Name of Sponsor/Company: Astellas Pharma Inc. (APGD Japan)		
Name of Finished Product: ASP3550		
Name of Active Ingredient: degarelix (INN)		

Synopsis

Title of Study:

ASP3550 Phase II Study - A Maintenance-Dose-Finding Study of Three-Month Depot in Patients with Prostate Cancer -

Investigators/Coordinating Investigator:

[redacted] ([redacted]) and investigators belong to 30 medical institutes in Japan.

[redacted] ([redacted]) and two coordinating investigators.

Study Center(s):

Thirty (30) medical institutes in Japan.

Publication Based on the Study:

N/A

Study Period:
Study Initiation Date (Date of First Enrollment):

2010/10/12

Study Completion Date (Date of Last Evaluation):

2012/04/24

Phase of Development:

2

Objectives:

To assess the effect of the ASP3550 3-month regimen on the maintenance of serum testosterone suppression (≤ 0.5 ng/mL) from Day 28 to Day 364 after ASP3550 administration in patients with prostate cancer, as the primary objectives. Following secondary objectives were also studied:

- Effects of ASP3550 on serum testosterone, serum PSA, serum LH and serum FSH.
- Pharmacokinetics and concentration-response relationship of ASP3550.
- Safety of ASP3550.

Methodology:

Patients with prostate cancer fulfilling all the inclusion criteria and falling under none of the exclusion criteria received ASP3550 at a maintenance dose of 360 mg (60 mg/mL) or 480 mg (60 mg/mL) for 3 months, after giving written informed consent. For comparison of the results obtained at these maintenance doses, the study was conducted as a randomized, multicenter, open-label, uncontrolled, parallel-group study.

The initial ASP3550 dose of 240 mg (40 mg/mL) was administered subcutaneously, followed by maintenance doses of 360 mg (60 mg/mL) or 480 mg (60 mg/mL) subcutaneously every 84 days, starting on Day 28 after the initial administration, for a total of 4 doses.

Number of Patients (Planned, Enrolled and Analyzed):

Number of patients planned: 120

Number of patients randomized: 155 (SAF: 152)

Diagnosis and Main Criteria for Inclusion:

Patients with prostate cancer who require endocrine therapy were indicated. Patients fulfilling all of the following criteria at screening enrolled in the study:

- Male patients with histologically proven prostate cancer (adenocarcinoma) of all stages.
- Patients in whom endocrine treatment is indicated. Patients with rising serum PSA after having prostatectomy or radiotherapy performed with curative intention may be included.
- Patients with serum testosterone > 2.2 ng/mL at screening.
- Patients with an ECOG (Eastern Co-operative Oncology Group) P.S. (Performance Status) score of 0 to 2.
- Patients with serum PSA ≥ 2 ng/mL at screening.
- Patients with a life expectancy of at least 12 months.
- Patients of 20 years of age or older at the time of giving consent.
- Patients who provide written consent on a voluntary basis.

Test Product, Dose and Mode of Administration, Batch Numbers:

ASP3550 was supplied in lyophilized formulation for subcutaneous injection with 3 different strengths. Each vial contained 120 mg, 180 mg and 240 mg of ASP3550, respectively accompanied with 5 mL ampoules of Water for Injection.

Patients received ASP3550 subcutaneously with the initial dose of 240 mg (40 mg/mL) solution on Day 0, followed with subcutaneous maintenance dose of either 360 mg (60 mg/mL) solution or 480 mg (60 mg/mL) on Day 28, Day 112, Day 196 and Day 280.

Lot numbers: [redacted].

Duration of Treatment:

Initial dose of 240 mg in 40 mg/mL solution: Day 0
Maintenance dose of either 360 mg in 60 mg/mL solution or 480 mg in 60 mg/mL: Day 28, Day 112, Day 196 and Day 280.

Reference Product, Dose and Mode of Administration, Batch Numbers:

N/A

Criteria for Evaluation:

Primary Variable: Accumulated castration rate in the serum testosterone level from Day 28 to Day 364 of treatment was chosen for the primary variable.

Statistical Methods:

Primary Analysis for Primary Variable: Kaplan-Meier method

Summary of Results/Conclusions:

One hundred and fifty five (155) Japanese patients with prostate cancer indicated for endocrine therapy, received ASP3550 subcutaneously with the initial dose of 240 mg in 40 mg/mL solution on Day 0, followed with subcutaneous maintenance dose of either 360 mg in 60 mg/mL solution or 480 mg in 60 mg/mL on Day 28, Day 112, Day 196 and Day 280. The cumulative probability of serum testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 (FAS) in 480 mg (60 mg/mL) was 97.2% (95% CI: 0.894–0.993), and it was higher than in 360 mg (60 mg/mL): 88.3% (95% CI: 0.779–0.940). The most frequent adverse events were injection site reactions in both dose groups, but they did not cause the discontinuation of the test drug treatment. The subcutaneous administration of ASP3550 3-month regimen with the employed dosages interval was generally safe for Japanese patients with prostate cancer.

