PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Sutent® / Sunitinib Malate

PROTOCOL NO.: A6181193

PROTOCOL TITLE: A Phase II Study of Sunitinib in Patients with Progressive Advanced/Metastatic Well-differentiated Pancreatic Neuroendocrine Tumors

Study Center(s): Four centers in Japan

Study Initiation Date and Primary Completion or Final Completion Dates:
28 July 2010 to 05 November 2013.

Phase of Development: Phase 2

Study Objective(s):

Primary objective:

To assess the clinical benefit response (CBR) rate in subjects with unresectable progressive advanced/metastatic well-differentiated pancreatic neuroendocrine tumors treated with sunitinib at a dose of 37.5 mg once daily in a continuous daily regimen.

Secondary objectives:

- To assess objective response rate (ORR)
- To assess tumor shrinkage in diameter
- To assess progression-free survival (PFS)
- To assess overall survival (OS)
- To assess safety and tolerability of sunitinib
- To assess pharmacokinetics (trough plasma concentrations) of sunitinib, SU012662 (active metabolite) and total drug (sunitinib + SU012662)

Exploratory objective:

- To evaluate biochemical markers (hormone concentrations and a tumor marker, chromogranin A)

METHODS

Study Design: This was a multi-center, open-label, uncontrolled, phase II study of sunitinib in subjects with unresectable progressive advanced/metastatic well-differentiated pancreatic neuroendocrine tumors. Sunitinib was orally given in a continuous daily dosing regimen at a dose of 37.5 mg once daily in the morning (regardless of fasting or not) with each cycle repeated every 4 weeks to evaluate the efficacy and safety. A dose increase to 50 mg/day after Week 9 was permitted at the discretion of the investigator if there was no response in a subject within the first 8 weeks of treatment based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, if the treatment-related non-hematological toxicity remained ≤ grade 1, and if the treatment-related hematological toxicity remained ≤ grade 2.

SCHEDULE OF ACTIVITIES

	Screening	Treatment with sunitinib				Post- treatment	
Study Procedures	**≤ 21 Days Prior to Dosing**	**Cycle 1**		**Cycle 2 and After**		**End of Treatment/ Withdrawal [4]**	**On and After 28 Days Post-treatment**
		Day 1 [2] –1/+0	**Day 15 –3/+3**	**Day 1 –3/+3**	**Day 15 [3] –3/+3**		
Informed Consent**[5]**	X						
Medical/Oncological History **[6]**	X						
Physical Examination **[7]**	X	(X)		X		X	(X)
Hematology, Blood Chemistry **[8]**	X	(X)	X	X	(X)	X	(X)
Coagulation **[9]**	X			X Every other cycle on and after Cycle 3		X	(X)
Thyroid Function Test **[10]**	X			X		X	(X)
Urinalysis **[11]**	X			X		X	(X)
Pregnancy Test **[12]**	(X)					(X)	
HIV Test **[13]**	(X)						
12-lead Electrocardiogram **[14]**	X			X Every other cycle on and after Cycle 3	(X)	X	
MUGA or Echocardiogram for LVEF assessment	X			X Every other cycle on and after Cycle 3		X	(X)
Ki-67 **[15]**	(X)						
Chromogranin A, Pancreatic hormone **[16]**	X			X Every other cycle on and after Cycle 3		X	
Brain CT or MRI scan, Bone scan **[17]**	(X)	(X)		(X)		(X)	
Tumor Imaging **[18]**	X			X Every other cycle on and after Cycle 3		X	
Registration **[19]**	X						
Symptom at baseline		X					
Sunitinib **[20]**		X->	->	X->	->		
Study Drug Compliance **[21]**			X	X		X	
Adverse Events **[22]**	X	X	X	X	X	X	X
Concomitant Medications/Treatments **[23]**	X	X	X	X	X	X	X
Blood sampling for Pharmacokinetics (trough level)**[24]**			X	X Up to Cycle 4			
Post-Study Survival Status **[25]**							X

1 cycle = 28 days; (X) = if necessary.

