Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897-908. DOI: 10.1056/NEJMoa1102673.

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Credit Roster for the Comparison of AMD Treatments Trials

Clinical Centers (Ordered by Number of Patients Enrolled)

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Elman Retina Group, P.A. (Baltimore, MD): Michael Elman, MD (PI); Tammy Butcher (CC); Theresa Cain (OP/OCT); Teresa Coffey, COA (VA/R); Dena Firestone (VA/R); Nancy Gore (VA/R); Pamela Singletary (VA/R); Peter Sotirakos (OP/OCT); JoAnn Starr (CC).

University of North Carolina at Chapel Hill (Chapel Hill, NC): Travis A. Meredith, MD (PI); Cassandra J. Barnhart, MPH (CC/VA/R); Debra Cantrell, COA (VA/R/OP/OCT); RonaLyn Esquejo-Leon (OP/OCT); Odette Houghton, MD (O); Harpreet Kaur (VA/R); Fatoumatta NDure, COA (CC).

Ophthalmologists Enrolling Patients but No Longer Affiliated with a CATT Center: Ronald Glatzer, MD (O); Leonard Joffe, MD (O); Reid Schindler, MD (O).

Resource Centers

Chairman's Office (Cleveland Clinic, Cleveland, OH): Daniel F. Martin, MD (Chair); Stuart L. Fine, MD (Vice-Chair; University of Colorado, Denver CO); Marilyn Katz (Executive Assistant).

Coordinating Center (University of Pennsylvania, Philadelphia, PA): Maureen G. Maguire, PhD (PI); Mary Brightwell-Arnold, SCP (Systems Analyst); Ruchira Glaser, MD (Medical Monitor); Judith Hall (Protocol Monitor); Sandra Harkins (Staff Assistant); Jiayan Huang, MS (Biostatistician); Alexander Khvatov, MS (Systems Analyst); Kathy McWilliams, CCRP (Protocol Monitor); Susan K. Nolte (Protocol Monitor); Ellen Peskin, MA, CCRP (Project Director); Maxwell Pistilli, MS, MEd (Biostatistician); Susan Ryan (Financial Administrator); Allison Schnader (Administrative Coordinator); Gui-shuang Ying, PhD (Senior Biostatistician).

OCT Reading Center (Duke University, Durham, NC): Glenn Jaffe, MD (PI); Jennifer Afrani-Sakyi (CATT PowerPoint Presentations); Brannon Balsley (OCT Technician Certifications); Linda S. Bennett (Project Manager); Adam Brooks (Reader/SD-Reader); Adrienne Brower-Lingsch (Reader); Lori Bruce (Data Verification); Russell Burns (Senior Technical Analyst/Senior Reader/SD Reader/OCT Technician Certifications); Dee Busian (Reader); John Choong (Reader); Lindsey Cloaninger (Reader Reliability Studies/ Document Creation/CATT PPT Files); Francis Char DeCroos (Research Associate); Emily DuBois (Data Entry); Mays El-Dairi (Reader/SD-Reader); Sarah Gach (Reader); Katelyn Hall (Reader Reliability Studies/ Data Verification/Document Creation); Terry Hawks (Reader); ChengChenh Huang (Reader); Cindy Heydary (Senior Reader/Quality Assurance Coordinator/SD Reader/Data Verification); Alexander Ho (Reader, Transcription); Shashi Kini (Data Entry/Transcription); Michelle McCall (Data Verification); Daaimah Muhammad (Reader Feedback); Jayne Nicholson (Data Verification); Jeanne Queen (Reader/SD-Reader); Pamela Rieves (Transcription); Kelly Shields (Senior Reader); Cindy Skalak (Reader); Adam Specker (Reader); Sandra Stinnett (Biostatistician); Sujatha Subramaniam (Reader); Patrick Tenbrink (Reader); Cynthia Toth, MD (Director of Grading); Aaron Towe (Reader); Kimberly Welch (Data Verification); Natasha Williams (Data Verification); Katrina Winter (Senior Reader); Ellen Young (Senior Project Manager).

Fundus Photograph Reading Center (University of Pennsylvania, Philadelphia, PA): Juan E. Grunwald, MD (PI); Judith Alexander (Director); Ebenezer Daniel, MBBS, MS, MPH, PhD (Director); Elisabeth Flannagan (Administrative Coordinator); E. Revell Martin (Reader); Candace Parker (Reader); Krista Sepielli (Reader); Tom Shannon (Systems Analyst); Claressa Whearry (Data Coordinator).

National Eye Institute, National Institutes of Health: Maryann Redford, DDS, MPH (Program Officer).

Committees

Executive Committee: Daniel F. Martin, MD (chair); Robert L. Avery, MD; Sophie J. Bakri, MD; Ebenezer Daniel, MBBS, MS, MPH; Stuart L. Fine, MD; Juan E. Grunwald, MD; Glenn Jaffe, MD, Marcia R. Kopfer, BS, COT; Maureen G. Maguire, PhD; Travis A. Meredith, MD; Ellen Peskin, MA, CCRP; Maryann Redford, DDS, MPH; David F. Williams, MD.

Operations Committee: Daniel F. Martin, MD (chair); Linda S. Bennett; Ebenezer Daniel, MBBS, MS, MPH; Frederick L. Ferris III, MD; Stuart L. Fine, MD; Juan E. Grunwald, MD; Glenn Jaffe, MD; Maureen G. Maguire, PhD; Ellen Peskin, MA, CCRP; Maryann Redford, DDS, MPH; Cynthia Toth, MD.

Clinic Monitoring Committee: Ellen Peskin, MA, CCRP (chair); Mary Brightwell-Arnold, SCP; Joan DuPont; Maureen G. Maguire, PhD; Kathy McWilliams, CCRP; Susan K. Nolte.

Data and Safety Monitoring Committee: Lawrence M. Friedman, MD (chair); Susan B. Bressler, MD; David L. DeMets, PhD; Martin Friedlander, MD, PhD; Mark W. Johnson, MD; Anne Lindblad, PhD; Douglas W. Losordo, MD, FACC; Franklin G. Miller, PhD.

Supplementary Material from Main Paper Table 1.
Baseline Characteristics by Treatment Group

Characteristic	Ranibizumab Monthly N=301		Bevacizumab Monthly N=286		Ranibizumab PRN N=298		Bevacizumab PRN N=300	
Lesion type- no. (%)								
Predominantly classic	70	(23.3)	55	(19.2)	67	(22.5)	71	(23.7)
Minimally classic	40	(13.3)	41	(14.3)	34	(11.4)	39	(13.0)
Occult only	137	(45.5)	138	(48.3)	138	(46.3)	126	(42.0)
RAP**	29	(9.6)	28	(9.8)	31	(10.4)	35	(11.7)
>50% hemorrhage	21	(7.0)	17	(5.9)	23	(7.7)	23	(7.7)
Can't grade/no lesion	4	(1.3)	7	(2.4)	5	(1.7)	6	(2.0)
Area of neovascularization, disc areas†								
Mean (SD)	1.9	(1.8)	1.7	(1.8)	1.9	(1.8)	1.6	(1.6)
Area of lesion, disc areas‡								
Mean (SD)	2.6	(2.8)	2.5	(2.6)	2.5	(2.4)	2.3	(2.2)
All eligibility criteria met - no. (%)								
Yes	291	(96.7)	274	(95.8)	286	(96.0)	292	(97.3)
No	10	(3.3)	12	(4.2)	12	(4.0)	8	(2.7)

**Retinal angiomatous proliferation

†Number in each group that could not be measured : 36, 38, 35, 32

‡Number in each group that could not be measured : 8,15,10,14

Treatment Group Codes Used in CATT Tables

- Treatment group codes are used in most CATT tables

  1 = Ranibizumab Monthly

  2 = Bevacizumab Monthly

  3 = Ranibizumab PRN

  4 = Bevacizumab PRN

Baseline Medical History by Treatment Groups

(as of December 31, 2010)

	Treatment Group								
	1 (N=301)		2 (N=286)		3 (N=298)		4 (N=300)		
Medical Condition	n	%	n	%	n	%	n	%	p-value
MI (heart attack)	34	(11.3)	40	(14.0)	30	(10.1)	36	(12.0)	0.53
Congestive heart failure	23	(7.6)	12	(4.2)	12	(4.0)	26	(8.7)	0.03
Stroke	14	(4.7)	18	(6.3)	22	(7.4)	16	(5.3)	0.52
TIA	12	(4.0)	25	(8.7)	12	(4.0)	19	(6.3)	0.05
Breast cancer	28	(9.3)	26	(9.1)	21	(7.0)	22	(7.3)	0.66
Colorectal cancer	10	(3.3)	10	(3.5)	15	(5.0)	8	(2.7)	0.48
Prostate cancer	18	(6.0)	23	(8.0)	19	(6.4)	21	(7.0)	0.77
Lung cancer	4	(1.3)	5	(1.7)	3	(1.0)	5	(1.7)	0.88
Other cancer	75	(24.9)	61	(21.3)	72	(24.2)	62	(20.7)	0.53
Angina/chest pain/discomfort	24	(8.0)	25	(8.7)	33	(11.1)	32	(10.7)	0.51
Arrhythmia/irregular heart beat	50	(16.6)	52	(18.2)	59	(19.8)	67	(22.3)	0.33
Palpitations	23	(7.6)	17	(5.9)	33	(11.1)	34	(11.3)	0.06
Hypertension (high blood pressure)	194	(64.5)	182	(63.6)	190	(63.8)	213	(71.0)	0.17
Shortness of breath	74	(24.6)	54	(18.9)	68	(22.8)	72	(24.0)	0.34
Heart murmur	27	(9.0)	25	(8.7)	32	(10.7)	27	(9.0)	0.84
Poor circulation to feet/legs	51	(16.9)	48	(16.8)	42	(14.1)	48	(16.0)	0.77
Hypercholesterolemia (high cholesterol)	167	(55.5)	159	(55.6)	167	(56.0)	178	(59.3)	0.75
Hypertriglyceridemia (excess fatty acids in the blood)	39	(13.0)	44	(15.4)	32	(10.7)	40	(13.3)	0.43
Phlebitis	11	(3.7)	11	(3.8)	16	(5.4)	17	(5.7)	0.55
Pneumonia	66	(21.9)	40	(14.0)	44	(14.8)	53	(17.7)	0.05
Asthma	32	(10.6)	31	(10.8)	31	(10.4)	29	(9.7)	0.97
Emphysema	17	(5.6)	16	(5.6)	15	(5.0)	22	(7.3)	0.67
Fractures/dislocations	77	(25.6)	81	(28.3)	66	(22.1)	75	(25.0)	0.40
Osteoarthritis	138	(45.8)	132	(46.2)	148	(49.7)	136	(45.3)	0.71

Adverse Event Reporting and Coding in CATT

- The definitions of adverse event and serious adverse events are those specified by the Food and Drug Administration (FDA) in 21 CFR 312. As stated in the CATT Manual of Operations, Chapter 6

  An **adverse event** (AE) is the development or worsening of any symptom, sign, illness or experience that is temporally associated with a protocol mandated intervention, regardless of causality. These include AEs that emerge during the reporting period that were not previously observed in the patient, complications that occur as a result of protocol-mandated interventions or preexisting medical conditions that are judged by the investigator to have worsened in severity or frequency, or have changed in character during the adverse event reporting period.

  Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

  - fatal
  - life-threatening
  - requires or prolongs inpatient hospital stay
  - results in persistent or significant disability or incapacity
  - a congenital anomaly or birth defect in a neonate or infant born to a mother exposed to the investigational product
  - considered by the investigator to be an important medical event (e.g., events that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the patient, and may require intervention to prevent one of the other serious outcomes noted above.)

- At each follow-up visit (every 28 days), the clinic coordinator asks the patient a series of questions about their health. The questions are noted below. If the answer to any of these questions is "yes", the patient asks the patient additional questions about the event and completes case report forms on adverse events.

  - "Since your most recent CATT visit, have you had any new symptoms, injuries, illness or side effects or worsening of pre-existing conditions?"
  - "Since your most recent CATT visit, have you had any hospitalizations?"
  - "Since your last treatment, have you had any pain in the study eye?"
  - "Other than localized redness at the injection site, have you had any new or unusual redness in the study eye since your last treatment?"

- Adverse events in CATT are coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. The MedDRA system provides a hierarchy of classifications for each adverse event:

  System Organ Class (SOC)

High-Level Group Term (HLGT)
High-Level Term (HLT)
Preferred Term (PT)
Lower Level Term (LLT)

- Adverse events are categorized into severity level with the following descriptors:

  1 Mild, little clinical significance
  2 Moderate, causing some limitation; minimal/no intervention required
  3 Severe
  4 Life-threatening or disabling
  5 Death

- CATT Coordinators select a Preferred Term or Lower Level Term matching the patient's description of the event and a severity level from an online, interactive database provided by the National Cancer Institute (Common Terminology Criteria for Adverse Events, v3 http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx). Only selected MedDRA codes are available within the CTC database and are particularly limited for ophthalmic events. A supplemental list of common ophthalmic events and codes are available on the CATT data management website and CATT coordinators call the Coordinating Center if a systemic or ocular code that matches the event is not available in the online database. Coordinating Center staff members have access to the full MedDRA set of codes.

- Serious adverse events receive special handling. Coordinators complete a Serious Adverse Event form and fax it to the Coordinating Center. The Project Director oversees the compilation of the patient's baseline medical history, baseline and current medications, intercurrent adverse events, treatment history, and any additional medical reports accompanying the Serious Adverse Event form. These materials are emailed to the CATT Medical Monitor, who is a cardiologist with experience as a medical monitor for clinical trials. The Medical Monitor reviews the materials, may ask for additional information, and changes the MedDRA code, severity, and/or attribution if the information provided is inconsistent with the original coding by the clinical coordinator or investigator.

- Prior to the initiation of the Lucentis-Avastin Trial, CATT leaders suggested using the Anti-Platelet Trialists Collaboration (APTC) definition of vascular event and vascular death. The definitions are:

  "vascular events, defined as non-fatal myocardial infarctions, non-fatal strokes, or vascular deaths." Outcome events were to be counted as "non-fatal" only if the patient subsequently survived to the end of the study treatment period scheduled for that patient: otherwise, only the death was to be counted.

Survivors could have suffered more than one type of non-fatal event. Causes of death were subdivided into "non-vascular" (that is, definitely non-vascular) and "vascular" (that is, definitely or possibly vascular, which includes all deaths attributed to cardiac, cerebral, haemorrhagic, embolic, other vascular, or unknown causes). Myocardial infarctions and strokes were to be counted if the investigator considered them to be either probable or definite. Transient ischaemic attacks (in brain or eye), angina, and "possible" myocardial infarctions or strokes were not to be counted as outcomes. Strokes (including subarachnoid haemorrhages) were to be counted only if symptoms persisted for at least 24 hours, and were subdivided into haemorrhagic (including those of "probably" haemorrhagic aetiology) and other (including those of probably ischaemic or of unknown aetiology)."

- The preferred terms for ocular adverse events have been grouped into 29 categories (see page the following 2 pages).

Ocular Adverse Event Categories

1. Endophthalmitis
ENDOPHTHALMITIS

2. Ocular Vessel Embolism or Occlusion
OPTIC ISCHAEMIC NEUROPATHY
RETINAL ARTERY EMBOLISM
RETINAL ARTERY OCCLUSION
RETINAL VEIN OCCLUSION

3. Uveitis, Scleritis, and Anterior Chamber Inflammation
ANTERIOR CHAMBER DISORDER
ANTERIOR CHAMBER FLARE
ANTERIOR CHAMBER INFLAMMATION
EPISCLERITIS
EYE INFLAMMATION
IRIDOCYCLITIS
IRITIS
UVEITIS

4. Detachment of the Retinal Pigment Epithelium or Choroid
DETACHMENT OF RETINAL PIGMENT EPITHELIUM

5. Macular Degeneration
CHOROIDAL NEOVASCULARISATION
MACULAR DEGENERATION

6. Retinal Tear
RETINAL TEAR

7. Retinal and Choroidal Hemorrhage
CHOROIDAL HAEMORRHAGE
RETINAL HAEMORRHAGE

8. Retinal and Choroidal Detachment
CHOROIDAL DETACHMENT
RETINAL DETACHMENT

9. Vitreous Hemorrhage
VITREOUS HAEMORRHAGE

10. Vitreous detachment
VITREOUS DETACHMENT

11. Retinal, choroidal, and vitreal disorders -
CHORIORETINAL ATROPHY
CHORIORETINAL DISORDER
MACULAR HOLE
MACULAR OEDEMA
MACULOPATHY
RETINAL ANEURYSM
RETINAL DEGENERATION
RETINAL DEPIGMENTATION
RETINAL EXUDATES
RETINAL NEOVASCULARISATION
RETINAL OEDEMA
RETINAL PIGMENT EPITHELIOPATHY
RETINAL PIGMENTATION
RETINAL SCAR
RETINAL VASCULAR DISORDER
RETINOPATHY PROLIFERATIVE
RETINOSCHISIS
SUBRETINAL FIBROSIS
VITREOUS DEGENERATION
VITREOUS DISORDER

12. Ocular hypertension
OCULAR HYPERTENSION

13. Glaucoma
ANGLE CLOSURE GLAUCOMA
BORDERLINE GLAUCOMA
GLAUCOMA
NORMAL TENSION GLAUCOMA
OPEN ANGLE GLAUCOMA
OPTIC NERVE CUPPING

14. Reduced or Blurred Vision

BLINDNESS
BLINDNESS UNILATERAL
VISION BLURRED
VISUAL ACUITY REDUCED
VISUAL DISTURBANCE

15. Temporary vision loss

AMAUROSIS FUGAX
BLINDNESS TRANSIENT
VISUAL ACUITY REDUCED TRANSIENTLY

16. Disturbed Vision

ALTERED VISUAL DEPTH PERCEPTION
CHARLES BONNET SYNDROME
CHROMATOPSIA
DIPLOPIA
GLARE
HALO VISION
METAMORPHOPSIA
NIGHT BLINDNESS
SCOTOMA

17. Photophobia

PHOTOPHOBIA

18. Conjunctival Hemorrhage

CONJUNCTIVAL HAEMORRHAGE
EYE DISORDER before July 18 2008 when code for conjunctive hemorrhage was provided

19. Eye Pain

ASTHENOPIA
EYE PAIN
OCULAR DISCOMFORT

20. Foreign Body Sensation, Eye Irritation

ABNORMAL SENSATION IN EYE
EYE IRRITATION
FOREIGN BODY SENSATION IN EYES

21. Floaters and Flashes

PHOTOPSIA
VITREOUS FLOATERS
VITREOUS OPACITIES

22. Conjunctivitis, Keratitis, other conjunctival and corneal disorders

CONJUNCTIVAL IRRITATION
CONJUNCTIVAL CYST
CONJUNCTIVAL DISCOLOURATION
CONJUNCTIVAL DISORDER
CONJUNCTIVAL FOLLICLES
CONJUNCTIVAL HYPERAEMIA
CONJUNCTIVAL IRRITATION
CONJUNCTIVAL OEDEMA
CONJUNCTIVAL VASCULAR DISORDER
CONJUNCTIVITIS
CONJUNCTIVITIS ALLERGIC
EYE DISCHARGE
EYELID PTOSIS
KERATITIS
PINGUECULA
PTERYGIUM
PUNCTATE KERATITIS
ULCERATIVE KERATITIS

23. Blepharitis, Dry Eye, other eyelid and tear disorders

BLEPHARITIS
BLEPHARITIS ALLERGIC
BLEPHAROCHALASIS
BLEPHAROSPASM
CHALAZION
DACRYOSTENOSIS ACQUIRED
DRY EYE
ECTROPION
EYE ALLERGY
EYE PRURITUS
EYELID BLEEDING

EYELID SENSORY DISORDER
EYELID VASCULAR DISORDER
EYELID CYST
EYELID DISORDER
EYELID EROSION
EYELID EXFOLIATION
EYELID MARGIN CRUSTING
EYELID PAIN
ENTROPION
ERYTHEMA OF EYELID
EYELID FUNCTION DISORDER
EYELID OEDEMA
KERATOCONJUNCTIVITS SICCA
LACRIMATION DECREASED
LACRIMATION INCREASED
MEIBOMIANITIS

24. Corneal disorders

CORNEAL DEFECT
CORNEAL DEPOSITS
CORNEAL DISORDER
CORNEAL EPITHELIUM DEFECT
CORNEAL OEDEMA
CORNEAL OPACITY
CORNEAL PIGMENTATION
CORNEAL SCAR
KERATOPATHY
TRICHIASIS

25. Hyphema

HYPHAEMA

26. Ocular Hyperemia and Swelling

EYE SWELLING
OCULAR HYPERAEMIA

27. Cataract and related conditions

ANTERIOR CAPSULE CONTRACTION
CATARACT
CATARACT CORTICAL
CATARACT NUCLEAR
CATARACT SUBCAPSULAR
POSTERIOR CAPSULE OPACIFICATION

28. Optic nerve conditions

OPTIC DISC HAEMORRHAGE
OPTIC NERVE SHEATH HAEMORRHAGE
OPTIC NEUROPATHY
PUPILLARY DISORDER
PUPILS UNEQUAL

29. Other

ARCUS LIPOIDES
EYE HAEMORRHAGE
EYE DISORDER after July 18, 2008 when code for conjunctival hemorrhage was provided
HYPERMETROPIA
HYPOTONY OF EYE
IRIS ADHESIONS
PRESBYOPIA
SCLERAL DISCOLOURATION

Causes of Death by Treatment Group through Week 052

(as of December 31, 2010)

Treatment	Cause
1	MYOCARDIAL INFARCTION
	COLON CANCER METASTATIC
	RESPIRATORY FAILURE
	MYOCARDIAL INFARCTION
2	CEREBRAL HAEMORRHAGE
	CEREBRAL HAEMORRHAGE
	MALIGNANT GLIOMA
	HYPERTENSIVE HEART DISEASE
3	RENAL FAILURE
	BILE DUCT CANCER*
	OVARIAN CANCER
	MYOCARDIAL INFARCTION
	PNEUMONIA
4	CARDIAC ARREST
	CEREBRAL HAEMORRHAGE
	FAILURE TO THRIVE
	CARDIO-RESPIRATORY ARREST
	SEPSIS
	SEPSIS
	CARDIAC ARREST
	FALL
	CARDIO-RESPIRATORY ARREST
	RENAL CANCER METASTATIC
	RENAL CANCER METASTATIC

* Death preceded by a cerebrovascular accident

Serious Adverse Events by System Organ Class and Treatment Group

through Week 052

(as of December 31, 2010)

	Treatment Group															
	1				2				3				4			
	People		Events		People		Events		People		Events		People		Events	
System Organ Class	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total	**67**	**(22.3)**	**91**	**30.2**	**73**	**(25.5)**	**122**	**42.7**	**76**	**(25.5)**	**102**	**34.2**	**93**	**(31.0)**	**135**	**45.0**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
CARDIAC DISORDERS	10	(3.3)	11	3.7	16	(5.6)	18	6.3	12	(4.0)	14	4.7	13	(4.3)	14	4.7
EAR AND LABYRINTH DISORDERS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
EYE DISORDERS	20	(6.6)	23	7.6	16	(5.6)	16	5.6	18	(6.0)	19	6.4	21	(7.0)	22	7.3
GASTROINTESTINAL DISORDERS	3	(1.0)	3	1.0	6	(2.1)	7	2.4	2	(0.7)	3	1.0	9	(3.0)	9	3.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5	(1.7)	5	1.7	3	(1.0)	3	1.0	3	(1.0)	3	1.0	3	(1.0)	3	1.0
HEPATOBILIARY DISORDERS	---	---	---	---	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	2	0.7
IMMUNE SYSTEM DISORDERS	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
INFECTIONS AND INFESTATIONS	6	(2.0)	7	2.3	11	(3.8)	14	4.9	12	(4.0)	13	4.4	18	(6.0)	18	6.0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	7	(2.3)	7	2.3	11	(3.8)	12	4.2	8	(2.7)	8	2.7	9	(3.0)	10	3.3
INVESTIGATIONS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
METABOLISM AND NUTRITION DISORDERS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	4	(1.3)	4	1.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2	(0.7)	2	0.7	6	(2.1)	7	2.4	4	(1.3)	4	1.3	5	(1.7)	5	1.7
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS A	7	(2.3)	7	2.3	5	(1.7)	5	1.7	10	(3.4)	10	3.4	9	(3.0)	9	3.0
NERVOUS SYSTEM DISORDERS	6	(2.0)	7	2.3	9	(3.1)	9	3.1	12	(4.0)	12	4.0	9	(3.0)	9	3.0
PSYCHIATRIC DISORDERS	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
RENAL AND URINARY DISORDERS	---	---	---	---	4	(1.4)	4	1.4	1	(0.3)	1	0.3	2	(0.7)	2	0.7
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6	(2.0)	8	2.7	3	(1.0)	4	1.4	3	(1.0)	3	1.0	6	(2.0)	8	2.7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
SURGICAL AND MEDICAL PROCEDURES	4	(1.3)	4	1.3	6	(2.1)	6	2.1	4	(1.3)	5	1.7	8	(2.7)	11	3.7
VASCULAR DISORDERS	2	(0.7)	2	0.7	6	(2.1)	7	2.4	4	(1.3)	4	1.3	3	(1.0)	4	1.3

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total		**67**	**(22.3)**	**91**	**30.2**	**73**	**(25.5)**	**122**	**42.7**	**76**	**(25.5)**	**102**	**34.2**	**93**	**(31.0)**	**135**	**45.0**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
CARDIAC DISORDERS	ANGINA PECTORIS	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	AORTIC VALVE DISEASE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ARRHYTHMIA	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	ATRIAL FIBRILLATION	2	(0.7)	2	0.7	4	(1.4)	5	1.7	4	(1.3)	4	1.3	2	(0.7)	2	0.7
	ATRIAL FLUTTER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BRADYCARDIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7
	CARDIAC ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CARDIAC FAILURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CARDIAC FAILURE CHRONIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIAC FAILURE CONGESTIVE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CARDIO-RESPIRATORY ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CONDUCTION DISORDER	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	CORONARY ARTERY DISEASE	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	CORONARY ARTERY OCCLUSION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	GASTROCARDIAC SYNDROME	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HYPERTENSIVE HEART DISEASE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MYOCARDIAL INFARCTION	4	(1.3)	4	1.3	2	(0.7)	2	0.7	4	(1.3)	4	1.3	1	(0.3)	1	0.3
	MYOCARDIAL ISCHAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SICK SINUS SYNDROME	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VENTRICULAR TACHYCARDIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
EAR AND LABYRINTH DISORDERS	VERTIGO	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
EYE DISORDERS	BLINDNESS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CATARACT	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	CATARACT SUBCAPSULAR	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHOROIDAL NEOVASCULARISATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CORNEAL SCAR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DETACHMENT OF RETINAL PIGMENT EPITHELIUM	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	ENDOPHTHALMITIS	2	(0.7)	2	0.7	4	(1.4)	4	1.4	---	---	---	---	---	---	---	---
	EYE DISORDER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HYPHAEMA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	MACULAR DEGENERATION	4	(1.3)	5	1.7	---	---	---	---	2	(0.7)	2	0.7	5	(1.7)	6	2.0
	MACULAR OEDEMA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MACULAR SCAR	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	RETINAL DETACHMENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7
	RETINAL HAEMORRHAGE	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0	3	(1.0)	3	1.0
	RETINAL OEDEMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	RETINAL VEIN OCCLUSION	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	VISUAL ACUITY REDUCED	5	(1.7)	5	1.7	7	(2.4)	7	2.4	7	(2.3)	8	2.7	4	(1.3)	4	1.3
	VISUAL ACUITY REDUCED TRANSIENTLY	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	3	(1.0)	3	1.0
	VITREOUS HAEMORRHAGE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
GASTROINTESTINAL DISORDERS	ABDOMINAL HERNIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ABDOMINAL PAIN	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COLITIS ULCERATIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CONSTIPATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DUODENAL ULCER HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	GASTRIC POLYPS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
GASTROINTESTINAL DISORDERS (continued)	GASTRIC ULCER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTRIC ULCER HAEMORRHAGE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTRITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	GASTROINTESTINAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	GASTROOESOPHAGEAL REFLUX DISEASE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ILEUS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LOWER GASTROINTESTINAL HAEMORRHAGE	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	NAUSEA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PANCREATITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RECTAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SMALL INTESTINAL OBSTRUCTION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VOMITING	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CHEST PAIN	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	GAIT DISTURBANCE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NON-CARDIAC CHEST PAIN	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	PYREXIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
HEPATOBILIARY DISORDERS	BILE DUCT OBSTRUCTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BILE DUCT STONE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CHOLECYSTITIS	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	CHOLELITHIASIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
IMMUNE SYSTEM DISORDERS	ANAPHYLACTIC REACTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DRUG HYPERSENSITIVITY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
INFECTIONS AND INFESTATIONS	BRONCHIECTASIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CELLULITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	CELLULITIS STREPTOCOCCAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CHOLECYSTITIS INFECTIVE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CLOSTRIDIUM DIFFICILE COLITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CYSTITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DIVERTICULITIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	GASTROENTERITIS VIRAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HERPES OPHTHALMIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HERPES ZOSTER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INFECTION	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	KIDNEY INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LIVER ABSCESS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OSTEOMYELITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PNEUMONIA	3	(1.0)	4	1.3	4	(1.4)	4	1.4	7	(2.3)	7	2.3	4	(1.3)	4	1.3
	PNEUMONIA BACTERIAL	---	---	---	---	2	(0.7)	3	1.0	---	---	---	---	---	---	---	---
	POST PROCEDURAL CELLULITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	POST PROCEDURAL SEPSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SEPSIS	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	URINARY TRACT INFECTION	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0	2	(0.7)	2	0.7
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ANKLE FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CERVICAL VERTEBRAL FRACTURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	COMPRESSION FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (continued)	DISLOCATION OF JOINT PROSTHESIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	FALL	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	FEMORAL NECK FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	FEMUR FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FOREIGN BODY IN EYE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HIP FRACTURE	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---	2	(0.7)	2	0.7
	HUMERUS FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INCISIONAL HERNIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	JAW FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MULTIPLE FRACTURES	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	PELVIC FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	POST PROCEDURAL HAEMORRHAGE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ROAD TRAFFIC ACCIDENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SKIN LACERATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SPINAL COMPRESSION FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	SPINAL FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	WRIST FRACTURE	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
INVESTIGATIONS	BLOOD GLUCOSE DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
METABOLISM AND NUTRITION DISORDERS	DEHYDRATION	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	FAILURE TO THRIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPERGLYCAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPOKALAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
METABOLISM AND NUTRITION DISORDERS (continued)	HYPONATRAEMIA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BUNION	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	CERVICAL SPINAL STENOSIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	EXOSTOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	INTERVERTEBRAL DISC COMPRESSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	JOINT SWELLING	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LUMBAR SPINAL STENOSIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	MUSCULAR WEAKNESS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MUSCULOSKELETAL CHEST PAIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	OSTEOARTHRITIS	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	ROTATOR CUFF SYNDROME	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	BASAL CELL CARCINOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BILE DUCT CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLADDER CANCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BLADDER CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BRAIN NEOPLASM	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BREAST CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	BREAST CANCER RECURRENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BREAST CANCER STAGE II	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BREAST CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHRONIC LYMPHOCYTIC LEUKAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	COLON CANCER	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (continued)	COLON CANCER METASTATIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DIFFUSE LARGE B-CELL LYMPHOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	LUNG NEOPLASM MALIGNANT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MALIGNANT GLIOMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NON-SMALL CELL LUNG CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NON-SMALL CELL LUNG CANCER METAST	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OVARIAN CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PANCREATIC CARCINOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PROSTATE CANCER	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	PROSTATE CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RENAL CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	SMALL CELL LUNG CANCER STAGE UNSPECIFIED	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SQUAMOUS CELL CARCINOMA OF SKIN	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
NERVOUS SYSTEM DISORDERS	CAROTID ARTERY STENOSIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	CEREBELLAR INFARCTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CEREBRAL HAEMORRHAGE	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	CEREBRAL INFARCTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CEREBROVASCULAR ACCIDENT	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEU	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CONVULSION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DEMENTIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DEMENTIA ALZHEIMERS TYPE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ENCEPHALOPATHY	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	FACIAL PALSY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
NERVOUS SYSTEM DISORDERS (continued)	HAEMORRHAGE INTRACRANIAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	LOSS OF CONSCIOUSNESS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MEMORY IMPAIRMENT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PRESYNCOPE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	SYNCOPE	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	SYNCOPE VASOVAGAL	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TRANSIENT ISCHAEMIC ATTACK	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7	3	(1.0)	3	1.0
	TRIGEMINAL NEURALGIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
PSYCHIATRIC DISORDERS	DEPRESSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	DEPRESSION SUICIDAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HALLUCINATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MENTAL STATUS CHANGES	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	PSYCHOTIC DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
RENAL AND URINARY DISORDERS	CALCULUS BLADDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CALCULUS URETERIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RENAL FAILURE	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	URETHRAL STENOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	URINARY RETENTION	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	BENIGN PROSTATIC HYPERPLASIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PELVIC PROLAPSE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ASTHMA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BRONCHOSPASM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CHRONIC OBSTRUCTIVE PULMONARY DISEASE	2	(0.7)	2	0.7	1	(0.3)	2	0.7	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	DYSPNOEA	2	(0.7)	3	1.0	---	---	---	---	---	---	---	---	---	---	---	---
	HYPOXIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INTERSTITIAL LUNG DISEASE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PNEUMONIA ASPIRATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	PULMONARY EMBOLISM	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	RESPIRATORY FAILURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	SKIN ULCER	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
SURGICAL AND MEDICAL PROCEDURES	BREAST CYST EXCISION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIAC PACEMAKER REPLACEMENT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CATARACT OPERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CHOLECYSTECTOMY	---	---	---	---	2	(0.7)	2	0.7	3	(1.0)	3	1.0	---	---	---	---
	HERNIA REPAIR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HIP ARTHROPLASTY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	KNEE ARTHROPLASTY	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	4	1.3
	LITHOTRIPSY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LUNG LOBECTOMY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NAIL OPERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SEPTOPLASTY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SIMPLE MASTECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SPINAL FUSION SURGERY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
SURGICAL AND MEDICAL PROCEDURES (continued)	SPINAL LAMINECTOMY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TRANSURETHRAL PROSTATECTOMY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VITRECTOMY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
VASCULAR DISORDERS	ACCELERATED HYPERTENSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ANEURYSM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	AORTIC ANEURYSM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DEEP VEIN THROMBOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	EMBOLISM	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HAEMATOMA	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---
	HYPERTENSION	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	HYPOTENSION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	INTERMITTENT CLAUDICATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ORTHOSTATIC HYPOTENSION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	THROMBOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3

Summary of Systemic Adverse Events (AEs) by Severity and Treatment Group

		Ranibizumab Monthly	**Bevacizumab Monthly**	**Ranibizumab PRN**	**Bevacizumab PRN**
		N=301	N=286	N=298	N=300
AEs		n (%)	n (%)	n (%)	n (%)
All	Yes	235 (78.1)	232 (81.1)	238 (79.9)	251 (83.7)
	No	66 (21.9)	54 (18.9)	60 (20.1)	49 (16.3)
Severity ≥ 2	Yes	141 (46.8)	152 (53.2)	154 (51.7)	171 (57.0)
	No	160 (53.2)	134 (46.9)	144 (48.3)	129 (43.0)
Severity ≥ 3	Yes	59 (19.6)	64 (22.4)	64 (21.5)	81 (27.0)
	No	242 (80.4)	222 (77.6)	234 (78.5)	219 (73.0)
Severity ≥ 4	Yes	10 (3.32)	13 (4.55)	11 (3.69)	20 (6.67)
	No	291 (96.7)	273 (95.5)	287 (96.3)	280 (93.3)

Severity Levels

1 Mild, little clinical significance
2 Moderate, causing some limitation; minimal/no intervention required
3 Severe
4 Life-threatening or disabling
5 Death

Systemic Adverse Events by System Organ Class and Treatment Group through Week 052

(as of December 31, 2010)

	Treatment Group															
	1				2				3				4			
	People		Events		People		Events		People		Events		People		Events	
System Organ Class	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total	**235**	**(78.1)**	**794**	**263.8**	**232**	**(81.1)**	**831**	**290.6**	**238**	**(79.9)**	**821**	**275.5**	**251**	**(83.7)**	**902**	**300.7**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3	(1.0)	4	1.3	11	(3.8)	12	4.2	7	(2.3)	8	2.7	8	(2.7)	9	3.0
CARDIAC DISORDERS	23	(7.6)	36	12.0	25	(8.7)	33	11.5	17	(5.7)	27	9.1	21	(7.0)	28	9.3
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	4	(1.3)	6	2.0	1	(0.3)	1	0.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7
EAR AND LABYRINTH DISORDERS	11	(3.7)	12	4.0	9	(3.1)	9	3.1	7	(2.3)	8	2.7	8	(2.7)	9	3.0
ENDOCRINE DISORDERS	4	(1.3)	5	1.7	8	(2.8)	8	2.8	5	(1.7)	6	2.0	2	(0.7)	2	0.7
GASTROINTESTINAL DISORDERS	44	(14.6)	67	22.3	46	(16.1)	69	24.1	44	(14.8)	60	20.1	55	(18.3)	76	25.3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	41	(13.6)	47	15.6	23	(8.0)	29	10.1	34	(11.4)	37	12.4	30	(10.0)	35	11.7
HEPATOBILIARY DISORDERS	1	(0.3)	1	0.3	4	(1.4)	4	1.4	2	(0.7)	2	0.7	2	(0.7)	6	2.0
IMMUNE SYSTEM DISORDERS	12	(4.0)	15	5.0	11	(3.8)	12	4.2	12	(4.0)	13	4.4	11	(3.7)	12	4.0
INFECTIONS AND INFESTATIONS	97	(32.2)	132	43.9	99	(34.6)	152	53.1	94	(31.5)	127	42.6	112	(37.3)	166	55.3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	48	(15.9)	71	23.6	64	(22.4)	85	29.7	53	(17.8)	77	25.8	50	(16.7)	71	23.7
INVESTIGATIONS	19	(6.3)	20	6.6	14	(4.9)	17	5.9	15	(5.0)	22	7.4	21	(7.0)	23	7.7
METABOLISM AND NUTRITION DISORDERS	14	(4.7)	15	5.0	14	(4.9)	14	4.9	17	(5.7)	18	6.0	21	(7.0)	25	8.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	61	(20.3)	81	26.9	65	(22.7)	89	31.1	78	(26.2)	113	37.9	66	(22.0)	92	30.7
CYSTS AND POLY	23	(7.6)	25	8.3	20	(7.0)	22	7.7	26	(8.7)	29	9.7	20	(6.7)	25	8.3
NERVOUS SYSTEM DISORDERS	42	(14.0)	62	20.6	55	(19.2)	67	23.4	49	(16.4)	61	20.5	51	(17.0)	63	21.0
PSYCHIATRIC DISORDERS	11	(3.7)	16	5.3	12	(4.2)	13	4.5	12	(4.0)	12	4.0	16	(5.3)	17	5.7
RENAL AND URINARY DISORDERS	8	(2.7)	10	3.3	12	(4.2)	13	4.5	7	(2.3)	7	2.3	12	(4.0)	14	4.7
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	4	(1.3)	4	1.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	55	(18.3)	80	26.6	49	(17.1)	71	24.8	60	(20.1)	89	29.9	62	(20.7)	89	29.7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	20	(6.6)	24	8.0	28	(9.8)	34	11.9	25	(8.4)	30	10.1	27	(9.0)	35	11.7
SURGICAL AND MEDICAL PROCEDURES	28	(9.3)	39	13.0	29	(10.1)	43	15.0	30	(10.1)	36	12.1	39	(13.0)	57	19.0
VASCULAR DISORDERS	20	(6.6)	22	7.3	29	(10.1)	32	11.2	29	(9.7)	35	11.7	37	(12.3)	44	14.7

