These data indicate that administration of BIG-IV Lot 2 results in a reduction in length of hospital stay equivalent to the reduction observed when patients were treated with BIG-IV Lot 1.

The safety data summarized for 79 patients treated with BIG-IV Lot 2 indicate that BIG-IV Lot 2 is safe and well tolerated. Similar to the AE profile of BIG-IV Lot I-treated patients, many of the AEs experienced by the BIG-IV Lot 2-treated patients were part of the known pathophysiology of infant botulism. The only AE that was considered possibly related to BIG-IV administration was erythematous rash. Erythematous rash or flushing has also been observed historically in patients with untreated infant botulism, and its prevalence and possible physiological basis are discussed more fully in Section 8.8.8.5.1 of the 29 June 2001 BLA submission. No anaphylactic events (bronchospasm, hypotension, or respiratory arrest) in any patient occurred within 24 hours of receiving BIG-IV.

There was not a statistically significant difference in the elimination rates of the two BIG-IV lots, although the BIG-IV Lot 1 elimination rate was slightly higher than the BIG-IV Lot 2 elimination rate. Similar to BIG-IV Lot 1, the half-life and

elimination rate of BIG-IV Lot 2 indicate that Lot 2 can provide patients protection from botulinum toxin for at least 6 months.

In summary, the efficacy, safety, and PK data indicate that BIG-IV Lot 2 is comparable to BIG-IV Lot 1, indicating that the safety and efficacy conclusions

20.5 REFERENCES

1. Long SS, Gajewski JL, Brown LW, Gilligan PH. Clinical, laboratory, and environmental features of infant botulism in southeastern Pennsylvania. Pediatrics 1985; 75:935-941.

2. Arnon SS, Maslanka SE, Schechter R, Hatheway CL. Development of serum antibodies to botulism neurotoxins in patients with infant botulism, International Conference on Basic and Therapeutic Aspects of Botulism and Tetanus Toxins, Orlando, Florida, November 1999.

Appendix 2. Submitted Antitoxin Levels for Botulinum Toxin Type A for Selected Subjects from the RCT and OLC

(TIND = treatment IND, EIN = emergency IND, CU = compassionate use, RCT = randomized controlled trial)

PATID	CONC (mIU/mL)	INFDATE	SAMPDATE	DAYS	SAMPLE	LOT
RCT-005	182.9	4/16/1992	5/5/1992	20		1
RCT-005	120.2	4/16/1992	5/14/1992	29		1
RCT-005	44.4	4/16/1992	6/11/1992	57		1
RCT-005	28.7	4/16/1992	8/11/1992	118		1
RCT-005	17.2	4/16/1992	9/3/1992	141		1
RCT-007	134.6	6/8/1992	6/22/1992	15		1
RCT-007	98.1	6/8/1992	7/6/1992	29		1
RCT-007	60.2	6/8/1992	8/3/1992	57		1
RCT-007	25.2	6/8/1992	8/31/1992	85		1
RCT-007	9.2	6/8/1992	9/28/1992	113		1
RCT-007	7.3	6/8/1992	10/26/1992	141		1
RCT-017	10	10/1/1992	10/16/1992	16		1
RCT-017	2.8	10/1/1992	10/28/1992	28		1
RCT-017	2.8	10/1/1992	11/23/1992	54		1
RCT-022	132.9	1/5/1993	1/18/1993	14		1
RCT-022	97.5	1/5/1993	2/3/1993	30		1
RCT-022	73.4	1/5/1993	3/1/1993	56		1
RCT-022	17.4	1/5/1993	4/2/1993	88		1
RCT-022	19.9	1/5/1993	4/28/1993	114		1
RCT-035	131.6	7/20/1993	8/2/1993	14		1
RCT-035	74.6	7/20/1993	8/18/1993	30		1
RCT-035	46.8	7/20/1993	9/14/1993	57		1
RCT-035	45.6	7/20/1993	10/13/1993	86		1
RCT-035	11.7	7/20/1993	11/10/1993	114		1
RCT-035	12.2	7/20/1993	12/6/1993	140		1
RCT-042	140.2	10/29/1993	11/12/1993	15		1
RCT-042	95.6	10/29/1993	11/26/1993	29		1
RCT-042	77.1	10/29/1993	12/24/1993	57		1
RCT-042	41.2	10/29/1993	1/21/1994	85		1
RCT-042	28.6	10/29/1993	2/18/1994	113		1
RCT-042	14	10/29/1993	3/18/1994	141		1
RCT-056	136.8	8/1/1994	8/15/1994	15		1
RCT-056	108.6	8/1/1994	8/30/1994	30		1
RCT-056	69.8	8/1/1994	9/27/1994	58		1
RCT-056	46.9	8/1/1994	10/25/1994	86		1
RCT-056	23.4	8/1/1994	11/23/1994	115		1
RCT-057	159.9	8/4/1994	8/18/1994	15		1
RCT-057	138.1	8/4/1994	9/1/1994	29		1
RCT-057	64.5	8/4/1994	9/29/1994	57		1
RCT-057	38.3	8/4/1994	10/31/1994	89		1
RCT-057	15.7	8/4/1994	11/22/1994	111		1
RCT-057	6.1	8/4/1994	12/21/1994	140		1
RCT-062	128.6	10/3/1994	10/17/1994	15		1

