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Sponsor: Pfizer, Inc.

Investigational Product: Sunitinib malate (SU011248, SUTENT®)

Clinical Study Report Synopsis: Protocol A6181202

Protocol Title: A single-arm open-label international multi-center study of the efficacy and safety of sunitinib malate (SU011248, SUTENT®) in patients with progressive advanced metastatic well-differentiated unresectable pancreatic neuroendocrine tumors

Investigators: [redacted] (* did not randomize patients)

Study Centers: Australia (2 sites), Belgium (1 site), China (9 sites), Czech Republic (2 sites), Estonia (1 site), France (3 sites), Hungary (1 site), India (1 site), Italy (2 sites), Japan (2 sites), Norway (1 site), Netherland (1 site), Poland (2 sites), Portugal (1 site), Romania (2 sites), Slovakia (1 site), South Africa (1 site), Spain (2 sites), United States (4 sites)

Publications Based on the Study: None

Study Initiation and Completion Dates: First Patient First Visit: 06 June 2012 to ongoing at data cutoff 19 March 2016

Report Date: 11 November 2016

Previous Report Dates: 07 October 2016

Phase of Development: Phase 4

Study Objectives:

Primary Objective

To confirm sunitinib treatment effect on progression-free survival (PFS) per investigator assessment in patients with advanced/metastatic, well-differentiated, unresectable pancreatic neuroendocrine tumors (pNETs) per Response Evaluation Criteria in Solid Tumors (RECIST 1.0).

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Secondary Objectives

- To assess PFS per independent radiological review;
- To assess time to tumor progression (TTP);
- To assess overall survival (OS);
- To assess objective response rate (ORR);
- To assess duration of response (DoR);
- To assess time to tumor response (TTR);
- To evaluate the use of Choi criteria;
- To evaluate Chromogranin A (CgA) response;
- To assess the safety and tolerability of sunitinib;
- To assess patient-reported outcomes (PROs);
- To explore the potential relationship between plasma soluble kinase insert domain for tyrosine (sKIT) levels and measures of efficacy including PFS;
- To assess sunitinib and SU12662 (active metabolite of sunitinib) plasma trough concentrations (C_{trough}) and to potentially explore the relationship between C_{trough} and safety, biomarker, and efficacy.

METHODS

Study Design: This study was a multinational, multi-center, open-label, Phase 4 clinical trial evaluating the efficacy and safety of sunitinib in patients with progressive, advanced/metastatic well-differentiated, unresectable pNETs.

A minimum target enrollment of approximately 80 men and women 18 years of age or older with progressive advanced/metastatic well-differentiated unresectable pNETs was established for this study population. Of these 80 patients, approximately 40 patients were not to have received any previous systemic therapies (ie, first-line systemic treatment-naïve cohort), including chemotherapy, immunotherapy, intravenous peptide receptor radiotherapy, or investigational anticancer agent other than somatostatin analogs. The remaining approximately 40 patients were to have experienced progressive disease on or after prior systemic therapy (ie, later-line/previously treated).

Patients had to have experienced documented disease progression within a year prior to the start of study enrollment. Eligible patients were enrolled to receive sunitinib orally at

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37.5 mg once a day on a continuous daily dosing (CDD) schedule. After discontinuation of treatment and mandated 28-day follow-up, patients were followed to collect information on further antineoplastic therapy and survival.

Diagnosis and Main Criteria for Inclusion: Patients were to be 18 years of age or older; have proven diagnosis of well-differentiated pNET with available Ki-67 index, and unresectable or metastatic disease documented on a scan and disease progression within 12 months prior to study enrollment. Presence of at least one measurable target lesion according to RECIST 1.0; adequate organ function; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Study Treatment:

Eligible subjects were enrolled to receive sunitinib orally at 37.5 mg once a day on a CDD regimen. Study medication, sunitinib, was supplied as hard gelatin oral capsules containing 12.5 mg and 25 mg equivalents of sunitinib free base. Cycles were defined as a 28-day period.

Efficacy Evaluations:

Primary Efficacy Endpoint:

PFS per investigator assessment according to RECIST 1.0: time from date of enrollment to first progression of disease or death for any reason in the absence of documented progressive disease (PD), whichever occurred first. If tumor progression data included more than 1 date, the first date was used. PFS (in months) was calculated as (first event date − enrollment date +1)/30.4.

Secondary Efficacy Endpoints:

PFS per independent radiological review according to RECIST 1.0: time from enrollment to first documentation of objective tumor progression or to death due to any cause, whichever occurred first.

TTP: time from enrollment to first documentation of objective tumor progression. If tumor progression data included more than 1 date, the first date was used. TTP (in months) was calculated as (first event date − enrollment date +1)/30.4.

TTR: time from date of enrollment to first documentation of objective tumor response that was subsequently confirmed. For patients proceeding from partial response (PR) to complete response (CR), the onset of PR was taken as the onset of response. If lesion assessment data included more than 1 date, the first date was used. TTR (in months) was calculated as (first response date – enrollment date + 1)/30.4. TTR was only calculated for the subgroup of patients with an objective tumor response.

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OS: time from date of enrollment to date of death due to any cause. OS (in months) was calculated as (date of death − enrollment date +1)/30.4. For patients still alive at the time of the analysis or without confirmation of death, the OS time was censored on the last date they were known to be alive. Patients lacking data beyond enrollment had their OS times censored at enrollment with a duration of 1 day.

DoR: time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. DoR was calculated as (the end date for DoR − first CR or PR that was subsequently confirmed +1)/30.4. DoR (in months) was only calculated for the subgroup of patients with a confirmed objective tumor response. For patients proceeding from PR to CR, the onset of PR was taken as the onset of response.

ORR: percent of patients with confirmed CR or confirmed PR according to the RECIST 1.0, relative to all enrolled patients. Confirmed responses were those that persisted on repeat imaging study at least 4 weeks after initial documentation of response. Designation of best response of stable disease (SD) required the criteria to be met at least 6 weeks after enrollment. Patients who did not have on-study radiographic tumor re-evaluation, who received antitumor treatment other than the study medication prior to reaching a CR or PR, or who died, progressed, or dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of ORR.

CgA response rate: percent of patients with a confirmed CgA CR or confirmed CgA PR, relative to the population with an elevated baseline CgA value. CR was defined as a decrease from a high baseline value to one that fell within the normal range, and a PR was defined as a decrease from a high baseline value to one that was at least 50% lower, but remained greater than the ULN range for CgA. PD was defined as at least a 50% increase in CgA level. Confirmed responses were those that persisted at least 4 weeks after initial documentation of response. Designation of best response of SD required the documentation of SD (<50% increase and <50% decrease from baseline) for at least 6 weeks.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

Plasma samples for determination of sKIT concentrations were obtained pre-dose on Days 1 and 15 of Cycle 1, Cycle 2 Day 1, Cycle 3 Day 1, and then every 2 cycles thereafter (Cycles 5, 7, 9, etc), and at the End of Treatment or time of investigator-assessed disease progression whenever possible.

Analysis of plasma samples was conducted at Intertek Pharmaceutical Services (Alta Bioscience Ltd). The sKIT was analyzed using an Enzyme-Linked Immunosorbent Assay (ELISA) kit.

In cases where readings were below the level of quantification (BLQ) for the assay, such readings have been excluded from the analyses.

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Ki-67 tumor index was collected at Screening as part of medical history. Ki-67 assessments based on previous tumor biopsy results or previous surgical resections had to be provided.

Plasma samples for determination of the trough concentrations (pre-dose) levels of sunitinib and SU012662 were obtained pre-dose at Day 15 of Cycle 1 and Day 1 of Cycles 2, 3, and 5. For each PK sample, actual time and date of sample collection in addition to the actual time and date of the last dose before sample collection were appropriately recorded on the case report form. Samples were analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

A 4 mL blood sample Prep D1 (dipotassium ethylenediamine tetraacetic acid whole blood collection optimized for deoxyribonucleic acid analysis) was collected at the baseline visit and retained for potential pharmacogenomic analyses related to drug response. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The retained pharmacogenomic samples were collected from all patients unless prohibited by local regulations.

Patient-reported outcomes (PROs) defined as health-related quality of life (QoL) using the self-administered European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ Gastrointestinal (GI) NET-21 (EORTC QLQ-G.I.NET21). The questionnaire was to be self-administered by the patient in the clinic. The questionnaire was to be completed before any interventions (eg, laboratory assessments or study drug administration) at baseline, every cycle post-baseline assessment including at the End of Treatment or withdrawal, and the visit 28 days post-treatment. In the event the patient was unable to visit the clinic for the 28 days post-treatment visit, assessments were not applicable.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure, temperature, weight), 12-lead electrocardiograms (ECGs), adverse events (AEs), safety laboratory tests, ECOG performance status, physical examination.

Statistical Methods: Detailed methodology for summarization and statistical analyses of the data collected in this trial was documented in a Statistical Analysis Plan (SAP).

RESULTS

Patient Disposition and Demography: A total of 123 patients were screened for this study (A6181202), of whom 106 received sunitinib treatment (61 patients in the treatment-naïve cohort and 45 patients in the later-line cohort). Sixty-eight (68) patients were still ongoing (either on treatment or in long-term survival follow-up) at the time of data cutoff (Table S1).

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Table S1. Patient Disposition

Screened = 123	Treatment-Naïve Cohort		Later-Line Cohort		Total	
	N	(%)	N	(%)	N	(%)
Assigned to Study	61		45		106	
Treated	61	(100.0)	45	(100.0)	106	(100.0)
Discontinued from Study	16	(26.2)	22	(48.9)	38	(35.8)
Patient Died	10	(16.4)	19	(42.2)	29	(27.4)
Relation to Study Drug not Defined	6	(9.8)	3	(6.7)	9	(8.5)
Lost to Follow-up	4	(6.6)	1	(2.2)	5	(4.7)
Other	0		2	(4.4)	2	(1.9)
Patient Refused Further Follow-up	2	(3.3)	0		2	(1.9)
Ongoing at Date of Cutoff	45	(73.8)	23	(51.1)	68	(64.2)
Discontinuations from Treatment	43	(70.5)	39	(86.7)	82	(77.4)
Patient Died	1	(1.6)	1	(2.2)	2	(1.9)
Relation to Study Drug not Defined	36	(59.0)	30	(66.7)	66	(62.3)
Global Deterioration of Health Status	2	(3.3)	2	(4.4)	4	(3.8)
Objective Progression or Relapse	26	(42.6)	23	(51.1)	49	(46.2)
Other	4	(6.6)	4	(8.9)	8	(7.5)
Patient Refused Continued Treatment for Reason Other Than Adverse Event	4	(6.6)	1	(2.2)	5	(4.7)
Related to Study Drug	4	(6.6)	5	(11.1)	9	(8.5)
Adverse Event	4	(6.6)	5	(11.1)	9	(8.5)
Not Related to Study Drug	2	(3.3)	3	(6.7)	5	(4.7)
Adverse Event	2	(3.3)	3	(6.7)	5	(4.7)

Full Analysis Set = all patients who were enrolled into the study regardless of whether patients received study drug or not.
Safety Analysis Set = all patients who received at least 1 dose of study medication.
Note: Percentage is based on the enrolled number of patients in each cohort.

All 106 patients enrolled into the study comprised the full analysis set (FAS) and were analyzed for efficacy, 61 patients in the treatment-naïve cohort and 45 patients in the later-line cohort. All patients in the FAS received at least a dose of sunitinib and were also included in the safety analysis set.

Data from the 61 treatment-naïve patients in the FAS were combined with the data from the treatment-naïve patients in the intention-to-treat population in A6181111 for the primary PFS analysis and pre-defined secondary efficacy analyses (ORR and OS). There were 76 first-line patients (41 treated with sunitinib and 35 treated with placebo) in Study A6181111. Thus, in the combined data there were 102 treatment-naïve patients that received sunitinib and 35 patients that received placebo.

The overall FAS population of this study was comprised of 63 (59.4%) male and 43 (40.6%) female patients. The mean age, mean weight, and mean height of the FAS were 54.6 years, 70.3 kg, and 169.1 cm, respectively. The majority of the demographic and baseline

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characteristics were similar between the 2 cohorts; however, the proportion of female and Asian patients was smaller in the later-line cohort.

All patients had an ECOG PS of 0 (64.2%) or 1 (35.8%) at baseline without notable differences between the 2 cohorts.

All patients had measurable disease at baseline and adequate baseline assessment. Overall, the majority of patients had lesions in the liver (98 [92.5%] patients) and pancreas (47 [44.3%] patients). Patients most commonly had 1, 2 or 3 involved disease sites. The treatment-naïve cohort had a larger proportion of patients with 1 involved disease site, compared to the later-line cohort (39.3% and 20.0%, respectively). A smaller proportion of patients in the treatment-naïve cohort had lesions in the pancreas (36.1%) than in the later-line cohort (55.6%).

Prior somatostatin analog therapy (SSA) was reported for 51 (48.1%) patients with 24 (39.3%) patients in the treatment-naïve cohort and 27 (60.0%) patients in the later line cohort. Patients with regimens that consisted only of SSAs were considered naïve.

In regards to loco regional treatment at screening, the most common were trans arterial chemoembolization (treatment-naïve cohort: 23.0%; later line cohort: 13.3%) followed by radiofrequency ablation (treatment-naïve cohort: 1.6%); later-line cohort: 6.7%). Patients who received previous chemoembolization without exposure to prior systemic chemotherapy were considered treatment-naïve.

