

NEUROSIS	1 (<1)	0 (0)	1 (<1)
STRESS REACTION	1 (<1)	0 (0)	1 (<1)
THINKING ABNORMAL	2 (<1)	0 (0)	2 (<1)
CONCENTRATION IMPAIRED	1 (<1)	0 (0)	1 (<1)
HYSTERIA	1 (<1)	0 (0)	1 (<1)
SUICIDE ATTEMPT	2 (<1)	0 (0)	2 (<1)
PSYCHOSIS	1 (<1)	0 (0)	1 (<1)
RED BLOOD CELL DISORDERS	1 (<1)	0 (0)	1 (<1)
SPLEEN DISORDER	1 (<1)	0 (0)	1 (<1)
RESISTANCE MECHANISM DISORDERS	9 (<1)	1 (<1)	10 (<1)
UPPER RESP TRACT INFECTION	1 (<1)	0 (0)	1 (<1)
URINARY TRACT INFECTION	2 (<1)	0 (0)	2 (<1)
INFECTION	1 (<1)	0 (0)	1 (<1)
PNEUMONIA	1 (<1)	0 (0)	1 (<1)
HERPES ZOSTER	2 (<1)	1 (<1)	3 (<1)
SEPSIS	1 (<1)	0 (0)	1 (<1)
PYELONEPHRITIS	1 (<1)	0 (0)	1 (<1)
RESPIRATORY SYSTEM DISORDERS	15 (<1)	2 (<1)	17 (<1)
COUGHING	1 (<1)	0 (0)	1 (<1)
PHARYNGITIS	2 (<1)	0 (0)	2 (<1)
DYSPTNOEA	6 (<1)	2 (<1)	8 (<1)
BRONCHOSPASM	1 (<1)	0 (0)	1 (<1)
PNEUMONIA	2 (<1)	0 (0)	2 (<1)
PNEUMOTHORAX	2 (<1)	0 (0)	2 (<1)
ATELECTASIS	1 (<1)	0 (0)	1 (<1)
RESPIRATORY INSUFFICIENCY	1 (<1)	0 (0)	1 (<1)
SKIN AND APPENDAGES DISORDERS	7 (<1)	1 (<1)	8 (<1)
RASH	3 (<1)	0 (0)	3 (<1)
PRURITUS	3 (<1)	0 (0)	3 (<1)
RASH ERYTHEMATOUS	0 (0)	1 (<1)	1 (<1)
SKIN ULCERATION	1 (<1)	0 (0)	1 (<1)
PHOTOSENSITIVITY REACTION	1 (<1)	0 (0)	1 (<1)
SPECIAL SENSES OTHER, DISORDERS	2 (<1)	1 (<1)	3 (<1)
TASTE PERVERSION	1 (<1)	0 (0)	1 (<1)
TASTE LOSS	1 (<1)	0 (0)	1 (<1)
PAROSMIA	0 (0)	1 (<1)	1 (<1)
URINARY SYSTEM DISORDERS	7 (<1)	1 (<1)	8 (<1)
URINARY INCONTINENCE	3 (<1)	0 (0)	3 (<1)
MICTURITION FREQUENCY	1 (<1)	0 (0)	1 (<1)
RENAL CALCULUS	0 (0)	1 (<1)	1 (<1)
URINARY RETENTION	1 (<1)	0 (0)	1 (<1)
RENAL FAILURE ACUTE	1 (<1)	0 (0)	1 (<1)
PROCEDURE NOS	1 (<1)	0 (0)	1 (<1)
VASCULAR (EXTRACARDIAC) DISORDERS	13 (<1)	5 (1)	18 (<1)
CEREBROVASCULAR DISORDER	5 (<1)	4 (<1)	9 (<1)
PERIPHERAL ISCHAEMIA	2 (<1)	0 (0)	2 (<1)
EMBOLISM PULMONARY	2 (<1)	0 (0)	2 (<1)

VASCULAR DISORDER	1 (<1)	0 (0)	1 (<1)
HAEMORRHAGE INTRACRANIAL	1 (<1)	0 (0)	1 (<1)
HAEMATOMA	1 (<1)	0 (0)	1 (<1)
ARTERITIS	0 (0)	1 (<1)	1 (<1)
PURPURA	1 (<1)	0 (0)	1 (<1)
VISION DISORDERS	2 (<1)	0 (0)	2 (<1)
VISION ABNORMAL	1 (<1)	0 (0)	1 (<1)
DIPLOPIA	1 (<1)	0 (0)	1 (<1)

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Appendix F - Adverse Events in Phase 3 Controlled Trials

Table 106: All Adverse Events in Phase 3 Controlled Trials (B303, B304, B351, B352)

Adverse Event	N	PBO	%	Exelon	%
NAUSEA	824	171	19.2	653	34.1
VOMITING	494	90	10.1	404	21.1
DIZZINESS	459	111	12.5	348	18.2
DIARRHEA	407	112	12.6	295	15.4
HEADACHE	404	116	13.0	288	15.1
ANOREXIA	286	58	6.5	228	11.9
ABDOMINAL PAIN	261	57	6.4	204	10.7
AGITATION	239	75	8.4	164	8.6
INSOMNIA	220	64	7.2	156	8.2
FATIGUE	183	36	4.0	147	7.7
DYSPEPSIA	186	47	5.3	139	7.3
SOMNOLENCE	124	26	2.9	98	5.1
DEPRESSION	136	42	4.7	94	4.9
ASTHENIA	119	29	3.3	90	4.7
BACK PAIN	124	39	4.4	85	4.4
CONSTIPATION	123	39	4.4	84	4.4
COUGHING	120	37	4.2	83	4.3
RHINITIS	104	21	2.4	83	4.3
ANXIETY	111	31	3.5	80	4.2
HALLUCINATION	110	31	3.5	79	4.1
MALAISE	96	25	2.8	71	3.7
HYPERTENSION	86	17	1.9	69	3.6
NERVOUSNESS	97	29	3.3	68	3.6
FLATULENCE	88	23	2.6	65	3.4
SWEATING INCREASED	75	18	2.0	57	3.0
TREMOR	74	18	2.0	56	2.9
AGGRESSIVE REACTION	70	16	1.8	54	2.8
RASH	77	23	2.6	54	2.8
URINARY INCONTINENCE	72	19	2.1	53	2.8
INFLUENZA-LIKE SYMPTOMS	67	20	2.2	47	2.5
SYNCOPE	63	19	2.1	44	2.3
OEDEMA PERIPHERAL	63	20	2.2	43	2.2
CHEST PAIN	56	15	1.7	41	2.1
DELUSION	54	15	1.7	39	2.0
VERTIGO	55	16	1.8	39	2.0
PRURITUS	49	14	1.6	35	1.8
WEIGHT DECREASE	42	7	0.8	35	1.8
DYSPNOEA	43	11	1.2	32	1.7
VISION ABNORMAL	39	7	0.8	32	1.7
MICTURITION FREQUENCY	41	11	1.2	30	1.6
ERUCTATION	38	9	1.0	29	1.5
GAIT ABNORMAL	31	4	0.4	27	1.4
PARONIRIA	30	6	0.7	24	1.3
TOOTH DISORDER	32	8	0.9	24	1.3
ATAXIA	32	9	1.0	23	1.2
MYALGIA	33	10	1.1	23	1.2
PAIN LEG(S)	30	8	0.9	22	1.2
HYPOTENSION	27	7	0.8	20	1.0
PALPITATION	27	7	0.8	20	1.0
PARAESTHESIA	26	6	0.7	20	1.0
SALIVA INCREASED	21	1	0.1	20	1.0
SINUSITIS	26	6	0.7	20	1.0

ALLERGY	23	4	0.4	19	1.0
PROCEDURE NOS	26	8	0.9	18	0.9
BEHAVIOURAL DISTURBANCE	22	5	0.6	17	0.9
STIFFNESS	20	3	0.3	17	0.9
ANGINA PECTORIS	18	2	0.2	16	0.8
FIBRILLATION ATRIAL	21	5	0.6	16	0.8
HOT FLUSHES	20	4	0.4	16	0.8
FEELING COLD	16	1	0.1	15	0.8
HYPOTENSION POSTURAL	21	6	0.7	15	0.8
EMOTIONAL LABILITY	15	1	0.1	14	0.7
CARDIAC FAILURE	16	4	0.4	12	0.6
GASTROENTERITIS	16	4	0.4	12	0.6
CATARACT	15	4	0.4	11	0.6
CRAMPS	15	4	0.4	11	0.6
DEHYDRATION	14	3	0.3	11	0.6
HERPES ZOSTER	16	5	0.6	11	0.6
HYPOAESTHESIA	15	4	0.4	11	0.6
BRADYCARDIA	14	4	0.4	10	0.5
CYSTITIS	12	2	0.2	10	0.5
HAEMATURIA	11	1	0.1	10	0.5
HYPOKALAEMIA	11	1	0.1	10	0.5
MUSCLE CONTRACTIONS INVOLUNTARY	12	2	0.2	10	0.5
MYOCARDIAL INFARCTION	12	2	0.2	10	0.5
TASTE PERVERSION	12	2	0.2	10	0.5
EARACHE	11	2	0.2	9	0.5
GASTROESOPHAGEAL REFLUX	13	4	0.4	9	0.5
HERNIA	13	4	0.4	9	0.5
INFECTION VIRAL	12	3	0.3	9	0.5
PALLOR	11	2	0.2	9	0.5
AMNESIA	11	3	0.3	8	0.4
CHOLELITHIASIS	8	0	0.0	8	0.4
DYSURIA	11	3	0.3	8	0.4
LIBIDO INCREASED	8	0	0.0	8	0.4
APATHY	7	0	0.0	7	0.4
NYSTAGMUS	8	1	0.1	7	0.4
APPETITE INCREASED	8	2	0.2	6	0.3
ARRHYTHMIA	8	2	0.2	6	0.3
CONVULSIONS	8	2	0.2	6	0.3
HERPES SIMPLEX	7	1	0.1	6	0.3
PHLEBITIS	8	2	0.2	6	0.3
RENAL CALCULUS	7	1	0.1	6	0.3
SKIN DRY	7	1	0.1	6	0.3
ANAEMIA HYPOCHROMIC	6	1	0.1	5	0.3
BREAST PAIN FEMALE	6	1	0.1	5	0.3
DERMATITIS CONTACT	7	2	0.2	5	0.3
DYSPHAGIA	6	1	0.1	5	0.3
DYSPHONIA	6	1	0.1	5	0.3
EXTRAPYRAMIDAL DISORDER	5	0	0.0	5	0.3
GI HAEMORRHAGE	6	1	0.1	5	0.3
GLAUCOMA	7	2	0.2	5	0.3
HYPOKINESIA	5	0	0.0	5	0.3
LACRIMATION ABNORMAL	6	1	0.1	5	0.3
LYMPHADENOPATHY	5	0	0.0	5	0.3
MELAENA	7	2	0.2	5	0.3
OESOPHAGITIS	7	2	0.2	5	0.3
RASH ERYTHEMATOUS	7	2	0.2	5	0.3
SKIN COLD CLAMMY	5	0	0.0	5	0.3
TASTE LOSS	5	0	0.0	5	0.3
BLADDER DISORDERS NOS	5	1	0.1	4	0.2