Efficacy/Pharmacokinetic Results:

The cumulative serum probability of serum testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 (FAS) was 88.3% (95% CI: 0.779–0.940) in 360 mg (60 mg/mL) and 97.2% (95% CI: 0.894–0.993) in 480 mg (60 mg/mL).

[redacted]

Safety Results:
The incidences of adverse events were 94.7% in 360 mg (60 mg/mL) and 96.1% in 480 mg (60 mg/mL).
The numbers and incidences (%) of patients with adverse events classified in Grade 3 and higher were 18 (23.7%) in 360 mg (60 mg/mL) and 14 (18.4%) in 480 mg (60 mg/mL).

The most frequent adverse events were injection site reactions in both dose groups, but they did not cause the discontinuation of the test drug treatment. The subcutaneous administration

of ASP3550 3-month regimen with the employed dosages interval was generally safe for Japanese patients with prostate cancer.

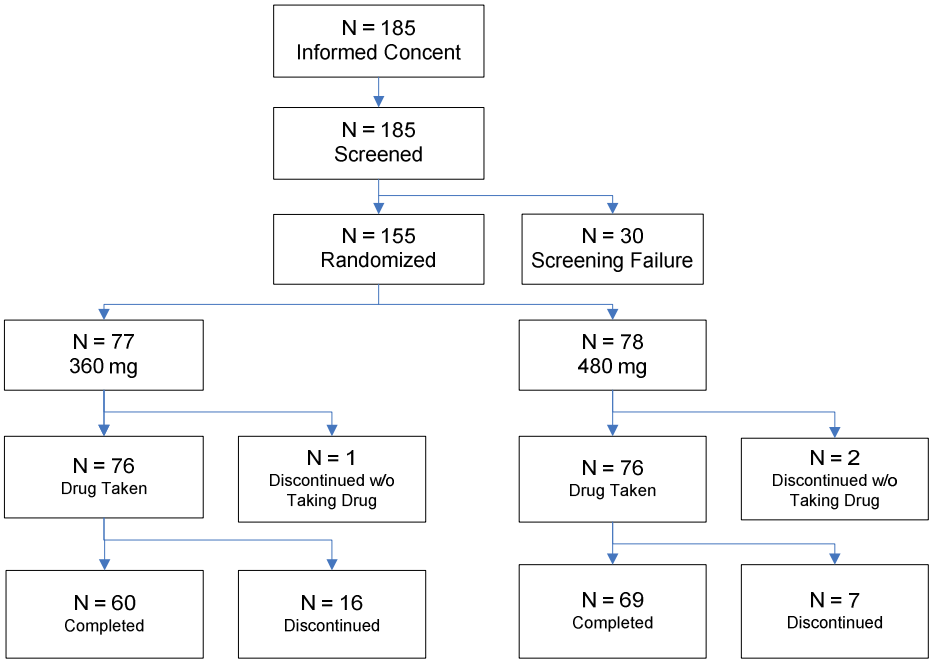
CONCLUSIONS:

The cumulative probability of serum testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 (FAS) in 480 mg (60 mg/mL) was 97.2% (95% CI: 0.894–0.993), and it was higher than in 360 mg (60 mg/mL): 88.3% (95% CI: 0.779–0.940). The most frequent adverse events were injection site reactions in both dose groups, but they did not cause the discontinuation of the test drug treatment. The subcutaneous administration of ASP3550 3-month regimen with the employed dosages interval was generally safe for Japanese patients with prostate cancer.

Date of Report:

201304/18

Figure 1 Disposition of Subjects



Source: Table 12.1.1.1, Table 12.1.1.2, Table 12.1.1.3, Table 12.1.1.4, Table 12.1.1.6