In general, the demographic characteristics from Study A6181111 were comparable to the treatment-naïve cohort in this study (A6181202).

Efficacy Results:

Study A6181202 Alone

The primary analysis showed that the median PFS as assessed by investigator was 13.2 months (95% CI: 10.9, 16.7). The median PFS as assessed by investigator was 13.2 months (95% CI: 7.4, 16.8) and 13.0 months (95% CI: 9.2, 20.4) in the treatment-naïve cohort and the later-line cohort, respectively (Table S2). A median PFS of 11.1 months (95% CI: 7.4, 16.6) was observed in the FAS based on the independent third-party radiology assessment according to RECIST 1.0 with a median PFS of 11.1 months (95% CI: 5.5, 16.7) in the treatment-naïve cohort and 9.5 months (95% CI: 7.4, 18.4) in the later-line cohort. The third-party assessments supported the primary investigator-assessed PFS analysis.

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Table S2 Progression-Free Survival (Based on the Investigator Assessment According to RECIST) Treatment-Naive Cohort vs. Later-Line Cohort - Full Analysis Set

	Treatment-Naive Cohort (N=61)	Later-Line Cohort (N=45)	Total (N=106)
Number with event	37 (60.7)	28 (62.2)	65 (61.3)
Type of event			
Progression of disease (PD)	35 (57.4)	26 (57.8)	61 (57.5)
Death without progression of disease	2 (3.3)	2 (4.4)	4 (3.8)
Number censored	24 (39.3)	17 (37.8)	41 (38.7)
Reason for censorship			
No adequate baseline assessments	0	0	0
No on-study disease assessments	0	0	0
Given new anti-cancer treatment prior to tumor progression	2 (3.3)	6 (13.3)	8 (7.5)
Unacceptable gap of >16 weeks between PD or Death to the most recent prior adequate assessment	0	3 (6.7)	3 (2.8)
In follow-up for progression	18 (29.5)	6 (13.3)	24 (22.6)
Removed from Study prior Documentation of PD or Death	4 (6.6)	2 (4.4)	6 (5.7)
Probability of being event free at Month 6[a] (95% CI[b])	66.7 [52.9, 77.4]	75.9 [58.7, 86.7]	70.5[60.2, 78.7]
Kaplan-Meier estimates of Progression Free Survival (Month) Quartiles (95% CI)[c]			
25%	5.0 [2.7, 7.4]	7.4 [3.7, 10.2]	5.6 [3.7, 7.5]
50%	13.2 [7.4, 16.8]	13.0 [9.2, 20.4]	13.2 [10.9, 16.7]
75%	20.2 [16.7, 26.2]	22.9 [14.7, 37.9]	22.9 [16.8, 33.2]

Abbreviations: CI = Confidence Interval; PD = Progression of Disease; PFS = Progression-Free Survival; RECIST= Response Evaluation Criteria In Solid Tumors

[a] Estimated from the Kaplan-Meier curve.

[b] Calculated from the product-limit method.

[c] Calculated from Brookmeyer and Crowley Method.

PFS is defined as the time from date of enrollment to first progression of disease (PD) or death for any reason in the absence of documented PD, whichever occurs first.

Comparisons were made regarding the independent third-party radiology assessment according to Choi criteria in addition to RECIST; the evaluation of tumor response according to Choi criteria has been considered particularly useful in patients with GIST to also capture changes in tumor density after treatment. A longer median PFS was observed in both cohorts compared to RECIST, with a median PFS of 18.7 months (95% CI: 5.6, not estimable) in the treatment-naïve cohort, and a median PFS of 16.5 months (95% CI: 7.4, 22.9) in the later-line cohort.

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Analyses of secondary efficacy endpoints supported the primary PFS analysis. The median TTP based on investigator assessment was 14.5 months (95% CI: 11.0, 16.7) in the FAS, with a median TTP of 14.8 months (95% CI: 7.5, 16.8) and 14.5 months (95% CI: 9.2, 20.4) for the treatment-naïve cohort and later line cohort, respectively. RECIST 1.0 confirmed ORR in the FAS based on investigator assessment was 24.5% (95% exact CI: 16.7, 33.8) with a CR rate of 2.8% and a PR rate of 21.7%. The ORR was 21.3% (95% exact CI: 11.9, 33.7) in the treatment-naïve cohort and 28.9% (95% exact CI: 16.4, 44.3) in the later line cohort. Responses were rapid, with a median TTR based on investigator assessment was 3.8 months (range: 1.0-11.1 months); there was no difference in median TTR between the treatment-naïve cohort and the later line cohort (both medians 3.8 months). Responses were also durable, with a median DoR based on investigator assessment of 14.7 months (95% CI: 10.1, 21.9); the median DoR in the treatment-naïve cohort was longer (19.1 months [95% CI: 10.1, not estimable]) than the median DoR in the later-line cohort (14.7 months [95% CI: 5.5, 21.9]).

In addition to PFS analysis according to Choi criteria, TTP was also analysed according to Choi and the median was 18.7 months (95% CI: 5.6, not estimable) for the treatment-naïve cohort and 16.7 months (95% CI: 7.4, 30.9) for the later-line cohort; which was greater than the investigator-assessed TTP by RECIST 1.0.. Furthermore, the ORR based on the independent third-party radiology assessment according to Choi criteria was higher than the ORR assessments according to RECIST 1.0: 52.5% (95% exact CI: 39.3, 65.4) and 55.6% (95% exact CI: 40.0, 70.4) in the treatment-naïve and later-line cohort, respectively. Although there was a trend in evaluating higher treatment response when Choi criteria were compared to RECIST criteria; however, further analysis is warranted to determine the role Choi criteria may play in assessing response in patients with pNET.

As the majority of patients were in follow-up at the time of data cutoff, the OS data were not mature as of the data cutoff date. An updated analysis of OS will be performed when the median OS can be accurately calculated and presented in a supplemental CSR.

In patients with confirmed CgA response, a greater proportion of patients in the treatment-naïve cohort had a confirmed objective CR or PR (16.4% [95% exact CI: 9.6, 32.5]) compared to the later line cohort (11.1% [95% exact CI: 4.0, 25.6]). However, a definitive conclusion on CgA response could not be made, as the sample size was small.

Combined Studies A6181202 and A6181111 Data

To strengthen the confirmed sunitinib treatment effect on PFS demonstrated in Study A6181202, PFS data from treatment-naïve patients in this study and Study A6181111 were combined and compared to PFS data from the placebo control arm of Study A6181111. A statistically significant and clinically meaningful improvement in investigator-assessed PFS was observed in favor of patients receiving sunitinib (ie, sunitinib arm treatment-naïve cohort) compared to patients receiving placebo (ie, placebo arm treatment-naïve cohort). A median PFS of 12.9 months (95% CI: 7.4, 16.7) was observed in the sunitinib arm treatment-naïve cohort, and a median PFS of 5.7 months (95% CI: 3.6, 7.9) was observed in

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the placebo arm treatment-naïve cohort, with an HR of 0.429 (95% CI: 0.245, 0.752) and a 1-sided p-value of 0.001 based on 50 events in the sunitinib arm treatment-naïve cohort and 19 events in the placebo arm treatment-naïve cohort. In order to ensure that the PFS endpoint was robust, an independent third-party radiology assessment according to RECIST 1.0 was conducted. A median PFS of 12.6 months (95% CI: 7.7, 16.6) was observed for the sunitinib arm treatment-naïve cohort and a median of 6.2 months (95% CI: 3.6, 8.1) for the placebo arm treatment-naïve cohort, with an HR of 0.552 (95% CI: 0.292, 1.042) and a 1-sided p-value of 0.031 based on 55 events (sunitinib arm treatment-naïve cohort: 41 [40.2%], placebo arm treatment-naïve cohort: 14 [40.0%]), which supported the robustness of the results of the primary investigator-assessed PFS analysis.

Controlling for baseline characteristics (age, ethnic origin, and performance status of PFS as assessed by Investigator) had no effect on the PFS HR as assessed by investigator (HR=0.424 [95% CI: 0.217, 0.827]) with a 1-sided p value of 0.005. The results of the sensitivity analysis supported the robustness of the primary analysis.

Patient-Reported Outcomes

The naïve cohort showed some declines in health-related QoL compared to the later-line cohort; however these changes manifest in later cycles. Conversely, the later-line cohort does not show notable declines in scales. In addition, both cohorts showed progressive decline in social functioning over time.

The combined cohort was not meaningful due to the scarcity of data from latter cycles from Study A6181111.

Pharmacokinetic and Pharmacodynamic Results:

Biomarkers

SKIT concentration was pharmacodynamically modulated upon sunitinib treatment. This observation is consistent with previous reports in patients with metastatic breast cancer and GIST. No statistically significant differences were seen when PFS curves were compared after stratification by median baseline sKIT concentration in the treatment-naïve and in the later-line cohorts. In the OS analysis in the treatment-naïve cohort, while OS data are still immature, the Kaplan-Meier estimate showed a potential trend in favor of patients with baseline sKIT ≥ median. However, this observation was not replicated in the later-line cohort but held in the combined cohorts.

No statistically significant differences were seen when PFS curves were compared after stratification by median baseline tumor Ki-67 index in the treatment-naïve and in the later-line cohorts. When OS curves were compared after stratification by median baseline tumor Ki-67 index in the treatment-naïve cohort, and while OS data are still immature, the Kaplan Meier estimation showed a trend in favor of the group with baseline tumor Ki-67 index ≥ median. However, this trend was not observed in the later-line cohort or in the

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combined cohorts. This observation is consistent with previous reports which showed sunitinib and/or everolimus may induce durable disease control in patients with well-differentiated pNET with a Ki-67 index above 15% and positive lesions on functional imaging with gallium^{68} dotatoc and/or Octreoscan®.

In summary, there were no clear predictive and/or prognostic biomarkers identified in this study for patients with advanced/metastatic, well-differentiated, unresectable pNETs with regard to PFS. With regard to OS, potential associations were observed in relation to baseline sKIT and Ki-67 index in the treatment-naïve cohort; however, the OS results are still immature and based on only few events. In addition, in the later-line cohort, the OS appeared to be similar between the sKIT or Ki-67 subgroups.

Pharmacokinetics and Pharmacokinetics-Pharmacodynamics

Another secondary objective of this study was to determine the C_{trough} values for sunitinib and its active metabolite SU012662 in pNET patients and to potentially explore the relationship between C_{trough} values and safety, efficacy, and biomarkers. Both sunitinib and its active metabolite appeared to reach steady state concentrations by Day 15 of Cycle 1. There appeared to be no additional accumulation of sunitinib and its active metabolite across subsequent cycles. Based on the results of the analyses exploring potential relationships between safety, efficacy, and biomarker parameters with Total Drug C_{trough} values on Day 15 of Cycle 1 and Day 1 of Cycles 2 and 3, there appeared to be weak correlations (ie, $r < 0.50$) between safety (ie, percent change from baseline in absolute neutrophil count, thrombocyte count, lymphocyte count, hemoglobin, and systolic blood pressure count) and biomarker (ie, fold change from baseline in sKIT) parameters with C_{trough} values. In addition, the incidence of any-grade palmar-plantar erythrodysesthesia syndrome, thrombocytopenia, hypertension, and anaemia appeared to be greater in patients with higher Total Drug C_{trough} values (ie, $\geq$ median C_{trough}) as compared to those with lower Total Drug C_{trough} values (ie, < median C_{trough}). Furthermore, the ORR (based on RECIST or CgA criteria) and median PFS appeared to be greater in patients with higher Total Drug C_{trough} values as compared to those with lower Total Drug C_{trough} values. There were no consistent trends with respect to median OS in patients with higher C_{trough} values as compared to those with lower C_{trough} values. Further analyses showed no correlations (ie, $-0.3<r<0.3$) between PFS or OS with C_{trough} values on Day 15 of Cycle 1 and Day 1 of Cycles 2 and 3.

Safety Results:

One hundred four (104) patients (98.1%) experienced at least 1 AE on sunitinib treatment, and 69 patients (65.1%) experienced Grade 3 or 4 AEs, which were generally manageable by dosing interruption (63.2%), dose reduction (18.9%), and/or supportive care. Neutropenia, diarrhoea, leukopenia, palmar-plantar erythrodysaesthesia syndrome, fatigue, and thrombocytopenia were the most commonly all-causality reported AEs. The most common treatment-related AEs in this study were consistent with those that have previously been reported with sunitinib, such as neutropenia, diarrhoea, leukopenia, thrombocytopenia, and palmar-plantar erythrodysaesthesia syndrome (Table S3). Twenty-six (26) patients (24.5%)

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experienced SAEs. Eighteen (18) patients (17%) discontinued treatment due to AEs, 10 of the 18 patients discontinued due to treatment-related AEs. There were no deaths due to treatment-related toxicity and all deaths were due to disease progression with the exception of 1 death in the later-line cohort with reason not clearly ascertainable. The sunitinib AE profile observed in this study was generally consistent with the known AE profile for sunitinib. There were no new safety findings identified in this study compared to those in Study A6181111 and previously reported sunitinib studies.