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total		**235**	**(78.1)**	**794**	**263.8**	**232**	**(81.1)**	**831**	**290.6**	**238**	**(79.9)**	**821**	**275.5**	**251**	**(83.7)**	**902**	**300.7**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	1	(0.3)	2	0.7	7	(2.4)	7	2.4	5	(1.7)	5	1.7	7	(2.3)	7	2.3
	BLOOD DISORDER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HAEMORRHAGIC ANAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LEUKOCYTOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LYMPHADENOPATHY	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MICROCYTIC ANAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SPLENOMEGALY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	THROMBOCYTOPENIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
CARDIAC DISORDERS	ANGINA PECTORIS	4	(1.3)	4	1.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	ANGINA UNSTABLE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	AORTIC VALVE CALCIFICATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	AORTIC VALVE DISEASE	1	(0.3)	1	0.3	1	(0.3)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	AORTIC VALVE INCOMPETENCE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ARRHYTHMIA	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7
	ARRHYTHMIA SUPRAVENTRICULAR	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ARTERIOSCLEROSIS CORONARY ARTERY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ARTERIOSPASM CORONARY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ATRIAL FIBRILLATION	6	(2.0)	6	2.0	10	(3.5)	11	3.8	8	(2.7)	9	3.0	3	(1.0)	3	1.0
	ATRIAL FLUTTER	---	---	---	---	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0
	ATRIOVENTRICULAR BLOCK	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ATRIOVENTRICULAR BLOCK FIRST DEGREE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BRADYCARDIA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	CARDIAC ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CARDIAC FAILURE	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	CARDIAC FAILURE CHRONIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIAC FAILURE CONGESTIVE	3	(1.0)	4	1.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
CARDIAC DISORDERS (continued)	CARDIAC PSEUDOANEURYSM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIO-RESPIRATORY ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CONDUCTION DISORDER	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	CORONARY ARTERY DISEASE	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	3	1.0	---	---	---	---
	CORONARY ARTERY OCCLUSION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	GASTROCARDIAC SYNDROME	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HEART VALVE INSUFFICIENCY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPERTENSIVE HEART DISEASE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LEFT ATRIAL DILATATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	LEFT VENTRICULAR DYSFUNCTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	LEFT VENTRICULAR HYPERTROPHY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MYOCARDIAL INFARCTION	4	(1.3)	4	1.3	2	(0.7)	2	0.7	4	(1.3)	4	1.3	1	(0.3)	1	0.3
	MYOCARDIAL ISCHAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NODAL RHYTHM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PALPITATIONS	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	PERICARDITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SICK SINUS SYNDROME	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	3	(1.0)	3	1.0
	SINUS BRADYCARDIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	SUPRAVENTRICULAR TACHYCARDIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	TRICUSPID VALVE INCOMPETENCE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	VENTRICULAR ARRHYTHMIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VENTRICULAR TACHYCARDIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	COLOUR BLINDNESS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CORNEAL DYSTROPHY	4	(1.3)	6	2.0	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	SICKLE CELL TRAIT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
EAR AND LABYRINTH DISORDERS	CERUMEN IMPACTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DEAFNESS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	EAR CONGESTION	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	EAR DISORDER	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	EAR HAEMORRHAGE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	EAR PAIN	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	EUSTACHIAN TUBE DYSFUNCTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	EXTERNAL EAR DISORDER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	EXTERNAL EAR INFLAMMATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	EXTERNAL EAR PAIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HEARING IMPAIRED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPOACUSIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MASTOID DISORDER	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	MIDDLE EAR INFLAMMATION	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	TINNITUS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VERTIGO	6	(2.0)	7	2.3	5	(1.7)	5	1.7	1	(0.3)	1	0.3	4	(1.3)	5	1.7
ENDOCRINE DISORDERS	ENDOCRINE DISORDER	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	3	1.0	---	---	---	---
	HYPERTHYROIDISM	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HYPOPARATHYROIDISM	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	HYPOTHYROIDISM	3	(1.0)	3	1.0	7	(2.4)	7	2.4	2	(0.7)	2	0.7	---	---	---	---
	THYROID DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	THYROID MASS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
GASTROINTESTINAL DISORDERS	ABDOMINAL DISTENSION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ABDOMINAL HERNIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ABDOMINAL PAIN	---	---	---	---	3	(1.0)	3	1.0	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	ABDOMINAL PAIN UPPER	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
GASTROINTESTINAL DISORDERS (continued)	ABNORMAL FAECES	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	APHTHOUS STOMATITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BARRETTS OESOPHAGUS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	COLITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COLITIS ISCHAEMIC	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	COLITIS ULCERATIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COLONIC OBSTRUCTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	COLONIC POLYP	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CONSTIPATION	3	(1.0)	3	1.0	3	(1.0)	3	1.0	5	(1.7)	6	2.0	5	(1.7)	5	1.7
	CROHNS DISEASE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DENTAL CARIES	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DIARRHOEA	18	(6.0)	22	7.3	8	(2.8)	10	3.5	9	(3.0)	9	3.0	9	(3.0)	10	3.3
	DIVERTICULUM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DIVERTICULUM INTESTINAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DRY MOUTH	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	DUODENAL ULCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DUODENAL ULCER HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	DYSPEPSIA	2	(0.7)	2	0.7	4	(1.4)	4	1.4	---	---	---	---	2	(0.7)	2	0.7
	DYSPHAGIA	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	ERUCTATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FLATULENCE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	GASTRIC HAEMORRHAGE	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTRIC POLYPS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	GASTRIC ULCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	3	(1.0)	3	1.0
	GASTRIC ULCER HAEMORRHAGE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTRITIS	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---	1	(0.3)	1	0.3
	GASTROINTESTINAL DISORDER	1	(0.3)	1	0.3	1	(0.3)	1	0.3	3	(1.0)	3	1.0	2	(0.7)	2	0.7
	GASTROINTESTINAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
GASTROINTESTINAL DISORDERS (continued)	GASTROOESOPHAGEAL REFLUX DISEASE	1	(0.3)	1	0.3	4	(1.4)	4	1.4	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	GINGIVAL PAIN	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	GLOSSODYNIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HAEMORRHOIDS	---	---	---	---	3	(1.0)	3	1.0	---	---	---	---	1	(0.3)	1	0.3
	HIATUS HERNIA	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	ILEUS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	INGUINAL HERNIA	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	IRRITABLE BOWEL SYNDROME	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LOWER GASTROINTESTINAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7	---	---	---	---
	MOUTH ULCERATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NAUSEA	7	(2.3)	8	2.7	7	(2.4)	9	3.1	9	(3.0)	11	3.7	12	(4.0)	12	4.0
	OBSTRUCTION GASTRIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OESOPHAGEAL POLYP	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OESOPHAGEAL STENOSIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OESOPHAGEAL ULCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	OESOPHAGITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ORAL PAIN	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ORAL SOFT TISSUE DISORDER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	PANCREATIC INSUFFICIENCY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PANCREATITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	PERIODONTAL DISEASE	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	PHARYNGOESOPHAGEAL DIVERTICULUM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	POLYP COLORECTAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RECTAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	REFLUX OESOPHAGITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RETCHING	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SALIVARY DUCT INFLAMMATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SMALL INTESTINAL OBSTRUCTION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
GASTROINTESTINAL DISORDERS (continued)	STOMACH DISCOMFORT	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	STOMATITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	TEETH BRITTLE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	TOOTH DISORDER	4	(1.3)	5	1.7	2	(0.7)	2	0.7	5	(1.7)	6	2.0	2	(0.7)	2	0.7
	TOOTH IMPACTED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TOOTH LOSS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TOOTHACHE	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	3	1.0	4	(1.3)	4	1.3
	VOMITING	5	(1.7)	5	1.7	5	(1.7)	5	1.7	3	(1.0)	3	1.0	6	(2.0)	6	2.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CALCINOSIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CHEST DISCOMFORT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CHEST PAIN	3	(1.0)	3	1.0	1	(0.3)	1	0.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	CHILLS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	CREPITATIONS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CYST	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	EXTRAVASATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FACE OEDEMA	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	FACIAL PAIN	3	(1.0)	3	1.0	---	---	---	---	---	---	---	---	---	---	---	---
	FATIGUE	5	(1.7)	6	2.0	5	(1.7)	5	1.7	6	(2.0)	6	2.0	8	(2.7)	8	2.7
	GAIT DISTURBANCE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	GENERAL SYMPTOM	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HERNIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ILL-DEFINED DISORDER	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	INFLUENZA LIKE ILLNESS	16	(5.3)	17	5.6	7	(2.4)	8	2.8	10	(3.4)	10	3.4	8	(2.7)	9	3.0
	MASS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	NODULE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (continued)	NON-CARDIAC CHEST PAIN	1	(0.3)	1	0.3	2	(0.7)	2	0.7	3	(1.0)	3	1.0	1	(0.3)	1	0.3
	OEDEMA PERIPHERAL	6	(2.0)	6	2.0	6	(2.1)	7	2.4	7	(2.3)	8	2.7	5	(1.7)	5	1.7
	PAIN	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	PYREXIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	3	(1.0)	3	1.0
HEPATOBILIARY DISORDERS	BILE DUCT OBSTRUCTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BILE DUCT STONE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CHOLANGITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CHOLECYSTITIS	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	CHOLELITHIASIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	HEPATIC VEIN THROMBOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	JAUNDICE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	JAUNDICE CHOLESTATIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
IMMUNE SYSTEM DISORDERS	ALLERGY TO ARTHROPOD STING	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ANAPHYLACTIC REACTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DRUG HYPERSENSITIVITY	3	(1.0)	4	1.3	3	(1.0)	4	1.4	4	(1.3)	5	1.7	1	(0.3)	1	0.3
	FOOD ALLERGY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HYPERSENSITIVITY	5	(1.7)	6	2.0	4	(1.4)	4	1.4	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	IMMUNE SYSTEM DISORDER	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	2	(0.7)	3	1.0
	SEASONAL ALLERGY	2	(0.7)	3	1.0	3	(1.0)	3	1.0	6	(2.0)	6	2.0	4	(1.3)	4	1.3
INFECTIONS AND INFESTATIONS	ABSCESS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ADENOVIRAL CONJUNCTIVITIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ADENOVIRAL UPPER RESPIRATORY INFECTION	11	(3.7)	12	4.0	11	(3.8)	11	3.8	10	(3.4)	10	3.4	12	(4.0)	14	4.7
	BACTERAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BACTERIAL INFECTION	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
INFECTIONS AND INFESTATIONS (continued)	BRONCHIECTASIS	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BRONCHITIS	7	(2.3)	9	3.0	8	(2.8)	9	3.1	9	(3.0)	9	3.0	6	(2.0)	7	2.3
	CARBUNCLE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CATHETER RELATED INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CELLULITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	4	(1.3)	4	1.3
	CELLULITIS STREPTOCOCCAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CHOLECYSTITIS INFECTIVE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CHRONIC SINUSITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CLOSTRIDIUM DIFFICILE COLITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CONJUNCTIVITIS INFECTIVE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	CYSTITIS	11	(3.7)	13	4.3	7	(2.4)	8	2.8	8	(2.7)	9	3.0	10	(3.3)	15	5.0
	DEVICE RELATED INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DIABETIC FOOT INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DIVERTICULITIS	5	(1.7)	5	1.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3	4	(1.3)	4	1.3
	EAR INFECTION	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	ENTERITIS INFECTIOUS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	EXTERNAL EAR CELLULITIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	EYELID INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FUNGAL INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	GASTRIC INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTRITIS BACTERIAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	GASTROENTERITIS	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	GASTROENTERITIS ROTAVIRUS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	GASTROENTERITIS VIRAL	3	(1.0)	3	1.0	1	(0.3)	1	0.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	GINGIVAL INFECTION	1	(0.3)	1	0.3	1	(0.3)	3	1.0	---	---	---	---	---	---	---	---
	HELICOBACTER GASTRITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HEPATITIS VIRAL	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HERPES OPHTHALMIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
INFECTIONS AND INFESTATIONS (continued)	HERPES SIMPLEX OPHTHALMIC	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	HERPES ZOSTER	4	(1.3)	4	1.3	5	(1.7)	6	2.1	4	(1.3)	4	1.3	5	(1.7)	5	1.7
	HORDEOLUM	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	HYPOPYON	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INFECTION	4	(1.3)	4	1.3	6	(2.1)	7	2.4	3	(1.0)	3	1.0	2	(0.7)	3	1.0
	INFLUENZA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	KIDNEY INFECTION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	LARYNGITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LIVER ABSCESS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LOCALISED INFECTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	LUNG INFECTION	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	MYCETOMA MYCOTIC	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NAIL INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	NASOPHARYNGITIS	14	(4.7)	15	5.0	12	(4.2)	12	4.2	15	(5.0)	20	6.7	12	(4.0)	13	4.3
	OESOPHAGEAL CANDIDIASIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ONYCHOMYCOSIS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	ORAL CANDIDIASIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ORAL HERPES	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ORAL INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OSTEOMYELITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OTITIS EXTERNA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	OTITIS MEDIA	3	(1.0)	3	1.0	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	PHARYNGITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7
	PHARYNGITIS STREPTOCOCCAL	---	---	---	---	---	---	---	---	---	---	---	---	4	(1.3)	4	1.3
	PNEUMONIA	7	(2.3)	8	2.7	6	(2.1)	6	2.1	9	(3.0)	9	3.0	9	(3.0)	10	3.3
	PNEUMONIA BACTERIAL	---	---	---	---	2	(0.7)	3	1.0	---	---	---	---	---	---	---	---
	POST PROCEDURAL CELLULITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	2	0.7
	POST PROCEDURAL INFECTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
INFECTIONS AND INFESTATIONS (continued)	POST PROCEDURAL SEPSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PSEUDOMONAS INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	RESPIRATORY TRACT INFECTION	---	---	---	---	2	(0.7)	3	1.0	---	---	---	---	---	---	---	---
	RHINITIS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SEPSIS	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	SINUSITIS	8	(2.7)	8	2.7	16	(5.6)	16	5.6	12	(4.0)	14	4.7	12	(4.0)	12	4.0
	SINUSITIS BACTERIAL	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	SKIN INFECTION	---	---	---	---	1	(0.3)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	SOFT TISSUE INFECTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	STAPHYLOCOCCAL INFECTION	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	TOOTH ABSCESS	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---	1	(0.3)	1	0.3
	TOOTH INFECTION	3	(1.0)	3	1.0	5	(1.7)	5	1.7	5	(1.7)	6	2.0	3	(1.0)	3	1.0
	UPPER RESPIRATORY TRACT INFECTION	7	(2.3)	7	2.3	3	(1.0)	3	1.0	2	(0.7)	2	0.7	5	(1.7)	5	1.7
	URINARY TRACT INFECTION	16	(5.3)	17	5.6	17	(5.9)	20	7.0	13	(4.4)	17	5.7	25	(8.3)	29	9.7
	URINARY TRACT INFECTION ENTEROCOCCAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VIRAL RHINITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	VIRAL UPPER RESPIRATORY TRACT INFECTION	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	VULVITIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	WOUND INFECTION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ANIMAL BITE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	ANKLE FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ARTHROPOD BITE	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CARDIAC PACEMAKER MALFUNCTION	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CARTILAGE INJURY	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	CATARACT OPERATION COMPLICATION	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	CERVICAL VERTEBRAL FRACTURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (continued)	CLAVICLE FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COMPRESSION FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	1	(0.3)	1	0.3
	CONJUNCTIVAL ABRASION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CONTUSION	9	(3.0)	12	4.0	14	(4.9)	15	5.2	8	(2.7)	9	3.0	10	(3.3)	10	3.3
	CORNEAL ABRASION	4	(1.3)	4	1.3	9	(3.1)	9	3.1	2	(0.7)	2	0.7	5	(1.7)	5	1.7
	DEVICE BREAKAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DISLOCATION OF JOINT PROSTHESIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DRUG ADMINISTERED AT INAPPROPRIATE SITE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	EXCORIATION	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	EXPOSURE TO TOXIC AGENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	FACIAL BONES FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FALL	13	(4.3)	16	5.3	11	(3.8)	12	4.2	15	(5.0)	17	5.7	15	(5.0)	15	5.0
	FEMORAL NECK FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	FEMUR FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FOOT FRACTURE	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	FOREIGN BODY IN EYE	2	(0.7)	2	0.7	2	(0.7)	3	1.0	1	(0.3)	1	0.3	---	---	---	---
	FRACTURE	4	(1.3)	4	1.3	8	(2.8)	8	2.8	5	(1.7)	5	1.7	2	(0.7)	3	1.0
	FRACTURED SACRUM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HAND FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	HEAD INJURY	5	(1.7)	6	2.0	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HIP FRACTURE	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---	2	(0.7)	2	0.7
	HUMERUS FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INCISIONAL HERNIA	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	INTRAOCULAR LENS DISLOCATION	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	INTRAOCULAR LENS OPACITY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	JAW FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	JOINT INJURY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (continued)	JOINT SPRAIN	---	---	---	---	2	(0.7)	2	0.7	4	(1.3)	4	1.3	3	(1.0)	3	1.0
	LACERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LIMB INJURY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MEDICAL DEVICE COMPLICATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	MENISCUS LESION	---	---	---	---	---	---	---	---	4	(1.3)	4	1.3	---	---	---	---
	MOUTH INJURY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MULTIPLE FRACTURES	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	MULTIPLE INJURIES	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MUSCLE INJURY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	NAIL AVULSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	OVERDOSE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PELVIC FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PERIORBITAL HAEMATOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	POST PROCEDURAL HAEMORRHAGE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	POST-TRAUMATIC PAIN	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	PROCEDURAL COMPLICATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	PROCEDURAL PAIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RECALL PHENOMENON	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	RIB FRACTURE	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	ROAD TRAFFIC ACCIDENT	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SKELETAL INJURY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SKIN LACERATION	7	(2.3)	7	2.3	4	(1.4)	4	1.4	4	(1.3)	5	1.7	5	(1.7)	5	1.7
	SPINAL COMPRESSION FRACTURE	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	SPINAL FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	SUNBURN	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SUPERFICIAL INJURY OF EYE	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---
	TENDON RUPTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (continued)	THERMAL BURN	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	UPPER LIMB FRACTURE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	WOUND	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	WOUND DEHISCENCE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	WRIST FRACTURE	---	---	---	---	4	(1.4)	4	1.4	3	(1.0)	3	1.0	---	---	---	---
INVESTIGATIONS	ANTIPHOSPHOLIPID ANTIBODIES POSITIVE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BIOPSY BILE DUCT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BIOPSY LYMPH GLAND ABNORMAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BIOPSY SKIN	1	(0.3)	1	0.3	2	(0.7)	3	1.0	3	(1.0)	4	1.3	2	(0.7)	2	0.7
	BIOPSY VOCAL CORD ABNORMAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLOOD CALCIUM INCREASED	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLOOD CHOLESTEROL INCREASED	3	(1.0)	3	1.0	4	(1.4)	5	1.7	3	(1.0)	3	1.0	2	(0.7)	2	0.7
	BLOOD CREATININE INCREASED	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLOOD GLUCOSE DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0
	BLOOD GLUCOSE INCREASED	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	2	0.7	2	(0.7)	2	0.7
	BLOOD MAGNESIUM DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BLOOD POTASSIUM DECREASED	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BLOOD POTASSIUM INCREASED	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLOOD PRESSURE INCREASED	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	BLOOD SODIUM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BLOOD SODIUM DECREASED	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	BLOOD TRIGLYCERIDES INCREASED	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	CARDIAC MURMUR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CARDIAC STRESS TEST	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	COLONOSCOPY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ELECTRCARDIOGRAM ABNORMAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
INVESTIGATIONS (continued)	HAEMOGLOBIN DECREASED	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	2	0.7	1	(0.3)	1	0.3
	IMMUNOGLOBULINS DECREASED	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INTERNATIONAL NORMALISED RATIO INCREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	INTRAOCULAR PRESSURE INCREASED	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7
	LABORATORY TEST ABNORMAL	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	PARACENTESIS EYE NORMAL	2	(0.7)	3	1.0	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PROSTATIC SPECIFIC ANTIGEN INCREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PULMONARY ARTERIAL PRESSURE ABNORMAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SCAN ADRENAL GLAND	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SMEAR CERVIX ABNORMAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	TROPONIN INCREASED	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	UREA RENAL CLEARANCE DECREASED	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	WEIGHT DECREASED	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	WEIGHT INCREASED	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
METABOLISM AND NUTRITION DISORDERS	ANOREXIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DECREASED APPETITE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	DEHYDRATION	2	(0.7)	2	0.7	4	(1.4)	4	1.4	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	DIABETES MELLITUS	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7
	DIABETES MELLITUS NON-INSULIN-DEPENDENT	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	FAILURE TO THRIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GLUCOSE TOLERANCE IMPAIRED	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	GOUT	1	(0.3)	1	0.3	1	(0.3)	1	0.3	5	(1.7)	5	1.7	2	(0.7)	4	1.3
	HYPERCHOLESTEROLAEMIA	2	(0.7)	2	0.7	1	(0.3)	1	0.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3
	HYPERGLYCAEMIA	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPERKALAEMIA	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
METABOLISM AND NUTRITION DISORDERS (continued)	HYPERLIPIDAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPERTRIGLYCERIDAEMIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HYPOCALCAEMIA	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	HYPOKALAEMIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	5	(1.7)	5	1.7
	HYPONATRAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	IRON DEFICIENCY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	MALNUTRITION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OBESITY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	VITAMIN B12 DEFICIENCY	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---
	VITAMIN D DEFICIENCY	3	(1.0)	3	1.0	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	4	(1.3)	4	1.3	10	(3.5)	10	3.5	15	(5.0)	15	5.0	10	(3.3)	12	4.0
	ARTHRITIS	9	(3.0)	9	3.0	10	(3.5)	12	4.2	14	(4.7)	16	5.4	6	(2.0)	7	2.3
	ARTHROPATHY	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	BACK PAIN	10	(3.3)	10	3.3	10	(3.5)	11	3.8	21	(7.0)	24	8.1	13	(4.3)	13	4.3
	BUNION	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	BURSITIS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	CERVICAL SPINAL STENOSIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	EXOSTOSIS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	FIBROMYALGIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	FLANK PAIN	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HIP DEFORMITY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	INTERVERTEBRAL DISC COMPRESSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	INTERVERTEBRAL DISC DEGENERATION	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	INTERVERTEBRAL DISC DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INTERVERTEBRAL DISC PROTRUSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	JOINT EFFUSION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (continued)	JOINT RANGE OF MOTION DECREASED	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	JOINT STIFFNESS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	JOINT SWELLING	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LUMBAR SPINAL STENOSIS	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	4	1.3	2	(0.7)	2	0.7
	MOBILITY DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MUSCLE SPASMS	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	3	1.0	5	(1.7)	5	1.7
	MUSCLE TIGHTNESS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MUSCULAR WEAKNESS	---	---	---	---	3	(1.0)	3	1.0	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	MUSCULOSKELETAL CHEST PAIN	2	(0.7)	2	0.7	3	(1.0)	3	1.0	1	(0.3)	1	0.3	3	(1.0)	4	1.3
	MUSCULOSKELETAL DISORDER	7	(2.3)	7	2.3	6	(2.1)	8	2.8	7	(2.3)	10	3.4	6	(2.0)	6	2.0
	MUSCULOSKELETAL PAIN	1	(0.3)	1	0.3	3	(1.0)	3	1.0	4	(1.3)	4	1.3	1	(0.3)	1	0.3
	MUSCULOSKELETAL STIFFNESS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7	---	---	---	---
	MYALGIA	2	(0.7)	2	0.7	3	(1.0)	3	1.0	3	(1.0)	5	1.7	3	(1.0)	3	1.0
	MYOSITIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	NECK PAIN	2	(0.7)	2	0.7	3	(1.0)	3	1.0	3	(1.0)	3	1.0	4	(1.3)	4	1.3
	NEUROPATHIC ARTHROPATHY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OSTEOARTHRITIS	3	(1.0)	4	1.3	4	(1.4)	4	1.4	5	(1.7)	5	1.7	4	(1.3)	4	1.3
	OSTEOPENIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OSTEOPOROSIS	4	(1.3)	4	1.3	1	(0.3)	1	0.3	3	(1.0)	3	1.0	3	(1.0)	3	1.0
	PAIN IN EXTREMITY	10	(3.3)	11	3.7	10	(3.5)	12	4.2	7	(2.3)	8	2.7	6	(2.0)	6	2.0
	PLANTAR FASCIITIS	3	(1.0)	3	1.0	---	---	---	---	---	---	---	---	---	---	---	---
	RHABDOMYOLYSIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	RHEUMATOID ARTHRITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ROTATOR CUFF SYNDROME	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	SPINAL OSTEOARTHRITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SYNOVIAL CYST	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7
	TENDONITIS	2	(0.7)	3	1.0	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (continued)	TOE DEFORMITY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	ACROCHORDON	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ANGIOCENTRIC LYMPHOMA RECURRENT	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BASAL CELL CARCINOMA	6	(2.0)	6	2.0	7	(2.4)	7	2.4	8	(2.7)	9	3.0	7	(2.3)	9	3.0
	BENIGN NEOPLASM	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	BILE DUCT CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLADDER CANCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BLADDER CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BLADDER NEOPLASM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BLEPHARAL PAPILLOMA	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	BRAIN NEOPLASM	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BREAST CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	BREAST CANCER RECURRENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BREAST CANCER STAGE II	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BREAST CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHOROIDAL NAEVUS	5	(1.7)	5	1.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	CHRONIC LYMPHOCYTIC LEUKAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	COLON CANCER	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	COLON CANCER METASTATIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DIFFUSE LARGE B-CELL LYMPHOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	EOSINOPHILIC LEUKAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	FIBROMATOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	GASTROINTESTINAL TRACT ADENOMA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LUNG NEOPLASM	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (continued)	LUNG NEOPLASM MALIGNANT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MALIGNANT GLIOMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MALIGNANT MELANOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	MORTONS NEUROMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NEOPLASM	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NEOPLASM SKIN	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	NON-HODGKINS LYMPHOMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NON-SMALL CELL LUNG CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NON-SMALL CELL LUNG CANCER METAST	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OVARIAN CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PANCREATIC CARCINOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PROSTATE CANCER	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	PROSTATE CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RENAL CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	SEBORRHOEIC KERATOSIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SKIN CANCER	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	SMALL CELL LUNG CANCER STAGE UNSPECIFIED	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SQUAMOUS CELL CARCINOMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SQUAMOUS CELL CARCINOMA OF SKIN	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	THYROID NEOPLASM	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
NERVOUS SYSTEM DISORDERS	AMNESIA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BALANCE DISORDER	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	CAROTID ARTERY STENOSIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	CARPAL TUNNEL SYNDROME	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CEREBELLAR INFARCTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CEREBRAL HAEMORRHAGE	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
NERVOUS SYSTEM DISORDERS (continued)	CEREBRAL INFARCTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CEREBROVASCULAR ACCIDENT	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	CERVICAL MYELOPATHY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CERVICOGENIC HEADACHE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEU	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	COGNITIVE DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7
	CONVULSION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DEMENTIA	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	DEMENTIA ALZHEIMERS TYPE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DIZZINESS	18	(6.0)	20	6.6	7	(2.4)	8	2.8	10	(3.4)	10	3.4	11	(3.7)	12	4.0
	ENCEPHALOPATHY	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	EXTRAPYRAMIDAL DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	FACIAL NEURALGIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	FACIAL PALSY	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HAEMORRHAGE INTRACRANIAL	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HEADACHE	12	(4.0)	16	5.3	21	(7.3)	23	8.0	18	(6.0)	19	6.4	6	(2.0)	7	2.3
	HEMIPARESIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPOAESTHESIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	LOSS OF CONSCIOUSNESS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MEMORY IMPAIRMENT	---	---	---	---	2	(0.7)	2	0.7	2	(0.7)	2	0.7	5	(1.7)	5	1.7
	MIGRAINE WITH AURA	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	NERVE COMPRESSION	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	NERVE ROOT COMPRESSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	NERVOUS SYSTEM DISORDER	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	3	1.0
	NEURALGIA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	NEUROPATHY PERIPHERAL	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OPHTHALMOPLEGIC MIGRAINE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PARAESTHESIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
NERVOUS SYSTEM DISORDERS (continued)	PARASTHESIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PARKINSON'S DISEASE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	PERIPHERAL SENSORY NEUROPATHY	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	PERONEAL NERVE PALSY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PRESYNCOPE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RADICULOPATHY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RESTLESS LEGS SYNDROME	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	SCIATICA	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	SINUS HEADACHE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	SOMNOLENCE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SPEECH DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SYNCOPE	2	(0.7)	4	1.3	5	(1.7)	5	1.7	4	(1.3)	4	1.3	5	(1.7)	5	1.7
	SYNCOPE VASOVAGAL	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TRANSIENT ISCHAEMIC ATTACK	1	(0.3)	2	0.7	---	---	---	---	3	(1.0)	3	1.0	3	(1.0)	3	1.0
	TREMOR	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TRIGEMINAL NEURALGIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VISUAL FIELD DEFECT	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	VITH NERVE PARALYSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
PSYCHIATRIC DISORDERS	ANXIETY	3	(1.0)	3	1.0	2	(0.7)	2	0.7	2	(0.7)	2	0.7	7	(2.3)	7	2.3
	CONFUSIONAL STATE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	3	(1.0)	3	1.0	2	(0.7)	2	0.7
	DEPRESSION	6	(2.0)	6	2.0	4	(1.4)	4	1.4	4	(1.3)	4	1.3	4	(1.3)	4	1.3
	DEPRESSION SUICIDAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HALLUCINATION	2	(0.7)	2	0.7	3	(1.0)	3	1.0	---	---	---	---	1	(0.3)	1	0.3
	HALLUCINATION VISUAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INSOMNIA	1	(0.3)	1	0.3	3	(1.0)	3	1.0	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	MENTAL STATUS CHANGES	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	PSYCHOTIC DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
RENAL AND URINARY DISORDERS	AZOTAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BLADDER SPASM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CALCULUS BLADDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CALCULUS URETERIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DYSURIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HAEMATURIA	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HYDRONEPHROSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPERTONIC BLADDER	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INCONTINENCE	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NEPHROLITHIASIS	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	POLLAKIURIA	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	POLYURIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RENAL CYST	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RENAL FAILURE	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RENAL FAILURE ACUTE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	RENAL FAILURE CHRONIC	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	URETHRAL STENOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	URINARY INCONTINENCE	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	URINARY RETENTION	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	URINARY TRACT PAIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	UROGENITAL DISORDER	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	UROGENITAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	BENIGN PROSTATIC HYPERPLASIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	OVARIAN CYST	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PELVIC PAIN	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PELVIC PROLAPSE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
REPRODUCTIVE SYSTEM AND BREAST DISORDERS (continued)	PENILE HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PROSTATITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	SEXUAL DYSFUNCTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VAGINAL DISCHARGE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ACUTE RESPIRATORY DISTRESS SYNDROME	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ACUTE RESPIRATORY FAILURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	APNOEA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ASPIRATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ASTHMA	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	ATELECTASIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BRONCHIAL DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BRONCHOSPASM	4	(1.3)	4	1.3	1	(0.3)	1	0.3	---	---	---	---	5	(1.7)	5	1.7
	CHRONIC OBSTRUCTIVE PULMONARY DISEASE	2	(0.7)	3	1.0	4	(1.4)	6	2.1	4	(1.3)	4	1.3	3	(1.0)	3	1.0
	CHRONIC RESPIRATORY FAILURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COUGH	22	(7.3)	26	8.6	11	(3.8)	11	3.8	19	(6.4)	21	7.0	20	(6.7)	21	7.0
	DIAPHRAGMATIC PARALYSIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DYSPHONIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	DYSPNOEA	15	(5.0)	16	5.3	5	(1.7)	5	1.7	1	(0.3)	1	0.3	3	(1.0)	4	1.3
	EMPHYSEMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	EPIGLOTTIC OEDEMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	EPISTAXIS	---	---	---	---	2	(0.7)	4	1.4	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	HICCUPS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HYPERCAPNIA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPOXIA	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	IDIOPATHIC PULMONARY FIBROSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (continued)	INTERSTITIAL LUNG DISEASE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	LUNG INFILTRATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NASAL CONGESTION	3	(1.0)	3	1.0	2	(0.7)	3	1.0	7	(2.3)	7	2.3	13	(4.3)	14	4.7
	NASAL POLYPS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NASAL SEPTUM DEVIATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NONINFECTIVE BRONCHITIS	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PHARYNGOLARYNGEAL PAIN	3	(1.0)	4	1.3	7	(2.4)	7	2.4	4	(1.3)	4	1.3	2	(0.7)	2	0.7
	PLEURAL EFFUSION	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	PLEURISY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PLEURITIC PAIN	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PNEUMONIA ASPIRATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	PNEUMONITIS	---	---	---	---	2	(0.7)	2	0.7	5	(1.7)	7	2.3	1	(0.3)	1	0.3
	POSTNASAL DRIP	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PRODUCTIVE COUGH	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PULMONARY CONGESTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PULMONARY EMBOLISM	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	PULMONARY HYPERTENSION	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	PULMONARY MASS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PULMONARY OEDEMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RESPIRATORY ACIDOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RESPIRATORY DISORDER	6	(2.0)	6	2.0	5	(1.7)	6	2.1	11	(3.7)	13	4.4	9	(3.0)	9	3.0
	RESPIRATORY FAILURE	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RESPIRATORY TRACT CONGESTION	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	RHINITIS ALLERGIC	4	(1.3)	4	1.3	2	(0.7)	2	0.7	10	(3.4)	10	3.4	6	(2.0)	7	2.3
	RHINORRHOEA	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	SINUS CONGESTION	1	(0.3)	1	0.3	3	(1.0)	5	1.7	---	---	---	---	1	(0.3)	1	0.3
	SINUS DISORDER	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (continued)	SLEEP APNOEA SYNDROME	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	SNEEZING	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ACTINIC KERATOSIS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	ALOPECIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ANGIOEDEMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CUTIS LAXA	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	DERMAL CYST	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	DERMATITIS	---	---	---	---	---	---	---	---	4	(1.3)	4	1.3	---	---	---	---
	DERMATITIS ACNEIFORM	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DERMATITIS ALLERGIC	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	DERMATITIS CONTACT	---	---	---	---	3	(1.0)	3	1.0	2	(0.7)	2	0.7	4	(1.3)	4	1.3
	DRY SKIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	ECCHYMOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ECZEMA	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	ERYTHEMA MULTIFORME	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	EXFOLIATIVE RASH	3	(1.0)	3	1.0	2	(0.7)	2	0.7	4	(1.3)	4	1.3	2	(0.7)	2	0.7
	HEAT RASH	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPERHIDROSIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	HYPERKERATOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INGROWING NAIL	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	NAIL DISORDER	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	ONYCHOMADESIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PAIN OF SKIN	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	PETECHIAE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PRURITUS	---	---	---	---	1	(0.3)	1	0.3	4	(1.3)	4	1.3	1	(0.3)	1	0.3
	PRURITUS ALLERGIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
SKIN AND SUBCUTANEOUS TISSUE DISORDERS (continued)	PSORIASIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RASH	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	RASH MACULO-PAPULAR	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ROSACEA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SEBORRHOEIC DERMATITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SKIN DISORDER	5	(1.7)	6	2.0	5	(1.7)	5	1.7	2	(0.7)	5	1.7	---	---	---	---
	SKIN EXFOLIATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SKIN INDURATION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7
	SKIN LESION	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	SKIN ULCER	---	---	---	---	3	(1.0)	4	1.4	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	SWELLING FACE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	TRANSIENT ACANTHOLYTIC DERMATOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	UMBILICAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	URTICARIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
SURGICAL AND MEDICAL PROCEDURES	ACROCHORDON EXCISION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ACUPUNCTURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	AORTIC VALVE REPLACEMENT	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	ATHERECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BAKERS CYST EXCISION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BLADDER HYDRODISTENSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BLEPHAROPLASTY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BLOOD PRODUCT TRANSFUSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BREAST CYST EXCISION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BUNION OPERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CARDIAC PACEMAKER INSERTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CARDIAC PACEMAKER REPLACEMENT	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	CARPAL TUNNEL DECOMPRESSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
SURGICAL AND MEDICAL PROCEDURES (continued)	CATARACT OPERATION	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	4	(1.3)	4	1.3
	CAUTERY TO NOSE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CENTRAL VENOUS CATHETERISATION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CERUMEN REMOVAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHEMOTHERAPY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7
	CHOLECYSTECTOMY	---	---	---	---	3	(1.0)	3	1.0	3	(1.0)	3	1.0	---	---	---	---
	CHONDROPLASTY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CORONARY ARTERIAL STENT INSERTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CORONARY ARTERY BYPASS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CRYOTHERAPY	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	4	1.3	1	(0.3)	1	0.3
	CYST REMOVAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DENTAL IMPLANTATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DENTAL TREATMENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ENDODONTIC PROCEDURE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3
	EPIDERMOID CYST EXCISION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	EYE LASER SURGERY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	FOOT OPERATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	FRACTURE TREATMENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	GAMMA RADIATION THERAPY TO SKIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HERNIA REPAIR	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	HIP ARTHROPLASTY	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	IMPLANTABLE DEFIBRILLATOR INSERTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INGUINAL HERNIA REPAIR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	INTERNAL FIXATION OF FRACTURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	IRIDOTOMY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	JOINT DISLOCATION REDUCTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	JOINT FLUID DRAINAGE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	JOINT MANIPULATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
SURGICAL AND MEDICAL PROCEDURES (continued)	KNEE ARTHROPLASTY	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	3	(1.0)	5	1.7
	KNEE OPERATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LASER THERAPY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	LITHOTRIPSY	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	LUNG LOBECTOMY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MASTECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	MAXILLARY ANTRUM OPERATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MENISCUS OPERATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MICROGRAPHIC SKIN SURGERY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MOLE EXCISION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	3	1.0	1	(0.3)	1	0.3
	NAIL OPERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	NERVE BLOCK	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OSTECTOMY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PELVIC FLOOR REPAIR	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PERIODONTAL OPERATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PHARYNGEAL OPERATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	POLYPECTOMY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RADIOTHERAPY	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	RADIOTHERAPY TO LUNG	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SEBACEOUS CYST EXCISION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SEPTOPLASTY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SHOULDER ARTHROPLASTY	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	SIMPLE MASTECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SINUS OPERATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	SKIN LESION EXCISION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	4	1.3
	SKIN NEOPLASM EXCISION	3	(1.0)	3	1.0	5	(1.7)	7	2.4	3	(1.0)	3	1.0	2	(0.7)	2	0.7
	SPINAL FUSION SURGERY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SPINAL LAMINECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
SURGICAL AND MEDICAL PROCEDURES (continued)	STENT PLACEMENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SURGICAL STAPLING	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SUTURE INSERTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	TENDON SHEATH INCISION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TOE OPERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7
	TOOTH EXTRACTION	4	(1.3)	4	1.3	2	(0.7)	4	1.4	4	(1.3)	5	1.7	6	(2.0)	7	2.3
	TRANSFUSION	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	TRANSURETHRAL PROSTATECTOMY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VASCULAR CAUTERISATION	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	VITRECTOMY	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	WOUND DEBRIDEMENT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	WRIST SURGERY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
VASCULAR DISORDERS	ACCELERATED HYPERTENSION	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---
	ANEURYSM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ANGIOPATHY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	AORTIC ANEURYSM	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ARTERIOSCLEROSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BLOOD PRESSURE FLUCTUATION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	DEEP VEIN THROMBOSIS	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	EMBOLISM	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HAEMATOMA	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7	5	(1.7)	5	1.7
	HAEMORRHAGE	---	---	---	---	---	---	---	---	2	(0.7)	3	1.0	1	(0.3)	2	0.7
	HOT FLUSH	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HYPERTENSION	12	(4.0)	13	4.3	17	(5.9)	17	5.9	17	(5.7)	19	6.4	19	(6.3)	21	7.0
	HYPOTENSION	1	(0.3)	1	0.3	4	(1.4)	4	1.4	3	(1.0)	3	1.0	8	(2.7)	8	2.7
	INTERMITTENT CLAUDICATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LYMPHOEDEMA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class, Preferred Term, and Treatment Group through Week 052

(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
VASCULAR DISORDERS (continued)	ORTHOSTATIC HYPOTENSION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PALLOR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PERIPHERAL ISCHAEMIA	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	PERIPHERAL VASCULAR DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PHLEBITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	THROMBOSIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	VARICOSE VEIN	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	VASCULAR CALCIFICATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VENOUS INSUFFICIENCY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class and Treatment Group through Week 052
Severity 2 or higher
(as of December 31, 2010)

	Treatment Group															
	1				2				3				4			
	People		Events		People		Events		People		Events		People		Events	
System Organ Class	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total	**141**	**(46.8)**	**318**	**105.6**	**152**	**(53.1)**	**390**	**136.4**	**154**	**(51.7)**	**341**	**114.4**	**171**	**(57.0)**	**455**	**151.7**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	(0.7)	3	1.0	7	(2.4)	7	2.4	4	(1.3)	5	1.7	2	(0.7)	2	0.7
CARDIAC DISORDERS	15	(5.0)	22	7.3	21	(7.3)	28	9.8	14	(4.7)	19	6.4	18	(6.0)	22	7.3
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
EAR AND LABYRINTH DISORDERS	6	(2.0)	6	2.0	2	(0.7)	2	0.7	3	(1.0)	4	1.3	1	(0.3)	1	0.3
ENDOCRINE DISORDERS	3	(1.0)	4	1.3	8	(2.8)	8	2.8	1	(0.3)	1	0.3	1	(0.3)	1	0.3
GASTROINTESTINAL DISORDERS	18	(6.0)	22	7.3	21	(7.3)	34	11.9	13	(4.4)	16	5.4	28	(9.3)	30	10.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	13	(4.3)	15	5.0	11	(3.8)	12	4.2	13	(4.4)	13	4.4	12	(4.0)	13	4.3
HEPATOBILIARY DISORDERS	1	(0.3)	1	0.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	5	1.7
IMMUNE SYSTEM DISORDERS	4	(1.3)	4	1.3	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	3	1.0
INFECTIONS AND INFESTATIONS	38	(12.6)	48	15.9	44	(15.4)	68	23.8	44	(14.8)	51	17.1	68	(22.7)	93	31.0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	26	(8.6)	32	10.6	29	(10.1)	35	12.2	28	(9.4)	33	11.1	31	(10.3)	38	12.7
INVESTIGATIONS	6	(2.0)	6	2.0	3	(1.0)	4	1.4	5	(1.7)	8	2.7	10	(3.3)	12	4.0
METABOLISM AND NUTRITION DISORDERS	8	(2.7)	8	2.7	6	(2.1)	6	2.1	6	(2.0)	7	2.3	8	(2.7)	10	3.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	26	(8.6)	30	10.0	30	(10.5)	43	15.0	38	(12.8)	55	18.5	29	(9.7)	37	12.3
CYSTS AND POLY	10	(3.3)	11	3.7	11	(3.8)	11	3.8	16	(5.4)	17	5.7	13	(4.3)	16	5.3
NERVOUS SYSTEM DISORDERS	19	(6.3)	24	8.0	23	(8.0)	25	8.7	24	(8.1)	25	8.4	33	(11.0)	41	13.7
PSYCHIATRIC DISORDERS	7	(2.3)	8	2.7	5	(1.7)	5	1.7	6	(2.0)	6	2.0	9	(3.0)	9	3.0
RENAL AND URINARY DISORDERS	2	(0.7)	3	1.0	5	(1.7)	5	1.7	6	(2.0)	6	2.0	8	(2.7)	8	2.7
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	25	(8.3)	31	10.3	20	(7.0)	28	9.8	23	(7.7)	30	10.1	24	(8.0)	36	12.0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	7	(2.3)	7	2.3	10	(3.5)	11	3.8	8	(2.7)	8	2.7	7	(2.3)	11	3.7
SURGICAL AND MEDICAL PROCEDURES	16	(5.3)	20	6.6	21	(7.3)	29	10.1	14	(4.7)	18	6.0	25	(8.3)	37	12.3
VASCULAR DISORDERS	11	(3.7)	12	4.0	21	(7.3)	22	7.7	18	(6.0)	18	6.0	24	(8.0)	29	9.7

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total		**141**	**(46.8)**	**318**	**105.6**	**152**	**(53.1)**	**390**	**136.4**	**154**	**(51.7)**	**341**	**114.4**	**171**	**(57.0)**	**455**	**151.7**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	1	(0.3)	2	0.7	6	(2.1)	6	2.1	3	(1.0)	3	1.0	2	(0.7)	2	0.7
	BLOOD DISORDER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HAEMORRHAGIC ANAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	THROMBOCYTOPENIA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
CARDIAC DISORDERS	ANGINA PECTORIS	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	ANGINA UNSTABLE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	AORTIC VALVE DISEASE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	ARRHYTHMIA	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7
	ARRHYTHMIA SUPRAVENTRICULAR	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ARTERIOSPASM CORONARY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ATRIAL FIBRILLATION	5	(1.7)	5	1.7	9	(3.1)	10	3.5	6	(2.0)	6	2.0	2	(0.7)	2	0.7
	ATRIAL FLUTTER	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	BRADYCARDIA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	CARDIAC ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CARDIAC FAILURE	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	CARDIAC FAILURE CHRONIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIAC FAILURE CONGESTIVE	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	CARDIAC PSEUDOANEURYSM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIO-RESPIRATORY ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CONDUCTION DISORDER	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	CORONARY ARTERY DISEASE	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	3	1.0	---	---	---	---
	CORONARY ARTERY OCCLUSION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	GASTROCARDIAC SYNDROME	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HYPERTENSIVE HEART DISEASE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	MYOCARDIAL INFARCTION	4	(1.3)	4	1.3	2	(0.7)	2	0.7	4	(1.3)	4	1.3	1	(0.3)	1	0.3
	MYOCARDIAL ISCHAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NODAL RHYTHM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PALPITATIONS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PERICARDITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SICK SINUS SYNDROME	---	---	---	---	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0
	SINUS BRADYCARDIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VENTRICULAR TACHYCARDIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	SICKLE CELL TRAIT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
EAR AND LABYRINTH DISORDERS	EAR CONGESTION	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	EAR DISORDER	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	EAR HAEMORRHAGE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	EAR PAIN	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HEARING IMPAIRED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MIDDLE EAR INFLAMMATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VERTIGO	4	(1.3)	4	1.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
ENDOCRINE DISORDERS	ENDOCRINE DISORDER	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPOPARATHYROIDISM	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HYPOTHYROIDISM	2	(0.7)	2	0.7	7	(2.4)	7	2.4	1	(0.3)	1	0.3	---	---	---	---
	THYROID DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	THYROID MASS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
GASTROINTESTINAL DISORDERS	ABDOMINAL HERNIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ABDOMINAL PAIN	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	ABDOMINAL PAIN UPPER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	COLITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COLITIS ISCHAEMIC	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	COLITIS ULCERATIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COLONIC POLYP	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CONSTIPATION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---
	DIARRHOEA	4	(1.3)	4	1.3	2	(0.7)	3	1.0	---	---	---	---	2	(0.7)	2	0.7
	DIVERTICULUM INTESTINAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DUODENAL ULCER HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	DYSPEPSIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DYSPHAGIA	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	GASTRIC HAEMORRHAGE	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTRIC POLYPS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	GASTRIC ULCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	3	(1.0)	3	1.0
	GASTRIC ULCER HAEMORRHAGE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTRITIS	---	---	---	---	3	(1.0)	3	1.0	---	---	---	---	1	(0.3)	1	0.3
	GASTROINTESTINAL DISORDER	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	GASTROINTESTINAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	GASTROOESOPHAGEAL REFLUX DISEASE	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	HIATUS HERNIA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ILEUS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	INGUINAL HERNIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	IRRITABLE BOWEL SYNDROME	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LOWER GASTROINTESTINAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7	---	---	---	---
	NAUSEA	3	(1.0)	3	1.0	2	(0.7)	2	0.7	1	(0.3)	1	0.3	6	(2.0)	6	2.0
	OBSTRUCTION GASTRIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OESOPHAGEAL STENOSIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OESOPHAGEAL ULCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	OESOPHAGITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PANCREATITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PHARYNGOESOPHAGEAL DIVERTICULUM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	POLYP COLORECTAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RECTAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RETCHING	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SMALL INTESTINAL OBSTRUCTION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	TEETH BRITTLE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	TOOTH DISORDER	1	(0.3)	1	0.3	2	(0.7)	2	0.7	3	(1.0)	3	1.0	---	---	---	---
	TOOTH IMPACTED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TOOTH LOSS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TOOTHACHE	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	VOMITING	2	(0.7)	2	0.7	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CHEST DISCOMFORT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHEST PAIN	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	CHILLS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CYST	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	FATIGUE	2	(0.7)	2	0.7	3	(1.0)	3	1.0	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	GAIT DISTURBANCE	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	ILL-DEFINED DISORDER	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INFLUENZA LIKE ILLNESS	3	(1.0)	4	1.3	2	(0.7)	2	0.7	4	(1.3)	4	1.3	3	(1.0)	3	1.0
	NON-CARDIAC CHEST PAIN	1	(0.3)	1	0.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	OEDEMA PERIPHERAL	1	(0.3)	1	0.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3	---	---	---	---
	PAIN	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	PYREXIA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
HEPATOBILIARY DISORDERS	BILE DUCT OBSTRUCTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BILE DUCT STONE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CHOLANGITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CHOLECYSTITIS	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	CHOLELITHIASIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	JAUNDICE CHOLESTATIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
IMMUNE SYSTEM DISORDERS	ANAPHYLACTIC REACTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DRUG HYPERSENSITIVITY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPERSENSITIVITY	2	(0.7)	2	0.7	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	IMMUNE SYSTEM DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SEASONAL ALLERGY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
INFECTIONS AND INFESTATIONS	ADENOVIRAL UPPER RESPIRATORY INFECTIC	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	BACTERAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BACTERIAL INFECTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BRONCHIECTASIS	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BRONCHITIS	3	(1.0)	5	1.7	5	(1.7)	5	1.7	6	(2.0)	6	2.0	3	(1.0)	4	1.3
	CATHETER RELATED INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CELLULITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	4	(1.3)	4	1.3
	CELLULITIS STREPTOCOCCAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CHOLECYSTITIS INFECTIVE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CHRONIC SINUSITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CLOSTRIDIUM DIFFICILE COLITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CYSTITIS	3	(1.0)	3	1.0	3	(1.0)	4	1.4	4	(1.3)	4	1.3	8	(2.7)	10	3.3
	DEVICE RELATED INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	DIABETIC FOOT INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DIVERTICULITIS	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	4	(1.3)	4	1.3
	ENTERITIS INFECTIOUS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FUNGAL INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	GASTRIC INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTROENTERITIS	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTROENTERITIS ROTAVIRUS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	GASTROENTERITIS VIRAL	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	GINGIVAL INFECTION	---	---	---	---	1	(0.3)	3	1.0	---	---	---	---	---	---	---	---
	HELICOBACTER GASTRITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HERPES OPHTHALMIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HERPES SIMPLEX OPHTHALMIC	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	HERPES ZOSTER	1	(0.3)	1	0.3	3	(1.0)	4	1.4	4	(1.3)	4	1.3	2	(0.7)	2	0.7
	HYPOPYON	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INFECTION	1	(0.3)	1	0.3	2	(0.7)	3	1.0	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	INFLUENZA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	KIDNEY INFECTION	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	LIVER ABSCESS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LOCALISED INFECTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	LUNG INFECTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MYCETOMA MYCOTIC	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NAIL INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	NASOPHARYNGITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	4	(1.3)	4	1.3
	ONYCHOMYCOSIS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	ORAL CANDIDIASIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ORAL INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OSTEOMYELITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OTITIS MEDIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	PHARYNGITIS	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	PHARYNGITIS STREPTOCOCCAL	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	PNEUMONIA	7	(2.3)	7	2.3	4	(1.4)	4	1.4	7	(2.3)	7	2.3	7	(2.3)	8	2.7
	PNEUMONIA BACTERIAL	---	---	---	---	2	(0.7)	3	1.0	---	---	---	---	---	---	---	---
	POST PROCEDURAL CELLULITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	POST PROCEDURAL SEPSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PSEUDOMONAS INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	RESPIRATORY TRACT INFECTION	---	---	---	---	2	(0.7)	3	1.0	---	---	---	---	---	---	---	---
	RHINITIS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SEPSIS	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	SINUSITIS	2	(0.7)	2	0.7	5	(1.7)	5	1.7	7	(2.3)	9	3.0	2	(0.7)	2	0.7
	SINUSITIS BACTERIAL	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	SKIN INFECTION	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	SOFT TISSUE INFECTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	STAPHYLOCOCCAL INFECTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	TOOTH ABSCESS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	TOOTH INFECTION	3	(1.0)	3	1.0	3	(1.0)	3	1.0	2	(0.7)	3	1.0	2	(0.7)	2	0.7
	UPPER RESPIRATORY TRACT INFECTION	3	(1.0)	3	1.0	1	(0.3)	1	0.3	2	(0.7)	2	0.7	3	(1.0)	3	1.0
	URINARY TRACT INFECTION	6	(2.0)	6	2.0	5	(1.7)	5	1.7	5	(1.7)	5	1.7	17	(5.7)	19	6.3
	URINARY TRACT INFECTION ENTEROCOCCAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VIRAL UPPER RESPIRATORY TRACT INFECTIC	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VULVITIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	WOUND INFECTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ANKLE FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ARTHROPOD BITE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIAC PACEMAKER MALFUNCTION	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	CARTILAGE INJURY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CATARACT OPERATION COMPLICATION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CERVICAL VERTEBRAL FRACTURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CLAVICLE FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COMPRESSION FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CONTUSION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CORNEAL ABRASION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7	5	(1.7)	5	1.7
	DISLOCATION OF JOINT PROSTHESIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	EXCORIATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	EXPOSURE TO TOXIC AGENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	FALL	5	(1.7)	6	2.0	5	(1.7)	5	1.7	6	(2.0)	7	2.3	8	(2.7)	8	2.7
	FEMORAL NECK FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	FEMUR FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FOOT FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	FOREIGN BODY IN EYE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	FRACTURE	4	(1.3)	4	1.3	7	(2.4)	7	2.4	4	(1.3)	4	1.3	2	(0.7)	3	1.0
	HEAD INJURY	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	HIP FRACTURE	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---	2	(0.7)	2	0.7
	HUMERUS FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INCISIONAL HERNIA	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	INTRAOCULAR LENS DISLOCATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INTRAOCULAR LENS OPACITY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	JOINT INJURY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	JOINT SPRAIN	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	LACERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LIMB INJURY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MEDICAL DEVICE COMPLICATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	MENISCUS LESION	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	MULTIPLE FRACTURES	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	OVERDOSE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PELVIC FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PERIORBITAL HAEMATOMA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	POST PROCEDURAL HAEMORRHAGE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	POST-TRAUMATIC PAIN	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	RIB FRACTURE	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7	---	---	---	---
	ROAD TRAFFIC ACCIDENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SKIN LACERATION	2	(0.7)	2	0.7	3	(1.0)	3	1.0	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	SPINAL COMPRESSION FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	SPINAL FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	SUNBURN	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SUPERFICIAL INJURY OF EYE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	TENDON RUPTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	THERMAL BURN	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	UPPER LIMB FRACTURE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	WRIST FRACTURE	---	---	---	---	3	(1.0)	3	1.0	2	(0.7)	2	0.7	---	---	---	---
INVESTIGATIONS	ANTIPHOSPHOLIPID ANTIBODIES POSITIVE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BIOPSY BILE DUCT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BIOPSY LYMPH GLAND ABNORMAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BIOPSY SKIN	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	BLOOD CHOLESTEROL INCREASED	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	BLOOD CREATININE INCREASED	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BLOOD GLUCOSE DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0
	BLOOD GLUCOSE INCREASED	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	2	(0.7)	2	0.7
	BLOOD MAGNESIUM DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BLOOD POTASSIUM DECREASED	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	BLOOD SODIUM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BLOOD SODIUM DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BLOOD TRIGLYCERIDES INCREASED	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CARDIAC MURMUR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HAEMOGLOBIN DECREASED	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	1	(0.3)	1	0.3
	IMMUNOGLOBULINS DECREASED	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INTERNATIONAL NORMALISED RATIO INCREA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PROSTATIC SPECIFIC ANTIGEN INCREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TROPONIN INCREASED	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	WEIGHT DECREASED	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
METABOLISM AND NUTRITION DISORDERS	ANOREXIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DEHYDRATION	2	(0.7)	2	0.7	3	(1.0)	3	1.0	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	FAILURE TO THRIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GLUCOSE TOLERANCE IMPAIRED	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	GOUT	1	(0.3)	1	0.3	---	---	---	---	3	(1.0)	3	1.0	1	(0.3)	3	1.0
	HYPERGLYCAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPERKALAEMIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HYPOKALAEMIA	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7
	HYPONATRAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OBESITY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	VITAMIN B12 DEFICIENCY	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
MUSCULOSKELETAL AND CONNE(	ARTHRALGIA	2	(0.7)	2	0.7	3	(1.0)	3	1.0	7	(2.3)	7	2.3	6	(2.0)	7	2.3
	ARTHRITIS	4	(1.3)	4	1.3	4	(1.4)	6	2.1	7	(2.3)	8	2.7	3	(1.0)	3	1.0
	ARTHROPATHY	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BACK PAIN	5	(1.7)	5	1.7	4	(1.4)	4	1.4	13	(4.4)	13	4.4	5	(1.7)	5	1.7