Table 1 Demographics 1, Categorical Data, FAS

Variable	Dose	360 mg	480 mg	Total
Age at Date of Informed Consent	<75	34 (45.3%)	35 (46.1%)	69 (45.7%)
	75<=	41 (54.7%)	41 (53.9%)	82 (54.3%)
	Total	75	76	151
Tobacco History - 1	No	19 (25.3%)	17 (22.4%)	36 (23.8%)
	Yes	56 (74.7%)	59 (77.6%)	115 (76.2%)
	Total	75	76	151
Tobacco History - 2	Never Used Tobacco	19 (25.3%)	17 (22.4%)	36 (23.8%)
	Former Tobacco User	43 (57.3%)	48 (63.2%)	91 (60.3%)
	Current Tobacco User	13 (17.3%)	11 (14.5%)	24 (15.9%)
	Total	75	76	151
Alcohol History - 1	No	11 (14.7%)	16 (21.1%)	27 (17.9%)
	Yes	64 (85.3%)	60 (78.9%)	124 (82.1%)
	Total	75	76	151
Alcohol History - 2	Never Used Alcohol	11 (14.7%)	16 (21.1%)	27 (17.9%)
	Former Alcohol User	14 (18.7%)	12 (15.8%)	26 (17.2%)
	Current Alcohol User	50 (66.7%)	48 (63.2%)	98 (64.9%)
	Total	75	76	151
ECOG P.S.	0	70 (93.3%)	74 (97.4%)	144 (95.4%)
	1	5 (6.7%)	2 (2.6%)	7 (4.6%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	75	76	151
Medical History (Past)	No	51 (68.0%)	46 (60.5%)	97 (64.2%)
	Yes	24 (32.0%)	30 (39.5%)	54 (35.8%)
	Total	75	76	151
Medical History (Present)	No	2 (2.7%)	3 (3.9%)	5 (3.3%)
	Yes	73 (97.3%)	73 (96.1%)	146 (96.7%)
	Total	75	76	151
Prior Treatment for Prostate Cancer (Overall)	No	68 (90.7%)	69 (90.8%)	137 (90.7%)
	Yes	7 (9.3%)	7 (9.2%)	14 (9.3%)
	Total	75	76	151
Prior Treatment for Prostate Cancer (Prostatic extirpation)	No	73 (97.3%)	74 (97.4%)	147 (97.4%)
	Yes	2 (2.7%)	2 (2.6%)	4 (2.6%)
	Total	75	76	151
Prior Treatment for Prostate Cancer (Chemoradiotherapy)	No	73 (97.3%)	74 (97.4%)	147 (97.4%)
	Yes	2 (2.7%)	2 (2.6%)	4 (2.6%)
	Total	75	76	151
Prior Treatment for Prostate Cancer (Neo Adjuvant/Adjuvant Therapy)	No	75 (100.0%)	76 (100.0%)	151 (100.0%)
	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	75	76	151
Prior Treatment for Prostate Cancer (Other Therapy)	No	75 (100.0%)	76 (100.0%)	151 (100.0%)
	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	75	76	151
Prior Treatment for Prostate Cancer (Watchful Waiting)	No	71 (94.7%)	71 (93.4%)	142 (94.0%)
	Yes	4 (5.3%)	5 (6.6%)	9 (6.0%)
	Total	75	76	151
TNM Stage/Primary Tumor (at diagnosing)	TX	0 (0.0%)	0 (0.0%)	0 (0.0%)
	T0	0 (0.0%)	0 (0.0%)	0 (0.0%)
	T1/2	48 (64.0%)	49 (64.5%)	97 (64.2%)
	T3/4	27 (36.0%)	27 (35.5%)	54 (35.8%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	75	76	151
TNM Stage/Regional Lymph Node (at diagnosing)	NX	1 (1.3%)	0 (0.0%)	1 (0.7%)
	N0	66 (88.0%)	64 (84.2%)	130 (86.1%)
	N1	8 (10.7%)	12 (15.8%)	20 (13.2%)
	Total	75	76	151
TNM Stage/Distant Metastasis (at	MX	2 (2.7%)	0 (0.0%)	2 (1.3%)