In summary, the sunitinib treatment effect was confirmed in patients with advanced/metastatic, well-differentiated, unresectable pNETs with an acceptable safety profile. The benefit/risk profile of sunitinib was confirmed to be favorable for this patient population.

Table S3. Summary of Key Treatment-Emergent Adverse Events Experienced by ≥15% of Patients in Any Cohort by Preferred Term, and Corresponding CTCAE Grade (Treatment-Related, All Cycles, All Grades and Grade 3/4)

	Treatment-Naïve Cohort (N=61)		Later-Line Cohort (N=45)		Total (N=106)	
Number (%) of Patients with Preferred Term Adverse Event	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Neutropenia	36 (59.0)	12 (19.7)	21 (46.7)	10 (22.2)	57 (53.8)	22 (20.8)
Diarrhoea	29 (47.5)	5 (8.2)	20 (44.4)	1 (2.2)	49 (46.2)	6 (5.7)
Leukopenia	25 (41.0)	4 (6.6)	21 (46.7)	3 (6.7)	46 (43.4)	7 (6.6)
Palmar-plantar erythrodysaesthesia syndrome	19 (31.1)	5 (8.2)	14 (31.1)	2 (4.4)	33 (31.1)	7 (6.6)
Thrombocytopenia	18 (29.5)	6 (9.8)	14 (31.1)	2 (4.4)	32 (30.2)	8 (7.5)
Fatigue	18 (29.5)	1 (1.6)	10 (22.2)	0 (0.0)	28 (26.4)	1 (0.9)
Dysgeusia	13 (21.3)	0 (0.0)	11 (24.4)	0 (0.0)	24 (22.6)	0 (0.0)
Nausea	9 (14.8)	0 (0.0)	13 (28.9)	1 (2.2)	22 (20.8)	1 (0.9)
Hypertension	14 (23.0)	4 (6.6)	7 (15.6)	2 (4.4)	21 (19.8)	6 (5.7)
Stomatitis	13 (21.3)	2 (3.3)	6 (13.3)	1 (2.2)	19 (17.9)	3 (2.8)
Dyspepsia	5 (8.2)	0 (0.0)	11 (24.4)	0 (0.0)	16 (15.1)	0 (0.0)

Abbreviations: AE=Adverse event; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities, N=Number of patients; PT=Preferred term; TEAE=Treatment Emergent Adverse Event.
Patients are counted once at the highest CTCAE grade on-study.
CTCAE v3.0 was used.
TEAEs are all AEs (serious and non-serious) occurred, for the first time, on or after the first day of study treatment. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
Maximum CTCAE Grade is defined as the maximum CTCAE grade value for the specific PT.
MedDRA (v19.0) coding dictionary applied.

2. CLINICAL STUDY REPORT SYNOPSIS

Conclusions:

- The sunitinib treatment effect was confirmed in patients with advanced/metastatic, well-differentiated, unresectable pNET, with an investigator-assessed median PFS of 13.2 months (95% CI: 10.9, 16.7). The sunitinib treatment effect in for treatment-naïve pNET patients was strengthened by the combination of PFS data from the treatment-naïve cohort of Study A6181202 with PFS data from Study A6181111, where investigator-assessed median PFS of 12.9 months (95% CI: 7.4, 16.7) was observed for the sunitinib arm treatment-naïve cohort and 5.7 months (95% CI: 3.6, 7.9) was observed for the placebo arm treatment-naïve cohort with an HR of 0.429 (95% CI: 0.245, 0.752) and a p-value of 0.001.

- The independent third-party radiology assessment according to RECIST 1.0 supported the primary investigator assessed PFS analysis with a median PFS of 11.1 months (95% CI: 7.4, 16.6).

- The secondary endpoints (TTP and ORR) assessments according to RECIST supported the primary PFS endpoint with an investigator-assessed median TTP of 14.5 months (95% CI: 11.0, 16.7) and an investigator-assessed ORR of 24.5% (95% exact CI: 16.7, 33.8), with responses that were rapid and durable with an investigator-assessed median TTR of 3.8 months (range: 1.0-11.1 months) and an investigator-assessed median DoR of 14.7 months (95% CI: 10.1, 21.9).

- Although there was a trend in evaluating higher treatment response when Choi criteria were compared to RECIST criteria, further analysis is warranted to determine the role Choi criteria may play in assessing response in patients with pNET.

- A definitive conclusion on CgA response could not be made, as the sample size was small.

- Sunitinib was associated with AEs that were consistent with the known safety profile, generally manageable by dosing interruption, dose reduction, and/or supportive care.

- In terms of global health-related quality of life and functioning domains (EORTC QLQ-C30 and EORTC QLQ-G.I.NET21), the treatment-naïve cohort showed a decline earlier than the later-line cohort, however, these changes were seen in later cycles.

- Global health-related quality of life and functioning domains (EORTC QLQ-C30) were maintained for patients in the sunitinib arm treatment-naïve cohort with limited adverse symptomatic effects.

- sKIT concentrations were pharmacodynamically modulated, decreasing steadily while on sunitinib treatment until Cycle 7, at which time the concentrations reached a low plateau and did not change notably until the End of Treatment, at which point the concentrations still remained below the baseline concentrations but started rising again.

2. CLINICAL STUDY REPORT SYNOPSIS

- sKIT and Ki-67 were not identified as clear predictive and/or prognostic biomarkers in this study for patients with advanced/metastatic, well-differentiated, unresectable pNETs.

- Potential associations were observed in regard to OS in relation to baseline sKIT and Ki-67 index in treatment-naïve pNET patients; however, the OS results are still immature and based on only few events. In addition, in the later-line pNET patients, the OS appeared to be similar between the sKIT or Ki-67 subgroups.

- The steady state concentrations for sunitinib and its active metabolite were reached by Day 15 of Cycle 1 and did not show additional accumulation across subsequent cycles.

- The incidence of all grades AEs of palmar-plantar erythrodysaesthesia syndrome, thrombocytopenia, hypertension, and anaemia appeared to be greater in patients with higher Total Drug C_{trough} concentrations as compared to those with lower Total Drug C_{trough}.

- The ORR (based on RECIST or CgA criteria) and median PFS appeared to be greater in patients with higher Total Drug trough concentrations as compared to those with lower Total Drug trough concentrations.

TITLE PAGE

Study Title:	A Single Arm Open-Label International Multi–Center Study Of The Efficacy And Safety Of Sunitinib Malate (SU011248, Sutent®) In Patients With Progressive Advanced Metastatic Well–Differentiated Unresectable Pancreatic Neuroendocrine Tumors Supplemental Clinical Study Report
Investigational Product:	Sunitinib malate (SU011248, SUTENT®)
Indication:	Pancreatic neuroendocrine tumors
Sponsor:	Pfizer Inc.
Protocol Number:	A6181202
Phase of Development:	Phase 4
Study Initiation Date:	First Patient First Visit (FPFV): 06 June 2012
Primary Completion Date:	19 March 2016
Study Completion Date:	Last Patient Last Visit (LPLV): 26 July 2018
Sponsor's Signatories:	Clinical Lead: PPD MD Statistical Line Head: PPD PhD
Final Signoff Date:	13 Dec 2018
Investigators:	See below.

Country	Center	Principal Investigator	Country	Center	Principal Investigator
Australia	CCI *	PPD	Australia	CCI	PPD
Belgium	CCI	PPD	China	CCI	PPD
China	CCI	PPD	China	CCI	PPD
China	CCI	PPD	China	CCI *	PPD
China	CCI	PPD	China	CCI	PPD
China	CCI *	PPD	China	CCI	PPD
Czech Republic	CCI	PPD	Czech Republic	CCI	PPD
Estonia	CCI *	PPD	France	CCI	PPD
France	CCI *	PPD	France	CCI *	PPD
Hungary	CCI	PPD	India	CCI	PPD
Italy	CCI	PPD	Italy	CCI *	PPD
Japan	CCI	PPD	Japan	CCI	PPD
Norway	CCI	PPD	Netherland	CCI *	PPD
Poland	CCI *	PPD	Poland	CCI *	PPD
Portugal	CCI *	PPD	Romania	CCI	PPD
Romania	CCI	PPD	Slovakia	CCI	PPD

South Africa	CCI	PPD	Spain	CCI	PPD
Spain	CCI *	PPD	United States	CCI *	PPD
United States	CCI *	PPD	United States	CCI	PPD
United States	CCI	PPD			

*Did not enrol patients.
Abbreviation: PI = Principle Investigator.

GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with Good Clinical Practice (GCP) guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

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14.2 Efficacy Data Summary

14.3 Safety Data Summary

14.3.1 Adverse Events

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16. APPENDICES

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16.1.4.1 Investigators and Corresponding Ethics Committees (IEC) or Institutional Review Boards (IRB), and Curriculum Vitae, (CV)

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16.2.8.7 Investigator Comments

16.3 Case Report Forms (CRFs)

All Case Report Forms (CRFs) or Data Collection Tools (DCTs) agreed upon with regulatory agencies to be submitted will be provided in Module 5 of the Common Technical Document (CTD) for New Drug Applications (United States of America) and in Section 5 of New Drug Submissions (Canada), and will be available upon request for Marketing Authorization Applications (Europe) and Japanese New Drug Applications (JNDA).

16.3.1 CRFs For Deaths, Other Serious Adverse Events, and Withdrawals For Adverse Events: Not applicable

16.3.2 Other CRF's Submitted: Not applicable

16.4 Individual Subject Data Listings: Not applicable

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
CDD	Continuous daily dosing
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CSR	Clinical study report
C_{trough}	plasma trough concentrations
DCT	Data collection tools
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FAS	Full Analysis Set
FLT3	FMS-like tyrosine kinase 3
FPFV	First Patient First Visit
GCP	Good Clinical Practice
HR	Hazard ratio
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
Ki-67 index	A biomarker for assessing the tumor grade
KIT	kinase insert domain for tyrosine
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	Mammalian target of rapamycin
NCI CTC	National Cancer Institute Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	Overall survival
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PK	Pharmacokinetic
pNET	Pancreatic neuroendocrine tumor
PS	Performance status
PT	Preferred Term
RDI	Relative dose intensity

RECIST	Response Evaluation Criteria In Solid Tumors
RET	REarranged during Transfection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set
sCSR	Supplemental Clinical Study Report
SD	Standard deviation
sKIT	Soluble kinase insert domain for tyrosine
SOC	System organ class
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

ETHICS

Independent Ethics Committee or Institutional Review Board

The final protocol and any amendments (Section 16.1.1) were reviewed and approved by the Institutional Review Boards (IRB) and/or Independent Ethics Committees (IEC) at each of the investigational centers participating in the study. The IRBs and IECs are listed in Section 16.1.4.

Ethical Conduct of the Study

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study participants.

INTRODUCTION

Study A6181202 primary analysis data have been reported previously in the primary clinical study report (CSR) for the global population[1] (dated 11 November 2016) and primary CSR for the China subgroup that comprised of patients enrolled at sites in China[2] (dated 09 November 2016). The present supplemental clinical study report (sCSR) presents the final planned analyses of selected efficacy and safety data for both the study populations up to the last patient last visit (LPLV), 26 July 2018.

Pancreatic neuroendocrine tumors (pNETs) are rare malignancies with an incidence of approximately 2.5 to 5 cases per 100,000 per year. Because of the relatively indolent nature of this disease, the majority of patients are diagnosed with disseminated metastases. For patients with metastatic disease, the 5-year survival rate is low, and cure is generally not possible.[3]

Their indolent nature and resistance to traditional treatment modalities distinguish well-differentiated neuroendocrine tumors from poorly differentiated carcinoma and small cell carcinoma. These latter tumors pursue a far more aggressive clinical course, are often responsive to platinum-based chemotherapy regimens, and are characterized histologically by the presence of frequent mitoses and areas of necrosis. Because of biological differences between poorly differentiated carcinoma and well-differentiated pNETs, treatment regimens and response to treatment for each differ.

At the start of the study, except for surgery for localized disease, there was a lack of available therapies with meaningful, clinical benefit for well-differentiated pNETs.[4] Available treatment options for unresectable disease have included the use of somatostatin analogs, which may relieve symptoms related to hormonal hypersecretion, but there is limited evidence to support a direct antitumor effect in progressive, well-differentiated pNETs. The palliative benefit of interferon-α, combination chemotherapy, radiotherapy, cryotherapy, and chemoembolization therapy have been questioned, given the resistance of these tumors to traditional treatment modalities and the associated toxicity of many of these treatments.

Therefore, newer agents with novel mechanisms of action were desperately needed for the treatment of this disease.

pNETs are highly vascular tumors. Several tumors, including pNETs, aberrantly express both the vascular endothelial growth factor (VEGF) ligand and its FLK-1/KDR receptor (VEGFR), both of which play critical roles in tumor angiogenesis.[5] The expression of VEGF upregulates intracellular anti-apoptotic proteins, facilitates tumor growth, and is associated with relatively short disease free and overall survival. In addition to VEGFR, platelet-derived growth factor receptor (PDGFR) is also activated by phosphorylation in several tumor types and is also involved in tumor neoangiogenesis. Inhibition of angiogenesis would therefore be expected to result in growth inhibition and regression of these tumors. In one study performed in a mouse model, treatment with the angiogenesis inhibitors angiostatin and endostatin reduced the tumor burden of pNETs by 60%.[6]

Investigation of angiogenesis inhibitors such as sunitinib in patients with pNETs is therefore of great interest. Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor of kinase insert domain for tyrosine (KIT), PDGFRs, VEGFRs, REarranged during Transfection (RET) kinase, and FMS-like tyrosine kinase 3 (FLT3). Sunitinib has been evaluated in patients with pNETs in 2 clinical trials, a pivotal Phase 3 double-blind placebo-controlled study (A6181111) and supportive Phase 2 open label study with a pNET cohort (RTKC 0511 015).