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	BUNION	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	BURSITIS	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7
	CERVICAL SPINAL STENOSIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	EXOSTOSIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	INTERVERTEBRAL DISC COMPRESSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	INTERVERTEBRAL DISC DEGENERATION	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	INTERVERTEBRAL DISC DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	JOINT EFFUSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	JOINT RANGE OF MOTION DECREASED	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	JOINT SWELLING	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LUMBAR SPINAL STENOSIS	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	4	1.3	2	(0.7)	2	0.7
	MOBILITY DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MUSCLE SPASMS	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	MUSCULAR WEAKNESS	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	MUSCULOSKELETAL CHEST PAIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7
	MUSCULOSKELETAL DISORDER	2	(0.7)	2	0.7	3	(1.0)	5	1.7	6	(2.0)	8	2.7	1	(0.3)	1	0.3
	MUSCULOSKELETAL PAIN	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MYALGIA	---	---	---	---	3	(1.0)	3	1.0	---	---	---	---	---	---	---	---
	MYOSITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NECK PAIN	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7
	OSTEOARTHRITIS	1	(0.3)	1	0.3	2	(0.7)	2	0.7	4	(1.3)	4	1.3	4	(1.3)	4	1.3
	OSTEOPOROSIS	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	PAIN IN EXTREMITY	3	(1.0)	3	1.0	5	(1.7)	5	1.7	2	(0.7)	3	1.0	2	(0.7)	2	0.7
	ROTATOR CUFF SYNDROME	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SYNOVIAL CYST	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	TENDONITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
NEOPLASMS BENIGN, MALIGNANT	BASAL CELL CARCINOMA	4	(1.3)	4	1.3	3	(1.0)	3	1.0	5	(1.7)	6	2.0	2	(0.7)	4	1.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	BENIGN NEOPLASM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BILE DUCT CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLADDER CANCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BLADDER CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BRAIN NEOPLASM	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BREAST CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	BREAST CANCER RECURRENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BREAST CANCER STAGE II	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BREAST CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHRONIC LYMPHOCYTIC LEUKAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	COLON CANCER	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	COLON CANCER METASTATIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DIFFUSE LARGE B-CELL LYMPHOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	FIBROMATOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LUNG NEOPLASM MALIGNANT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MALIGNANT GLIOMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MALIGNANT MELANOMA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MORTONS NEUROMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NEOPLASM	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NON-SMALL CELL LUNG CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NON-SMALL CELL LUNG CANCER METAST	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OVARIAN CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PANCREATIC CARCINOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PROSTATE CANCER	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	PROSTATE CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RENAL CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	SKIN CANCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	SMALL CELL LUNG CANCER STAGE UNSPECIF	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	SQUAMOUS CELL CARCINOMA OF SKIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
NERVOUS SYSTEM DISORDERS	CAROTID ARTERY STENOSIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	CARPAL TUNNEL SYNDROME	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CEREBELLAR INFARCTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CEREBRAL HAEMORRHAGE	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	CEREBRAL INFARCTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CEREBROVASCULAR ACCIDENT	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	CERVICAL MYELOPATHY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CERVICOGENIC HEADACHE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHRONIC INFLAMMATORY DEMYELINATING P	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	COGNITIVE DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CONVULSION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DEMENTIA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	DEMENTIA ALZHEIMERS TYPE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DIZZINESS	7	(2.3)	7	2.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	5	(1.7)	5	1.7
	ENCEPHALOPATHY	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	EXTRAPYRAMIDAL DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	FACIAL PALSY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HAEMORRHAGE INTRACRANIAL	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HEADACHE	4	(1.3)	4	1.3	5	(1.7)	5	1.7	3	(1.0)	3	1.0	1	(0.3)	1	0.3
	HEMIPARESIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPOAESTHESIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	LOSS OF CONSCIOUSNESS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MEMORY IMPAIRMENT	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	4	(1.3)	4	1.3
	MIGRAINE WITH AURA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	NERVE COMPRESSION	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	NERVE ROOT COMPRESSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	NERVOUS SYSTEM DISORDER	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	NEUROPATHY PERIPHERAL	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PARKINSON'S DISEASE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PERIPHERAL SENSORY NEUROPATHY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PERONEAL NERVE PALSY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PRESYNCOPE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RADICULOPATHY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RESTLESS LEGS SYNDROME	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SCIATICA	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	SINUS HEADACHE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SPEECH DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SYNCOPE	---	---	---	---	4	(1.4)	4	1.4	3	(1.0)	3	1.0	5	(1.7)	5	1.7
	SYNCOPE VASOVAGAL	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TRANSIENT ISCHAEMIC ATTACK	1	(0.3)	2	0.7	---	---	---	---	2	(0.7)	2	0.7	3	(1.0)	3	1.0
	TREMOR	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TRIGEMINAL NEURALGIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VITH NERVE PARALYSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
PSYCHIATRIC DISORDERS	ANXIETY	---	---	---	---	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	CONFUSIONAL STATE	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	3	1.0	2	(0.7)	2	0.7
	DEPRESSION	5	(1.7)	5	1.7	---	---	---	---	---	---	---	---	4	(1.3)	4	1.3
	DEPRESSION SUICIDAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HALLUCINATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HALLUCINATION VISUAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INSOMNIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MENTAL STATUS CHANGES	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	PSYCHOTIC DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
RENAL AND URINARY DISORDERS	BLADDER SPASM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CALCULUS BLADDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CALCULUS URETERIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HAEMATURIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	NEPHROLITHIASIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	POLLAKIURIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	RENAL FAILURE	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RENAL FAILURE ACUTE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RENAL FAILURE CHRONIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	URINARY INCONTINENCE	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	URINARY RETENTION	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	BENIGN PROSTATIC HYPERPLASIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PELVIC PROLAPSE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PENILE HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
RESPIRATORY, THORACIC AND MI	ACUTE RESPIRATORY DISTRESS SYNDROME	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ACUTE RESPIRATORY FAILURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ASPIRATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ASTHMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7
	ATELECTASIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BRONCHIAL DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BRONCHOSPASM	4	(1.3)	4	1.3	1	(0.3)	1	0.3	---	---	---	---	4	(1.3)	4	1.3
	CHRONIC OBSTRUCTIVE PULMONARY DISEAS	2	(0.7)	3	1.0	2	(0.7)	4	1.4	3	(1.0)	3	1.0	3	(1.0)	3	1.0
	CHRONIC RESPIRATORY FAILURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	COUGH	6	(2.0)	7	2.3	1	(0.3)	1	0.3	4	(1.3)	4	1.3	4	(1.3)	4	1.3
	DYSPNOEA	9	(3.0)	10	3.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3	2	(0.7)	2	0.7

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	EMPHYSEMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	EPISTAXIS	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	HICCUPS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HYPERCAPNIA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPOXIA	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	IDIOPATHIC PULMONARY FIBROSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	INTERSTITIAL LUNG DISEASE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	NASAL CONGESTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	NASAL SEPTUM DEVIATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PHARYNGOLARYNGEAL PAIN	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	PLEURAL EFFUSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	PLEURISY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PNEUMONIA ASPIRATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	PNEUMONITIS	---	---	---	---	2	(0.7)	2	0.7	4	(1.3)	4	1.3	---	---	---	---
	PRODUCTIVE COUGH	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PULMONARY EMBOLISM	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	PULMONARY HYPERTENSION	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	RESPIRATORY ACIDOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RESPIRATORY DISORDER	---	---	---	---	---	---	---	---	3	(1.0)	5	1.7	4	(1.3)	4	1.3
	RESPIRATORY FAILURE	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RHINITIS ALLERGIC	2	(0.7)	2	0.7	1	(0.3)	1	0.3	5	(1.7)	5	1.7	---	---	---	---
	RHINORRHOEA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SINUS CONGESTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SINUS DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
SKIN AND SUBCUTANEOUS TISSU	ACTINIC KERATOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CUTIS LAXA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DERMAL CYST	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	DERMATITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DERMATITIS ACNEIFORM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DERMATITIS CONTACT	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	3	1.0
	DRY SKIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	ECZEMA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	EXFOLIATIVE RASH	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HEAT RASH	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INGROWING NAIL	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	NAIL DISORDER	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	ONYCHOMADESIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PAIN OF SKIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PETECHIAE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PRURITUS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RASH	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ROSACEA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SEBORRHOEIC DERMATITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SKIN DISORDER	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	SKIN INDURATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SKIN LESION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	SKIN ULCER	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
SURGICAL AND MEDICAL PROCED	ACROCHORDON EXCISION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	AORTIC VALVE REPLACEMENT	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	ATHERECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BAKERS CYST EXCISION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BREAST CYST EXCISION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BUNION OPERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CARDIAC PACEMAKER INSERTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	CARDIAC PACEMAKER REPLACEMENT	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	CARPAL TUNNEL DECOMPRESSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CATARACT OPERATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CERUMEN REMOVAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHEMOTHERAPY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7
	CHOLECYSTECTOMY	---	---	---	---	3	(1.0)	3	1.0	3	(1.0)	3	1.0	---	---	---	---
	CHONDROPLASTY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CORONARY ARTERIAL STENT INSERTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CORONARY ARTERY BYPASS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CRYOTHERAPY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CYST REMOVAL	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ENDODONTIC PROCEDURE	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	FRACTURE TREATMENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	GAMMA RADIATION THERAPY TO SKIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HERNIA REPAIR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	HIP ARTHROPLASTY	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	IMPLANTABLE DEFIBRILLATOR INSERTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INTERNAL FIXATION OF FRACTURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	IRIDOTOMY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	JOINT DISLOCATION REDUCTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	JOINT MANIPULATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	KNEE ARTHROPLASTY	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	3	(1.0)	5	1.7
	LASER THERAPY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	LUNG LOBECTOMY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MASTECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	MAXILLARY ANTRUM OPERATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MICROGRAPHIC SKIN SURGERY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MOLE EXCISION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	3	1.0	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	NAIL OPERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OSTECTOMY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PELVIC FLOOR REPAIR	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PHARYNGEAL OPERATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	POLYPECTOMY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RADIOTHERAPY	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	RADIOTHERAPY TO LUNG	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SEPTOPLASTY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SHOULDER ARTHROPLASTY	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	SIMPLE MASTECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SKIN LESION EXCISION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	3	1.0
	SKIN NEOPLASM EXCISION	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	SPINAL FUSION SURGERY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SPINAL LAMINECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	STENT PLACEMENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SURGICAL STAPLING	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SUTURE INSERTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	TOE OPERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7
	TOOTH EXTRACTION	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	3	1.0
	TRANSFUSION	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	TRANSURETHRAL PROSTATECTOMY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VASCULAR CAUTERISATION	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---	---	---	---	---
	VITRECTOMY	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	WOUND DEBRIDEMENT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	WRIST SURGERY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
VASCULAR DISORDERS	ACCELERATED HYPERTENSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ANEURYSM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity 2 or higher
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	ANGIOPATHY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	AORTIC ANEURYSM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ARTERIOSCLEROSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DEEP VEIN THROMBOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	EMBOLISM	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HAEMATOMA	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	HYPERTENSION	6	(2.0)	7	2.3	14	(4.9)	14	4.9	10	(3.4)	10	3.4	16	(5.3)	18	6.0
	HYPOTENSION	1	(0.3)	1	0.3	2	(0.7)	2	0.7	3	(1.0)	3	1.0	6	(2.0)	6	2.0
	INTERMITTENT CLAUDICATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ORTHOSTATIC HYPOTENSION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PERIPHERAL ISCHAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PHLEBITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	THROMBOSIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	VARICOSE VEIN	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Systemic Adverse Events by System Organ Class and Treatment Group through Week 052
Severity≥ 3
(as of December 31, 2010)

	Treatment Group															
	1				2				3				4			
	People		Events		People		Events		People		Events		People		Events	
System Organ Class	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total	**59**	**(19.6)**	**86**	**28.6**	**64**	**(22.4)**	**125**	**43.7**	**64**	**(21.5)**	**100**	**33.6**	**81**	**(27.0)**	**149**	**49.7**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	---	---	---	---	3	(1.0)	3	1.0	1	(0.3)	1	0.3	2	(0.7)	2	0.7
CARDIAC DISORDERS	10	(3.3)	13	4.3	16	(5.6)	22	7.7	11	(3.7)	14	4.7	14	(4.7)	15	5.0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
EAR AND LABYRINTH DISORDERS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
GASTROINTESTINAL DISORDERS	2	(0.7)	2	0.7	8	(2.8)	13	4.5	2	(0.7)	3	1.0	6	(2.0)	6	2.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4	(1.3)	4	1.3	4	(1.4)	4	1.4	3	(1.0)	3	1.0	4	(1.3)	4	1.3
HEPATOBILIARY DISORDERS	1	(0.3)	1	0.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	4	1.3
IMMUNE SYSTEM DISORDERS	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
INFECTIONS AND INFESTATIONS	7	(2.3)	8	2.7	10	(3.5)	12	4.2	11	(3.7)	11	3.7	17	(5.7)	19	6.3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	9	(3.0)	10	3.3	8	(2.8)	9	3.1	7	(2.3)	7	2.3	11	(3.7)	12	4.0
INVESTIGATIONS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	3	(1.0)	3	1.0	4	(1.3)	4	1.3
METABOLISM AND NUTRITION DISORDERS	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	3	1.0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5	(1.7)	6	2.0	5	(1.7)	7	2.4	9	(3.0)	11	3.7	6	(2.0)	6	2.0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYST	7	(2.3)	7	2.3	5	(1.7)	5	1.7	9	(3.0)	9	3.0	9	(3.0)	9	3.0
NERVOUS SYSTEM DISORDERS	6	(2.0)	7	2.3	12	(4.2)	13	4.5	13	(4.4)	13	4.4	11	(3.7)	11	3.7
PSYCHIATRIC DISORDERS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
RENAL AND URINARY DISORDERS	1	(0.3)	1	0.3	4	(1.4)	4	1.4	2	(0.7)	2	0.7	2	(0.7)	2	0.7
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9	(3.0)	10	3.3	4	(1.4)	6	2.1	5	(1.7)	6	2.0	8	(2.7)	15	5.0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	---	---	---	---	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	3	1.0
SURGICAL AND MEDICAL PROCEDURES	6	(2.0)	6	2.0	5	(1.7)	7	2.4	4	(1.3)	6	2.0	12	(4.0)	15	5.0
VASCULAR DISORDERS	5	(1.7)	5	1.7	9	(3.1)	10	3.5	6	(2.0)	6	2.0	10	(3.3)	14	4.7

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total		**59**	**(19.6)**	**86**	**28.6**	**64**	**(22.4)**	**125**	**43.7**	**64**	**(21.5)**	**100**	**33.6**	**81**	**(27.0)**	**149**	**49.7**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	HAEMORRHAGIC ANAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
CARDIAC DISORDERS	ANGINA PECTORIS	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	AORTIC VALVE DISEASE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	ARRHYTHMIA	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7
	ARRHYTHMIA SUPRAVENTRICULAR	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ATRIAL FIBRILLATION	2	(0.7)	2	0.7	6	(2.1)	7	2.4	4	(1.3)	4	1.3	1	(0.3)	1	0.3
	ATRIAL FLUTTER	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CARDIAC ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CARDIAC FAILURE	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	CARDIAC FAILURE CHRONIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIAC FAILURE CONGESTIVE	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	CARDIAC PSEUDOANEURYSM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIO-RESPIRATORY ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CONDUCTION DISORDER	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	CORONARY ARTERY DISEASE	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	CORONARY ARTERY OCCLUSION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	HYPERTENSIVE HEART DISEASE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MYOCARDIAL INFARCTION	4	(1.3)	4	1.3	2	(0.7)	2	0.7	4	(1.3)	4	1.3	1	(0.3)	1	0.3
	MYOCARDIAL ISCHAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NODAL RHYTHM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PERICARDITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VENTRICULAR TACHYCARDIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
CONGENITAL, FAMILIAL AND GENE	SICKLE CELL TRAIT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
EAR AND LABYRINTH DISORDERS	EAR CONGESTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HEARING IMPAIRED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	VERTIGO	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
GASTROINTESTINAL DISORDERS	ABDOMINAL HERNIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ABDOMINAL PAIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	COLITIS ULCERATIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DUODENAL ULCER HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DYSPHAGIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	GASTRIC POLYPS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	GASTRIC ULCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	GASTRIC ULCER HAEMORRHAGE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTRITIS	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---
	GASTROINTESTINAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ILEUS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LOWER GASTROINTESTINAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7	---	---	---	---
	NAUSEA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	PANCREATITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RECTAL HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SMALL INTESTINAL OBSTRUCTION	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	VOMITING	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
GENERAL DISORDERS AND ADMIN	ASTHENIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CHEST PAIN	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7
	FATIGUE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	GAIT DISTURBANCE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	INFLUENZA LIKE ILLNESS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	NON-CARDIAC CHEST PAIN	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
HEPATOBILIARY DISORDERS	BILE DUCT OBSTRUCTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BILE DUCT STONE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	CHOLECYSTITIS	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	CHOLELITHIASIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	JAUNDICE CHOLESTATIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
IMMUNE SYSTEM DISORDERS	ANAPHYLACTIC REACTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DRUG HYPERSENSITIVITY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
INFECTIONS AND INFESTATIONS	BACTERAEMIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BRONCHIECTASIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BRONCHITIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CELLULITIS	---	---	---	---	---	---	---	---	---	---	---	---	3	(1.0)	3	1.0
	CELLULITIS STREPTOCOCCAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CHOLECYSTITIS INFECTIVE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CLOSTRIDIUM DIFFICILE COLITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CYSTITIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DIVERTICULITIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	ENTERITIS INFECTIOUS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	GASTROENTERITIS VIRAL	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HERPES OPHTHALMIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HERPES ZOSTER	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---
	INFECTION	---	---	---	---	1	(0.3)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	LIVER ABSCESS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OSTEOMYELITIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	PNEUMONIA	3	(1.0)	3	1.0	1	(0.3)	1	0.3	5	(1.7)	5	1.7	5	(1.7)	5	1.7
	PNEUMONIA BACTERIAL	---	---	---	---	2	(0.7)	3	1.0	---	---	---	---	---	---	---	---
	POST PROCEDURAL CELLULITIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	POST PROCEDURAL SEPSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PSEUDOMONAS INFECTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SEPSIS	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	URINARY TRACT INFECTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	4	1.3
INJURY, POISONING AND PROCED	ANKLE FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CARDIAC PACEMAKER MALFUNCTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CATARACT OPERATION COMPLICATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CERVICAL VERTEBRAL FRACTURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	COMPRESSION FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CORNEAL ABRASION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	EXCORIATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	FALL	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	FEMORAL NECK FRACTURE	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	FOREIGN BODY IN EYE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	FRACTURE	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	HIP FRACTURE	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---	2	(0.7)	2	0.7
	HUMERUS FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	INCISIONAL HERNIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	INTRAOCULAR LENS DISLOCATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LACERATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MEDICAL DEVICE COMPLICATION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	MULTIPLE FRACTURES	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	OVERDOSE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PELVIC FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	POST PROCEDURAL HAEMORRHAGE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	RIB FRACTURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	SKIN LACERATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	SPINAL COMPRESSION FRACTURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	WRIST FRACTURE	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
INVESTIGATIONS	BIOPSY BILE DUCT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BIOPSY LYMPH GLAND ABNORMAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BIOPSY SKIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BLOOD MAGNESIUM DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BLOOD SODIUM DECREASED	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CARDIAC MURMUR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HAEMOGLOBIN DECREASED	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	INTERNATIONAL NORMALISED RATIO INCREA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TROPONIN INCREASED	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
METABOLISM AND NUTRITION DIS	DEHYDRATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	FAILURE TO THRIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPERGLYCAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPERKALAEMIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HYPOKALAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPONATRAEMIA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
MUSCULOSKELETAL AND CONNE	ARTHRALGIA	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---
	ARTHRITIS	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BACK PAIN	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	BUNION	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---	---	---	---	---
	CERVICAL SPINAL STENOSIS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	EXOSTOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	INTERVERTEBRAL DISC COMPRESSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	JOINT RANGE OF MOTION DECREASED	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	LUMBAR SPINAL STENOSIS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	MUSCLE SPASMS	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	MUSCULAR WEAKNESS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MUSCULOSKELETAL DISORDER	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7	---	---	---	---
	OSTEOARTHRITIS	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	3	(1.0)	3	1.0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLY	BILE DUCT CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLADDER CANCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BLADDER CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BRAIN NEOPLASM	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BREAST CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	BREAST CANCER RECURRENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BREAST CANCER STAGE II	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	BREAST CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CHRONIC LYMPHOCYTIC LEUKAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	COLON CANCER	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	COLON CANCER METASTATIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	DIFFUSE LARGE B-CELL LYMPHOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	LUNG NEOPLASM MALIGNANT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MALIGNANT GLIOMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NON-SMALL CELL LUNG CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NON-SMALL CELL LUNG CANCER METAST	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OVARIAN CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	PANCREATIC CARCINOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PROSTATE CANCER	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	PROSTATE CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RENAL CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	SMALL CELL LUNG CANCER STAGE UNSPECIF	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SQUAMOUS CELL CARCINOMA OF SKIN	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
NERVOUS SYSTEM DISORDERS	CAROTID ARTERY STENOSIS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	CEREBELLAR INFARCTION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	CEREBRAL HAEMORRHAGE	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	CEREBRAL INFARCTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CEREBROVASCULAR ACCIDENT	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	CHRONIC INFLAMMATORY DEMYELINATING P	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	COGNITIVE DISORDER	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CONVULSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	DEMENTIA ALZHEIMERS TYPE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	DIZZINESS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ENCEPHALOPATHY	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	FACIAL PALSY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HEADACHE	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	HEMIPARESIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	LOSS OF CONSCIOUSNESS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PRESYNCOPE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	SPEECH DISORDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SYNCOPE	---	---	---	---	3	(1.0)	3	1.0	2	(0.7)	2	0.7	4	(1.3)	4	1.3
	SYNCOPE VASOVAGAL	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	TRANSIENT ISCHAEMIC ATTACK	1	(0.3)	2	0.7	---	---	---	---	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	TRIGEMINAL NEURALGIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
PSYCHIATRIC DISORDERS	DEPRESSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DEPRESSION SUICIDAL	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HALLUCINATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MENTAL STATUS CHANGES	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
RENAL AND URINARY DISORDERS	CALCULUS BLADDER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CALCULUS URETERIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HAEMATURIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	RENAL FAILURE	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	RENAL FAILURE ACUTE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	URINARY RETENTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
REPRODUCTIVE SYSTEM AND BRI	PELVIC PROLAPSE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PENILE HAEMORRHAGE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
RESPIRATORY, THORACIC AND MI	ACUTE RESPIRATORY FAILURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ASPIRATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BRONCHOSPASM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CHRONIC OBSTRUCTIVE PULMONARY DISEAS	1	(0.3)	1	0.3	1	(0.3)	2	0.7	1	(0.3)	1	0.3	3	(1.0)	3	1.0
	CHRONIC RESPIRATORY FAILURE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DYSPNOEA	4	(1.3)	5	1.7	---	---	---	---	---	---	---	---	---	---	---	---
	HYPERCAPNIA	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPOXIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	IDIOPATHIC PULMONARY FIBROSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	INTERSTITIAL LUNG DISEASE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	PLEURAL EFFUSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PLEURISY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	PNEUMONIA ASPIRATION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	3	1.0
	PNEUMONITIS	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	PULMONARY EMBOLISM	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	PULMONARY HYPERTENSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RESPIRATORY ACIDOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RESPIRATORY FAILURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
SKIN AND SUBCUTANEOUS TISSU	DERMATITIS CONTACT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	ONYCHOMADESIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PAIN OF SKIN	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	PRURITUS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	RASH	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SKIN ULCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
SURGICAL AND MEDICAL PROCED	AORTIC VALVE REPLACEMENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ATHERECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BREAST CYST EXCISION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIAC PACEMAKER INSERTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CARDIAC PACEMAKER REPLACEMENT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	CHOLECYSTECTOMY	---	---	---	---	3	(1.0)	3	1.0	3	(1.0)	3	1.0	---	---	---	---
	CORONARY ARTERIAL STENT INSERTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CORONARY ARTERY BYPASS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HERNIA REPAIR	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	HIP ARTHROPLASTY	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	IMPLANTABLE DEFIBRILLATOR INSERTION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	KNEE ARTHROPLASTY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	3	(1.0)	5	1.7
	LUNG LOBECTOMY	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	MASTECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥3
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	SKIN LESION EXCISION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SPINAL FUSION SURGERY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	SPINAL LAMINECTOMY	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	STENT PLACEMENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	TRANSFUSION	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	TRANSURETHRAL PROSTATECTOMY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	VITRECTOMY	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	WOUND DEBRIDEMENT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
VASCULAR DISORDERS	ACCELERATED HYPERTENSION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	ANEURYSM	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	AORTIC ANEURYSM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	ARTERIOSCLEROSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	DEEP VEIN THROMBOSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	HAEMATOMA	---	---	---	---	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	HYPERTENSION	3	(1.0)	3	1.0	5	(1.7)	5	1.7	2	(0.7)	2	0.7	5	(1.7)	7	2.3
	HYPOTENSION	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	INTERMITTENT CLAUDICATION	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	THROMBOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Systemic Adverse Events by System Organ Class and Treatment Group through Week 052
Severity ≥4
(as of December 31, 2010)

	Treatment Group															
	1				2				3				4			
	People		Events		People		Events		People		Events		People		Events	
System Organ Class	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total	**10**	**(3.3)**	**12**	**4.0**	**13**	**(4.5)**	**17**	**5.9**	**11**	**(3.7)**	**12**	**4.0**	**20**	**(6.7)**	**22**	**7.3**
CARDIAC DISORDERS	3	(1.0)	4	1.3	4	(1.4)	5	1.7	3	(1.0)	3	1.0	4	(1.3)	4	1.3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
IMMUNE SYSTEM DISORDERS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
INFECTIONS AND INFESTATIONS	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	2	(0.7)	3	1.0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
METABOLISM AND NUTRITION DISORDERS	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
CYSTS AND POLY	4	(1.3)	4	1.3	3	(1.0)	3	1.0	4	(1.3)	4	1.3	5	(1.7)	5	1.7
NERVOUS SYSTEM DISORDERS	1	(0.3)	1	0.3	3	(1.0)	3	1.0	2	(0.7)	2	0.7	1	(0.3)	1	0.3
PSYCHIATRIC DISORDERS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
RENAL AND URINARY DISORDERS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	(0.3)	1	0.3	1	(0.3)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
SURGICAL AND MEDICAL PROCEDURES	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
VASCULAR DISORDERS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥4
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total		**10**	**(3.3)**	**12**	**4.0**	**13**	**(4.5)**	**17**	**5.9**	**11**	**(3.7)**	**12**	**4.0**	**20**	**(6.7)**	**22**	**7.3**
CARDIAC DISORDERS	AORTIC VALVE DISEASE	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CARDIAC ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CARDIAC FAILURE CONGESTIVE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	CARDIO-RESPIRATORY ARREST	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	CORONARY ARTERY DISEASE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	HYPERTENSIVE HEART DISEASE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	MYOCARDIAL INFARCTION	2	(0.7)	2	0.7	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---
	VENTRICULAR TACHYCARDIA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
GENERAL DISORDERS AND ADMIN	GAIT DISTURBANCE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
IMMUNE SYSTEM DISORDERS	ANAPHYLACTIC REACTION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
INFECTIONS AND INFESTATIONS	ENTERITIS INFECTIOUS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PNEUMONIA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	POST PROCEDURAL SEPSIS	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	SEPSIS	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
INJURY, POISONING AND PROCED	FALL	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HUMERUS FRACTURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
METABOLISM AND NUTRITION DIS	FAILURE TO THRIVE	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	HYPERGLYCAEMIA	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
MUSCULOSKELETAL AND CONNE	LUMBAR SPINAL STENOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥4
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
NEOPLASMS BENIGN, MALIGNANT	BILE DUCT CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	BLADDER CANCER	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BRAIN NEOPLASM	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BREAST CANCER RECURRENT	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	BREAST CANCER STAGE III	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	COLON CANCER METASTATIC	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	LUNG NEOPLASM MALIGNANT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	MALIGNANT GLIOMA	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	NON-SMALL CELL LUNG CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	NON-SMALL CELL LUNG CANCER METAST	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	OVARIAN CANCER	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PANCREATIC CARCINOMA	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	PROSTATE CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	RENAL CANCER METASTATIC	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	SMALL CELL LUNG CANCER STAGE UNSPECIF	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
NERVOUS SYSTEM DISORDERS	CEREBRAL HAEMORRHAGE	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	CEREBRAL INFARCTION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CEREBROVASCULAR ACCIDENT	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	ENCEPHALOPATHY	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	TRANSIENT ISCHAEMIC ATTACK	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
PSYCHIATRIC DISORDERS	DEPRESSION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
RENAL AND URINARY DISORDERS	RENAL FAILURE	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
RESPIRATORY, THORACIC AND MI	ACUTE RESPIRATORY FAILURE	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Adverse Events by System Organ Class, Preferred Term, and Treatment Group
Severity ≥4
(as of December 31, 2010)

		Treatment Group															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
System Organ Class	Preferred Term	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
	CHRONIC OBSTRUCTIVE PULMONARY DISEAS	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	PNEUMONIA ASPIRATION	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	PULMONARY EMBOLISM	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	RESPIRATORY FAILURE	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
SURGICAL AND MEDICAL PROCED	AORTIC VALVE REPLACEMENT	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	BREAST CYST EXCISION	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	CARDIAC PACEMAKER REPLACEMENT	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
VASCULAR DISORDERS	THROMBOSIS	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Eye Disorder Adverse Events Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total		**248**	**(82.4)**	**1,063**	**353.2**	**235**	**(82.2)**	**1,000**	**349.7**	**229**	**(76.8)**	**851**	**285.6**	**230**	**(76.7)**	**895**	**298.3**
Endophthalmitis	Study Eye Only	2	(0.7)	2	0.7	4	(1.4)	4	1.4	---	---	---	---	---	---	---	---
	Fellow Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
Ocular Vessel Embolism or Occlusion	Study Eye Only	---	---	---	---	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	3	1.0
	Fellow Eye Only	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
Uveitis, Scleritis, and Anterior Chamber Inflammation	Study Eye Only	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	2	(0.7)	5	1.7
	Fellow Eye Only	2	(0.7)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
	Both Eyes	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
Detachment of the Retinal Pigment Epithelium	Study Eye Only	11	(3.7)	11	3.7	9	(3.1)	9	3.1	10	(3.4)	10	3.4	10	(3.3)	12	4.0
	Fellow Eye Only	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
Macular Degeneration	Study Eye Only	7	(2.3)	8	2.7	5	(1.7)	5	1.7	6	(2.0)	7	2.3	6	(2.0)	7	2.3
	Fellow Eye Only	12	(4.0)	12	4.0	7	(2.4)	7	2.4	6	(2.0)	6	2.0	18	(6.0)	19	6.3
Retinal Tear	Study Eye Only	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	Fellow Eye Only	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
Retinal and Choroidal Hemorrhage	Study Eye Only	4	(1.3)	4	1.3	7	(2.4)	8	2.8	6	(2.0)	6	2.0	12	(4.0)	13	4.3
	Fellow Eye Only	6	(2.0)	7	2.3	6	(2.1)	6	2.1	3	(1.0)	3	1.0	2	(0.7)	2	0.7
Retinal and Choroidal Detachment	Study Eye Only	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	3	(1.0)	6	2.0
	Fellow Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7

Eye Disorder Adverse Events Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Vitreous Hemorrhage	Study Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	Fellow Eye Only	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---
Vitreous detachment	Study Eye Only	6	(2.0)	6	2.0	7	(2.4)	7	2.4	12	(4.0)	12	4.0	5	(1.7)	5	1.7
	Fellow Eye Only	6	(2.0)	6	2.0	6	(2.1)	6	2.1	1	(0.3)	1	0.3	5	(1.7)	5	1.7
	Both Eyes	3	(1.0)	3	1.0	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	Unknown	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
Retinal, choroidal, and vitreal disorders	Study Eye Only	14	(4.7)	14	4.7	15	(5.2)	18	6.3	13	(4.4)	15	5.0	11	(3.7)	14	4.7
	Fellow Eye Only	8	(2.7)	9	3.0	5	(1.7)	5	1.7	7	(2.3)	7	2.3	5	(1.7)	5	1.7
	Both Eyes	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
Ocular hypertension	Study Eye Only	18	(6.0)	32	10.6	13	(4.5)	23	8.0	15	(5.0)	21	7.0	12	(4.0)	22	7.3
	Fellow Eye Only	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	Both Eyes	---	---	---	---	3	(1.0)	3	1.0	2	(0.7)	2	0.7	1	(0.3)	1	0.3
Glaucoma	Study Eye Only	1	(0.3)	1	0.3	3	(1.0)	3	1.0	3	(1.0)	4	1.3	5	(1.7)	5	1.7
	Fellow Eye Only	2	(0.7)	2	0.7	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7
	Both Eyes	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
Reduced or Blurred Vision	Study Eye Only	38	(12.6)	48	15.9	36	(12.6)	46	16.1	40	(13.4)	53	17.8	39	(13.0)	49	16.3
	Fellow Eye Only	15	(5.0)	16	5.3	14	(4.9)	15	5.2	9	(3.0)	11	3.7	15	(5.0)	18	6.0
	Both Eyes	13	(4.3)	17	5.6	11	(3.8)	12	4.2	12	(4.0)	12	4.0	14	(4.7)	19	6.3
	Unknown	2	(0.7)	2	0.7	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7
Temporary vision loss	Study Eye Only	3	(1.0)	3	1.0	---	---	---	---	1	(0.3)	2	0.7	2	(0.7)	2	0.7
	Fellow Eye Only	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	Both Eyes	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3

Eye Disorder Adverse Events Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Disturbed Vision	Study Eye Only	8	(2.7)	10	3.3	2	(0.7)	2	0.7	5	(1.7)	5	1.7	3	(1.0)	3	1.0
	Fellow Eye Only	2	(0.7)	3	1.0	4	(1.4)	4	1.4	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	Both Eyes	6	(2.0)	6	2.0	5	(1.7)	5	1.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7
Photophobia	Study Eye Only	3	(1.0)	3	1.0	3	(1.0)	3	1.0	3	(1.0)	3	1.0	2	(0.7)	2	0.7
	Fellow Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	Both Eyes	2	(0.7)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	2	0.7	---	---	---	---
	Unknown	1	(0.3)	1	0.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7	---	---	---	---
Conjunctival Hemorrhage	Study Eye Only	129	(42.9)	340	113.0	134	(46.9)	379	132.5	119	(39.9)	252	84.6	118	(39.3)	282	94.0
	Fellow Eye Only	10	(3.3)	12	4.0	3	(1.0)	5	1.7	8	(2.7)	13	4.4	6	(2.0)	8	2.7
	Both Eyes	3	(1.0)	3	1.0	1	(0.3)	2	0.7	2	(0.7)	2	0.7	2	(0.7)	3	1.0
	Unknown	20	(6.6)	30	10.0	7	(2.4)	13	4.5	8	(2.7)	15	5.0	15	(5.0)	27	9.0
Eye Pain	Study Eye Only	60	(19.9)	92	30.6	55	(19.2)	79	27.6	53	(17.8)	77	25.8	45	(15.0)	65	21.7
	Fellow Eye Only	10	(3.3)	13	4.3	7	(2.4)	8	2.8	16	(5.4)	21	7.0	9	(3.0)	10	3.3
	Both Eyes	6	(2.0)	6	2.0	5	(1.7)	5	1.7	6	(2.0)	7	2.3	2	(0.7)	2	0.7
	Unknown	7	(2.3)	8	2.7	3	(1.0)	3	1.0	6	(2.0)	6	2.0	2	(0.7)	3	1.0
Foreign Body Sensation, Eye Irritation	Study Eye Only	18	(6.0)	29	9.6	25	(8.7)	40	14.0	22	(7.4)	25	8.4	20	(6.7)	27	9.0
	Fellow Eye Only	5	(1.7)	8	2.7	1	(0.3)	1	0.3	3	(1.0)	3	1.0	4	(1.3)	4	1.3
	Both Eyes	3	(1.0)	3	1.0	4	(1.4)	7	2.4	3	(1.0)	3	1.0	4	(1.3)	5	1.7
	Unknown	2	(0.7)	2	0.7	---	---	---	---	2	(0.7)	2	0.7	2	(0.7)	2	0.7

Eye Disorder Adverse Events Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Floaters and Flashes	Study Eye Only	69	(22.9)	87	28.9	54	(18.9)	70	24.5	45	(15.1)	56	18.8	48	(16.0)	62	20.7
	Fellow Eye Only	13	(4.3)	15	5.0	13	(4.5)	16	5.6	10	(3.4)	10	3.4	12	(4.0)	15	5.0
	Both Eyes	6	(2.0)	8	2.7	6	(2.1)	10	3.5	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	Unknown	4	(1.3)	4	1.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	5	(1.7)	6	2.0
Conjunctivitis, Keratitis, other conjunctival and corneal disorders	Study Eye Only	11	(3.7)	13	4.3	14	(4.9)	18	6.3	8	(2.7)	8	2.7	13	(4.3)	14	4.7
	Fellow Eye Only	5	(1.7)	7	2.3	4	(1.4)	5	1.7	5	(1.7)	6	2.0	5	(1.7)	6	2.0
	Both Eyes	5	(1.7)	5	1.7	9	(3.1)	10	3.5	7	(2.3)	7	2.3	8	(2.7)	8	2.7
	Unknown	3	(1.0)	3	1.0	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
Blepharitis, Dry Eye, other eyelid and tear disorders	Study Eye Only	28	(9.3)	38	12.6	28	(9.8)	34	11.9	22	(7.4)	23	7.7	27	(9.0)	30	10.0
	Fellow Eye Only	8	(2.7)	8	2.7	10	(3.5)	10	3.5	7	(2.3)	9	3.0	6	(2.0)	7	2.3
	Both Eyes	22	(7.3)	30	10.0	15	(5.2)	23	8.0	34	(11.4)	43	14.4	18	(6.0)	22	7.3
	Unknown	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7	---	---	---	---
Corneal disorders	Study Eye Only	1	(0.3)	2	0.7	3	(1.0)	3	1.0	5	(1.7)	6	2.0	3	(1.0)	6	2.0
	Fellow Eye Only	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	Both Eyes	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
Hyphema	Study Eye Only	2	(0.7)	3	1.0	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
Ocular Hyperemia and Swelling	Study Eye Only	6	(2.0)	11	3.7	8	(2.8)	10	3.5	11	(3.7)	12	4.0	9	(3.0)	13	4.3
	Fellow Eye Only	3	(1.0)	3	1.0	1	(0.3)	1	0.3	3	(1.0)	3	1.0	1	(0.3)	2	0.7
	Both Eyes	3	(1.0)	3	1.0	1	(0.3)	2	0.7	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	Unknown	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---

Eye Disorder Adverse Events Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Cataract and related conditions	Study Eye Only	11	(3.7)	13	4.3	10	(3.5)	11	3.8	6	(2.0)	7	2.3	5	(1.7)	5	1.7
	Fellow Eye Only	8	(2.7)	8	2.7	7	(2.4)	7	2.4	7	(2.3)	8	2.7	8	(2.7)	9	3.0
	Both Eyes	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3
Optic nerve conditions	Study Eye Only	1	(0.3)	1	0.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	1	0.3
	Fellow Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7
Other	Study Eye Only	6	(2.0)	6	2.0	6	(2.1)	7	2.4	6	(2.0)	6	2.0	3	(1.0)	4	1.3
	Fellow Eye Only	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	---	---	---	---
	Both Eyes	3	(1.0)	3	1.0	---	---	---	---	3	(1.0)	3	1.0	1	(0.3)	2	0.7