Footnotes for Schedule of Assessments
1. During Treatment: All examination and assessments were performed prior to dosing with sunitinib unless otherwise indicated within an allowance in the scheduled visit. One cycle was 28 days. All examination and assessment were to be performed at the calendar days after the first dose of study drug, regardless of treatment delays.
2. Cycle 1 Day 1: Hematology, blood chemistry, and physical examination were not required if acceptable screening assessment had been performed within 7 days prior to the first dose of the study drug. Subjects were fasted at least for 10 hours before scheduled visit.
3. Day 15 Beyond Cycle 2: On and after Week 9, subjects could have dose escalated from 37.5 mg to 50 mg daily if subjects did not show response at Week 8 after the study drug initiation with non-hematologic toxicity ≤ grade 1 and hematologic toxicity ≤ grade 2. If dose was escalated to 50 mg daily, scheduled examination and assessment were performed at Day 15.
4. End of Study Treatment/Withdrawal: All procedures had to be performed within 4 weeks after the last dose if they had not been performed at the last dose. The radiological tumor assessments (brain CT or MRI, bone scan, if necessary) were not required if they had been performed within 6 weeks prior to the last dose or the end of study.
5. Informed Consent: Had to be obtained prior to undergoing any study specific procedure.
6. Medical/Oncology History and Demographics: Included information on prior treatment regimens, dosing and duration of administration, and description of best response observed and treatment failure.
7. Physical Examination: Physical examination, ECOG performance status, body weight, height (at screening visit only), and vital signs (temperature, blood pressure(seated), pulse). Blood pressure was to be measured on the same arm at each examination.
8. Hematology, Blood Chemistry: Performed at screening, Cycle 1 Days 1 and 15, Days 1 and 15 (if required) of Cycle 2 and after. Subjects were fasted at least for 10 hours at the scheduled visit.
9. Coagulation test: Prothrombin Time (PT) or International Normalized Ratio (INR) were examined at screening, Cycle 2 Day 1, Cycle 3 Day 1 and every other cycle afterwards. Subjects were fasted at least for 10 hours at the scheduled visit.
10. Thyroid function test including TSH were required at screening and every 4 weeks after. Subsequent thyroid function testing were performed if required.(recommended: freeT_4, total T_3 and thyroglobulin). Subjects were fasted at least for 10 hours at the scheduled visit.
11. Urinalysis (Dip stick): In cases of urine protein resulted ≥2+, urine protein/creatinine ratio was measured to assess NCI CTCAE grade and dose interruption or modification were made according to the severity. Repeat as clinically indicated.
12. Pregnancy test was conducted within 7 days of starting study treatment and at the end of study treatment.
13. If patients had a negative HIV test within 6 months prior to the registration, the test did not have to be performed at screening.
14. ECG: Three consecutive 12-lead ECGs approximately 2 minutes apart to determine the mean QTc interval. If the mean QTc interval was prolonged (>500 msec), the ECGs had to be over read by a cardiologist at the site for confirmation. Additional ECGs were performed as clinically indicated and at 14 days (+/-7 days) after sunitinib dose escalation. The ECGs were to be performed at the time matched (+/- 1 hour) to the screening examination.
15. Ki-67 Assessment: Assessed based on previous tumor biopsy results or previous surgical resections prior to the study participation. No new assessment performed for this study.
16. Chromogranin A, Pancreatic hormones were evaluated at screening, Cycle 2 Day 1, Cycle 3 Day 1, and every other cycle until 6 months had passed since the initiation of the study. Chromogranin A was evaluated in all subjects and pancreatic hormones were evaluated in subjects with functional pNET. Subjects were fasted at least for 10 hours at the scheduled visit.
17. Brain CT or MRI, bone scans: Brain and/or bone scan was evaluated at screening if brain or bone metastasis were suspected. Subsequent brain or bone scan were performed if clinical sign/symptoms of disease suggested brain or bone metastases or disease progression.
18. Tumor Imaging: Performed at screening, Cycle 2 Day 1, Cycle 3 Day 1, and every other cycle afterward. CT or MRI scan of chest, abdomen and pelvis in addition to any other applicable sites of disease were assessed. Additional scan were performed whenever disease progression was suspected (eg, symptomatic deterioration), to confirm a partial or complete response (at least 4 weeks after initial documentation of response), followed by every other cycle assessment. Allowance of Cycle 7 Day 1 visit (Week 25) was +3 days. The assessment was performed until median PFS or 2 years after the last subject start of the study treatment, whichever was longer
19. Registration: Subjects were registered at least 3 days prior to the planned dosing date
20. Study Treatment: Treatment started on Day 1 after completing all pre-dose assessments at a starting dose of 37.5 mg. The dose was adjusted according to individual patient tolerance.
21. Study Drug Compliance: The study drug medication bottle(s) including any unused capsules were returned to the site for drug accountability.
22. Adverse Events: Subjects were followed for adverse events from initiation of the study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or were determined to be “chronic” or “stable,” whichever was later. If a subject started other anti-cancer medication, non-serious adverse event monitoring was completed at the point. Serious adverse events including deaths were monitored and reported from the time that the subject provided informed consent. Safety assessment was continued until the median PFS or 2 years after the last subject study treatment initiation, whichever was longer.
23. Concomitant Medications and Treatments: Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment until 28 days after last treatment.
24. Trough Drug Level Sampling: A blood sample taken at pre-dose on Cycle 1 Day 15 (+/- 1 day) and Day 1 of Cycles 2 to 4.
25. Post-Study Survival Status: After discontinuation of study treatment, post-study survival status was collected every 6 months. The assessment was continued until median OS or 3 years after the last subject start the study treatment, whichever was shorter. If OS failed to achieve median value, final confirmation of survival status were provided at timing when 3 years had passed since completion of subject registration. In addition, this was not required if confirmation of survival status had been provided within 2 months before timing when 3 years had passed since completion of subject registration.