Phase 3 study A6181111 had previously demonstrated a clinically meaningful improvement in progression-free survival (PFS) in subjects with progressive well-differentiated pNETs, with a median PFS of 11.4 months (95% confidence interval [CI]: 7.4, 19.8) in the sunitinib arm and 5.5 months (95% CI: 3.6, 7.4) in the placebo arm with a hazard ratio (HR) of 0.418 (95% CI: 0.263, 0.662) (2-sided p=0.0001).[7] Additionally, sunitinib treatment was associated with longer survival compared with placebo, with a HR for overall survival (OS) of 0.409 (95% CI: 0.187-0.894; p=0.0204; 30 OS events; data cutoff 15 April 2009). OS was updated 5 years after the last subject first visit (data cutoff of 15 April 2014) and continued to show a favorable longer survival trend compared to placebo, with a HR of 0.730 (95% CI: 0.504, 1.057; 2-sided p=0.0940). Median OS was 38.6 months (95% CI: 25.6, 56.4) in the sunitinib group and 29.1 months (95% CI: 16.4, 36.8) in the placebo group.[8] Although the OS improvement was confounded by the unblinding of the study and subjects receiving placebo crossing over to the sunitinib group, the OS still showed a favorable trend towards sunitinib.

The objectives of the Phase 4 study A6181202 were to confirm the safety and efficacy findings of the pivotal Phase 3 study A6181111, provide additional information on the study population, and to meet regulatory post-approval commitments. Study A6181202 met its primary objective of confirming sunitinib treatment effect on PFS per investigator assessment in patients with progressive advanced metastatic, well-differentiated, unresectable pNETs per Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0), with a median investigator-assessed PFS of 13.2 months (95% CI: 10.9, 16.7). There were no new safety findings identified in this study compared to those in Study A6181111 or other previous sunitinib studies, and the benefit-risk profile of sunitinib was confirmed to be favorable for this patient population.

STUDY OBJECTIVES

Primary Objective

- To confirm sunitinib treatment effect on PFS per investigator assessment in subjects with advanced/metastatic, well-differentiated, unresectable, pNETs per RECIST 1.0.

Secondary Objectives

- To assess PFS per independent radiological review; time-to-tumor-progression, OS, objective response rate; duration of response; and time-to-tumor response;
- To evaluate the use of Choi criteria and Chromogranin A response; explore the potential relationship between plasma soluble KIT (sKIT) levels and measures of efficacy including PFS;
- To assess the safety and tolerability of sunitinib;
- To assess patient-reported outcomes;
- To assess sunitinib and its active metabolite, SU12662, plasma trough concentrations (C_{trough}) and to potentially explore the relationship between C_{trough} and safety, biomarker, and efficacy.

After completion of the primary analysis of Study A6181202 and confirmation that the primary study objective was met, patients who were still showing clinical benefit from study treatment according to the investigator were candidates for continued sunitinib treatment. The purpose of this sCSR is to provide the final planned analyses of OS data and selected safety data collected up to the LPLV, 26 July 2018 for the global population. In addition, selected data that were separately analyzed for the China subgroup are also presented.

INVESTIGATIONAL PLAN

The primary objective of the A6181202 study was to confirm the safety and efficacy findings from the pivotal Phase 3 study of sunitinib in patients with progressive advanced metastatic well-differentiated, unresectable pNETs, Study A6181111. The study was conducted to provide additional information in this population and meet regulatory post-approval commitments.

Eligible patients were enrolled to receive sunitinib orally at 37.5 mg once a day on a continuous daily dosing (CDD) schedule. Patients continued treatment until they experienced death or unacceptable toxicity, withdrew consent, met other withdrawal criteria, or until the final analysis for the study was performed. Patients with evidence of disease progression could continue treatment if judged to have clinical benefit.

After discontinuation of treatment and the mandated 28-day follow-up, patients were followed-up to collect information on survival and further antineoplastic therapy.

The primary analysis period of the study was from the first patient first visit (FPFV) on 06 June 2012 until the data cutoff on 19 March 2016. As the majority of patients were in follow-up at the time of data cutoff, the OS data were not mature at the time. An updated analysis of OS is reported in the present sCSR. In addition, summaries of the planned safety data collected up to LPLV, 26 July 2018, are also provided.

Study Design

A6181202 was a single arm, multinational, multi-center, open label, Phase 4 clinical study evaluating the efficacy and safety of sunitinib in patients with progressive, advanced metastatic well-differentiated, unresectable pNETs.[1,2]

All enrolled patients received the same treatment with sunitinib. After treatment discontinuation there was a mandated 28-day follow-up, followed by a long-term follow-up to collect information on patient survival and selected safety measures.

Enrolled patients were divided into 2 cohorts:

- Treatment-naïve cohort comprising of patients who had not received any previous systemic therapies (ie, first-line systemic), including chemotherapy, immunotherapy, intravenous peptide receptor radiotherapy, or investigational anticancer agent other than somatostatin analogs;

- Later-line cohort comprising of patients who had experienced progressive disease on or after prior systemic therapy.

Selection of Study Population

Inclusion and Exclusion Criteria

Following primary analysis, patients who were clinically benefiting from study treatment as judged by the investigator continued study treatment and follow-up.

Patients had to meet the eligibility criteria to participate in this study. Eligibility criteria were similar to those established for the previous study, A6181111.[7] A detailed list of the selection criteria is provided in the primary CSRs,[1,2] and an abbreviated list is presented below.

Inclusion criteria included:

1. Histologically or cytologically proven diagnosis of well-differentiated pNETs (according to World Health Organization 2000 classification)[9] with available Ki-67 (biomarker for assessing the tumor goals) index.

2. Unresectable (as assessed by the investigator) or metastatic disease documented on a scan (computed tomography, magnetic resonance imaging, or Octreoscan®) taken within 28 days of study enrollment. Disease progression (per RECIST 1.0) within 12 months prior to study enrollment.

3. Disease that was not amenable to surgery, radiation, or combined modality therapy with curative intent.

4. Eastern Cooperative Oncology Group (ECOG) Performance status (PS) 0 or 1.

5. Life expectancy ≥3 months.

Exclusion criteria included:

1. Prior treatment with any tyrosine kinase inhibitors, anti-VEGF angiogenesis inhibitors, non-VEGF targeted angiogenesis inhibitors, or mammalian target of rapamycin (mTOR) inhibitors.

2. Diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or in situ carcinoma of the cervix uteri.

3. Abnormal cardiac function with abnormal 12-lead electrocardiogram (ECG). Ongoing Grade ≥2 cardiac dysrhythmias by National Cancer Institute Common Toxicity Criteria (NCI CTC version 3.0), atrial fibrillation of any grade, or prolongation of the QTc interval to >450 msec for males or >470 msec for females.

4. Symptomatic brain metastases, spinal cord compression, or new evidence of brain or leptomeningeal disease.

5. Left ventricular ejection fraction ≤50% as measured by either multigated acquisition scan or echocardiogram.

Treatments

Sunitinib was available as an oral drug formulation as 30 hard gelatin capsules of the doses 12.5 mg or 25 mg equivalents of sunitinib free base.

Eligible patients were enrolled to receive sunitinib orally at 37.5 mg once a day on a CDD regimen. Dose escalation to 50 mg daily was allowed after the first 8 weeks of treatment for patients not experiencing a complete response or partial response according to RECIST 1.0, provided their treatment-related non-hematological or hematological adverse events (AEs), if any, were Grade ≤1 or Grade ≤2, respectively. For patients experiencing severe toxicity, the dose of 37.5 mg could be reduced to 25 mg daily, which is the minimum dose acceptable for daily dosing of sunitinib. Intra-patient re-escalation of study drug back to previous dose was permitted at the discretion of the investigator and considering the patient's clinical status.

Efficacy, Pharmacokinetic, and Safety

Efficacy Evaluations

The primary efficacy analysis was for PFS, defined as the time from the date of enrollment to the first objective progressive disease or death due to any cause, whichever occurred first. The primary efficacy endpoint results were summarized in the primary CSR, dated

11 November 2016.[1] An updated analysis of the OS is reported in the present sCSR. OS was defined as the time from date of enrollment to date of death due to any cause as described in the Statistical Analysis Plan (SAP; Section 16.1.9.1).

Safety Evaluations

Safety evaluations were based on assessment of AEs (type, incidence, severity [graded by National Cancer Institute Common Terminology Criteria for Adverse Events {NCI-CTCAE}, version 3.0, dated August 9, 2006], seriousness, and relatedness), serious adverse events (SAEs), and laboratory safety (hematology, blood chemistry, urinalysis, and liver function). Medical Dictionary for Regulatory Activities (MedDRA) version 21 coding was applied.

Pharmacokinetic Evaluations

No pharmacokinetic (PK) evaluations were planned after the completion of the primary analysis. Updated patient listings for PK data are provided in the present sCSR.

Statistical Methods Planned in the Protocol

Time to event endpoints were summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% CI for each median were provided.

Descriptive statistics, including the mean, standard deviation (SD), median, minimum, and maximum values, were provided for continuous data.

The number and percentage of patients in each category were provided for categorical variables.

For the OS analysis in this report, data from the treatment-naïve cohort of the global population were combined with data from the treatment-naïve patients in the intention-to-treat population from Study A6181111.

Further details on statistical methods are provided in the SAP (Section 16.1.9.1).

Data Sets Analyzed

The following analysis populations were defined for the global population and China subgroup. The China subgroup analyses sets were a subset of the corresponding global population analyses sets.

Full Analysis Set (FAS) included all patients who were enrolled into the study regardless of whether patients received study drug or not. The FAS was the analysis population for evaluating patient characteristics and efficacy endpoints.

Safety Analysis Set (SAS) included all patients who received at least 1 dose of study drug. The SAS population was the analysis population for evaluating treatment administration and compliance, and safety.

Changes in the Conduct of the Study

There were 3 amendments to the clinical study protocol as follows.

Protocol Amendment 1, dated 31 July 2012

The following changes were made.

- Updated medication errors language;
- Updated AE reporting language;
- Minor administrative changes.

Protocol Amendment 2, dated 25 January 2013

The following changes were made.

- Updated AE reporting language;
- Included changes only applicable to Japan (eg, central laboratory for Chromogranin A assessment, inclusion age for Japan ≥20);
- Clarified usage of validated analytical methods in PK analyses.

Protocol Amendment 3, dated 05 July 2016

The following changes were made after the data cutoff point for the primary analysis, 19 March 2016.

- Reduced the number of efficacy assessments after collection of data for the primary and most secondary endpoints;
- Minor administrative changes and updates to the safety reporting language.

The most recent version of the protocol including all amendments is provided in Section 16.1.1.

Changes in the Planned Analysis

The SAP applicable to the global population was amended twice.

SAP version 2 that was approved on 14 September 2015 provided detailed description of biomarker data analysis.

SAP version 3 that was approved on 3 December 2015 removed unnecessary supportive analyses and provided additional clarifications on populations for each analysis. The applicable SAP for the China subgroup analyses is version 1.0, dated 25 January 2016.[2]

SAP version 3 and China subgroup SAP are provided in Section 16.1.9.1.

RESULTS

Results of data analyzed up to the data cutoff date of the primary analyses were reported previously in the primary CSRs for the global population,[1] dated 11 November 2016 and for the China subgroup,[2] dated 09 November 2016. Analyses of OS and the planned safety data collected up to the LPLV, 26 July 2018, are presented in this sCSR.

The China subgroup is a subset of the global population. Some efficacy and safety analyses were performed separately for the China subgroup (Section 14), while patient listings (Section 16) for this subgroup are part of the listings of the global population.

Patient Disposition

In the global population, a total of 106 patients were enrolled and treated with sunitinib. Of these, 61 patients were in the treatment-naïve cohort and 45 patients in the later-line cohort. Patient discontinuations from the study and treatment phases are presented in Table 1. At the data cutoff date of the primary CSR (19 March 2016), a total of 68 (64.2%) patients were ongoing, either on-treatment or in long-term survival follow-up.[1] At the LPLV, of the 106 enrolled patients, 47 (44.3%) patients discontinued from the study due to death and the remaining 59 (55.7%) patients discontinued due to loss to follow-up (10 [9.4%] patients), refusal for continued follow-up (4 [3.8%] patients) or for other reasons including end of the study by the sponsor (45 [42.5%] patients). Death was reported as the reason for study discontinuation in a smaller proportion of patients in the treatment-naïve cohort (19 [31.1%] patients) than in the later-line cohort (28 [62.2%] patients).

During the treatment phase, discontinuation due to objective progression or relapse was reported in 64 (60.4%) patients overall, with similar proportions in the treatment-naïve and later-line cohorts (36 [59.0%] patients and 28 [62.2%] patients, respectively). Treatment discontinuation due to death was reported in 1 patient each in the treatment-naïve cohort (1.6%) and the later-line cohort (2.2%). Treatment discontinuation due to study drug-related AE(s) were reported in 11 (10.4%) patients overall, with similar proportions in the treatment-naïve (9.8%) and later-line (11.1%) cohorts. Overall, 5 (4.7%) patients discontinued treatment due to global deterioration of health status.