BUNDLE BRANCH BLOCK	4	0	0.0	4	0.2
CORONARY ARTERY DISORDER	5	1	0.1	4	0.2
DEAFNESS	5	1	0.1	4	0.2
DIPLOPIA	5	1	0.1	4	0.2
DREAMING ABNORMAL	5	1	0.1	4	0.2
MYOCARDIAL ISCHAEMIA	5	1	0.1	4	0.2
NOCTURIA	5	1	0.1	4	0.2
URINARY RETENTION	5	1	0.1	4	0.2
ABSCCESS	4	1	0.1	3	0.2
CACHEXIA	3	0	0.0	3	0.2
FURUNCULOSIS	4	1	0.1	3	0.2
GASTRIC ULCER	3	0	0.0	3	0.2
HYPERGLYCAEMIA	4	1	0.1	3	0.2
NEUROPATHY PERIPHERAL	3	0	0.0	3	0.2
OEDEMA PERIORBITAL	4	1	0.1	3	0.2
PERIPHERAL ISCHAEMIA	4	1	0.1	3	0.2
RASH PSORIAFORM	4	1	0.1	3	0.2
RENAL CYST	3	0	0.0	3	0.2
SPEECH DISORDER	4	1	0.1	3	0.2
STOMATITIS ULCERATIVE	4	1	0.1	3	0.2
STRESS REACTION	4	1	0.1	3	0.2
TENDINITIS	3	0	0.0	3	0.2
THIRST	3	0	0.0	3	0.2
THROMBOPHLEBITIS	3	0	0.0	3	0.2
VASCULAR DISORDER	4	1	0.1	3	0.2
APHASIA	2	0	0.0	2	0.1
AV BLOCK	2	0	0.0	2	0.1
BLEPHARITIS	2	0	0.0	2	0.1
BONE DISORDER	2	0	0.0	2	0.1
CIRCULATORY DISORDER	2	0	0.0	2	0.1
CYST, SKIN	2	0	0.0	2	0.1
GENITALIA ABNORMAL FEMALE	2	0	0.0	2	0.1
HICCUP	2	0	0.0	2	0.1
HYPERTRICHOSIS	2	0	0.0	2	0.1
HYPONATRAEMIA	2	0	0.0	2	0.1
HYPOREFLEXIA	2	0	0.0	2	0.1
JOINT MALFORMATION	2	0	0.0	2	0.1
MACULA LUTEA DEGENERATION	2	0	0.0	2	0.1
NAIL DISORDER	2	0	0.0	2	0.1
NEUROSIS	2	0	0.0	2	0.1
PARALYSIS	2	0	0.0	2	0.1
PERINEAL PAIN FEMALE	2	0	0.0	2	0.1
RENAL PAIN	2	0	0.0	2	0.1
SERUM IRON DECREASED	2	0	0.0	2	0.1
SKIN HYPERTROPHY	2	0	0.0	2	0.1
SPASM GENERALIZED	2	0	0.0	2	0.1
TUMOR BENIGN	2	0	0.0	2	0.1
UVEITIS	2	0	0.0	2	0.1
VAGINITIS ATROPHIC	2	0	0.0	2	0.1
VEIN VARICOSE	2	0	0.0	2	0.1
VESTIBULAR DISORDER	2	0	0.0	2	0.1
WEIGHT INCREASE	2	0	0.0	2	0.1
APNOEA	1	0	0.0	1	0.1
ATELECTASIS	1	0	0.0	1	0.1
ATRIAL FLUTTER	1	0	0.0	1	0.1
BONE PAIN	1	0	0.0	1	0.1
BREAST PAIN MALE	1	0	0.0	1	0.1
CARDIOMEGALY	1	0	0.0	1	0.1
CHEILITIS	1	0	0.0	1	0.1

CHEST PAIN SUBSTERNAL	1	0	0.0	1	0.1
CHOLECYSTITIS	1	0	0.0	1	0.1
COLON CARCINOMA	1	0	0.0	1	0.1
CORNEAL ULCERATION	1	0	0.0	1	0.1
DEPRESSION PSYCHOTIC	1	0	0.0	1	0.1
DUODENAL ULCER	1	0	0.0	1	0.1
EAR DISCHARGE	1	0	0.0	1	0.1
EMBOLISM ARTERIAL	1	0	0.0	1	0.1
EMBOLISM LIMB	1	0	0.0	1	0.1
ENCEPHALOPATHY	1	0	0.0	1	0.1
ENDOCRINE DISORDER NOS	1	0	0.0	1	0.1
EOSINOPHILIA	1	0	0.0	1	0.1
EPIDERMAL NECROLYSIS	1	0	0.0	1	0.1
EUPHORIA	1	0	0.0	1	0.1
FOLLICULITIS	1	0	0.0	1	0.1
GENERALIZED INFLAMMATION LEG(S)	1	0	0.0	1	0.1
GENERALIZED INFLAMMATION OF THE EXTREMITIES	1	0	0.0	1	0.1
GLYCOSURIA	1	0	0.0	1	0.1
GOITRE	1	0	0.0	1	0.1
GRANULOMATOUS LESION	1	0	0.0	1	0.1
HAEMATEMESIS	1	0	0.0	1	0.1
HAIR DISCOLOURATION	1	0	0.0	1	0.1
HEART VALVE DISORDERS	1	0	0.0	1	0.1
HEPATITIS	1	0	0.0	1	0.1
HEPATOCELLULAR DAMAGE	1	0	0.0	1	0.1
HYPERACUSIS	1	0	0.0	1	0.1
HYPERAESTHESIA	1	0	0.0	1	0.1
HYPERKALAEMIA	1	0	0.0	1	0.1
HYPOTHERMIA	1	0	0.0	1	0.1
HYSTERIA	1	0	0.0	1	0.1
ILLUSION	1	0	0.0	1	0.1
INFECTION PARASITIC	1	0	0.0	1	0.1
IRRITABLE COLON	1	0	0.0	1	0.1
JAUNDICE	1	0	0.0	1	0.1
LEUKOCYTOSIS	1	0	0.0	1	0.1
LIBIDO DECREASED	1	0	0.0	1	0.1
LIVER FATTY	1	0	0.0	1	0.1
MIOSIS	1	0	0.0	1	0.1
MUSCLE ATROPHY	1	0	0.0	1	0.1
OEDEMA GENITAL	1	0	0.0	1	0.1
PAPILLOEDEMA	1	0	0.0	1	0.1
PEPTIC ULCER	1	0	0.0	1	0.1
PHOTOPHOBIA	1	0	0.0	1	0.1
PNEUMOTHORAX	1	0	0.0	1	0.1
POST-MENOPAUSAL BLEEDING	1	0	0.0	1	0.1
PSORIASIS AGGRAVATED	1	0	0.0	1	0.1
PULMONARY OEDEMA	1	0	0.0	1	0.1
PYELONEPHRITIS	1	0	0.0	1	0.1
RASH FOLLICULAR	1	0	0.0	1	0.1
RECTAL DISORDER	1	0	0.0	1	0.1
RESPIRATORY DISORDER	1	0	0.0	1	0.1
RESPIRATORY INSUFFICIENCY	1	0	0.0	1	0.1
SALIVARY DUCT OBSTRUCTION	1	0	0.0	1	0.1
SEPSIS	1	0	0.0	1	0.1
SOMNAMBULISM	1	0	0.0	1	0.1
SUDDEN DEATH	1	0	0.0	1	0.1
SUICIDE ATTEMPT	1	0	0.0	1	0.1
TACHYCARDIA VENTRICULAR	1	0	0.0	1	0.1
TETANY	1	0	0.0	1	0.1

THROMBOPHLEBITIS DEEP	1	0	0.0	1	0.1
URETERAL DISORDER	1	0	0.0	1	0.1

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Appendix G - AE's in Patients with Concomitant Medical Conditions

The tables are generated from patients in phase 3 controlled trials (B303, B304, B351, B352)

Table 107: Hypertension

Preferred Term Current Med. Condition Status	EMC		Placebo		Difference in EMC - Placebo		Total		EMC vs Placebo
	N	n	N	n	p	N	n		
AE causing death	1856	6	1856	1	0.01	1856	1	1	0.01
With CMC	466	0	466	0	0	466	0	0	0
Without CMC	1390	6	1390	1	0.01	1390	1	1	0.01
Fatal AE	1856	0	1856	0	0	1856	0	0	0
With CMC	466	0	466	0	0	466	0	0	0
Without CMC	1390	0	1390	0	0	1390	0	0	0
Leading to discontinuation	1856	19	1856	19	0	1856	19	19	0
With CMC	466	0	466	19	0	466	19	19	0
Without CMC	1390	19	1390	0	0	1390	0	0	0
Resulting in dose change	1856	33	1856	52	0.001	1856	85	85	0.001
With CMC	466	19	466	52	0.001	466	71	71	0.001
Without CMC	1390	14	1390	0	0	1390	0	0	0
Severe Effect	1856	1	1856	1	0	1856	2	2	0
With CMC	466	0	466	1	0	466	1	1	0
Without CMC	1390	1	1390	0	0	1390	1	1	0
Clinically Significant	1856	9	1856	10	0	1856	19	19	0
With CMC	466	0	466	10	0	466	10	10	0
Without CMC	1390	9	1390	0	0	1390	0	0	0

1. Data from controlled studies - B303, B304, B351, and B352
 2. Current Med. Condition
 3. Adverse Events that first occurred after the initial onset of CMC
 4. p < 0.05 Breslow-Day test for homogeneity of odds ratio
 5. Clinically Notable Weight Increase defined as an increase of 7% or greater from baseline

Table 108: Dyspepsia

Preferred Term Current Med. Condition Status	EMC		Placebo		Difference in EMC - Placebo		Total		EMC vs Placebo
	N	n	N	n	p	N	n		
AE causing death	1856	0	1856	0	0	1856	0	0	0
With CMC	466	0	466	0	0	466	0	0	0
Without CMC	1390	0	1390	0	0	1390	0	0	0
Fatal AE	1856	0	1856	0	0	1856	0	0	0
With CMC	466	0	466	0	0	466	0	0	0
Without CMC	1390	0	1390	0	0	1390	0	0	0
Leading to discontinuation	1856	0	1856	0	0	1856	0	0	0
With CMC	466	0	466	0	0	466	0	0	0
Without CMC	1390	0	1390	0	0	1390	0	0	0
Resulting in dose change	1856	33	1856	52	0.001	1856	85	85	0.001
With CMC	466	19	466	52	0.001	466	71	71	0.001
Without CMC	1390	14	1390	0	0	1390	0	0	0
Severe Effect	1856	1	1856	1	0	1856	2	2	0
With CMC	466	0	466	1	0	466	1	1	0
Without CMC	1390	1	1390	0	0	1390	1	1	0
Clinically Significant	1856	9	1856	10	0	1856	19	19	0
With CMC	466	0	466	10	0	466	10	10	0
Without CMC	1390	9	1390	0	0	1390	0	0	0

1. Data from controlled studies - B303, B304, B351, and B352
 2. Current Med. Condition
 3. Adverse Events that first occurred after the initial onset of CMC
 4. p < 0.05 Breslow-Day test for homogeneity of odds ratio
 5. Clinically Notable Weight Increase defined as a decrease of 7% or greater from baseline

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Table 109: Diabetes Mellitus

Population Test Adverse Event Condition Status	ENL		Placebo		ENL - Placebo	Total		ENL % of Patients
	N	n (%)	N	n (%)		n	n (%)	
All Diabetes Events	1266	3	1266	17	14	2532	2	0.08
With DM	1266	3	1266	17	14	2532	2	0.08
Without DM	1266	4	1266	17	13	2532	2	0.08
Diabetes AD	1266	23	1266	73	50	2532	32	0.13
With DM	1266	23	1266	73	50	2532	32	0.13
Without DM	1266	23	1266	73	50	2532	32	0.13
Diabetes in Discontinuation	1266	19	1266	59	40	2532	14	0.05
With DM	1266	19	1266	59	40	2532	14	0.05
Without DM	1266	19	1266	59	40	2532	14	0.05
Fluctuating in Baseline Change	1266	133	1266	123	100	2532	92	0.37
With DM	1266	133	1266	123	100	2532	92	0.37
Without DM	1266	133	1266	123	100	2532	92	0.37
Severe Event	1266	13	1266	17	4	2532	14	0.05
With DM	1266	13	1266	17	4	2532	14	0.05
Without DM	1266	13	1266	17	4	2532	14	0.05
Requiring Therapy	1266	94	1266	173	79	2532	57	0.23
With DM	1266	94	1266	173	79	2532	57	0.23
Without DM	1266	94	1266	173	79	2532	57	0.23