Eye Disorder Adverse Events Severity ≥ 2 by Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Total		**56**	**(18.6)**	**96**	**31.9**	**59**	**(20.6)**	**123**	**43.0**	**54**	**(18.1)**	**81**	**27.2**	**68**	**(22.7)**	**102**	**34.0**
Endophthalmitis	Study Eye Only	2	(0.7)	2	0.7	4	(1.4)	4	1.4	---	---	---	---	---	---	---	---
	Fellow Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
Ocular Vessel Embolism or Occlusion	Study Eye Only	---	---	---	---	---	---	---	---	---	---	---	---	2	(0.7)	3	1.0
Uveitis, Scleritis, and Anterior Chamber Inflammation	Study Eye Only	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	Fellow Eye Only	2	(0.7)	3	1.0	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
Detachment of the Retinal Pigment Epithelium	Study Eye Only	2	(0.7)	2	0.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	Fellow Eye Only	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
Macular Degeneration	Study Eye Only	4	(1.3)	5	1.7	1	(0.3)	1	0.3	2	(0.7)	2	0.7	3	(1.0)	3	1.0
	Fellow Eye Only	4	(1.3)	4	1.3	2	(0.7)	2	0.7	4	(1.3)	4	1.3	6	(2.0)	6	2.0
Retinal Tear	Study Eye Only	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
Retinal and Choroidal Hemorrhage	Study Eye Only	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	6	(2.0)	6	2.0
	Fellow Eye Only	1	(0.3)	1	0.3	3	(1.0)	3	1.0	1	(0.3)	1	0.3	1	(0.3)	1	0.3
Retinal and Choroidal Detachment	Study Eye Only	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---	1	(0.3)	1	0.3
	Fellow Eye Only	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	2	0.7
Vitreous Hemorrhage	Study Eye Only	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	Fellow Eye Only	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

Eye Disorder Adverse Events Severity ≥ 2 by Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Retinal, choroidal, and vitreal disorders	Study Eye Only	2	(0.7)	2	0.7	3	(1.0)	3	1.0	2	(0.7)	2	0.7	1	(0.3)	1	0.3
	Fellow Eye Only	1	(0.3)	1	0.3	1	(0.3)	1	0.3	4	(1.3)	4	1.3	---	---	---	---
Ocular hypertension	Study Eye Only	3	(1.0)	3	1.0	3	(1.0)	7	2.4	2	(0.7)	2	0.7	2	(0.7)	2	0.7
	Fellow Eye Only	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
	Both Eyes	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
Glaucoma	Study Eye Only	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	2	0.7	---	---	---	---
	Fellow Eye Only	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	Both Eyes	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
Reduced or Blurred Vision	Study Eye Only	7	(2.3)	8	2.7	7	(2.4)	10	3.5	6	(2.0)	7	2.3	8	(2.7)	8	2.7
	Fellow Eye Only	1	(0.3)	1	0.3	1	(0.3)	1	0.3	3	(1.0)	4	1.3	2	(0.7)	2	0.7
	Both Eyes	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	4	(1.3)	4	1.3
Temporary vision loss	Study Eye Only	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
	Fellow Eye Only	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
Disturbed Vision	Study Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	Both Eyes	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
Photophobia	Study Eye Only	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
	Both Eyes	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
Conjunctival Hemorrhage	Study Eye Only	7	(2.3)	11	3.7	14	(4.9)	17	5.9	8	(2.7)	8	2.7	9	(3.0)	16	5.3
	Fellow Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	1	(0.3)	1	0.3

Eye Disorder Adverse Events Severity ≥ 2 by Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Eye Pain	Study Eye Only	13	(4.3)	17	5.6	11	(3.8)	13	4.5	6	(2.0)	6	2.0	9	(3.0)	9	3.0
	Fellow Eye Only	---	---	---	---	1	(0.3)	1	0.3	3	(1.0)	3	1.0	---	---	---	---
Foreign Body Sensation, Eye Irritation	Study Eye Only	---	---	---	---	4	(1.4)	13	4.5	---	---	---	---	1	(0.3)	1	0.3
	Fellow Eye Only	---	---	---	---	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3
	Both Eyes	---	---	---	---	2	(0.7)	5	1.7	---	---	---	---	---	---	---	---
Floaters and Flashes	Study Eye Only	1	(0.3)	1	0.3	2	(0.7)	2	0.7	1	(0.3)	1	0.3	5	(1.7)	5	1.7
	Fellow Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	Both Eyes	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---	---	---	---	---
Conjunctivitis, Keratitis, other conjunctival and corneal disorders	Study Eye Only	3	(1.0)	4	1.3	4	(1.4)	5	1.7	---	---	---	---	2	(0.7)	2	0.7
	Fellow Eye Only	1	(0.3)	2	0.7	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	Both Eyes	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	1	0.3
Blepharitis, Dry Eye, other eyelid and tear disorders	Study Eye Only	2	(0.7)	2	0.7	5	(1.7)	6	2.1	1	(0.3)	1	0.3	4	(1.3)	4	1.3
	Fellow Eye Only	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	---	---	---	---
	Both Eyes	3	(1.0)	3	1.0	3	(1.0)	3	1.0	4	(1.3)	5	1.7	4	(1.3)	4	1.3
Corneal disorders	Study Eye Only	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
	Fellow Eye Only	---	---	---	---	---	---	---	---	2	(0.7)	2	0.7	1	(0.3)	1	0.3
Hyphema	Study Eye Only	2	(0.7)	3	1.0	---	---	---	---	---	---	---	---	---	---	---	---
Ocular Hyperemia and Swelling	Study Eye Only	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	1	(0.3)	2	0.7

Eye Disorder Adverse Events Severity ≥ 2 by Ocular Category, Eye Involved, Treatment Group through Week 052

(as of December 31, 2010)

		Treatment															
		1				2				3				4			
		People		Events		People		Events		People		Events		People		Events	
Ocular_Category	Eye Involved	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100	N	%	N	Per 100
Cataract and related conditions	Study Eye Only	6	(2.0)	7	2.3	4	(1.4)	5	1.7	3	(1.0)	3	1.0	2	(0.7)	2	0.7
	Fellow Eye Only	5	(1.7)	5	1.7	6	(2.1)	6	2.1	5	(1.7)	6	2.0	5	(1.7)	5	1.7
	Both Eyes	---	---	---	---	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---
Optic nerve conditions	Study Eye Only	---	---	---	---	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---
Other	Study Eye Only	---	---	---	---	2	(0.7)	2	0.7	3	(1.0)	3	1.0	---	---	---	---
	Fellow Eye Only	1	(0.3)	1	0.3	1	(0.3)	1	0.3	---	---	---	---	---	---	---	---

CATT

Comparison of
Age-related Macular Degeneration
Treatments
Trials

CATT: Lucentis® - Avastin® Trial

Manual of Procedures

May 2010

COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENTS TRIALS (CATT)
CATT: LUCENTIS® – AVASTIN® TRIAL

MANUAL OF PROCEDURES

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CHAPTER 1

BACKGROUND

1.1. PUBLIC HEALTH IMPORTANCE

Age related macular degeneration (AMD) is the leading cause of severe vision loss in people over the age of 65 in the United States and other Western countries (Tielsch, 1994; Sommer, 1991; Leibowitz, 1980; Klein, 1992; Sorsby, 1966; Buch, 2001). More than 1.6 million people in the US currently have one or both eyes affected by the advanced stage of AMD (Friedman, 2002) and it is estimated that there are another 7 million individuals "at risk" (The Eye Diseases Prevalence Research Group 2004). Once advanced AMD occurs in one eye, the risk for developing advanced AMD in the second eye over a 5 year period is 43% (AREDS, 2001) and the impact is substantial; more than 230,000 people in the United States are believed to be legally blind due to AMD (Tielsch, 1994). These numbers are expected to increase as the proportion of the American population over the age of 65 years increases. Projections by the US Census Bureau indicate the US population aged 65 years and older will increase 54% from 2000 to 2020 (US Census Bureau, 2002).

1.2. CLINICAL FEATURES OF AMD

The hallmark findings in an eye with AMD are the presence of drusen, atrophy of the retinal pigment epithelium (RPE), and pigmentary changes in the macula. These changes of early AMD are not usually associated with significant visual loss. However, progression to a more advanced stage may occur and is often associated with severe loss of vision. The advanced stage of AMD consists of either choroidal neovascularization (neovascular AMD) or central geographic atrophy. This progression to neovascular AMD or geographic atrophy is influenced by a variety of factors: smoking, advancing age, family history, white race, and low dietary intake of antioxidants (AREDS, 2005; Wang, 2003; Snow, 2000; Schaumberg, 2001; Pollack, 1998; Klein, 1998a, 1998b). However, the strongest risk factor is the size and extent (area) of the drusen and RPE changes themselves (AREDS, 2005).

The majority (90%) of the severe visual loss due to advanced AMD is attributable to the development of choroidal neovascularization (CNV) (Ferris, 1983; Sommer, 1991). These new vessels, which originate from the choroid, grow through breaks in Bruch's membrane and extend under the RPE and/or into the subretinal space. Approximately 70%-80% of neovascular lesions are subfoveal at the time of presentation (Berkow, 1984; Freund, 1993; Moisseiev, 1995; Margherio, 2000) and most of the lesions that develop outside the fovea, unless treated, expand into the fovea within one to two years. By three years after diagnosis, approximately 50% to 90% of eyes will have visual acuity of 20/200 or worse, depending in part on the fluorescein angiographic pattern of the lesion at presentation (MPS Group, 1991, 1993, 1994; Stevens, 1997; TAP, 2001; VIP, 2001). Neovascular lesions with a "classic" pattern of fluorescence generally deteriorate more rapidly and severely than eyes with an "occult" pattern of fluorescence (MPS Group, 1991).

1.3. PATHOGENESIS OF AMD

A variety of theories has been proposed regarding the pathogenesis of AMD which are well summarized in the literature (D'Amato, 1998; Husain, 2002; Ambati, 2003). There is good evidence that oxidative stress is involved in the development of AMD, a theory that received support from the beneficial effects of anti-oxidant vitamins that were observed in the Age-Related Eye Disease Study (Beatty, 2000; AREDS, 2001). Immune mediated processes have also been implicated in drusen formation and the inflammatory response associated by them may be an angiogenic stimulus (Penfold, 1985; Johnson, 2000; Hageman, 2001). The role that inflammation might play in the pathogenesis of AMD has been further elucidated by the finding by four independent laboratories that a variation in the factor H gene (HF1/CFH) dramatically increases the likelihood of developing AMD (Hageman, 2005; Haines, 2005; Edwards, 2005; Klein, 2005). Factor H is the major soluble inhibitor of the alternative pathway of complement activation and sustained complement activation can lead to chronic inflammation, aggravate local tissue damage, and contribute significantly to disease progression, such as that which occurs in Alzheimer's disease and atherosclerosis (Shen, 2003; Bok, 2005). It is not difficult to imagine how dysfunction of the complement system, which functions by creating holes in cell membranes as a first line of defense against microorganisms and other foreign particles (Bok, 2005), could produce RPE apoptosis as well as promote the development of microscopic breaks in Bruch's membrane which is preferentially thinner in the macula (Chong 2005).

The specific mechanism by which CNV develops is unclear. However, it is increasingly evident that a variety of cytokines that regulate angiogenesis play an important role. The delicate balance of polypeptide angiopromoters and angioinhibitors may be tipped in favor of neovascularization by the diffusion barrier that is created by diffuse thickening of Bruch's membrane from progressive accumulation of extracellular material containing lipid (drusen). This in turn interferes with normal functioning of the RPE (Ambati, 2003). RPE cells harbor a variety of growth factors that promote the growth and development of CNV and are easily implicated because of their proximity to choroidal vessels. In addition, choroidal blood flow has been shown to be impaired and choroidal perfusion altered in eyes with early AMD; these changes may also contribute to the accumulation of debris from the RPE and stimulation of angiogenesis (Pauleikhoff, 1990; Friedman, 1998). Examinations of surgical specimens excised from patients with CNV have provided immunohistopathologic evidence that growth factors such as vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (bFGF), transforming growth factor beta (TGF beta), angiopoietin 1, angiopoietin 2, and connective tissue growth factor (CTGF) are involved in the formation of CNV (Amin, 1994; Reddy, 1995; Kvanta, 1996, Otani, 1999; He, 2003). Of all of these cytokines, the one that has received the greatest attention to date is VEGF.

VEGF is a naturally occurring protein that is a potent inducer of angiogenesis. In addition, it is an even more potent inducer of vascular permeability (50,000 times greater than histamine) (Ferrara, 1992). There is also data that suggests that VEGF may also have pro-inflammatory properties (Ishida, 2003). The evidence that VEGF plays an important role in CNV is compelling. First, VEGF and VEGF receptors are expressed at high levels in areas of CNV in a primate model (Miller, 1994). Second, VEGF expression has been demonstrated in pathological examination of surgically excised CNV membranes of patients with AMD (Lopez, 1996). Third, VEGF has been shown to be present in CNV membranes of autopsied eyes with AMD (Frank, 1996). Finally, studies have shown that VEGF accumulates in vascular endothelial cells of

AMD patients (Asayama, 2000). These observations stimulated the development of several drugs that inhibit VEGF. The positive clinical trial results (discussed below) from the studies of these drugs validate the importance of VEGF in the pathogenesis of CNV and establish VEGF inhibition as an important treatment for neovascular AMD.

1.4. TREATMENTS FOR AMD

Prior to 2005, there had been a number of advances in the treatment of neovascular AMD including the use of thermal laser, photodynamic therapy with verteporfin, and intravitreal injections of pegaptanib. While each of these treatments had been shown to be modestly effective at slowing the rate of visual loss, the overall experience with these treatments had been disappointing. The development of Lucentis®, a monoclonal antibody directed against VEGF, represents a major therapeutic improvement over existing therapies that has altered physicians' and patients' expectations regarding the extent of visual loss that can be prevented or reversed. The discussion that follows will first cover the treatments of AMD that preceded anti-VEGF therapy followed by discussion of the development of those drugs that inhibit VEGF.

1.4.1. Prevention

In 2001, the Age-Related Eye Disease Study (AREDS) Group reported that daily supplementation with high-dose anti-oxidant vitamins (A, C, and E) and zinc reduced the 5-year incidence of a 3-line loss in vision from 29% to 23%, among patients with extensive drusen or with unilateral advanced AMD (AREDS, 2001). While this finding is of major importance, there is still much room for improvement in the prevention of vision loss from AMD. Specifically, 23% of patients still suffer loss of vision even if they are compliant with the AREDS supplements. Non-compliance with taking 2-4 tablets daily may be considerable among patients outside the environment of a clinical trial. Supplements cost $200 per year and are not covered by health insurance.

Other preventative strategies being studied in randomized clinical trials include prophylactic laser treatment to eyes with extensive drusen (Complications of AMD Prevention Trial (CAPT Study Group, 2004; Prophylactic Treatment for AMD (Rodanant, 2002)) and posterior juxtascleral injections of anecortave acetate (Retaane™) to the fellow eye in patients with unilateral advanced AMD. While there is hope that these strategies will be effective, neither is expected to eliminate the need for effective treatments for neovascular AMD.

1.4.2. Thermal Laser

Between 1979 and 1994, the Macular Photocoagulation Study Group conducted clinical trials of thermal laser treatment for well-defined CNV (typically a classic pattern of leakage on fluorescein angiography). While treated eyes in all trials lost less visual acuity than untreated eyes, thermal laser treatment has serious limitations (MPS Group 1991, 1993, 1994). Not more than 20% of eyes that develop CNV are amenable to thermal laser treatment. Recurrent CNV develops in approximately half of treated eyes (MPS Group, 1986, 1990). In addition, thermal laser to subfoveal CNV causes an immediate drop in vision that many patients and ophthalmologists find unappealing despite the long term (18 to 24 months and beyond) benefit of treatment.

1.4.3. Photodynamic Therapy with Verteporfin

In 1999, the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group reported that photodynamic treatment (PDT) with verteporfin for eyes with subfoveal, predominantly classic CNV reduced the risk of loss of visual acuity (TAP Group, 1999). The proportion who lost fewer than 3 lines of visual acuity was 39% in the placebo group versus 67% in the treated group. Treatment benefit extends through at least 2 years (TAP Group, 2001). As a result, photodynamic therapy superseded thermal laser as the treatment of choice for subfoveal, classic CNV.

In 2001, the results of a clinical trial of PDT for eyes with subfoveal, occult CNV showed that treated eyes had better visual acuity at 2 years than untreated eyes (VIP Group, 2001). However, reduction in the risk of loss of fewer than 3 lines of visual acuity did not accrue until after 12 months and is modest (32% versus 45% at 24 months). In addition, PDT must be repeated up to every 3 months; the average number of treatments in the first 2 years is 5 to 6. Costs associated with treatment over 2 years are $10,000 to $15,000. These results and additional analyses led the Centers for Medicare and Medicaid Services (CMS) to cover PDT for predominantly classic CNV and occult and minimally classic lesions <4 disc areas in size (Blinder, 2003).

While the advent of PDT was a welcome addition to the treatment of neovascular AMD, the magnitude of the treatment effect was disappointing. At one year, the average patient in the TAP study lost vision despite treatment (mean of 10 letters). Only 6% of treated patients gained ≥3 lines and only 5% of patients retained vision of 20/40 or better (TAP Group, 1999). In an effort to improve visual outcomes, a number of investigators have begun to evaluate PDT in combination with an intravitreal injection of triamcinolone. Triamcinolone has the potential added benefit of reducing retinal edema and/or subretinal fluid and inhibits a number if cytokines that may contribute to CNV including VEGF. Consecutive case series have suggested that this combination treatment may be more effective than PDT alone (Spaide, 2005; Augustin, 2006). A randomized clinical trial designed to evaluate PDT and triamcinolone was suspended because the data from the Lucentis® trials and the availability of Avastin® resulted in no patients being enrolled.

1.4.4. Retaane®

Retaane® (anecortave acetate) is an angiostatic steroid that is not associated with intraocular pressure rise or acceleration of cataract (D'Amico, 2003). It has been shown to inhibit endothelial proliferation, endothelial migration and plasminogen activation. It is administered as a periocular posterior juxtascleral depot injection every 6 months. In a phase II trial, visual acuity in patients (80%) with predominantly classic CNV treated with Retaane® 15 mg was better than in patients in the placebo group at one year by 3 measures: mean change from baseline vision ($P = 0.01$), stabilization of vision (<3 line change, 79% Retaane® versus 53% placebo; $P = 0.03$), and prevention of severe vision loss (decrease of ≥ 6 lines; $P = 0.02$). A phase III trial involved 530 patients with predominantly classic CNV who were assigned to treatment with Retaane® or PDT. At one year, 45% of patients treated with Retaane® lost <3 lines of vision compared to 49% for patients treated with PDT ($P = 0.43$). Although the point estimates of the two treatments were similar, Retaane® failed to meet its primary non-inferiority limit (Slakter, 2006). No clinically relevant drug or administration related safety issues have been identified in any clinical trial. At the time of this writing, Retaane® had been submitted to the FDA for consideration of approval. An additional clinical trial evaluating Retaane® for

prevention of CNV in 2500 patients at high risk for developing neovascular AMD is ongoing. Final results are not expected until 2010.

1.4.5. Macugen®

Macugen® (pegaptanib sodium) is an anti-VEGF aptamer that selectively binds to and neutralizes VEGF isoform 165 (Eyetech Study Group, 2002, 2003). In a phase III trial, 1186 patients with subfoveal CNV (all lesion types) were randomly assigned to treatment with one of three doses of Macugen versus sham injections (control) every 6 weeks for up to two years. At one year, the proportion of patients who had lost fewer than 15 letters (3 lines) was 70% for Macugen 0.3 mg versus 55% for the controls ($p<0.001$). No dose response relationship was observed. The therapeutic effect was not restricted to any lesion type. Like PDT, patients treated with Macugen continued on average to lose vision (7 letter mean loss at one year) and only 6% gained ≥3 lines. The most common serious adverse event was endophthalmitis which occurred in 1.3% of patients. Macugen received FDA approval in December, 2004.

1.4.6. Lucentis®

Lucentis® (ranibizumab, formerly RhuFab V2) is a modified fragment of an anti-VEGF antibody (Avastin®) that binds and inhibits all VEGF isoforms (Krzystolik, 2002). Initial studies with the full length antibody suggested that it did not penetrate the retina when injected into the vitreous cavity (Mordenti(a), 1999). However, the Fab fragment passed easily through the retina to reach the target (subretinal) space. An affinity maturation process was applied to increase the binding affinity to VEGF 140-fold, and Lucentis® was moved into clinical studies. The results from four large randomized clinical trials have been reported to date.

In a phase III trial (entitled MARINA), 716 patients with occult and minimally classic CNV were randomly assigned to one of two doses of Lucentis® (0.3 mg or 0.5 mg) versus sham injections every 4 weeks (fixed schedule) for up to two years. At one year, the proportion of patients who had lost <15 letters (3 lines) was 95% for both 0.3 mg and 0.5 mg of Lucentis® versus 62% for the controls ($p<0.001$). Unlike all previous AMD studies, the average patient gained vision with a mean improvement from baseline of 7 letters (compared to a 10 letter loss among controls). The proportion of treated patients who gained ≥3 lines was 25% for Lucentis® 0.3 mg and 34% for the 0.5 mg dose. The proportion of patients who retained vision of 20/40 or better was 39% and 40% respectively (Rosenfeld, 2006). The 2-year results showed that the large treatment benefit was maintained with injections given every 28 days. The mean difference between controls and the Lucentis® treatment groups was 20.3 letters for the 0.3mg dose and 21.3 for the 0.5mg group.

In a second study (entitled FOCUS), 162 patients with predominantly classic subfoveal CNV were randomly assigned to PDT versus Lucentis® 0.5 mg + PDT. At one year, the proportion of patients who had lost <15 letters (3 lines) was 91% in the combined Lucentis® + PDT group versus 68% for the PDT alone group ($p<0.003$). Patients treated with PDT + Lucentis® gained vision on average while those treated with PDT alone lost vision (mean change of +5 letters versus -8 letters) The proportion of patients who gained ≥3 lines was 24% for Lucentis® + PDT versus 5% for PDT alone. The mean number of PDT treatments was 3.4 in the PDT alone group versus 1.3 in the combined group (unpublished data, presented at the ASRS Meeting, July, 2005). Two year results, with data complete on approximately 85% of patients, were similar on all outcome measures; e.g., the difference in mean change in visual acuity was 12.4 letters at two

years whereas the difference at 1 year was 13.1 letters (unpublished data, presented at the ASRS Meeting, September, 2006).

In a third study (entitled ANCHOR), 423 patients with predominantly classic subfoveal CNV were randomly assigned 2:1 to Lucentis® (0.3 mg or 0.5 mg) given every 4 weeks (fixed schedule) versus PDT every 3 months as needed for up to two years. At one year, the proportion of patients who had lost <15 letters (3 lines) was 94% in the 0.3 mg group, 96% percent in the Lucentis® 0.5 mg group versus 64% percent for the PDT group ($p<0.0001$). Patients treated with Lucentis® gained vision on average while those treated with PDT lost vision. (Brown, 2006)

In a fourth study (entitled PIER), 184 patients with predominantly classic, minimally classic or occult with no classic lesions received a 0.3-mg or 0.5-mg intravitreal injection of Lucentis® or sham injection once a month for the first three months followed by injections once every three months. At month three, on average, patients treated with Lucentis® gained 2.9 letters (0.3mg) or 4.3 letters (0.5mg) and patients in the sham injection group lost 8.7 letters. At month 12, on average, patients treated with Lucentis® lost 1.6 letters (0.3mg) or 0.2 letters (0.5mg) and patients in the sham group lost 16.3 letters ($p<0.0001$). The proportion of patients in the fixed, quarterly schedule Lucentis® groups losing < 15 letters at 12 months was 83% (0.3mg) or 90% (0.5mg) compared to 49% for patients receiving sham injections. (Genentech press release, June 2, 2006).

Adverse events reported to date been minimal. Conjunctival hemorrhage, eye pain, and increased intraocular pressure are common, mild to moderate side effects. The incidence of endophthalmitis was 0.4% – 0.8% in the MARINA study. Intraocular inflammation was noted in 8.6% of patients in the FOCUS study. However, the FOCUS trial employed a lypholyzed formulation that was discontinued before MARINA and ANCHOR began. The rate of inflammation was 0.8% in MARINA using the newer formulation. There were no reported cases of endophthalmitis in the PIER study.

There is an ongoing study evaluating a less frequent dosing schedule. PRONTO is a single center, uncontrolled, case series of 40 patients treated with Lucentis. After an initial 3 (0.5 mg) injections, additional injections are given only if specific clinical criteria are met: a loss of 5 letters in conjunction with fluid in the macula as detected by OCT, an increase in OCT central retinal thickness of at least 100 μm, new onset classic CNV, new macular hemorrhage, or persistent macular fluid detected by OCT at least 1 month after the previous injection. The mean number of treatments within the first year was 5.5. The proportion of eyes with an increase in visual acuity of 3 or more lines was 35% and the mean gain was 9.3 letters.

Lucentis® received approval (US BL 125156) for treatment of neovascular AMD on June 30, 2006.

1.4.7. Avastin®

1.4.7.1. Rationale for use of Avastin®

Bevacizumab (Avastin®) and Lucentis® are derived from the same monoclonal antibody. Avastin® was FDA-approved in 2003 for intravenous use in patients with colorectal cancer (Hurwitz, 2004). In a series of 18 patients with CNV, intravenous administration of Avastin®

was associated with improved visual acuity and reduced retinal thickness (Michels, 2005). Systemic administration of Avastin® is associated with an increased risk of thromboembolic events in cancer patients (Herbert, 2005).

Following the encouraging clinical trial results with Lucentis®, several investigators began evaluating intravitreal Avastin® for the treatment of CNV. Given its molecular similarity to Lucentis, its low cost, and its availability, the interest in Avastin® has been considerable. Within 6 months of its public introduction as a single case report at the ASRS meeting in July 2005 (Rosenfeld, 2005) it has been adopted as a first line therapy for CNV by many retina specialists in the United States, despite the absence of any randomized clinical trial data to support its intraocular use. In our discussions with a number of prospective collaborators for this study, it became apparent that the number of patients treated with intravitreal Avastin® in the last 3 months alone far exceeds the number of patients in all of the Lucentis® trials combined. The reasons for this are its apparent beneficial effect and its availability for off-label use. Although preclinical primate data suggested that a 149 kD antibody the size of Avastin® injected into the vitreous cavity would not penetrate the retina, in clinical practice, intravitreal Avastin® has been found to have a significant biological effect on retinal edema, subretinal fluid, and pigment epithelial detachments secondary to AMD with concomitant improvement in visual acuity (Avery, 2006; Rich, 2006; Yoganathan, 2006). In addition, when Avastin® was injected into the vitreous of rabbits, it showed full penetration of the retina (Shahar, 2006; Feiner, 2006; Schraemeyer, ARVO 2006).

1.4.7.2. Dose of Avastin®

The Avastin® dose most commonly used in the United States is 1.25 mg in 0.05 ml. This dose was derived from consideration of the molecular weight and binding affinity differences between Lucentis® and Avastin, as well as the differences in presumed retinal penetration. It is estimated that Avastin® 1.25 mg may be roughly equivalent to Lucentis® 0.3 to 0.5 mg in terms of the number and affinity of the binding sites that are delivered to the eye (Rosenfeld, 2005). However, outside of the United States, 2.50 mg in 0.10 ml is used frequently. (Bashshur, 2006). A dose-escalation study of a single injection of Avastin® to 15 patients in each of 3 dose groups (1.0mg, 1.5 mg, and 2.0 mg) showed nearly identical improvements in LogMAR visual acuity for the 1.5 mg and 2.0 mg doses at 1 and 6 weeks after injection (Costa, 2006). However, at 12 weeks, the mean improvement decreased from the 6-week level in the 1.5 mg group but was stable in the 2.0 mg group. Improvements in visual acuity in the 1.0 mg group were less than in the higher dose groups and also decreased between 6 and 12 weeks. The dose-response effect for change in visual acuity from baseline across the 3 groups at 12 weeks was statistically significant at the $p=0.02$ level. These data provide some evidence that the longevity of the treatment effect is dose-dependent in the 1.0 to 2.0 mg range.

1.4.7.3. Duration of activity

The intravitreal half-life of Avastin® is estimated to be twice that of Lucentis® (Mordenti(b), 1999). This is thought to be due to the increased size of Avastin® (149 kD versus 48 kD for Lucentis®) as well as the presence of the Fc portion. A longer half-life may allow a therapeutic effect to be achieved with less frequent injections. However, the optimal dosing schedule is unknown. As a result, retreatment with Avastin® has been primarily "as needed," that is, driven by the clinical response.

1.4.7.4. Safety of Avastin® as reported in the grant application for the clinical trial

To date, the safety profile of Avastin® has been very good. The solution is non-preserved and is not known to contain any additives that would be toxic to the retina (Rosenfeld, 2005). Avastin® is non-toxic, as measured by electroretinogram, to the retina of the rabbit, mouse, and cow (Shahar, 2006; Feiner, 2006; Manzano, 2006; Heiduschka, ARVO 2006; Luke, ARVO 2006) Electroretinography after injection of Avastin® in human eyes has also not shown any deleterious effect (Maturi, 2006). No negative effects were observed on retinal pigment epithelial, neurosensory retinal, or microvascular endothelial cells in vitro when treated with doses similar to or above the doses in clinical use (Luthra, 2006).

There has been widespread use throughout the world of Avastin® for neovascular AMD as well as for diabetic macular edema and other retinal-vascular diseases. Large, systematic studies of the safety of Avastin® are lacking; however, a review of 47 abstracts for the ARVO 2006 meeting provided data on 4,845 patients receiving one or more intravitreal injections of Avastin. In 30 of the studies, no adverse events were reported. In addition to the more severe adverse events listed below, corneal abrasions (8), inflammation (6), foreign body sensation and subconjuncival hemorrhage (5), ocular pain (2), punctuate keratitis (1), and elevated IOP (1) were reported.

Non-Ocular Adverse Events	**Ocular Adverse Events**
2 Deaths*	1 Endophthalmitis
2 Cerebrovascular accidents	1 Retinal detachment
1 Transient ischemic attack	1 CRAO
1 Ischemic colitis 2 wks post injection	1 Vitreous hemorrhage
1 Bowel stricture (history of bowel surgery)	4 Acute vision loss
	1 lost 4 lines of VA
10 elevated blood pressure	3 new/increased subretinal hemorrhage

* 1 cerebral hemorrhage 2 weeks after injection in a patient with pre-existing hypertension, diabetes, and anti-coagulation, 1 cause unknown.

While the types of reporting cited above may underestimate the true incidence of adverse events, the widespread use and very low reported incidence of serious side effects provide sufficient evidence of safety to move forward with a well-controlled clinical trial involving Avastin.

1.4.8. Summary of Treatment Efficacy for Neovascular AMD at One Year

	< 3 Line Loss	≥ 3 lines gained	≥ 20/40
Natural History			
Pred Classic	39%	2%	1%
Occult	51%	2%	7%
Thermal Laser	50%	1%	----
Photodynamic Therapy			
Pred Classic	67%	6%	5%
Occult	55%	3%	15%
Anti-VEGF agents			
Macugen	70%	6%	----
Lucentis*			
Pred Classic	95%	38%	35%
Min Classic/Occult	95%	34%	40%

*Percentages average over the 0.3mg and 0.5mg groups which had nearly identical results.

1.5. RATIONALE FOR TREATMENT COMPARISONS

Lucentis® is the most effective treatment for neovascular AMD studied to date and has become the standard of care. However, widespread implementation of a fixed, every 4 week dosing schedule has obvious practical limitations and the cost of such repeated injections is considerable. Avastin® has not been evaluated relative to Lucentis®. Although the half-life of Avastin® may be longer than the half-life of Lucentis, dosing as frequently as every 28 days with Avastin® may still be necessary to achieve the same beneficial effects as Lucentis®. Previous studies do not answer the question of whether a reduced dosing schedule is as effective as a fixed schedule of monthly injections. The PIER study showed that a schedule of dosing every three month was more effective than a sham injection, but did not allow comparison with either a fixed schedule or a schedule dependent upon clinical response. The PRONTO study showed that a dosing schedule for Lucentis® dependent on clinical response could be carried out and achieve favorable responses, however, there was no comparison with fixed schedule treatment. Treatment dependent on clinical response has the potential to reduce the treatment burden to patients as well as to reduce the overall cost of therapy.

In September 2006, the National Eye Institute (NEI) awarded funding for the Comparison of AMD Treatments Trials: Lucentis-Avastin Trial. NEI funds support research activities in the clinical centers, Coordinating Center, Reading Centers, and Study Chair's Office. The multicenter, randomized, clinical trial will involve 4 treatment groups:

1) Lucentis® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Lucentis® every 4 weeks or to variable dosing.
2) Avastin® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Avastin® every 4 weeks or to variable dosing.

3) Lucentis® on a variable dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.
4) Avastin® on a variable dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.

CHAPTER 2

OVERVIEW OF THE CATT: LUCENTIS-AVASTIN TRIAL DESIGN

2.1. COMPARISION OF AMD TREATMENT TRIALS (CATT)

CATT is envisioned as a set of multicenter, randomized clinical trials of treatments for neovascular age-related macular degeneration (AMD). The trials will differ predominantly in the treatments under evaluation. The trials will share the same overall methods and structure; e.g., common standardized procedures for measurement of outcome measures, data collection and management methods, and similar committee and administrative structure. The Lucentis-Avastin Trial will be the first CATT clinical trial.

2.2. CATT: LUCENTIS-AVASTIN TRIAL

The CATT: Lucentis-Avastin Trial will identify the best approach to anti-VEGF therapy to be used as the standard of comparison for subsequent clinical trials for neovascular age-related macular degeneration. A summary of the trial design elements are displayed in Table 2-1. While the remainder of this manual of procedures addresses details of many of the topics, some comments about the choice of specific approaches are provided below:

- **Eligibility criteria** are designed to be as inclusive as possible in order to maximize generalizability of the results without jeopardizing the ability to observe a treatment effect because of interfering causes of visual loss. There are no criteria regarding the angiographic pattern of leakage (classic, occult choroidal neovascularization {CNV}) or the size of the lesion. Lucentis® has shown efficacy in preserving visual acuity in clinical trials involving eyes with both types of leakage. Patients with visual acuity in the eligible range (20/25 to 20/320) may benefit from stabilization or improvement of vision, regardless of the initial size of the lesion. The vast majority of patients with new, subfoveal CNV are eligible for the CATT: Lucentis-Avastin Trial.
- **Treatment in the CATT: Lucentis-Avastin Trial will be in two phases**, the first year and the second year. The primary outcome assessment is at 12 months; however, it will be important to know the need for and outcome of treatment beyond one year. In addition, the results of the Study will not be known when patients complete 12 months of follow-up, so there will be no evidence-based guidelines for treatment beyond 12 months. Patients in the two variable dosing arms will continue with their initially assigned treatments. However, even if Lucentis® or Avastin® on fixed schedule provides better visual acuity at one year than the other treatment arms, there will still be the question of whether treatment every four weeks must continue indefinitely. A randomly selected half of the patients assigned initially to fixed schedule treatment will be assigned to variable treatment (with the originally assigned study drug) for the second year. Re-randomization allows for estimation of the change in visual acuity during the second year under the two treatment strategies and allows for relatively precise estimation of (95% confidence interval of ±3 letters) of the difference between the two groups. This information will be very valuable if the two variable dosing arms prove inferior to fixed schedule Lucentis® at 1 year.

Table 2-1. CATT: Lucentis-Avastin Trial Design Summary

Feature	Criteria
Objective	Evaluate the relative efficacy and safety of treatment of subfoveal neovascular AMD with Lucentis® on a fixed schedule, Avastin® on a fixed schedule, Lucentis® on a variable schedule, and Avastin® on a variable schedule
Major Eligibility Criteria	Active subfoveal choroidal neovascularization (CNV) Fibrosis < 50% of total lesion area Visual acuity (VA) 20/25-20/320 Age ≥ 50 yrs ≥1 drusen (>63μ) in either eye or late AMD in fellow eye No previous treatment for CNV in study eye No other progressive retinal disease likely to compromise VA No contraindications to injections with Lucentis® or Avastin®
Randomization Unit	Person, only one eye of each person may be enrolled
Masking	VA examiner; image graders masked to drug and schedule; Ophthalmologist masked to drug
Treatments	1) Lucentis® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Lucentis® every 4 weeks or to variable dosing. 2) Avastin® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Avastin® every 4 weeks or to variable dosing. 3) Lucentis® on a variable dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity. 4) Avastin® on a variable dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.
Outcome Measures 1°	Mean change in VA at 1 year (non-inferiority limit of 5 letters)
2° (at 1 year and 2 years)	Number of treatments 3-line change in VA (15 letters on ETDRS chart) Change in subretinal and intraretinal fluid on optical coherent tomography Change in lesion size on fluorescein angiography Incidence of endophthalmitis, retinal detachment, cataract, uveitis Incidence of adverse events Cost
Sample size	300 per group, or 1200 total
Follow-up	Every 4 weeks through 2 years

- **The guiding principle for variable dosing schedule Lucentis® or Avastin®** is that Lucentis® and Avastin®, as anti-VEGF agents, have anti-permeability and anti-angiogenesis properties and that treatment should be given only when there are signs of neovascular AMD that are associated with abnormal vessel permeability or vessel growth.
- The fact that patients in the fixed schedule Lucentis® and Avastin® arms receive injections every month regardless of response to treatment, while those in the two variable dosing arms do not, unmasks the patient, the ophthalmologist, and Clinic Coordinator to whether the patient is in a fixed schedule group or a variable dosing arm. However, ophthalmologists and visual function examiners are masked to whether patients are receiving Lucentis® or Avastin®. **Thus, interpretations of OCTs and angiograms by the ophthalmologist with respect to meeting requirements for retreatment <u>are masked.</u>** Including sham injections for patients who do not meet the criteria for retreatment was considered by the Planning Committee but rejected for the follow reasons: 1) patients receiving both types of injection may be able to distinguish between a real injection and a sham injection; 2) the logistical aspects of allowing for the possibility of a sham injection or real injection at each visit increases the likelihood of mistakes in treatment and increases the overall complexity of the trial.
- Given the underlying continuous measurement scale of visual acuity, the high likelihood for both increases and decreases in visual acuity score, and the inability of the traditional 3-line loss dichotomy to accommodate measurement of further improvements in treatment efficacy, **mean change is a strong choice for the primary outcome.** The higher precision in estimation of a mean relative to a proportion is desirable in non-inferiority trials where the interpretation is driven by the width of the confidence interval. The only major drawback to the choice of using mean change is the absence of a description of differences between groups in clinically meaningful changes in the distribution. However, this shortcoming can be overcome by secondary outcome measures and through the use of descriptive statistics.
- Despite the strong reliance in the Trial on OCT for determining the need for treatment, there is a need for assessing whether OCT, FA, and visual acuity associations present at the time of diagnosis of CNV persist over the course of treatment and whether the short-term responses to treatment in these features provide prognostic information independent of the prognostic information at baseline. **The OCT and Fluorescein Angiography Substudy addresses this need.**
- CATT procedures for refraction, visual acuity measurement, and photography are the same as those used in other multicenter clinical trials for retinal diseases.

CHAPTER 3

PATIENT SELECTION

3.1. PATIENT SELECTION

Patients will be randomized in a 1:1:1:1 ratio among 1) Lucentis® treatment on a fixed schedule of every 4 weeks, 2) Avastin® treatment on a fixed schedule of every 4 weeks 3) Lucentis® on a variable dosing schedule and 3) Avastin® on a variable dosing schedule. Patient inclusion and exclusion criteria in the CATT: Lucentis-Avastin Trial are based in large part on the criteria specified in the protocols for the previous clinical trials of Lucentis®. Lucentis-Avastin Trial patients will have only one eye enrolled in the study.

Written informed consent will be obtained before initiation of any study-specific procedures. Screening evaluations may be performed at any time within the 7 days preceding the day of randomization when the first study injection is expected to be given.

3.1.1. Inclusion Criteria

All patients must meet the following criteria for entry into the CATT: Lucentis-Avastin Trial:

- Signed informed consent form
- Age ≥ 50 years of either gender
- Women must be postmenopausal for at least 12 months prior to trial entry, or surgically sterile. If of child bearing potential, a serum pregnancy test with a negative result must be obtained within 14 days prior to the first treatment. Women of child bearing potential must be practicing effective contraception implemented during the trial and for at least 60 days following the last dose of study medication.
- No condition that precludes follow-up for 2 years.
- No contraindication to intravitreal injection of Lucentis® or Avastin®, as specified in the exclusion criteria below.

3.1.2. Eligibility criteria for study eyes

Study eyes must meet the following criteria for entry into the CATT: Lucentis-Avastin Trial:

- Newly diagnosed, angiographically documented, previously untreated, active CNV lesion (i.e., leakage on fluorescein angiography AND subretinal, intraretinal, or sub-RPE fluid on OCT) secondary to age-related macular degeneration.
- Best corrected visual acuity in the study eye, using e-ETDRS testing, between 20/25 and 20/320 (Snellen equivalent), inclusive.

  Only one eye will be enrolled in the Study. If both eyes are eligible, the patient and study ophthalmologist will select the eye for entry.

- The CNV or sequela of the CNV (i.e., pigment epithelium detachment, subretinal or sub-RPE hemorrhage, blocked fluorescence, macular edema, or subretinal sub-RPE or intraretinal fluid) must involve the center of the fovea.
- The total area of fibrosis must comprise less than 50% of the total lesion.
- ≥ 1 drusen (>63 microns) in either eye OR late AMD in fellow eye
- No previous treatment for CNV in the study eye
- Clear ocular media and adequate pupillary dilation to permit good quality fundus imaging.
- Disc and macula color stereoscopic photographs and fluorescein angiogram within 7 days of randomization.
- OCT of the macula within 7 days of randomization.

3.2. EXCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from study entry:

3.2.1. Prior/Concomitant Treatment

- Previous treatment with verteporfin PDT, Macugen®, Lucentis®, intravitreal Avastin®, thermal laser, external beam radiation or other AMD therapy in the study eye. Prophylactic treatment such as CAPT/CNVPT treatment does not exclude the patient.
- Previous treatment with intravenous Avastin®
- Concurrent treatment with an investigational drug or device in the non-study eye for any ocular condition
- History of submacular surgery or other surgical intervention for AMD in the study eye
- Previous participation in any studies of investigational drugs likely to have ocular effects within 30 days preceding the initial study treatment
- Concurrent use of systemic anti-VEGF agents.

3.2.2. Exclusionary Lesion Characteristics

- Fibrosis or geographic atrophy involving the center of the fovea in the study eye
- CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia
- Retinal pigment epithelial tear involving the macula in the study eye

3.2.3. Exclusionary Concurrent Ocular Conditions

- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 2 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 2 year follow-up period.
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye
- Current vitreous hemorrhage in the study eye
- History of rhegmatogenous retinal detachment or macular hole in the study eye
- History of vitrectomy in the study eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
- For subjects who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot exceed 8 diopters of myopia.
- Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding the first study treatment.
- Uncontrolled glaucoma in the study eye (defined as intraocular pressure $\geq$25 mmHg despite treatment with antiglaucoma medication)
- Patients who are unable to be photographed to document CNV due to known allergy to fluorescein dye, lack of venous access or cataract obscuring the CNV.
- Patients with other progressive retinal disease likely to affect visual acuity within the next 2 years. Patients with pattern dystrophy with CNV and drusen determined to be definitely AMD are eligible.
- Patients with other ocular diseases that can compromise the visual acuity of the study eye such as amblyopia and anterior ischemic optic neuropathy

3.2.4. Concurrent Systemic Conditions

- Premenopausal women not using adequate contraception (see Section 3.3)
- Pregnancy or lactation
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications
- Current treatment for active systemic infection

- Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders
- History of recurrent significant infections or bacterial infections
- Inability to comply with study or follow-up procedures

3.3. DEFINITION OF TERMS PERTAINING TO ELIGIBILITY CRITERIA

Informed Consent: Written informed consent must be obtained from each patient prior to performing any study-specific procedures. The patient should be asked to sign the consent form only after the patient has been introduced to the study and had questions answered.

Age: Few patients below the age of 50 are anticipated to meet the criteria below. Patients below the age of 50 may have forms of macular degeneration other than age-related macular degeneration.

Images: Stereoscopic color photographs of the disc and macula of both eyes are required. In addition, a fluorescein angiogram with the early phase on the study eye is mandatory. An OCT of each eye is also required. All images must be taken within 7 days prior to randomization.

Effective Contraception: Acceptable methods of birth control are surgical sterilization, use of oral contraceptives, barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel, an intrauterine device (IUD), or contraceptive hormone implant or patch.

Condition Precluding Follow-Up: Patients must have a high probability of completing 2 years of follow-up. The mere presence of serious health conditions in this population does not disqualify the patient from enrollment. However, if the severity of the condition is such that progression to a state where travel to the clinical center for regular follow-up visits would place undue burden on the patient or is such that death is almost certain to occur during the follow-up period, the patient should not be enrolled in the study. Patients with known plans to move to an area of the country without a nearby CATT clinical center should not be enrolled.

Contraindications to Lucentis® or Avastin® injections: No previous inflammatory reactions following intravitreal Lucentis® or Avastin® treatment in the non-study eye.