Table 1. Discontinuations from Study Phase (Full Analysis Set) and Treatment Phase (Safety Analysis Set): Global Population

Screened = 123	Treatment-Naïve Cohort N = 61	Later-Line Cohort N = 45	Total N = 106
	n (%)	n (%)	n (%)
Discontinuations from Study Phase			
Patient died	19 (31.1)	28 (62.2)	47 (44.3)
Relation to study drug not defined	42 (68.9)	17 (37.8)	59 (55.7)
Lost to follow-up	8 (13.1)	2 (4.4)	10 (9.4)
Other[a]	30 (49.2)	15 (33.3)	45 (42.5)
Patient refused further follow-up	4 (6.6)	0	4 (3.8)
Total	61 (100.0)	45 (100.0)	106 (100.0)
Discontinuations from Treatment Phase			
Patient died	1 (1.6)	1 (2.2)	2 (1.9)
Relation to study drug not defined	52 (85.2)	36 (80.0)	88 (83.0)
Global deterioration of health status	3 (4.9)	2 (4.4)	5 (4.7)
Objective progression or relapse	36 (59.0)	28 (62.2)	64 (60.4)
Other	8 (13.1)	5 (11.1)	13 (12.3)
Patient refused continued treatment for reason other than adverse event	5 (8.2)	1 (2.2)	6 (5.7)
Adverse event related to study drug	6 (9.8)	5 (11.1)	11 (10.4)
Adverse event not related to study drug	2 (3.3)	3 (6.7)	5 (4.7)
Total	61 (100.0)	45 (100.0)	106 (100.0)

Sources: Table 14.1.1.3 and Table 14.1.1.4
[a]Includes discontinuation due to end of study.
Percentage is based on the number of enrolled patients in each cohort.
Abbreviations: N = number of patients enrolled; n = number of patients who met the criteria.

The China subgroup comprised of 31 patients enrolled in China and treated with sunitinib. At the data cutoff date of the primary CSR (19 March 2016),[2] 26 (83.9%) patients were ongoing, either on-treatment or in long-term survival follow-up. Patient discontinuations from the study and treatment phase are presented in Table 2. At the LPLV, of the 31 enrolled patients, 9 (29.0%) patients discontinued from the study due to death, and the remaining 22 (71.0%) patients discontinued due to loss to follow-up (2 [6.5%] patients) or for other reasons including end of the study by the sponsor (20 [64.5%] patients).

During the treatment period, discontinuation because of objective progression or relapse was reported in 21 (67.7%) patients and due to death in 1 patient (3.2%). Overall, treatment discontinuation due to AE(s) related to the study drug were reported in 2 (6.5%) patients.

Table 2. Discontinuations from Study Phase (Full Analysis Set) and Treatment Phase (Safety Analysis Set): China Subgroup

Assigned to Study Treatment	Total N = 31
	n (%)
Discontinuations from Study Phase	
Patient died	9 (29.0)
Relation to study drug not defined	22 (71.0)
Lost to follow-up	2 (6.5)
Other[a]	20 (64.5)
Total	31 (100.0)
Discontinued from Treatment Phase	
Patient died	1 (3.2)
Relation to study drug not defined	26 (83.9)
Objective progression or relapse	21 (67.7)
Other	2 (6.5)
Patient refused continued treatment for reason other than adverse event	3 (9.7)
Adverse event related to study drug	2 (6.5)
Adverse event not related to study drug	2 (6.5)
Total	31 (100.0)

Sources: Table 14.1.1.3.1 and Table 14.1.1.4.1
[a]Includes discontinuation due to end of study.
Percentage is based on the enrolled number of patients.
Abbreviations: N = number of patients enrolled; n = number of patients who met the criteria.

By patient listings for discontinuation from the study or treatment are provided in Tables 16.2.1.3 and 16.2.1.4, respectively; and patients not meeting the eligibility criteria are listed in 16.2.1.5.

Demography

Demographic characteristics were described in the primary CSRs for the global population and China subgroup.[1,2]

Briefly, in the global population, the overall FAS population was comprised of 63 (59.4%) male and 43 (40.6%) female patients. The majority of the demographic and baseline characteristics were similar between the 2 cohorts; however, the proportion of female and Asian patients was comparatively lower in the later-line cohort. All patients had an ECOG PS of either 0 (64.2%) or 1 (35.8%) at baseline with no notable differences between the 2 cohorts.

In the China subgroup, the overall FAS population was comprised of 31 patients, 19 (61.3%) male and 12 (38.7%) female patients. All patients had an ECOG PS of either 0 (58.1%) or 1 (41.9%) at baseline.

By patient listings are provided for demographic characteristics in Table 16.2.4.1, primary diagnoses and durations in Table 16.2.4.2, medical history in Table 16.2.4.3, and pregnancy test results by visit in Table 16.2.4.4.

Protocol Deviations

Section 16.2.2 lists the protocol deviations recorded for this study after the primary CSR data cutoff date, 19 March 2016. Overall, of the 181 protocol deviations recorded, 10 were considered as major protocol deviations. The majority of the minor protocol deviations were related to study procedures or tests not done. Of the 10 major protocol deviations, 4 were related to study procedures or tests not done, 3 to AEs or SAEs, 2 to signing of informed consent form, and 1 to administration of the study drug.

None of the protocol deviations was considered to significantly impact patient safety or the interpretation of study results.

A formal acknowledgment by the study team was made that deviations were reviewed and GCP compliance was maintained.

Prior and Concomitant Treatments

Prior and concomitant treatments were described in the primary CSRs for the global population and the Chinese subgroup.[1,2]

Updated patient listings are provided for prior systemic therapies in Table 16.2.5.2.1.1, prior surgery in Table 16.2.5.2.2.2, concomitant drug treatments in Table 16.2.5.2.3, concomitant nondrug treatments in Table 16.2.5.2.4, concurrent somatostatin therapy in Table 16.2.5.2.5, and follow-up systemic therapy in Table 16.2.5.2.6.

Efficacy Results

Overall Survival: Global Population

For the global population, the overall OS data for the FAS up to the LPLV, 26 July 2018, were analyzed. The overall OS data for the treatment-naïve and later-line cohorts are presented in Table 3 and Figure 1. At the end of the study, 20 (32.8%) patients in the treatment-naïve cohort and 28 (62.2%) patients in the later-line cohort died, primarily due to disease under study. A total of 58 (54.7%) patients were censored, of which 50 (47.2%) patients were lost to follow-up (includes patients who were alive at the time the study was ended by the sponsor). A higher proportion of the patients were censored in the treatment-naïve cohort (41 [67.2%] patients) than in the later-line cohort (17 [37.8%] patients).

Overall, the median OS for the global population was estimated to be 54.1 months (95% CI: 37.9, not reached). The median OS could not be determined for the treatment-naïve cohort; and was 37.9 months (95% CI: 22.9, 56.1) for the later-line cohort.

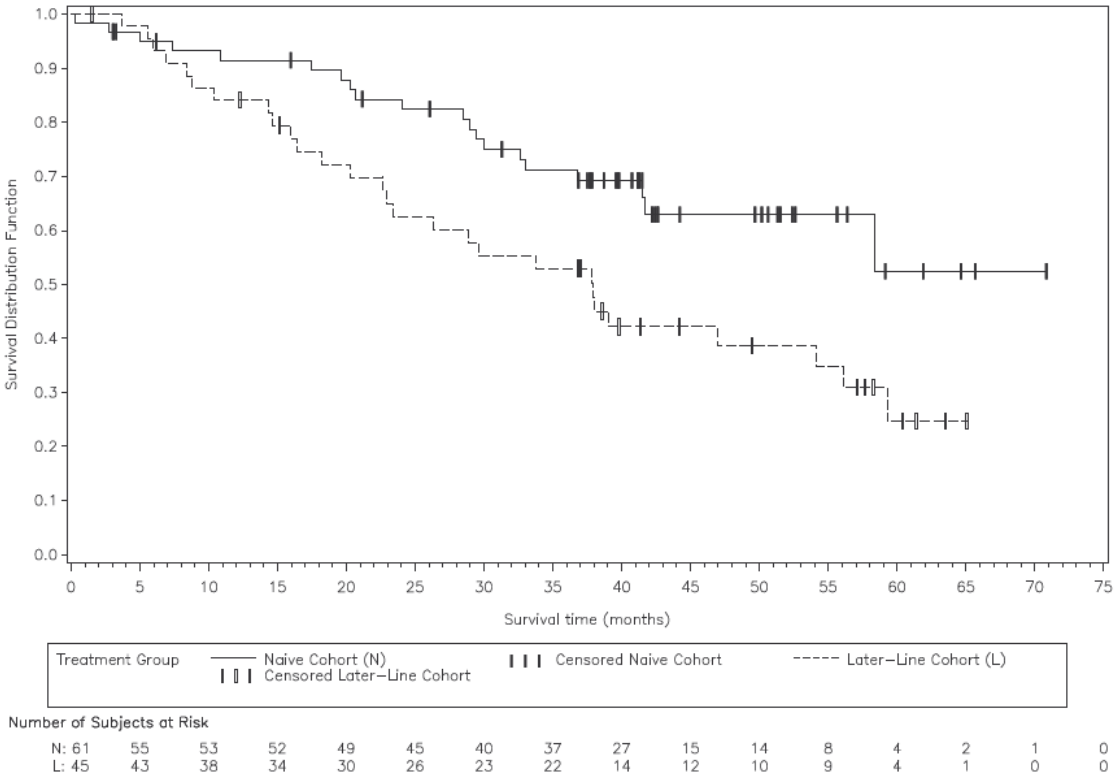
Survival probability at Year 1 was 88.3% (95% CI: 80.3, 93.2) for the total population: 91.5% (95% CI: 80.9, 96.4) for the treatment-naïve cohort and 84.3% (95% CI: 69.8, 92.2) for the later-line cohort; and at Year 2 was 75.0% (95% CI: 65.3, 82.4) for the total population: 84.4% (95% CI: 72.2, 91.6) for the treatment-naïve cohort and 63.0% (95% CI: 46.8, 75.5) for the later-line cohort.

Table 3. Overall Survival – Full Analysis Set; Global Population

	Treatment-Naïve Cohort N = 61	Later-Line Cohort N = 45	Total N = 106
Number of deaths, n (%)[a]	20 (32.8)	28 (62.2)	48 (45.3)
Cause of death, n (%)			
Disease under study	16 (26.2)	26 (57.8)	42 (39.6)
Study treatment toxicity	0	0	0
Unknown	2 (3.3)	0	2 (1.9)
Other	2 (3.3)	2 (4.4)	4 (3.8)
Number censored, n (%)	41 (67.2)	17 (37.8)	58 (54.7)
Reason for censorship, n (%)			
Patient withdrew consent for additional follow-up	4 (6.6)	4 (8.9)	8 (7.5)
Lost to follow-up or alive when study ended[b]	37 (60.7)	13 (28.9)	50 (47.2)
Survival probability at Year 1[c] (95% CI)[d], %	91.5 (80.9, 96.4)	84.3 (69.8, 92.2)	88.3 (80.3, 93.2)
Survival probability at Year 2[c] (95% CI)[d], %	84.4 (72.2, 91.6)	63.0 (46.8, 75.5)	75.0 (65.3, 82.4)
Kaplan-Meier estimates of time to event (months) quartiles (95% CI[e])			
25%	30.0 (20.3, 41.7)	16.4 (8.4, 26.3)	23.4 (17.5, 30.0)
50%	- (41.7, -)	37.9 (22.9, 56.1)	54.1 (37.9, -)
75%	-	59.3 (46.9, -)	- (59.3, -)

Sources: Tables 14.2.6.2 and 14.2.6.3
A patient could have more than 1 cause of death.
[a]Investigator was notified of death of 1 patient enrolled in China in the treatment-naïve cohort after the patient discontinued from study.
[b]Includes patients who were alive at the last survival follow-up visit.
[c] Estimated from Kaplan-Meier curve.
[d]Calculated from the log [-log (1 or 2-year survival probability)] using a normal approximation and back transformation.
[e]Calculated from Brookmeyer and Crowley Method.
Abbreviations: CI = confidence interval, N = number of patients enrolled; n = number of patients who met the criteria.

Figure 1. Overall Survival – Treatment-Naïve Cohort and Later-Line Cohort - Full Analysis Set; Global Population



Source: Figure 14.2.5.2

For the global population, a combined analysis was done to compare treatment-naïve sunitinib-treated patients pooled from 2 studies, A6181202 and A6181111 (sunitinib arm), with placebo-treated patients from A6181111 study (placebo arm) (Table 4 and Figure 2). A total of 22 (21.6%) patients in the sunitinib arm and 6 (17.1%) patients in the placebo arm died, mostly due to the disease under study. A high proportion of the patients were censored in the 2 arms: 80 (78.4%) and 29 (82.9%) patients, respectively, either because the patients were in long-term survival follow-up at the data cutoff date in Study A6181111 (38 [37.3%] and 28 [80.0%] patients, respectively) or were alive when Study A6181202 ended or were lost to follow-up (37 [36.3%] patients and 1 [2.9%] patient, respectively) or refused follow-up (5 [4.9%] patients and none, respectively).