Table 1 Demographics 1, Categorical Data, FAS

Variable	Dose	360 mg	480 mg	Total
diagnosing)	M0	64 (85.3%)	65 (85.5%)	129 (85.4%)
	M1	9 (12.0%)	11 (14.5%)	20 (13.2%)
	Total	75	76	151
TNM Stage/Primary Tumor (Now)	TX	0 (0.0%)	0 (0.0%)	0 (0.0%)
	T0	0 (0.0%)	0 (0.0%)	0 (0.0%)
	T1/2	45 (60.0%)	46 (60.5%)	91 (60.3%)
	T3/4	28 (37.3%)	28 (36.8%)	56 (37.1%)
	Not Applicable†	2 (2.7%)	2 (2.6%)	4 (2.6%)
	Total	75	76	151
TNM Stage/Regional Lymph Node (Now)	NX	0 (0.0%)	0 (0.0%)	0 (0.0%)
	N0	67 (89.3%)	64 (84.2%)	131 (86.8%)
	N1	8 (10.7%)	12 (15.8%)	20 (13.2%)
	Total	75	76	151
TNM Stage/Distant Metastasis (Now)	MX	0 (0.0%)	0 (0.0%)	0 (0.0%)
	M0	66 (88.0%)	65 (85.5%)	131 (86.8%)
	M1	9 (12.0%)	11 (14.5%)	20 (13.2%)
	Total	75	76	151
Pathological Stage/pT Category	pT2	1 (50.0%)	0 (0.0%)	1 (25.0%)
	pT3MR-	1 (50.0%)	1 (50.0%)	2 (50.0%)
	pT3MR+	0 (0.0%)	1 (50.0%)	1 (25.0%)
	Not Done	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	2	2	4
Pathological Stage/pN Category	pN0	2 (100.0%)	2 (100.0%)	4 (100.0%)
	pN1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	pN2/3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Done	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	2	2	4
Histological Stage	Highly differentiated/ Gleason Scores 2-4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderately differentiated/ Gleason Scores 5-6	16 (21.3%)	12 (15.8%)	28 (18.5%)
	Poorly differentiated/ Gleason Scores 7-10	59 (78.7%)	64 (84.2%)	123 (81.5%)
	Total	75	76	151
The Stage of Prostate Cancer at Date of Registration	Localized Prostate Cancer	44 (58.7%)	44 (57.9%)	88 (58.3%)
	Locally Advanced Prostate Cancer	20 (26.7%)	19 (25.0%)	39 (25.8%)
	Metastatic Prostate Cancer	9 (12.0%)	11 (14.5%)	20 (13.2%)
	Not Classifiable	2 (2.7%)	2 (2.6%)	4 (2.6%)
	Total	75	76	151
PSA at Date of Screening	<20	46 (61.3%)	48 (63.2%)	94 (62.3%)
	20<=	29 (38.7%)	28 (36.8%)	57 (37.7%)
	Total	75	76	151
PSA at Date of Baseline - 1	<10	29 (38.7%)	24 (31.6%)	53 (35.1%)
	10<= - <20	19 (25.3%)	25 (32.9%)	44 (29.1%)
	20<= - <50	11 (14.7%)	12 (15.8%)	23 (15.2%)
	50<=	16 (21.3%)	15 (19.7%)	31 (20.5%)
	Total	75	76	151
PSA at Date of Baseline - 2	<20	48 (64.0%)	49 (64.5%)	97 (64.2%)
	20<=	27 (36.0%)	27 (35.5%)	54 (35.8%)
	Total	75	76	151
Testosterone at Date of Baseline	<3.5	16 (21.3%)	15 (19.7%)	31 (20.5%)
	3.5<= - <5	29 (38.7%)	36 (47.4%)	65 (43.0%)
	5<=	30 (40.0%)	25 (32.9%)	55 (36.4%)
	Total	75	76	151
Prior Treatment (Drug)	No	9 (12.0%)	12 (15.8%)	21 (13.9%)
	Yes	66 (88.0%)	64 (84.2%)	130 (86.1%)

Table 1 Demographics 1, Categorical Data, FAS

Variable	Dose	360 mg	480 mg	Total
	Total	75	76	151
Prior Treatment (Therapy)	No	52 (69.3%)	61 (80.3%)	113 (74.8%)
	Yes	23 (30.7%)	15 (19.7%)	38 (25.2%)
	Total	75	76	151
Combination Treatment (Drug)	No	2 (2.7%)	1 (1.3%)	3 (2.0%)
	Yes	73 (97.3%)	75 (98.7%)	148 (98.0%)
	Total	75	76	151
Combination Treatment (Therapy)	No	41 (54.7%)	43 (56.6%)	84 (55.6%)
	Yes	34 (45.3%)	33 (43.4%)	67 (44.4%)
	Total	75	76	151

† Patients who underwent a radical prostatectomy.
Source: Table 12.1.3.1

Table 2 Demographics 2, Numerical Data, FAS

Variable	Dose	N	Mean	STD	Min	Max	Median	Q1	Q3
Age at Date of Informed Consent	360mg	75	74.3	6.68	54	85	76.0	71.0	79.0
	480mg	76	73.3	6.26	52	83	75.0	69.0	78.0
Height	360mg	75	162.38	5.901	144.1	176.9	161.20	158.30	166.10
	480mg	76	163.30	5.591	150.2	174.0	163.45	158.95	167.00
Weight	360mg	75	61.63	7.921	45.0	93.3	61.30	55.10	66.70
	480mg	76	64.26	8.867	46.0	90.5	65.15	58.55	68.85
BMI	360mg	75	23.35	2.469	18.3	30.0	22.95	21.79	24.77
	480mg	76	24.07	2.898	16.5	34.5	23.93	21.96	26.25
BSA	360mg	75	1.656	0.1195	1.38	2.10	1.663	1.562	1.726
	480mg	76	1.692	0.1259	1.40	1.95	1.692	1.602	1.768
Duration of Disease (days)	360mg	75	103.2	312.11	0	2366	24.0	14.0	45.0
	480mg	76	104.2	304.71	0	1777	23.5	13.0	47.0

Source: Table 12.1.3.2

Table 3 Cumulative Probability of Serum Testosterone ≤ 0.5 ng/mL from Day 28 to Day 364, 360 mg (60 mg/mL), FAS

Dose	Day	Estimate	95% CI*	
			Lower limit	Upper limit
360 mg (60 mg/mL)	0	1.000	1.000	1.000
	28	0.987	0.909	0.998
	112	0.973	0.898	0.993
	168	0.973	.	.
	196	0.973	.	.
	224	0.959	0.878	0.987
	252	0.944	0.858	0.979
	280	0.930	0.839	0.970
	308	0.914	0.819	0.961
	336	0.914	.	.
	364	0.883	0.779	0.940

* Calculated by Greenwood Formula
Source: Table 12.3.1

Table 4 Cumulative probability of Serum Testosterone ≤ 0.5 ng/mL from Day 28 to Day 364, 480 mg (60 mg/mL), FAS

Dose	Day	Estimate	95% CI*	
			Lower limit	Upper limit
480 mg (60 mg/mL)	0	1.000	1.000	1.000
	112	1.000	.	.
	140	1.000	.	.
	196	0.986	0.907	0.998
	280	0.986	.	.
	308	0.972	0.894	0.993
	364	.	.	.