ENL = Enalapril Studies = E101, E104, E107, and E108
 AD = Current Medical Condition
 DM = Current Medical Condition
 AD = Adverse Events that first occurred after the initial onset of DM
 p < 0.05 = Breslow-Day test for homogeneity of odds ratios
 Clinically Notable Weight Decrease defined as a decrease of 7% or greater from baseline

Table 110: Arthritis

Population Test Adverse Event Condition Status	ENL		Placebo		ENL - Placebo	Total		ENL % of Patients
	N	n (%)	N	n (%)		n	n (%)	
All Arthritis Events	1266	1	1266	1	0	2532	1	0.01
With DM	1266	1	1266	1	0	2532	1	0.01
Without DM	1266	0	1266	0	0	2532	0	0.00
Diabetes AD	1266	1	1266	1	0	2532	1	0.01
With DM	1266	1	1266	1	0	2532	1	0.01
Without DM	1266	0	1266	0	0	2532	0	0.00
Diabetes in Discontinuation	1266	1	1266	1	0	2532	1	0.01
With DM	1266	1	1266	1	0	2532	1	0.01
Without DM	1266	0	1266	0	0	2532	0	0.00
Fluctuating in Baseline Change	1266	133	1266	123	100	2532	92	0.37
With DM	1266	133	1266	123	100	2532	92	0.37
Without DM	1266	133	1266	123	100	2532	92	0.37
Severe Event	1266	13	1266	17	4	2532	14	0.05
With DM	1266	13	1266	17	4	2532	14	0.05
Without DM	1266	13	1266	17	4	2532	14	0.05
Requiring Therapy	1266	94	1266	173	79	2532	57	0.23
With DM	1266	94	1266	173	79	2532	57	0.23
Without DM	1266	94	1266	173	79	2532	57	0.23

ENL = Enalapril Studies = E101, E104, E107, and E108
 AD = Current Medical Condition
 DM = Current Medical Condition
 AD = Adverse Events that first occurred after the initial onset of DM
 p < 0.05 = Breslow-Day test for homogeneity of odds ratios
 Clinically Notable Weight Decrease defined as a decrease of 7% or greater from baseline

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**Review of Clinical Data
March 9, 1998 Amendment Evaluating the Mortality in the Rivastigmine NDA**

NDA: 20-823
Sponsor: Novartis
Drug: Rivastigmine
Route of Administration: Oral
Reviewer: Greg Burkhart, M.D., M.S.
Review Completion Date: March 26, 1998

ISL
-26-98

In Dr. Oliva's initial review of the rivastigmine NDA, he found about a 2 fold increase in all-cause mortality on drug compared to placebo in the phase 2/3 RCTs. To evaluate the issue further, Dr. Racoosin and I conducted a nested case control study based upon data in the 120 day safety update [*Update*] database and found that all-cause mortality increased with increasing rivastigmine dose. These findings were summarized in a January 28, 1998 memorandum, authored by Dr. Racoosin.

To verify the findings of the case-control study, Novartis conducted a person-time analysis on the *Update* database. Since we had randomly selected a small percentage of eligible patients as controls, the relative difference in mortality by dose group was estimated and not exact. The person-time analysis would provide an exact quantification of the mortality rates and relative differences between dose groups. Novartis informally submitted their findings in a February 12, 1998 fax and hand delivered the datasets.

The person-time analysis conducted by Novartis using the *Update* database generally confirmed the case control study finding that at all-cause mortality increased with increasing dose. Novartis then proceed to add additional follow-up experience with the new database referred to by Novartis as an extended update [*Extended*] database.

On March 9, Novartis amended the NDA with a person-time analysis of the *Extended* database. At the time of submission, we learned that the analysis had not only been based upon additional follow-up experience but also added 3 deaths that had been excluded in previous analyzes. These 3 deaths had been classified as occurring more than 30 days after last use when, in fact, they occurred within 30 days of the last prescribed dose (LPD).

In addition to a written report of the analysis conducted on the *Extended* database, the submission also contained the supporting datasets. The primary datasets consisted of a

(1) demography file that contained general information on each patient as well as the date of death, (2) Drug Administration Record (DAR) file that contained multiple rows per patient with each row providing the beginning and ending dates of each dose used along with the study number, and (3) the grouped person-time file used by Novartis in the analysis.

This memorandum reviews the findings from the person-time analyzes of both the *Update* and *Extended* databases after first reviewing the initial case control study findings as well additional analyzes that have been conducted on that dataset since Dr. Racoosin's memorandum.

Overview of the Patient Population Used in All Three Analyzes

The case control analysis as well as the person-time analyzes of the *Update* and *Extended* databases all used the same patient population with the only difference being that additional follow up was captured in the *Extended* database.

Overall, 3350 patients have contributed experience to the databases with 3162 of these exposed at some point to rivastigmine. The remaining 188 patients were only exposed to placebo (never entered an extension). These 3350 patients were enrolled in the 4 RCTs (303,304,351, or 352) along with their extensions (305 and 353), or in 2 open label titration studies (354 and 355).

In the 4 RCTs, 2791 patients were randomized with 868 and 1923 assigned to placebo and drug, respectively. Based upon the data in the demography file, 2010 of the 2791 patients entered an extension. However, in the DAR file, it appears to me that 7 of the 2010 (2 placebo and 5 drug patients) did not have any exposure in an extension. Thus, based upon the DAR file, 2003 patients (678 placebo and 1325 drug exposed) actually had exposure in an extension.

The 788 RCT patients¹ who did not enter the extensions may be an additional source of data on the "expected" mortality much as the experience of patients who discontinued clozapine provided data on the possible background mortality rate in clozapine users.² As in the analysis of the clozapine registry data, one will have to stratify the experience on "time since last-use" of drug since mortality may be higher shortly following discontinuation because concomitant disease processes may be related to the reason for discontinuation. Ideally, one would one to focus on patients dropping out for self limited AEs or for lack of efficacy.

The 2003 patients who entered the extensions did not necessarily complete the RCT portion. Patients were allowed to discontinue from the RCT and enter the extensions after waiting till what would have been their RCT ending date. For example, of the 678

¹ Calculated by subtracting 2003 from 2791.

² Walker AM. *Epidemiology*; 1997 page 671.

patients who had rivastigmine exposure in an extension who were exposed to placebo in the RCT (according to the DAR file), 14 discontinued from the RCT and waited to enter the extension.

The 2003 patients entering extension were re-started on rivastigmine with the titration schedule reportedly less controlled than in the RCTs. Apparently the objective was still to achieve the highest dose tolerated up to 12 mg. Since some patients entering the extensions had been randomized to lower doses (in dose ranges), one would expect more experience at higher doses in the RCTs, if such doses were tolerated.

The extension studies have essentially captured the experience of 2 distinct groups of patients; those with and without preceding exposure to rivastigmine. Thus, it will be important to examine the mortality rates separately for these two groups.

The remaining 559 patients in the databases (3350-2791) were in the titration studies with 544 of these in study 355. These patients were studied under open label using a more rapid titration schedule.

One should note that in addition to the 3350 patients that have contributed experience to the *Update* and *Extended* databases, there have been additional patients exposed to rivastigmine worldwide. In fact, there were about 5000 worldwide patients currently on rivastigmine at the time the NDA was filed. The 3350 patients reported on by Novartis represented a systematic sample of all exposed patients and were selected because they had the opportunity to have completed at least 52 weeks of observation.

Dates of Follow Up in the *Update* and *Extended* Databases

In the *Update* Database (same dataset used for the case control study), events could have been captured in the data for patients enrolled in RCT/Extensions up through their 52 week visits (about 52 weeks + 14 days), and in some patients, up through the 78 week visits. Experience in the 2 titration studies were inclusive of 26 weeks. The *Extended* Database added experience for patients in RCT/Extensions up through either 52 or 104 week visits while patients in the titration studies were updated through 52 weeks.

The *Update* Database summarized experience that occurred no later than December 31, 1996 while the *Extended* Database captured experience that occurred no later than June 30, 1997.³

³Admittedly, we did not understand the effect of Novartis's approach on the extent of experience (including each patient's person-time at a dose) until after extensive discussions as well as a review of a separate written description of these methods that was faxed to us on March 12 after the amendment was submitted

The approach used by Novartis to capture experience in 26 week blocks was based upon the methods used for data collection. CRFs were removed from investigative sites for data entry after patients completed 26, 52, 78 and 104 week visits.

Focusing on patients who had the opportunity⁴ to complete at least 52 weeks of study in an RCT/extension was a reasonable approach in reducing the scope of the task of providing extensive follow-up for a sufficient number of patients with exposure to rivastigmine. By itself, such a restriction would not create any systematic bias. Of course, if the risk was only present with extended use beyond 104 weeks or only in more recent calendar time then the database would not be capable of observing the risk. Neither of these possible concerns seem very likely in this case.

Figure 1 shows how the effect of the definitions used by Novartis to construct the *Extended* database have impacted the person-time captured in it. As shown, the 915 patients who entered an RCT before 6/30/95 could have contributed up to 104 weeks to the database while 1874 patients who entered an RCT after 6/30/95 but before 7/1/96 could have contributed up to 52 weeks. A consequence of this approach and the basis for the confusion was that events occurring as early as 7/1/96 may have been excluded from the *Extended* Database if patients entered shortly after 6/30/95. Thus, when Novartis refers to an update date of June 30, 1997, they mean that the included experience could have occurred no later than that date not that all events are reported as of that date.

Methods used by Novartis to Calculate Mortality Rates in the *Update* and *Extended* Databases

Selection of Deaths to be Used in the Analyses

As in the case-control study, the analyses of the *Update* and *Extended* databases have focused on deaths occurring within 30 days of the LPD. While there are some deaths identified in the database that occurred after 30 days, there is less certainty as one gets further from last use that all possible deaths have been identified. Most survival and epidemiological studies will have vital status dates that censor follow-up. Since sponsors, as in this case, do not routinely conduct follow-up for every patient at specified intervals following drug discontinuation, it is a matter of belief as to whether deaths are ascertained. Thus, we believed, as is usually assumed in an NDA safety analysis, that Novartis would have identified all deaths within 30 days of stopping the drug.

While we considered "cause-specific" mortality in a general way in the case control study by examined cardiovascular deaths (including sudden deaths) as a separate

⁴ Patients did not have to actually complete 52 weeks. They just had to have the opportunity. Thus, dropouts and deaths that occurred earlier than 52 weeks would be included if they otherwise would have completed the appropriate length of follow-up.

outcome, the analyzes conducted by Novartis have, so far, focused on all-cause mortality. As in most NDAs, the clinical materials may be somewhat limited to assign causes to deaths and it may be difficult to develop a case definition given the non-specific nature of deaths. One could focus on sudden death or focus on the deaths remaining after excluding those that could not possibly have been caused by drug, but the approach can be difficult with the findings possibly difficult to interpret. Should a motor vehicle death to the driver be excluded? What about an occupant? I am sure that most can construct scenarios, in either case, where a suspect exposure was at least indirectly responsible for the accident. Thus, it may be difficult to conduct a meaningful analysis of cause-specific mortality unless there are a large number of deaths for study and/or if one can develop a specific case definition.

Additionally, the person-time analyzes have not yet examined the effect of restricting deaths to those occurring on drug. Of course the necessity to consider the timing of death to last dose reflects a concern about increasing the likelihood that a death could have been caused by the drug. Such a concern has more merit when focusing on sudden deaths. Deaths that result from an illness course that began on drug but where death occurred after discontinuation may still be of interest can not necessarily be discounted. Thus, while there would be merit to examining the effect of restricting the analysis to deaths, say within a few days of drug use, such findings have to be considered carefully.

Methods of Analysis

To calculate the mortality rates, each patient day was classified according to daily dose. This allows each patient contributed to each daily dose group making the groups mutually exclusive with respect to time, but not with respect to patients. Presumably, the DAR file⁵ was used to compute the time at dose for each patient. It was then a matter of grouping the deaths and person-time according to dose group, age, gender, US vs foreign, and study type.

