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Study No.: ARI40005
Title: A randomized, double-blind, parallel group study to investigate the efficacy and safety of treatment with dutasteride (0.5 mg) and tamsulosin (0.4 mg), administered once daily for 4 years, alone and in combination, on the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic benign prostatic hyperplasia (Year 4 analysis)
Rationale: Combination therapy with finasteride and doxazosin was a more effective treatment for reduction in the overall risk of benign prostatic hyperplasia (BPH) clinical progression than either monotherapy in select subjects over a 4-year treatment period. The primary aim was to investigate whether combination therapy of dutasteride with the alpha-1-adrenoreceptor antagonist, tamsulosin, for up to 4 years, could provide superior benefits to monotherapy alone with respect to improvement in symptoms and the longer term clinical outcomes of acute urinary retention (AUR) or BPH-related prostatic surgery in subjects with moderate to severe BPH and at risk for BPH clinical progression.
Phase: III
Study Period: 14 November 2003 – 11 May 2009
Study Design: An international, multicenter, randomized, double-blind, parallel group study of dutasteride (0.5 mg) and tamsulosin (0.4 mg) given alone or in combination to male subjects ≥ 50 years old with a clinical diagnosis of moderate to severe symptomatic BPH. The study consisted of a 4-week single-blind placebo run-in period, a 4-year double-blind treatment period, and a 16-week safety follow-up period. The total study duration for each subject was up to 229 weeks.
Centres: 443 investigators in 35 countries
Indication: Benign prostatic hyperplasia
Treatment: Dutasteride was supplied as yellow capsules containing 0.5 mg active ingredient or matched placebo capsules. Tamsulosin was supplied as over-encapsulated pink capsules containing 0.4 mg active ingredient or matched placebo capsules. All subjects were instructed to take two capsules consisting of one dutasteride-matched placebo capsule and one tamsulosin-matched placebo capsule once daily during the 4-week placebo run-in period. During the treatment period, subjects were randomized in a ratio of 1:1:1 to receive either dutasteride 0.5 mg + tamsulosin 0.4 mg, dutasteride 0.5 mg + tamsulosin placebo, or dutasteride placebo + tamsulosin 0.4 mg once daily for 208 weeks.
Objectives: To assess efficacy of combination treatment in providing superior symptomatic improvement to BPH patients compared with dutasteride and/or tamsulosin monotherapy after 2 years of treatment; and to assess efficacy of combination treatment in providing superior improvement in the clinical outcomes of AUR or BPH-related prostatic surgery to BPH patients compared with tamsulosin or dutasteride monotherapy after 4 years of treatment.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint at Year 4 was time to first event of AUR or BPH-related prostatic surgery. The proportion of subjects experiencing AUR or BPH-related prostatic surgery was a supportive endpoint to the primary analysis.
Secondary Outcome/Efficacy Variable(s): The secondary efficacy endpoints at Year 4 were time to BPH clinical progression (composite endpoint comprising symptom deterioration by ≥ 4 International Prostate Symptom Score [IPSS] points on 2 consecutive visits, BPH-related AUR, overflow or urge incontinence, recurrent urinary tract infection [UTI] or urosepsis, and BPH-related renal insufficiency), time to event/proportion of subjects for each of the five components of BPH clinical progression, time to event/proportion of subjects undergoing BPH-related prostatic surgery; proportion of subjects with BPH-related macroscopic hematuria post-baseline; and proportion of subjects with BPH-related macroscopic hematospermia post-baseline. The efficacy endpoints initially tested at Year 2 were considered secondary efficacy endpoints at Year 4; these include IPSS, prostate volume, and Qmax.
Statistical Methods: The Intent-to-Treat (ITT) population was the primary population for analyses and consisted of all subjects randomized to the double-blind treatment period. Demographic and baseline characteristics, baseline measures for efficacy, safety, and health outcomes, along with current medical conditions including those of special interest in the BPH population, breast and prostate cancer history/family history, and sexual function were summarized overall and by treatment group. All planned treatment group comparisons were between combination therapy and each monotherapy; comparisons between dutasteride and tamsulosin were not planned or performed.
Statistical testing of the multiple primary and secondary endpoints, and at multiple timepoints for each endpoint, was

performed in a pre-specified hierarchical step down manner (producing a closed test procedure) at the 0.01 level of significance (i.e., a priori-defined multiplicity guidelines). The primary comparisons of interest at Year 4 were combination therapy versus each monotherapy in terms of time to first event of AUR or BPH-related prostatic surgery, defined as number of days from the date of the first dose of randomized study drug to the date of the initial event. The primary analysis compared treatments in terms of time to first AUR or BPH-related surgery for the ITT using a log rank test stratified by cluster. The relative risk (hazard ratio) for the treatment effect and associated two-sided 95% confidence intervals was estimated using a Cox proportional hazards model with treatment as the only covariate and stratified by cluster. Estimates and corresponding confidence intervals for the relative risk (hazard ratio) and risk reduction (1-hazard ratio) of combination therapy versus each monotherapy were presented along with the log rank p-value. The crude rate of AUR or BPH-related surgery incidence was calculated using the ITT population of each treatment as the denominator; the associated 95% confidence interval was output. This crude rate was compared for combination therapy versus each monotherapy using the Mantel-Haenszel test stratified by cluster.

Other secondary endpoints designated as "time to" including clinical progression of BPH, each of the five components of clinical progression of BPH, and BPH-related prostatic surgery were analyzed and reported in a manner similar to the primary endpoint. BPH-related macroscopic hematuria and BPH-related hematospermia were each summarized as a crude rate; treatment group comparisons for combination therapy versus each monotherapy in terms of these proportions were performed using a Mantel-Haenszel test controlling for investigative site cluster.

Change in baseline IPSS, Qmax, BII, and Q8 of the IPSS (BPH-related Health Status [BHS]) were compared at each scheduled post-baseline assessment for combination therapy versus each monotherapy using t-tests from a general linear model with effects for treatment, cluster, and baseline value at $\alpha=0.01$. The adjusted mean estimates, the adjusted mean differences, and 95% confidence intervals in terms of the adjusted mean differences were presented. The adjusted mean differences were in terms of combination therapy minus each monotherapy. Percentage change in baseline prostate volume or in transition zone volume were similarly analyzed except that treatment groups were compared using t-tests from the general linear model $\log(\text{post baseline value}/\text{baseline value}) = \log(\text{baseline value}) + \text{treatment} + \text{cluster}$. Patient's Perception of Study medication (PPSM) grouped response categories were compared at each scheduled visit for combination therapy versus each monotherapy using a Mantel-Haenszel test controlling for cluster.

Treatment group comparisons for combination therapy versus each monotherapy for the proportion of subjects with AEs, drug-related AEs, SAEs, and AE withdrawals from study/investigational product were performed using Fisher's exact test. For AEs of special interest, time to first event was summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves. Also for AEs of special interest, relative risk estimates (hazard ratios) for treatment and the corresponding 95% confidence intervals were presented based on a Cox proportional hazards model, with treatment as the only covariate.