Number of Subjects (Planned and Analyzed): Targeted number of subjects was 10. A total of 12 subjects were enrolled and analyzed.

Diagnosis and Main Criteria for Inclusion: The study included Japanese patients 20 years or older with a histologically or cytologically proven diagnosis of well-differentiated pancreatic neuroendocrine tumor and with local, locally advanced or metastatic disease documented as having shown progression on a scan (CT or MRI) taken within 12 months prior to baseline compared to a previous scan (taken at any time in the past) in accordance with RECIST. Eligible subjects also had to have at least one measurable target lesion for further evaluation in accordance with RECIST, disease that was not amenable to surgery, radiation, or combined modality therapy with curative intent, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and a life expectancy of at least 3 months.

Study Treatment: Sunitinib capsule was orally administered from Day 1 in a continuous daily dosing regimen at a dose of 37.5 mg once daily with each cycle repeated every 4 weeks. The starting dose was 37.5 mg/day and sunitinib was administered once daily in the morning regardless of fasting or not. Dose reductions were allowed depending on the individual tolerability.

Efficacy Endpoints:

Tumor assessments were performed at baseline, on Day 1 of Cycle 2, on Day 1 of Cycle 3, and then at 8-week intervals during the study. Additional assessments of disease were performed when progression of disease was suspected.

Primary Endpoint:

- CBR rate defined as the percentage of subjects with a best overall response of confirmed complete response (CR), confirmed partial response (PR), or stable disease (SD) $\geq$ 24 weeks in the analysis population.

Secondary Endpoints:

- ORR defined as the percentage of subjects with a best overall response of confirmed CR or confirmed PR in the analysis population.
- Tumor shrinkage defined as the percent change from baseline in the sum of the longest diameter of target lesions in subjects calculated as:

$$\text{Tumor shrinkage (\%)} = \frac{(\text{Sum of the diameter after treatment}) - (\text{Sum of the diameter at baseline})}{(\text{Sum of the diameter at baseline})} \times 100$$

- PFS defined as the time from registration to first documentation of progressive disease (PD) or to death due to any cause, whichever occurred first.

- OS defined as the time from registration to documentation of death due to any cause.