To analyze the rates in each database, Novartis used standard methodology by descriptively examining the data and then conducting poisson regression. Novartis defined the daily dose (mg) groups as follows: placebo, 1-<4, ≥4- ≤6, >6-≤9 and >9.

Some confusion has occurred regarding the definitions of the dose groups. In our initial case-control analysis, we used less than 4 mg. After Novartis, as well as other members of the review team, pointed out to us that patients in the RCTs were randomized to dose ranges where the lowest range included 4 mg, we reanalyzed the case control study, but

⁵ While I did not formally evaluate the DAR file for data errors, I did find a significant error. In reviewed a subgroup of these data, the 38 deaths, patient 35211009 had 382 extra days on placebo that resulted from a clear data entry error of the dates.

the findings did not change.⁶ However, in their analysis of the *Update Database*, Novartis, for some reason, used our original definition.

In my opinion this is a relatively minor issue since we do not think the description of the mortality pattern hinged on what was used for the lower dose group and since statistical inference has no validity for most of the data in the databases.⁷ In any case, it is relatively easy to examine the mortality pattern both ways. To be compelling, the pattern observed should not be susceptible to minor changes in definitions used to defined dose groups.

Case Control Study Findings

Cases were defined as the 24 phase 3 deaths that occurred in the *Update* database that were classified as occurring within 30 days of last use of rivastigmine. Phase 2 deaths were not included in our analysis since the update did not contain data on time at dose for all patients in phase 2 studies.

For comparison, 5 randomly selected controls were matched to each of the 24 deaths by study number and country (US or foreign). To be an eligible control, the patient could have died any earlier in study than the case.

We found a clear increase the odds ratios for death by LPD category that was not model dependent. A second random sample of 5 controls confirmed the findings of the first sample.

The analysis considered a number of rivastigmine dose variables. The strength of the findings increased when the LPD per kg baseline weight was used as the exposure variable. (The database did not contain information on body weight during study.) There was no relationship with cumulative dose and there was no evidence that there was significant changing of a patient's daily dose within 30 days of the last dose. For a more extensive description of the findings, please see Dr. Racoosin's memorandum.

At the time of the initial analysis, we also examined cause-specific mortality even though it was not mentioned in Dr. Racoosin's memorandum because of the limited number of cases of interest. To identify the cases, Dr. Oliva reviewed the clinical materials for the 24 cases and using implicit judgment, he classified each death as to whether could have been caused by rivastigmine focusing on cardiovascular and sudden deaths. Of the 24 deaths, 8 meet his criteria. While the findings did not change using these 8 cases in a re-analysis, the estimates were even more imprecise.

⁶ There was no material effect on the findings in the case-control study in that it still suggested increasing mortality with increasing dose.

⁷ Even in the RCTs, person-time aggregated to the low dose group will include time for patients who were randomized to a higher dose range since they all started low in the RCTs. If statistical inference can be used anywhere in these data, it would be for drug vs. placebo in the RCTs.

More recently, we examined the effect of using deaths that occurred within one week of the LPD and baseline mental status score on the relative difference in mortality by dose group and found no change in the findings.⁸

Mortality Rates in the *Update Database*

Table 1 shows the 25 deaths and person-years (PYs) of use according to the LPD. Of the 25 deaths included in Table 1, one occurred in a patient assigned placebo. The remaining 24 deaths are the same cases that we used in our case-control analysis.

Table 2 shows the mortality rates by dose group across the *Update Database*. As we saw in the "nested" case control study, which incidentally matched by study number and hence study type, use of 10 or 12 mg was associated with an increased mortality rate when compared with 1-4 mg and lower dose groups. Also, quite apparent is the absence of deaths in the placebo group despite having a moderate amount of experience (almost 400 PYs).

Table 3 shows the mortality rates by dose group separately for the RCT, titration and extension studies. The all-cause mortality rate across the titration studies was about 4 fold greater than across the RCTs. Additionally, while the high dose group (10 and 12 mg) had the largest mortality rate in the extensions, it was the mid dose groups in the RCTs and the titration studies.

My conclusions upon seeing these data was that the mortality rates in the *Update Database* was generally consistent with the relative increase in mortality with increasing dose that was observed in the case control study and reason for more evaluation. In addition, as pointed by Novartis in the amendment, the variation in mortality by study type raises concern about pooling the data. Of course the case control study did not pool the data, but in fact matched on study number.

Mortality in the *Extended Database*

Combined Experience Across All Study Types

Table 4 shows the distribution of the additional deaths and PYs by daily dose. Table 5 shows the mortality by dose group (as before with 4 mg in the lower dose). There now are a total of 38 deaths, 37 on drug that has occurred in 2856.3 PYs.⁹ The placebo experience, of course has not changed from the time the NDA was filed. In effect, Novartis has added 13 additional deaths along with about 464 PYs of experience (a rate

⁸ Of the 24 deaths, 14 occurred within 7 days of the last dose, 5 from 7-14 days of the last dose and 5 from 14-30 days of the last dose.

⁹ In the submission, Novartis reported 2869.3 PYs for the *Extended database*. However, I could not reproduce this number from the DAR file from which I computed the PYs to be 2856.3.

of 28 per 1000 PYs). Table 9 provides a listing of all 38 deaths that lists the study type, LPD, time at LPD, and time till death.

Of the 13 additional deaths, only 7 occurred within the additional follow-up. Three others were added, which had been excluded from the case control study and the *Extended* database because they had been misclassified as occurring more than 30 days after the last dose. In fact, after a systematic review of the timing of death to the LPD using the narrative summaries, the 3 cases were shown to be within 30 days. The misclassification occurred because the project database was missing key dates (date of death for 2 cases and date of LPD for the other) which were present in the narratives. Our review of the narratives confirmed Novartis's findings and there were no other cases that appeared to have been excluded inappropriately.¹⁰

Three other deaths were added that occurred in the titration study 355 just after each patient's cutoff date but within 30 days of drug, and thus should have been counted.

As shown in Table 5, the effect of the additional follow-up and deaths has been to increase the rates in the lower dose groups reducing the relative difference between dose groups, but making the difference with placebo even more striking.

Mortality by Study Type

Table 6 shows the mortality rates by study type. Across the titration studies the mortality is about 6 fold greater than that across the RCTs. As before, the only relative increase in mortality with the high dose group was in the extension studies, more evident by comparing the 10 and 12 mg experience (13/623 PYs = 21 per 1000 PYs) with the lower doses (6/669 PYs = 9 per 1000 PYs) or about a 2.3 fold difference. Of the 3 deaths that were added to the extension experience because of misclassification in the project database, 2 have added to the low dose group.

In the RCTs combining all dose groups, there were 6 deaths in 811 PYs of rivastigmine use compared to 1 death in 396 PYs of placebo or about 3 fold increase (exact one tailed; 0.26, 95% CI; 0.4, 136). Based upon Novartis's separate analysis of the first 100 days of use from use thereafter, there were 4 deaths in 475.7 PYs of use (8.4 per 1000 PYs) compared to 2 deaths in 335.3 PYs of use after 100 days (6 per 1000 PYs). While this is certainly not striking difference, 100 days may have been a little broad to check for a potential early increase in mortality. Of the 4 deaths, 3 were within 30 days of starting the drug. Thus, if the rates are re-computed for the first 30 days separately, the mortality rate will likely be significantly higher in the first 30 days that time thereafter since 3 of the 6 deaths occurred there and patient dropout was not that extensive.

¹⁰ Dr. Oliva verified that the narrative submitted in the 120 safety update contained these dates.

The PIDs for the 6 deaths on drug in the RCTs are **30309004**, **30334018**, **30409003**, **35103011**, **35105003**, and **35215039**.¹¹ The bolded numbers are those that occurred within 30 days of starting the drug. Of the 6, there are 2 that appear to be sudden and unexplained by some event, 1 that occurred just after a diagnosis of "metastatic prostate cancer" that had few clinical details and may have been sudden in nature, and 1 that also may have been sudden but after being hospitalized for anorexia and weight loss.¹²

Novartis also examined the rates by time since start in the titration studies. In the first 100 days there were 4 deaths in 129.8 PYs of use (30.8 per 1000 PYs) compared 8 deaths in 239 PYs thereafter (33.5 per 1000 PYs). Of the 4 deaths within 100 days 1 occurred in the first 30 days of use. The PIDs for the 12 deaths that have been observed in the titration studies are **35502104**, **35507116**, **35515108**, **35516101**, **35516104**, **35518102**, **35522103**, **35524116**, **35526102**, **35528101**, **35528121**, and **35528126**.

Novartis did not examine the mortality in the extension studies separately for patients with and without preceding exposure to the drug in the RCTs. Such an analysis would, in my opinion, be critical before assuming that such patients were comparable.

Of the 2003 patients who entered the extension studies with exposure in the DAR file, 678 were had used placebo in the RCTs while the remaining 1325 were exposed to drug in the RCTs. I identified these patients using the DAR file where dose recorded as "0" appears to identify placebo use. Patients who were on drug, but with short periods of no use appeared to have been represented by gaps in the time periods. There was no specific variable included with any of the files that denoted group assignment in the RCTs. (My error to some extent since I didn't think to add this variable when the files built.) I then computed the person-time for the extension studies by dose group separately for patients with and without prior rivastigmine exposure.

Table 7 shows the all-cause mortality rates for the 678 placebo patients who entered the extension while Table 8 shows the rates for the 1325 patients who were exposed to drug in the RCTs. While there was only a slight difference in all-cause mortality in the 2 groups of patients (1.5 fold increase in placebo patients who went on drug), there was a striking difference in the pattern of deaths and rates by dose group. Of the 8 deaths in the drug naïve patients, 5 were at low dose. Strikingly, all 11 deaths in the previously exposed patients occurred at high dose. Thus, in my view, the mortality pattern seen with the 2 groups of patients would preclude combining their experience.

For patients with previously exposure to drug in an RCT, the all-cause mortality rate with use of 10 or 12 mg was 24.5 per 1000 PYs (11 deaths in about 449 PYs). At doses

¹¹ Dr. Oliva describes the deaths in his review in section 8.2.3.

¹² As an aside, reviewing the clinical details for these 6 deaths illustrates the problem with evaluating cause-specific mortality from such data - limited details on the event(s) and the non-specific nature of most deaths.

lower than 10 mg, there were 0 deaths in 416 PYs of use (two tailed Fishers exact; $p = .001$). The PIDs for the 11 deaths in extension patients who had been on drug in the RCTs are ~~30304001~~, 30312016, 30331002, 30413013, 35106045, 35112014, 35203003, 35203025, 35213004, 35213019, and 35220009. As shown in Table 9, the shortest length of use at the LPD in these patients was 27 days. Thus, temporal changes in dose were unrelated to death assuming that LPD reflects actual use.

The PIDs for the 8 patient deaths that occurred in extension patients who were assigned placebo in an RCT are 30302004, 30342006, 30431015, 35105021, 35204022, 35206021, 35211009, and 35215011. In reviewing the clinical details from the death summaries provided by Novartis, there is little information on the experience leading up to the event associated with death. For example, patient 30302004 was reportedly hospitalized for "respite care" falling shortly after entering the hospital, fracturing a hip and then dying from sepsis following surgical repair of the fracture. There was no information about the actual reason for hospitalization. If the patient was dehydrated or orthostatic because of AEs caused by the drug, then the death may be attributable to drug. Patient 35215011, on 12 mg, apparently had weight loss, malaise and then had a sudden death. Again there were few details about the events leading up to death. Patient 30342006, on 12mg, also appears to have been a sudden death.

While age, gender and country did not confound the differences between dose groups in most analyzes, any effect on the two groups of patients entering the extension has not yet been examined.