Study Population: Males ≥ 50 years of age with clinically diagnosed BPH, an International Prostate Symptom Score (IPSS) screening score of ≥ 12 points, prostate volume ≥ 30 cc, a total serum Prostate Specific Antigen (PSA) level ≥ 1.5 to ≤ 10.0 ng/mL, a maximum flow rate (Qmax) > 5 mL/sec and ≤ 15 mL/sec, and minimum voided volume of ≥ 125 mL at Screening were included. Subjects with a history or evidence of prostate cancer or previous prostate surgery were excluded.

	Combination	Dutasteride	Tamsulosin
Number of Subjects:			
Planned, N	4500		
Randomised, N	1610	1623	1611
Completed Treatment, n (%)	1113 (69)	1093 (67)	989 (61)
Total Number Subjects Withdrawn From Treatment, N (%)	497 (31)	530 (33)	622 (39)
Withdrawn due to Adverse Events, n (%)	211 / 497 (42)	185 / 530 (35)	210 / 622 (34)
Withdrawn due to Lack of Efficacy, n (%)	53 / 497 (11)	71 / 530 (13)	104 / 622 (17)
Withdrawn for any other reasons, n (%)	233 / 497 (47)	274 / 530 (52)	308 / 622 (50)
Demographics	Combination	Dutasteride	Tamsulosin
N (ITT)	1610	1623	1611
Males	1610	1623	1611
Mean Age, years (SD)	66.0 (7.05)	66.0 (6.99)	66.2 (7.00)
Race (White), n (%)	1421 (88)	1433 (88)	1405 (87)

Primary Efficacy Results:						
	Combination N=1610		Dutasteride N=1623		Tamsulosin N=1611	
Period of First AUR or BPH-Related Surgery	No. events / No. at risk		No. events / No. at risk		No. events / No. at risk	
Year 1	29 / 1610		27 / 1623		40 / 1611	
Year 2	14 / 1457		22 / 1484		62 / 1464	
Year 3	15 / 1347		16 / 1365		44 / 1307	
Year 4	9 / 1274		19 / 1277		45 / 1176	
Log Rank p-value ^a	--		0.18		<0.001	
Relative Risk Estimate ^b (95% CI)	--		0.80 (0.58, 1.11)		0.34 (0.26, 0.45)	
Risk Reduction Estimate (95% CI)	---		19.6% (-10.9, 41.7)		65.8% (54.7, 74.1)	
a. P-value vs. Dut+Tam based on log-rank test with stratification by cluster.						
b. Relative risk (hazard ratio) vs. monotherapy is based on Cox proportional hazards model with stratification by cluster.						
Summary of AUR or BPH-Related Surgery						
Incidence, n (%) [95% CI]	67 (4.2)		84 (5.2)		191 (11.9)	
AUR	35 / 67 (52)		44 / 84 (52)		109 / 191 (57)	
BPH-related surgery	32 / 67 (48)		40 / 84 (48)		82 / 191 (43)	
95% CI	3.2, 5.1		4.1, 6.3		10.3, 13.4	
p-value ^c	--		0.18		<0.001	
c. P-value vs. Dut+Tam based on Mantel-Haenszel test with stratification by cluster.						
Secondary Outcome Variable(s):						
	Combination N=1610		Dutasteride N=1623		Tamsulosin N=1611	
Period of First BPH Clinical Progression	No. events / No. at risk		No. events / No. at risk		No. events / No. at risk	
Year 1	126 / 1610		184 / 1623		171 / 1611	
Year 2	31 / 1264		54 / 1240		78 / 1262	
Year 3	30 / 1135		29 / 1082		67 / 1048	
Year 4	16 / 1047		22 / 959		31 / 880	
Relative Risk Estimate ^d (95% CI)	--		0.69 (0.57, 0.82)		0.56 (0.47, 0.66)	
Risk Reduction Estimate (95% CI)	--		31.2% (17.7, 42.5)		44.1% (33.6, 53.0)	
d. Relative risk (hazard ratio) vs. monotherapy is based on Cox proportional hazards model with stratification by cluster.						
Summary of BPH Clinical Progression						
	Combination N=1610		Dutasteride N=1623		Tamsulosin N=1611	
Incidence, n (%) [95% CI]	203 (12.6) [11.0, 14.2]		289 (17.8) [15.9, 19.7]		347 (21.5) [19.5, 23.5]	
Symptom deterioration	132 / 203 (65)		203 / 289 (70)		221 / 347 (64)	
BPH-related AUR	22 / 203 (11)		31 / 289 (11)		64 / 347 (18)	
BPH-related incontinence	46 / 203 (23)		49 / 289 (17)		56 / 347 (16)	
Recurrent BPH-related UTI	2 / 203 (<1)		5 / 289 (2)		3 / 347 (<1)	
BPH-related renal insufficiency	1 / 203 (<1)		2 / 289 (<1)		5 / 347 (1)	
IPSS change from baseline (Last Observation Carried Forward [LOCF] Analysis)						
	Adjusted Mean Change From Baseline (Standard Error [SE])					
	N	Comb	N	Dutasteride	N	Tamsulosin
Month 12	1575	-5.6 (0.15)	1592	-4.2 (0.15)	1582	-4.5 (0.15)
Month 24	1575	-6.2 (0.15)	1592	-4.9 (0.15)	1582	-4.3 (0.15)
Month 36	1575	-6.3 (0.16)	1592	-5.2 (0.16)	1582	-4.0 (0.16)
Month 48	1575	-6.3 (0.16)	1592	-5.3 (0.16)	1582	-3.8 (0.16)
	Adjusted mean difference (combination therapy minus monotherapy (SE) [95% CI]) ^e					
Month 12	--	--	--	-1.4 (0.202) [-1.80, -1.01]	--	-1.1 (0.203) [-1.53, -0.73]