Pharmacokinetic Endpoints:

For pharmacokinetic analysis, trough plasma concentrations of sunitinib, its active metabolite, SU012662, and total drug (sunitinib + SU012662) were assessed. Total drug concentrations were calculated as the sum of sunitinib and SU012662 concentrations. Plasma samples were collected before sunitinib dosing to determine trough concentrations on Day 15 of Cycle 1 and on day 1 of Cycles 2 to 4. Concentrations of sunitinib and its active metabolite, SU012662 were assayed using a validated high performance liquid chromatography / tandem mass spectrometry.

To evaluate biochemical markers in an exploratory manner in sunitinib-treated subjects, blood hormone concentrations and tumor marker (chromogranin A) concentrations were measured at screening, on Day 1 of Cycle 2, on Day 1 of Cycle 3, and then at 8-week intervals until 6-month follow period for all subjects. Chromogranin A was measured in all subjects. As for blood hormone, the produced hormones were measured only in subjects with a diagnosis of functional pancreatic neuroendocrine tumor.

Safety Evaluations:

Subjects were followed for adverse events from Day 1 of study treatment until the last visit and for serious adverse events from the time of informed consent until 28 days after the last on-study treatment. Laboratory tests, vital signs (temperature, blood pressure, pulse, body weight), 12-lead electrocardiogram (ECG), left ventricular ejection fraction (LVEF), physical examination, and ECOG PS were also used to evaluate subject safety.

Statistical Methods:

Full Analysis Set (FAS) was defined as the population of all enrolled subjects in whom well-differentiated pancreatic neuroendocrine tumor had been diagnosed and who received at least one dose of study medication. The FAS was used for efficacy analysis. For the analysis of the primary endpoint, CBR rate and its exact 95% confidence interval (CI) were calculated. For the analysis of the secondary endpoints, ORR and its exact 95% CI, and the percent change from baseline in the sum of the longest diameter of target lesions were calculated. PFS and OS were summarized by Kaplan-Meier methods.

Pharmacokinetic Analysis Set was defined as the population of subjects who received at least one dose of study medication and in whom trough concentrations at steady state were assessed. Trough plasma concentrations of sunitinib, SU012662, and total drug were listed, summarized with descriptive statistics, and plotted.

To evaluate biochemical markers, data of hormone concentrations and tumor marker (chromogranin A) concentrations were listed.

Safety Analysis Set was defined as all subjects enrolled in the study who received at least one dose of study medication. Safety endpoints were summarized according to Pfizer data standards (PDS) specifying the sponsor's standards of reporting clinical study data. Safety endpoints included adverse events, laboratory abnormalities, vital signs, 12-lead ECG,

LVEF, physical examination, and ECOG PS. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

The primary analysis of this study was conducted after all the subjects enrolled in the study discontinued treatment or completed the 6-month follow period

RESULTS

Subject Disposition and Demography:

Subject disposition was shown in Table 1.

Table 1. Subject Disposition

	Number of Subjects
Enrolled	12
Assigned to Treatment	12
Completed	0
Discontinued	12
Tumor progression or recurrence	8
Study discontinuation initiated by Sponsor	1
Consent withdrawal not due to adverse event	1
Others (interruption of study treatment exceeding 4 weeks was required)	1
Adverse event	1
Analyzed for Efficacy	12
Analyzed for Pharmacokinetics	11
Analyzed for Safety	12

Subjects assigned to treatment were 8 males and 4 females with the mean age of 54.1 years (range: 34 to 79 years).

Efficacy Results:

Primary endpoint

A summary of investigator-assessed CBR rate and ORR values was shown in Table 2.

Table 2. Clinical Benefit Rate (CBR)

Number of Evaluable Subjects	12
Best overall response	Number of subjects (%)
CR	0
PR	6 (50.0)
SD ≥24 weeks (168 days)	3 (25.0)
The number of subjects with CBR (CBR rate) ［95%CI］ a)	9 (75.0) [42.8 to 94.5]
The number of subjects with objective response (ORR) ［95%CI］ a)	6 (50.0) [21.1 to 78.9]

CBR = Clinical benefit response, ORR = Objective response rate, CR = Complete response, PR = Partial response, SD = Stable disease, CI = Confidence interval

a) Two-sided 95% CIs were calculated using exact method based on binomial F-distribution.