RCT-062	69.4	10/3/1994	10/31/1994	29		1
RCT-062	26.4	10/3/1994	11/28/1994	57		1
RCT-062	8.9	10/3/1994	12/26/1994	85		1
RCT-062	2.8	10/3/1994	1/23/1995	113		1
RCT-062	2.8	10/3/1994	2/21/1995	142		1
RCT-067	108.9	12/7/1994	12/20/1994	14		1
RCT-067	148.8	12/7/1994	1/6/1995	31		1
RCT-067	89.6	12/7/1994	2/2/1995	58		1
RCT-067	55.9	12/7/1994	3/2/1995	86		1
RCT-067	17.5	12/7/1994	4/1/1995	116		1
RCT-067	11.9	12/7/1994	4/28/1995	143		1
RCT-074	34.1	3/30/1995	4/13/1995	15		1
RCT-074	65.3	3/30/1995	5/30/1995	62		1
RCT-074	2.8	3/30/1995	6/22/1995	85		1
RCT-074	2.8	3/30/1995	7/27/1995	120		1
RCT-083	130.8	6/23/1995	7/7/1995	15		1
RCT-083	66.2	6/23/1995	7/21/1995	29		1
RCT-083	56.4	6/23/1995	8/18/1995	57		1
RCT-083	2.8	6/23/1995	9/15/1995	85		1
RCT-083	16.9	6/23/1995	10/13/1995	113		1
RCT-083	2.8	6/23/1995	11/10/1995	141		1
RCT-091	67.8	8/20/1995	9/3/1995	15		1
RCT-091	45.2	8/20/1995	9/18/1995	30		1
RCT-091	7.3	8/20/1995	10/16/1995	58		1
RCT-112	111.8	7/30/1996	8/13/1996	15		1
RCT-112	124.3	7/30/1996	8/27/1996	29		1
RCT-112	2.8	7/30/1996	12/17/1996	141		1
RCT-121	65.8	10/23/1996	11/6/1996	15		1
RCT-121	73.2	10/23/1996	11/20/1996	29		1
RCT-121	32.3	10/23/1996	12/18/1996	57		1
RCT-121	6.8	10/23/1996	1/15/1997	85		1
TIND-093	3.005	8/23/2000	8/22/2000	0	93-082200	2
TIND-093	429.019	8/23/2000	8/23/2000	1	93-082300	2
TIND-093	124.748	8/23/2000	9/6/2000	15	93-090600	2
TIND-093	134.727	8/23/2000	9/20/2000	29	93-092000	2
TIND-093	67.394	8/23/2000	10/19/2000	58	93-101900	2
TIND-094	0	8/24/2000	8/24/2000	0	94-082400a	2
TIND-094	560.912	8/24/2000	8/24/2000	1	94-082400b	2
TIND-094	195.997	8/24/2000	9/7/2000	15	94-090700	2
TIND-094	160.708	8/24/2000	9/19/2000	27	94-091900	2
TIND-094	84.494	8/24/2000	10/19/2000	57	94-101900	2
TIND-094	47.508	8/24/2000	11/16/2000	85	94-111600	2
TIND-094	50.229	8/24/2000	12/14/2000	113	94-121400	2
TIND-094	16.956	8/24/2000	1/11/2001	141	94-011101	2
TIND-104	7.741	9/26/2000	9/26/2000	0	104-092600a	2
TIND-104	448.649	9/26/2000	9/26/2000	1	104-092600b	2
TIND-104	95.237	9/26/2000	10/10/2000	15	104-101000	2
TIND-104	104.208	9/26/2000	10/24/2000	29	104-102400	2
TIND-104	51.59	9/26/2000	11/21/2000	57	104-112100	2
TIND-104	34.175	9/26/2000	12/19/2000	85	104-121900	2