Month 24	--	-1.3 (0.211) [-1.69, -0.86]	-1.8 (0.212) [-2.23, -1.40]			
Month 36	--	-1.1 (0.221) [-1.55, -0.68]	-2.3 (0.221) [-2.76, -1.90]			
Month 48	--	-0.96 (0.226) [-1.40, -0.52]	-2.5 (0.226) [-2.96, -2.07]			
e. Estimates are based on the adjusted (least squares) means from the general linear model: Change from Baseline IPSS = Treatment + Cluster + Baseline IPSS. Adjusted mean differences are based on Dut+Tam therapy minus each monotherapy.						
Adjusted Mean Change From Baseline Urinary Flow Rate (Qmax) (LOCF Analysis)						
	Adjusted Mean Change From Baseline (SE)					
	N	Comb	N	Dutasteride	N	Tamsulosin
Month 12	1477	2.0 (0.12)	1482	1.5 (0.12)	1510	0.9 (0.12)
Month 24	1492	2.4 (0.12)	1501	1.9 (0.12)	1519	0.9 (0.12)
Month 36	1495	2.6 (0.12)	1504	1.9 (0.12)	1521	0.6 (0.12)
Month 48	1495	2.4 (0.13)	1505	2.0 (0.13)	1523	0.7 (0.13)
	Adjusted mean difference (combination therapy minus monotherapy (SE) [95% CI])					
Month 12	--	0.50 (0.164) [0.18, 0.82]	1.12 (0.163) [0.81, 1.44]			
Month 24	--	0.52 (0.172) [0.18, 0.86]	1.53 (0.172) [1.20, 1.87]			
Month 36	--	0.65 (0.171) [0.31, 0.99]	2.00 (0.171) [1.66, 2.33]			
Month 48	--	0.35 (0.179) [0.00, 0.70]	1.66 (0.178) [1.31, 2.01]			
Adjusted Mean Percentage Change from Baseline in Prostate Volume (LOCF Analysis)						
	Adjusted Mean Change From Baseline (SE)					
	N	Comb	N	Dutasteride	N	Tamsulosin
Month 12	1411	-24.1 (0.60)	1442	-25.2 (0.59)	1451	-1.5 (0.77)
Month 24	1427	-26.9 (0.62)	1451	-28.0 (0.61)	1465	-0.0 (0.84)
Month 36	1430	-27.6 (0.68)	1455	-28.8 (0.66)	1468	1.6 (0.94)
Month 48	1430	-27.3 (0.66)	1455	-28.0 (0.65)	1468	4.6 (0.94)
	Adjusted mean difference (combination therapy minus monotherapy (SE) [95% CI])					
Month 12	--	1.1 (0.83) [-0.6, 2.7]	-22.6 (0.96) [-24.5, -20.7]			
Month 24	--	1.1 (0.86) [-0.6, 2.8]	-26.9 (1.03) [-28.9, -24.9]			
Month 36	--	1.2 (0.93) [-0.6, 3.0]	-29.2 (1.14) [-31.4, -26.9]			
Month 48	--	0.7 (0.91) [-1.1, 2.5]	-31.9 (1.13) [-34.1, -29.7]			
Adjusted Mean Percentage Change from Baseline in Transition Zone Volume (LOCF Analysis)						
	Adjusted Mean Change From Baseline (SE)					
	N	Comb	N	Dutasteride	N	Tamsulosin
Month 12	150	-17.2 (3.29)	159	-15.6 (3.39)	160	5.6 (4.09)
Month 24	153	-23.4 (5.63)	164	-22.8 (5.86)	160	8.7 (8.22)
Month 36	155	-20.9 (3.97)	164	-26.7 (3.90)	162	14.7 (5.89)
Month 48	155	-17.9 (4.45)	164	-26.5 (4.21)	163	18.2 (6.54)
	Adjusted mean difference (combination therapy minus monotherapy (SE) [95% CI])					
Month 12	--	-1.7 (4.20) [-9.9, 6.6]	-22.8 (4.76) [-32.2, -13.4]			
Month 24	--	-0.5 (3.94) [-8.3, 7.2]	-32.1 (5.36) [-42.6, -21.6]			

Month 36	--	5.8 (4.04) [-2.1, 13.7]	-35.6 (5.41) [-46.2, -24.9]			
Month 48	--	8.6 (4.45) [-0.1, 17.4]	-36.1 (6.02) [-47.9, -24.3]			
Health Outcomes: Medical resource utilization						
(i) Fewer unscheduled outpatient visits related to AUR or BPH-related surgery were made to the general practitioner / urologist in the combination therapy group compared with either monotherapy group.						
(ii) For unscheduled visits related to AUR made during the 4-year treatment period, 61.9% and 14.8% fewer visits were made in the combination therapy group compared with the tamsulosin and dutasteride monotherapy groups, respectively.						
(iii) For unscheduled visits related to BPH-related surgery made during the 4-year treatment period, 67.1% and 40.4% fewer visits were made in the combination therapy group compared with the tamsulosin and dutasteride monotherapy groups, respectively.						
Health Outcomes: Changes from Baseline in BII (LOCF Analysis)						
	Adjusted Mean Change From Baseline (SE)					
	N	Comb	N	Dutasteride	N	Tamsulosin
Month 12	1574	-1.9 (0.06)	1593	-1.5 (0.06)	1582	-1.6 (0.06)
Month 24	1574	-2.1 (0.07)	1593	-1.7 (0.07)	1582	-1.5 (0.07)
Month 36	1574	-2.2 (0.07)	1593	-1.8 (0.07)	1582	-1.3 (0.07)
Month 48	1574	-2.2 (0.07)	1593	-1.8 (0.07)	1582	-1.2 (0.07)
	Adjusted mean difference (combination therapy minus monotherapy (SE) [95% CI])					
Month 12	--			-0.38 (0.088) [-0.55,-0.21]		-0.33 (0.088) [-0.51,-0.16]
Month 24	--			-0.34 (0.092) [-0.52,-0.16]		-0.62 (0.092) [-0.80,-0.44]
Month 36	--			-0.36 (0.095) [-0.55,-0.18]		-0.85 (0.096) [-1.04,-0.66]
Month 48	--			-0.32 (0.098) [-0.51,-0.13]		-0.94 (0.098) [-1.13,-0.75]
Health Outcomes: Changes from Baseline in BHS (LOCF Analysis)						
	Adjusted Mean Change From Baseline (SE)					
	N	Comb	N	Dutasteride	N	Tamsulosin
Month 12	1575	-1.2 (0.03)	1592	-1.0 (0.03)	1583	-1.0 (0.03)
Month 24	1575	-1.4 (0.03)	1592	-1.1 (0.03)	1583	-1.1 (0.03)
Month 36	1575	-1.5 (0.03)	1592	-1.2 (0.03)	1583	-1.1 (0.03)
Month 48	1575	-1.5 (0.03)	1592	-1.3 (0.03)	1583	-1.1 (0.03)
	Adjusted mean difference (combination therapy minus monotherapy (SE) [95% CI])					
Month 12	--			-0.25 (0.043) [-0.33,-0.16]		-0.18 (0.043) [-0.26,-0.09]
Month 24	--			-0.23 (0.045) [-0.32,-0.14]		-0.30 (0.045) [-0.39,-0.21]
Month 36	--			-0.24 (0.046) [-0.33,-0.15]		-0.39 (0.046) [-0.48,-0.30]
Month 48	--			-0.23 (0.047) [-0.32,-0.13]		-0.46 (0.047) [-0.55,-0.37]
Health Outcomes: PPSM						
Combination therapy was significantly superior to both monotherapies for all 12 questions of the PPSM at 4 years, with the exception of change in pain prior to urination (Q5) for combination therapy versus tamsulosin monotherapy.						
Safety Results: Treatment-emergent AEs and SAEs were defined as AEs and SAEs with onset on or after randomization (or missing onset of treatment date), and included data from the 16-week safety follow-up period.						
		Combination N=1610	Dutasteride N=1623	Tamsulosin N=1611		
Most Frequent Adverse Events – On-Therapy		n (%)	n (%)	n (%)		
Subjects with any AE(s), n (%)		1182 (73)	1182 (73)	1167 (72)		