Secondary endpoints

Secondary endpoints are summarized in Table 3.

Of best overall response in accordance with RECIST, ORR defined as the percentage of subjects with a best overall response of confirmed complete response (CR) or confirmed PR was 50.0% (95% CI: 21.1% to 78.9%).

During the study (including 28 days after the last on-study treatment), 8 of 12 subjects (66.7%) had progressive disease (PD). Of 4 subjects in whom event did not occur, 3 had discontinued study treatment prior to PD, and 1 had received other anti-cancer agent prior to PD, and thus, they were censored. No death occurred during the study.

The probability of progression-free survival (PFS) at 6-month, 12-month, and 24-month was 91.7%, 71.3%, and 35.6%, respectively; the median PFS was estimated to be 16.8 months (95% CI: 9.3 to 26.2 months).

In survival follow-up, 4 deaths (33.3%) due to progression of underlying disease, and 1 death (8.3%) due to other reason (multiple organ failure caused by infectious enteritis) were reported. Of 7 subjects whose investigation was censored at the end of the study, survival of 6 subjects were confirmed, but 1 was no longer being followed for survival. The probability of OS at 6-month, 12-month, 24-month, and 36-month was 90.9%, 90.9%, 81.8%, and 54.5%, respectively; the median OS could not be estimated due to lack of sufficient number of events.

Table 3. Secondary Endpoints

Number of Evaluable Subjects	**12**
Best Overall Response	Number of subjects (%)
CR	0
PR	6 (50.0)
SD	5 (41.7)
PD	1 (8.3)
The number of subjects with ORR ［95%CI］ a)	6 (50.0) [21.1 to 78.9]
Percent changes from baseline to each assessment time point in sum of the longest diameter of target lesions	Mean ± SD
Cycle 1 (n=1)	-20.0 ± NA
Cycle 2 (n=11)	-14.4 ± 13.43
Cycle 3 (n=12)	-18.0 ± 17.70
Cycle 5 (n=9)	-26.0 ± 10.03
Cycle 7 (n=9)	-28.5 ± 11.86
Cycle 9 (n=9)	-31.8 ± 17.20
Cycle 11 (n=9)	-36.4 ± 30.11
Cycle 13 (n=9)	-28.8 ± 16.92
Cycle 14 (n=1)	1.7 ± NA
Cycle 15 (n=7)	-32.5 ± 17.29
Cycle 16 (n=1)	-34.7 ± NA
Cycle 17 (n=5)	-38.7 ± 15.41
Cycle 18 (n=1)	-43.1 ± NA
Cycle 19 (n=4)	-37.8 ± 19.21
Cycle 21 (n=4)	-35.8 ± 19.19
Cycle 23 (n=4)	-35.1 ± 22.82
Cycle 25 (n=4)	-32.6 ± 19.64
Cycle 27 (n=3)	-30.8 ± 26.68
Cycle 28 (n=2)	-40.4 ± 9.72
Cycle 29 (n=1)	3.3 ± NA
Maximum Reduction (n=12)	-34.8 ± 28.76
Progression-free Survival (PFS) (Months)	Median ［95%CI］ 16.8 (9.3 to 26.2)
Overall Survival (OS) (Months)	Median ［95%CI］ NA (22.0 to NA)

CI = Confidence interval, CR = Complete response, NA = not applicable, ORR = Objective response rate, PR = Partial response, PD = Progressive Disease, SD = Stable disease

a) Two-sided 95% CIs were calculated using exact method based on binomial F-distribution.

Pharmacokinetic Endpoint

Dose-corrected Trough Plasma Concentrations of Sunitinib, SU012662 and Total Drug (Sunitinib + SU012662) is summarized in Table 4.