TIND-104	22.795	9/26/2000	1/16/2001	113	104-011601	2
TIND-104	16.299	9/26/2000	2/13/2001	141	104-021301	2
TIND-106	4.156	9/28/2000	9/28/2000	0	106-092800a	2
TIND-106	346.61	9/28/2000	9/28/2000	1	106-092800b	2
TIND-106	109.209	9/28/2000	10/12/2000	15	106-101200	2
TIND-106	90.891	9/28/2000	10/26/2000	29	106-102600	2
TIND-106	56.677	9/28/2000	11/28/2000	62	106-112800	2
TIND-106	51.918	9/28/2000	12/21/2000	85	106-122100	2
TIND-106	16.543	9/28/2000	1/26/2001	121	106-012601	2
TIND-106	15.863	9/28/2000	3/1/2001	155	106-030101	2
TIND-113	309.784	10/26/2000	11/9/2000	15	113-110900	2
TIND-113	186.937	10/26/2000	12/4/2000	40	113-120400	2
TIND-113	173.043	10/26/2000	12/20/2000	56	113-122000	2
TIND-113	131.1	10/26/2000	1/18/2001	85	113-011801	2
TIND-113	69.571	10/26/2000	2/21/2001	119	113-022101	2
TIND-113	34.528	10/26/2000	3/20/2001	146	113-032001	2
TIND-114	0	10/27/2000	10/27/2000	0	114-102700a	2
TIND-114	526.848	10/27/2000	10/27/2000	1	114-102700b	2
TIND-114	179.864	10/27/2000	11/10/2000	15	114-111000	2
TIND-114	113.232	10/27/2000	11/25/2000	30	114-112500	2
TIND-114	95.437	10/27/2000	12/22/2000	57	114-122200	2
TIND-114	102.28	10/27/2000	1/19/2001	85	114-011901	2
TIND-114	19.46	10/27/2000	2/19/2001	116	114-021901	2
TIND-114	9.902	10/27/2000	3/15/2001	140	114-031501	2
TIND-116	0	10/31/2000	10/31/2000	0	116-103100a	2
TIND-116	920.089	10/31/2000	10/31/2000	1	116-103100b	2
TIND-116	276.386	10/31/2000	11/15/2000	16	116-111500	2
TIND-116	263.076	10/31/2000	11/29/2000	30	116-112900	2
TIND-116	144.495	10/31/2000	1/4/2001	66	116-010401	2
TIND-116	138.291	10/31/2000	1/23/2001	85	116-012301	2
TIND-116	93.197	10/31/2000	2/20/2001	113	116-022001	2
TIND-116	32.662	10/31/2000	3/20/2001	141	116-032001	2
TIND-118	3.768	11/4/2000	11/4/2000	0	118-110400a	2
TIND-118	412.345	11/4/2000	11/4/2000	1	118-110400b	2
TIND-118	167.278	11/4/2000	11/17/2000	14	118-111700	2
TIND-118	127.762	11/4/2000	12/1/2000	28	118-120100	2
TIND-118	66.217	11/4/2000	12/29/2000	56	118-122900	2
TIND-118	37.459	11/4/2000	1/26/2001	84	118-012601	2
TIND-118	22.632	11/4/2000	2/23/2001	112	118-022301	2
TIND-118	22.005	11/4/2000	3/23/2001	140	118-032301	2
TIND-120	0	11/17/2000	11/16/2000	0	120-111600	2
TIND-120	605.419	11/17/2000	11/17/2000	1	120-111700	2
TIND-120	261.834	11/17/2000	11/30/2000	14	120-113000	2
TIND-120	193.753	11/17/2000	12/15/2000	29	120-121500	2
TIND-120	127.098	11/17/2000	1/16/2001	61	120-011601	2
TIND-120	23.331	11/17/2000	4/5/2001	140	120-040501	2
TIND-122	0	11/30/2000	11/30/2000	0	122-113000a	2
TIND-122	741.291	11/30/2000	11/30/2000	1	122-113000b	2
TIND-122	252.568	11/30/2000	12/15/2000	16	122-121500	2
TIND-122	179.755	11/30/2000	1/2/2001	34	122-010201	2