The median OS could not be determined for either arm. Survival probability at Year 1 was 92.0% (95% CI: 83.8, 96.1) for the sunitinib arm and 86.3% (95% CI: 67.4, 94.7) for the placebo arm; and at Year 2 was 85.1% (95% CI: 74.2, 91.6) for the sunitinib arm and could not be determined for placebo arm. The estimated HR was 0.303 (95% CI: 0.100, 0.921), indicating a 69.7% reduction in the risk of death with sunitinib treatment compared with placebo; and the difference was statistically significant (p-value = 0.013).

It should be noted that survival follow-up was shorter in Study A6181111 (data cutoff date, 15 April 2009; range for survival follow-up: 0.03 to 20.63 months)[7] compared with

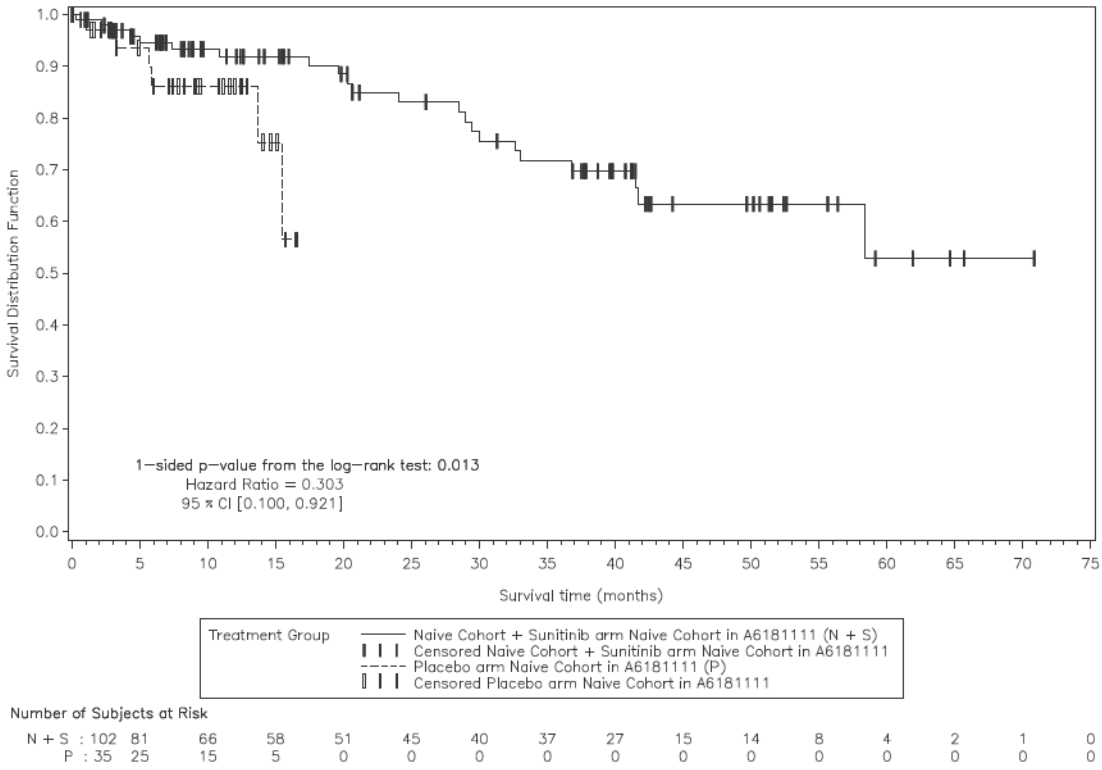
Study A6181202 (data cutoff date, 26 July 2018; range of survival follow-up, 0.03 to 70.83 months; Table 16.2.6.5) leading to an imbalance in the follow-up between sunitinib and placebo arms.

Table 4. Overall Survival – Treatment-Naïve Cohort in Study A6181202 + Sunitinib Arm Treatment-Naïve Cohort in Study A6181111 versus Placebo Arm Treatment-Naïve Cohort in Study A6181111 – Full Analysis Set; Global Population

	Sunitinib Arm N = 102	Placebo Arm N = 35
Number of deaths, n (%)[a]	22 (21.6)	6 (17.1)
Cause of death, n (%)		
Disease under study	17 (16.7)	4 (11.4)
Study treatment toxicity	0	0
Unknown	2 (2.0)	0
Other	3 (2.9)	2 (5.7)
Number censored, n (%)	80 (78.4)	29 (82.9)
Reason for censorship, n (%)		
In follow-up as of data cutoff in Study A6181111	38 (37.3)	28 (80.0)
Patient withdrew consent for additional follow-up	5 (4.9)	0
Lost to follow-up or alive when study ended[b]	37 (36.3)	1 (2.9)
Survival probability at Year 1[c] (95% CI)[d], %	92.0 (83.8, 96.1)	86.3 (67.4, 94.7)
Survival probability at Year 2[c] (95% CI)[d], %	85.1 (74.2, 91.6)	-
Kaplan-Meier estimates of OS (month)		
Quartiles (95% CI[e])		
25%	32.6 (20.6, 58.4)	15.5 (5.7, -)
50%	- (41.7, -)	- (13.7, -)
75%	-	- (15.5, -)
Versus placebo arm naïve cohort in Study A6181111		
HR[f]	0.303	
95% CI of HR	0.100, 0.921	
p-value[g]	0.013	

Source: Table 14.2.6.1
[a]Investigator was notified of death of 1 patient enrolled in China in the treatment-naïve cohort after the patient discontinued from study.
[b]Includes patients who were alive at the last survival follow-up visit.
[c] Estimated from Kaplan-Meier curve.
[d]Calculated from the log [-log (1 or 2-year survival probability)] using a normal approximation and back transformation.
[e]Calculated from Brookmeyer and Crowley Method.
[f]Based on the Cox Proportional hazards model.
[g]One-sided p-value from the log-rank test.
Abbreviations: CI = confidence interval, HR = hazard ratio; N = number of patients enrolled; n = number of patients who met the criteria; OS = overall survival.

Figure 2. Overall Survival – Treatment-Naïve Cohort in Study A6181202 + Sunitinib Arm Treatment-Naïve Cohort in Study A6181111 versus Placebo Arm Treatment-Naïve Cohort in Study A6181111 - Full Analysis Set



Source: Figure 14.2.5.1

Overall Survival: China Subgroup

For the China subgroup, the overall OS data for the FAS at the data cutoff date of this report, 26 July 2018, are presented in Table 5 and Figure 3. Overall, 10 (32.3%) patients died, mostly due to disease under study (6 [19.4%] patients). A high proportion of the patients were censored (21 [67.7%] patients), primarily because the patients were alive when the study ended or were lost to follow-up (18 [58.1%] patients).

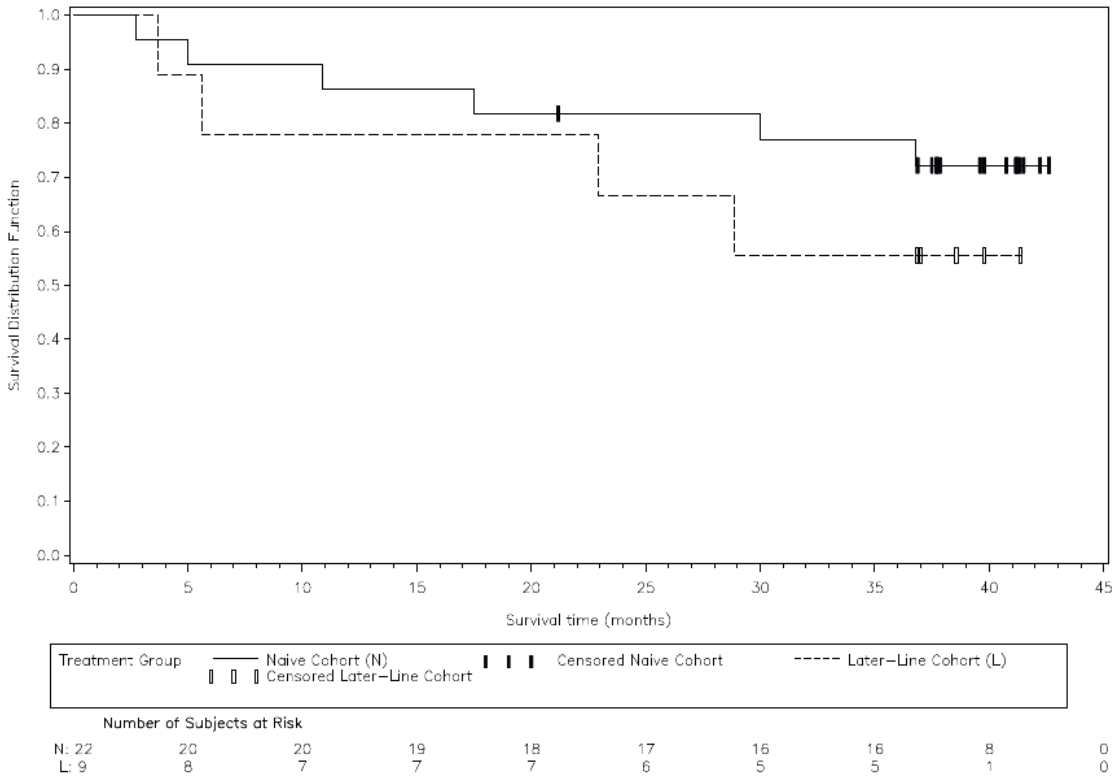
The median OS could not be determined. Survival probability at Year 1 was 84.1% (95% CI: 66.0, 93.1) and at Year 2 was 77.7% (95% CI: 58.7, 88.7). These estimates were comparable with survival probability estimates for the overall global population at Year 1 and Year 2: 88.3% (95% CI: 80.3, 93.2) and 75.0% (95% CI: 65.3, 82.4), respectively (Table 3).

Table 5. Overall Survival – Full Analysis Set; China Subgroup

	Sunitinib N = 31
Number of deaths, n (%)[a]	10 (32.3)
Cause of death, n (%)	
Disease under study	6 (19.4)
Study treatment toxicity	0
Unknown	1 (3.2)
Other	3 (9.7)
Number censored, n (%)	21 (67.7)
Reason for censorship, n (%)	
Patient withdrew consent for additional follow-up	3 (9.7)
Lost to follow-up or alive when study ended[b]	18 (58.1)
Survival probability at Year 1[c] (95% CI)[d], %	84.1 (66.0, 93.1)
Survival probability at Year 2[c] (95% CI)[d], %	77.7 (58.7, 88.7)
Kaplan-Meier estimates of time to event (month)	
Quartiles [95% CI[e]]	
25%	28.8 (5.0, -)
50%	- (36.8, -)
75%	-

Source: Table 14.2.3.1.1
A patient could have more than 1 cause of death.
[a]Investigator was notified of death of 1 patient enrolled in China in the treatment-naïve cohort after the patient discontinued from study.
[b]Includes patients who were alive at the last survival follow-up visit.
[c]Estimated from the Kaplan-Meier curve.
[d]Calculated from the log [-log (1 or 2-year survival probability)] using a normal approximation and back transformation.
[e]Calculated from Brookmeyer and Crowley Method.
Abbreviations: CI = confidence interval, HR = hazard ratio; N = number of patients enrolled; n = number of patients who met the criteria; OS = overall survival.

Figure 3. Overall Survival – Treatment-Naïve Cohort versus Later-Line Cohort – Full Analysis Set; China Subgroup



Source: Figure 14.2.2.1.1

Pharmacokinetic, Pharmacodynamic and Other Results

Listing of patients with PK/pharmacodynamic data were provided for the global population in the primary CSR.[1] Updated listing of patients with data on levels of protein biomarker sKIT changes from baseline is provided in Table 16.2.5.3.6.

Updated patient listing for Chromogranin A response is provided in Table 16.2.6.8.

Updated patient listing for analyses of patient-reported outcomes is provided for European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) assessments in Table 16.2.8.5.1, derived EORTC QLQ-C30 questionnaire in Table 16.2.8.5.2, EORTC QLQ - G.I.NET21 (Carcinoid/Neuroendocrine) questionnaire assessments in Table 16.2.8.5.3, and derived EORTC QLQ - G.I.NET21 (Carcinoid/Neuroendocrine) questionnaire in Table 16.2.8.5.4.

Safety Results

Extent of Exposure

The global population SAS comprised of 106 patients, all of whom had received at least 1 dose of the study drug. Most patients (90 [84.9%] patients) received treatment for

≥91 days, with a median duration of treatment of 364.0 days (Table 6). The median treatment duration was longer in the treatment-naïve cohort (394.0 days) than in the later-line cohort (311.0 days).

Table 6. Duration of Treatment – Safety Analysis Set; Global Population

	Treatment-Naïve Cohort N = 61	Later-Line Cohort N = 45	Total N = 106
Duration category (days)			
≤1	0	0	0
2-7	1	0	1
8-14	0	1	1
15-28	0	0	0
29-60	5	4	9
61-90	3	2	5
≥91	52	38	90
Median duration (days)	394.0	311.0	364.0
Range (days)	7 - 1939	14 - 1806	7 - 1939

Source: Table 14.4.1
Duration of treatment is the time period starting from the date of first dose and ending at the last dose.
Abbreviation: N = number of patients with at least 1 dose of study drug.