Erectile dysfunction	167 (10)	147 (9)	109 (7)
Hypertension	137 (9)	150 (9)	144 (9)
Nasopharyngitis	134 (8)	130 (8)	149 (9)
Back pain	109 (7)	89 (5)	113 (7)
Bronchitis	80 (5)	75 (5)	70 (4)
Influenza	77 (5)	75 (5)	83 (5)
Upper respiratory tract infection	77 (5)	55 (3)	57 (4)
Retrograde ejaculation	75 (5)	11 (<1)	19 (1)
Libido decreased	71 (4)	57 (4)	31 (2)
Arthralgia	70 (4)	57 (4)	68 (4)
Diarrhoea	67 (4)	53 (3)	48 (3)
Dizziness	61 (4)	63 (4)	69 (4)
Osteoarthritis	52 (3)	56 (3)	43 (3)
Hypercholesterolaemia	44 (3)	62 (4)	53 (3)
Prostate cancer	37 (2)	41 (3)	63 (4)
Headache	32 (2)	68 (4)	46 (3)
	Combination N=1610	Dutasteride N=1623	Tamsulosin N=1611
	n (%) [related]	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%) [related]	276 (17) [12]	311 (19) [11]	313 (19) [12]
Prostate cancer	20 (1) [0]	17 (1) [1]	25 (2) [0]
Coronary artery disease	14 (<1) [2]	14 (<1) [2]	15 (<1) [1]
Angina pectoris	14 (<1) [0]	13 (<1) [1]	15 (<1) [1]
Pneumonia	13 (<1) [0]	8 (<1) [0]	6 (<1) [0]
Myocardial infarction	11 (<1) [0]	18 (<1) [0]	10 (<1) [1]
Atrial fibrillation	10 (<1) [0]	7 (<1) [0]	9 (<1) [0]
Osteoarthritis	9 (<1) [0]	13 (<1) [0]	11 (<1) [0]
Cerebrovascular accident	8 (<1) [0]	10 (<1) [0]	6 (<1) [1]
Bladder cancer	6 (<1) [1]	5 (<1) [0]	4 (<1) [0]
Syncope	6 (<1) [1]	1 (<1) [1]	3 (<1) [0]
Transient ischaemic attack	5 (<1) [0]	5 (<1) [0]	4 (<1) [0]
Dyspnoea	5 (<1) [0]	4 (<1) [0]	1 (<1) [0]
Abdominal pain	5 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Coronary artery stenosis	4 (<1) [1]	5 (<1) [1]	2 (<1) [0]
Inguinal hernia	4 (<1) [0]	17 (1) [0]	11 (<1) [0]
Cholelithiasis	4 (<1) [0]	6 (<1) [0]	6 (<1) [0]
Pulmonary embolism	4 (<1) [0]	3 (<1) [0]	3 (<1) [0]
Hypertension	4 (<1) [0]	3 (<1) [0]	8 (<1) [1]
Renal failure acute	4 (<1) [0]	2 (<1) [0]	3 (<1) [0]
Femur fracture	4 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Chronic obstructive pulmonary disease	4 (<1) [0]	1 (<1) [0]	3 (<1) [0]
Acute myocardial infarction	4 (<1) [0]	0	3 (<1) [0]
Cardiac failure congestive	4 (<1) [0]	0	1 (<1) [0]
Dehydration	3 (<1) [1]	2 (<1) [0]	0
Colon cancer	3 (<1) [0]	9 (<1) [0]	3 (<1) [0]
Myocardial ischaemia	3 (<1) [0]	3 (<1) [0]	3 (<1) [0]
Acute coronary syndrome	3 (<1) [0]	3 (<1) [0]	1 (<1) [0]
Bradycardia	3 (<1) [0]	2 (<1) [1]	0
Cellulitis	3 (<1) [0]	3 (<1) [0]	0
Cholecystitis acute	3 (<1) [0]	3 (<1) [0]	4 (<1) [0]
Aortic aneurysm	3 (<1) [0]	2 (<1) [0]	1 (<1) [0]
Cholecystitis	3 (<1) [0]	2 (<1) [0]	0
Urinary tract infection	3 (<1) [0]	1 (<1) [0]	3 (<1) [0]
Hip fracture	3 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Nasal polyps	3 (<1) [0]	1 (<1) [0]	0

Colon neoplasm	3 (<1) [0]	0	1 (<1) [0]
Cerebral ischaemia	3 (<1) [0]	0	1 (<1) [0]
Tibia fracture	3 (<1) [0]	0	2 (<1) [0]
Hypotension	2 (<1) [2]	0	1 (<1) [0]
Gastric ulcer	2 (<1) [1]	1 (<1) [0]	1 (<1) [0]
Loss of consciousness	2 (<1) [1]	0	0
Urinary retention	2 (<1) [0]	6 (<1) [0]	15 (<1) [0]
Calculus ureteric	2 (<1) [0]	4 (<1) [0]	4 (<1) [0]
Non-cardiac chest pain	2 (<1) [0]	4 (<1) [0]	0
Rotator cuff syndrome	2 (<1) [0]	3 (<1) [0]	2 (<1) [0]
Aortic stenosis	2 (<1) [0]	2 (<1) [0]	1 (<1) [0]
Cataract	2 (<1) [0]	2 (<1) [0]	4 (<1) [0]
Malignant melanoma	2 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Head injury	2 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Arthralgia	2 (<1) [0]	1 (<1) [0]	3 (<1) [0]
Arthritis	2 (<1) [0]	1 (<1) [0]	0
Back pain	2 (<1) [0]	1 (<1) [0]	0
Depression	2 (<1) [0]	1 (<1) [0]	0
Cardiac failure	2 (<1) [0]	0	3 (<1) [0]
Pancreatic carcinoma	2 (<1) [0]	0	1 (<1) [0]
Pancreatitis	2 (<1) [0]	0	2 (<1) [1]
Rectal polyp	2 (<1) [0]	0	0
Bronchitis	2 (<1) [0]	0	3 (<1) [0]
Lumbar vertebral fracture	2 (<1) [0]	0	0
Asthma	2 (<1) [0]	0	1 (<1) [0]
Peripheral ischaemia	2 (<1) [0]	0	0
Hydrocele	2 (<1) [0]	0	0
Renal cell carcinoma	1 (<1) [1]	3 (<1) [0]	0
Myeloid leukaemia	1 (<1) [1]	0	1 (<1) [0]
Hepatic mass	1 (<1) [1]	0	0
Eye haemorrhage	1 (<1) [1]	0	0
Intervertebral disc protrusion	1 (<1) [0]	6 (<1) [0]	1 (<1) [0]
Sick sinus syndrome	1 (<1) [0]	4 (<1) [0]	0
Colonic polyp	1 (<1) [0]	4 (<1) [0]	1 (<1) [0]
Renal colic	1 (<1) [0]	4 (<1) [0]	0
Angina unstable	1 (<1) [0]	3 (<1) [0]	4 (<1) [0]
Coronary artery occlusion	1 (<1) [0]	3 (<1) [0]	1 (<1) [0]
Rectal cancer	1 (<1) [0]	3 (<1) [0]	1 (<1) [0]
Cerebral infarction	1 (<1) [0]	3 (<1) [0]	2 (<1) [0]
Dizziness	1 (<1) [0]	2 (<1) [1]	1 (<1) [1]
Nephrolithiasis	1 (<1) [0]	3 (<1) [0]	1 (<1) [0]
Renal failure	1 (<1) [0]	3 (<1) [0]	0
Supraventricular tachycardia	1 (<1) [0]	2 (<1) [0]	4 (<1) [1]
Lung neoplasm malignant	1 (<1) [0]	2 (<1) [0]	2 (<1) [0]
Bladder transitional cell carcinoma	1 (<1) [0]	2 (<1) [0]	1 (<1) [0]
Rectal haemorrhage	1 (<1) [0]	2 (<1) [0]	0
Lobar pneumonia	1 (<1) [0]	2 (<1) [0]	1 (<1) [0]
Cartilage injury	1 (<1) [0]	2 (<1) [0]	0
Cervical vertebral fracture	1 (<1) [0]	2 (<1) [0]	0
Arteriosclerosis	1 (<1) [0]	2 (<1) [0]	0
Pyrexia	1 (<1) [0]	2 (<1) [0]	2 (<1) [0]
Hyponatraemia	1 (<1) [0]	2 (<1) [0]	2 (<1) [0]
Anxiety	1 (<1) [0]	2 (<1) [0]	0
Atrial flutter	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Mitral valve incompetence	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]