* Calculated by Greenwood Formula
Source: Table 12.3.1

Table 5 Number of Patients with Treatment Emergent Adverse Events, SAF

	Dose	Number of Patients	95% CI
All AEs	360 mg	72/76 (94.7%)	(87.07, 98.55)
	480 mg	73/76 (96.1%)	(88.89, 99.18)
	Total	145/152 (95.4%)	(90.74, 98.13)
ADRs (Probable/Possible)	360 mg	68/76 (89.5%)	(80.31, 95.34)
	480 mg	71/76 (93.4%)	(85.31, 97.83)
	Total	139/152 (91.4%)	(85.82, 95.37)
ADRs (Probable/Possible/Unlikely)	360 mg	72/76 (94.7%)	(87.07, 98.55)
	480 mg	71/76 (93.4%)	(85.31, 97.83)
	Total	143/152 (94.1%)	(89.06, 97.26)
Serious AEs	360 mg	13/76 (17.1%)	(9.43, 27.47)
	480 mg	7/76 (9.2%)	(3.78, 18.06)
	Total	20/152 (13.2%)	(8.23, 19.59)
Serious ADRs (Probable/Possible)	360 mg	5/76 (6.6%)	(2.17, 14.69)
	480 mg	2/76 (2.6%)	(0.32, 9.18)
	Total	7/152 (4.6%)	(1.87, 9.26)
Serious ADRs (Probable/Possible/Unlikely)	360 mg	6/76 (7.9%)	(2.95, 16.40)
	480 mg	2/76 (2.6%)	(0.32, 9.18)
	Total	8/152 (5.3%)	(2.30, 10.11)
AEs Leading to Discontinuation	360 mg	3/76 (3.9%)	(0.82, 11.11)
	480 mg	1/76 (1.3%)	(0.03, 7.11)
	Total	4/152 (2.6%)	(0.72, 6.60)
ADRs Leading to Discontinuation (Probable/Possible)	360 mg	2/76 (2.6%)	(0.32, 9.18)
	480 mg	1/76 (1.3%)	(0.03, 7.11)
	Total	3/152 (2.0%)	(0.41, 5.66)
ADRs Leading to Discontinuation (Probable/Possible/Unlikely)	360mg	2/76 (2.6%)	(0.32, 9.18)
	480mg	1/76 (1.3%)	(0.03, 7.11)
	Total	3/152 (2.0%)	(0.41, 5.66)
AEs Leading to Death	360 mg	1/76 (1.3%)	(0.03, 7.11)
	480 mg	0/76 (0.0%)	(0.00, 4.74)
	Total	1/152 (0.7%)	(0.02, 3.61)
ADRs Leading to Death (Probable/Possible)	360 mg	1/76 (1.3%)	(0.03, 7.11)
	480 mg	0/76 (0.0%)	(0.00, 4.74)
	Total	1/152 (0.7%)	(0.02, 3.61)
ADRs Leading to Death (Probable/Possible/Unlikely)	360 mg	1/76 (1.3%)	(0.03, 7.11)
	480 mg	0/76 (0.0%)	(0.00, 4.74)
	Total	1/152 (0.7%)	(0.02, 3.61)

Adverse events judged as “Probable” or “Possible” were defined as “adverse events whose relationship to the study drugs could not be ruled out” and called as “adverse drug reactions”.
Source: Table 12.6.1.1.1

Table 6 Number of Subjects of Treatment Emergent Adverse Events, as Classified by MedDRA SOC and PT (Grade 3 and Higher)