Active CNV includes **both** of the following: leakage on fluorescein angiography AND subretinal or intraretinal fluid on OCT.

CNV lesion: A contiguous area of abnormal tissue in the macula that encompasses angiographically documented CNV with possible additional components of subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the retinal pigment epithelium, and fibrosis.

AMD: Clinical and/or angiographic signs consistent with AMD (e.g., drusen, retinal pigment epithelial changes, choroidal neovascularization) with no other likely etiologic explanations for the degenerative changes.

Sequela of CNV: Sequela of the lesion includes pigment epithelial detachment, subretinal , sub-RPE hemorrhage, blocked fluorescence, macular edema, or subretinal, sub-RPE or intraretinal fluid contiguous with the CNV lesion.

Visual Acuity Score: The best corrected E-ETDRS visual acuity score for a study eye must be $\geq$ 23 letters (20/320 or better) and $\leq$ 82 letters (20/25 or worse).

Cataract Surgery: Eyes that have had lens extraction or lens implantation within the last 2 months are ineligible. Eyes that have had a capsulotomy within the past 2 months are ineligible.

Lens Opacities: Lens opacities may be present but must be such that at enrollment and for the next 2 years the view of the posterior pole for ophthalmoscopy and photography is unobstructed. Patients likely to undergo cataract extraction in the study eye within the next 2 years should not be enrolled in the Lucentis-Avastin Trial Study.

Myopia: Eyes with fundus changes consistent with high myopia, such as lacquer cracks, are ineligible. Eyes with a spherical equivalent more negative than –8.00 diopters are ineligible even if there are no myopic changes apparent in the fundus.

Progressive Ocular Disease: Any condition that is likely to decrease visual acuity over the course of 2 years excludes the patient from the study.

3.4. PATIENT RECRUITMENT AND SCREENING

3.4.1. Patient Recruitment

Lucentis-Avastin Trial patients will be recruited through a variety of methods. Most patients will be identified from the clinical practices at the participating centers and from referring ophthalmologists in the community. To aid recruitment efforts, the CATT Coordinating Center will develop materials both for referring ophthalmologists and for patients explaining the study. All centers must submit these materials to their local IRB for approval prior to their distribution to potential patients.

3.4.2. Patient Screening

The Study enrolling ophthalmologist must determine a patient's eligibility prior to enrollment. All patients must undergo an ophthalmological examination, fluorescein angiography, color photography and OCT to assess whether the patient meets ocular eligibility criteria, visual function testing conducted according to Lucentis-Avastin Trial study protocol to determine if visual acuity requirements are met, and respond to questions concerning medical history that may impact their eligibility for the Lucentis-Avastin Trial. All procedures to determine eligibility must be completed within 7 days prior to randomization with the exception (14 days) of pregnancy testing for women of childbearing potential. (For details on these procedures, refer to section 5.2 of this protocol).

3.4.3. Participation in Other Clinical Trials

3.4.3.1. AREDS2 Participation

Patients who are participating in the Age-Related Eye Diseases Study 2 (AREDS2) may participate in the CATT: Lucentis-Avastin Trial if they meet all other Study eligibility criteria.

Pre-enrollment approval from the Coordinating Center is not required; however, the clinic coordinator must note AREDS2 participation on the Baseline General Information Form.

3.4.3.2. Participation in Other Studies

If a prospective patient is participating in another study other than AREDS2, either ocular or non-ocular, the enrolling ophthalmologist or clinic coordinator must contact the Director of the Coordinating Center prior to enrolling the patient into CATT. The ophthalmologist and clinic coordinator should obtain as much information as possible about the other study so that an appropriate decision, that safeguards both the patient's safety and the objectives of the study, can be made.

CHAPTER 4

STUDY DRUG AND TREATMENT

4.1. INTRODUCTION

The treatment protocols used in the CATT: Lucentis-Avastin Trial have evolved from the methods used by other investigators in earlier studies of intravitreal anti-VEGF agents for subfoveal choroidal neovascularization. Injection procedures have been adapted from the DRCRnet standard procedures.

Patients will be randomized in a 1:1:1:1 ratio to one of the four treatment groups listed below. Criteria for additional treatment in the two variable dosing schedule arms are defined in section 4.4.2:

a. Lucentis® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re randomization to Lucentis® every 4 weeks or to variable dosing
b. Avastin® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Avastin® every 4 weeks or to variable dosing
c. Lucentis® on variable schedule dosing for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity
d. Avastin® on variable schedule dosing for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity

Patients will follow their assigned protocols for two years after their enrollment.

4.2. TREATMENT OF PATIENTS INITIALLY ASSIGNED TO FIXED SCHEDULE LUCENTIS® OR AVASTIN®

All patients who are assigned to receive study drugs on a fixed schedule will receive an intravitreal injection of either Lucentis® or Avastin®, as appropriate, immediately after receipt of the randomized treatment assignment and every 4 weeks through 48 weeks of follow-up. The intent of the study protocol for patients assigned to fixed schedule treatment is treatment every 4 weeks (e.g., 28 days) but the *minimal* interval between treatments may be 23 days. The protocol will continue to use the term "monthly" treatments to reflect the study's objective of 28 day treatment intervals. Patients should receive 12 additional injections during the first 48-week follow-up period, unless contraindications develop. The dose per injection will be:

- 0.5 mg (0.05 mL) of Lucentis®
- 1.25 mg (0.05 mL) of Avastin®

At week 52 there is a second randomization for patients originally assigned to one of the fixed schedule treatment groups. Half of the patients in each fixed schedule group will continue on the fixed schedule (injection every month), while the other half will be assigned to a variable schedule for the next year.

- Patients assigned to remain on fixed schedule injections will receive injections at week 52 and every 4 weeks through 100 weeks. Patients should receive 13 additional injections during this period, unless contraindications develop.
- Patients assigned to variable schedule injections will be assessed for treatment at week 52 and every 4 weeks through 100 weeks. The decision to treat patients will follow the treatment guidelines described below in section 4.3.

At 104 weeks, the last follow-up visit for the clinical trial will occur. No treatment will be performed during the visit at 104 weeks as part of the clinical trial treatment protocol.

4.2.1. Policy on Treatment Futility for Patients Assigned to Fixed Monthly Treatments

Patients assigned to a fixed schedule of Lucentis or Avastin should receive monthly injections throughout the period of treatment assignment, either 1 or 2 years. However, during the course of treatment, some patients will develop severe permanent loss of vision due to progression of their disease. If in the best medical judgment of the treating ophthalmologist it is believed that there is no chance of any benefit to the patient from additional intravitreal injections in terms of preserving vision or retinal anatomy, intravitreal injections of the study drug may be suspended. Examples of this scenario would include patients with very large areas of central atrophy or subretinal fibrosis who have no evidence of residual macular function.

These patients will continue to be followed in the study at regular monthly intervals. It would be exceedingly uncommon to reach a point of treatment futility during the first 12 months of follow-up

4.3. LUCENTIS® AND AVASTIN® TREATMENT ON VARIABLE SCHEDULE DOSING FOR THE FIRST 104 WEEKS

4.3.1. Initial Treatment

All patients who are randomized to receive study treatment on variable scheduled dosing will receive an intravitreal injection of either Lucentis® or Avastin®, as appropriate, immediately after receipt of the randomized treatment assignment. This is the only mandatory treatment for these patients. The dose per injection will be:

- 0.5 mg (0.05 mL) of Lucentis®
- 1.25 mg (0.05 mL) of Avastin®

An ophthalmologist, who remains masked to the identity of the study drug (Lucentis® or Avastin®), performs the ophthalmologic examination during follow-up, and evaluates OCTs and fluorescein angiograms (when performed) to determine if the eye should be treated. The ophthalmologist administers the injection to the patient whenever he/she judges that treatment is warranted based on the guidelines below.

4.3.2. Re-Treatment Guidelines

All patients who are randomized to receive study treatment on variable schedule dosing will be evaluated by the Study investigator every four weeks. Additional treatment is administered during follow-up visits if the Study-certified ophthalmologist determines that

treatment is warranted based on the guidelines below. The *minimal* interval between treatments may be 23 days.

Treatment is warranted if there are signs of active CNV. **It is anticipated that most re-treatment decisions will be driven by the presence or absence of fluid (subretinal, intraretinal fluid, or sub-RPE) on the OCT.** Eyes with fluid on OCT should be treated, with the exception of eyes in which there has been no decrease in fluid after three consecutive monthly injections. For such eyes, it is possible that continued treatment may be futile and the ophthalmologist and patient may choose to suspend treatment. Treatment may be reinstituted in these eyes at a later visit if there is increased fluid (relative to the visit when treatment was stopped) on OCT.

If there is no fluid on OCT, but there are other signs of active CNV, the eye should be treated. These signs include new subretinal or intraretinal hemorrhage, persistent subretinal or intraretinal hemorrhage, decreased visual acuity relative to the last visit without another explanation, increased lesion size on fluorescein angiography relative to the last angiogram, or leakage on fluorescein angiography.

Fluorescein angiography is required at specific visits and may be used in deciding whether treatment is warranted. Fluorescein angiography may be obtained at other visits to aid in the decision on whether treatment should be applied. Fluorescein angiography may also be obtained when there is no fluid on OCT and the decision to treat is based on new subretinal or intraretinal hemorrhage or decreased visual acuity relative to the last visit without another explanation. All fluorescein angiography should be submitted to the CATT Fundus Photograph Reading Center.

Patients who present for a "non-scheduled" study examination may be retreated if they meet the above criteria for retreatment and at least four weeks have elapsed since the last study treatment (variable dosing schedule patients only.) If the patient is retreated, no additional intravitreal study treatment may be administered for the next 23 days**.**

4.4. WITHHOLDING TREATMENT DUE TO POST-TREATMENT ADVERSE EVENT IN STUDY EYE – ALL TREATMENT GROUPS

If a patient experiences a serious adverse event in the study eye after treatment, the Investigator may, at her/his discretion withhold additional treatment until the event has resolved. Such events in the study eye include, but are not limited to:

- intraocular inflammation $\geq$2+ (anterior chamber cells >10 cells per mm^2)
- intraocular pressure $\geq$ 30 mmHG
- vitreous hemorrhage with a $\geq$ 30 letter loss in visual acuity
- new sensory rhegmatogenous retinal break or detachment (including macular hole)
- local infection

Refer to Exhibit 4-2 for more detailed definitions and procedures for withholding treatment for eyes with post treatment adverse events.

4.5. METHODS FOR ORDERING, HANDLING, AND STORING STUDY DRUG

4.5.1. Methods for ordering. handling and storing Avastin®

The CATT Investigational Drug Service (IDS) supplies kits for injections of Avastin®. Each kit will contain one 2-cc glass vial of study drug, one 25-gauge x 1½ inch needle for withdrawal of the vial contents, and one 30-gauge x ½ inch injection needle for the intravitreal injection. Vials are for single eye use only.

The initial supply of Avastin® is ordered by the Coordinating Center when a site has achieved CATT certification. Subsequent supplies are ordered by the clinic coordinator by faxing the Drug Re-Order Form to the IDS. Coordinators are encouraged to order as many vials as can be stored and used until the drug expires. The Coordinating Center is responsible for initiating replacements for expiring drug.

The IDS uses next day shipping and sends the designated drug recipient at the center information to track the package. The clinic coordinator must track packages not received by the following afternoon and the IDS needs to be immediately notified about lost shipments. The IDS ships the drug in a foam shipper with cold packs. The staff at each receiving site will inspect the conditions of each shipment of medication kits upon arrival, and immediately transfer the contents into appropriate, refrigerated storage locations. Kits received with warm or broken cold packs will be rejected, placed in quarantine, and the Drug Distribution Service notified. Study drug should be refrigerated at 2°-8°C (36°-46°F). DO NOT FREEZE. Do not use drug beyond the date printed on the packaging. Vials should be protected from light. Store in the original carton until time of use. See Chapter 5.2.12 for requirements for record keeping. Unused or outdated vials must be destroyed at the Clinical Center or returned to the Drug Distribution Center for destruction, as specified in the CATT Medication Manual and in Exhibit 4-3.

Vials of study drug must be stored securely in the clinic (if a separate pharmacy is not used) or in the local or on-site pharmacy (if one is used). It is important that vials are not accessible to non-study staff. If the medication must be stored in a refrigerator that is accessible to other staff, it is recommended that a separate locked box be used.

All medication vials received must be logged in and documented on the Avastin® inventory form. Similarly, each time Avastin® is dispensed to a CATT patient, it must be documented on the Inventory Log by affixing the tear-off portion of each vial label on the Inventory Label indicating the patient's study ID number, alpha code and date dispensed.

4.5.2. Methods for handling and storing Lucentis®

Staff at each clinical center will be responsible for obtaining Lucentis® for use in the Study. Procedures identical or similar to those used for non-Study patients should be used. In most centers, Lucentis® will be obtained from a center-affiliated pharmacy or from onsite supplies. Lucentis® should be refrigerated at 2°-8°C (36°-46°F). DO NOT FREEZE. Do not use beyond the date printed on the packaging. Vials should be protected from light. Store the vial and accompanying materials in the original carton until time of use.

Each time Lucentis® is dispensed to a CATT patient for study treatment, it must be documented on the Lucentis® Inventory Log distributed by the Coordinating Center or in a way that provides the same information as the Log. The information must include the lot number and expiration date (or vial label), the patient's study ID number, alpha code and date dispensed.

4.5.3. Preparation of the syringe and maintaining masking of the CATT ophthalmologist

The Clinic Coordinator is responsible for having the syringe presented in a masked manner to the CATT ophthalmologist. The Clinic Coordinator will obtain the drug to be injected from their local supply of each drug. The Clinic Coordinator, or another designated individual at the clinical center, fills the syringe as indicated in step 2 of Exhibit 4-1 and labels the syringe with the words "CATT Study Drug", along with the patient's ID number, alphabetic code and study eye. (Syringe labels are provided by the Coordinating Center.) The Clinic Coordinator presents the filled syringe to the CATT-certified ophthalmologist who will perform the injection. **The Clinic Coordinator, and the person filling the syringe if different from the Clinic Coordinator, may not reveal the content of the syringe to anyone else at the clinical center.** Timing and the exact steps performed by the Clinic Coordinator should be as similar as possible for the two study drugs. For example, if the time to acquire one drug is longer than the time required for the other drug, the Clinic Coordinator should adjust the time of delivering the syringe to the CATT ophthalmologist so that it is identical for the two drugs.

4.6. INTRAVITREAL INJECTION PROTOCOL

4.6.1. Administration

The injection protocol used in the Trial has been adapted from the protocol developed by the Diabetic Retinopathy Clinical Research Network (DRCRnet) and from the Lucentis® preparation guidelines (Genentech, Inc. 2006). Procedures will be implemented to minimize the risk of potential adverse events associated with serial intraocular injections (e.g., endophthalmitis). Aseptic technique must be observed by clinic staff involved in the injection tray assembly, anesthetic preparation and administration, and study drug preparation and administration. In addition to the procedures outlined in the protocol, added safety measures in adherence to specific institutional policies associated with intraocular injections should be observed.

Study drug will be administered in the study eye only. Intravitreal injection must be performed by the CATT-certified ophthalmologist following a slit lamp examination. See Exhibit 4-1 for detailed pre-injection procedures.

The needle of the syringe containing 50 μL of study drug solution will be inserted through the pre-anesthetized conjunctiva and sclera, approximately 3.0–4.0 mm posterior to the limbus, avoiding the horizontal meridian and aiming toward the center of the globe. The injection volume should be delivered slowly. The needle should then be removed slowly to ensure that all drug solution is in the eye. (See Exhibit 4-1 for detailed instructions for administration.)

At the discretion of the ophthalmologist, antimicrobial drops may be administered immediately following the intraocular injection or may be self-administered by the patient four times daily for 3 days following each intraocular injection.

4.7. POST ADMINISTRATION SAFETY TELEPHONE CALL

Clinic Coordinators telephone the patients 3-5 days after the first intraocular injection to assess whether the patient has experienced an adverse effect(s) of treatment. If the coordinator believes that such an event may have occurred, the patient is asked to return to the Clinical Center immediately for an evaluation. Patients with complications are treated according to best medical judgment.

4.8. TREATMENT DISCONTINUATION BECAUSE OF ADVERSE EVENTS

Exhibit 4-2 lists recommended criteria to guide clinical decision-making. Should any of the events in Exhibit 4-2 occur, and the managing ophthalmologist decides to withhold treatment, the reason should be recorded on the Treatment Evaluation Form for the visit and, if applicable, on the Adverse Event Log.

4.9. PRIOR AND CONCOMITANT THERAPY

Patients with previous treatment for CNV in the study eye are excluded from the Study. However prior treatment for CNV in the non-study eye is NOT an exclusion and will be documented on study forms. Concomitant treatment with Lucentis®, Avastin® and non-investigational agents is allowed. At all follow-up visits, patients will be asked about any additional treatments for any ocular condition, in either the study or non-study eye.

4.9.1. Concomitant Therapy for the Study Eye

No other treatment for choroidal neovascularization should be given to the study eye, including, but not limited to, laser photocoagulation, photodynamic therapy, Macugen® therapy, transpupillary thermotherapy, external beam radiation therapy, submacular surgery, or other surgical intervention for AMD. No other experimental or investigational treatments are permitted during this study; this includes ocular experimental and investigational treatments in the study eye (see Section 3.2.1).

Elective vitrectomy surgery is not allowed in the study eye during study participation. Onset of glaucoma during study participation should be treated as clinically indicated. Cataract surgery in the study eye may be performed if clinically indicated and should occur > 30 days after the previous study injection; the next study injection will be held for ≥ 30 days following cataract surgery.

If patients choose to discontinue their Study treatment in favor of an alternative treatment for choroidal neovascularization, certain precautions must be taken. If an anti-VEGF agent is to be administered, treatment must not be initiated in the study eye < 23 days following the last Study treatment.

4.9.2. Concomitant Therapy for the Non-Study Eye

Treatment of CNV that develops in the non-study eye during the follow-up period should follow the best medical judgment for the patient. Every effort should be made to decide

on the treatment for the non-study eye without unmasking the CATT ophthalmologist managing the patient. Possible treatments include thermal laser, photodynamic therapy, Macugen®, Lucentis®, or Avastin®. Other investigational agents should not be used for treatment of the non-study eye.

4.9.3. Follow-up of Patients Who Have Discontinued Lucentis-Avastin Trial Study Treatment

Patients who discontinue treatment will continue to be followed in the Study. Collecting data about the follow-up status of the eyes of patients who discontinue treatment is crucial in fully evaluating the treatment groups. If treatment is discontinued due to concomitant therapy or treatment related adverse events in the study eye, patients are expected to complete follow-up visits and undergo visual acuity testing, OCT, color photography and fluorescein angiography as specified for their treatment group in this protocol.

4.10. MANAGEMENT OF PATIENTS WHO DEVELOP INJECTION-RELATED COMPLICATIONS

Complications that arise from study treatment (e.g. endophthalmitis following an intravitreal injection) will be treated according to best medical judgment.

EXHIBIT 4-1

LUCENTIS-AVASTIN TRIAL INTRAVITREAL INJECTION PROCEDURES

The following procedures will be implemented to minimize the risk of potential adverse events associated with serial intravitreal injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration. In addition to the procedures outlined below, added safety measures in adherence to specific institutional policies associated with intravitreal injections will be observed.

The injection protocol used in Lucentis-Avastin Trial is the protocol developed by the Diabetic Retinopathy Clinical Research Network (DRCRnet), with the specific injection volume and needle gauges adjusted for injection of Lucentis® or Avastin® in this study. The following procedures (except where noted) will be performed by a CATT-certified treating ophthalmologist.

1. **Pre-Injection**
   a. On the day of injection, topical antibiotic drops may be administered at the discretion of the investigator.

   b. Remove the study drug vial from the refrigerator.

   c. When the patient is ready for the injection, apply a drop of topical anesthetic to the eye.

   d. Additional anesthesia will be at the discretion of the investigator but the use of lidocaine gel is not recommended since the gel may interfere with the action of povidone iodine. Additional anesthesia may include application of a cotton-tipped applicator soaked in topical anesthetic over the intended injection site, use of a subconjunctival anesthetic including subconjunctival lidocaine, etc.

   e. The eye will then be prepared for injection using one of the following sequence of steps:

      - Place 2-3 drops of 5% povidone iodine in the lower fornix. (Optional: Using sterile cotton-tipped applicators soaked in 5% povidone iodine, scrub the upper and lower eyelid margins and the upper and lower eyelashes.)
      - Place a sterile eyelid speculum to stabilize the eyelids.
      - A cotton-tipped applicator soaked in 5% povidone iodine is applied to the conjunctiva directly over and surrounding the intended injection site. Encourage the patient to look superonasally during the application of 5% povidone iodine to the intended injection site. Allow 30-60 seconds for the povidone iodine to dry before injection.

      OR

      - Place a sterile eyelid speculum to stabilize the eyelids.
      - Apply either a cotton-tipped applicator soaked in 5% povidone iodine or a 10% povidone iodine Swabstick directly over the intended injection site. Encourage the patient to look superonasally during the application of povidone iodine to the intended injection site. Allow 30-60 seconds for the povidone iodine to dry before injection.

OR

- A 5% povidone-iodine flush can be performed. Start by using a sterile needle to draw up at least 10cc of 5% povidone-iodine into a syringe. Following this, the needle should be discarded and a sterile angio-catheter should be attached to the syringe and used for irrigation. If desired, the catheter tubing may be trimmed using sterile scissors. Next the fornices and the caruncle should be irrigated with at least 10 cc of 5% povidone-iodine using a forced stream from the angio-catheter.
- Place a sterile eyelid speculum to stabilize the eyelids.

OR IF THE PATIENT IS ALLERGIC TO IODINE

- Apply one drop of topical antibiotic every 5 minutes for 3 doses prior to injection.
- Place a sterile eyelid speculum to stabilize the eyelids.

2. Filling the Syringe

a. Disinfect the rubber stopper on the vial of study drug with isopropyl alcohol. Disinfect hands.

b. Aseptically attach the 1½ inch needle onto the syringe, and carefully remove the needle cap.

c. Insert the sterile needle through the center of the stopper and draw the entire contents of the vial into the syringe. The 1½ inch needle should then be removed and a sterile 30-gauge, ½ inch needle should be placed onto the syringe. Fluid is expelled at an approximately 45-degree angle over a sterile surface until the plunger is advanced to 50 µL. The syringe is now ready for injection.

3. Injection

a. Sterile calipers or the blunt end of a sterile Tuberculin syringe (diameter equal to approximately 4.0mm) are used to locate the position of the injection site. The entry site for the intravitreal injection should be 3.0mm-4.0mm posterior to the limbus.

b. Inject the study drug into the vitreous cavity pointing toward the optic nerve via the pars plana.

4. Post-Injection

a. Remove the lid speculum and avoid any excess pressure on the eye.

b. Indirect ophthalmoscopy is performed to confirm that the central retinal artery is perfused and to assess any complications.

c. At the discretion of the investigator, a bottle of topical antibiotic may be provided to the patient and used QID for 3 days (inclusive of the day of injection).

NOTE: The patient should not be permitted to leave the physician's office until perfusion of the central retinal artery is confirmed. IOP may be checked ≥10 minutes after injection. The last IOP taken before the patient leaves the physician's office should be recorded.

EXHIBIT 4-2

TREATMENT DISCONTINUATION CRITERIA DUE TO ADVERSE EVENTS IN THE STUDY EYE

Event in Study Eye	Drug Dose-Holding Criteria
Intraocular inflammation	Hold dose if intraocular inflammation is ≥ 2+ (anterior chamber cells >10 cells per mm^2) in the study eye).
Intraocular pressure	Hold dose if intraocular pressure in the study eye is ≥ 30 mmHg. Treatment will be permitted when intraocular pressure has been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the Investigator.
Vitreous hemorrhage	Hold dose if there is a vitreous hemorrhage sufficient to produce a ≥ 30-letter decrease in visual acuity in the study eye compared with the last assessment of visual acuity prior to the onset of the vitreous hemorrhage. Treatment will be permitted when the vitreous hemorrhage improves to allow a visual acuity score improvement to a < 30-letter decrease.
Sensory rhegmatogenous retinal break or detachment (including macular hole)	Hold dose if a new retinal break is identified in the study eye. Treatment may be resumed ≥ 23 days after the retinal break has been successfully treated.
Local infection	Hold dose if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis or endophthalmitis in either eye.

The ophthalmologist may discontinue a patient from additional treatment for other safety reasons if in the best medical judgment of the treating ophthalmologist it is believed that there is no chance of any benefit to the patient from additional intravitreal injections in terms of preserving vision or retinal anatomy.

Returning or Destroying Expired or Damaged Drug

Expired or Damaged drug can either be destroyed on-site, or shipped back to the coordinating center pharmacy (IDS). The same form is used in both cases, and the inventory log must be updated. Do this as follows:

1. Contact the IDS and ask for a Destruction/Return Form. This will be faxed or emailed to you.
2. Document the # of vials and the reason.
3. Fill in the lot # and use-by date.
4. Sign the form.
5. **If destroying on-site,** fax the form back to the coordinating center pharmacy (IDS) and keep the original in your study records. Acceptable methods of destruction include incineration, yellow-bag (chemotherapy) waste or red-bag (biohazard) waste. If your site uses a different method than these, contact the central pharmacy to discuss and determine if your method is acceptable.
6. **If sending back**, pack the vials/kits well (sealed plastic bag to catch leaks, and bubble wrap or foam peanuts to prevent breakage). Send ambient (room temperature) along with a copy of the form. Keep the original in your study records.
7. On the inventory record, enter the quantity you removed from inventory, and enter the new balance. Hand-write the lot # and use-by date of the vials you removed from inventory.

Note that the empty packaging does not need to be saved, as long as the tear-off label from the vial is properly affixed to the inventory record and the inventory record is properly completed.

CHAPTER 5

PATIENT VISITS AND EXAMINATIONS

5.1. INTRODUCTION

Each patient enrolled in the Study is required to have study visits at the CATT clinical center every four weeks through the first 104 weeks (2 years) (See Exhibit 5-1). Patients are enrolled in the Trial, randomized to one of four treatment groups and treated in one eye during one or more encounters comprising a baseline visit. Patients assigned to either the Lucentis® on fixed schedule group or the Avastin® on fixed schedule group will be re-randomized at 52 weeks either to continue following a fixed schedule of injections every 4 weeks or to follow a variable dosing schedule.

Activities to be completed at each follow-up visit are specified in Exhibit 5-1 and vary by treatment group (fixed schedule vs. variable). At least one Study data collection form must be completed documenting each of the required visits.

Study patients may be seen in the clinical center between their regularly scheduled visits. Patients are encouraged to call the Clinic Coordinator at any time a decrease in vision is noticed so that the patient may be scheduled for an examination in the clinical center to assess the cause of the decrease in vision. Alternatively, the Study Investigator may believe that examining the patient more frequently than required by the Study schedule is in the patient's best interest. No data collection forms are required for these extra visits unless the investigator determines that additional treatment is required. However, study treatment may not be administered any more frequently than once every 23 days.

If any study visit is missed and cannot be rescheduled within the time window printed on the patient's appointment schedule, a Missed Visit Form should be completed and submitted to the Web based CATT data system.

5.2. PRE-ENROLLMENT PROCEDURES

Pre-enrollment procedures encompass the activities of evaluating the patient for eligibility by performing visual acuity testing, fundus photography, fluorescein angiography, OCT, an ophthalmological examination, and by questioning the patient about concurrent conditions. The order in which these procedures are performed may vary from clinic to clinic, subject to the restrictions discussed below. All procedures must be completed within 7 days prior to randomization.

5.2.1. Patient Identification

Each patient will be assigned a permanent identification number and alphabetic code to be used on all study forms, photographs and OCTs. The patient identification number is a two-part identifier consisting of a two-digit clinic number and three-digit sequence number. Patients will also have a four-letter randomly generated alphabetic code that is not linked to their name. The patient identification number and alpha code are available on pre-printed patient registration logs.

Each patient is also associated with a site within a clinical center. The patient's site is identified by a two-digit clinic number followed by a single digit site number. The patient's site identifies the address that is used for sending all patient specific correspondence, such as edit queries and appointment reminders. At some point in follow-up, a patient may move from one site to another within a clinical center or from one clinical center to another. If the patient moves to another site or clinical center, a Transfer of Patient Form must be completed. The patient's identification number and alphabetic code are permanent and do not change even if a patient is transferred.

5.2.2. Informed Consent

Informed consent must be obtained before the patient undergoes Study-specific procedures. Specifically, if the procedures used routinely in the clinical center for OCT, photography, refraction, or visual acuity testing are not identical to those specified by the CATT protocol, then consent MUST be obtained prior to the performing the procedure. The Coordinating Center has distributed a script (Exhibit 13-2) to the Clinical Centers that may be used to obtain patient consent for conducting screening studies prior to obtaining the patient's consent to participate in the full study. Clinical Centers may use this script with the approval of the local IRB. The Clinic Coordinator and the enrolling CATT Ophthalmologist share responsibility for the patient's orientation into the Study, but the ophthalmologist must take responsibility for the initial discussion with the patient and family. The Clinic Coordinator should be present for the discussion and should make every effort to ensure that all of the patient's questions and those of the family are answered satisfactorily. The patient should not be asked to sign the consent form until either the Clinic Coordinator or the CATT Ophthalmologist has answered all questions. It is important that the patient understands the concept of randomization in clinical trials.

If the patient is not ready to sign the consent form during the baseline visit, the patient may go home to think about enrolling in the trial. All parts of the baseline visit must be completed within 7 days prior to randomization. Before information is submitted to the CATT Web-based Data Entry System, a patient must sign the consent form.

5.2.3. Patient History

The Clinic Coordinator and Ophthalmologist, as appropriate, should review with the patient those questions on the Baseline General Information Form, Baseline Medical History Form and Assessment of Eligibility Form that can be answered prior to ophthalmoscopy and photography to ensure that the patient is eligible. Participation in other clinical trials is not an automatic exclusion; however, the Clinic Coordinator must call the Director of the Coordinating Center to discuss the treatment and follow-up required for any study in which the patient is already participating. If the patient is participating in the AREDS2 study, it should be noted on the form but the Clinic Coordinator does not need to contact the Coordinating Center.

Clinic Coordinators must complete the Patient Information Form so that the patient can be traced if contact is lost later in follow-up. Completion of this form may be delayed until after eligibility has been established, but it must be completed before requesting a treatment assignment.

5.2.4. Testing Visual Acuity

Refraction and testing of visual acuity to fulfill study eligibility criteria must be performed before the patient's eyes are dilated and before fundus photography and OCT if these procedures are to be

carried out on the same day. Refraction must precede visual acuity testing. If the Clinic Coordinator is also certified as a Refractionist and Visual Acuity Examiner, the Clinic Coordinator may perform the refraction and visual acuity during the baseline visit only. Standardized procedures as described in Chapter 7 must be followed. The Coordinator cannot refract the patient or test visual acuity during follow-up visits.

5.2.5. Ophthalmological Examination

A Study-certified Ophthalmologist performs a dilated eye examination of each eye of the patient to establish that the ocular inclusion criteria are met and that none of the ocular exclusionary conditions are present.

5.2.6. Fundus Photography

A Study-certified Photographer takes mydriatic stereoscopic color photographs and a fluorescein angiogram of both eyes according to the standardized procedures described in Chapter 8. Photography must be performed after testing visual acuity if these procedures are carried out on the same day.

5.2.7. Optical Coherence Tomography (OCT)

An OCT of both eyes is taken by a Study-certified OCT Technician according to the standardized procedures described in Chapter 9. Because the eye must be dilated for OCT, it must be performed after testing visual acuity if these procedures are carried out on the same day.

5.2.8. Use of Medications and Dietary Supplements

The Clinic Coordinator must complete a Baseline Concomitant Medication Form to indicate if the patient currently takes medications or dietary supplements. If they do, the appropriate forms must be completed prior to enrolling and randomizing the patient.

5.2.9. Patient Enrollment and Randomized Treatment Assignment

All procedures involved in the baseline visit must be performed within a **7**-day period preceding the randomization. Thus, if the OCT, color photographs, the fluorescein angiogram, or visual acuity testing are more than 7 days old on the day that the patient is to be randomized, the procedure(s) must be repeated.

After the Ophthalmologist assesses from photography, ophthalmic examination, OCT, visual acuity testing and medical history that the patient is eligible for the trial and if the patient has signed a consent form, the Clinic Coordinator will enter the data into the CATT Data Management system. (See Section 5.8 for information on submitting data to the CATT Data Management System.) The data system will check all entered responses against all eligibility criteria and will indicate which items, if any, need correction or confirmation. If all required data have been received and the patient is eligible, the Clinic Coordinator opens a form, answers questions about data collection completeness, and saves the form to generate a randomized treatment assignment for the patient. The system will then generate a report that provides the treatment to which the patient has been assigned. The Coordinator will print the treatment assignment report and the follow-up visit schedule. The baseline visit materials and follow-up visit schedule are filed in the

patient's Study chart. The treatment assignment screen should be filed with the Patient Log in a notebook and kept in a locked cabinet.

5.2.10. Re-Randomization of Patients Assigned to the "Fixed Treatment" Group

At 52 weeks, patients assigned to either of the two fixed schedule treatment groups will be randomized again to either continue with the fixed dosing schedule or to begin a variable dosing schedule for the next year. The study medication will not change from the original assignment of Lucentis® or Avastin®. This will be done by the clinic coordinator submitting the patient's ID number to the Web-based CATT data management system and requesting a 52-week randomized assignment. After confirming that the patient was previously randomized to a fixed schedule treatment group, the system will issue the treatment assignment for the next year. If the week 52 visit is missed, the re-randomization procedure can occur at any time after the visit window has closed.

5.2.11. Masking to Treatment Assignment

There are different levels of masking within the study. The Refractionist and Visual Acuity Examiner are masked to the treatment assignment (study drug and dosing schedule) for all follow-up visits. The Ophthalmologist knows the dosing schedule but is masked to whether the patient is receiving Lucentis® or Avastin®. The Clinic Coordinator is unmasked to both the study drug and dosing schedule. Patients are initially masked to the study drug but may find out the identity of the drug from billing documents. To ensure that the Ophthalmologist remains masked to the study drug assigned to the patient, an important task of the Clinic Coordinator is to remind the patient not to discuss the drug they are receiving with the Ophthalmologist. Similarly, patients (and clinic staff) must be reminded not to discuss the dosing schedule or drug received with either the Refractionist or Visual Acuity Examiner prior to each examination.

All personnel in the CATT Fundus Photograph Reading Center and the CATT OCT Reading Center will be masked to whether the patient is receiving Lucentis® or Avastin®.

5.2.12. Medication and Record Keeping

During the randomization process, each participant is assigned to receive either Lucentis® or Avastin®. The study supplies the Avastin® through the Drug Distribution Service. Lucentis® is purchased and stored by the clinical center in a manner identical to its use outside of the study (i.e., standard practice).

If the patient is assigned to Lucentis®, the Clinic Coordinator will obtain a box of Lucentis® from the practice inventory. Using the 19 gauge filter needle provided in the Lucentis® packaging, the Clinic Coordinator will draw up the medication into a syringe and then attach a 30 gauge injection needle. The Clinic Coordinator will affix to the syringe a label with the patient's ID number, alphabetic code and study eye and give it to the Ophthalmologist to administer treatment. The dispensed vial must be recorded on the Lucentis® Inventory Log or similar document by the Clinic Coordinator.

If the patient is assigned to Avastin®, the Clinic Coordinator will obtain a package consisting of a single use medication vial supplied by the Drug Distribution Service. Using the 25 gauge needle provided in the package, the Clinic Coordinator will draw up the medication into a syringe and

then attach a 30 gauge injection needle. The Clinic Coordinator will affix to the syringe a label with the patient's ID number, alphabetic code and study eye and give it to the Ophthalmologist to administer treatment. The Clinic Coordinator will affix the label from the medication kit to the Medication Inventory Log.

Federal law requires documentation of receipt, use, and disposition of every dose of investigational medication. The CATT Drug Distribution Center has the responsibility to assure the FDA that systems for medication accountability are being maintained by investigators at the Clinical Centers. To assist in fulfilling these requirements, a set of drug accountability records has been prepared for use by each site.

A Medication Inventory Log is supplied to simplify the accountability of the study-supplied Avastin® from receipt to return/destruction of unused product. When study-supplied Avastin® is used for treatment, the date of treatment and the treating physician's initials are recorded. Finally, when medication is returned to the CATT Drug Distribution Center or destroyed on site, there is a place to record this as well. Medication Dispensing Logs for Lucentis® are also supplied to record the use of Lucentis® for each CATT treatment.

5.2.13. Treatment

Patients and CATT-certified Ophthalmologists should be prepared to commence treatment to the study eye immediately after randomization. (See Chapter 4.6 for the detailed treatment protocol.) An Intravitreal Injection Treatment Form is completed using information provided by the treating Ophthalmologist. Before the patient leaves the clinical center, the Clinic Coordinator schedules a time to call the patient to conduct a short safety telephone call 3-5 days later and schedules the patient's next study visit in four weeks.

5.3. SAFETY CHECK TELEPHONE CALL

A safety check telephone call is scheduled for 3-5 days after the first study injection. The Clinic Coordinator should schedule this telephone call with the patient prior to the patient leaving the office after the first treatment. The purpose of the call is to assess whether or not the patient has experienced an untoward effect of the study injection and address concerns that the patient may have. A brief form is completed to document the telephone call and is entered into the CATT database by the Clinic Coordinator. Documentation of the telephone call is also recorded in the patient's medical record and signed and dated by the clinic coordinator.

5.4. REGULARLY SCHEDULED FOLLOW-UP VISITS THROUGH 104 WEEKS

Follow-up visits are scheduled every four weeks for a total of 104 weeks (2 years after enrollment into the Study).

5.4.1. Preparing for Follow-Up Visits

The following tasks should be performed before the patient arrives for a scheduled follow-up visit.

- Remind the patient of the scheduled appointment by telephone or by mail in advance of the date.

- Retrieve the patient's Study file.
- Log onto the CATT database and print a packet of all forms and logs required for the specific follow-up visit. Each page of the printed forms will be pre-populated with the patient's Study identification number, alphabetic identification code, and visit code. When printing forms for each visit, the clinic coordinator must remember to print the Concomitant Medication Log and Adverse Event Log located in separate "tabs" in the CATT database. In the rare event the system cannot print the forms required for the visit, the clinic coordinator will photocopy the forms from the Forms Notebook resident at the site and must label each page with the identifying information.
- Be sure that any pertinent information received since the last examination is available to the investigators.
- Put the Patient Information Form in the folder as a reminder to review and update the information.

5.4.2. Follow-Up Visit Procedures

The procedures to be performed at each follow-up visit are displayed in Exhibit 5-1. Patient history, visual acuity testing, ophthalmological examination, and evaluation for treatment are performed at every visit. Treatments are performed on a fixed or variable dosing schedule. As during the baseline visit, visual acuity testing must be performed before dilation of pupils, and OCT testing and ophthalmological examination after dilation of pupils. Photography is performed in both eyes at weeks 052 and 104 at sites that do not participate in the fluorescein substudy; at sites participating in the fluorescein substudy, photography is performed in both eyes at weeks 012, 024, 052 076 and 104. OCT is performed at weeks 004, 008, 012, 024 052, 076 and 104 for the patients in the fixed schedule group; OCT is performed at every visit for patients in the variable dosing schedule groups.

Assessing Interim Medical History During Follow-up Visits: The CATT General Follow-Up Visit Form specifies collection of data from the patient regarding their health, medications, vision, other ocular treatments, and possible adverse events (AEs) since the patient's last Lucentis-Avastin Trial visit. All AEs must be recorded on the AE Log. If the investigator identifies an adverse event as serious, it must also be reported to the Coordinating Center on the CATT Serious Adverse Event Reporting Form as detailed in Section 6.9 of this manual. Either the Clinic Coordinator or Study Ophthalmologist may ask the patient these items. Visual Acuity Examiners are never to ask these items as the patient's response may jeopardize the Visual Acuity Examiner's masking to treatment schedule and study medication. If additional or follow-up information is obtained about a previously reported serious adverse event, the Clinic Coordinator or Ophthalmologist must complete a SAE Follow-Up Reporting Form.

Visual Acuity Testing: A certified Visual Acuity Examiner must perform the standardized, e-ETDRS visual acuity testing (Chapter 7). To minimize potential bias, the Clinic Coordinators may not perform visual acuity testing during follow-up visits. The Clinic Coordinator should supply the Visual Acuity Examiner with the patient's record of subjective refraction from the previous test. In the rare occurrence of a malfunctioning e-ETDRS system, the coordinator should provide the Visual Acuity Examiner with the paper ETDRS Chart Worksheet to record the results of visual acuity testing.

Refraction: Refraction is required only at follow-up visits for which the visual acuity score will be used to evaluate treatment efficacy (see Exhibit 5-1). A CATT-certified Refractionist must perform the standardized, e-ETDRS refraction (Chapter 7). The Clinic Coordinator may not perform refraction during follow-up visits.

Fundus Photography: Fluorescein angiography and color photography of the study eye are required as specified in Exhibit 5-1. A CATT certified photographer takes mydriatic stereoscopic color photographs and a fluorescein angiogram according to the standardized procedures described in Chapter 8. Photography must be performed after testing visual acuity if these procedures are carried out on the same day. If not performed on the same day, photography must be performed within 7 days of the visual acuity test.

Patient Information: At all follow-up visits, the Clinic Coordinator asks the patient if any contact information has changed since the last visit to the clinic and updates the Patient Information form accordingly.

5.4.3. Follow-Up Visit Procedures if the Week 52 Visit is Missed

Because the primary outcome of the CATT study is visual acuity at one year, a missed visit at week 52 has a greater negative impact on CATT results than when other visits are missed. If the week 52 visit is missed, a protocol refraction, visual acuity testing, OCT, fundus photographs and angiography must be completed for all patients at the next completed study visit that occurs within the week 56, 60 or 64 visit window. In addition, if the patient is assigned to fixed monthly treatments, you must re-randomize the patient prior to evaluating the need for treatment.

Data collected at these visits must be entered in the visit week during which the testing actually occurred (e.g., if you are testing visual acuity at week 60 enter the data in the week 60 tab). Do NOT enter the data in week 52 if the visit occurred outside of the week 52 visit window. The exception to this is the re-randomization (RAND2) form, which resides on the week 52 visit tab and must be completed there.

5.4.4. Study Treatment During Follow-up Visits

Fixed Schedule Lucentis® and Avastin® Patient Groups

All patients assigned to fixed schedule group will receive additional study treatment during each study visit, unless a contraindication to injection develops (see Exhibit 4-2) or unless the ophthalmologist believes that additional treatment is futile (see section 4.2.1). Results of the OCT, visual acuity testing, and fluorescein angiogram (if performed) will not affect treatment decisions.

Variable Schedule Lucentis® and Avastin® Patient Groups

Patients who are assigned to treatment with either variable schedule Lucentis® or Avastin® will receive additional treatment if there are signs of lesion activity and no contraindication to injection has developed. See Section 4.3.2 for guidelines on retreatment decisions. If a fluorescein angiogram was done to aid the ophthalmologist in his/her determination of the need for additional treatment, the angiogram must be submitted to the Fundus Photograph Reading Center.

5.4.5. Study Treatment During "Non-Regularly Scheduled" Study Visits (Variable Schedule Patients Only)

There may be times when a Study patient returns to the Clinical Center before their next regularly scheduled study visit, either because the Study Ophthalmologist wishes to re-examine the patient sooner than in 4 weeks or because the patient reports symptoms. During these "non-scheduled" visits, the Study Ophthalmologist may decide that the patient should be retreated if at least 23 days have elapsed since the prior study treatment (variable dosing schedule patients only.) If the patient is retreated, he/she cannot be treated again at their next scheduled study visit if the next visit occurs sooner than 23 days later.

5.4.6. Reporting Adverse Events

All adverse events (AEs) that occur from the time the patient enrolls into the Lucentis-Avastin Trial through the end of the study follow-up period must be reported. The Clinic Coordinator is responsible for entering the AE data into the Web-based system. If a Serious Adverse Event (SAE) occurs, the Clinic Coordinator is responsible for submitting the SAE Reporting Form to the CATT Coordinating Center and for submitting a SAE report to the local IRB (if required by local IRB rules). If additional information is obtained on a serious adverse event that was previously reported it must be reported on the SAE Follow-Up Reporting Form. (See Chapter 6 for a detailed discussion on reporting adverse events.)

5.4.7. Scheduling Required Visits and Procedures

It is extremely important that both the Clinic Coordinator and the patient adhere to the follow-up appointment schedule. The patient's appointment schedule should be consulted whenever the patient is given an appointment for a follow-up examination. It is especially important to refer to the schedule when an examination date is changed.

Each visit should be scheduled as close as possible to the target date. Whenever a visit is completed near the end of a time window, an attempt should be made to get the patient back on schedule. Visits not completed within the specified time limits are classified as missed.

The Clinic Coordinator plays a crucial role in ensuring that the required procedures and visits occur on schedule. Before the patient leaves the Clinical Center, the Clinic Coordinator schedules the next visit. Thus, whenever a patient leaves a Study visit, he/she should have an appointment card with the date of the next visit.

When scheduling each study visit, the Clinic Coordinator should consult the "Required Study Visits and Visit Procedures" chart (Exhibit 5-1) to ensure that all requisite tests are scheduled.

5.4.8. Follow-up of Patients Unable to Return for Scheduled Visits

Because of poor health or for other reasons, some patients may not be able to return to the Clinical Center for scheduled study visits despite their original intentions to do so. Information regarding unresolved SAEs can be obtained by the Clinic Coordinator through telephone calls or, after obtaining patient consent, records from a non-study physician whom the patient has seen may be obtained. If the patient cannot be located through family members or friends, a Patient Search Form should be initiated. Coordinators must still complete Missed Visit Forms for these patients.