Ventricular extrasystoles	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Ventricular tachycardia	1 (<1) [0]	1 (<1) [0]	0
Lymphoma	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Pancreatitis acute	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Abdominal hernia	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Gastric haemorrhage	1 (<1) [0]	1 (<1) [0]	0
Intestinal obstruction	1 (<1) [0]	1 (<1) [0]	0
Carotid artery stenosis	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Tendon rupture	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Fibula fracture	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Contusion	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Post procedural haemorrhage	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Wound	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Wound dehiscence	1 (<1) [0]	1 (<1) [0]	0
Spinal column stenosis	1 (<1) [0]	1 (<1) [0]	4 (<1) [0]
Flank pain	1 (<1) [0]	1 (<1) [0]	0
Lumbar spinal stenosis	1 (<1) [0]	1 (<1) [0]	0
Haematuria	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Hypoxia	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Aortic aneurysm rupture	1 (<1) [0]	1 (<1) [0]	0
Aortic dissection	1 (<1) [0]	1 (<1) [0]	0
Peripheral vascular disorder	1 (<1) [0]	1 (<1) [0]	0
Varicose vein	1 (<1) [0]	1 (<1) [0]	0
Deep vein thrombosis	1 (<1) [0]	1 (<1) [0]	0
Chest pain	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Retinal detachment	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Bipolar disorder	1 (<1) [0]	1 (<1) [0]	0
Pericardial effusion	1 (<1) [0]	0	1 (<1) [0]
Cardiac asthma	1 (<1) [0]	0	0
Cardiac failure chronic	1 (<1) [0]	0	0
Cardio-respiratory arrest	1 (<1) [0]	0	0
Coronary artery aneurysm	1 (<1) [0]	0	0
Cardiovascular deconditioning	1 (<1) [0]	0	0
Basal cell carcinoma	1 (<1) [0]	0	1 (<1) [0]
Lung adenocarcinoma	1 (<1) [0]	0	1 (<1) [0]
Oesophageal carcinoma	1 (<1) [0]	0	1 (<1) [0]
Adenocarcinoma	1 (<1) [0]	0	0
Bladder cancer recurrent	1 (<1) [0]	0	0
Bronchial carcinoma	1 (<1) [0]	0	0
Central nervous system lymphoma	1 (<1) [0]	0	0
Metastases to bone	1 (<1) [0]	0	0
Multiple myeloma	1 (<1) [0]	0	0
Tracheal cancer	1 (<1) [0]	0	0
Renal oncocytoma	1 (<1) [0]	0	0
Bladder transitional cell carcinoma stage III	1 (<1) [0]	0	0
Abdominal pain upper	1 (<1) [0]	0	1 (<1) [0]
Duodenal ulcer	1 (<1) [0]	0	1 (<1) [0]
Gastritis	1 (<1) [0]	0	1 (<1) [0]
Gastrooesophageal reflux disease	1 (<1) [0]	0	1 (<1) [0]
Diarrhoea	1 (<1) [0]	0	0
Gastritis haemorrhagic	1 (<1) [0]	0	0
Mallory-Weiss syndrome	1 (<1) [0]	0	0
Volvulus	1 (<1) [0]	0	0
Vomiting	1 (<1) [0]	0	0
Intra-abdominal haemorrhage	1 (<1) [0]	0	0

Urosepsis	1 (<1) [0]	0	3 (<1) [0]
Bronchopneumonia	1 (<1) [0]	0	1 (<1) [0]
Device related infection	1 (<1) [0]	0	1 (<1) [0]
Cystitis	1 (<1) [0]	0	0
Endocarditis bacterial	1 (<1) [0]	0	0
Gastroenteritis	1 (<1) [0]	0	0
Gastroenteritis salmonella	1 (<1) [0]	0	0
Wound infection	1 (<1) [0]	0	0
Anal abscess	1 (<1) [0]	0	0
Cholecystitis infective	1 (<1) [0]	0	0
Cellulitis of male external genital organ	1 (<1) [0]	0	0
Gastroenteritis norovirus	1 (<1) [0]	0	0
Ischaemic stroke	1 (<1) [0]	0	4 (<1) [0]
Dementia Alzheimer's type	1 (<1) [0]	0	0
Extrapyramidal disorder	1 (<1) [0]	0	0
Neuritis	1 (<1) [0]	0	0
Psychomotor hyperactivity	1 (<1) [0]	0	0
Sciatica	1 (<1) [0]	0	0
Senile dementia	1 (<1) [0]	0	0
Carotid artery occlusion	1 (<1) [0]	0	0
Lumbar radiculopathy	1 (<1) [0]	0	0
Radicular pain	1 (<1) [0]	0	0
Ischaemic cerebral infarction	1 (<1) [0]	0	0
Nerve root compression	1 (<1) [0]	0	0
Rib fracture	1 (<1) [0]	0	2 (<1) [0]
Hand fracture	1 (<1) [0]	0	0
Muscle rupture	1 (<1) [0]	0	0
Wrist fracture	1 (<1) [0]	0	0
Anaemia postoperative	1 (<1) [0]	0	0
Face injury	1 (<1) [0]	0	0
Device failure	1 (<1) [0]	0	0
Medical device complication	1 (<1) [0]	0	0
Skin laceration	1 (<1) [0]	0	0
Limb injury	1 (<1) [0]	0	0
Skull fracture	1 (<1) [0]	0	0
Chest injury	1 (<1) [0]	0	0
Upper limb fracture	1 (<1) [0]	0	0
Limb traumatic amputation	1 (<1) [0]	0	0
Lower limb fracture	1 (<1) [0]	0	0
Neck pain	1 (<1) [0]	0	0
Nose deformity	1 (<1) [0]	0	0
Calculus urinary	1 (<1) [0]	0	1 (<1) [0]
Bladder neck obstruction	1 (<1) [0]	0	0
Renal failure chronic	1 (<1) [0]	0	0
Haemothorax	1 (<1) [0]	0	0
Nasal septum deviation	1 (<1) [0]	0	0
Peripheral artery aneurysm	1 (<1) [0]	0	1 (<1) [0]
Malignant hypertension	1 (<1) [0]	0	0
Orthostatic hypotension	1 (<1) [0]	0	0
Phebitis	1 (<1) [0]	0	0
Haemorrhage	1 (<1) [0]	0	0
Aortic dilatation	1 (<1) [0]	0	0
Arterial disorder	1 (<1) [0]	0	0
Prostatitis	1 (<1) [0]	0	1 (<1) [0]
Epididymal cyst	1 (<1) [0]	0	0