Discussion of the Findings from the Mortality Analyses Conducted to Date

The division's concern that there may be an association between rivastigmine use and increased mortality began when Dr. Oliva noted the apparent excess of deaths on drug compared to placebo in the RCTs. Across the phase 2/3 RCTs, there were 8 deaths in the 2039 patients assigned rivastigmine and 2 in 921 patients assigned placebo (deaths within 30 days)¹³, about a 2 fold increase (one tailed exact; $p = .28$).

Novartis, acknowledging the apparent excess in mortality in the RCTs as an issue, included a section in the ISS arguing that the excess wasn't a signal of risk. Based upon my conversations with Dr. Oliva, Novartis makes the points that (1) the apparent increase in mortality results from an absence of mortality in the placebo group, (2) the overall morality with rivastigmine is similar to that seen with Tacrine and Aricept, and (3) there were no unusual causes of death with the causes consistent with that expected in an elderly population.

¹³ The numerators are different from those shown in Dr. Oliva's review because of our focus on deaths within 30 days. He also reported in his review that there were 869 placebo patients in the phase 3 studies with his information based upon the 120 safety update report. In the files that we have, there were 868 placebo patients.

Of course, it is always true that when a difference exists between groups that there is both an apparent deficit in one group as well as an excess in the other. How one knows which is correct isn't clear, and in this case, there were almost 400 PYs of placebo experience, not an insignificant amount of exposure. Thus, one would have to interpret the excess of death on drug in the RCTs as a signal requiring further investigation. Certainly, one might be willing to dismiss it as a "signal" if deaths on drug were very unlikely to have been related to use of the drug, an argument that will be difficult to make in this population because it is difficult to know what type of death might be attributable. Additionally, there are some deaths that are not inconsistent with a drug etiology. It's just hard to know with limited clinical data and the non-specific nature of most deaths in the NDA which to focus on. Thus, I don't find the argument that the "causes of death were those expected" to be particularly compelling at this point.

Given the size of the rivastigmine NDA, we do have additional data in which to evaluate mortality. In fact, there is more experience in the extension studies of this NDA than in the total NDA experience with many other drugs. It is also this experience from which I think the most troubling signal has arisen.

When the mortality of patients entering the extension studies is evaluated separately in patients with and without prior rivastigmine exposure (meaning placebo versus drug in RCT), the patterns that are observed seem completely different. In patients who were exposed to drug in an RCT, all 11 deaths occurred with 10 or 12 mg as the LPD. This occurs despite about 400 PYs at doses less than 10 mg (exact fisher's two tailed; .001). While I agree that the p value in the comparison has no inferential quality since patients have not been randomized to dose, the finding is nevertheless significant.

My interpretation of the p value would be that there is strong evidence that mortality did not randomly distribute according to time at a dose. This is not to say that the drug caused such a pattern, however. As has been pointed out by others in the division, if tolerance to rivastigmine dose increased with increasing severity of disease, then there may be a "confounding by indication" in a sense. Patients most likely to die are those at increased doses not because of the drug but for other correlated factors. No evidence has been collected to speak to this issue one way or the other although Dr. Racoonin and I did examine baseline mental status score in the case control study, finding no evidence of confounding. Incidentally, all these 11 deaths have occurred after significant time at use so that it is unlikely that changes in dose is related to death if LPD reflects use.

The mortality pattern in patients in extension studies who had placebo in the RCTs is also of interest. Mortality was greatest in the lowest dose. While the rates have not been formally examined to see if mortality is highest during initial use, 3 of the 8 deaths occurred in the first month of entering the extension. In addition, there may also be an early hazard in the RCT data, although it also needs to be formally analyzed for such. While one would expect an early mortality hazard (on or off drug) in stroke, head

trauma, and other trials of acute life-threatening events, I don't see a compelling reason why one would expect such in AD studies.

The fact that there is not a dose response in patients newly exposed to the drug is not a particularly supportive that no risk exists. Titration designs that start each patient at the same dose irrespective of what the ending dose can be, can have event rates by dose that are difficult to interpret. In fact, it may not even be that unexpected that higher doses appear to have even a lower rates in short term studies.

What seems even more difficult to understand is the surprising disparity in the shape of the hazard by dose that emerges depending on whether patients have or have not had prior exposure. One explanation would be that all findings are chance although the finding in the extension patients with prior exposure is compelling. Thus, another would be that the findings the RCTs are chance and that there is confounding by indication in the extension patients with prior exposure. Another would be that there are 2 time periods of risk. One occurring during early use and the other occurring as a function of dose with long term use.

I do not see a good way of picking from among the possible explanations, and I am also sure that many more can be offered by health professionals. One could focus on the extension patients with prior exposure and evaluate that aspect of the signal, but waiting for additional data may also help by adding more experience in such patients.

There are an additional 18 deaths that have occurred in the extensions on or before June 30, 1997 that are within 30 days of last use. In Figure 1 this additional experience is represented by the shaded areas and, based upon my estimates, represents about 600-700 patients. Of these 18, 12 appear to have been in patients with prior exposure to the drug in an RCT.

Because Novartis summarized these 18 deaths in the amendment we also know their LPD. Of the 18 deaths, none are at or less than 4 mg, 9 are in the mid dose categories and 9 are at 10 or 12 mg. Of the 12 deaths that will be added to the experience of patients in extension studies who had drug in an RCT, 4 deaths are at 6 mg, 2 are at 8 mg, 1 was at 10 mg, and 5 are at 12 mg. Of course, we do not know the person-time by dose at this point.

Conclusion

In my opinion, there are 4 lines of evidence suggesting that rivastigmine use is associated with increased mortality although the association could exist because of confounding. First, there was a 2 fold excess in mortality with drug compared to placebo in the phase 2/3 studies although the statistical confidence for the relative increase was weak. Second, and requiring additional analysis for confirmation, there appears to be increased mortality with early use of rivastigmine in the RCTs. Third, there may also be increased mortality shortly after initial use in patients who had

placebo in the RCTs and then started drug in the extension. Finally, and the most compelling observation in my opinion, is that all 11 deaths in extension patients with prior exposure in the RCTs occurred at doses of 10 or 12 mg despite substantial experience at lower doses.

Recommendation

- 1) Update the database through June 30, 1997 adding the additional 18 deaths and person-time to the extension experience. I believe the sponsor has started this update.
- 2) Conduct more detailed review of the individual deaths examining the course prior to death examining any events that preceding death. Dr. Knudsen, from the division's safety team, has started this review.
- 3) More formally analyze the hazard in the RCTs and in placebo patients going to the extension studies.
- 4) I still believe that a nested case control study of the extension experience will be necessary to investigate for explanatory factors, some of which could be confounders.

Greg Burkhart, M.D., M.S.

Safety Team Leader, Neuropharmacological Drug Products, HFD-120

cc:HFD-120\Burkhart\Leber\Oliva\Levin\Racoosin\Knudsen

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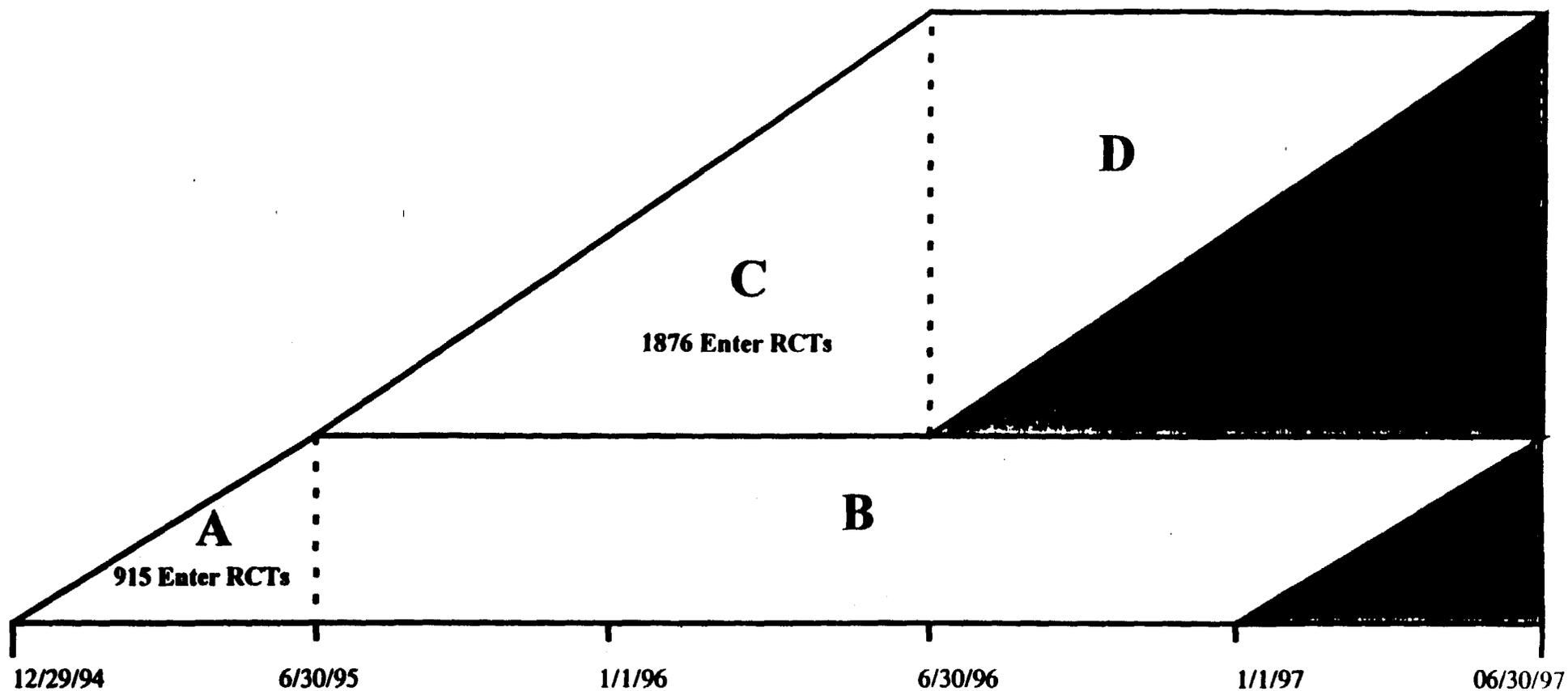


Figure 1. Theoretical Person-Time Included in the Extended Database for Patients Entering RCTs and Going to Extension. The time is theoretical since it does not account for patient dropout. Of the 2791 patients that entered an RCT (counting placebo), 915 entered before 6/30/95 with their theoretical person-time represented by Areas A + B. About 67% of patients (1876) entered after 6/30/95 but no later than 6/30/96 with their theoretical person-time represented by areas C + D. The shaded areas represent potential experience not included in the extended database. From IND safety reporting, we know there have been 18 deaths identified in the person-time represented by the shaded area essentially doubling the number of deaths in the extensions. From the data provided by Novartis in the demography file, the experience in the shaded area comes from 600-700 patients.