Table 4. Dose-corrected Trough Plasma Concentrations of Sunitinib, SU012662 and Total Drug (Sunitinib + SU012662)

Number of Participants Analyzed Mean ± Standard Deviation (ng/mL)	11
Sunitinib (Cycle 1 Day 15, n=10)	53.9 ± 17.6
Sunitinib (Cycle 2 Day 1, n=2)	41.7 ± 21.9
Sunitinib (Cycle 3 Day 1, n=8)	49.9 ± 19.7
Sunitinib (Cycle 4 Day 1, n=5)	53.5 ± 24.6
SU012662 (Cycle 1 Day 15, n=10)	23.7 ± 7.00
SU012662 (Cycle 2 Day 1, n=2)	21.2 ± 6.36
SU012662 (Cycle 3 Day 1, n=8)	25.7 ± 9.14
SU012662 (Cycle 4 Day 1, n=5)	19.6 ± 7.44
Total drug (Cycle 1 Day 15, n=10)	77.5 ± 20.9
Total drug (Cycle 2 Day 1, n=2)	62.9 ± 28.3
Total drug (Cycle 3 Day 1, n=8)	75.5 ± 26.5
Total drug (Cycle 4 Day 1, n=5)	73.0 ± 28.8

Safety Results:

All 12 subjects (100%) had a total of 198 all-causality adverse events, and a total of 169 treatment-related adverse events. Summary of adverse events are presented in Table 5.

Table 5. Summary of Adverse Events

Causality with study treatment Number of Evaluable Subjects	All-causality 12	Treatment-related 12
Number of subjects with AE	12 (100)	12 (100)
Number of AEs	198	169
Number of subjects with SAE [a)]	3 (25.0)	2 (16.7)
Number of subjects with AE of Grade 3 or 4	12 (100)	11 (91.7)
Number of subjects with AE of Grade 5 [a)]	0	0
Number of subjects who discontinued study due to adverse event	1 (8.3)	1 (8.3)
Number of subjects with dose reduction due to AE [b)]	1 (8.3)	1 (8.3)
Number of subjects with dose interruption due to AE [c)]	12 (100)	11 (91.7)

a) Number of subjects reported during the study (including 28 days after the last on-study treatment) (%)
b) Subjects who needed only dose reduction but did not need treatment interruption
c) Subjects who needed treatment interruption only, and those who needed both treatment interruption and dose reduction

No deaths occurred during the study. Serious adverse events are summarized in Table 6.

Table 6. Serious Adverse Events

System Organ Class/Preferred Term MedDRA (v14.0)	All-causality 12	Treatment-related 12
Total, serious adverse events	3 (25.0)	2 (16.7)
Gastrointestinal disorders		
Enterocolitis	1 (8.3)	1 (8.3)
Hepatobiliary disorders		
Cholangitis	1 (8.3)	0
Cholecystitis acute	1 (8.3)	0
Nervous system disorders		
Convulsion	1 (8.3)	1 (8.3)
Loss of consciousness	1 (8.3)	1 (8.3)

MedDRA = ICH Medical Dictionary for Regulatory Activities Number of subjects (%)

All-causality and treatment related adverse events are summarized in Table 7. The most common all-causality adverse events included diarrhea in 10 subjects (83.3%), palmar-plantar erythrodysaesthesia syndrome, and hypertension in 8 subjects each (66.7%), headache and fatigue in 7 subjects each (58.3%), nausea, vomiting, pyrexia, nasopharyngitis, and dysgeusia in 5 subjects each (41.7%).

Table 7. Adverse Events[a]