Priapism	1 (<1) [0]	0	0
Asthenia	1 (<1) [0]	0	0
Macular degeneration	1 (<1) [0]	0	2 (<1) [0]
Diabetes mellitus inadequate control	1 (<1) [0]	0	0
Aggression	1 (<1) [0]	0	0
Confusional state	1 (<1) [0]	0	0
Delirium	1 (<1) [0]	0	0
Haemolytic anaemia	1 (<1) [0]	0	0
Thrombocytopenia	1 (<1) [0]	0	0
Aplasia	1 (<1) [0]	0	0
Hereditary sideroblastic anaemia	1 (<1) [0]	0	0
Vertigo	1 (<1) [0]	0	0
Vestibular disorder	1 (<1) [0]	0	0
Sudden hearing loss	1 (<1) [0]	0	0
Arrhythmia	0	3 (<1) [0]	1 (<1) [0]
Gastric cancer	0	3 (<1) [0]	0
Balance disorder	0	2 (<1) [1]	0
Calculus bladder	0	3 (<1) [0]	4 (<1) [0]
Sleep apnoea syndrome	0	3 (<1) [0]	0
Aortic valve incompetence	0	2 (<1) [0]	0
Pericarditis	0	2 (<1) [0]	0
AV dissociation	0	1 (<1) [1]	0
Chronic left ventricular failure	0	1 (<1) [1]	0
Bladder neoplasm	0	2 (<1) [0]	0
Prostate cancer stage I	0	1 (<1) [1]	0
Ileus	0	2 (<1) [0]	1 (<1) [0]
Anal fissure	0	2 (<1) [0]	0
Duodenal ulcer haemorrhage	0	2 (<1) [0]	0
Diverticulitis	0	2 (<1) [0]	2 (<1) [0]
Appendicitis	0	2 (<1) [0]	0
Arthritis bacterial	0	2 (<1) [0]	0
Convulsion	0	2 (<1) [0]	0
Epilepsy	0	2 (<1) [0]	0
Parkinson's disease	0	2 (<1) [0]	0
Spinal fracture	0	2 (<1) [0]	1 (<1) [0]
Sternal fracture	0	2 (<1) [0]	0
Pneumonia aspiration	0	2 (<1) [0]	0
Jaundice	0	1 (<1) [1]	0
Benign prostatic hyperplasia	0	2 (<1) [0]	10 (<1) [0]
Anaemia	0	2 (<1) [0]	1 (<1) [0]
Intraocular pressure increased	0	1 (<1) [1]	0
Aortic valve disease mixed	0	1 (<1) [0]	0
Tricuspid valve incompetence	0	1 (<1) [0]	0
Hepatic neoplasm malignant	0	1 (<1) [0]	2 (<1) [0]
Acute myeloid leukaemia	0	1 (<1) [0]	1 (<1) [0]
Benign colonic neoplasm	0	1 (<1) [0]	0
Cholesteatoma	0	1 (<1) [0]	0
Malignant palate neoplasm	0	1 (<1) [0]	0
Metastases to liver	0	1 (<1) [0]	0
Neoplasm malignant	0	1 (<1) [0]	0
Squamous cell carcinoma	0	1 (<1) [0]	0
Tonsil cancer	0	1 (<1) [0]	0
Transitional cell carcinoma	0	1 (<1) [0]	0
Colon cancer metastatic	0	1 (<1) [0]	0
Retroperitoneal neoplasm	0	1 (<1) [0]	0

Metastatic neoplasm	0	1 (<1) [0]	0
Urinary tract neoplasm	0	1 (<1) [0]	0
Colorectal cancer	0	1 (<1) [0]	0
Salivary gland cancer	0	1 (<1) [0]	0
Gastric neoplasm	0	1 (<1) [0]	0
Haemorrhoids	0	1 (<1) [0]	2 (<1) [0]
Gastric ulcer haemorrhage	0	1 (<1) [0]	1 (<1) [0]
Gastrointestinal haemorrhage	0	1 (<1) [0]	1 (<1) [0]
Inguinal hernia, obstructive	0	1 (<1) [0]	1 (<1) [0]
Colitis	0	1 (<1) [0]	0
Crohn's disease	0	1 (<1) [0]	0
Diverticulum	0	1 (<1) [0]	0
Haematemesis	0	1 (<1) [0]	0
Haematochezia	0	1 (<1) [0]	0
Large intestine perforation	0	1 (<1) [0]	0
Oesophagitis	0	1 (<1) [0]	0
Small intestinal obstruction	0	1 (<1) [0]	0
Umbilical hernia	0	1 (<1) [0]	0
Pharyngoesophageal diverticulum	0	1 (<1) [0]	0
Intestinal haemorrhage	0	1 (<1) [0]	0
Appendix disorder	0	1 (<1) [0]	0
Sepsis	0	1 (<1) [0]	2 (<1) [0]
Upper respiratory tract infection	0	1 (<1) [0]	2 (<1) [0]
Viral infection	0	1 (<1) [0]	1 (<1) [0]
Abscess intestinal	0	1 (<1) [0]	0
Amoebiasis	0	1 (<1) [0]	0
Ear infection	0	1 (<1) [0]	0
Epiglottitis	0	1 (<1) [0]	0
Gangrene	0	1 (<1) [0]	0
Gastroenteritis Escherichia coli	0	1 (<1) [0]	0
Infective myositis	0	1 (<1) [0]	0
Nasopharyngitis	0	1 (<1) [0]	0
Pneumonia streptococcal	0	1 (<1) [0]	0
Streptococcal sepsis	0	1 (<1) [0]	0
Escherichia urinary tract infection	0	1 (<1) [0]	0
Pseudomonas infection	0	1 (<1) [0]	0
Biliary tract infection	0	1 (<1) [0]	0
Epidemic nephropathy	0	1 (<1) [0]	0
Cerebral haemorrhage	0	1 (<1) [0]	1 (<1) [0]
Grand mal convulsion	0	1 (<1) [0]	1 (<1) [0]
Altered state of consciousness	0	1 (<1) [0]	0
Brain stem ischaemia	0	1 (<1) [0]	0
Dysarthria	0	1 (<1) [0]	0
Hemiparesis	0	1 (<1) [0]	0
Monoplegia	0	1 (<1) [0]	0
Intracranial hypotension	0	1 (<1) [0]	0
Cerebral cyst	0	1 (<1) [0]	0
Subdural haematoma	0	1 (<1) [0]	3 (<1) [0]
Concussion	0	1 (<1) [0]	1 (<1) [0]
Radius fracture	0	1 (<1) [0]	1 (<1) [0]
Spinal compression fracture	0	1 (<1) [0]	1 (<1) [0]
Ulna fracture	0	1 (<1) [0]	1 (<1) [0]
Accidental overdose	0	1 (<1) [0]	0
Ankle fracture	0	1 (<1) [0]	0
Cardiac pacemaker malfunction	0	1 (<1) [0]	0