Table 1. Deaths and Person-time by Dose (Update Database)

<u>Dose Group</u>	<u>Deaths</u>	<u>Person Years</u>
Placebo	1	396
1 mg	1	59
1.5 mg	0	17
2 mg	1	113
2.5 mg	0	20
3 mg	0	142
3.5 mg	0	7
4 mg	2	273
4.5 mg	0	4
5 mg	2	35
6 mg	3	320
7 mg	0	39
8 mg	0	176
9 mg	3	110
10 mg	2	114
10.5 mg	0	33
12 mg	10	547

Table 2. Mortality Rate by Dose Group (Update Database)

<u>Dose Group</u>	<u>Deaths</u>	<u>Person Years</u>	<u>Rate / 1000 PYs</u>
Placebo	1	396	2.5
1-4 mg	4	630	6.3
>4-6 mg	5	631	13.9
>6-9 mg	3	324	9.2
>9 mg	12	694	17.3
ALL	25	2405	10.4

Table 3. Mortality Rates by Dose and Study Type (Update Database)

<u>Study Group</u>	<u>Dose Group</u>	<u>Deaths</u>	<u>Person Years</u>	<u>Rate / 1000 Pys</u>
RCTs	Placebo	1	396	2.5
RCTs	1-4 mg	2	377	5.3
RCTs	>4-6 mg	3	125	23.9
RCTs	>6-9 mg	0	145	0
RCTs	>9 mg	1	165	6.1
RCTs	All Doses	7	1208	5.8
<hr/>				
Titration	1-4mg	0	56	0
Titration	>4-6 mg	2	57	34.9
Titration	>6-9 mg	3	41	73.2
Titration	>9 mg	0	64	0
Titration	All Doses	5	218	22.9
<hr/>				
Extension	1- 4mg	2	198	10.1
Extension	>4-6 mg	0	176	0
Extension	>6-9 mg	0	139	0
Extension	>9 mg	11	465	23.7
Extension	All Doses	13	978	13.3

Table 4. Deaths and Person-time by Dose (Extended Database)

<u>Dose Group</u>	<u>Deaths</u>	<u>Person Years</u>
Placebo	1	396
1 mg	1	59
1.5 mg	0	17
2 mg	3	139
2.5 mg	0	20
3 mg	2	176
3.5 mg	0	7
4 mg	3	304
4.5 mg	0	4
5 mg	2	35
6 mg	5	413
7 mg	0	39
8 mg	1	220
9 mg	5	140
10 mg	3	150
10.5 mg	0	33
12 mg	12	718

The PYs comes from the grouped person-time file used by Novartis. When I construct PYs by dose from the DAR file I get slightly different numbers. For example, for 12 mg I got 714.2 PYs as opposed to 718.

Table 5. Mortality Rate by Dose Group (Extended Database)

<u>Dose Group</u>	<u>Deaths</u>	<u>Person Years</u>	<u>Rate / 1000 PYs</u>
Placebo	1	396	2.5
1-4mg	9	722	12.5
>4-6 mg	7	451	15.5
>6-9 mg	6	398	15.1
>9 mg	15	902	16.6
All	38	2869	13.2

Derived from the grouped person-time file.

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Table 6. Mortality Rates by Dose and Study Type (Extended Database)

<u>Study Group</u>	<u>Dose Group</u>	<u>Deaths</u>	<u>Person Years</u>	<u>Rate / 1000 Pys</u>
RCTs	Placebo	1	396	2.5
RCTs	1-4 mg	2	376	5.3
RCTs	>4-6 mg	3	125	23.9
RCTs	>6-9 mg	0	145	0
RCTs	>9 mg	1	165	6.1
RCTs	ALL Doses	7	1207	5.8
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Titration	1-4 mg	2	89	22.3
Titration	>4-6 mg	4	96	41.9
Titration	>6-9 mg	5	71	70.4
Titration	>9 mg	1	113	8.9
Titration	ALL Doses	12	369	32.5
<hr/>				
Extension	1-4mg	5 (5)	256 (103)	19.5 (48.5)
Extension	>4-6 mg	0 (0)	231 (87)	0 (0)
Extension	>6-9 mg	1 (1)	183 (59)	5.5 (16.9)
Extension	>9 mg	13 (2)	624 (172)	20.9 (11.6)
Extension	ALL Doses	19	1293	14.7

Derived from the grouped person-time file.

Table 7. Mortality Rates by Dose Group For 678 Patients in Extension Who Were Assigned Placebo in RCT

<u>Dose Group</u>	<u>Deaths</u>	<u>Person Years</u>	<u>Rate / 1000 PYs</u>
1-4mg	5	104	48.1
>4-6 mg	0	87	0
>6-9 mg	1	59	16.8
>9 mg	2	172	11.6
All	8	422	18.9

Derived by me from the DAR file. The PYs from Table 7 and Table 8 total to 1287 slightly different than the total of 1293 in the grouped person-time file.

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**Table 8. Mortality Rates by Dose Group for Patients in the Extension
Who Did were Assigned Rivastigmine in RCT**

<u>Dose Group</u>	<u>Deaths</u>	<u>Person Years</u>	<u>Rate / 1000 PYs</u>
1-4mg	0	151	0
>4-6 mg	0	143	0
>6-9 mg	0	122	0
>9 mg	11	449	24.5
All	11	865	12.7

Derived by me from the DAR file. The PYs from Table 7 and Table 8 total to 1287 slightly different than the total of 1293 in the grouped person-time file.

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Table 9. Summary of the 38 Deaths in the Extended Database that were Within 30 days of the Last Prescribed Dose (LPD)

30304001	Extension (Drug in RCT)	died 63 days into ext, at 12 Mg for 27 days (max in RCT was 7 mg)
30312016	Extension (Drug in RCT)	died 185 days into the ext, at 12 Mg for 129 days (max in RCT was 4 mg)
30331002	Extension (Drug in RCT)	died 531 days into the ext, at 10 Mg for 490 days (max in RCT was 9 mg)
30413013	Extension (Drug in RCT)	died 100 days into the ext, at 12 mg for 64 days (max in RCT was 12 mg)
35106045	Extension (Drug in RCT)	died 139 days into the ext, LPD was 12 mg for 102 days (max in RCT was 9 mg)
35112014	Extension (Drug in RCT)	died 438 days into the ext, LPD was 12 mg for 377 days (max in RCT was 9 mg)
35203003	Extension (Drug in RCT)	died 201 days into the ext, LPD was 10 mg for 25 days (max in RCT was 4 mg)
35203025	Extension (Drug in RCT)	died 97 days into the ext, LPD was 12 mg for 60 days (max in RCT was 4 mg)
35213004	Extension (Drug in RCT)	died 126 days into the ext, LPD was 12 mg for 66 days (max in RCT was 12 mg)
35213019	Extension (Drug in RCT)	died 138 days into the ext, LPD was 12 mg for 86 days (max in RCT was 4 mg)
35220009	Extension (Drug in RCT)	died 187 days into the ext, LPD was 10 mg for 38 days (max in RCT was 4 mg)
30302004	Extension (Placebo in RCT)	died 140 days into ext at 8 Mg for 55 days (max was 12 mg)
30342006	Extension (Placebo in RCT)	died 143 days into the ext, at 12 Mg for 108 days
30431015	Extension (Placebo in RCT)	died 113 days into the ext, LPD was 2 Mg for 52 days (max was 4 mg)
35105021	Extension (Placebo in RCT)	died 389 days into the ext, LPD was 2 Mg for 325 days (max was 6 mg)
35204022	Extension (Placebo in RCT)	died 37 days into the ext, LPD was 4 mg for 23 days (this was max)
35206021	Extension (Placebo in RCT)	died 137 days into the ext, LPD was 4 mg for 28 days, (max; 8 mg)
35211009	Extension (Placebo in RCT)	died 416 days into the ext, LPD was 2 mg for 26 days, (this was the max)
35215011	Extension (Placebo in RCT)	died 191 days into the ext, LPD was 12 mg for 124 days
30309004	RCT (Assigned Drug)	died 30 days into the RCT at 5 Mg for 2 days
30334018	RCT (Assigned Drug)	died 103 days into the RCT, at 12 Mg for 45 days
30409003	RCT (Assigned Drug)	died 118 days into the RCT, at 5 Mg for 79 days
35103011	RCT (Assigned Drug)	died 14 days into the RCT, LPD was 1 mg for 9 days, this was the max
35105003	RCT (Assigned Drug)	died 47 days into RCT, LPD was 4 Mg for 5 days
35215039	RCT (Assigned Drug)	died 24 days into the RCT, LPD was 5 mg for 7 days (this was the max)
30411001	RCT (Assigned Placebo)	died 135 days into the RCT, on placebo
35502104	Titration Study 355	died 460 days into study, LPD was 6 mg for 97 days, max was 9 mg for 13 days
35507116	Titration Study 355	died 70 days into study, LPD was 6 mg for 28 days, max was 12 mg for 5 days
35515108	Titration Study 355	died 186 days into study, LPD was 3 mg for 121 days, max was 9 mg for 37 days
35516101	Titration Study 355	died 430 days into study, LPD was 3 mg for 71 days, max was 12 mg
35516104	Titration Study 355	died 269 days into study, LPD was 9mg for 169 days, max was 12 mg
35518102	Titration Study 355	died 146 days into study, LPD was 9mg for 91 days, max was 12 mg
35522103	Titration Study 355	died 320 days into study, LPD was 9mg for 267 days, max was 12 mg
35524116	Titration Study 355	died 96 days into study, LPD was 9mg for 79 days, this was the max
35526102	Titration Study 355	died 407 days into study, LPD was 12 mg for 43 days
35528101	Titration Study 355	died 8 days into study, LPD was 3 mg for 6 days, this was max
35528121	Titration Study 355	died 44 days into study, LPD was 9 mg for 5 days, this was max
35528126	Titration Study 355	died 199 days into study, LPD was 6 mg for 191 days, this was max

RECEIVED APR 15 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS (HFD-110)
MEDICAL OFFICER'S CONSULT REVIEW

NDA 20-823

Name of Drug : EXELON (rivastigmine tartrate)

Consult Request :by Armando Oliva, MD, HFD-120

Sponsor : Novartis

Date of Consult Request: 3/10/98

Date Received: 3/16/98

Date of Review : 4/13/98

Reviewer : Sughok K. Chun, M.D.

Exelon is an acetylcholinesterase (AChE) inhibitor and is indicated for the treatment of Alzheimer's disease. Review of the cardiovascular safety data suggest that Exelon use is associated with first degree AV block. In addition, there is evidence for a dose-dependent increase in mortality with Exelon use. The reason for the increased mortality with higher doses is as yet unexplained.

According to Dr. Oliva' medical review (pages 72 to 79 of 168) :

- There were no significant mean changes from the baseline (BL) for all ECG parameters measured (PR, QRS, QTc intervals and Ventricular rate) in study B351(randomized to 4 fixed dose groups) [Table 52, page 72]. When comparing high dose to placebo, the only PR-interval prolongation (change with placebo 0.2 msec vs. with Exelon 9mg/d 2.0 msec) was noted. Similar trend was observed with studies B303 and B352 [Table 53, page 75].
In study B351 showed increased incidence of prolonged PR-intervals from BL >260 msec to ≤260 msec. seen only after treatment with Exelon
placebo 0/173, Exelon 3 mg 1/175, 6 mg 6/176; 9 mg 3/178 pts.
- I agree to the Dr. Oliva's conclusion that, although PR-intervals overall did not increase substantially, there was a subset of pts treated with Exelon experienced PR prolongation with treatment.
- ECG data of 3 cases be noted :

B351 02080 : 81 y/m, at BL had a RBBB and 1st degree AV block PR-interval 224 msec prolonged to 312 msec after 2 wks treatment with Exelon 3.5 mg/d. D/C of Exelon for 4 days PR-interval 260 msec. Pt was also on Procordia.

B304 3006 : 67 y/f, at BL PR-interval 172 msec to 204 msec (fluctuated between 186 and 204 msec) after ~6months treatment of Exelon 12 mg/d.

B353 213002 : 79 y/f, at BL RBBB and left anterior hemiblock, developed dizziness and HR 30 bpm due to 3rd degree AV block after 1 yr on Exelon 6 mg/d. Pacemaker was inserted.

COMMENTS

Exelon is an AChE inhibitor and it may augment vagal influence on the heart and result in bradycardia and prolonged SA node and AV node conduction time (PR-interval prolongation). PR-intervals vary with heart rate (longer with slower HR), daily activities, and changes of

parasympathetic tone in normal healthy subjects [Johnson RL et al.: Electrocardiographic findings in 67,375 asymptomatic individuals, Part VII. A-V block. Am.J.Cardiol. 1960:6, 153].