TIND-122	147.301	11/30/2000	1/25/2001	57	122-012501	2
TIND-122	77.005	11/30/2000	2/22/2001	85	122-022201	2
TIND-122	26.473	11/30/2000	3/22/2001	113	122-032201	2
TIND-123	5.854	12/2/2000	12/1/2000	0	123-120100	2
TIND-123	162.916	12/2/2000	12/2/2000	1	123-120200a	2
TIND-123	267.294	12/2/2000	12/2/2000	1	123-120200b	2
TIND-123	170.689	12/2/2000	12/3/2000	2	123-120300	2
TIND-123	145.331	12/2/2000	12/18/2000	17	123-121800	2
TIND-123	90.36	12/2/2000	1/2/2001	32	123-010201	2
TIND-123	42.172	12/2/2000	1/29/2001	59	123-012901	2
TIND-123	23.224	12/2/2000	2/26/2001	87	123-022601	2
TIND-123	9.103	12/2/2000	3/26/2001	115	123-032601	2
TIND-123	9.673	12/2/2000	4/23/2001	143	123-042301	2
TIND-125	7.151	12/16/2000	12/16/2000	0	125-121600	2
TIND-125	128.672	12/16/2000	12/30/2000	15	125-123000	2
TIND-125	167.958	12/16/2000	1/13/2001	29	125-011301	2
TIND-125	122.39	12/16/2000	2/9/2001	56	125-020901	2
TIND-125	70.093	12/16/2000	3/9/2001	84	125-030901	2
TIND-125	33.914	12/16/2000	4/6/2001	112	125-040601	2
TIND-125	27.384	12/16/2000	5/4/2001	140	125-050401	2
TIND-128	4.333	1/8/2001	1/8/2001	0	128-010801a	2
TIND-128	590.461	1/8/2001	1/8/2001	1	128-010801b	2
TIND-128	144.773	1/8/2001	1/22/2001	15	128-012201	2
TIND-128	142.202	1/8/2001	2/5/2001	29	128-020501	2
TIND-128	61.102	1/8/2001	3/5/2001	57	128-030501	2
TIND-128	53.723	1/8/2001	4/2/2001	85	128-040201	2
TIND-128	22.174	1/8/2001	4/30/2001	113	128-043001	2
TIND-128	6.596	1/8/2001	5/29/2001	142	128-052901	2
TIND-133	2.84	2/5/2001	2/5/2001	0	133-020501a	2
TIND-133	658.471	2/5/2001	2/5/2001	1	133-020501b	2
TIND-133	271.948	2/5/2001	2/19/2001	15	133-021901	2
TIND-133	189.903	2/5/2001	3/5/2001	29	133-030501	2
TIND-133	125.028	2/5/2001	4/2/2001	57	133-040201	2
TIND-133	74.938	2/5/2001	4/30/2001	85	133-043001	2
TIND-133	33.546	2/5/2001	5/29/2001	114	133-052901	2
TIND-133	16.869	2/5/2001	6/26/2001	142	133-062601	2
TIND-137	366.107	3/2/2001	3/2/2001	0	137-030201	2
TIND-137	170.656	3/2/2001	3/21/2001	20	137-032101	2
TIND-137	141.137	3/2/2001	3/31/2001	30	137-033101	2
TIND-137	91.823	3/2/2001	4/26/2001	56	137-042601	2
TIND-137	46.767	3/2/2001	5/24/2001	84	137-052401	2
TIND-137	22.618	3/2/2001	6/21/2001	112	137-062101	2
TIND-137	9.668	3/2/2001	7/26/2001	147	137-072601	2
TIND-138	0.522	3/2/2001	3/2/2001	0	138-030201a	2
TIND-138	365.608	3/2/2001	3/2/2001	1	138-030201b	2
TIND-138	133.589	3/2/2001	3/15/2001	14	138-031501	2
TIND-138	265.726	3/2/2001	3/30/2001	29	138-033001	2
TIND-138	105.421	3/2/2001	4/27/2001	57	138-042701	2
TIND-138	55.534	3/2/2001	5/24/2001	84	138-052401	2
TIND-138	35.402	3/2/2001	6/22/2001	113	138-062201	2