Clavicle fracture	0	1 (<1) [0]	0
Epicondylitis	0	1 (<1) [0]	0
Fall	0	1 (<1) [0]	0
Patella fracture	0	1 (<1) [0]	0
Seroma	0	1 (<1) [0]	0
Vascular graft occlusion	0	1 (<1) [0]	0
Postoperative ileus	0	1 (<1) [0]	0
Cervical spinal stenosis	0	1 (<1) [0]	0
Muscular weakness	0	1 (<1) [0]	0
Osteoporosis	0	1 (<1) [0]	0
Polymyalgia rheumatica	0	1 (<1) [0]	0
Rheumatoid arthritis	0	1 (<1) [0]	0
Musculoskeletal discomfort	0	1 (<1) [0]	0
Bladder obstruction	0	1 (<1) [0]	0
Hydronephrosis	0	1 (<1) [0]	0
Micturition disorder	0	1 (<1) [0]	0
Nephrotic syndrome	0	1 (<1) [0]	0
Urinary bladder polyp	0	1 (<1) [0]	0
Ureteral polyp	0	1 (<1) [0]	0
Pneumothorax	0	1 (<1) [0]	3 (<1) [0]
Haemoptysis	0	1 (<1) [0]	1 (<1) [0]
Acute pulmonary oedema	0	1 (<1) [0]	0
Respiratory failure	0	1 (<1) [0]	0
Sinus polyp	0	1 (<1) [0]	0
Allergic granulomatous angiitis	0	1 (<1) [0]	0
Bronchial hyperreactivity	0	1 (<1) [0]	0
Circulatory collapse	0	1 (<1) [0]	1 (<1) [1]
Hypertensive crisis	0	1 (<1) [0]	0
Thrombophlebitis	0	1 (<1) [0]	0
Venous thrombosis	0	1 (<1) [0]	0
Aortic disorder	0	1 (<1) [0]	0
Bile duct stone	0	1 (<1) [0]	1 (<1) [0]
Cholecystitis chronic	0	1 (<1) [0]	1 (<1) [0]
Prostatic intraepithelial neoplasia	0	1 (<1) [0]	0
Prostatism	0	1 (<1) [0]	0
Retinal tear	0	1 (<1) [0]	0
Vitreous haemorrhage	0	1 (<1) [0]	0
Hypercalcaemia	0	1 (<1) [0]	0
Mental status changes	0	1 (<1) [0]	0
Pernicious anaemia	0	1 (<1) [0]	0
Alanine aminotransferase increased	0	1 (<1) [0]	0
Aspartate aminotransferase increased	0	1 (<1) [0]	0
ChestX-ray abnormal	0	1 (<1) [0]	0
Heart rate irregular	0	1 (<1) [0]	0
Blood alkaline phosphatase increased	0	1 (<1) [0]	0
Purpura senile	0	1 (<1) [0]	0
Stevens-Johnson syndrome	0	1 (<1) [0]	0
Goitre	0	1 (<1) [0]	0
Atrioventricular block	0	0	1 (<1) [0]
Atrioventricular block complete	0	0	1 (<1) [0]
Cardiac tamponade	0	0	1 (<1) [0]
Left ventricular failure	0	0	1 (<1) [0]
Mitral valve prolapse	0	0	1 (<1) [0]
Tachycardia	0	0	1 (<1) [1]
Congestive cardiomyopath	0	0	1 (<1) [0]

Cardiac valve disease	0	0	1 (<1) [0]
Brain neoplasm	0	0	3 (<1) [0]
Renal cancer	0	0	2 (<1) [0]
Thyroid neoplasm	0	0	2 (<1) [0]
Laryngeal cancer	0	0	1 (<1) [0]
Malignant neoplasm of ampulla of Vater	0	0	1 (<1) [0]
Mesothelioma	0	0	1 (<1) [0]
Metastatic pain	0	0	1 (<1) [0]
Non-small cell lung cancer stage I	0	0	1 (<1) [0]
Retinal melanoma	0	0	1 (<1) [0]
Urinary bladder adenoma	0	0	1 (<1) [0]
Hepatic cancer metastatic	0	0	1 (<1) [0]
Thyroid cancer	0	0	1 (<1) [0]
Bladder transitional cell carcinoma stage II	0	0	1 (<1) [0]
Abdominal distension	0	0	1 (<1) [0]
Abdominal rigidity	0	0	1 (<1) [0]
Anal fistula	0	0	1 (<1) [0]
Barrett's oesophagus	0	0	1 (<1) [0]
Diverticulum intestinal	0	0	1 (<1) [0]
Duodenitis	0	0	1 (<1) [0]
Dysphagia	0	0	1 (<1) [0]
Gastric ulcer perforation	0	0	1 (<1) [0]
Melaena	0	0	1 (<1) [0]
Peptic ulcer haemorrhage	0	0	1 (<1) [0]
Proctitis	0	0	1 (<1) [0]
Lower gastrointestinal haemorrhage	0	0	1 (<1) [0]
Mechanical ileus	0	0	1 (<1) [0]
Bowel movement irregularity	0	0	1 (<1) [0]
Erosive oesophagitis	0	0	1 (<1) [0]
Anal prolapse	0	0	1 (<1) [0]
Inguinal hernia strangulated	0	0	1 (<1) [0]
Respiratory tract infection	0	0	2 (<1) [0]
Bronchiectasis	0	0	1 (<1) [0]
Carbuncle	0	0	1 (<1) [0]
Chronic sinusitis	0	0	1 (<1) [0]
Dengue fever	0	0	1 (<1) [0]
Localised infection	0	0	1 (<1) [0]
Orchitis	0	0	1 (<1) [0]
Osteomyelitis	0	0	1 (<1) [0]
Prostatic abscess	0	0	1 (<1) [0]
Pyelonephritis acute	0	0	1 (<1) [0]
Salmonellosis	0	0	1 (<1) [0]
Subcutaneous abscess	0	0	1 (<1) [0]
Tinea pedis	0	0	1 (<1) [0]
Postoperative abscess	0	0	1 (<1) [0]
Central line infection	0	0	1 (<1) [0]
Pseudomonas sepsis	0	0	1 (<1) [0]
Implant site infection	0	0	1 (<1) [0]
Post procedural sepsis	0	0	1 (<1) [0]
Autonomic nervous system imbalance	0	0	1 (<1) [0]
Encephalopathy	0	0	1 (<1) [0]
Haemorrhage intracranial	0	0	1 (<1) [0]
Multiple sclerosis	0	0	1 (<1) [0]
Presyncope	0	0	1 (<1) [0]
Somnolence	0	0	1 (<1) [0]