PR-prolongation seen in Pt#B351 02080 probably due to Exelon. The pt was on Procardia. Calcium channel blockers often prolong PR-interval specially with verapamil and diltiazem, but rarely with Procardia.; B304 3006 may be normal variation + Exelon effect; B353 213002 had bifascicular block (RBBB + left hemiblock) prior to Exelon a result of underlying cardiac disease. Pts with bifascicular block is a one of common precursor of complete AV block specially with prolongation of PR-interval. PR-interval prior to Exelon was not given this pt. Treatment with Exelon may or may not contributed to the development of 3rd degree AV block of this pt. Development of complete AV block is rather common with trifascicular block (1st degree AV block, RBBB and anterior hemiblock). Use of Exelon in the presence of sick sinus syndrome, 2nd degree and 3rd degree AV block should be listed in CONTRAINDICATIONS and bifascicular block with prolonged PR interval be listed in PRECAUTIONS.

RESPONSES TO THE QUESTIONS

Q1. Should a baseline or routine ECG monitoring be recommended for patients on Exelon ?

A: We do not recommend baseline or routine ECG monitoring to the drugs which cause some prolongation of PR interval like verapamil or diltiazem. However, Alzheimer's disease occurred mostly in the elderly population and sick sinus syndrome (bradycardia tachycardia syndrome) and coronary heart disease are common in this population that baseline ECG is necessary to detect sick sinus syndrome, AV block, and bifascicular block in this elderly population when HR is ≤ 50 bpm..

Q2. Should 1st degree AV block at BL be a contraindication to treatment ? .. or should pts with AV block be followed differently than those with normal AV conduction ?

A. No. The 1st degree AV block itself is not contraindicated. However, pts with 1st degree AV block with wide QRS may be treated with Exelon with PRECAUTION. First degree AV block associated with wide QRS complex due to RBBB, LBBB or bifascicular block is precursor of complete AV block. Frequent measurement of pulse be made in these patients. If pulse rate is < 50 bpm, ECG should be taken to detect higher degree AV block and Exelon be discontinued.

HR $\sim \leq 40$ bpm is accompanied by signs and symptoms of reduced cardiac output, syncope or presyncope, angina, and/or palpitations due to ventricular tachyarrhythmias. There is no statistic data to show how many pts with 1st degree AV block develop to 2nd or 3rd degree AV block. Many of Type II 2nd degree and lesser degree with Type I 2nd degree AV block progressed to 3rd degree AV block in pts with myocardial diseases. About 40% of pts with bifascicular block with prolonged PR interval (trifascicular block) developed 3rd degree AV block during acute myocardial infarction [Hindman MC et al.: The clinical significance of bundle branch block complicating acute myocardial infarctions for temporary and permanent pacemaker insertion. Circulation 58:689, 1978].

Exelon be **CONTRAINDICATED** patients with sick sinus syndrome, 2nd or 3rd degree AV block unless there is a functioning cardiac pacemaker in place.

Q3. It is my understanding that 1st degree AV block is in most cases benign. Some of the pts treated with Exelon exhibited marked PR prolongation. Is there a degree of PR prolongation that would require intervention ?

A : Yes. Almost all 1st degree AV block is benign. There is no safe limit of PR interval defined. Normal PR interval is defined as ≤ 200 msec or ≤ 240 msec. Three out of 1000 healthy aircrew applicants had PR interval ≥ 240 msec.

**APPEARS THIS WAY
ON ORIGINAL**

cc: Original
cc: HFD-110
cc: HFD-110 Project Manager
cc: HFD-110 GanleyC
cc: HFD-110 ChunS

From: (OLIVAA)
Date: 4/03/1998 10:48 AM
To: 1 Charles Ganley
Subject: Exelon Exclusion Criteria



Here's the information that I didn't have earlier:

Exclusion Criteria for cardiovascular disease were similar for all phase 3 studies. The exact wording is as follows:

unstable, severe or clinically significant cardiovascular disease such as myocardial infarction within the previous 6 months, unstable angina pectoris, cardiac failure of NYHA functional class II or more or second or third degree atrioventricular (AV) block.

There is no specific exclusion criterion for a specific ECG abnormalities, and certainly not for 1st degree AV block.

Let me know if there's any other info you might need.

Thanks
Armando

**APPEARS THIS WAY
ON ORIGINAL**

Review of Clinical Data
May 12, 1998 Amendment Updating the Mortality Experience
with Rivastigmine Through June 30, 1997

NDA: 20-823

Sponsor: Novartis

Drug: Rivastigmine

Route of Administration: Oral

Reviewer: Greg Burkhart, M.D., M.S.

Review Completion Date: May 28, 1998

This memorandum reviews the mortality experience in the rivastigmine NDA development program that has been captured through June 30, 1997. This additional follow-up substantially expands the overall experience for the 3162 patients with exposure to rivastigmine, but does not add any additional patients.

In a March 26, 1998 review of the March 9 amendment to the NDA, I provided some background to this issue as well as an overview of the experience from the rivastigmine development program that has been captured in the safety updates. In it, I also summarized the findings that have lead to a concern about rivastigmine's capacity to cause death as a consequence of its use. While I will provide some details about the methods used to compute the person-time and to analyze the data, the reader may still want to read the March 28 memorandum first since much of the context of current review depends upon the findings in the March 28 review.

Methods of Review

Both myself and the sponsor have computed person-time by prescribed dose using the primary data collected by the sponsor on the CRFs and then entered into a computerized dataset. This dataset contains multiple rows of data for each patient with each row having beginning and ending dates for the prescribed dose for the corresponding interval of time. The first date in the first row of each patient's data is the study start date while the latest date in the last row was the last day of exposure for that patient either representing the update date, death date, or end of study date.

By subtracting the dose interval dates on each row (adding a day since the last date was represented a full day of use by definition), person-time was computed for each dose and then summed across the population according to age, gender, dose, study number and

time since starting a study. The computations of the person-time by myself and the sponsor resulting in similar totals although they vary by a few years.

As before, the death date and other demographic variables are contained in a separate demographic file. All analyses conducted to date have focused on deaths occurring within 30 days of last use. In this memorandum, I also analyzed deaths within 7 days.

While the sponsor did not provide a discussion of any methods they used to QA the primary data, the error that I identified in the prior submission (patient 35211009) has now been corrected. Although I examined some patient data records (maybe 20) and found no logical errors in the data as they had been entered, I did not make a systematic evaluation of the primary dataset nor have I compared the entered data with that on patient CRFs.

Both myself and sponsor used similar methods to analyze the data. Tabular displays were used to visually examine mortality patterns. To evaluate the mortality rates as a function of dose, age, sex, study and time since study entry (TSSE), we each used poisson regression. I used the poisson regression module of the Epicure software package while the sponsor used the SAS module.

The variable TSSE was defined differently by the sponsor and myself. They focused on a dichotomous definition split at 100 days and I looked at 4 levels in some cases. This becomes important when considering the sponsor's argument that TSSE is a confounding factor. While I had suggested using a 100 day cut to the sponsor, it was not my intention to be rigid in that definition if there was a need to really check the hazard over time which has become an issue for these data. Thus, I decided that a dichotomous split was not adequate

The sponsor's submission summarized their analysis of the data showing the findings for the phase 2 and 3 RCTs separately, the "titration" studies¹, and the RCT extensions, and also on the full phase 3 database. I focused principally on the RCT extension database although I had checked the RCTs and "titration" studies for an "early" hazard after the March 26 memorandum.

To evaluate whether a variable and/or an interaction between variables was a "significant" predictor of mortality, I used likelihood ratio testing of two hierarchical models where the second model with the variable or interaction was compared to the previous model containing all variables but the variable or interaction of interest. I am not sure what the sponsor did to address this issue, but they appeared to have focused on the wald test for individual variables which is not helpful for evaluating the statistical evidence for interaction.

¹ The open label titration studies used a faster titration schedule. All phase studies administered the drug with some schedule of titration so referring to these open label studies as "titration" studies is somewhat misleading.

Of course, once we leave the comparison between overall drug group with placebo, the p values have no probabilistic interpretation since patients have not been randomly assigned to an ending dose. In addition, I do not consider p values generated from LRTs to have any strict probabilistic interpretation even if the data were generated using randomized assignment. Thus, the statistical results that are discussed and displayed are useful only for descriptive purposes helping to determine what is the best description, if there is one, of the mortality pattern that was observed. In general, the interpretation of any signal must be based upon the size of the effect given the sample size and data quality, and not so much the p value.

Overall Experience across the Phase 3 studies

Novartis's Table 12 on page 32 of their submission summarizes the updated experience separately for the RCTs, "titration" studies and RCT extensions.² To get the overall deaths, PYRs and mortality rates by dose group across the phase 3 program, I pooled the data from Novartis's table 12.

As shown in Table 1, there are now 56 deaths in about 3629 person-years (PYRs) of use with rivastigmine with the dose group for 10/12 mg having the highest mortality rate. As in the March submission, the sponsor is still placing the 4 mg experience in the second dose group although, as pointed out to me by Novartis and other members of the review team, 4 mg was included in the lowest dose group during randomization. Since this was a minor issue in my opinion with the findings not dependent on such classification, I did not re-compute across the full database.

From Novartis's Table 12, we can also see that 990.6 person-years of the 1290.3 total for 10/12 mg is coming from extension experience (76.7%). In addition, about 56% of the overall experience at 10/12 mg is coming from RCT extensions in patients who had prior exposure to drug in the RCT. Thus, the overall safety of these upper doses is heavily dependent on RCT extension experience.

Overall, the RCT experience has not changed from prior updates and there has been some additional experience added from the open-label titration studies, but the mortality rates in the "titration" studies have not changed a great deal. (I show the RCT rates by time in the discussion section.)

As before, the open label "titration" studies still appear to have materially greater mortality than the RCTs or RCT extensions. Within the "titration" studies, the mid dose groups still have the greatest mortality. The sponsor continues to state that patients entered into the "titration" studies were sicker at baseline although no evidence is presented to make this case.

² I have included the sponsor's tables that I refer to at the end of the memorandum.

As a reminder, the fact that the "titration" studies administered the drug more rapidly has raised some concern. However, I would generally expect that if more rapid titration was correlated with increased mortality, then we should have observed increased mortality early in the study corresponding somewhat with the titration period. However, as can be seen from the sponsor's Table 14, there is no evidence of an early hazard in these studies. Thus, if there is a signal from these "titration" studies, I doubt that is secondary to a faster titration schedule.

RCT Extension Experience Updated Through June 30, 1997

As shown in the sponsor's Table 12, we now have 35 deaths observed in about 1986 PYRs of extension experience substantially increasing the overall experience. The "extended database" in the March 9 update had 19 deaths in 1293 PYRs of extension experience.

Table 2 shows mortality rates for RCT experience and RCT extension experience for patients assigned placebo and drug in the RCTs. For the 680 patients in RCT extensions who had placebo in an RCT, the mortality was 8 fold greater than the placebo mortality rate in RCTs (20.3 compared to 2.5 to per 1000 PYRs). For the 1330 extension patients who had drug in the RCT, their mortality was about 2 fold higher than drug mortality in the RCT (16.3 compared to 7.5 to per 1000 PYRs).

Table 3 shows the mortality rates and 95% CIs by dose group for the RCT extensions irrespective of assignment in the RCT. As before, the largest mortality rate is in the 10/12 mg dose group. The lowest dose group has a similar rate, but it is based upon more sparse data as reflected by the wider CI. The LRT for the dose variable suggested that there was little, if any, evidence that the mortality rates varied by dose group level ($p = .20$).³

Table 3A shows rates by dose group when only deaths within 7 days of last dose are used in the numerator. There is no material change in the relative relationship although the numbers are quite small. While not shown, it is also true that deaths between 7-30 days after the last dose, generally follow the same pattern. Thus, even if an analysis focused on sudden deaths that occur on drug, one may be excluding a good part of the signal.

Table 4 shows the rates by age, sex, and assignment in RCT. Other than the rates increasing with age, there was no material difference between males and females, and between patients who were assigned drug or placebo in an RCT.