Adverse Events	Adverse Events (Incidence:145, Events:1359)					
	360 mg			480 mg		
	Grade 1 and Grade 2	Grade 3 and Higher	Total	Grade 1 and Grade 2	Grade 3 and Higher	Total
Number of Subjects			76			76
Number of Incidence	54	18	72	59	14	73
Incidence (%)	71.1%	23.7%	94.7%	77.6%	18.4%	96.1%
Number of Events	571	28	599	743	17	760
Events						
Blood and lymphatic system disorders	9.2% (7,7)	0.0% (0,0)	9.2% (7,7)	6.6% (5,5)	0.0% (0,0)	6.6% (5,5)
Anaemia	7.9% (6,6)	0.0% (0,0)	7.9% (6,6)	5.3% (4,4)	0.0% (0,0)	5.3% (4,4)
Eosinophilia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Microcytic anaemia	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Cardiac disorders	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,2)	1.3% (1,2)	2.6% (2,4)
Angina pectoris	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Aortic valve stenosis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Bundle branch block left	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Bundle branch block right	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Tachycardia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Congenital, familial and genetic disorders	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Dermoid cyst	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Ear and labyrinth disorders	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Vertigo	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Eye disorders	7.9% (6,10)	2.6% (2,2)	10.5% (8,12)	2.6% (2,3)	0.0% (0,0)	2.6% (2,3)
Cataract	1.3% (1,1)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Conjunctival haemorrhage	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Conjunctivitis	2.6% (2,3)	0.0% (0,0)	2.6% (2,3)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Dry eye	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Glaucoma	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Macular degeneration	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Maculopathy	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Retinal vein occlusion	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Macular hole	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Retinal aneurysm	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Gastrointestinal disorders	18.4% (14,16)	5.3% (4,4)	23.7% (18,20)	25.0% (19,38)	3.9% (3,3)	28.9% (22,41)
Abdominal discomfort	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Abdominal pain	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	3.9% (3,9)	0.0% (0,0)	3.9% (3,9)
Abdominal pain upper	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Aphthous stomatitis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Colitis ischaemic	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Colonic polyp	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Constipation	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	5.3% (4,6)	1.3% (1,1)	6.6% (5,7)
Dental caries	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	1.3% (1,1)	3.9% (3,3)
Diarrhoea	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	5.3% (4,7)	0.0% (0,0)	5.3% (4,7)
Diverticulum intestinal haemorrhagic	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Dry mouth	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Dyspepsia	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,3)	0.0% (0,0)	1.3% (1,3)
Enterocolitis	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Gastric polyps	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Gingivitis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Haemorrhoids	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Inguinal hernia	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Lip swelling	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Nausea	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Periodontal disease	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Periodontitis	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Reflux oesophagitis	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Toothache	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Vomiting	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Polyp colorectal	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Hypoaesthesia oral	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
General disorders and administration site conditions	55.3% (42,313)	0.0% (0,0)	55.3% (42,313)	76.3% (58,462)	0.0% (0,0)	76.3% (58,462)

Table 6 Number of Subjects of Treatment Emergent Adverse Events, as Classified by MedDRA SOC and PT (Grade 3 and Higher)

Adverse Events	Adverse Events (Incidence:145, Events:1359)					
	360 mg			480 mg		
	Grade 1 and Grade 2	Grade 3 and Higher	Total	Grade 1 and Grade 2	Grade 3 and Higher	Total
Number of Subjects			76			76
Number of Incidence	54	18	72	59	14	73
Incidence (%)	71.1%	23.7%	94.7%	77.6%	18.4%	96.1%
Number of Events	571	28	599	743	17	760
Events						
Chest discomfort	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Chills	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Fatigue	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Feeling abnormal	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Injection site erythema	38.2% (29,58)	0.0% (0,0)	38.2% (29,58)	40.8% (31,83)	0.0% (0,0)	40.8% (31,83)
Injection site induration	19.7% (15,31)	0.0% (0,0)	19.7% (15,31)	19.7% (15,38)	0.0% (0,0)	19.7% (15,38)
Injection site inflammation	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Injection site mass	13.2% (10,34)	0.0% (0,0)	13.2% (10,34)	15.8% (12,41)	0.0% (0,0)	15.8% (12,41)
Injection site pain	42.1% (32,103)	0.0% (0,0)	42.1% (32,103)	52.6% (40,141)	0.0% (0,0)	52.6% (40,141)
Injection site pruritus	6.6% (5,13)	0.0% (0,0)	6.6% (5,13)	9.2% (7,11)	0.0% (0,0)	9.2% (7,11)
Malaise	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	10.5% (8,12)	0.0% (0,0)	10.5% (8,12)
Oedema peripheral	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)
Pyrexia	11.8% (9,14)	0.0% (0,0)	11.8% (9,14)	27.6% (21,39)	0.0% (0,0)	27.6% (21,39)
Thirst	1.3% (1,3)	0.0% (0,0)	1.3% (1,3)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Injection site swelling	22.4% (17,40)	0.0% (0,0)	22.4% (17,40)	31.6% (24,73)	0.0% (0,0)	31.6% (24,73)
Injection site nodule	3.9% (3,12)	0.0% (0,0)	3.9% (3,12)	5.3% (4,16)	0.0% (0,0)	5.3% (4,16)
Hepatobiliary disorders	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)	3.9% (3,4)	0.0% (0,0)	3.9% (3,4)
Cholecystitis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Cholelithiasis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Hepatic steatosis	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Liver disorder	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Immune system disorders	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Seasonal allergy	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Infections and infestations	28.9% (22,41)	3.9% (3,3)	32.9% (25,44)	38.2% (29,52)	1.3% (1,1)	39.5% (30,53)
Bronchitis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Herpes zoster	2.6% (2,2)	1.3% (1,1)	3.9% (3,3)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Influenza	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Nasopharyngitis	25.0% (19,27)	0.0% (0,0)	25.0% (19,27)	32.9% (25,41)	0.0% (0,0)	32.9% (25,41)
Otitis media	1.3% (1,2)	0.0% (0,0)	1.3% (1,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Otitis media chronic	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Pharyngitis	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Pulpitis dental	0.0% (0,0)	2.6% (2,2)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Rhinitis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,2)	0.0% (0,0)	1.3% (1,2)
Sialoadenitis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Sinusitis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Tinea pedis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Urinary tract infection	1.3% (1,2)	0.0% (0,0)	1.3% (1,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Injection site cellulitis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Dental fistula	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Injury, poisoning and procedural complications	9.2% (7,8)	3.9% (3,4)	13.2% (10,12)	7.9% (6,7)	1.3% (1,1)	9.2% (7,8)
Cerebral haemorrhage traumatic	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Injury	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Multiple injuries	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Rib fracture	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Face injury	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Contusion	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Wound	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Thermal burn	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Meniscus lesion	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Skin laceration	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Skeletal injury	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Lower limb fracture	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Tooth fracture	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Heat illness	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)