If the Clinic Coordinator discovers that the patient has died, the Clinic Coordinator follows procedures for reporting a serious adverse event and completes a Patient Death form in the Web-based CATT system.

5.4.8.1. Missed Visits

Any time a patient misses a scheduled visit, the Clinic Coordinator should contact the patient immediately and arrange another appointment. Whenever it is not possible to examine the patient in a CATT Clinical Center, the following procedures should be followed to provide as much useful information as possible.

- If a Study patient cannot complete a scheduled visit within the time window for that visit, the Coordinating Center should be notified by completion and entry of a Missed Visit Form within one week of the close of the visit window.
- The patient should be contacted by telephone to schedule the next visit or to confirm the appointment for the next visit.
- The patient should be asked whether they have been examined during the time period covered by another ophthalmologist. If so, the name(s) of the other physician(s), the address, and telephone number, if possible, should be obtained from the patient. The patient must be asked to sign a medical record release form allowing the outside physician(s) to provide information on the patient.

If the patient cannot be located, an intensive search should be instituted immediately by the Clinic Coordinator. The Clinic Coordinator should use all available resources to locate the patient, including writing or telephoning each contact provided by the patient at time of enrollment or added since then. Because this search may be long and time-consuming, it is important that it be started as soon as any member of the clinic staff is aware that there is a problem. The steps taken to locate the patient should be documented on a Patient Search Form. In extreme cases when the clinic staff has exhausted all avenues and the patient has not been located, the Coordinating Center should be notified. Missed visit forms must be completed for these patients for each visit the patient missed.

5.5. CHANGING THE SITE FOR PATIENT FOLLOW-UP

During the course of their follow-up, some patients may choose to be seen at another CATT-certified site within the clinical center. A Transfer of Patient Form must be completed so that materials relating to the patient are sent to the correct location. The patient's study chart should be transferred to the new site.

Patients may move to another area of the country. If another CATT clinical center is located closer to the patient's new home, a permanent transfer may be arranged and documented with a Transfer of Patient Form. The CATT staff at the new clinical center must accept responsibility for the follow-up of the patient before the patient can be transferred. The Clinic Coordinator from both clinics must sign the form indicating approval of the transfer, and fax the completed form to the Coordinating Center. The clinic at which the patient was originally enrolled should copy the patient's study chart and send it to the receiving clinic.

5.6. PATIENT DEATH

As soon as clinic personnel become aware that a patient has died, the Clinic Coordinator follows procedures for reporting a serious adverse event, requests a death certificate, completes a Patient Death form, and enters the form into the CATT Web-based data system. The patient will then be removed from later reminders for visits.

5.7. GUIDELINES FOR DOCUMENTATION OF LUCENTIS-AVASTIN TRIAL ACTIVITIES

In accordance with good research practice, it is essential that all study patient-related activities be documented so that information at the clinical centers can be compared with the data in the trial database and in source documents by study site visitors and/or outside auditors as necessary.

Information should be included that documents the following information:

- That all reported procedures and tests were conducted according to protocol.
- That all procedures and examinations were performed by the reported personnel on the dates reported.
- That the reported treatment regime was administered and explained to the patient per protocol by the specified personnel or that protocol deviations have been reported.

In addition to Lucentis-Avastin Trial forms, other clinical information is valuable for providing complete documentation of study-related procedures. The following section specifies the types of documentation that are recommended.

5.7.1. Information to be Included in the Medical Chart

- Examination notes, dated and signed by the individual(s) performing the examination, and completed at the time of the examination.
- Copies of lab reports
- Copies of all internal or external patient-related correspondence.
- Signed and dated notes from telephone calls and other contacts with patients, their families, friends and physicians.
- Signed notes documenting patient education, counseling, and enrollment decisions regarding the Trial.

Patient names and other identifiers should be retained on all such documentation so that the identity of the patient and the correspondence of examination results to the reported data may be confirmed. This information need not be retained in the study files but may be kept in separate clinic files for each patient. The structure of these files may vary depending on local guidelines or requirements. However, some Clinic Coordinators find it expeditious to attach copies of all documents from which data were abstracted to the corresponding forms in the study charts.

5.7.2. Maintaining the Patient's Lucentis-Avastin Trial File

All study visit materials are filed in the patient's study chart as is a copy of the follow-up appointment schedule. The following things should be done to keep the patient's study file as complete and up-to-date as possible at all times:

- The patient's contact information, such as telephone numbers, place of employment, persons who can be contacted about the patient's whereabouts, etc., should be reviewed and updated at each visit. Contacts already listed should be confirmed. If any changes are made, the information should be added to the Patient Information Form.
- Be sure that copies of the forms and all other information submitted to the CATT Coordinating Center and Reading Centers are in the patient's file.

5.8. SUBMISSION OF VISIT DATA TO THE CATT RESOURCE CENTERS

One major responsibility of the Clinic Coordinator is to gather the data obtained at the study visit and submit it to the Coordinating Center, OCT Reading Center and (if necessary) to the Fundus Photograph Reading Center. Study forms should be entered in to the data system as soon as possible after the visit; forms entered more than 7 days later will be considered late. Photographic materials and OCTs should be submitted to the respective Reading Centers according to the procedures discussed in Chapters 8 and 9 of this manual.

The Clinic Coordinator should carefully check all data collection forms before entering the data in the web-based CATT data system. This process is extremely important because correcting errors that have entered the data system is far more time-consuming and expensive than taking the appropriate steps to prevent errors. Every response on the forms should be checked for completeness, consistency with other information reported for the patient, and legibility. In addition, the person performing each procedure should initial or sign the appropriate component of the form, as indicated on the forms.

5.8.1. Entering Data into the On-Line Patient Enrollment and Randomization System

At any point after the patient has signed a patient consent form, the Clinic Coordinator may enter baseline data into the on-line system in real time. For example, the Clinic Coordinator may enter the results of the OCT and visual acuity testing before the interpretation of the fluorescein angiogram is made.

The first step in entering data for a patient is to complete a Patient Registration Form. This form may be completed after the patient consent form has been signed. More information on entering data may be found in the CATT Database Management System Manual.

5.8.2. Submission of Data to the OCT Reading Center

All patients enrolled in the trial are required to undergo OCT at the baseline visit and as specified in Exhibit 5-1. The results of the scans will be interpreted by the OCT Reading Center. The Clinic Coordinator has the responsibility to send the scan output to the OCT Reading Center, as specified in Chapter 9.

5.8.3. Submission of Photographic Materials to the Fundus Photograph Reading Center

All patients enrolled in the trial are required to undergo photography (color photographs and fluorescein angiography) at the baseline visit and as specified in Exhibit 5-1. The results of the images will be interpreted by the Fundus Photograph Reading Center. The Clinic Coordinator has the responsibility to send the photographic images to the Fundus Photograph Reading Center, as specified in Chapter 8.

5.8.4. Completeness of Submitted Data

Each data form should be checked for completeness and to assure that all pages of all components are included and in the correct order. In addition, the clinic coordinator should check the data screen before saving the data into the database. Data will be validated during the entry process. Whenever there is doubt about how an item is to be answered, the Protocol Monitors or Director at the CATT Coordinating Center should be contacted by telephone. Items for which an answer always is required usually appear on the left-hand side of each page of each form and data entry screen.

5.8.5. Consistency

Questions that should be answered only for certain patients appear in boxes in the right hand column of each page of each form and data entry screen. An arrow leading from a specific response to a box indicates that whenever that response is checked, the additional information in the box also is required. Otherwise, items in the box should be left unanswered. Dates should be checked for accuracy. In particular, the date of an examination recorded on a data form should be the actual date the patient was examined and not the date when the data are entered into the database.

5.9. EDITS AND CORRECTIONS

5.9.1. Edit Queries

The information submitted to the CATT database is edited for anomalies by means of special computer programs. When a question exists regarding the answer to one or more of the items on a component, the item is flagged by the data system. The Clinic Coordinator should first check for a data entry error by comparing the response on the paper copy of the form against the database response. If the edit query is due to a data entry error, the Clinic Coordinator may immediately correct the error. If the edit query is not due to a data entry error, the Clinic Coordinator should refer to the patient's record and determine the correct answer for each item flagged. The Clinic Coordinator may need to consult with the physicians or other technical staff for specific medical information. In this case, whenever a correction to an earlier value on the paper form is required, the Clinic Coordinator corrects the earlier response on the original data collection form filed at the site by striking through it (so that it is still legible), writing the correct response, and initialing and dating the corrected item(s). The original response should not be obliterated with white-out, marker, or by scratching through it. The database is similarly updated. After edit queries are resolved, the responses of the database and paper forms must be the same.

5.9.2. Errors Discovered in Other Ways

On occasion, when errors are detected by the Coordinating Center through audits or data summary reports, Coordinating Center staff will have the ability to flag a database response for review by the Clinic Coordinator. A correction to the database and paper form as described above may be required.

5.10. QUALITY ASSURANCE RESPONSIBILITIES

The validity and credibility of the study depends to a large degree on the collection and reporting of high quality, accurate data. Each study staff member should be aware of his/her responsibility for following the protocol, reporting data accurately and promptly, and resolving any problems that occur in trial-related activities. Although the local Principal Investigator bears primary responsibility for the accuracy and integrity of study data, much of the responsibility falls to the Clinic Coordinator.

In addition to the routine procedures described in previous sections, the primary quality assurance mechanisms to be implemented at the Clinical Center are:

- The person completing each examination and taking responsibility for the examination must be identified by initials and certification number at the end of the section where the data from the examination is recorded.
- Hard-copy documentation of all tests, and procedures should be obtained and kept in patients' study files.
- Any errors or discrepancies discovered at the clinical center are corrected, regardless of the time elapsed since the data were collected, and updated in the database system.
- Systematic data collection or reporting problems are brought to the attention of the responsible individual, the local Principal Investigator and the Coordinating Center for review and resolution.

EXHIBIT 5-1

CATT REQUIRED VISITS & PROCEDURES

----------FOLLOW-UP WEEK----------

	000	004	008	012	016	020	024	028	032	036	040	044	048	052
History	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Refraction	B	B		B			B			B				B*
Visual Acuity	B	B	B	B	B	B	B	B	B	B	B	B	B	B*
OCT	X	X	X	X	V	V	X	V	V	V	V	V	V	X*
Ophthalmologic Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography	B			F			F							B*
Treatment+	X	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+

----------FOLLOW-UP WEEK----------

	056	060	064	068	072	076	080	084	088	092	096	100	104
History	X	X	X	X	X	X	X	X	X	X	X	X	X
Refraction			B			B			B				B
Visual Acuity	B	B	B	B	B	B	B	B	B	B	B	B	B
OCT	V	V	V	V	V	X	V	V	V	V	V	V	X
Ophthalmologic Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography						F							B
Treatment	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	

LEGEND:

000: Denotes 'Baseline visit'
X: All patients
V: Only patients assigned to the variable dosing schedule.
B: Both eyes
F: Only for the 300 patients in the fluorescein angiography sub-study (75 patients per treatment arm)
+: Treatment for those in the fixed schedule groups. For the variable dosing schedule groups, evaluation for treatment.
***** If Week 052 visit is missed, procedure should be done at the next completed study visit that occurs within the week 56, 60 or 64 visit window.

Photography includes both color photography and fluorescein angiography.

CHAPTER 6

SAFETY AND ADVERSE EVENTS

6. SAFETY AND ADVERSE EVENTS

6.1. Medical Monitoring in the CATT

Medical monitoring in the Study is the responsibility of the CATT Data & Safety Monitoring Committee (DSMC). A Medical Safety Monitor, who holds an MD, reviews reports of serious adverse events (SAEs) as they occur. On a monthly basis, the Coordinating Center provides the Monitor with the number and type of SAEs at each clinical center, and will provides statistical and analytical expertise to ascertain the presence of site-specific patterns of safety issues.

6.2. Independent Data and Safety Monitoring Board

The Data and Safety Monitoring Committee (DSMC) was appointed by the National Eye Institute and is comprised of ophthalmologists with expertise in age-related macular degeneration and CNV, a specialist in cardiovascular medicine, a physician with expertise in angiogenesis, biostatistician/epidemiologists, and a patient advocate as voting members. The NEI Project Officer serves as an ex officio member. The committee is responsible for the review of performance, safety, and efficacy data. At the first DSMC meeting, the Committee reviewed the study protocol, offered advice to the Study Executive Committee, and approved the study design. Statistical guidelines for early stopping and procedures for recording and reporting adverse events were presented by the Coordinating Center and accepted by the DSMC. The DSMC meets semi-annually.

A Medical Safety Monitor reviews reports of serious adverse events. The Coordinating Center submits periodic reports masked to treatment group to the DSMC and Study Chairman.

6.3. Overview of Adverse Events Definitions and Reporting System

Because the CATT Study is examining the treatment effect of an off-label use of a pharmaceutical agent (Avastin®), the study is operating under an IND. Hence this study will comply with the adverse events definitions and reporting requirements for clinical trials established by the Food and Drug Administration (FDA) in 21 CFR 312.

6.4. Definition of Adverse Events

An adverse event (AE) is the development or worsening of any symptom, sign, illness or experience that is temporally associated with a protocol mandated intervention, regardless of causality. These include AEs that emerge during the reporting period that were not previously observed in the patient, complications that occur as a result of protocol-mandated interventions or preexisting medical conditions that are judged by the investigator to have worsened in severity or frequency, or have changed in character during the adverse event reporting period.

6.5. Definition of Serious Adverse Events

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs inpatient hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect in a neonate or infant born to a mother exposed to the investigational product
- considered by the investigator to be an important medical event (e.g., events that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the patient, and may require intervention to prevent one of the other serious outcomes noted above.)

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Keep in mind that the definition of a SAE focuses on the "outcome" of the event, and the SAE may involve only one, or possibly more, of the above criteria. All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

6.5.1. Severity vs. Serious

The terms "serious" and "severe" are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (e.g., a mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is ***not*** the same as "serious", which is based on patient or event ***outcome or action*** criteria, usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. When recording AEs and SAEs, severity and seriousness must be independently assessed.

6.5.2. Preexisting Conditions

Preexisting conditions should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. If there is a question as to whether a medical development should be reported as an adverse event, the Investigator or Clinic Coordinator must contact the Study Chairman for guidance.

6.5.3. Worsening of Symptoms and Signs of Choroidal Neovascularization

Developing symptoms and signs that are consistent with the natural history of choroidal neovascularization secondary to AMD are not considered reportable adverse events. Such developments are, however, recorded on the study data collection forms. For example, moderate loss of visual acuity over time, expansion of the size of the lesion, and increased intraretinal or subretinal fluid are common developments associated with AMD. Such developments are

recorded on study forms by either clinical center staff or staff at the two Reading Centers, but are not reportable adverse events.

Worsening of symptoms and signs of choroidal neovascularization should be recorded as an AE or SAE only if judged by the investigator to have unexpectedly worsened in severity and/or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of choroidal neovascularization, it is important to convey why the development was unexpected. For further guidance see 6.5.6. below.

6.5.4. Abnormal Laboratory Values

Abnormal laboratory results will generally not be recorded as an AE. A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.
- The abnormality results in study withdrawal.

6.5.5. Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in a hospitalization should be documented and reported as a SAE. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event when the hospitalization or prolonged hospitalization was for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

6.5.6. Vision Threatening Adverse Events

An AE is considered to be vision-threatening and is a reportable SAE if it meets one or more of the following criteria:

- It caused a decrease in visual acuity of >30 letters (compared with the last assessment of visual acuity prior to the most recent treatment) lasting >1 hour.
- It caused a decrease in visual acuity to the level of Light Perception or worse lasting > 1 hour
- It required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- It is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis).

- In the investigator's opinion, it may require medical intervention to prevent permanent loss of vision.

Note that the development of endophthalmitis is a reportable serious adverse event.

6.5.7. Deaths

All deaths that occur during the AE reporting period (section 6.6), regardless of attribution to study intervention, must be recorded on a CATT Patient Death Form, entered into the CATT database and immediately reported to the Coordinating Center and local IRB as an SAE. A death certificate must be requested and when obtained, a copy must be sent to the Coordinating Center and the original retained in the patient's CATT file.

6.6. Adverse Event Reporting Period

The reporting period during which adverse events must be reported is the period from enrollment to the end of the study follow-up. All unresolved adverse events must be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled study visit, the Investigator will instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to prior study treatment. Such events should be reported if the Investigator attributes the event to study treatment. Patients who withdraw early from the study will be contacted by the Clinic Coordinator 30 days after their last visit to ascertain whether any AEs have occurred.

6.7. Collecting Adverse Event Information

During each study visit, investigators and clinic coordinators will assess the occurrence, status change and resolution of AEs and SAEs by examination and by questioning the patient. Complete reporting information includes the following:

- Specific condition or event and direction or change
- Grade/severity
- Event type
- Dates of onset and (if applicable) resolution
- Outcome
- Whether event necessitated a change in study treatment
- Abnormal laboratory value (SAEs only)
- Attribution to study drug (SAEs only)

Whenever an SAE is associated with a hospital stay, the clinic coordinator must ask the patient to sign a release to obtain the hospital discharge summary. Upon receipt, a copy of the report must be sent to the Coordinating Center and the original filed in the patient's CATT file.

6.8. Assessment of Adverse Events

All events will be coded by the Clinic Coordinator using an on-line version of the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute (National Cancer Institute, 2006). The CTCAE version 3.0 provides definitions for a large subset of adverse event terms and a grading (severity) scale for each adverse event. The CTCAEv3.0 and its associated grading criteria are very specific, providing an adverse event term (MedDRA name and number) and grade that precisely describes the event. (Refer to the CATT Oracle Clinical™ Training Manual for instructions in accessing and using the CTCAEv3.0.) If the event is not found in the CTCAEv3.0, the Clinic Coordinator contacts the Coordinating Center for assistance. The Director, Protocol Monitor and Systems Analyst uses MedDRA Browser Version 10 (Northrup Grumman, 2005), which is linked to a database of all MedDRA numbers and terms.

6.8.1. Coding Ocular Adverse Events

When coding an ocular adverse event, the clinic coordinator should first consult the CTCAEv3.0 as described above. If the event is not found, the clinic coordinator should next consult the list of the Common Ocular Adverse Events, which is accessible from the CATT Landing Page (https://rt4.cceb.med.upenn.edu/crcu_html/crcu_rdc_launch.html). If the event is not on this list, the coordinator then searches the full list of Ocular MedDRA terms, which is also accessible from the CATT Landing Page.

6.8.2. Grading the Severity of Adverse Events

All events must be graded for severity by the Investigator, using a 5 point scale:

1 = Mild: Awareness of sign or symptom, but easily tolerated
2 = Moderate: Interference with normal daily activities
3 = Severe: Inability to perform normal daily activities
4 = Life threatening or disabling: Immediate risk of death or disablement
5 = Death

6.8.3. Attributing the Causality of Serious Adverse Events

Attribution is the determination of whether a serious adverse event is related to a medical treatment or procedure. To report on attribution, clinicians must evaluate each SAE the patient experiences to determine what might have caused the event or what interventions or conditions might have been associated with the event.

A SAE is related to the investigational agents when 1) the onset is temporally related to the administration of the study drug and the SAE is not explainable by the patient's concomitant conditions or therapies, and/or 2) the SAE follows a pattern of response to the study drug or injection and/or 3) the SAE lessens or resolves when the drug is reduced or discontinued, and (if applicable) 4) reoccurs when drug is reintroduced. A non-related SAE has an etiology other than the study drugs (e.g., preexisting medical condition, underlying disease or concomitant medication) or a SAE whose onset is not plausibly related temporally to the administration of the study drug. When ascertaining whether a SAE is related to the drugs under study, or to the injection procedure, investigators should use the following criteria:

Unrelated:	The SAE is clearly not related to the investigational agents
Unlikely:	The SAE is doubtfully related to the investigational agents
Possible:	The SAE may be related to the investigational agents
Probable:	The SAE is likely related to the investigational agents
Definite:	The SAE is clearly related to the investigational agents
Related to Injection	**The SAE is not related to the investigational agent but is related to the injection procedure alone**

6.8.3.1. Attribution of Causality by the Medical Safety Monitor

The Medical Safety Monitor will also evaluate all reported SAEs against accumulating knowledge of the study drugs to identify and communicate new safety findings to investigators and to the FDA. In cases when the evaluation of the Medical Monitor regarding causality differs from the Investigator's, the Monitor's assessment will prevail with regard to filing MedWatch reports.

6.9. Recording of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs that are observed during the study are recorded on the CATT Adverse Event Log and in the patient's clinical record. All SAEs are also reported on the CATT Serious Adverse Event Initial Reporting Form (or SAE Follow-up Reporting Form) and submitted to the CATT Coordinating Center. The information recorded on the CATT Adverse Event Log should be based on the signs or symptoms detected during the clinical evaluation of the patient and on information obtained from the patient. The AE Log is included in the on-line CATT database, and with the submission of each log entry the computer performs an automatic data check to ensure that all required reporting elements have been entered into the system.

All serious adverse events are reported on the SAE Initial Reporting Form (or SAE Follow-up Reporting Form) and submitted to a secured fax machine at the CATT Coordinating Center. The Coordinating Center maintains a database of all SAEs and confirms receipt of materials in conjunction with a reminder to the Clinic Coordinator to report the event to the local IRB if the event meets the IRB's reporting requirements. Reports of all SAEs and all accompanying documentation will be electronically sent to the Medical Monitor by the Coordinating Center.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Adverse events that are still ongoing at the end of the study period must be followed up for one month to determine the final outcome. Any AE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

6.9.1. Diagnosis vs. Symptoms

If a disease is known at the time an AE is reported, this diagnosis should be recorded on the Adverse Event Log and (if appropriate) on the SAE Reporting Form rather than listing individual symptoms. However, if a cluster of symptoms cannot be identified as a single diagnosis, each individual event should be reported separately. If a diagnosis is subsequently known, it should be reported as follow-up information.

6.10. Reporting of Serious Adverse Events

The time frame within which an adverse event must be reported by clinical center staff depends on whether or not it is drug related, expected or unexpected, and degree of severity. The following table summarizes the Requirements for Reporting Serious Adverse Events.

SUMMARY OF SERIOUS ADVERSE EVENT REPORTING REQUIREMENTS

Drug Related*	Unexpected†	Alarming††		Coordinating Center	IRB
		±	Serious Not Drug-Related Expected ± Alarming	Within 48 hours	Within 5 working days
✓		±	Serious Drug-Related Expected ± Alarming	Within 24 hours	Within 5 working days
✓	✓		Serious Drug-Related Unexpected Not Alarming	Within 24 hours	Within 5 working days
✓	✓	✓	Serious Drug-Related Unexpected Alarming	Immediately	Within 24 hours

***Drug Related** - There is reasonable possibility the experience may have been caused by the drug/device

†**Unanticipated/Unexpected** - An event not noted as expected in the protocol

††**Alarming** - (Grade 3 or above))

NOTE: Each participating clinical site is required to conform to the reporting rules of their local IRB.

6.10.1. Reporting Serious Adverse Events to the Coordinating Center

When CATT Clinical Center staff becomes aware of a serious adverse event, the investigator or clinic coordinator notifies the Coordinating Center via secure fax transmission of the SAE Reporting Form within the time period listed in the table above. Copies of all such correspondence must be maintained in the patient's study folder at the site.

In turn, the Coordinating Center sends an electronic copy of the Serious Adverse Event Report Form and other supporting documentation to the CATT Medical Monitor, CATT Study Chairman and NEI Project Officer within 24 hours of notification by the Clinical Center.

6.10.2. IND Safety Reports

The CATT Study Chairman holds the IND for the use of Avastin® in this trial. He, or at his direction, the Principal Investigator of the Coordinating Center is responsible for notifying the FDA and all participating CATT Investigators of any adverse events that are associated with the study drugs that are both serious and unexpected. Follow-up information to a safety report will be submitted as soon as the relevant information is available.

6.10.3. Written IND Safety Reports

The CATT Study Chairman or, at his direction, the Principal Investigator of the Coordinating Center notifies the FDA and all participating CATT investigators in a written IND safety report of any event associated with the use of the study drugs that is both serious and unexpected and any finding from laboratory animal testing suggesting a significant risk for humans. Notification occurs as soon as possible, but no later than 15 calendar days after notification of the event. In each written IND safety report, the Chairman will identify all safety reports previously filed with the IND concerning a similar adverse experience and will analyze the significance of the SAE in light of the previous similar reports.

6.10.3.1. Telephone/Faxed Transmission of IND Safety Reports

The Study Chairman or at his direction, the Principal Investigator of the Coordinating Center, will notify the FDA by telephone or fax of any unexpected fatal or life-threatening event that is associated with the use of the study drugs. Notification will occur as soon as possible, but no later than 7 calendar days after notification of the event.

6.10.4. IRB Notification of SAEs Occurring at Their Center

The Clinical Center must inform their local IRB of all serious adverse events occurring at the center, in accordance with the IRB's reporting requirements. The Clinic Coordinator indicates on the Serious Adverse Event Report Form the status of this notification or that the SAE does not meet the requirements for IRB notification. Until she/he indicates that the IRB has been notified, or that no notification is required, the Protocol Monitor will contact the Clinic Coordinator on daily basis until she/he submits documentation to indicate that IRB notification has been made. During site visits to the clinical centers, the Protocol Monitor will ensure that documentation exists to confirm that the local IRB was notified of all reportable SAEs that occurred at the site.

6.10.5. IRB Notification of SAEs Occurring at Other Centers

Upon receipt of an IND Safety Report, each Clinical Center is responsible for copying the IND report and submitting the copy to their local IRB within 10 working days (or shorter if the local IRB requires a shorter reporting period). The original report and dated documentation of IRB submission (via cover letter) must be maintained at the clinical center. During site visits to the clinical centers, the Protocol Monitor will ensure that documentation exists to confirm that the local IRB was notified of all reportable SAEs.

6.10.6. DSMC Notification of Serious Adverse Events by the Coordinating Center

The Director of the Coordinating Center informs the full DSMC in writing of all serious adverse event reports at semi-annual committee meetings. The Medical Monitor may, at her discretion, instruct the Coordinating Center to notify the full DSMC immediately of a serious adverse event, and may request a meeting or teleconference of the committee prior to its next scheduled meeting.

The following information will be provided to the DSMC by the Coordinating Center:

- Clinical Center
- Patient ID Number
- Description of event (MedRA code)
- Date of onset
- Current status
- Severity of the event
- Whether study treatment was discontinued
- Medical Monitor's assessment of association between SAE and study drugs
- Reason the event is classified as serious

6.11. Annual Reports

Every year, within 60 days of the anniversary date of the IND, the Study Chairman, or at his direction, the Principal Investigator of the Coordinating Center, will submit to the FDA a report that includes a status report for the study as well as annual summary that includes:

- Tables of the most frequent and serious SAEs by body system
- Summary of all IND Safety Reports
- A list of deceased patients and causes of death
- Drops-out due to adverse events
- (If relevant) a description of new understanding of the study drugs' actions

6.12. Reporting and Analysis of Serious Adverse Events

Biostatisticians at the Coordinating Center will, on an annual basis, report to the DSMC, the NEI and the FDA their analysis of all cumulative serious adverse events. The analysis will include:

- Number of events
- Frequency of each type of event
- Severity of events
- Attribution of event
- Number of patients who had study drug stopped
- Whether Study drug could be reinstituted

- Number of patients requiring medication after stopping Study drug at one and two years
- Number of deaths

6.13. Managing Adverse Events

When a patient enrolled in the study experiences an adverse event, the Investigator at the Clinical Site will manage the patient with the best medical treatment protocol for the condition or, if appropriate, will refer the patient to a specialist or to the patient's personal physician.

6.14. Stopping Due to Safety Concerns

At the first meeting of the Data and Safety Monitoring Committee, the topic of stopping the clinical trial was addressed. Specific complications of treatment are anticipated and specific boundaries, in terms of magnitude of incidence or statistical significance may be adopted. For unanticipated adverse events associated with treatment, the DSMC will consider the severity of the adverse event, the magnitude of the excess incidence, the biological plausibility of a causal relation with the intervention, and the statistical significance of the difference in incidence between treatment groups.

CHAPTER 7
REFRACTION AND VISUAL ACUITY TESTING PROTOCOLS

7. INTRODUCTION

The refraction and visual acuity testing protocol designed by the Diabetic Retinopathy Clinical Research Network (DRCRnet, 2005) will be used in the Study. The CATT Research Group is indebted to the DRCRnet for sharing their protocol.

ALL refractionists should be proficient in the following optical fundamentals:

- Spherical equivalency
- Plus/minus spheres and cylinders
- Hyperopia, myopia, and astigmatism
- "Push plus" refraction principles.

7.1. REFRACTION CHART

Use of the refraction chart on the Electronic Visual Acuity Tester (EVA) at a distance of 3 meters is preferred; however, ETDRS chart R (Exhibit 7-1) at 4 meters/1 meter may be used in the rare event that the EVA is not working.

- For the EVA, the refraction chart on the EVA is displayed by tapping on the [Refraction Chart] icon on the Main Menu of the Palm Handheld or tapping the dropdown in upper right corner of screen and selecting 'Refraction Chart'; select [Refraction Chart] icon
- If the EVA is not functioning and the ETDRS chart R is used for refraction, the refraction protocol described beginning in section 7.4 "Steps in Refraction" should be performed, starting at 4 meters. If the subject is unable to read at least 3 letters on both the 20/200 and 20/160 lines, the subject should be moved to 1 meter, a +0.75 diopter (D) sphere added to the spherical power in the trial frame, and the refraction performed using the appropriate lenses according to the vision level. The refraction obtained at 1 meter must be reported as a 4-meter equivalent by subtracting +0.75 (D) from the spherical power.
- Under no circumstances should the ETDRS charts be used interchangeably with the EVA during the same refraction session.

Check the room lighting level before the refraction. For the EVA, dim incandescent lighting is required; fluorescent lighting should not be used. There should be no glare on the EVA screen and no spotlights. After warming up the EVA for at least 10 minutes, it should be calibrated for size and brightness (see section 7.5.2 for details) For the ETDRS charts, ambient room lighting is approximately 50 foot-candles, with uniform lighting maintained between the subject and the ETDRS charts.

7.2. TRIAL FRAMES/PHOROPTER

Trial frames are preferred for use in refraction. If trial frames/lenses are not used, a phoropter may be used. If a phoropter is used, the final refraction MUST be put in trial frames and the final

spherical refinement performed at 3 meters with the EVA, if the EVA is used, or at 4 meters with the ETDRS chart, if the EVA is not functioning.

If a phoropter is used for a subject whose acuity is worse than 20/80, the +/-0.25 D or +/-0.50 D strength of the phoropter's mounted cross cylinder may not allow the subject to notice any change when checking for cylindrical axis and power. In this case, a separate +/-1.00 D handheld cross cylinder (as in Exhibit 7-2 Protocol Summary at the end of this chapter) held in front of the phoropter instead of the mounted cross cylinder is recommended.

The protocol for the subjective refraction is described in terms of a trial frame, but a similar method can be followed with a phoropter.

The trial frame is placed and adjusted on the subject's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. The left eye is occluded and the starting refraction is placed in the right lens cells, with the cylindrical correction anterior. The steps for the procedure are detailed below.

7.3. CONTACT LENS USE

If the subject wears contact lenses and has spectacle glasses as well, he/she should be instructed to refrain from wearing the contact lenses on the day of each examination. In the event that the subject either has no glasses or has forgotten the instructions and has reported for the examination wearing contact lenses, these should be removed and at least one-half hour should elapse before the refraction is performed. In this latter event, careful attention should be given to the cornea during the slit-lamp examination: any abnormalities should be noted in the subject's clinic record.

7.4. STEPS IN REFRACTION

The following steps must be used during refraction and are explained in more detail below

1. Determine initial starting refraction
2. Refine sphere for the right eye
3. Refine cylinder axis for the right eye
4. Refine cylinder power for the right eye
5. Recheck sphere for the right eye
6. Repeat the process for the left eye

7.4.1. Determine Initial Starting Refraction

If subject has had a study refraction at a prior visit, use the refraction results from the most recent visit.

If this is the first study refraction for the subject, use one of the following for the starting refraction:

- Retinoscopy
- Autorefractor

- Current spectacles
- Previous refraction (available in subject chart)

In the exceptional case that none of the above is available, then start the refraction with 'plano'.

The refraction steps below are for visual acuities of 20/20 to 20/80 with the initial starting refraction. For acuities worse than 20/80, refer to the charts for appropriate sphere and cylinder powers to use. Whenever the acuity improves to a better range by improved correction (e.g. from 20/80 – 20/160 range to 20/20 – 20/80 range) smaller sphere and cylinder powers for the better acuity range according to the charts should be used.

7.4.2. Refine Sphere

7.4.2.1 Increase Plus

	Sphere for Checking	Sphere Incremental Change
20/20-20/80	+0.50	+0.50
<20/80 – 20/160	+1.00	+1.00
20/200 – 20/320	+2.00	+1.00
<20/320	+2.00	+1.00

The right eye is tested first and then the left eye. The starting refraction is placed in the trial frame; the left eye is occluded with an occluder lens and tissue or eye patch and the refractionist determines the lowest line that the subject can read.

With the subject focused on the smallest letters that he/she can read, a +0.50 D sphere is held in front of the trial frame over the right eye and the subject is asked if the lens makes the vision clearer, blurrier, or keeps the vision exactly the same.

- NOTE: "Clearer, Blurrier, or No Change" preferred, but "Better, Worse, or No Change" can be used. If vision is clearer or there is no change, the sphere in the trial frame is replaced with a sphere that is 0.50 D more plus or less minus.
- The +0.50 D sphere is again held in front of the trial frame over the right eye and the subject is asked again if the lens makes the vision clearer, blurrier, or keeps the vision exactly the same.
    - If vision is again clearer or there is no change, the sphere in the trial frame is replaced with a sphere that is 0.50 D more plus or less minus.
- This process of increasing the plus sphere or decreasing the minus sphere in the right eye is repeated until the +0.50 D sphere makes the vision blurrier.
- When the +0.50 D sphere makes the vision blurrier, no additional change in the sphere is made at this time.

By this process the highest plus or least minus sphere for best vision is determined.

7.4.2.2. Increase Minus

	Sphere for Checking	Sphere Incremental Change
20/20-20/80	-0.50 (or -0.37)	-0.25
<20/80 – 20/160	-1.00	-0.50
20/200 – 20/320	-2.00	-1.00
<20/320	-2.00	-1.00

After determining the highest plus or least minus sphere, the subject is asked to read the smallest line possible (the reading should be at least as good as the initial reading).

The -0.50 (or –0.37) D sphere is held in front of the trial frame before the right eye and the subject is asked if the vision is improved so he/she can actually read more letters.

- If vision is not improved, the +0.50 D sphere is held in front of the trial frame before the right eye once again to see if the subject will accept more plus.

- If the subject reports that the –0.50 (or -0.37) D lens improves vision, the subject is requested to read the smallest line possible while the –0.50 (or –0.37) D lens is held in front of the trial frame.

    - If there is an actual improvement in acuity and the examiner is convinced that the subject is able to read at least one additional letter, then the sphere in the trial frame is replaced by a sphere that is 0.25 D less plus or more minus.

Minus spherical power is added in –0.25 D increments in this fashion as long as the subject continues to read at least one additional letter.

- If the subject is unable to read any more letters, the sphere is not changed, even if the subject reports that the vision with the extra minus is better (or sharper and darker or more distinct).

The final check in the initial sphere evaluation is the presentation of a +0.50 D sphere to determine if any more plus sphere will be accepted initially.

> **Example:** Assume that following the check with plus sphere, the sphere in the trial frame is -0.50. The subject is asked to read the lowest line possible with this correction and reads the 20/20 line perfectly and no letters on the 20/16 line. Then -0.50 (or -0.37) D is held in front of the trial frame and the subject is asked if the lens makes the vision clearer or blurrier. If the subject reports that the vision is clearer, he is again asked to read the chart. If more letters are read (e.g., $20/20^{+2}$), then the sphere in the trial frame is changed to -0.75.

The process is repeated with a -0.50 (or -0.37) D added over –0.75. If again the subject reports that vision is improved, but he/she cannot read any additional letters, the sphere should remain at –0.75 and a final sphere check with a +0.50 D lens done.

7.4.3. Refine Cylinder Axis

For purposes of this discussion, only plus cylinder techniques are presented. Minus cylinders may be used instead of plus cylinders to determine the axis and power of the cylinder. If minus cylinders are used, the procedure described must be revised to reflect this change in sign.

If the starting refraction contains a cylinder correction, changes in cylindrical axis are tested by holding a 0.50 D cross cylinder in front of the trial frame (or the appropriate cross cylinder based on level of acuity), first with the positive axis 45 degrees to one side of the cylinder axis, and then with the positive axis 45 degrees to the opposite side of the cylinder axis (in most cases, the handle of the Jackson Cross Cylinder lens should be aligned directly over the axis of the cylinder lens in the trial frame.

Instruct the subject to focus on an "O" or "C" one-two lines above the smallest line of letters that he can read.

Explain to the subject: *I am going to show you two views of this "C" and neither view may be clearer than the view you have right now. I would like to know which of the two views is the clearer of the two, or are both views pretty much about the same or equally blurry.* Ask: *Is the "C" clearer on view 1 [flip the lens] or view 2, or are both views about the same or equally blurred?*

- Since neither position may produce a clear image, the subject is encouraged to select the position of least blur.

If the subject cannot choose between the two positions of the cross cylinder at the beginning of this test, the axis of the cylinder is moved 5-15 degrees, first in one direction and then in the other, with the cross cylinder being checked in each position to confirm that the original axis was indeed correct.

- If the subject does prefer one position of the cross cylinder to the other, the axis of the cylinder is moved 5-15 degrees toward the positive axis of the cross cylinder when in the position the subject said was better.

When the power of the cylinder is low and/or the subject's discrimination is poor, larger shifts will produce more clear-cut responses.

The cross cylinder is tried again with the positive axis 45 degrees to one side of the new cylinder axis and then with the positive axis 45 degrees to the opposite side of the new cylinder axis; the subject is asked which position he/she prefers.

- If the subject prefers one position to the other, the axis of the plus cylinder is moved toward the positive axis of the cross cylinder.

Testing for change of axis is repeated until the subject cannot decide that one position of the cross cylinder is clearer than the other by reporting that both views are about the same or equally blurry.

7.4.4. Refine Cylinder Power

Change in cylinder power is now tested by adding the 0.25 D cross cylinder (or appropriate cross cylinder based on level of acuity), first with the positive axis and then with the negative axis coincident with the cylinder axis.

Again, instruct the subject to focus on an "O" or "C" one-two lines above the smallest line of letters that he/she can read or on the smallest line of letters he can read. Explain to the subject: *Once again I am going to show you two views of this "C" and neither view may be clearer than the view you have right now. I would like to know which of the two views is the clearer of the two, or are both views pretty much about the same or equally blurry.* Ask: *Is the "C" clearer on view 1 [flip the lens] or view 2, or are both views about the same or equally blurred?*

- If the subject prefers the positive axis coincident with cylinder axis, the power of the correcting plus cylinder is increased by an additional plus 0.25 D.

- If the subject prefers the negative axis coincident with the cylinder, the power of the cylinder is reduced by 0.25 D.

The process is repeated until the subject cannot choose one of the cross cylinder positions as better than the other (i.e., until both positions are about the same or equally blurred).

Whenever the cylinder is changed by 0.50 D, 0.25 D of sphere of opposite sign is added as well (the changing of the sphere occurs during the procedure as soon as the cylinder has been changed by 0.50 D rather than making the adjustment following the completion of the refinement).

7.4.4.1 Checking Cylinder When Beginning Refraction is a Sphere

If the beginning refraction is a sphere and does not contain a cylinder, the presence of astigmatism can be tested by one of two methods:

1) Instruct the subject to focus on a letter "C" or "O" one-two lines above the smallest line of letters that he can read. Arbitrarily place a plus cylinder (for plus cylinder refraction) appropriate for the current acuity at 90 degrees, 180 degrees, 45 degrees, and 135 degrees in the trial frame and ask the subject if the lens makes the "C" or "O" clearer. If the subject reports that the cylinder makes the "C" or "O" clearer in any of these locations, continue the refraction by modifying the cylinder axis and power as described above.

2) Arbitrarily insert a +0.25 cylinder (or power appropriate for the current acuity) into the trial frame at 90 degrees, 180 degrees, 45 degrees, and 135 degrees. Using a Jackson Cross Cylinder appropriate for the current acuity, check the cylinder power at 90 degrees, 180 degrees, 45 degrees, and 135 degrees. If the subject accepts the cylinder in any of these locations, insert a cylinder of that strength at the accepted axis in the trial frame and continue the refraction by modifying the cylinder axis and power as described above.

7.4.5. Refraction Recheck/Final Sphere Refinement

The power of the sphere is rechecked according to the sphere refinement protocol above by using +0.37 D and -0.37 D spheres and changing the spherical power by 0.25 D increments of the appropriate sign until the subject reports that the +0.37 lens blurs the vision and the -0.37 does not improve vision.. If the sphere is changed at this point by 0.50 D or more, the cylinder axis and power should be rechecked. This process is repeated until no further significant lens changes are made. In refractions using the phoropter and the EVA, a final check of the sphere as described above **must** be repeated using the EVA (at a distance of 3 meters) and trial frames.

The entire process is then repeated for the left eye .

7.4.6. Refraction for Subjects with Poor Visual Acuity

For subjects with acuity worse than 20/100, the strong preference is to use the EVA at 3 meters since letters can be projected as large as 20/800. The EVA chart is a three-meter chart and should not be moved closer to the subject.

When the ETDRS chart R is used, if the subject is unable to read at least 3 letters on both the 20/200 and 20/160 lines, the subject should be moved to 1 meter, a +0.75 diopter (D) sphere added to the spherical power in the trial frame, and the refraction performed using the appropriate lenses according to the vision level. The refraction obtained at 1 meter must be reported as a 4-meter equivalent by subtracting +0.75 (D) from the spherical power.

If the subjective refraction cannot be performed because the subject's visual acuity is too poor, then the subject's most recent distance subjective refraction obtained at a previous visit should be considered as the refraction.

> **Example 1:** ETDRS chart R is used for refraction which could not be performed at 4 meters in the study eye because the subject could not see any letters on the refraction chart at that distance. When the subject was moved up to 1 meter, the following was obtained: + 2.00 + 1.00 x 180 degrees
>
> In order to make this finding appropriate for visual acuity testing at 4 meters, a +0.75 D sphere must be subtracted from the above correction, resulting in + 1.25 + 1.00 x 180 degrees for the final refraction.
>
> **Example 2 :** ETDRS chart R is used for refraction which could not be performed at 4 meters in the right eye because the subject could not see any letters on the refraction chart at that distance. When the subject was moved up to 1 meter, the following was obtained: - 1.00 + 1.00 x 180 degrees. In order to make this finding appropriate for visual acuity testing at 4 meters, a +0.75 D sphere must be subtracted from the above correction, resulting in -1.75 +1.00 x180 degrees for the final refraction.

7.5. VISUAL ACUITY TESTING

It is essential to have standardized visual acuity measurements for each examination at each of the participating clinics to minimize the effects of acuity examiner and subject bias. Visual acuity testing is performed with the Electronic Visual Acuity Tester (EVA) using a protocol called the Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol. This protocol has been developed to provide a visual acuity score that is comparable to that using the manual testing protocol used in the Early Treatment of Diabetic Retinopathy Study (ETDRS). The ETDRS chart testing is used as a back-up in case the EVA is not functioning.

Visual acuity measurements for each eye are obtained by a CATT-certified visual acuity examiner before the subject's pupils have been dilated.

7.5.1. Electronic Visual Acuity Tester

7.5.1.1 EVA System Description

The EVA (Figure 1) utilizes a programmed Palm handheld device (or tablet PC) that communicates with a personal computer running a Linux (or Windows XP) operating system.

Stimuli are high-contrast, black-and-white letters with luminance of 85 to 105 candels/meter2 and contrast of 98%. The system can present single letters or lines of letters. Single letter testing is used in the Electronic ETDRS program whereas lines of letters can be used for refraction. Single letters are framed with crowding bars spaced a letter width around the letter. For lines of letters, five letters are displayed for sizes smaller than 20/160; a decreasing number of letters is displayed as letter size increases. With a high-resolution (1600x1200) 17-inch monitor, the system is capable of displaying letters from 20/800 (1.6 logMAR) to 20/12 (-0.2 logMAR) at a test distance of 3 meters. Letter size is a close, but not exact, approximation of the logMAR progression of the ETDRS charts (within about 2% of the letter size at each logMAR level).

The Palm™ handheld device (Figure 2), communicating with the EVA through a connected cable or wirelessly with Bluetooth, provides instructions for the technician, allows entry of identification data, displays the letter that is being shown on the monitor, records the responses, and sends instructions to the EVA with regard to the sequence of letter presentations. The size of each letter presentation is determined by a computer program based on the subject's responses.

Figure 1: Electronic Visual Acuity Tester (EVA)

Figure 2: Palm Handheld

7.5.2. System Calibration

Two system calibrations are performed at regular intervals: (1) size calibration to confirm letters are accurately displayed and (2) luminance calibration to confirm the monitor screen is sufficiently bright for testing.

7.5.1.1 Size Calibration

Size calibration must be performed at each study visit. For non-study use, size calibration is recommended at least quarterly.

Size Calibration Instructions:

1. Display the EVA calibration square (this is the initial screen when the system starts up). Length of each side of the black square should be **114 mm**

2. Repeat the following steps on the top and left side of square:

a) Place EVA ruler (or similar ruler with millimeter scale) against side of black square. Check whether length of the side is **114 mm**.