System Organ Class/Preferred Term MedDRA (v14.0)	All-causality 12	Treatment Related 12
Number (%) of Subjects with adverse events	12 (100)	12 (100)
Blood and lymphatic system disorders		
Anaemia	2 (16.7)	2 (16.7)
Disseminated intravascular coagulation	1 (8.3)	0
Neutropenia	2 (16.7)	2 (16.7)
Thrombocytopenia	1 (8.3)	1 (8.3)
Cardiac disorders		
Left ventricular dysfunction	2 (16.7)	2 (16.7)
Endocrine disorders		
Hypothyroidism	4 (33.3)	4 (33.3)
Eye disorders		
Conjunctival haemorrhage	1 (8.3)	1 (8.3)
Diplopia	1 (8.3)	0
Eyelash discolouration	1 (8.3)	1 (8.3)
Ocular hyperaemia	1 (8.3)	1 (8.3)
Gastrointestinal disorders		
Abdominal distension	1 (8.3)	1 (8.3)
Abdominal pain	1 (8.3)	1 (8.3)
Ascites	2 (16.7)	2 (16.7)
Constipation	1 (8.3)	
Diarrhoea	10 (83.3)	10 (83.3)
Dyspepsia	1 (8.3)	1 (8.3)
Dysphagia	1 (8.3)	0
Gastritis	1 (8.3)	1 (8.3)
Gingivitis	2 (16.7)	2 (16.7)
Glossitis	1 (8.3)	1 (8.3)
Haemorrhoids	1 (8.3)	1 (8.3)
Hypoaesthesia oral	1 (8.3)	1 (8.3)
Loose tooth	1 (8.3)	0
Nausea	5 (41.7)	4 (33.3)
Oral dysaesthesia	2 (16.7)	2 (16.7)
Periodontitis	1 (8.3)	1 (8.3)
Reflux oesophagitis	2 (16.7)	2 (16.7)
Stomatitis	2 (16.7)	2 (16.7)
Toothache	1 (8.3)	1 (8.3)
Vomiting	5 (41.7)	4 (33.3)
General disorders and administration site conditions		
Face oedema	1 (8.3)	1 (8.3)
Fatigue	7 (58.3)	5 (41.7)
Malaise	2 (16.7)	2 (16.7)
Mucosal inflammation	3 (25.0)	3 (25.0)
Oedema	4 (33.3)	4 (33.3)
Oedema peripheral	2 (16.7)	2 (16.7)
Pyrexia	5 (41.7)	5 (41.7)
Hepatobiliary disorders		
Cholangitis	1 (8.3)	0
Hepatic failure	1 (8.3)	0

Table 7. Adverse Events[a]

System Organ Class/Preferred Term MedDRA (v14.0)	All-causality 12	Treatment Related 12
Infections and infestations		
Encephalitis herpes	1 (8.3)	1 (8.3)
Enteritis infectious	1 (8.3)	0
Enterocolitis infectious	1 (8.3)	1 (8.3)
Hordeolum	1 (8.3)	1 (8.3)
Infected epidermal cyst	1 (8.3)	0
Nasopharyngitis	5 (41.7)	4 (33.3)
Oral herpes	1 (8.3)	1 (8.3)
Pharyngitis	1 (8.3)	1 (8.3)
Pneumonia	1 (8.3)	1 (8.3)
Pyoderma	1 (8.3)	0
Skin candida	1 (8.3)	1 (8.3)
Trichophytosis	2 (16.7)	1 (8.3)
Injury, poisoning and procedural complications		
Contusion	2 (16.7)	0
Fall	1 (8.3)	0
Wound	1 (8.3)	0
Investigations		
Blood alkaline phosphatase increased	1 (8.3)	0
Blood urine present	1 (8.3)	1 (8.3)
Electrocardiogram QT prolonged	3 (25.00)	3 (25.00)
Gamma-glutamyltransferase increased	1 (8.3)	0
Lipase increased	2 (16.7)	2 (16.7)
Lymphocyte count decreased	1 (8.3)	1 (8.3)
Neutrophil count decreased	4 (33.3)	4 (33.3)
Platelet count decreased	2 (16.7)	2 (16.7)
Protein urine present	2 (16.7)	2 (16.7)
Urine output decreased	1 (8.3)	0
White blood cell count decreased	3 (25.00)	3 (25.00)
Metabolism and nutrition disorders		
Decreased appetite	4 (33.3)	4 (33.3)
Hyperamylasaemia	1 (8.3)	1 (8.3)
Hypercholesterolaemia	1 (8.3)	1 (8.3)
Hypoalbuminaemia	1 (8.3)	1 (8.3)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (8.3)	1 (8.3)
Back pain	2 (16.7)	1 (8.3)
Muscle spasms	3 (25.0)	3 (25.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Skin papilloma	1 (8.3)	0
Nervous system disorders		
Dysaesthesia	1 (8.3)	1 (8.3)
Dysgeusia	5 (41.7)	5 (41.7)
Headache	7 (58.3)	6 (50.0)
Hypoaesthesia	1 (8.3)	1 (8.3)