TIND-142	3.386	3/15/2001	3/14/2001	0	142-031401	2
TIND-142	931.712	3/15/2001	3/15/2001	1	142-031501	2
TIND-142	227.59	3/15/2001	3/29/2001	15	142-032901	2
TIND-142	152.333	3/15/2001	4/12/2001	29	142-041201	2
TIND-142	126.674	3/15/2001	5/10/2001	57	142-051001	2
TIND-142	40.355	3/15/2001	6/7/2001	85	142-060701	2
TIND-142	34.767	3/15/2001	7/5/2001	113	142-070501	2
TIND-142	55.656	3/15/2001	8/2/2001	141	142-080201	2
TIND-144	2.952	3/17/2001	3/17/2001	0	144-031701a	2
TIND-144	879.854	3/17/2001	3/17/2001	1	144-031701b	2
TIND-144	273.044	3/17/2001	3/30/2001	14	144-033001	2
TIND-144	179.392	3/17/2001	4/12/2001	27	144-041201	2
TIND-144	110.32	3/17/2001	5/11/2001	56	144-051101	2
TIND-144	69.515	3/17/2001	6/12/2001	88	144-061201	2
TIND-144	19.968	3/17/2001	7/20/2001	126	144-072001	2
TIND-144	7.231	3/17/2001	8/10/2001	147	144-081001	2
TIND-146	1.358	4/5/2001	4/5/2001	0	146-040501a	2
TIND-146	600.052	4/5/2001	4/5/2001	1	146-040501b	2
TIND-146	257.218	4/5/2001	4/18/2001	14	146-041801	2
TIND-146	188.513	4/5/2001	5/4/2001	30	146-050401	2
TIND-146	40.287	4/5/2001	7/13/2001	100	146-071301	2
TIND-148	4.866	4/14/2001	4/14/2001	0	148-041401a	2
TIND-148	767.3	4/14/2001	4/14/2001	1	148-041401b	2
TIND-148	225.795	4/14/2001	4/30/2001	17	148-043001	2
TIND-148	176.809	4/14/2001	5/14/2001	31	148-051401	2
TIND-148	116.789	4/14/2001	6/11/2001	59	148-061101	2
TIND-150	2.161	4/24/2001	4/24/2001	0	150-042401	2
TIND-150	19.366	4/24/2001	5/8/2001	15	150-050801	2
TIND-150	9.124	4/24/2001	5/24/2001	31	150-052401	2
TIND-150	13.926	4/24/2001	6/28/2001	66	150-062801	2
TIND-150	3.76	4/24/2001	7/16/2001	84	150-071601	2
TIND-150	1.623	4/24/2001	8/15/2001	114	150-081501	2
TIND-150	0.522	4/24/2001	9/11/2001	141	150-091101	2
TIND-156	13.971	5/7/2001	5/7/2001	0	156-050701a	2
TIND-156	471.203	5/7/2001	5/7/2001	1	156-050701b	2
TIND-156	209.027	5/7/2001	5/21/2001	15	156-052101	2
TIND-156	119.919	5/7/2001	6/7/2001	32	156-060701	2
TIND-156	99.513	5/7/2001	7/6/2001	61	156-070601	2
TIND-156	50.864	5/7/2001	8/1/2001	87	156-080101	2
TIND-156	30.415	5/7/2001	8/29/2001	115	156-082901	2
TIND-159	0.335	5/24/2001	5/24/2001	0	159-052401	2
TIND-159	545.575	5/24/2001	5/25/2001	2	159-052501	2
TIND-159	204.645	5/24/2001	6/7/2001	15	159-060701	2
TIND-159	208.601	5/24/2001	6/21/2001	29	159-062101	2
TIND-159	116.297	5/24/2001	7/19/2001	57	159-071901	2
TIND-159	53.557	5/24/2001	8/21/2001	90	159-082101	2
TIND-161	0.522	5/28/2001	5/27/2001	0	161-052701	2
TIND-161	462.829	5/28/2001	5/28/2001	1	161-052801	2
TIND-161	157.706	5/28/2001	6/11/2001	15	161-061101	2
TIND-161	74.613	5/28/2001	7/24/2001	58	161-072401	2

TIND-161	56.141	5/28/2001	8/20/2001	85	161-082001	2
TIND-162	0.335	6/2/2001	6/2/2001	0	162-060201a	2
TIND-162	487.105	6/2/2001	6/2/2001	1	162-060201b	2
TIND-162	108.177	6/2/2001	6/21/2001	20	162-062101	2
TIND-162	202.398	6/2/2001	7/3/2001	32	162-070301	2
TIND-162	83.76	6/2/2001	7/30/2001	59	162-073001	2
TIND-162	100.023	6/2/2001	8/27/2001	87	162-082701	2
TIND-163	242.365	6/9/2001	6/21/2001	13	163-062101	2
TIND-163	154.75	6/9/2001	7/5/2001	27	163-070501	2
TIND-163	63.829	6/9/2001	8/3/2001	56	163-080301	2
TIND-163	31.752	6/9/2001	8/30/2001	83	163-083001	2