IMPORTANT: When viewing, use only one eye and move your head as necessary such that your eye is directly on line with side.

b) If needed, adjust side to 114 mm by changing horizontal and/or vertical setting on the monitor. Refer to the EVA Users Manual for instructions specific to your monitor.

7.5.2.1 Luminance Calibration

Luminance calibration must be performed at each study visit.

Luminance Calibration Instructions:

1. Allow monitor to warm up for at least 10 minutes.
2. Display the EVA calibration square (this is the initial screen when the system starts up).
3. For luminance calibration instructions specific to your EVA Model, monitor, and light meter, refer to the EVA Users Manual .

7.5.3. Adjusting the Monitor Settings

If the EVA monitor needs size or luminance adjustment, refer to your EVA Users Manual for instructions specific to your EVA model, monitor, and light meter.

7.5.4. E-ETDRS Testing Protocol

The EVA runs a visual acuity testing program called E-ETDRS (which stands for Electronic Early Treatment of Diabetic Retinopathy). The program has been developed to provide a visual acuity letter score that is comparable to the ETDRS chart testing score.

As part of the development of the E-ETDRS protocol, a study was conducted in which high validity and test-retest reliability were demonstrated (Moke et al., 2001).

7.5.4.1 Overview of E-ETDRS Visual Acuity Testing Protocol

In brief, the E-ETDRS Visual Acuity Testing Protocol consists of an initial screening phase to obtain an approximation of the visual acuity threshold and then a testing phase to obtain the visual acuity score.

The protocol is summarized below (Figure 3). The complete algorithm is depicted in Figure 4 that follows.

Figure 3
Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol Overview

The E-ETDRS testing protocol:

- Screening phase: With single letter presentations, determines smallest logMAR level at which a letter is correctly identified.
- Testing phase: Starts testing letters by intermixing letter sizes of screening phase score and one level smaller.
- Test progress: If a letter is missed at a level, one level larger is added to the testing mix; if a letter is correct at a level, one level smaller is added to the testing mix.
- Acuity determination: Tests 5 letters at each level until smallest level with 5/5 correct and the smallest level with 0/5 correct are determined.

IN THE FOLLOWING EXAMPLE, C = CORRECT AND M = MISSED

Example:

Screening: 20/400c, 20/200c, 20/100c, 20/50c, 20/25m, 20/40m Score = 20/50

Test progress

1. Start by intermixing 20/50 and 20/40 letters: 20/50c, 20/40m, 20/50c, 20/40m, 20/50m
2. Because a 20/50 letter was missed, add 20/63 to the letter mix (so now will have letters of 20/40, 20/50, and 20/63 intermixed): 20/63c, 20/50c, 20/40c
3. Because 20/40 was correct, add 20/32 to the letter mix (mix is now 20/32, 20/40, 20/50, and 20/63): 20/32m, 20/63c, 20/63c, 20/50m
4. Five letters at 20/50 have been tested, so it drops out of the mix (mix is now 20/32, 20/40, and 20/63): 20/63c, 20/40c, 20/32m, 20/40m
5. Five letters at 20/40 have been tested, so it drops out of the mix (mix is now 20/32 and 20/63): 20/32m, 20/32m, 20/63c
6. Five letters at 20/63 have been tested, so it drops out of the mix (mix is now 20/32 only): 20/32m
7. Five letters at 20/32 have been tested; there are no letters left in the mix so test is over

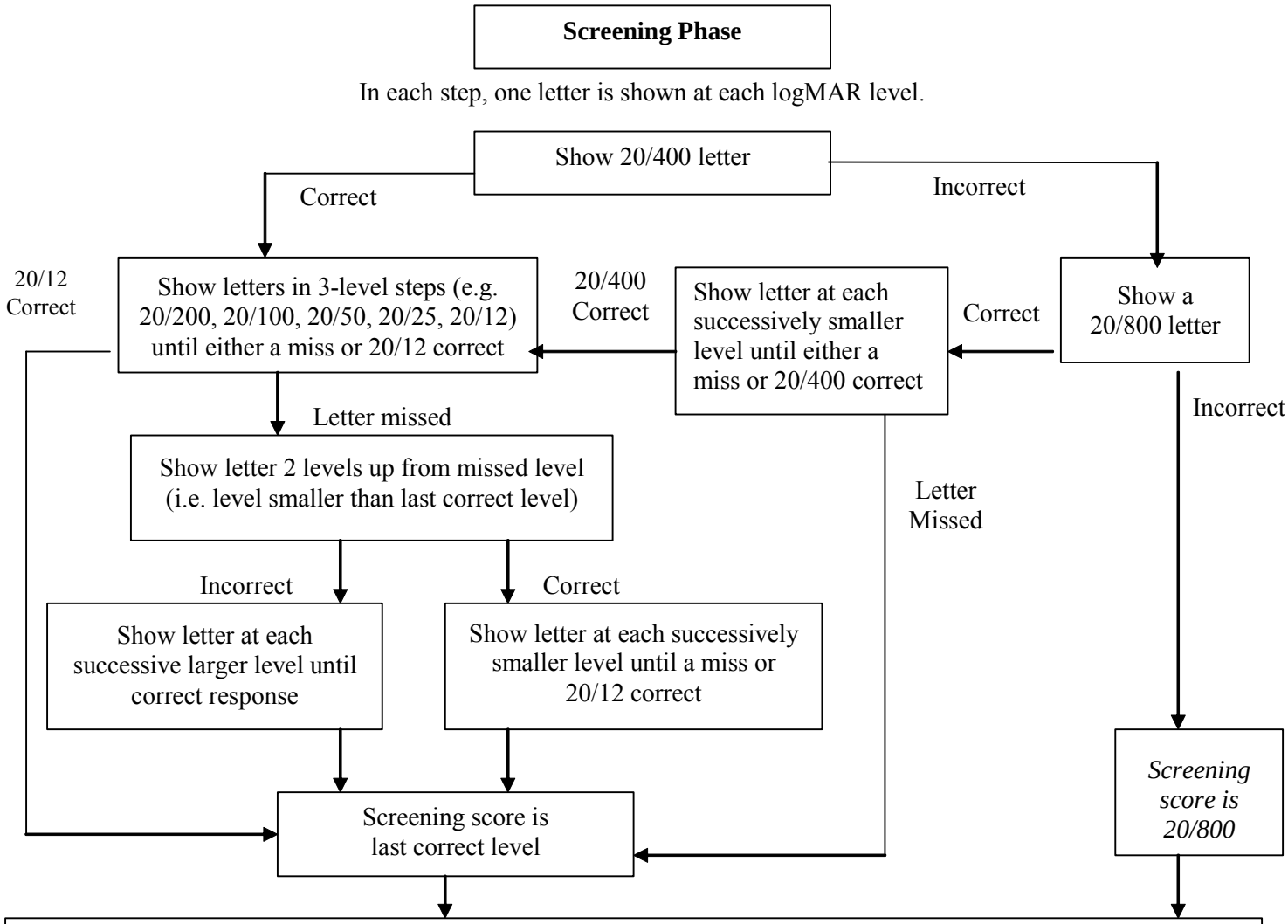
Test summary

20/63 5/5 correct
20/50 3/5 correct
20/40 2/5 correct
20/32 0/5 correct

Letter Score: 10 (number of letters correctly identified)
+ 55 (5 times the number of lines above (larger than) 20/63 and through 20/800)
= 65

Snellen Notation (smallest line with at least 3 of 5 letters correct): 20/50

Figure 4
Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol Algorithm



Threshold Phase

1. To start, letter pool consists of letters from 2 levels*: level of screening phase score and one level smaller.
2. Each letter presentation is randomly selected from active pool of letters with the stipulation that every third letter must be from the largest level in active letter pool.
3. A level remains in active pool until 5 letters are tested at the level.
4. A new level is added to active letter pool when:
   a. A letter from largest level in the pool is missed: one level larger is added to letter pool†
   b. A letter from smallest level in the pool is correct: one level smaller is added to letter pool‡
5. Testing continues until an upper logMAR level with 5 of 5 letters correct and a lower logMAR level with 0 of 5 letters correct are determined and 5 letters are tested on all levels in between upper and lower logMAR levels.§
6. Visual acuity score is the number of letters correctly identified during threshold testing, plus 5 letters for each logMAR line above the upper logMAR level through 20/800.

The screening phase uses the letters V, R, K and D. The threshold phase uses the same 5 letters from the Sloan letter set that appear on the original ETDRS charts for right and left eyes.
*Unless screening score was 20/12, in which case letter pool consists of only 20/12 level letters.
†Unless 20/800 letter is missed.
‡Unless 20/12 is correct.
§If 20/12 becomes part of the active letter pool, it will be the lower logMAR level.

Before each subject study visit:

- Calibrate monitor for letter size
- Check monitor luminance
- Check room lighting level (dim incandescent lighting is recommended; fluorescent lighting should not be used; no glare on screen; no spotlights)

Before Every Test

- Verify testing distance from EVA to center of exam chair is 3 meters (118 inches)
- Turn on Palm and remove stylus

CATT Subject Testing (must be used for study subjects)

- Turn on Palm and remove stylus
- On main menu, tap E-ETDRS icon, then choose CATT from studies list
  OR
  Tap dropdown in upper right corner of screen, tap EVA Applications; select E-ETDRS icon; then choose CATT from studies list
- Follow instructions on Palm

Shut Down System

- Turn off the PC tester by selecting [Shutdown] icon on main menu
  OR
  Briefly press and release the power button on the EVA tower.

7.5.5. Visual Acuity Testing Procedures

7.4.5.1 Trial frames are to be used for refractive correction. In addition to the occluder in the trial frame, for testing the right eye, left eye is occluded with an eye patch or pad placed beneath the trial frames and vice versa.

- If refraction is required at a visit, then the correction determined by the protocol refraction will be used for the visual acuity testing. If refraction is not required at a visit, then the correction determined in the most recent refraction will be used.
- If during a visit when refraction is not required the subject appears to have experienced a loss of vision that cannot be explained by clinical findings on OCT and/or fluorescein angiography and the subject has already had their eye dilated, the subject may be asked to return to the clinic within a week for refraction and visual acuity testing before a decision on treatment is made.

7.5.5.2 Testing both eyes at Study Visits

Both eyes are tested at CATT study visits. The right eye is always tested first, then the left eye.

7.6. SAFEGUARDS TO AVOID BIAS

Masking of the visual acuity examiner is an important feature in avoiding bias in measuring what is the CATT primary outcome. In addition to masking, the automated nature of the computerized EVA testing minimizes the potential for induction of bias on the part of the examiner.

Technician instructions to the subject are to be minimal.

a. The subject should be told that there are only letters and no numbers and that each letter is "bracketed" by lines on all four sides.

b. For subjects with poor central vision, it may be suggested that the subject fixate eccentrically or turn or move his/her head in any manner if this improves visual acuity. If the subject employs these maneuvers, care must be taken to ensure that the fellow eye remains covered.

c. When the subject cannot read a letter, he/she is told to guess. If the subject states that a letter is one of two letters, then he/she is asked to choose only one letter and, if necessary, to guess.

d. When the subject gives one response but then gives a second response before the first response has been finalized (i.e., before the technician has verified the response as correct or incorrect and before the letter presentation on the EVA screen changes), the subject should be asked if that is his/her final answer; if the subject equivocates, ask the subject to choose one letter. Once the technician has verified the response and the letter presentation has changed on the EVA, no changes can be made in the subject's response.

e. If the subject provides a number or any other response other than one of the 26 letters of the alphabet, the subject should be told again that there are only letters on the chart and to respond with a letter.

7.7. POOR VISION TESTING (TESTING LIGHT PERCEPTION)

If the subject cannot identify any letters on visual acuity testing of an eye (i.e., letter score = 0), the eye is tested for light perception with the indirect ophthalmoscope as the light source. The testing procedure can be performed according to the investigator's usual routine. The following procedure is suggested:

- Room lighting should remain at the level of normal visual acuity testing. The subject should close the opposite eye and occlude it by making a tight seal with the palm around the orbit and the bridge of the nose. The indirect ophthalmoscope light should be in focus at three feet, and the rheostat set at six volts. From a distance of three feet the beam should be directed in and out of the eye at least four times; the subject should be asked to respond when he/she sees the light. If the examiner is convinced that the subject perceives the light, vision should be recorded as light perception, otherwise as no light perception.

7.8. STANDARD ETDRS VISUAL ACUITY PROTOCOL

The Standard ETDRS Visual Acuity Protocol should only be used as a back-up in the event the Electronic Visual Acuity Tester (EVA) is not functioning.

7.8.1. Visual Acuity Chart: Modified Bailey-Lovie

The ETDRS visual acuity charts 1 and 2 will be employed for standardized measurement of visual acuity. Acuity testing of all subjects, regardless of visual acuity, begins at four meters. Two ETDRS Visual Acuity Charts are used for the measurement of visual acuity, each with a different letter sequence. The right eye will always be tested with Chart 1 and the left eye with Chart 2.

7.8.2. Illumination of Visual Acuity Charts and Room

Each clinic must have/use an ETDRS light box for the ETDRS visual acuity charts during any CATT protocol acuity testing when the EVA is not functioning. The light box should be hung at eye level on the wall or placed on a stand (that can be purchased from the Lighthouse for the Blind in New York). Room lighting should be at office levels and should be uniform between the subject and the light box. The distance from the center of the exam chair to the Visual Acuity Chart should be 4.0 meters.

7.8.3. Best-Corrected Visual Acuity Measurements

The right eye is tested first and then the left eye. The subject is seated such that the distance from the center of the exam chair to the ETDRS Visual Acuity Chart should be 4.0 meters. This testing distance is always used first even if the subject could not be refracted at four meters. In addition to the occluder in the trial frame, the left eye is occluded with an eye patch or pad placed beneath the trial frames. With the lens correction obtained by subjective refraction in the trial frame, the subject is asked to read ETDRS Visual Acuity Chart 1 from the top with the right eye. It is emphasized to the subject that each answer will be scored so that adequate time should be allowed for each letter in order to achieve the best identification. The subject is instructed that all of the figures to be read are letters and that there are no numbers.

The examiner records each letter identified correctly by the subject as he/she reads the chart by circling the corresponding letter on the CATT ETDRS Chart worksheet data collection form. Letters read incorrectly, or for which no guesses are made, are not marked on this form. Each letter read correctly is scored as one point. The score for each line (including zero if no letters were read correctly on that line) and the total score for the eye must be recorded on the form after the testing has been completed.

If the number of letters read correctly at four meters is less than twenty, the test should be repeated at one meter and both the four-meter and one-meter totals should be recorded on the CATT ETDRS Chart worksheet data collection form. Both eyes should be tested at four meters before the subject is moved up to the one-meter test distance. Prior to actual testing at one-meter, + 0.75 sphere should be added to the correction already in the trial frame to compensate for the new distance. The subject must sit for testing at the one-meter distance.

The same procedure for obtaining visual acuity for the right eye is used for the left eye, except that ETDRS Visual Acuity Chart 2 is used.

7.8.4. Poor Vision Testing

Follow the procedures described in section 7.7.

7.8.5. Calculating the Visual Acuity Score

After each measurement of visual acuity, the visual acuity score for the visit is calculated. The visual acuity score is defined as follows:

- If twenty or more letters are read correctly at the four-meter test distance, the visual acuity score is equal to the number of letters (N) read correctly at four meters +30. If one or more but less than twenty letters are read correctly at four-meter distance, the visual acuity score is equal to the number of letters read correctly at four meters plus the number of letters read correctly at one meter in the first six lines.

- If no letters are read correctly at either the four-meter distance or the one-meter distance, the visual acuity score is 0.

EXHIBIT 7-1

ETDRS CHART R

20/200	H V Z D S
20/160	N C V K D
20/125	C Z S H N
20/100	O N V S R
20/80	K D N R O
20/63	Z K C S V
20/50	D V O H C
20/40	O H V C K
20/32	H Z C K O
20/25	N C K H D
20/20	Z H C S R
20/16	S Z R D N
20/12.5	H C D R O
20/10	R D O S N

EXHIBIT 7-2

CATT REFRACTION PROTOCOL SUMMARY

FLOW CHART OF CATT REFRACTION PROTOCOL

1. SPHERE

a. Plus → → → Clearer → → → Increase plus.
(lowest line) No Change → → Increase plus.
Blurrier → → → STOP

b. Minus → → → Clearer → → → Increase minus if additional letter(s) read.
(lowest line) No Change → → STOP
Blurrier → → → STOP

c. Plus → → → Clearer → → → Increase plus.
(lowest line) No Change → → Increase plus.
Blurrier→ → → STOP

2. CYLINDER **a. Axis** → → → Clearer at → → Move axis toward preferred plus axis
(C or O above smallest line) 1 or 2 until position 1 and 2 are equal.

3. CYLINDER **a. Power** → → → Clearer at → → Increase or decrease plus power
(C or O on smallest line) 1 or 2 until neither position 1 or 2 is better.
If power changes by >=0.50 adjust sphere.

(Not present) → → → → → JCC at 90/180; Place 0.25D cylinder at preferred axis.
JCC at 45/135 Then, check cylinder axis and power as above.

4. REFINE SPHERE Refine with +/- spheres as in step #1 until no improvement in vision.

NOTE: "Clearer, Blurrier, No change" preferred; "Better, Worse, No change" may also be used

Vision with Best Correction	**Sphere**		**Cylinder**			**Sphere Refinement**	
	Power **(1)**	Increment **(1)**	Axis **(2)**	Power **(3)**	Increment **(3)**	Power **(4)**	Increment **(4)**
20/20 – 20/80	a. +.50	+.50	a..50 JCC	a..25 JCC	+.25 -.25	a.+.37	+.25
	b. -.50/-.37	-.25				b. -.37	-.25
	c. +.50	+.50				c.+.37	+.25
<20/80 – 20/160	a. +1.00	+1.00	a.1.00 JCC	a.1.00 JCC	+1.00 -1.00	a.+.50	+.50
	b. -1.00	-0.50				b. -.50	-.50
	c. +1.00	+1.00				c.+.50	+.50
20/200 – 20/320	a. +2.00	+1.00	a.1.00 JCC	a.1.00 JCC	+1.00 -1.00	a.+1.00	+1.00
	b. -2.00	-1.00				b.-1.00	-1.00
	c. +2.00	+1.00				c.+1.00	+1.00
<20/320	a. +2.00	+1.00	No cylinder test			No refinement	
	b. -2.00	-1.00					
	c. +2.00	+1.00					

CHAPTER 10

DATA ANALYSIS, STATISTICAL ISSUES, AND DATA MONITORING

10.1. STUDY DESIGN CHARACTERISTICS AFFECTING DATA ANALYSIS AND STATISTICAL ISSUES

The CATT: Lucentis-Avastin Trial is a prospective, randomized, non-inferiority clinical trial involving four treatment arms. The design of the trial is summarized in Chapter 2. Key aspects of the design and rationale that have major bearing on the approach to data analysis, statistical issues, and data monitoring are noted below:

- There are 4 treatment arms. Lucentis® on a fixed schedule of injections every month has the best demonstrated treatment efficacy at the beginning of the trial. Lucentis® on a variable schedule, Avastin® on a variable schedule and Avastin® on a fixed schedule are alternative approaches that would be preferred to Lucentis® on a fixed schedule if their treatment efficacy was as good as or better than ("non-inferior" to) the efficacy of fixed schedule Lucentis®. Given non-inferior efficacy, Lucentis® on a variable dosing schedule would be preferred to fixed schedule Lucentis®, and Avastin® on a variable dosing schedule would be preferred to fixed schedule Avastin®, because patients would have fewer injections, decreasing cost and decreasing risk of injection-related side effects. Avastin® on a variable dosing schedule or on fixed schedule would be preferred to Lucentis® on a variable schedule or on a fixed schedule if treatment efficacy were not inferior because Avastin® is much less expensive than Lucentis® on a per injection basis.
- At 12 months, the patients in the Lucentis® on fixed schedule arm will be randomized to continue with Lucentis® on fixed schedule or to Lucentis® on a variable dosing schedule for the next 12 months. Similarly, at 12 months, the patients in the Avastin® on fixed schedule arm will be randomized to continue with Avastin® on fixed schedule or to Avastin® a variable dosing schedule for the next 12 months.
- The primary outcome measure is mean change in visual acuity (VA) between the Initial Visit and the visit 12 months later (FV52).
- Secondary outcome measures at 1 year and 2 years are
  - Number of treatments
  - Percentage of eyes with a decrease in visual acuity of 3 lines or more (15 letters or more on the E-ETDRS chart)
  - Change in subretinal and intraretinal fluid on optical coherence tomography (OCT)
  - Change in lesion size on fluorescein angiography (FA)
  - Incidence of potential side effects of endophthalmitis, retinal detachment, cataract and uveitis
  - Incidence of systemic side effects
  - Cost

- The unit of randomization is eye. Only one eye of a person can be enrolled.
- Although the primary outcome is assessed at 12 months, longer term outcomes of treatment are of great interest because of the continued risk of loss of vision beyond 12 months.
- A subset of patients will have the grading of FAs and OCTs more frequently than other patients to allow analysis of the interplay of information from visual acuity, OCTs and FAs in predicting changes in visual acuity.

10.2. NON-INFERIORITY TRIAL DESIGN

10.2.1. Statistical modeling of the CATT: Lucentis-Avastin Trial design

The CATT: Lucentis-Avastin Trial is, in statistical terms, a non-inferiority trial among four active treatment arms; i.e., there is no placebo or untreated comparison arm. Non-inferiority trials are different conceptually from more familiar superiority trials and their design and analysis must be considered carefully (Garrett, 2003; Musch, 2006; European Medicines Agency, 2005; European Agency for the Evaluation of Medicinal Products, 2000). In the CATT: Lucentis-Avastin Trial, the Lucentis® on fixed schedule group is considered the reference group to which each of the two variable schedule arms and Avastin® on fixed schedule arm will be compared. The comparison of variable schedule Avastin® to variable schedule Lucentis®, variable schedule Avastin® to fixed schedule Avastin®, and fixed schedule Avastin® to variable schedule Lucentis® are also of interest. In terms of classic hypothesis testing, the six sets of hypotheses involved in the four-armed study are:

$$\begin{array}{lll} H_0: \mu_{LV} - \mu_{LF} \leq -\delta & \text{and} & H_A: \mu_{LV} - \mu_{LF} > -\delta \\ H_0: \mu_{AV} - \mu_{LF} \leq -\delta & \text{and} & H_A: \mu_{AV} - \mu_{LF} > -\delta \\ H_0: \mu_{AF} - \mu_{LF} \leq -\delta & \text{and} & H_A: \mu_{AF} - \mu_{LF} > -\delta \end{array}$$

$$\begin{array}{lll} H_0: \mu_{AV} - \mu_{LV} \leq -\delta & \text{and} & H_A: \mu_{AV} - \mu_{LV} > -\delta \\ H_0: \mu_{AV} - \mu_{AF} \leq -\delta & \text{and} & H_A: \mu_{AV} - \mu_{AF} > -\delta \\ H_0: \mu_{AF} - \mu_{LV} \leq -\delta & \text{and} & H_A: \mu_{AF} - \mu_{LV} > -\delta \end{array}$$

where μ_i = is the mean change in visual acuity between initial visit and FV52 in group i,

δ = the maximum clinically acceptable true difference for treatments to be considered non-inferior, the "non-inferiority margin", $\delta > 0$

LV denotes treatment with Lucentis® on variable schedule,

LF denotes treatment with Lucentis® on fixed schedule,

AV denotes treatment with Avastin® on variable schedule,

AF denotes treatment with Avastin® on fixed schedule,

and change in visual acuity is defined as the FV52 score minus the initial visit score (i.e., positive change means improvement).

In non-inferiority trials, if α is the significance level used for hypothesis testing, then observed treatment group differences that are associated with rejecting the null hypothesis are the same as those that fall below the lower limit of the (1-2α) confidence interval. (European Agency for the Evaluation of Medicinal Products, 2000). Thus, hypothesis testing at the 0.025 level corresponds to setting 95% confidence intervals. This choice allows easy and

valid switching of the interpretation of a non-inferiority trial to the interpretation of a superiority trial if the new treatment results in a better mean change than the referent treatment. Using confidence intervals is promoted as the best way to interpret trial results.

10.2.2. Special issues in non-inferiority trials

The FDA sets forth in section 1.5 of "Guidance for industry. E 10. Choice of control group and related issues in clinical trials" four major criteria for making valid conclusions from non-inferiority trials. (FDA, 2001). These criteria are listed below with comments on their application to the CATT: Lucentis-Avastin Trial.

1. *Historical evidence of sensitivity to drug effects*; i.e.; there is strong evidence that the reference treatment is efficacious.

   Results released by Genentech on the results of their Phase III clinical trials provide strong evidence of a large treatment effect for Lucentis® on fixed schedule. Specifically, in the MARINA trial of fixed schedule Lucentis® versus sham treatment, 95% versus 62% of eyes with occult and minimally classic choroidal neovascularization lost less than 3 lines of visual acuity (15 letters) at 12 months. (Genentech press release, July 18, 2005). In the ANCHOR trial of fixed schedule Lucentis® versus photodynamic therapy with verteporfin (PDT), 94% and 95% (2 doses of Lucentis®) versus 64% of eyes with predominantly classic choroidal neovascularization lost less than 3 lines of visual acuity. (Genentech Press Release Nov 7, 2005). Thus, fixed schedule Lucentis® has been shown superior to both sham treatment and to an approved active treatment (PDT).

2. *The design of the trial should be similar to the design of the trials used to establish that the drug is efficacious*. Design features such as study population, concomitant therapy, and outcome measures should be similar.

   The CATT: Lucentis-Avastin Trial and the ANCHOR and MARINA trials have similar eligibility criteria, use change from baseline ETDRS visual acuity after protocol refraction as the primary outcome measure, and similarly restrict use of concomitant therapy for choroidal neovascularization.

3. *The trial conduct should be similar to the trials used to establish that the drug is efficacious and is of high quality*.

   The CATT: Lucentis-Avastin Trial and the ANCHOR and MARINA trials share many of the same clinical centers. Fixed schedule Lucentis® in the CATT: Lucentis-Avastin Trial is administered with one of the 2 efficacious doses, at the same time intervals, without regard to OCT or angiographic findings. CATT has a full program of certification and quality assurance to ensure a high quality trial (adherence to study protocol, high follow-up rate, etc). In both the previous studies and the CATT: Lucentis-Avastin Trial, the primary analysis is an intention to treat analysis.

4. *An acceptable non-inferiority margin exists (non-zero) and takes into account historical data on efficacy and relevant clinical and statistical considerations.* The non-inferiority margin must be smaller than the believed smallest effect of the reference treatment.

Ophthalmologists are willing to accept a small, non-zero decrement in efficacy in return for fewer injections, substantially lower costs, and decreased risk of endophthalmitis and other injection-related adverse effects.

Factors leading to treatment group differences that are artificially small are of particular concern in non-inferiority trials, as reflected in criteria 2 and 3 above. Administering the reference drug in a manner different than that used to establish efficacy (thereby possibly decreasing efficacy), including patients with characteristics that disqualified participation in the earlier trials, and treatment group crossovers are some of the factors that can produce results that lead to the conclusion that two drugs are equally efficacious.

10.3. CHOICE OF PRIMARY OUTCOME

The primary outcome measure for each treatment group is the mean change in visual acuity between initial visit and 52 weeks. Visual acuity, as measured with the E-ETDRS or ETDRS testing protocol, may be considered an interval scaled (Log MAR scale), continuous variable taking on values ranging from -82 to +77 (based on the eligibility criteria for the CATT: Lucentis-Avastin Trial). The mean is a precise summary measure for assessing whether one treatment has shifted the distribution of visual acuity towards improvement more than an alternative treatment.

Until the advent of Lucentis®, the vast majority of eyes with newly diagnosed subfoveal choroidal neovascularization lost vision over the next 1 to 3 years; only a small percentage of patients had improved vision over time. The distributions of change in visual acuity were fairly well characterized by the percentages in specified tail areas (e.g., 15 letter loss or 30 letter loss corresponding to 3 and 6 line loss of a doubling or quadrupling, respectively of the minimum angle of resolution). In addition, such losses have a clinically significant impact on the patient's function. However, the results from the MARINA and ANCHOR trials show that with fixed schedule Lucentis®, visual acuity can improve substantially (several lines) and that there is little room to show improvements in treatment efficacy by decreasing the 5% of eyes suffering a 3-line loss (15 letters) with treatment.

Given the underlying continuous measurement scale, the high likelihood for both increases and decreases in visual acuity score, and the inability of the traditional 3-line loss dichotomy to accommodate measurement of further improvements in treatment efficacy, mean change is a strong choice for the primary outcome. The higher precision of a mean relative to a proportion is desirable in non-inferiority trials where the interpretation is driven by the width of the confidence interval. The only major drawback to the choice of using mean change is the absence of description of differences in clinically meaningful changes in the distribution. However, this shortcoming can be overcome by secondary outcome measures and through the use of descriptive statistics.

10.4. SAMPLE SIZE CONSIDERATIONS

10.4.1. Approach to Sample Size

A non-inferiority trial approach to sample size and power calculations is used for the main treatment group comparisons in the CATT: Lucentis-Avastin Trial. The sample size for

comparisons between groups created by the second randomization at 52 weeks for patients in the initial fixed arms of Lucentis® and Avastin® is based on a non-inferiority approach. The calculations for the substudy on fluorescein angiography and OCT are based on achieving high power for detecting dichotomized risk factors.

10.4.2. Assumptions for the Sample Size Calculations for the CATT: Lucentis-Avastin Trial – Primary Analysis

Several assumptions must be made in order to calculate sample size:

- Overall Type I (α) error rate of 0.025 (see 10.2.1 above)
- Bonferroni adjustment for 6 primary comparisons yields an adjusted α error rate of 0.025/6 or 0.0042.
- Statistical power of 90%.
- The standard deviation of the distribution of changes **(σ)** in visual acuity is 15 letters (3 lines). This assumption is based on the observed standard deviations in recent trials of treatments for choroidal neovascularization. At 1 year, the published standard deviation in the verteporfin group in the VIP study for occult or minimally classic lesions was 13.4 letters. (VIP Therapy Study Group, 2001). Other studies have not published standard deviations of the treated group; however, back calculations based on knowing the mean change, the percentages with 15 letters lost or gained, and the percentile distribution of the normal (Gaussian) distribution provides additional estimates. (Genentech press release, July 18, 2005) In Genentech's MARINA trial, the mean change in both the Lucentis® dose groups was 7 letters improvement and 5% lost 15 or more letters. In the 0.3mg dose group, 25% of patients had a gain of 15 letters or more, in the 0.5mg group, 34% had a gain of 15 or more letters. These three percentages from the same group of patients yield estimates of σ of 13.4, 11.9, and 19.4 letters, respectively. In Alcon's Phase III of anecortave acetate versus PDT for eyes with predominantly classic lesions, the difference between treatment groups in mean change at 12 months was 0.06 Log MAR, or 3 letters, with a p-value of 0.03. Back calculating from the p-value with a t-distribution, yields an estimate of σ = 16 letters from the pooled estimate of variance. Based on the 5 estimates (11.9, 13.4, 13.4, 16, and 19.4) an estimate of 14 or 15 is reasonable.
- The maximum clinically acceptable true difference for new treatments to be considered non-inferior, $\boldsymbol{\delta_L}$ or the "non-inferiority margin", is 5 letters (just 1 line on the visual acuity chart). Factors considered in choosing this important value include:
  - Ophthalmologists and patients are reluctant to sacrifice visual acuity to gain the benefit of large cost savings and decreased number of injections.
  - The observed difference in mean change in visual acuity at 52 weeks between fixed schedule Lucentis® and sham treatment was 17 letters (3.4 lines) in the MARINA study. A $\boldsymbol{\delta_L}$ of 5 letters would be approximately 29% of the estimated treatment effect from the MARINA study.

- Historically, treatments for neovascular AMD with a difference in mean change in visual acuity of 1.2 to 1.4 lines (6 to 7 letters) between active treatment and placebo/sham control have been accepted as sufficiently efficacious to be used in clinical practice and/or approved by the FDA. The non-inferiority margin should be smaller than the difference that separates an efficacious treatment from no treatment. Therefore, δ_L for the CATT: Lucentis-Avastin Trial should be less than 1.2 lines (6 letters).

		Mean Change (VA Lines)				**Percent with 3-line loss**
Trial/Treatment	**Time**	**Drug**	**Control**	**Difference**		**Difference**
MPS / Laser[1]	24 mo	-3.0	-4.4	1.4		20%
TAP/PDT[2]	12 mo	-2.2	-3.5	1.3		15%
TAP/PDT[2]	24 mo	-2.7	-3.9	1.2		15%
VIP/PDT[3]	24 mo	-3.8	-5.1	1.3		12%
Eye001/Macugen[4]	12 mo	-1.6	-3.0	1.4		15%

[1] Macular Photocoagulation Study Group, 1991
[2] TAP Study Group, 1999
[3] VIP Therapy Study Group, 2001
[4] Gragoudas, 2004

- The anticipated true difference between treatment groups **(δ_1)** is 0. That is, both treatment arms are expected to have the same efficacy.
- The statistical test used to compare the two treatment groups at 12 months is an independent t-test on the mean change in visual acuity from the initial visit.
- The percentage of patients completing visit FV52 is 95%. Patient death, illness, and re-location may result in incomplete data. This assumption is reasonable given the 94% completion rate in the TAP PDT trial (TAP Study Group, 1999) and the 98% completion rate in the Complications of AMD Prevention Study.

10.4.3. Sample Size and Power Calculations – CATT: Lucentis-Avastin Trial

The sample size is calculated by using the above assumptions and the sample size formula for comparing two means in a non-inferiority trial as implemented in the statistical software program PASS 2005 (Number Cruncher Statistical System, Kaysville, Utah). The total number of patients required for analysis in each treatment group is 277, or 1108 total for the entire study. If approximately 8% do not complete the examination at 52 weeks, 300 patients in each group (1200 total) will need to be recruited.

Additional calculations in the table below show that the sample size of 277 patients in each arm for analysis will provide high statistical power to reject non-inferiority under a number of reasonable alternative value of σ and alternative number of multiple comparisons.

Sample Size Needed for Analysis for Each of 4 Treatment Groups

			Power	
Number of comparisons	**α**	**σ**	**80%**	**90%**
2	0.0125	14	150	195
6	0.00417	14	191	242
2	0.0125	15	172	224
6	0.00417	15	219	277
2	0.0125	16	195	255
6	0.00417	16	249	316

10.4.4. Sample Size and Power Calculations – OCT and FA Substudy

All patients will have their FAs and OCTs from baseline, 52 weeks and 104 weeks graded and analyzed for the purposes of outcome assessments. A subset of patients in the CATT: Lucentis-Avastin Trial will be chosen from among the first patients enrolled to have grading and analysis of additional FAs and OCTs as part of the OCT and FA Substudy. These patients also will have the FAs taken at 12, 24 and 80 weeks and the OCTs taken at 4, 8, 12, 24,and 80 weeks graded and analyzed. To better understand the relation between OCT and FA before and during treatment with anti-VEGF agents, correlations will be examined among OCT characteristics and FA characteristics at each time angiograms are taken. In addition, FA and OCT characteristics before and after the initial treatment will be explored for their prognostic value for visual acuity at 52 and 104 weeks. Patients from all four patient arms will be pooled because the relations among OCT, FA, and visual acuity are not expected to vary between Lucentis® and Avastin®.

Only 300 patients will have the additional gradings of FAs and OCTs. Because the proposed analysis is exploratory in nature, the precise analysis on which to base sample size calculations cannot be specified. The power to detect prognostic factors from among the FA characteristics from these additional time points will depend on the proportion of patients with the candidate risk factor (e.g., proportion with FA leakage at 8 weeks), the risk of the defined indicator of poor visual acuity outcome (e.g., visual acuity at 52 weeks worse than at initial visit), and the strength of the risk factor (relative risk). The table below shows that for a wide range of scenarios, 300 patients provides high statistical power (80% or better highlighted) of identifying (α=0.05) a clinically important prognostic factor (relative risk above 1.5). During analysis, efforts will be made to define poor VA outcome measures that are present in approximately a third of the patients (such as the worst tertile). Power calculations were performed using the statistical software program PS (version 2.1.31; Dupont, 1990).

Proportion with risk factor	Risk of poor VA outcome in those without factor	Relative Risk		
		2.00	1.75	1.5
50%	50%	1.00	1.00	0.99
	30%	1.00	0.98	0.77
	15%	0.88	0.67	0.38
25%	50%	1.00	1.00	0.98
	30%	1.00	0.94	0.66
	15%	0.80	0.59	0.34
15%	50%	1.00	1.00	0.90
	30%	0.97	0.83	0.51
	15%	0.66	0.47	0.27

With four times the number of patients available for analyses involving OCT scans and/or the annual FAs, there will be high power for detecting much lower relative risks.

10.4.5. Precision of the Estimate of the Difference in Change in Visual Acuity in each of the Two Groups Initially Assigned to Fixed Schedule of Lucentis® and Avastin®

After randomization at 52 weeks to either continuation of fixed schedule or on variable schedule for both Lucentis® and Avastin®, there will be approximately 143 patients in each of these subgroups (95% completion rate at 52 weeks). At 104 weeks, if the standard deviation of change in visual acuity remains at 15, the 95% confidence interval will be approximately (mean difference) ± 1.96 √ (2/143) * σ, or (mean difference) ± 3.5 letters.

10.5. DATA ANALYSIS

10.5.1. Statistical Methods to be Applied

Data analysis will be conducted using standard statistical techniques for comparing two independent groups: chi-squared tests for equality of proportions, independent t-test for equality of means, Wilcoxon rank sum test, multiple logistic and linear regression, and proportional hazards modeling. The distribution of continuous variables will be assessed by measures of normality and graphical displays so that non-parametric methods or data transformations may be applied when appropriate.

10.5.2. .Assessment of Baseline Comparability of Treatment Groups

Tables will be generated and inspected to compare, by treatment group, the distribution of key baseline variables having descriptive and prognostic importance. These variables will include, but not be limited to, patient age, race, ethnicity, gender, cigarette smoking status, hypertension, use of anti-oxidant vitamins, visual acuity, lesion size, lesion composition, presence of retinal angiomatous proliferation (RAP) features, retinal thickness, and presence of cysts on OCT.

10.5.3. Data Analyses of the Primary Outcome Variable

The primary statistical analyses will be performed on an intent-to-treat basis. There is some controversy about whether the "per protocol" study population should be used for the primary analysis in non-inferiority trials; however, recent examination of the question does not yield any clear benefit in using the "per protocol" subset of patients (Garrett, 2003). Furthermore, use of a per protocol study population may creates problems if inferiority is rejected and a test for superiority is conducted because intention-to-treat study populations are generally preferred for superiority trials.

The primary outcome measure is the mean change in visual acuity (VA) at 52 weeks. The primary assessment of efficacy will be based on pairwise comparisons in mean change in VA between groups. If there are no imbalances on important prognostic factors at baseline, a simple independent t-test and corresponding confidence intervals will be used for evaluation of treatment differences. If there are imbalances in the key prognostic factors at baseline (baseline visual acuity score and lesion size) linear regression models will be used to estimate the difference in mean change in VA between treatment groups and the confidence intervals derived from the corresponding standard error of the estimate. These models will also include indicator variables for clinical center because the randomization is stratified by center. The Bonferroni adjustment will be used to accommodate the 6 main pairwise comparisons of interest (see section 10.2.1 above); therefore an α level of 0.0042 will be used for hypothesis testing and confidence intervals will be (1-2 α) or 99.16% confidence intervals. If the null hypothesis of inferiority is rejected, testing for superiority will be performed. That is, if the lower confidence limit for the difference in mean VA change lies within $(-5, \infty)$, the null hypothesis of inferiority will be rejected and the non-inferiority will be established. Furthermore, if the lower confidence limit lies within $(0, \infty)$, superiority will be established (European Agency for the Evaluation of Medicinal Products, 2000).

Analyses will be performed to assess the robustness of the results with respect to dropouts and non-compliance with the eligibility criteria and the treatment protocol. In addition to the above-described analysis of results from all patients who complete the 52-week examination (completed cases) with their treatment group assignment classified as assigned at randomization ("intent-to-treat"), an intent-to-treat analysis will be performed using "last observation carried forward (LOCF)" for the visual acuity value of patients who do not complete the 52-week examination. Also, a "per protocol" analysis, including only those patients who met all eligibility criteria at baseline and whose assigned treatment was carried out as specified in the protocol, will be performed.

Additional analyses to more fully characterize the relation of mean visual acuity over time will be performed using longitudinal data analysis methods (Liang, 1986). Visual acuity scores from all visits with protocol refraction preceding measurement of visual acuity will be incorporated. Both the relation of visual acuity with follow-up time and the influence of possibly prognostic factors will be evaluated using these models. Subgroup analyses will be performed to assess the consistency of the treatment effect across clinics and the levels of important baseline covariates. To date, no effect modifiers have been identified for the anti-VEGF agents Macugen® and Lucentis® (Gragoudas, 2004; Genentech Press releases of July 18 and November 7, 2005). However, the role of specific OCT characteristics has not been fully explored and the decision on not prespecifying particular subgrouping factors as candidates for effect modification will be

reconsidered prior to the first data analyses of visual acuity data for the Data and Safety Monitoring Committee.

10.5.4. Data Analyses of Secondary Outcome Variables

Specific secondary outcome variables for the CATT: Lucentis-Avastin Trial are number of treatments, 3-line change in VA (15 letters on ETDRS chart), change in subretinal and intraretinal fluid on OCT, change in lesion size on fluorescein angiography, cost of treatment, and incidence of endophthalmitis, retinal detachment, cataract and uveitis. These secondary outcome measures are assessed at Year 1 and Year 2.

10.5.4.1. Number of Treatments

The number of treatments after initial treatment is an especially important secondary outcome measure because if either or both of the "on a variable schedule arms" is not found inferior to fixed schedule, then the major criterion for choosing treatment will be the number of injections required. This variable has a limited range (0-12 in the first year and 0-25 through the second year) and is likely to be highly skewed. The median number of treatments will be the primary summary measure and comparisons between the two "on a variable schedule arms" of the trial will be with the Wilcoxon rank sum test. In addition, Poisson regression will be used to compare groups and consider the influence of other factors.

10.5.4.2. 3-line Change in Visual Acuity

As noted above in 10.3, 3-line decrease (15-letter decrease, doubling of the minimum angle of resolution) in visual acuity have been used historically as a primary outcome variable. The proportion with 3-line increase and with 3-line decrease in each treatment group will be compared to supplement the statistical analysis of mean change in visual acuity. Results at 52 weeks and 104 weeks will be of particular importance.

10.5.4.3. Change in Subretinal and Intraretinal Fluid

Changes from initial visit in subretinal and intraretinal fluid will be assessed using both discrete and continuous variables. Presence and absence of fluid at 52 weeks and 104 weeks will be evaluated among treatment groups using chi-square tests of proportions supplemented with logistic regression. Change in retinal thickness at 52 and 104 weeks will be evaluated among groups using analysis of variance (ANOVA) and linear regression techniques. As for the primary outcome variable, longitudinal models will be used to more fully characterize the relation of these OCT characteristics over time and to identify factors other that treatment group that influence intraretinal and subretinal fluid.

10.5.4.4. Change in Size of Lesion

Changes from initial visit in size of lesion will be assessed using as a continuous variable (area of lesion on fluorescein angiography at 52 weeks and 104 weeks. Analysis of variance (ANOVA) and linear regression techniques will be used to compare changes in lesion size among the treatment groups. Longitudinal models will be used to more fully characterize the relation of lesion size over time and to identify factors other that treatment group that influence intraretinal and subretinal fluid.

10.5.4.5. Cost

The cost of delivery of each of the treatment arms through 1 and 2 years will be determined by using the observed number of treatments and the Medicare reimbursable rates for the study drug, injections, office visits, and diagnostic tests (OCT and photography) needed to deliver the treatment. The cost of treatment will be compared between treatment arms.

10.5.4.6. Incidence of Adverse Events

Systemic adverse events and ocular adverse events such as endophthalmitis, retinal detachment, cataract, and uveitis are expected at a very low rate in all of the treatment groups. Comparisons across treatment groups of these rates will be made using survival analysis techniques – Kaplan-Meier curves with differences assessed with the logrank test.

10.5.5. Handling Missing Data

Major efforts will be made by the entire CATT group to avoid loss to follow-up and subsequent missing data. However, despite these efforts some data for the primary and secondary outcome measures may be missing. The percentage of data missing for major analyses will be tabulated. The characteristics at baseline, and during follow-up, of patients who ultimately are unavailable for follow-up will be assessed by comparing distributions between those under follow-up to those who are lost to follow-up. When available, the reasons for loss to follow-up will be reviewed. If missing data from living patients account for more than a small percentage of expected data (>5%), key analyses will be performed not only with the actual observed data on patients under follow-up, but also, using multiple imputation methods (Rubin, 1987; Heyting, 1992; Lavori, 1995). Both predictive model based methods and propensity score methods will be used to evaluate the impact of missing data on the key analyses of the CATT. Multiple imputation methods have better statistical properties than alternatives such as complete case analyses or single imputation.

10.5.6. Data Analyses for OCT and Fluorescein Angiography Substudy

Analysis of the data from the OCT and fluorescein angiogram (FA) gradings of participants in the OCT and Fluorescein Angiography Substudy will focus on the relationships among OCT characteristics and FA characteristics at different points in follow-up time and on the time relationships between resolutions and reappearances of fluid on OCT and fluorescein leakage and subsequent visual acuity. These analyses will first be developed combining all treatment groups and will be examined to see if the relationships vary by treatment group (interaction).