Tables 5 and 6 show the rates by dose group for patients in extension assigned either drug or placebo in the RCT, respectively. In my opinion, the mortality patterns are

³ This is not a test for "trend" but just asking the question whether dose as defined, adds anything to predicting mortality. If the 2nd level had a much higher rate than the others, the dose variable may have explained a lot of the deviance and hence had a compelling LRT. Testing for trend would ask a different question.

different between tables 5 and 6 with the 10/12 mg dose group having about a 3 fold increase in mortality compared to lower doses in extension patients who had been assigned drug in an RCT. There was little difference by dose group in extension patients who had been assigned placebo in an RCT.

To statistically evaluate this apparent difference in mortality depending on whether a patient had prior exposure to drug in an RCT, I used the full extension data set and fit the following terms.

Mortality rate = Dose + Prior Exposure;

where dose was categorized into the 4 levels already defined and prior exposure was coded as yes/no. "No" meaning the patient had placebo in the RCT.

I then fit another model with the following terms and compared the deviance from it to the previous model using the LRT.

Mortality rate = Dose + Prior Exposure + Dose*Prior Exposure.

The p value for the LRT comparing the two models was 0.10 suggesting that there was some evidence that the mortality rates varied by dose level depending on whether patients had been assigned drug or placebo in the RCTs. From Table 5 and the fact that the dose variable was somewhat predictive of mortality in Table 5 but not Table 6, we know this effect was due to patients with prior exposure in RCTs. Tables 5A and 6A show the rates when only deaths within 7 days are used and there appears to be little change in the patterns although the data are sparse.

Table 7 collapses the dose group so that we can compare the 10/12 mg dose group with all lower doses. Although there is a slight increase in the high dose group compared to lower doses in patients assigned placebo in the RCTs, the difference is 3 fold greater in the 10/12 mg group in patients with prior exposure to drug in RCTs. The LRT of the dose variable in the extensions patients that had prior drug exposure provided moderate degree of statistical evidence that the dose group (now with two levels) with 10/12 mg had a higher rate (p = 0.02)

When I fit the same two models that were shown above for the full RCT extension dataset with the dose variable was now collapsed to the high and lower dose groups, the p value for the LRT was 0.20 suggesting that there was less evidence that the pattern of mortality across the 2 doses varied as a function of prior exposure to drug in the RCTs. This is not too surprising since there is an numerical increase from the lower doses to the 10/12 mg dose group in both subgroups, and hence, less evidence of variation when considering prior exposure in the RCTs.

Tables 8-11 focus on the argument put forth by the sponsor that the apparent increase in mortality at 10/12 mg is due to confounding (my term) by TSSE. In Novartis's

submission, they stratified the data at 100 days showing that the rates increase after the first 100 days. As shown in Tables 7 and 9, however, it is clear that the rates do not increase indefinitely and in fact appear to fall somewhat later in follow-up with the largest mortality observed from days 61-180.

The sponsor's argument was that since patients take a while to get to high dose and since mortality is also increasing with time, then high dose appears to have increased mortality because of time (TSSE). However, since mortality rate does not increase with time, it would seem very unlikely that TSSE could be confounding the apparent increase in mortality with 10/12 mg. Table 12 goes on to show that there is no statistical evidence of confounding by TSSE or age/sex on the rate ratios.

Discussion

In my opinion, weighing all lines of evidence, I think there is a *moderate* signal of concern in the rivastigmine NDA mortality experience. However the signal is far from clear cut and there is no one finding that conclusively shows that the drug caused events resulting in death. In fact, we have not been able to identify a specific cause of death that appears to be associated with use of the drug. Dr. Oliva's 5/28/98 review updates the mortality table so that all 56 deaths in the phase 3 studies that have been included in this analysis are listed. We have carefully reviewed the information provided on these deaths and other than the concern that has already been expressed about body weight, no striking clinical event associated with death was found.

Certainly the finding of a highly specific cause of death, such as aplastic anemia, that was clearly associated with use of the drug would provide compelling evidence of risk. Even a dose response for SUDs could be compelling even though SUDs is clinically nonspecific. However, the absence of a cause to explain the increase does not mean that the drug is free of risk. In fact, in an elderly population where deaths are expected to some extent, it is easy to envision the difficulties of finding an explanatory cause, and like most development programs, this one has not been designed to formally evaluate causes of death. Thus, I don't think the absence of a clear cause means there is no signal of concern. Perhaps, one could conduct an analysis where deaths that clearly can't be associated with drug could be excluded, but even this type of analysis can be difficult.

What lines of evidence contribute to the signal? First, in the phase 3 RCTs, the mortality rate was about 3 fold greater on drug compared to placebo; 7.3 per 1000 PYRs (6 deaths in 805 PYRs) compared to 2.5 per 1000 PYRs (1 death in 396 PYRs). However, the statistical evidence of an increase was weak ($p=.26$, Fishers exact⁴). In fact, given the extensive degree of experience in the extensions, I don't think most reviewers would have

⁴ The sponsor raised concern about the appropriateness of Fisher's exact test for person-time data. In theory, I agree with their argument. However, so long as time is in person-years, their concern is of little practical benefit particularly when the number of person-years is not that different than the number of patients. Of course, changing person-years to person-seconds would dramatically affect the p value obtained using Fisher's exact.

been alarmed by the RCT finding given no additional evidence suggesting concern, and with no clear specific cause of death in the RCTs.

There is also some evidence of an early hazard in the RCTs, but I don't think it adds much to the signal. In the patients assigned drug in the RCTs, 3 of the 6 deaths occurred in the first 30 days giving a rate of 19.4 per 1000 PYRs (3/154.3 PYRs) compared to a rate of 4.6 per 1000 PYRs after the first 30 days (3/651.3). While one would expect an "early hazard" in studies of acute disease states like stroke and head trauma, there is no reason to expect it with AD studies that I know of. While the observation is based upon a small amount of data, the "p" value reflecting time stratified at 30 days is 0.08. My interpretation would be that there is weak evidence of an early hazard, but given "all the looks", the p value would have had to be much smaller to be compelling. In addition, there was no evidence of earlier mortality in the open label "titration" studies even though they used a more rapid titration. Likewise, there was no evidence of earlier mortality in placebo patients switched to drug in the RCT extensions. Since there was one death in the placebo portion and 680 of 805 went on to the extensions, its hard to see how "susceptible" patients would have been removed from that subgroup of patients.

The fact there was no evidence of hazard in the placebo patients who went into the extensions does not necessarily mean, however that this extension experience of patients switched from placebo was not suggestive of risk. Overall, there were 13 deaths in 641 PYRs of experience on drug in the 680 patients who entered extensions who were assigned placebo in the RCTs giving a rate of 20.3 per 1000 PYRs. Recall that there was 1 death in 396 PYRs for the 868 patients assigned placebo in the RCTs and that the RCT length was about 182 days. From Table 5, most of the follow-up in the extensions for these patients is in the first year after entering the extension. Thus, from the first 6 months to the next year of follow-up, the mortality rate has jumped about 8 fold peaking several months after drug was started. The mortality in these patients was falls after 180 days of extension experience.

While the apparent increase in mortality in patients assigned placebo in RCTs in the extensions follows initiation of the drug, there was also an increase in mortality in the extensions for patients assigned drug in the RCTs from 7.5 per 1000 PYRs to 16.3 per 1000 PYRs, but much of this increase is secondary to increased mortality in the high dose group which is third aspect of the signal. As in Table 5, the mortality rate also peaks before 180 days and appears to decline thereafter.

Thus, in my opinion, the apparent increase in mortality in placebo patients switched to drug in the extension is of concern. The sponsor has argued that the placebo experience in the RCTs was much lower than it should have been. It is certainly true that both of the first two aspects of the signal, which were described above, depend upon the RCT placebo experience. If 5 deaths would have been observed rather than 1, I don't think these two aspects of the signal would have been relevant, although the 3rd part described next would still be an issue. But, how could we ever know what the placebo experience "should have been". Perhaps, it is bad luck, but I don't see how we can dismiss these two

aspects of the signal because only 1 death was observed with placebo especially since there was almost 400 PYRs of placebo experience.

Finally, the 3 fold increase in mortality in the 10/12 mg dose group compared to lower doses in patients with prior exposure in RCTs is a compelling finding with some statistical support. While the sponsor has argued that this increase is secondary to time which I interpret to mean that it is confounded by TSSE, I can find no evidence of such confounding. While the open label "titration studies" and RCTs do not show a higher rates for the 10/12 mg experience, the overall experience in these studies at higher doses was relatively small. In my opinion, we would still have a signal of concern even if this was the only finding since 56% of our experience with 10/12 mg is coming from patients in RCT extensions with prior exposure.

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Conclusion

In summary, as I consider the phase 3 data, I find the mortality experience perplexing and somewhat confusing. However, when I consider (1) the increase in mortality on drug in the RCTs, (2) the increase in patients switched from placebo to drug in RCT extensions and (3) the increase in the 10/12 mg dose group in patients in RCT extensions who had drug in the RCT, I find the mortality experience in total to constitute a *moderate* signal of concern.

Recommendation

I don't believe that additional follow-up is going to eliminate the concern that we have although trying to investigate the effect of other factors on mortality would be helpful. While the nested case-control study found that dose per baseline body weight was a better predictor of mortality than dose alone, this issue has not been investigated any further in the updates. The deaths that happened on high dose, as shown in Dr. Oliva 05/28/98 review, seem to have more weight loss. As I suggested before, conducting a case-control study to evaluate many patient factors where the controls are selected based upon person-time, may be helpful in understanding the mortality patterns that have been observed.

However, to resolve the issue, I believe Novartis will have to conduct a large randomized study. One could randomly assign patients to 4 groups; 2 groups with rivastigmine titrated to 6 mg and 12 mg, two dose groups of Aricept. Of course, if all cholinesterase inhibitors cause increased mortality without showing a dose response, this design would miss it, since there is no placebo. Such a study need not be double blinded and could focus entirely on mortality. Of course, the panel reviewing deaths needs to be blinded to drug assignment and needs to evaluate the data in real time.

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Table 1. Mortality Rates by Dose Group Across the Phase 3 Studies Through June 30, 1997

<u>Dose Group</u>	<u>Deaths</u>	<u>PYRs</u>	<u>Rate per 1000 PYRs</u>
Placebo	1	396.1	2.5
1-<4*	6	456.1	13.1
4-6	15	972.7	15.4
>6-9	8	514.0	15.6
>9	26	1290.3	20.1

*Note that the 4 mg dose is in the lowest category.

Table 2. Mortality Rates (per 1000 PYRs) for Patients in RCTs and RCT Extensions by Assignment in the RCT

	<u>Patients</u>	<u>PYRs</u>	<u>Deaths</u>	<u>Mortality Rate</u>
RCTs	2791	1191	7	5.9
Placebo	868	396	1	2.5
Drug	1923	805	6	7.5
RCT Extensions*	2010	1988	35	17.6
Placebo in RCT	680 of 868 (78%)	641	13	20.3
Drug in RCT	1330 of 1923 (69%)	1347	22	16.3

*All extension patients received drug.

Table 3. Mortality Rates by Dose Group for All Patients Entering RCT Extensions (95% CI)

<u>Dose Group</u>	<u>PYRs</u>	<u>Deaths</u>	<u>Rate per 1000 PYRs</u>
1-4 mg	135	3	22.2 (7.1,68.7)
5-6 mg	577	6	10.4 (4.7,23.1)
7-9 mg	285	3	10.5 (3.4,32.6)
10-12 mg	991	23	23.2 (15.4, 34.9)

Note: The LRT for the variable "dose group" had a p value of 0.20.

Table 3A. Mortality Rates by Dose Group for All Patients In An RCT Extension Using Deaths that were within 7 Days of the Last Dose

<u>Dose Group</u>	<u>PYRs</u>	<u>Deaths</u>	<u>Rate per 1000 PYRs</u>
1-4 mg	135	1	7.4
5-6 mg	577	2	3.5
7-9 mg	285	3	10.5
10-12 mg	991	14	14.1

Note: The LRT for the variable "dose group" had a p value of 0.18.