Appendix 3. Listing of Submitted Adverse Events by Study and Treatment

	Number of AEs (Number of Subjects with the AE)			
MedDra Preferred Name	RCT BIG-IV	RCT IGIV	OLS	Grand Total
Abdominal distension			85 (38)	85 (38)
Abdominal pain NOS			10 (2)	10 (2)
Accident NOS			1 (1)	1 (1)
Acne infantile			3 (2)	3 (2)
Activated partial thromboplastin time prolonged			1 (1)	1 (1)
Acute respiratory distress syndrome		2 (1)		2 (1)
Agitation			116 (27)	116 (27)
Alanine aminotransferase increased			8 (6)	8 (6)
Anaemia NOS	2 (2)	12 (11)	73 (18)	87 (31)
Anuria			1 (1)	1 (1)
Apnoea			19 (12)	19 (12)
Aspartate aminotransferase increased			10 (8)	10 (8)
Aspiration			1 (1)	1 (1)
Atelectasis			357 (107)	357 (107)
Atrial septal defect NOS			1 (1)	1 (1)
Bacteraemia			1 (1)	1 (1)
Bacterial infection NOS			3 (1)	3 (1)
Balanitis NOS			8 (1)	8 (1)
Band neutrophil count increased			10 (6)	10 (6)
Biliary tract disorder NOS			1 (1)	1 (1)
Birth mark NOS			3 (2)	3 (2)
Blister			1 (1)	1 (1)
Blood albumin decreased			21 (11)	21 (11)
Blood alkaline phosphatase NOS decreased			1 (1)	1 (1)
Blood alkaline phosphatase NOS increased			9 (5)	9 (5)
Blood bilirubin decreased			1 (1)	1 (1)
Blood bilirubin increased			6 (4)	6 (4)
Blood calcium decreased			2 (2)	2 (2)
Blood calcium increased			12 (7)	12 (7)
Blood cholinesterase decreased			1 (1)	1 (1)
Blood creatine kinase low			1 (1)	1 (1)
Blood creatine phosphokinase increased			8 (2)	8 (2)
Blood culture positive		1 (1)	1 (1)	2 (2)
Blood glucose increased			1 (1)	1 (1)
Blood in stool			4 (3)	4 (3)
Blood iron decreased			1 (1)	1 (1)
Blood lactate dehydrogenase increased			3 (3)	3 (3)
Blood lactic acid decreased			1 (1)	1 (1)
Blood lactic acid increased			1 (1)	1 (1)
Blood magnesium decreased			5 (5)	5 (5)
Blood magnesium increased			4 (3)	4 (3)
Blood phosphate decreased			1 (1)	1 (1)
Blood phosphorus decreased			2 (1)	2 (1)
Blood phosphorus increased			13 (8)	13 (8)

Blood pressure decreased		1 (1)	150 (46)	151 (47)
Blood pressure increased		1 (1)	1691 (216)	1692 (217)
Blood pyruvic acid decreased			1 (1)	1 (1)
Blood sodium increased			1 (1)	1 (1)
Blood triglycerides increased			2 (2)	2 (2)
Body temperature decreased			125 (46)	125 (46)
Body temperature increased			13 (4)	13 (4)
Bone mass decreased			2 (2)	2 (2)
Bradycardia NOS			24 (11)	24 (11)
Bradypnoea			1 (1)	1 (1)
Breath sounds decreased			50 (30)	50 (30)
Bronchiolitis		1 (1)	4 (1)	5 (2)
Cachexia			1 (1)	1 (1)
Calcium ionized decreased			1 (1)	1 (1)
Calcium ionized increased			14 (5)	14 (5)
Cardiac murmur NOS			122 (49)	122 (49)
Carnitine decreased			1 (1)	1 (1)
Carnitine increased			1 (1)	1 (1)
Central line management			1 (1)	1 (1)
Cephalhaematoma			6 (1)	6 (1)
Cerumen impaction			2 (1)	2 (1)
Cholelithiasis			1 (1)	1 (1)
Coagulation disorder NOS			4 (2)	4 (2)
Colitis NOS			9 (2)	9 (2)
Colitis pseudomembranous	1 (1)	1 (1)	9 (6)	11 (8)
Conjunctivitis NEC			34 (11)	34 (11)
Constipation		2 (1)		2 (1)
Convulsions NOS		12 (3)	5 (3)	17 (6)
Cough			121 (39)	121 (39)
C-reactive protein increased			3 (3)	3 (3)
CSF glucose decreased			1 (1)	1 (1)
CSF glucose increased			1 (1)	1 (1)
CSF pressure increased			2 (1)	2 (1)
CSF protein increased			1 (1)	1 (1)
Cyanosis NOS			13 (7)	13 (7)
Dehydration			96 (40)	96 (40)
Dermatitis allergic			53 (10)	53 (10)
Dermatitis contact			180 (67)	180 (67)
Dry skin			10 (3)	10 (3)
Dysphagia			1106 (183)	1106 (183)
Dyspnoea NOS			47 (21)	47 (21)
Ear infection NOS			2 (2)	2 (2)
Ecchymosis			4 (1)	4 (1)
Echocardiogram abnormal NOS			3 (1)	3 (1)
Eczema NOS			4 (1)	4 (1)
Electrocardiogram abnormal NOS			1 (1)	1 (1)
Electroencephalogram abnormal			5 (2)	5 (2)
Enterovirus infection			1 (1)	1 (1)
Eosinophilia (exc pulmonary)			2 (2)	2 (2)
Erythema NEC			3 (3)	3 (3)