In this study, patients followed a CDD treatment regimen. For purposes of analysis, a cycle was defined 28-days. For the global population, dose administration data are summarized in Table 7. Patients received between 1 and 64 cycles, with a median of 13 cycles. Of the 73 events of dose reduction, 56 events were in the treatment-naïve cohort and 17 events in the later-line cohort. Overall, 51 (48.1%) patients had dose reductions, of which, the majority had 1 dose reduced (47 [44.3%] patients) and 4 (3.8%) patients had ≥2 doses reduced. Of the 557 events of dose interruptions, 360 events were in the treatment-naïve cohort and 197 events in the later-line cohort. Overall, 84 (79.2%) patients had dose interruptions, of which 73 (68.9%) patients had a dose interruption due to an AE (treatment-naïve cohort: 46 [75.4%] patients; later-line cohort: 27 [60.0%] patients). Overall, 20 (18.9%) patients had at least 1 dose increase.

Table 7. Summary of Dose Administration – Safety Analysis Set; Global Population

	Treatment-Naïve Cohort N = 61	Later-Line Cohort N = 45	Total N = 106
Total number of cycles	1011	762	1773
Median (Range) of cycles administered	15 (1 – 60)	11 (1 – 64)	13 (1 – 64)
Patients with cycles administered, n (%):			
1 cycle	2 (3.3)	1 (2.2)	3 (2.8)
2 cycles	3 (4.9)	3 (6.7)	6 (5.7)
3 cycles	4 (6.6)	2 (4.4)	6 (5.7)
4 cycles	4 (6.6)	4 (8.9)	8 (7.5)
5 cycles	5 (8.2)	4 (8.9)	9 (8.5)
6 cycles	5 (8.2)	2 (4.4)	7 (6.6)
7 cycles	1 (1.6)	3 (6.7)	4 (3.8)
8 cycles	2 (3.3)	1 (2.2)	3 (2.8)
10 cycles	0	1 (2.2)	1 (0.9)
11 cycles	0	2 (4.4)	2 (1.9)
12 cycles	1 (1.6)	1 (2.2)	2 (1.9)
13 cycles	2 (3.3)	1 (2.2)	3 (2.8)
14 cycles	1 (1.6)	2 (4.4)	3 (2.8)
15 cycles	2 (3.3)	1 (2.2)	3 (2.8)
16 cycles	4 (6.6)	0	4 (3.8)
17 cycles	0	1 (2.2)	1 (0.9)
18 cycles	3 (4.9)	0	3 (2.8)
Patients with dose reductions, n (%)	34 (55.7)	17 (37.8)	51 (48.1)
Patients with 1 dose reduction, n (%)	30 (49.2)	17 (37.8)	47 (44.3)
Patients with ≥2 dose reductions, n (%)	4 (6.6)	0	4 (3.8)
Total number of dose reductions	56	17	73
Patients with dose increase, n (%)	11 (18.0)	9 (20.0)	20 (18.9)
Patients with 1 dose increase, n (%)	7 (11.5)	9 (20.0)	16 (15.1)
Patients with ≥2 dose increase, n (%)	4 (6.6)	0	4 (3.8)
Total number of dose increase	31	9	40
Patients with dose interruptions, n (%)	51 (83.6)	33 (73.3)	84 (79.2)
Total number of dose interruptions	360	197	557
Reason for dose interruptions, n (%)			
Adverse Event(s)	46 (75.4)	27 (60.0)	73 (68.9)
Not reported	1 (1.6)	0	1 (0.9)
Other	29 (47.5)	23 (51.1)	52 (49.1)

Source: Table 14.4.1.2
If there were no patients receiving a particular number of cycles, this was not displayed in the table.
Patient can contribute to more than one reason.
Patients are counted only once for each reason. Per protocol the patients were enrolled to receive drug treatment at 37.5 mg once a day.
If a patient receives treatment dose greater than the last dose received, then it is considered as dose increase.
If a patient receives treatment dose less than the last dose received, then it is considered as dose reduction.
Abbreviation: N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria.

For the global population, overall cumulative dose and relative dose intensity (RDI) are summarized in Table 8. The overall median RDI was 92.5% with a lower RDI in the treatment-naïve (86.9%) than the later-line (97.4%) cohort. The median average daily dose administered was 34.7 mg.

Table 8. Overall Cumulative Dose and Relative Dose Intensity – Safety Analysis Set; Global Population

	Treatment-Naïve Cohort N = 61	Later-Line Cohort N = 45	Total N = 106
Actual cumulative dose (mg)			
Median	11712.5	10237.5	10912.5
Mean	14442.8	16370.8	15261.3
SD	13510.79	16307.51	14719.56
Range	187.5 - 70687.5	525.0 - 67200.0	187.5 - 70687.5
Relative dose intensity (%)			
Median	86.9	97.4	92.5
Mean	83.7	91.1	86.8
SD	19.57	20.74	20.31
Range	34.2 - 129.6	47.3 - 130.9	34.2 - 130.9
Average daily dose as administered (mg)			
Median	32.6	36.5	34.7
Mean	31.4	34.1	32.6
SD	7.34	7.78	7.62
Range	12.8 - 48.6	17.7 - 49.1	12.8 - 49.1

Source: Table 14.4.1.3
Actual Cumulative Dose is actual total dose taken in the cycle.
Actual Dose Intensity is actual total dose taken in the cycle divided by actual number of days in the cycle including delays.
Relative Dose Intensity is % of Actual to Intended Dose Intensities.
Average Daily Dose is actual total dose taken divided by actual number of days in the study including delays.
Abbreviations: N = number of patients with at least 1 dose of study drug; SD = standard deviation.

The China subgroup SAS comprised of 31 patients, all of whom had received at least 1 dose of the study drug. The majority of patients (27 [87.1%] patients) received study drug for ≥91 days, and the median treatment duration was 329 days (Table 9).

Table 9. Duration of Treatment – Safety Analysis Set; China Subgroup

	Total N = 31
Duration category (days)	
≤1	0
2-7	0
8-14	0
15-28	0
29-60	4
61-90	0
≥91	27
Median duration (days)	329.0
Range (days)	29 - 1268

Source: Table 14.4.1.1
Duration of treatment is the time period starting from the date of first dose and ending at the last dose.
Abbreviation: N = number of patients with at least 1 dose of study drug.

In the China subgroup, patients received between 1 and 39 cycles, with a median of 12 cycles (Table 10). Overall, 13 (41.9%) patients had dose reductions, of which, the majority of patients had 1 dose reduction (10 [32.3%] patients) and 3 (9.7%) patients had 2 or more dose reductions. Of the 24 (77.4%) patients who had dose interruptions, the majority had the dose interruption due to an AE (21 [67.7%] patients), similar to the global cohort (68.9%) (Table 7). Overall 5 (16.1%) patients had at least 1 dose increase.

Table 10. Summary of Dose Administration – Safety Analysis Set; China Subgroup

	Total N = 31
Total number of cycles	459
Median (Range) of cycles administered	12 (1-39)
Patients with cycles administered, n (%):	
1 cycle	1 (3.2)
2 cycles	2 (6.5)
4 cycles	3 (9.7)
5 cycles	2 (6.5)
6 cycles	3 (9.7)
8 cycles	3 (9.7)
11 cycles	1 (3.2)
12 cycles	1 (3.2)
13 cycles	1 (3.2)
14 cycles	1 (3.2)
16 cycles	3 (9.7)
Patients with dose reductions, n (%)	13 (41.9)
Patients with 1 dose reduction, n (%)	10 (32.3)
Patients with ≥2 dose reductions, n (%)	3 (9.7)
Total number of dose reductions	34
Patients with dose increase, n (%)	5 (16.1)
Patients with 1 dose increase, n (%)	2 (6.5)
Patients with ≥2 dose increase, n (%)	3 (9.7)
Total number of dose increase	24
Patients with dose interruptions, n (%)	24 (77.4)
Total number of dose interruptions	134
Reason for dose interruptions, n (%)	
Adverse Event(s)	21 (67.7)
Not reported	1 (3.2)
Other	11 (35.5)

Source: Table 14.4.1.2.1
If there were no patients receiving a particular number of cycles, this is not displayed in the table.
Patient can contribute to more than one reason.
Patients are counted only once for each reason. Per protocol the patients were enrolled to receive drug treatment at 37.5 mg once a day.
If a patient receives treatment dose greater than the last dose received, then it is considered as dose increase.
If a patient receives treatment dose less than the last dose received, then it is considered as dose reduction.
Abbreviation: N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria.

For the China subgroup, cumulative dose and RDI are summarized in Table 11. Overall, the median RDI was 91.9% and median average daily dose administered was 34.5 mg.

Table 11. Overall Cumulative Dose and Relative Dose Intensity – Safety Analysis Set; China Subgroup

	Total N = 31
Actual cumulative dose (mg)	
Median	10100.0
Mean	14583.9
SD	13194.37
Range	1087.5 - 47550.0
Relative dose intensity (%)	
Median	91.9
Mean	87.3
SD	14.74
Range	56.6 - 100.0
Average daily dose as administered (mg)	
Median	34.5
Mean	32.7
SD	5.53
Range	21.2 - 37.5

Source: Table 14.4.1.3.1
Actual Cumulative Dose is actual total dose taken in the cycle.
Actual Dose Intensity is actual total dose taken in the cycle divided by actual number of days in the cycle including delays.
Relative Dose Intensity is a percentage of Actual to Intended Dose Intensities.
Average Daily Dose is actual total dose taken divided by actual number of days in the study including delays.
Abbreviations: N = number of patients with at least 1 dose of study drug; SD = standard deviation.

For the global population, by patient listings are provided for study drug administration schedule in Table 16.2.5.1, dose modification in Table 16.2.5.1.1, cumulative dose and RDI in 16.2.5.1.2, and for medication error in Table 16.2.5.1.3.

Adverse Events

Brief Summary of Adverse Events

In the global population, 1377 treatment-emergent adverse events (TEAEs) were reported in 104 (98.1%) patients, of which 770 TEAEs were reported in 59 (96.7%) patients in the treatment-naïve cohort and 607 TEAEs in 45 (100.0%) patients in later-line cohort (Table 12). A total of 29 (27.4%) patients experienced an SAE, with similar proportions in the 2 cohorts. Grade 5 TEAEs were reported in 4 (3.8%) patients, with similar proportions in the 2 cohorts. Of the Grade 5 events reported, none was related to the study treatment (Table 14.3.1.3.1) and all were reported as a TEAE of disease progression (Table 14.3.1.2.9.1). Grade 3 or 4 TEAEs were reported in a higher proportion of patients in the treatment-naïve (73.8%) than the later-line (66.7%) cohort. TEAEs resulted in temporary discontinuation of the study drug were reported in 68 (64.2%) patients, and permanent discontinuation in 22 (20.8%) patients. The study drug was reduced due to a TEAE in

25 (23.6%) patients, with a higher proportion of patients in the treatment-naïve (19 [31.1%] patients) than the later-line (6 [13.3%] patients) cohort.

Table 12. All-Causality Treatment-Emergent Adverse Events – Safety Analysis Set; Global Population

	Treatment-Naïve Cohort N = 61	Later-Line Cohort N = 45	Total N = 106
Number of AEs	770	607	1377
Patients, n (%)			
Patients with AEs	59 (96.7)	45 (100.0)	104 (98.1)
Patients with SAEs	17 (27.9)	12 (26.7)	29 (27.4)
Patients with Grade 3 or 4 AEs	45 (73.8)	30 (66.7)	75 (70.8)
Patients with Grade 5 AEs	2 (3.3)	2 (4.4)	4 (3.8)
Patients permanently discontinued due to AEs	11 (18.0)	11 (24.4)	22 (20.8)
Patients with dose reduced due to AEs	19 (31.1)	6 (13.3)	25 (23.6)
Patients with temporary discontinuation due to AEs	41 (67.2)	27 (60.0)	68 (64.2)

Source: Table 14.3.1.2.1
TEAEs were all AEs (serious and non-serious) that occurred for the first time on or after the first day of study drug and include data up to 9999 days after last dose of study drug. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
Except for the number of AEs patients are counted only once per cohort in each row.
SAEs - according to the investigator's assessment.
MedDRA (version 21) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria; SAE = serious adverse event; TEAE = treatment-emergent adverse events.

In the China subgroup, all patients experienced at least 1 TEAE regardless of the causality (Table 13). A total of 414 TEAEs were reported in 31 patients. Overall, 8 (25.8%) patients experienced an SAE. No Grade 5 TEAEs were reported. Overall, Grades 3 or 4 TEAEs were reported in 25 (80.6%) patients compared with 70.8% in the global population (Table 12). Permanent or temporary discontinuations due to TEAEs or dose modifications due to TEAEs were reported in a similar proportion of patients as in the global population. In general, the proportions of patients experiencing TEAEs from the categories analyzed were similar to those in the global population.