Correlation between FA characteristics (change in lesion size, dye leakage, retinal angiomatous proliferation) and OCT characteristics may change over time. For example, after the initial treatments, persistent subretinal fluid on OCT may be associated with lesion growth on FA, but by 12 months of follow-up there may be no association between subretinal fluid and further lesion growth. Analyses aimed at clarifying the relationship between presence of fluid on OCT and leakage on FA will be performed.

Exploration of the prognostic role of FA and OCT will be done in several ways. In the text that follows, the analyses are described for leakage on FA, but an identical approach will be take for fluid and retinal thickness on OCT.

- Longitudinal models of visual acuity over time with the presence of leakage as a time dependent covariate, with exploration of time-lagged variables;
- Exploration of patterns over follow-up time of leakage and VA at 12 and 24 months; e.g. do eyes that have resolution leakage by 2 months with no reappearance have better VA at 12 months than eyes without such resolution or eyes with intermittent periods of leakage?
- Repeat of analyses described above with VA at 24 months as the outcome measure;
- Addition of other covariates that may be indicators of treatment efficacy to the models developed above, especially OCT characteristics, to estimate the incremental information gained from knowledge of fluorescein leakage.

10.5.7. Identification of outliers, incorrectly collected data, and possibly fraudulent data

With each freeze of the database, a set of statistical and data analytic algorithms will be applied to detect data warranting further investigation and/or action. True values of data that are very different from the majority of values are known as outliers and may have undue influence on such statistical procedures as estimating the mean and variance and regression analyses. However, apparent outliers are often attributable to error: data recording error, data entry error, error in recoding in computer programs, error in the way in which the measurement is performed or the question asked. Another source of outliers is fraud.

As part of the preparation for any of the data analyses above, continuous variables, including dates, are subjected to the techniques of exploratory data analysis in order to fully understand the distribution of the variable. SAS, which is the main software package for data analysis, has built in procedures to flag and list values that meet certain criteria for outliers based on the median and interquartile range. The identification number of the patient can be attached to the extreme value. The Director reviews the exploratory analyses and determines whether an investigation of the accuracy of the value should begin. If the outlier values are valid, statistical methods that minimize the impact of outliers will be used.

Other data patterns will also be explored. Dates of clinical procedures will be examined by day of the week to identify the unlikely occurrence of procedures on weekends. Clusters of data values near cutoff values will be investigated. An inordinate percentage of 0 change values may indicate that the values from the last examination were merely copied. When such data patterns are identified, they will be brought to the attention of the Project Director for further investigation.

10.5.8. Software for Statistical Analysis

SAS/STAT software (SAS Institute, Inc., 100 SAS Campus Dr., Cary, NC, 27513-2414) is used for performing most statistical analyses. SAS Procedures are available for the vast majority of analysis methods described above, including the multiple imputation methods. Additional software packages are resident on the computer system for the Coordinating Center to handle specialized applications, such as Confidence Interval Analysis (CIA) for Windows (University of Southampton School of Medicine (www.medschool.soton.ac.uk/cia/)). When the application can be accommodated more easily by other software packages, Stata (StataCorp, 4905 Lakeway

Drive,College Station, Texas 77845) and S-Plus (1700 Westlake Avenue North, Suite 500, Seattle, WA 98109-3044) are available.

10.6. DATA MONITORING

The CATT Data and Safety Monitoring Committee (DSMC) will follow "NIH Policy For Data And Safety Monitoring" - release date: June 10, 1998) and the "National Eye Institute Guidelines for Data and Safety Monitoring of Clinical Trials" NOTICE: EY-01-002, release date March 2001. The NEI guidelines provide explicit guidelines on responsibilities of the Committee, membership, meeting format, recommendations, release of data, and conflict of interest which have been incorporated into CATT DSMC Charter and will not be repeated here in full. A few areas of particular importance to CATT will be noted below.

10.6.1. Initial Meeting

In addition to the review of protocol required by NEI guidelines, during the first meeting of the Data and Safety Monitoring Committee, the biostatisticians in the Coordinating Center will provide the members with background on the statistical and practical aspects of decisions on treatment efficacy or safety before the scheduled end of the clinical trial (Wittes, 1993). The overall statistical analysis plan and the plan for safety monitoring will be reviewed.

The biostatisticians will recommend that statistical monitoring of the CATT: Lucentis-Avastin Trial, a non-inferiority trial, for early stopping be managed through the approach of repeated confidence intervals (Durrleman, 1990; Jennison, 1984). This method applies the sequential monitoring Z values that would be applied to interim hypothesis testing to the construction of confidence intervals at each interim analysis. The approach of O'Brien and Fleming for calculation of the Z values will be suggested for adoption by the Data and Safety Monitoring Committee.

10.6.2. Safety Monitoring

The Medical Monitor, chosen by the study chair and NEI staff before subject enrollment begins, will bear special responsibility for review of adverse events. All serious adverse events reports will be transferred to the Medical Monitor upon receipt by the Coordinating Center as described in Chapter 6 on Adverse Events. The Medical Monitor will alert the study chair and the chair of the DSMC if there is a safety issue that warrants immediate discussion by teleconference.

The full DSMC will review all serious adverse events and tabulations of non-serious events during meetings held twice yearly. The chair of the DSMC must provide an annual report for submission to local Institutional Review Board (IRBs) that the Committee has reviewed the safety data with a recommendation for continuation or modification of the trial.

10.6.3. Stopping because of Safety

There will be no formal statistical guidelines for stopping because of safety considerations. The magnitude of the difference in safety outcomes, as well as their severity, will be considered in deciding whether the trial should be stopped. In addition, review of efficacy may be necessary in order to weigh the negative effects of the drug relative to the positive effects. In general, the

strength of evidence that the study drug is unsafe does not need to be as strong as the strength of evidence needed to stop a trial because of beneficial treatment effects on efficacy.

10.6.4. Other Considerations in Early Stopping

The statistical guidelines described above are only part of any decision to stop a trial early. Additional considerations include:

- Whether the results are consistent among various subgroups of patients and across the various clinical centers;
- Whether the results could be explained by imbalances in the baseline characteristics of the groups;
- Whether the results could be biased by patient or examiner expectations;
- Whether the results are consistent across the primary and secondary outcome measures;
- Whether it is likely that the current trends could be reversed if the trial were to be continued unmodified;
- Whether the medical community would question the validity or strength of the results of the trial because of early stopping.

CHAPTER 11

QUALITY ASSURANCE ACTIVITIES

11.1 OVERVIEW

The Coordinating Center has primary responsibility for assuring that the quality of the data collected and reported in the study are of consistently high quality. Many factors contribute to the quality of the data, from the design and procedures of the trial to the analytic methods employed. The Coordinating Center works with the Fundus Photograph Reading Center and OCT Reading Center on the design and implementation of a quality assurance program for grading photographs and OCTs. Similarly, Coordinating Center staff work with the Drug Distribution Service to implement a quality assurance program for tracking study drug inventory.

11.2 GENERAL QUALITY ASSURANCES

The major quality assurance features of the study are:

- Standard data collection forms and procedures;
- Common protocol for eligibility, examination, and follow-up of all patients in all clinical centers;
- Computerized treatment allocation with eligibility review preceding enrollment;
- **MASKED** assessment of the primary outcome measure and secondary outcome measures;
- Ophthalmologists **MASKED** to study drug when deciding on retreatment;
- Central masked grading of photographs and OCTs;
- Direct data entry into the study database at the Clinical Centers
- Central, computer driven data editing for missing, invalid, and suspect responses;
- Regular reporting on performance of all Clinical Centers;
- Monitoring visits to all centers;
- Specific data analyses to identify incorrect or fraudulent data collection processes;
- Certification of clinic staff and of imaging equipment;
- Regular meetings of the Investigative Group to review methods and discuss problems.

Staff at the Coordinating Center and Reading Centers participate in the design of all data collection forms, coordinate modifications to existing forms, and develop new forms as needed. Because the Coordinating Center supplies all centers with master copies of forms, it

ensures that the current versions of all forms and components are available to the clinical centers in the rare event that the on-line system is temporarily unavailable.

The members of the CATT Planning Committee played a major role in developing the Lucentis®-Avastin® Trial protocol and preparing the *Manual of Procedures*. Coordinating Center personnel and those from the Reading Centers update the chapters of the *Manual of Procedures* and are responsible for periodically distributing updates to all centers.

Biostatisticians and the Systems Analyst at the Coordinating Center prepare the treatment allocation schedules for each clinic. Treatment group allocations are issued only after verification of eligibility via the on-line database management system.

Coordinating Center staff members are responsible for ensuring that all data processing activities in the study proceed smoothly, as described in Chapter 16, and for timely editing, resolution of problems, and reporting. Concurrent data processing and editing are important for providing feedback to each individual involved in data collection and submission and to those involved in patient care to ensure that the procedures specified in the protocol are properly interpreted and applied.

Protocol Monitors of the Coordinating Center have primary responsibility for visiting the Clinical Centers to ensure protocol adherence and to assist in identifying and resolving problems. Other Coordinating Center staff also assist with these visits as necessary. Staff at the Coordinating Center provides information to the Director to facilitate the activities of overseeing clinical center operations.

Biostatisticians at the Coordinating Center develop a set of data analytic routines meant to identify patterns in the data that might indicate incorrect or fraudulent data collection processes. Further investigation of these findings will be conducted. Guidelines set by the NEI and the Office of Research Integrity will be followed.

The Director of the Coordinating Center is responsible for the certification program for the study (see Chapter 16). In addition to the initial training of Clinic Coordinators, the Director and Protocol Monitor also organize and chair sessions for the Clinic Coordinators at the annual meetings. Problems and issues related to following the protocol, handling of study medications and submission of data and images are reviewed and discussed to identify methods for resolving problems and improving or easing operations.

The yearly meeting of the Investigative Group is an important component of quality assurance. These meetings provide a mechanism of sharing information among CATT investigators and other personnel. The Coordinating Center staff, with input from the Chairman's Office and Operations Committee, plays a major role in organizing these meetings and preparing reports and presentations to be made to the Investigative Group.

11.3 CLINICAL CENTER MONITORING COMMITTEE

The Clinical Center Monitoring Committee has responsibility for the quality assurance activities required to maintain standardization of procedures and adherence to the CATT protocol. Membership and specific functions may be found in Section 12.11. Problems in Clinical Center performance or adherence to the protocol are normally resolved by the Director and Protocol Monitor working directly with the staff of the clinic. When these efforts fail, the problem is referred to the entire committee. If necessary, the Clinical Center Monitoring Committee reports failure to resolve the issue to the Operations Committee or the Executive Committee.

11.4 SITE VISITS TO CLINICAL CENTERS

Periodic site visits by an independent observer are necessary to ensure that there is standardization of procedures, that clinic personnel have been trained adequately, that the clinic facilities meet standards, and that patients and their data are being managed as specified in the protocol. The site visitor also provides assistance in solving logistical problems by conveying efficient, accurate solutions used in one clinical center to other clinical centers. All sites will be visited within a few months of the initiation of patient recruitment and will then be performed every other year on a staggered schedule. Clinical Centers may be visited more frequently if the Clinic Monitoring Committee deems it necessary due to problematic performance or clinic staff turnover.

11.4.1. Scheduling and Preparation

The site visit should be scheduled so that the clinic staff members may arrange their day appropriately, usually a month or more in advance. A copy of the site visit agenda is sent to the Principal Investigator of the clinic and to the Clinic Coordinator. The site visitors re-arrange the agenda to meet the scheduling constraints of the clinical center.

Site visitors prepare for the visit by reviewing previous site visit reports, notes from recent triannual telephone calls, clinic report cards issued by the Clinical Center Monitoring Committee and any comments or concerns from the Fundus Photograph and OCT Reading Centers regarding the Clinical Center. The data processing staff prepares data to be checked against clinic forms and original source materials.

The Clinic Coordinator prepares by making sure that patients and staff are available for the site visitor to observe the Refractionist, Visual Acuity Examiner, Photographer, OCT technician and Clinic Coordinator perform the entire set of study protocols. The site visitors may ask the Clinic Coordinator to assist in making arrangements for local lodging and transportation.

11.4.2. Conduct of the Visit

Site visits will begin early in the morning and will generally require 1-2 days. Strict adherence to the protocol is stressed throughout the visit. If clinical center staff view some part of the protocol as unreasonable or difficult to implement, the clinic personnel are instructed to follow the protocol. The site visitors bring the issue to the Operations Committee, Executive

Committee, Director of the Coordinating Center, Study Chairman or other person as warranted by the particular issue.

General areas of review during the site visit are listed below:

- Clinic staff, facilities and equipment
- Storage and access to study medications and drug accounting procedures
- Flow of patients through the clinic during study visits with special emphasis on procedures for OCT, photography and visual acuity testing
- Up-to-date study documentation including the *Manual of Procedures*, data collection form masters, protocol memoranda, study medication inventory and tracking documentation, documentation confirming reports of serious adverse events to the local IRB and other regulatory documents.
- Review of signed consent forms for 100% of patients during the enrollment period
- Review of a sample (approximately 5%) of data collection forms for comparison with data in the CATT database and source documents
- Observation of the Clinic Coordinator during at least one patient visit
- Observation of the Refractionist and Visual Acuity Examiner(s) performing the refraction or visual acuity testing, respectively, on a study patient.
- Storage and access to study patient files, including proper storage of signed consent forms and handling of edit messages
- Discussion of individual patients with follow-up problems
- Meeting with the Principal Investigator of the clinic to discuss recruitment, follow-up, and areas of concern

11.4.3. Site Visit Reports

A written summary prepared by the site visitor will be sent to the Clinic Coordinator, Principal Investigator and members of the Clinical Center Monitoring Committee. A copy of the report is also maintained in the Coordinating Center library of study documentation.

11.5 REGULARLY SCHEDULED TELEPHONE CALLS

A telephone call is scheduled once every 4 months (unless a site visit has recently occurred) between the Protocol Monitor and clinic coordinator to ensure that changes (if any) in study personnel, facilities, and equipment have been communicated and that progress is being made in any problem areas of performance. The status of certifications and re-certification requirements are reviewed. The Clinic Coordinators bring any problems, either within the clinical center, or with the Coordinating Center, to the attention of the Protocol Monitor or Director.

11.6 PREVENTING DROP-OUTS AND MISSED VISITS

Each Clinical Center must make visits as pleasant as possible by minimizing wait time, and providing comfortable waiting and examination facilities. The Coordinator and the PI for each Clinical Center will continually educate the patient as to the nature of the Study, the need for the patient's continued participation, and answer questions concerning AMD, CNV, medications used in the Study and if necessary, provide assistance with erroneous billing.

The Coordinator will contact patients to remind them of a follow up visit within the week of the appointment. The contact can be by telephone or email but a patient response is necessary. To ensure patient compliance for scheduled visits, early morning, evening or weekend hours may be provided. Every effort must be made by the Clinical Center to remain in contact with patients, even if they do not want to return to be examined or follow the protocol.

11.7 QUALITY ASSURANCE RELATED TO DRUG STORAGE AND ACCOUNTABILITY

Vials of Avastin® will be supplied to each center by the Drug Distribution Service. Lucentis® will be purchased by the clinical center in a manner consistent with non-study patients. Each Clinical Center will store both drugs in a refrigerator in their local pharmacy or in locked areas at the Clinical Center in a manner consistent with their standard clinical practice. All refrigerators will have a temperature alarm to alert staff if the temperature deviates beyond the boundaries of 2°-8°C (36°-46°F). At the time of treatment with either study drug, the clinic coordinator will record the identifying vial information onto the drug inventory logs. The Drug Distribution Center provides a "CATT Medication Ordering, Distribution, and Accountability Manual" to each clinical center. Outdated supplies will be recalled by the Drug Distribution Center and replacement supplies provided.

All drug storage facilities and study treatment records will be made available to the site visitor for inspection during site visits.

11.8 ENSURING DATA INTEGRITY AND QUALITY

Ensuring the integrity and quality of data collected in the CATT is critical. Refer to Section 16.5 for CATT Quality Assurance activities related to data management.

CHAPTER 13

STUDY POLICIES

13. Protection of Human Subjects

The protection of patients participating in the CATT: Lucentis-Avastin Trial has been paramount in the design and implementation of the study. This includes consideration of the risks and benefits of participation, plans for the consent process, and inclusion and exclusion criteria.

13.1 Institutional Review Board Review and Informed Consent

Each patient must provide written informed consent in order to participate in the Study. The consent form is prepared locally based on a prototype provided by the CATT Coordinating Center and is submitted to the local IRB for approval. (See Exhibit 13-1 for the template consent form.) All consent forms must be fully HIPAA compliant. Each participating Clinical Center must provide the Coordinating Center with a copy of the approved form before the site is certified to enroll patients into the Study.

Consent must be obtained from each patient prior to performing any study-specific procedures. Clinical Center staff may obtain verbal consent from the patient to perform study-specific procedures, such as a protocol refraction and visual acuity test. The fact that verbal consent is obtained should be noted in the patient's chart. A script for obtaining verbal consent is provided to the Clinical Centers by the CATT Coordinating Center (see Exhibit 13-2). Clinical Centers must obtain approval for the verbal consent process and the script from their local IRB. If the patient is determined to be eligible after all screening tests have been performed, WRITTEN informed consent must be obtained from the patient before enrollment into CATT.

Informed consent must be documented through the signature of the participating patient on the locally approved consent form. A copy of the signed/dated consent must be provided to the patient and the original will be maintained at each Clinical Center. The signed consent form must be available for inspection during site visits.

Investigators at each center are responsible for conducting the consent process, describing study procedures, discussing the risks and benefits and alternatives to participation, and discussing the voluntary nature of participation with the potential subject. The patient should be asked to sign the consent form only after the patient has been introduced to the study and had all questions answered to his or her satisfaction.

All investigators and clinic staff must complete training programs in ethics and maintaining the safety of human subjects in clinical research and in complying with HIPAA regulations prior to becoming eligible for CATT certification. Training may be provided by the individual institutions' approved training program or by the NIH website. If the local institution requires additional training for those engaged in human research at their institution, this too must be completed before commencing with any CATT procedures. Certificates documenting the successful completion of ethics and patient safety programs must be submitted to the Coordinating Center by all members of the investigative group prior to CATT certification.

13.1.1 Patient Confidentiality

Participating Clinical Centers must take all appropriate measures to protect the confidentiality of CATT patients. All scans, photographic materials and study forms that leave the Clinical Center do not identify the patient by name. Patients are assigned a unique numeric and letter code that is not related to their birth date, social security number or name. All study materials are kept in locked file cabinets at the Coordinating Center, OCT Reading Center and Fundus Photograph Reading Center. Patient identities are not be revealed in any publication that may result from this Study. The participating Clinical Centers maintain a log of patients' names, social security numbers, and assigned patient ID numbers, which are kept in a locked cabinet. Clinical information is not to be released without written permission of the patient, except as necessary for monitoring by the IRB, FDA, the NEI, the OHRP, and Protocol Monitors.

13.2 Patient Costs

Patients do not pay any charges for study drugs. Lucentis® is be supplied to Study patients by the clinical center using the same supply system as used outside of the Study. Claims for Lucentis® are to be submitted to Medicare, or the patient's primary insurance if different from Medicare. Claims are also submitted to the patient's supplemental insurance for the co-pay not covered by Medicare or other primary insurance. Any residual payment due for Lucentis® after all secondary and supplemental insurance payments have been made is covered by Study funds. Avastin® is supplied by the Study at no cost to the clinical center or patient.

Charges for Study office visits, imaging, and injection fees are the responsibility of the patient, Medicare, or the patient's other insurance. The frequency of visits and procedures within the CATT: Lucentis-Avastin Trial are within the norms of standard care for patients with neovascular age-related macular degeneration. In addition, insurance companies will be charged for any treatment for side effects that may occur as a result of participation in the study.

13.3 Publicity

All publicity and press releases on behalf of the CATT: Lucentis-Avastin Trial are to have prior approval of the Executive Committee. CATT investigators who are approached by the press for information concerning the study should refer these inquiries to the Study Chairman. It is recognized that when information is sought from an individual investigator by the local press in his or her own community, it is sometimes necessary or desirable for the investigator to handle the request him/herself. In such an event, the participating investigator who gives information should speak as an individual and not as the official representative of the CATT: Lucentis-Avastin Trial. This fact should be made clear to the press; however, the information given should be accurate and reflect the general policy and views of the group.

During the recruitment phase of the study, announcements (pre-approved by the CATT Executive Committee) may be placed in local media (newspaper, radio, television). The Coordinating Center also prepared for each clinical center a set of slides to present at local professional society meetings to aid in recruitment and study visibility. On a national level, study publicity will be increased by postings on the NEI and ClinicalTrials.gov web sites, and by mailings to AMD patient organizations.

13.4 Publication Plan

CATT: Lucentis-Avastin Trial papers are defined as those that use data, documents, or other information collected during the course of the Study. Publication of the results of CATT trials will be governed by the policies and procedures developed by the Executive Committee. The Executive Committee reviews all written reports prepared for publication.

A subcommittee of the Executive Committee ensures that the preparation of the results for abstract presentation or publication complies with NIH policies and guidelines, and appropriate analysis and conclusions are reached.

13.4.1 Authorship

All reports from the Comparisons of Age-related Macular Degeneration Treatments Trials Group that involve comparison of treatment groups and/or the major outcome measures of CATT studies will list the "Comparisons of Age-related Macular Degeneration Treatments Trials Group (CATT)" as author. All professional participants of the Group are listed at the end of each paper and are considered as contributors. In addition, all CATT personnel, past and present, may be listed with the approval of the principal investigator for whom they have worked. With the approval of the Executive Committee, publications may list members of the writing team in a footnote on the title page

13.4.2 Manuscript Writing Teams

The CATT Operations Committee will determine potential manuscript topics based on interim analyses and hypotheses. Investigative Group members are invited to volunteer for writing assignments and to suggest additional topics where appropriate. The Coordinating Center solicits members for the writing committees for CATT papers from among the CATT Investigative Group. Final designation of the writing committee will be made by the chair of the writing committee. The Executive Committee may recommend particular members of the Investigative Group for inclusion in the writing committee of specific papers. Along with the Operations Committee, each writing team will select the journal to receive the submission.

13.4.3 Manuscript Pre-Submission Review

Papers prepared for publication must be sent to the CATT Chairman or to the Coordinating Center Director for review and advance approval by the Executive Committee. If approved by the Executive Committee, the manuscript is then sent to the Data and Safety Monitoring Committee (DSMC) for review and approval.

Oral presentations of more than local scope must be approved in advance by the Executive Committee. Abstracts to be printed must be approved by the Executive Committee. The DSMC, at their initial meeting, may also decide to mandate their review of oral presentations and abstracts in advance. No unpublished study results may be used for oral presentations, local or otherwise, unless the Executive Committee grants a specific exception. The above restrictions do not apply to local presentations on the design of the CATT: Lucentis-Avastin Trial, provided these presentations contain no unpublished Study results. Such presentations are encouraged to stimulate recruitment.

Copies of Study papers are sent to all Principal Investigators as well as members of the Executive Committee and the Data and Safety Monitoring Committee (DSMC) for information before publication. Reprints of published papers are mailed to members of the DSMC and to each center for distribution among the staff.

Manuscripts emanating from ancillary studies must be sent to the Executive Committee for review before submission for publication. See also Section 13.6.

13.4.4 Acknowledgements

Each publication must acknowledge support from the National Eye Institute (NEI).

13.5 Data Sharing

NIH released "Final NIH Statement on Sharing Research Data" (NOT-OD-03-032) on February 26, 2003 which modified "NIH Announces Draft Statement on Sharing Research Data" (NOT-OD-02-035). In accord with NIH guidelines, a summary, de-identified data set will be made available through the CATT website at the time of publication and through direct inquiries to the Study Chair or Coordinating Center. The CATT data sets will be largely self-documenting in that an item identifier is embedded within the label for each variable. In addition, key derived variables will also be contained in the data sets.

The rights and privacy of people who participated in the Study will be protected at all times by stripping the data from all identifiers that could lead to disclosing the identity of individual research participants. This commitment to privacy-protected data sharing will be incorporated in all levels of database design.

By the end of the funding period, de-identified SAS data sets and form images corresponding to all data collection forms used, as well as key derived variables, will be put on file with a data repository such as the National Technical Information Service (NTIS).

The full SAS databases (not de-identified) associated with CATT will be kept on secured computer systems maintained by the Study Chair and by the Director of the Coordinating Center. Researchers may request limited access data sets and will need to enter into a data sharing agreement. Guidelines for the process of requesting such data sets and their content have been put forth recently by NHLBI (Geller, 2004). Access to the CATT database will be similar to these guidelines. Researchers requesting limited access data sets will bear the cost of their preparation.

13.6 Ancillary Studies

Individual investigators who wish to carry out ancillary studies are encouraged to do so. It is believed that such ancillary studies may greatly enhance the value of the CATT and ensure the continued interest of many capable investigators. However, to protect the integrity of the CATT, such ancillary studies must be reviewed and approved by the Executive Committee and Data and Safety Monitoring Committee before their execution, whether or not they involve the need for supplementary funds.

13.6.1 Definition of a CATT Ancillary Study

An ancillary study is a research study that requires either

- Supplementary observations or procedures to be performed upon all or a subgroup of CATT patients according to a set protocol, or,
- Additional effort or activity by either the Coordinating Center, OCT Reading Center or Fundus Photograph Reading Center staff beyond the current scope of CATT.

13.6.2 Reasons for Requirement of Approval

Everyone concerned with CATT is entitled to prior assurance that no ancillary study will:

- Complicate the interpretation of the CATT results;
- Adversely affect patient cooperation;
- Jeopardize the public image of CATT;
- Create a serious diversion of CATT resources locally or at the Resource Centers.

13.6.3 Preparation of Request for Approval of a CATT Ancillary Study

The request for approval of an ancillary study should be in narrative form. It should contain a brief description of the objectives, methods, and significance of the study. Full details should be given concerning any procedures to be carried out on any CATT patients, such as visual function tests, psychiatric interviews, psychological testing, radiological procedures, venipuncture, etc. Mention should be made of any substances to be injected or otherwise administered to the patients. Any observations to be made or procedures to be performed on a patient outside of the Clinical Center should be described. Mention should be made of the extent to which the ancillary study will require extra clinic visits by the patient or will lengthen the patient's usual clinic visits.

13.6.4 Procedures for Obtaining Ancillary Study Approval

The investigator concerned should send the ancillary study request to the Director of the Coordinating Center for distribution to all members of the Executive Committee. Within a reasonable time, the Director will summarize any questions and/or objections raised by members of the Executive Committee and send this summary to the applicant so that he/she may amplify, clarify, and/or withdraw the request. The members of the Executive Committee will then have another opportunity to review the request. The Director of the Coordinating Center then prepares a statement of the Executive Committee consensus, including any remaining reservations or objections. This statement is forwarded to the investigator who requested approval for the ancillary study. After Executive Committee approval is obtained, the information is then forwarded to the DSMC for its approval.

13.6.5 Funding of Ancillary Studies

If no additional funds are required, the investigator may proceed with the ancillary study as soon as the Executive Committee and Data and Safety Monitoring Committee approve it. If additional funds are needed, the investigator may prepare and submit a new research grant application to the Division of Research Grants, National Institutes of Health, or any other

potential sponsor, for review in the same manner as any other new research grant application. It is understood that the investigator is not to activate the ancillary study until approval has been received from the CATT Executive Committee and DSMC.

13.6.6 Publication of Ancillary CATT Results

All manuscripts or presentations for scientific meetings based on ancillary study data must be reviewed and approved by the CATT Executive Committee before publication or presentation. Such review will pertain to the expected impact on CATT Study objectives and not to scientific merit alone. Appropriate acknowledgment of CATT resources used—whether data, patients, or CATT investigators— should be included.

13.6.7 Progress Reports to Executive Committee

The investigator of each approved ancillary study is required to provide a written progress report for review by the Executive Committee at each scheduled meeting. The Coordinating Center reminds the investigators of the deadline and collects progress reports for distribution to the Executive Committee.

13.7 Related Studies

Individual CATT investigators who carry out studies related to ongoing, completed, or proposed CATT studies should be aware that their conclusions and interpretations might be viewed by non-CATT investigators as reflecting the position of the CATT Group. The study may be related because of types of patients included, types of treatment evaluated, or similarity of methods to those used in the CATT Study. Therefore, investigators are encouraged to submit reports from related studies to the Executive Committee for review prior to presentation or submission for publication in order to assure that the goals of the CATT Study are not jeopardized.

13.8 APPROVAL OF CHANGES IN PROTOCOL

All significant changes to the CATT protocol must be approved by the CATT Operations Committee, Executive Committee and the DSMC. In some circumstances, approval from NEI may also be required. When a change in protocol is implemented, a protocol memorandum will be issued to clinical center staff. All CATT clinical center staff will be required to acknowledge receipt of the protocol memorandum and that they understand its contents by signing and dating a form that is sent to the Coordinating Center. During site visits, the Protocol Monitor reviews whether all CATT protocols, forms and other documents are up to date.

13.8.1 Changes to the Manual of Procedures

The CATT Manual of Procedures will be revised to reflect changes to the protocol. All revised manual chapters are distributed by the Coordinating Center. Any revisions to chapters that originate in other CATT resource centers (i.e., the OCT Reading Center or Fundus Photograph Reading Center) must be sent to the Coordinating Center for distribution to the clinical centers.

EXHIBIT 13-1

University of Pennsylvania

Research Subject

Informed Consent Form

Protocol Title:	CATT: Lucentis-Avastin Trial
Principal Investigator:	**Insert Name of the Principal Investigator** **Address** **Insert Phone Numbers**
Sponsors:	**National Eye Institute (NEI)**
Emergency Contact:	**Insert Emergency Contact** **Insert Phone Number/Pager, etc.**

Why am I being asked to volunteer?

You are being asked to participate in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT): Lucentis-Avastin Trial, a randomized clinical treatment trial, because you have previously untreated, active, subfoveal choroidal neovascularization (CNV) secondary to Age-related Macular Degeneration (AMD) (also known as neovascular or "wet" AMD), you are at least 50 years of age and you meet other requirements for enrollment into this study. Your participation in this study is voluntary, which means that you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do to participate. The ophthalmologist (eye doctor) who is working on this study and his/her study assistant (the study coordinator) will explain the study to you, and have given you this consent form to read. You may also decide to discuss it with your family, friends or your personal doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the study coordinator to explain any words or sections of this form you do not understand. If you decide to participate, you will be asked to sign this form and will be provided a copy for your records.

What is the purpose of this research study?

Neovascular (wet) AMD is one of the leading causes of vision loss in people aged 60 and older. The purpose of the Lucentis-Avastin Trial study is to compare two drug treatments for neovascular "wet" AMD for their effects on vision and for safety. The two drugs being compared are Lucentis® (ranibizumab) and Avastin® (bevacizumab). The study is sponsored by the National Eye Institute (NEI), a branch of the National Institutes of Health, an agency within the U.S. Government.

What is Lucentis®?

Lucentis® is a drug that was approved by the U.S. Food and Drug Administration (FDA) in 2006 to treat "wet" AMD. Lucentis® interferes with the growth of new vessels and prevents leakage of fluid from new blood vessels. The clinical trials that showed the best results for Lucentis® called for an injection of a small amount (0.5 mg) of Lucentis® into the eye every four weeks. Lucentis® costs approximately $2100 per injection.

What is Avastin®?

Avastin® is a drug that has been approved by the FDA for the treatment of cancer. Patients with cancer have Avastin administered to them through a vein in their arm. Avastin® interferes with the growth of new vessels and prevents leakage of fluid from new blood vessels. It has NOT been approved to treat AMD; however, many doctors have been injecting it into the eye to treat AMD. Avastin® costs approximately $50 per injection.

What exactly will the study compare?

Avastin® and Lucentis® have similar actions, but it is not known whether Avastin® is more effective, less effective or the same as Lucentis® for treating AMD. Also, doctors want to know whether treating less frequently than every four weeks can provide the same benefits as treating every 28 days. This study will compare four (4) treatment plans for AMD:

1) An injection into the eye of 0.5 mg.(0.05ml) of Lucentis® given every four weeks
2) An injection into the eye of 1.25 mg (0.05ml) of Avastin® given every four weeks
3) An injection into the eye of 0.5 mg. of Lucentis® given on the advice of your study doctor. The study doctor's decision is based on an examination of your eye and on other clinical test results that can indicate CNV is active.
4) An injection into the eye of 1.25 mg of Avastin® given on the advice of your study doctor. The study doctor's decision is based on an examination of your eye and on other clinical test results that can indicate CNV is active.

Both Lucentis® and Avastin® are given by injection into the vitreous of the eye through the sclera. (The sclera is the "white of the eye" and the vitreous is the clear, jelly-like substance in the middle of the eye.) The procedure is called an "intravitreal injection".

How long will I be in the study? How many other people will be in the study?

You will be in the study for two years of treatment. The study will include the initial visit and follow up office visits that are scheduled every four weeks for two years. There will be 1200 patients participating in this study in approximately 45 clinical centers (doctor's offices) throughout the United States. Each of the four treatment groups will have a total of 300 participants.

What am I being asked to do?

Your consent to participate in this study means that you agree to be treated according to one

of the four study treatment plans. Your treatment plan will be selected randomly, like the flip of a coin, from among the four treatment plans rather than having your treatment selected by your study doctor and you. Everyone in the study will receive some kind of treatment. We do not know which treatment is best.

If you are randomized into one of the groups that receives injections every four weeks, you will continue this treatment schedule for one (1) year. At the end of one year you will again be randomly assigned to either treatment every 4 weeks for the next year or treatment only when your study doctor decides that the CNV is active. The same drug that you were originally assigned to, either Lucentis® or Avastin® will be used during the second year.

If you are assigned initially to treatment only when your study doctor decides that the CNV is active, your treatment will continue this way for two years.

Your study doctor and the person who will test your vision will not know which study drug (Lucentis® or Avastin®) you are being given. This is done so that that this knowledge cannot influence the results of vision testing and treatment decisions. However, for safety reasons, information on which drug you are receiving will be available to your doctor if medically necessary. You will not be told by the study team about which study drug you have been assigned. You may learn which drug you are receiving from billing and insurance statements. If this happens and you have questions about your billing, we ask that you speak only to the study coordinator about your statements and study drug.

Whether or not you choose to participate in this study, there is an approximate 10% chance per year that your other eye will develop CNV if it has not already done so. In that case, we would encourage you to speak with your study doctor and with your personal doctor about the choices for treatment of your other eye.

What happens during study visits?

You will have an eye doctor's visit every four weeks for two years. At **all** study visits, you will be examined by an ophthalmologist (an eye doctor) who will check how your eye is doing and you will have your vision tested. At each clinic visit you will also be questioned about your health and the medications you are taking. If you have been hospitalized, we will ask for your hospital records. Other tests will be done at all or some of the study visits. Patients assigned to receive treatment only when the study doctor decides that CNV is active will undergo a procedure called "**O**ptical **C**oherence **T**omography" or OCT at every visit. An OCT is a quick, painless, non-invasive procedure that scans the inside of your eye. Patients assigned to treatment every 4 weeks will have an OCT for their first 4 study visits and then at 6, 12, 18, and 24 months.

At the first study visit and at 3, 6, 12, 18, and 24 months, you may have eye photographs taken and a fluorescein angiogram. A fluorescein angiogram is a procedure in which fluorescein dye is injected into a vein in your arm and special pictures that show blood vessels are taken of your eye.

If you have been assigned to the treatment groups that receive treatment every four weeks, you will receive treatment at all study visits. If you have been assigned to the treatment groups that receive treatment only when your study doctor decides that the CNV is active, you will be treated only if the CNV appears active. After the first time you are treated, you will receive a telephone call from the Clinic Coordinator within 3-5 days, to see if you are experiencing any problems from the treatment.

What are the possible risks or discomforts?

During your participation in this study, you are at risk for the side effects described below. You should discuss these with the study doctor. There may also be other side effects that we cannot predict. Other medicines may be given to lessen the side effects and discomfort. Many side effects go away shortly after you stop treatment, but in some cases, side effects can be serious, long lasting, or permanent.

Possible Risks Associated with Lucentis® and Avastin®

Both Lucentis® and Avastin® have been studied in humans in **previously** completed clinical trials and research studies. The following side effects have been observed in treatment with each drug: temporary redness of the injected eye, minor bleeding at the injection site that resolves on its own (doesn't require treatment), dull pain in the injected eye, sensitivity to light, mild and temporary burning and stinging, vision disturbances, including decrease in vision, bleeding inside the injected eye that resolves on its own, infection outside the treated eye, and mild and self-resolving inflammation on the inside of the eye. Injection of the numbing medication may lead to minor bleeding under the surface of your eyeball; the bleeding will usually stop on its own, and the surface of your eye should return to its usual appearance. Antiseptic cleaning of the eye is done before each injection to minimize the risk of infection.

Less frequent side effects include infection inside the eye (endophthalmitis) severe inflammation in the inside of the eye (uveitis), blockage of the blood flow in the main vein inside the eye (central retinal vein occlusion), temporary increase in the pressure inside the eye (intraocular pressure), damage to the lens inside the eye (cataract formation), a tear through the retinal tissue in the eye (retinal tear/detachment), a rip in the pigment cell layer that lies beneath and nourishes the retina (retinal pigment epithelial [RPE] tear) and inadequate response of the pupil to light entering the eye. Some of the complications listed above may result in permanent loss of vision or loss of the eye.

If you have a history of glaucoma, you may be at more risk for experiencing increased pressure within your eye after an injection of any substance, including Lucentis® and Avastin®. To participate in this study, it must be shown that your glaucoma is well controlled with medication and that you take your medication as it has been prescribed by your doctor.

There is a chance that your vision may worsen. Worsened vision could be due to progression of your AMD, to a side effect of Lucentis® and Avastin® injection, or for other reasons. There is a chance that you will experience an allergic reaction to Lucentis® and Avastin®. Allergic reactions may be mild, such as skin rash or hives, or severe, such as breathing difficulties or shock. A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death. An allergic reaction can also cause a red, dry or itchy eye. It

is not possible to predict in advance if any of these problems will develop, but if they do, you will be promptly treated.

Tests have shown that low levels of Lucentis® and Avastin® can reach your blood stream after injection into the eye. The significance of this is not well understood. However, in one recent study, 1.2% of the people who took 0.5 mg of Lucentis® injected into the eye every 4 weeks developed stroke while only 0.3% of those who had an injection of a lower dose (0.3 mg) had a stroke. Among those people who had a history of prior stroke, the risk for another stroke was higher than among those with no prior stroke. The risk of having another side effect involving a body system other than the eye is unknown but is believed to be very small. Additional serous side effects have been associated with Avastin when it is given at high levels (more than 300 times the amount injected into the eye) directly into the blood stream for cancer patients. Strokes, transient ischemic attacks (TIAs), heart attacks, and angina (heart-related chest pain) were 2 to 3 times more common in cancer patients receiving Avastin® than in cancer patients not receiving Avastin®. In addition, intestinal perforations, wound healing complications, bleeding, high blood pressure, protein in the urine, infections, and congestive heart failure have been more common in cancer patients receiving Avastin®.

As is true for any drug, unknown and potentially serious or life-threatening side effects could occur with Lucentis® and Avastin®.

Risks on fetuses

The effects of Lucentis® and Avastin® on a fetus (unborn child) are unknown and may be harmful; therefore, females should not become pregnant while in this study. To participate in this study, females who are capable of bearing children must agree to use an effective, medically accepted method of birth control to prevent pregnancy and will be required to take a pregnancy test before entry into this study. If you are pregnant, you cannot be in this study because of possible harm to the fetus. If at any time during the study you suspect that you have become pregnant, you must notify the study doctor immediately. If after your participation in the study is over, you suspect that you have become pregnant within 90 days of the last administration of study drug, you must notify your study doctor immediately. Further, you understand that if you do become pregnant, you must stop study treatment. You must not breast feed a baby while in this study because Lucentis® and Avastin® may enter breast milk and possibly harm your child.

Risks and discomfort associated with Optical Coherence Tomography (OCT)

OCT takes approximately 10 minutes to perform. It is non-invasive and is not painful. No radiation is used. You will sit at a machine and look straight ahead as the machine takes pictures of the back of your eyes. No side effects from this test have been reported.

Risks and discomfort associated with fluorescein angiography

Patients having a fluorescein angiogram sometimes have side effects from the injection of the dye into the vein in their arm. Side effects include nausea and/or vomiting (5% risk), hives and itching (0.5% risk), and rarely a life-threatening allergic reaction (<0.01% risk).

POTENTIAL BENEFITS

Previous studies have shown that an intravitreal injection of Lucentis® every 4 weeks leads to much less loss of vision when compared to people not treated with Lucentis®. Intravitreal injections of Avastin® may provide similar beneficial effects. In addition, your participation in this study means that you will have the benefit of receiving treatment for AMD without any out-of-pocket expense to you for the drug, although Medicare and/or your insurance will be billed. Your participation in this study may lead to new treatment standards for people who have "wet" AMD.

What if new information becomes available about the study?

An independent committee of physicians, statisticians and patient advocates (known as a Data and Safety Monitoring Committee) will review the study findings while the study is ongoing. The committee will keep the results confidential unless there is new important information on the study drugs. The committee will disclose findings to the study doctors when there is new information on the safety of the study drugs or when there is proof beyond a reasonable doubt that one treatment is better than the other. We will notify you as soon as possible if such information becomes available. In addition, if information from other studies becomes available during your participation in this study, we will notify you as soon as possible.

What other choices do I have if I do not participate?

Your participation in this research study is voluntary. Instead of participating in this study, you may choose a specific treatment plan after discussion with your doctor. Both Lucentis® and Avastin® are routinely available to your eye doctor outside of this study. Your doctor will discuss your options with you. You may want to discuss your choice with your family, friends and/or your personal physician. Your choice not to participate in this study or will not affect your medical care in any way.

Will I be paid for being in this study?

There will be no payment or compensation for your participation.

Will I have to pay for anything?

You and/or your health insurance will be billed for clinic visits, the study doctor's fee for injections, tests and other procedures outlined in this consent form as well as for the costs of medical care during this study if these expenses would have been charged even if you were not in the study. Your health insurance may be charged for the study drug. You must either be enrolled in Medicare, or have private insurance that will cover at least 80% of the charge for the study drugs, or commit to pay personally for the study drug (self-insured). If any drug charges remain after your insurance plans have paid the bill for the drug, the study will pay them. The charge for study drug may appear on your billing account while the insurance payments are being processed. However, you will not have to pay for charges for the study drug.

What happens if I am injured or hurt during the study?

If you have a medical emergency during the study you may contact Dr. _____ or the emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise available from the University of Pennsylvania. If you have an illness or injury during this research trial that is not directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.

When is the study over? Can I leave before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. Your participation in the study will end in 2 years, after you have completed all your study visits. You may decide to leave the study at any time before the end, and your withdrawal from the study will not interfere with your future care. Should your physician find it necessary, and/or in your best interest, he/she may withdraw you from the study treatment but will ask for you to continue to be followed as part of the study. This study may also be stopped at any time by your physician, the National Eye Institute, or the Food and Drug Administration (FDA) without your consent, but you will be informed if such a decision is made and the reason for this decision

Who can see or use my information? How will my personal information be protected?

The investigator and staff involved with the study will keep your personal health information collected for the study strictly confidential. Please refer to the separate "Confidentiality & Privacy Rights" document that explains more specifically how your personal information will be protected. Information about your AMD, vision and photographs will be submitted to researchers at the University of Pennsylvania. Your OCT scans will be sent to a Reading Center at Duke University. All your information will be labeled with only number and letter codes. When the results of the study are reported in publications, your information will be reported as part of a group. You will not be identified in any way.

Your information may be reviewed by designated representatives of the CLINICAL INSTITUTIONS, the University of Pennsylvania, the National Eye Institute, and the U.S. Food and Drug Agency (FDA) who may need to review study records to ensure the quality and integrity of data collected in this study.

Who can I call about my rights as a research participant?

If you have questions regarding your participation in this research study or if you have any questions about your rights as a research participant don't hesitate to speak with Dr. _____, whose phone number is listed on page one of this form. Concerning your

rights as a research participant, you may also contact the Office of Regulatory Affairs at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in the Comparisons of Age-related Macular degeneration Treatments Trial. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you. You will also be given the University of Pennsylvania Health System and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your health information.

_____	_____	
Name of Subject (Please Print)	Signature of Subject	Date

_____	_____	
Name of Person Obtaining Consent (Please Print)	Signature	Date

For Use With Authorized Representative Signature

For subjects unable to give authorization, the authorization is given by the following authorized subject representative:

_____	_____	
Authorized subject representative **[print]**	Authorized subject representative Signature	Date

Provide a brief description of above person authority to serve as the subject's authorized representative.

EXHIBIT 13-2

Script Approved by University of Pennsylvania's IRB for Obtaining Verbal Consent for Eligibility Screening

Good morning __{Patient Name}__,

I'm {Clinic Staff Member Name}. As you know, you are going to be evaluated today to determine if you are a candidate for treatment for macular degeneration. We will perform some tests including measuring your vision, taking photographs, and obtaining an image of your macula to document the extent of fluid leakage in the macula that may be affecting your vision.

In all likelihood, you will be a candidate for treatment. There actually are two effective treatments. We are involved in a research study supported by the National Institutes of Health to compare which of these treatments might be better at preserving vision.

This study will enroll 1,200 patients at more than 45 centers across the entire U.S. If you are eligible for the study, I will describe the study in more detail and ask if you want to participate.

The first thing, however, is to measure your vision. Because we want the vision measured in patients all over the country to be standardized, I need your verbal consent to measure your vision in a standardized way. If you give me your verbal consent, there is no need to sign anything now.

NOTES:

This script is a sample. The script can be modified at your center to include other study-specific screening procedures.

The verbal consent process is optional; however, if it is not used, written informed consent for the entire study must be obtained prior to performing any study-specific procedures.

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