Extubation			1 (1)	1 (1)
Eye discharge			20 (12)	20 (12)
Faecal abnormality NOS			10 (5)	10 (5)
Faecal occult blood positive			22 (13)	22 (13)
Faeces discoloured			2 (2)	2 (2)
Feeding disorder NOS			36 (14)	36 (14)
Femur fracture NOS		2 (2)		2 (2)
Flatulence			13 (8)	13 (8)
Fluid retention			2 (1)	2 (1)
Fontanelle bulging			5 (3)	5 (3)
Frequent bowel movements			11 (5)	11 (5)
Fungus urine test positive		1 (1)		1 (1)
Gasping			1 (1)	1 (1)
Gastro-oesophageal reflux disease	2 (2)	2 (2)	1 (1)	5 (5)
Gastrostomy			1 (1)	1 (1)
Grunting			12 (8)	12 (8)
Haematemesis			3 (2)	3 (2)
Haematuria present			3 (3)	3 (3)
Haemoglobin decreased			92 (29)	92 (29)
Heart rate decreased			4 (3)	4 (3)
Heart rate increased			26 (9)	26 (9)
Hepatomegaly			1 (1)	1 (1)
Hiccups			4 (3)	4 (3)
Hoarseness			5 (5)	5 (5)
Humerus fracture		1 (1)		1 (1)
Hyperammonaemia			2 (2)	2 (2)
Hyperbilirubinaemia			3 (2)	3 (2)
Hyperkalaemia			16 (11)	16 (11)
Hypertension NOS		4 (3)	23 (6)	27 (9)
Hypervolaemia			1 (1)	1 (1)
Hypogammaglobulinaemia NOS			1 (1)	1 (1)
Hypoglycaemia NOS			1 (1)	1 (1)
Hypokalaemia			23 (20)	23 (20)
Hyponatraemia	4 (3)	14 (9)	36 (19)	54 (31)
Hypoproteinaemia			6 (1)	6 (1)
Hypotension NOS			9 (4)	9 (4)
Hypothermia			27 (10)	27 (10)
Hypoventilation			23 (15)	23 (15)
Injection site bruising			2 (2)	2 (2)
Injection site erythema			14 (12)	14 (12)
Injection site haemorrhage			3 (2)	3 (2)
Injection site oedema			12 (11)	12 (11)
Injection site reaction NOS			41 (20)	41 (20)
Intertrigo			1 (1)	1 (1)
Intubation NOS			52 (40)	52 (40)
Iron binding capacity total decreased			1 (1)	1 (1)
Irritability			466 (123)	466 (123)
Jaundice NOS			7 (4)	7 (4)
Lacrimation increased			7 (5)	7 (5)
Leucocytosis NOS			25 (15)	25 (15)