Thrombotic stroke	0	0	1 (<1) [0]
Cerebral arteriosclerosis	0	0	1 (<1) [0]
Road traffic accident	0	0	2 (<1) [0]
Extradural haematoma	0	0	1 (<1) [0]
Vascular pseudoaneurysm	0	0	1 (<1) [0]
Traumatic brain injury	0	0	1 (<1) [0]
Joint injury	0	0	1 (<1) [0]
Pelvic fracture	0	0	1 (<1) [0]
Lung injury	0	0	1 (<1) [0]
Procedural hypotension	0	0	1 (<1) [0]
Post procedural haematoma	0	0	1 (<1) [0]
Post procedural constipation	0	0	1 (<1) [0]
Psoriatic arthropathy	0	0	1 (<1) [0]
Spinal osteoarthritis	0	0	1 (<1) [0]
Foot deformity	0	0	1 (<1) [0]
Intervertebral disc degeneration	0	0	1 (<1) [0]
Spondylolisthesis	0	0	1 (<1) [0]
Dysuria	0	0	2 (<1) [0]
Urine flow decreased	0	0	2 (<1) [0]
Urethral stenosis	0	0	2 (<1) [0]
Urinary bladder haemorrhage	0	0	1 (<1) [0]
Urinary hesitation	0	0	1 (<1) [0]
Urinary tract disorder	0	0	1 (<1) [0]
Urinary tract obstruction	0	0	1 (<1) [0]
Renal artery arteriosclerosis	0	0	1 (<1) [0]
Pleural effusion	0	0	5 (<1) [0]
Pulmonary oedema	0	0	2 (<1) [0]
Acute respiratory failure	0	0	1 (<1) [0]
Lung disorder	0	0	1 (<1) [0]
Pleurisy	0	0	1 (<1) [0]
Pulmonary hypertension	0	0	1 (<1) [0]
Asthmatic crisis	0	0	1 (<1) [0]
Peripheral arterial occlusive disease	0	0	2 (<1) [0]
Arteriovenous fistula	0	0	1 (<1) [0]
Venous stenosis	0	0	1 (<1) [0]
Arterial stenosis limb	0	0	1 (<1) [0]
Cholangitis acute	0	0	1 (<1) [0]
Hepatitis	0	0	1 (<1) [1]
Hydrocholecystis	0	0	1 (<1) [0]
Epididymitis	0	0	1 (<1) [0]
Fatigue	0	0	1 (<1) [0]
Local swelling	0	0	1 (<1) [0]
Malaise	0	0	1 (<1) [0]
Implant site erosion	0	0	1 (<1) [0]
Glaucoma	0	0	1 (<1) [1]
Hyperkalaemia	0	0	1 (<1) [0]
Idiopathic thrombocytopenic purpura	0	0	1 (<1) [0]
Lymphadenopathy	0	0	1 (<1) [0]
Coagulation factor decreased	0	0	1 (<1) [0]
Electrocardiogram abnormal	0	0	1 (<1) [0]
Prostatic specific antigen increased	0	0	1 (<1) [0]
Deafness	0	0	1 (<1) [0]
Hyperhidrosis	0	0	2 (<1) [0]
	n (%) [related]	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%) [related]	40 (2) [0]	39 (2) [1]	46 (3) [0]

Myocardial infarction	5 (<1) [0]	7 (<1) [1]	10 (<1) [0]
Cerebrovascular accident	3 (<1) [0]	5 (<1) [0]	2 (<1) [0]
Cardiac failure	3 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Acute myocardial infarction	3 (<1) [0]	1 (<1) [0]	0
Colon cancer	3 (<1) [0]	0	2 (<1) [0]
Cardiac arrest	2 (<1) [0]	0	1 (<1) [0]
Lung neoplasm malignant	2 (<1) [0]	0	3 (<1) [0]
Pancreatic carcinoma	2 (<1) [0]	0	1 (<1) [0]
Hepatic neoplasm malignant	1 (<1) [0]	1 (<1) [0]	0
Multi-organ failure	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Road traffic accident	1 (<1) [0]	1 (<1) [0]	0
Sepsis	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Completed suicide	1 (<1) [0]	1 (<1) [0]	0
Coronary artery insufficiency	1 (<1) [0]	0	1 (<1) [0]
Atrial fibrillation	1 (<1) [0]	0	0
Cardio-respiratory arrest	1 (<1) [0]	0	0
Coronary artery thrombosis	1 (<1) [0]	0	0
Hypertensive cardiomyopathy	1 (<1) [0]	0	0
Glioblastoma multiforme	1 (<1) [0]	0	0
Large intestine carcinoma	1 (<1) [0]	0	0
Metastasis to central nervous system	1 (<1) [0]	0	0
Prostate cancer	1 (<1) [0]	0	0
Death	1 (<1) [0]	0	1 (<1) [0]
Generalised oedema	1 (<1) [0]	0	0
Injury	1 (<1) [0]	0	0
Procedural complication	1 (<1) [0]	0	0
Bronchopneumonia	1 (<1) [0]	0	0
Idiopathic pulmonary fibrosis	1 (<1) [0]	0	0
Aortic aneurysm rupture	1 (<1) [0]	0	2 (<1) [0]
Renal failure acute	1 (<1) [0]	0	0
Haemolytic anaemia	1 (<1) [0]	0	0
Pneumonia	0	3 (<1) [0]	0
Metastases to liver	0	2 (<1) [0]	1 (<1) [0]
Septic shock	0	2 (<1) [0]	0
Pulmonary embolism	0	2 (<1) [0]	1 (<1) [0]
Angina pectoris	0	1 (<1) [0]	0
Arteriosclerosis coronary artery	0	1 (<1) [0]	0
Cardiopulmonary failure	0	1 (<1) [0]	0
Acute left ventricular failure	0	1 (<1) [0]	0
Pancreatic neoplasm	0	1 (<1) [0]	1 (<1) [0]
Bladder cancer	0	1 (<1) [0]	0
Bronchial carcinoma	0	1 (<1) [0]	0
Gallbladder cancer	0	1 (<1) [0]	0
Gastrointestinal carcinoma	0	1 (<1) [0]	0
Metastases to lung	0	1 (<1) [0]	0
Gastrointestinal cancer metastatic	0	1 (<1) [0]	0
Metastatic squamous cell carcinoma	0	1 (<1) [0]	0
Cerebral infarction	0	1 (<1) [0]	1 (<1) [0]
Sudden death	0	1 (<1) [0]	0
Multiple injuries	0	1 (<1) [0]	2 (<1) [0]
Diverticulitis	0	1 (<1) [0]	0
Asphyxia	0	1 (<1) [0]	0
Pulmonary oedema	0	1 (<1) [0]	0
Respiratory failure	0	1 (<1) [0]	0
Aortic dissection	0	1 (<1) [0]	0

Peritonitis	0	1 (<1) [0]	0
Lymphoma	0	0	2 (<1) [0]
Brain neoplasm benign	0	0	1 (<1) [0]
Brain neoplasm malignant	0	0	1 (<1) [0]
Myeloide leukaemia	0	0	1 (<1) [0]
Pancreatic carcinoma metastatic	0	0	1 (<1) [0]
Renal cancer	0	0	1 (<1) [0]
Cerebral haemorrhage	0	0	1 (<1) [0]
Pyrexia	0	0	1 (<1) [0]
Carbon monoxide poisoning	0	0	1 (<1) [0]
Gun shot wound	0	0	1 (<1) [0]
Traumatic haematoma	0	0	1 (<1) [0]
Pleural effusion	0	0	1 (<1) [0]
Abdominal pain	0	0	1 (<1) [0]
Gastrointestinal haemorrhage	0	0	1 (<1) [0]
Hydronephrosis	0	0	1 (<1) [0]
Renal failure	0	0	1 (<1) [0]
Granulocytopenia	0	0	1 (<1) [0]
Jaundice	0	0	1 (<1) [0]

Conclusion: Publication(s) of 4 year data pending. Citations listed are for analyses of 2 year results.