Table 7. Adverse Events[a]

System Organ Class/Preferred Term MedDRA (v14.0)	All-causality 12	Treatment Related 12
Psychiatric disorders		
Insomnia	1 (8.3)	1 (8.3)
Renal and urinary disorders		
Haematuria	1 (8.3)	1 (8.3)
Nephrotic syndrome	1 (8.3)	1 (8.3)
Pollakiuria	1 (8.3)	1 (8.3)
Proteinuria	2 (16.7)	2 (16.7)
Reproductive system and breast disorders		
Scrotal haematocoele	1 (8.3)	0
Respiratory, thoracic and mediastinal disorders		
Cough	1 (8.3)	1 (8.3)
Epistaxis	2 (16.7)	2 (16.7)
Pleural effusion	1 (8.3)	1 (8.3)
Pneumomediastinum	1 (8.3)	0
Skin and subcutaneous tissue disorders		
Dermatitis acneiform	1 (8.3)	1 (8.3)
Dry skin	1 (8.3)	1 (8.3)
Eczema	1 (8.3)	1 (8.3)
Hair colour changes	1 (8.3)	1 (8.3)
Nail disorder	1 (8.3)	1 (8.3)
Onychomadesis	1 (8.3)	1 (8.3)
Palmar-plantar erythrodysaesthesia syndrome	8 (66.7)	8 (66.7)
Pruritus	2 (16.7)	2 (16.7)
Rash	2 (16.7)	2 (16.7)
Skin discolouration	1 (8.3)	1 (8.3)
Skin reaction	1 (8.3)	1 (8.3)
Vascular disorders		
Hypertension	8 (66.7)	8 (66.7)

MedDRA = ICH Medical Dictionary for Regulatory Activities
a. Not including serious adverse events

One subject discontinued the study due to an adverse event (Table 8).

Table 8. Adverse Event Resulted in Discontinuation of the Study

Serial number	Serious adverse event MedDRA v14.0 Preferred Term	Causality	Day of onset/ Day of recovery [a]	Intervention to study treatment	Outcome
1	Enterocolitis	Related	403/426	Discontinued	Resolved

MedDRA = ICH Medical Dictionary for Regulatory Activities
a. Day relative to start of study treatment. First day of study treatment = day 1.

CONCLUSIONS:

Conclusions from the primary analysis are as follows.

- Sunitinib orally administered to Japanese patients with pancreatic neuroendocrine tumor was effective in a continuous daily dosing regimen at a dose of 37.5 mg once daily with each cycle repeated every 4 weeks. CBR rate was 75.0% (95% CI, 42.8% to 94.5%) and ORR was 41.7% (95% CI, 15.2% to 72.3%).

- Following a continuous daily dosing with sunitinib, the steady state sunitinib, SU012662 and total drug concentrations were reached by Day 15 of Cycle 1 without disproportionate accumulation after that.

- Adverse events reported in this study were manageable with dose interruption/reduction or palliative care and were generally tolerable. Common adverse events were consistent with the known safety profiles of sunitinib.

Conclusions from the final efficacy and safety analysis were mostly the same as that of the primary analysis. The updated conclusions based on the final analysis are as follows.

- In Japanese patients with pancreatic neuroendocrine tumor orally given sunitinib in a continuous daily dose regimen at a dose of 37.5 mg once daily with each cycle repeated every 4 weeks, the CBR rate was the same as Primary Analysis, which was 75.0% (95% CI, 42.8% to 94.5%). Meanwhile ORR was 50.0% (95% CI, 21.1% to 78.9%) since PR increased by 1 subject.
- The probability of PFS at 12-month was 71.3%, and median PFS was estimated to be 16.8 months. The probability of OS at 12-month and 36-month was 90.9% and 54.5%, respectively. The median OS could not be estimated due to lack of sufficient number of events.
- Enteritis was newly reported in 1 subject as a treatment-related serious adverse event.