Leukopenia NOS			8 (3)	8 (3)
Lip dry			10 (7)	10 (7)
Loose stools			198 (73)	198 (73)
Lower respiratory tract infection NOS			49 (24)	49 (24)
Lung infiltration NOS			6 (2)	6 (2)
Lymphadenopathy			1 (1)	1 (1)
Metabolic acidosis NOS			31 (21)	31 (21)
Metabolic alkalosis			14 (5)	14 (5)
Mottled skin			19 (13)	19 (13)
Mouth haemorrhage			1 (1)	1 (1)
Mucosal dryness NOS			15 (9)	15 (9)
Nasal congestion			164 (56)	164 (56)
Nasal passage irritation			3 (2)	3 (2)
Nasogastric tube insertion			2 (2)	2 (2)
Neurogenic bladder			101 (16)	101 (16)
Neutropenia			1 (1)	1 (1)
Neutrophilia			1 (1)	1 (1)
Oedema NOS			201 (53)	201 (53)
Oliguria			13 (9)	13 (9)
Oral candidiasis			73 (25)	73 (25)
Otitis media NOS	7 (6)	8 (6)	11 (8)	26 (20)
Oxygen saturation decreased			121 (61)	121 (61)
Packed red blood cell transfusion			1 (1)	1 (1)
Pallor			388 (88)	388 (88)
Parotitis			1 (1)	1 (1)
Periorbital oedema			2 (1)	2 (1)
Peripheral coldness			56 (28)	56 (28)
Petechiae			1 (1)	1 (1)
Physical examination NOS abnormal			9 (5)	9 (5)
Pigmentation disorder NOS			6 (1)	6 (1)
Pigmented naevus			4 (1)	4 (1)
Pneumonia aspiration		1 (1)		1 (1)
Pneumonia NOS	8 (7)	11 (10)		19 (17)
Pneumothorax NOS		2 (2)		2 (2)
Posturing			7 (1)	7 (1)
Prealbumin decreased			2 (2)	2 (2)
Pressure sore			9 (5)	9 (5)
Procedural site reaction			1 (1)	1 (1)
Protein total decreased			18 (8)	18 (8)
Prothrombin time abnormal NOS			1 (1)	1 (1)
Pulmonary congestion			1 (1)	1 (1)
Pulse pressure decreased			5 (1)	5 (1)
Pyrexia			96 (54)	96 (54)
Rales			145 (41)	145 (41)
Rash erythematous	35 (16)	25 (13)	152 (68)	212 (97)
Rash papular			15 (8)	15 (8)
Rash pustular			3 (1)	3 (1)
Rash vesicular			4 (1)	4 (1)
Respiratory acidosis			7 (5)	7 (5)
Respiratory alkalosis			22 (3)	22 (3)

Respiratory arrest (exc neonatal)	2 (2)	7 (7)	1 (1)	10 (10)
Respiratory distress			4 (1)	4 (1)
Rhinorrhoea			15 (11)	15 (11)
Rhonchi			662 (104)	662 (104)
Scratch			2 (1)	2 (1)
Seborrhoea			1 (1)	1 (1)
Serology abnormal			1 (1)	1 (1)
Sinusitis NOS			1 (1)	1 (1)
Skin candida NOS			7 (1)	7 (1)
Skin infection NOS			6 (1)	6 (1)
Sneezing			2 (2)	2 (2)
Spinal muscular atrophy			1 (1)	1 (1)
Staphylococcal infection NOS			1 (1)	1 (1)
Stridor			46 (24)	46 (24)
Subcutaneous emphysema		1 (1)		1 (1)
Subglottic stenosis	2 (2)	1 (1)		3 (3)
Sweating increased			4 (3)	4 (3)
Tachycardia NOS			68 (22)	68 (22)
Tachypnoea			11 (11)	11 (11)
Teething			1 (1)	1 (1)
Throat irritation			2 (1)	2 (1)
Thrombocythaemia			12 (1)	12 (1)
Thrombocytopenia			2 (1)	2 (1)
Tongue coated			3 (3)	3 (3)
Toxic dilatation of colon	1 (1)			1 (1)
Transfusion reaction		1 (1)		1 (1)
Tricuspid valve incompetence			1 (1)	1 (1)
Tympanic membrane disorder NOS			3 (1)	3 (1)
Ultrasound kidney abnormal			2 (2)	2 (2)
Upper respiratory tract infection NOS			5 (3)	5 (3)
Upper respiratory tract infection viral NOS			1 (1)	1 (1)
Urinary tract infection NOS		12 (8)	13 (8)	25 (16)
Urine analysis abnormal NOS			7 (3)	7 (3)
Urine delta aminolevulinate increased			1 (1)	1 (1)
Urine osmolarity decreased			1 (1)	1 (1)
Vaginal discharge			1 (1)	1 (1)
Viral infection NOS			7 (7)	7 (7)
Vomiting NOS			124 (58)	124 (58)
White blood cell count abnormal NOS			1 (1)	1 (1)
X-ray NOS chest abnormal			2 (1)	2 (1)
X-ray NOS gastrointestinal tract abnormal			1 (1)	1 (1)
Grand Total	64 (42)	126 (89)	8845 (2604)	9035 (2735)