Table 6 Number of Subjects of Treatment Emergent Adverse Events, as Classified by MedDRA SOC and PT (Grade 3 and Higher)

Adverse Events	Adverse Events (Incidence:145, Events:1359)					
	360 mg			480 mg		
	Grade 1 and Grade 2	Grade 3 and Higher	Total	Grade 1 and Grade 2	Grade 3 and Higher	Total
Number of Subjects			76			76
Number of Incidence	54	18	72	59	14	73
Incidence (%)	71.1%	23.7%	94.7%	77.6%	18.4%	96.1%
Number of Events	571	28	599	743	17	760
Events						
Investigations	30.3% (23,47)	3.9% (3,4)	34.2% (26,51)	31.6% (24,38)	0.0% (0,0)	31.6% (24,38)
Alanine aminotransferase increased	6.6% (5,9)	1.3% (1,1)	7.9% (6,10)	7.9% (6,6)	0.0% (0,0)	7.9% (6,6)
Aspartate aminotransferase increased	5.3% (4,8)	1.3% (1,1)	6.6% (5,9)	5.3% (4,4)	0.0% (0,0)	5.3% (4,4)
Blood cholesterol increased	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Blood potassium decreased	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Blood triglycerides increased	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Electrocardiogram QT prolonged	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	3.9% (3,5)	0.0% (0,0)	3.9% (3,5)
Gamma-glutamyltransferase increased	7.9% (6,8)	0.0% (0,0)	7.9% (6,8)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Glucose urine present	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Blood urine present	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Haemoglobin decreased	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Weight decreased	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Weight increased	15.8% (12,12)	1.3% (1,1)	17.1% (13,13)	13.2% (10,10)	0.0% (0,0)	13.2% (10,10)
White blood cell count decreased	1.3% (1,2)	0.0% (0,0)	1.3% (1,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
White blood cell count increased	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Blood alkaline phosphatase increased	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	5.3% (4,4)	0.0% (0,0)	5.3% (4,4)
Occult blood positive	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Metabolism and nutrition disorders	10.5% (8,11)	2.6% (2,2)	13.2% (10,13)	5.3% (4,4)	2.6% (2,2)	7.9% (6,6)
Dehydration	0.0% (0,1)	1.3% (1,1)	1.3% (1,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Diabetes mellitus	5.3% (4,4)	1.3% (1,1)	6.6% (5,5)	2.6% (2,2)	2.6% (2,2)	5.3% (4,4)
Gout	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Hypercholesterolaemia	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Hyperglycaemia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Hyperuricaemia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Increased appetite	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Decreased appetite	1.3% (1,3)	0.0% (0,0)	1.3% (1,3)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Musculoskeletal and connective tissue disorders	17.1% (13,16)	0.0% (0,0)	17.1% (13,16)	25.0% (19,21)	1.3% (1,1)	26.3% (20,22)
Arthralgia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	6.6% (5,5)	0.0% (0,0)	6.6% (5,5)
Back pain	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)
Bursitis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Groin pain	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Lumbar spinal stenosis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Muscle spasms	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Musculoskeletal pain	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Myalgia	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Osteoarthritis	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Periarthritis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Spinal column stenosis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Spinal osteoarthritis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Tendonitis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Tenosynovitis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Trigger finger	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Intervertebral disc protrusion	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Musculoskeletal stiffness	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Tenosynovitis stenosans	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Spinal ligament ossification	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Gastric cancer	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Thyroid cancer	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Nervous system disorders	14.5% (11,16)	3.9% (3,4)	18.4% (14,20)	15.8% (12,20)	0.0% (0,0)	15.8% (12,20)
Carotid artery stenosis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Cerebral infarction	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Dementia	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)

Table 6 Number of Subjects of Treatment Emergent Adverse Events, as Classified by MedDRA SOC and PT (Grade 3 and Higher)

Adverse Events	Adverse Events (Incidence:145, Events:1359)					
	360 mg			480 mg		
	Grade 1 and Grade 2	Grade 3 and Higher	Total	Grade 1 and Grade 2	Grade 3 and Higher	Total
Number of Subjects			76			76
Number of Incidence	54	18	72	59	14	73
Incidence (%)	71.1%	23.7%	94.7%	77.6%	18.4%	96.1%
Number of Events	571	28	599	743	17	760
Events						
Dizziness	1.3% (1,2)	0.0% (0,0)	1.3% (1,2)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Dizziness postural	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Headache	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	3.9% (3,11)	0.0% (0,0)	3.9% (3,11)
Hydrocephalus	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Hyperaesthesia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Hypoaesthesia	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Loss of consciousness	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Neuralgia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Post herpetic neuralgia	1.3% (1,1)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Somnolence	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Syncope	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Tension headache	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Tremor	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Intercostal neuralgia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Cerebral haematoma	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Cerebral artery stenosis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Brachial plexopathy	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Psychiatric disorders	3.9% (3,3)	1.3% (1,1)	5.3% (4,4)	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)
Cardiac neurosis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Completed suicide	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Delirium	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Insomnia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Listless	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Renal and urinary disorders	3.9% (3,4)	1.3% (1,1)	5.3% (4,5)	10.5% (8,9)	1.3% (1,1)	11.8% (9,10)
Calculus bladder	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Dysuria	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Haematuria	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Nocturia	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Pollakiuria	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Pyuria	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Renal disorder	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Renal failure acute	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Urethral pain	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Urinary incontinence	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Urinary retention	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Reproductive system and breast disorders	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)	9.2% (7,7)	0.0% (0,0)	9.2% (7,7)
Balanoposthitis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Benign prostatic hyperplasia	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Breast pain	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Gynaecomastia	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)
Scrotal oedema	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Erectile dysfunction	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Respiratory, thoracic and mediastinal disorders	5.3% (4,7)	0.0% (0,0)	5.3% (4,7)	9.2% (7,9)	0.0% (0,0)	9.2% (7,9)
Asthma	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Atelectasis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Chronic obstructive pulmonary disease	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Cough	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	3.9% (3,5)	0.0% (0,0)	3.9% (3,5)
Emphysema	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Pulmonary embolism	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Rhinorrhoea	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Upper respiratory tract inflammation	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Oropharyngeal pain	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)

Table 6 Number of Subjects of Treatment Emergent Adverse Events, as Classified by MedDRA SOC and PT (Grade 3 and Higher)

Adverse Events	Adverse Events (Incidence:145, Events:1359)					
	360 mg			480 mg		
	Grade 1 and Grade 2	Grade 3 and Higher	Total	Grade 1 and Grade 2	Grade 3 and Higher	Total
Number of Subjects			76			76
Number of Incidence	54	18	72	59	14	73
Incidence (%)	71.1%	23.7%	94.7%	77.6%	18.4%	96.1%
Number of Events	571	28	599	743	17	760
Events						
Skin and subcutaneous tissue disorders	27.6% (21,29)	0.0% (0,0)	27.6% (21,29)	11.8% (9,20)	1.3% (1,1)	13.2% (10,21)
Actinic keratosis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Alopecia	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Dermatitis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	1.3% (1,1)
Dermatitis allergic	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Dermatitis contact	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	1.3% (1,2)	0.0% (0,0)	1.3% (1,2)
Drug eruption	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Dry skin	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Eczema	6.6% (5,7)	0.0% (0,0)	6.6% (5,7)	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)
Eczema asteatotic	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)
Eczema nummular	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Hyperhidrosis	2.6% (2,2)	0.0% (0,0)	2.6% (2,2)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Nail disorder	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Papule	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Penile ulceration	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Pruritus	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Rash	5.3% (4,5)	0.0% (0,0)	5.3% (4,5)	5.3% (4,5)	0.0% (0,0)	5.3% (4,5)
Seborrhoeic dermatitis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Stasis dermatitis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Swelling face	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Vascular disorders	38.2% (29,34)	2.6% (2,2)	40.8% (31,36)	40.8% (31,36)	2.6% (2,4)	43.4% (33,40)
Essential hypertension	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,2)	1.3% (1,2)
Flushing	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)
Hypertension	0.0% (0,0)	2.6% (2,2)	2.6% (2,2)	2.6% (2,2)	1.3% (1,2)	3.9% (3,4)
Hypotension	3.9% (3,3)	0.0% (0,0)	3.9% (3,3)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Deep vein thrombosis	1.3% (1,1)	0.0% (0,0)	1.3% (1,1)	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Hot flush	36.8% (28,30)	0.0% (0,0)	36.8% (28,30)	39.5% (30,33)	0.0% (0,0)	39.5% (30,33)

**% (*,*): Incidence (Number of Incidence, Number of Events)
NCI-CTCAE V4.0: Grade 1, Grade 2, Grade 3, Grade 4, Grade 5
MedDRA 13.1
Source: Table 12.6.1.1.20