Table 13. All-Causality Treatment-Emergent Adverse Events – Safety Analysis Set; China Subgroup

	Total N = 31
Number of AEs	414
Patients, n (%):	
Patients with AEs	31 (100.0)
Patients with SAEs	8 (25.8)
Patients with Grade 3 or 4 AEs	25 (80.6)
Patients with Grade 5 AEs	0
Patients permanently discontinued due to AEs	5 (16.1)
Patients with dose reduced due to AEs	6 (19.4)
Patients with temporary discontinuation due to AEs	18 (58.1)

Source: Table 14.3.1.2.1.1
TEAEs were all AEs (serious and non-serious) that occurred for the first time on or after the first day of study drug and include data up to 9999 days after last dose of study drug. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
Except for the number of AEs patients are counted only once per cohort in each row.
SAEs - according to the investigator's assessment.
MedDRA (version 21.0) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria; SAE = serious adverse event; TEAE = treatment-emergent adverse events.

Incidence of Adverse Events

All-Causality Treatment-Emergent Adverse Events

In the global population, the most common TEAEs reported in ≥5% of patients in either cohort regardless of causality are summarized by System Organ Class (SOC) and Preferred Term (PT) in Table 14. Overall, the SOC with TEAEs reported at the highest by-patient frequency was Gastrointestinal disorders reported in 94 (88.7%) patients, followed by Blood and lymphatic system disorders in 70 (66.0%) patients and Skin and subcutaneous tissue disorders in 67 (63.2%) patients. Similar to the results reported in the primary CSR,[1] the 3 most commonly reported TEAEs were neutropenia reported in 60 (56.6%) patients, followed by diarrhea in 55 (51.9%) patients, and leukopenia in 47 (44.3%) patients. These 3 TEAEs were reported in 60.7%, 54.1%, and 42.6% of patients in the treatment-naïve cohort, respectively, compared to 51.1%, 48.9%, and 46.7% in the later-line cohort, respectively.

Table 14. All-Causality Treatment-Emergent Adverse Events Experienced by ≥5% of Patients in Either Cohort by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; Global Population

System Organ Class Preferred Term	Treatment-Naïve Cohort N = 61 n (%)	Later-Line Cohort N = 45 n (%)	Total N = 106 n (%)
Any AE	59 (96.7)	45 (100.0)	104 (98.1)
Blood and Lymphatic System Disorders	38 (62.3)	32 (71.1)	70 (66.0)
Anaemia	11 (18.0)	9 (20.0)	20 (18.9)
Leukopenia	26 (42.6)	21 (46.7)	47 (44.3)
Lymphopenia	4 (6.6)	3 (6.7)	7 (6.6)
Neutropenia	37 (60.7)	23 (51.1)	60 (56.6)
Thrombocytopenia	18 (29.5)	15 (33.3)	33 (31.1)
Endocrine Disorders	5 (8.2)	4 (8.9)	9 (8.5)
Hypothyroidism	5 (8.2)	3 (6.7)	8 (7.5)
Eye disorders	8 (13.1)	6 (13.3)	14 (13.2)
Lacrimation increased	3 (4.9)	0	3 (2.8)
Gastrointestinal disorders	53 (86.9)	41 (91.1)	94 (88.7)
Abdominal distension	4 (6.6)	3 (6.7)	7 (6.6)
Abdominal pain	16 (26.2)	11 (24.4)	27 (25.5)
Abdominal pain upper	6 (9.8)	7 (15.6)	13 (12.3)
Ascites	1 (1.6)	3 (6.7)	4 (3.8)
Constipation	3 (4.9)	7 (15.6)	10 (9.4)
Diarrhoea	33 (54.1)	22 (48.9)	55 (51.9)
Dyspepsia	8 (13.1)	14 (31.1)	22 (20.8)
Dysphagia	2 (3.3)	3 (6.7)	5 (4.7)
Flatulence	3 (4.9)	1 (2.2)	4 (3.8)
Gastrooesophageal reflux disease	4 (6.6)	4 (8.9)	8 (7.5)
Gingival bleeding	3 (4.9)	0	3 (2.8)
Mouth ulceration	4 (6.6)	5 (11.1)	9 (8.5)
Nausea	14 (23.0)	14 (31.1)	28 (26.4)
Oral Pain	1 (1.6)	3 (6.7)	4 (3.8)
Regurgitation	3 (4.9)	0	3 (2.8)
Stomatitis	15 (24.6)	6 (13.3)	21 (19.8)
Vomiting	8 (13.1)	10 (22.2)	18 (17.0)
General disorders and administration site conditions	35 (57.4)	29 (64.4)	64 (60.4)
Asthenia	11 (18.0)	7 (15.6)	18 (17.0)
Face oedema	3 (4.9)	1 (2.2)	4 (3.8)
Fatigue	20 (32.8)	13 (28.9)	33 (31.1)
Mucosal inflammation	6 (9.8)	5 (11.1)	11 (10.4)
Oedema	5 (8.2)	2 (4.4)	7 (6.6)
Oedema peripheral	5 (8.2)	3 (6.7)	8 (7.5)
Pain	1 (1.6)	3 (6.7)	4 (3.8)

Table 14. All-Causality Treatment-Emergent Adverse Events Experienced by ≥5% of Patients in Either Cohort by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; Global Population

System Organ Class Preferred Term	Treatment-Naïve Cohort N = 61 n (%)	Later-Line Cohort N = 45 n (%)	Total N = 106 n (%)
Pyrexia	6 (9.8)	8 (17.8)	14 (13.2)
Hepatobiliary Disorders	13 (21.3)	5 (11.1)	18 (17.0)
Hepatic function abnormal	3 (4.9)	0	3 (2.8)
Liver injury	3 (4.9)	0	3 (2.8)
Immune System Disorders	3 (4.9)	1 (2.2)	4 (3.8)
Hypersensitivity	3 (4.9)	0	3 (2.8)
Infections and Infestations	25 (41.0)	23 (51.1)	48 (45.3)
Influenza	1 (1.6)	3 (6.7)	4 (3.8)
Nasopharyngitis	6 (9.8)	2 (4.4)	8 (7.5)
Upper respiratory tract infection	3 (4.9)	2 (4.4)	5 (4.7)
Urinary tract infection	6 (9.8)	3 (6.7)	9 (8.5)
Investigations	32 (52.5)	22 (48.9)	54 (50.9)
Alanine aminotransferase increased	3 (4.9)	8 (17.8)	11 (10.4)
Aspartate aminotransferase increased	5 (8.2)	7 (15.6)	12 (11.3)
Blood alkaline phosphatase increased	2 (3.3)	3 (6.7)	5 (4.7)
Blood bilirubin increased	1 (1.6)	3 (6.7)	4 (3.8)
Blood creatinine increased	1 (1.6)	3 (6.7)	4 (3.8)
Blood potassium decreased	3 (4.9)	0	3 (2.8)
Blood thyroid stimulating hormone increased	5 (8.2)	2 (4.4)	7 (6.6)
Blood urine present	3 (4.9)	0	3 (2.8)
Haemoglobin decreased	4 (6.6)	2 (4.4)	6 (5.7)
Neutrophil count decreased	5 (8.2)	3 (6.7)	8 (7.5)
Protein urine present	1 (1.6)	3 (6.7)	4 (3.8)
Red blood cell count decreased	2 (3.3)	3 (6.7)	5 (4.7)
Weight decreased	11 (18.0)	7 (15.6)	18 (17.0)
Weight increased	5 (8.2)	2 (4.4)	7 (6.6)
White blood cell count decreased	6 (9.8)	1 (2.2)	7 (6.6)
White blood cells urine positive	3 (4.9)	0	3 (2.8)
Metabolism and Nutrition Disorders	22 (36.1)	21 (46.7)	43 (40.6)
Decreased appetite	7 (11.5)	7 (15.6)	14 (13.2)
Hyperglycaemia	3 (4.9)	3 (6.7)	6 (5.7)
Hypocalcaemia	2 (3.3)	6 (13.3)	8 (7.5)
Hypoglycaemia	3 (4.9)	4 (8.9)	7 (6.6)
Hypokalaemia	7 (11.5)	4 (8.9)	11 (10.4)
Hypomagnesaemia	5 (8.2)	3 (6.7)	8 (7.5)

Table 14. All-Causality Treatment-Emergent Adverse Events Experienced by ≥5% of Patients in Either Cohort by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; Global Population

System Organ Class Preferred Term	Treatment-Naïve Cohort N = 61 n (%)	Later-Line Cohort N = 45 n (%)	Total N = 106 n (%)
Hypophosphataemia	2 (3.3)	7 (15.6)	9 (8.5)
Musculoskeletal and Connective Tissue Disorders	20 (32.8)	21 (46.7)	41 (38.7)
Arthralgia	4 (6.6)	4 (8.9)	8 (7.5)
Back pain	2 (3.3)	7 (15.6)	9 (8.5)
Muscle spasms	4 (6.6)	3 (6.7)	7 (6.6)
Myalgia	3 (4.9)	7 (15.6)	10 (9.4)
Pain in extremity	7 (11.5)	2 (4.4)	9 (8.5)
Nervous System Disorders	32 (52.5)	22 (48.9)	54 (50.9)
Dizziness	3 (4.9)	7 (15.6)	10 (9.4)
Dysgeusia	14 (23.0)	11 (24.4)	25 (23.6)
Headache	12 (19.7)	9 (20.0)	21 (19.8)
Paraesthesia	3 (4.9)	0	3 (2.8)
Psychiatric Disorders	3 (4.9)	5 (11.1)	8 (7.5)
Insomnia	0	3 (6.7)	3 (2.8)
Renal and Urinary Disorders	10 (16.4)	11 (24.4)	21 (19.8)
Proteinuria	5 (8.2)	7 (15.6)	12 (11.3)
Respiratory, Thoracic and Mediastinal Disorders	20 (32.8)	17 (37.8)	37 (34.9)
Cough	2 (3.3)	6 (13.3)	8 (7.5)
Dyspnoea	2 (3.3)	4 (8.9)	6 (5.7)
Epistaxis	7 (11.5)	5 (11.1)	12 (11.3)
Oropharyngeal pain	4 (6.6)	5 (11.1)	9 (8.5)
Skin and Subcutaneous Tissue Disorders	42 (68.9)	25 (55.6)	67 (63.2)
Alopecia	7 (11.5)	1 (2.2)	8 (7.5)
Dry skin	4 (6.6)	2 (4.4)	6 (5.7)
Erythema	0	4 (8.9)	4 (3.8)
Hair colour changes	0	6 (13.3)	6 (5.7)
Hyperkeratosis	5 (8.2)	1 (2.2)	6 (5.7)
Nail discolouration	3 (4.9)	0	3 (2.8)
Palmar-plantar erythrodysaesthesia subcutaneous tissue syndrome	19 (31.1)	14 (31.1)	33 (31.1)
Pigmentation disorder	5 (8.2)	1 (2.2)	6 (5.7)
Pruritus	1 (1.6)	3 (6.7)	4 (3.8)
Rash	7 (11.5)	3 (6.7)	10 (9.4)
Skin exfoliation	8 (13.1)	1 (2.2)	9 (8.5)
Vascular disorders	19 (31.1)	15 (33.3)	34 (32.1)

Table 14. All-Causality Treatment-Emergent Adverse Events Experienced by ≥5% of Patients in Either Cohort by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; Global Population

System Organ Class Preferred Term	Treatment-Naïve Cohort N = 61 n (%)	Later-Line Cohort N = 45 n (%)	Total N = 106 n (%)
Deep vein thrombosis	3 (4.9)	1 (2.2)	4 (3.8)
Hypertension	16 (26.2)	13 (28.9)	29 (27.4)

Source: Table 14.3.1.2.9.1
Patients are only counted once per cohort for each row.
TEAEs were all AEs (serious and non-serious) that occurred for the first time on or after the first day of study drug and include data up to 9999 days after last dose of study drug. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
MedDRA (version 21.0) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria; TEAE = treatment-emergent adverse event.

In the China subgroup, TEAEs reported in ≥3 patients regardless of causality are summarized by SOC and PT in Table 15. Overall, the SOC with TEAEs reported at the highest by-patient frequency was Blood and lymphatic system disorders reported in 27 (87.1%) patients, followed by Gastrointestinal disorders and Skin and subcutaneous tissue disorders, both in 25 (80.6%) patients. Similar to the results reported in the China subgroup primary CSR,[2] the 3 most commonly reported TEAEs were leukopenia reported in 24 (77.4%) patients, followed by neutropenia in 23 (74.2%) patients, and thrombocytopenia in 15 (48.4%) patients, all in the SOC Blood and lymphatic disorders. Diarrhea, which was one of the most commonly reported TEAEs in the global cohort (Table 14), was reported in a high proportion of patients in the China subgroup as well (14 [45.2%] patients).

In general, the type and frequency of the TEAEs reported in the global population and China subpopulation were similar to those reported in the respective primary CSRs.[1,2]

Table 15. All-Causality Treatment-Emergent Adverse Events Experienced by ≥3 Patients by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; China Subgroup

System Organ Class Preferred Term	Total N = 31 n (%)
Any AE	31 (100%)
Blood and Lymphatic System Disorders	27 (87.1)
Anaemia	7 (22.6)
Leukopenia	24 (77.4)
Neutropenia	23 (74.2)
Thrombocytopenia	15 (48.4)
Endocrine disorders	4 (12.9)
Hypothyroidism	3 (9.7)
Eye disorders	5 (16.1)
Eyelid oedema	3 (9.7)
Gastrointestinal Disorders	25 (80.6)
Abdominal distension	4 (12.9)
Abdominal pain	8 (25.8)
Abdominal pain upper	6 (19.4)
Diarrhoea	14 (45.2)
Gastrooesophageal reflux disease	3 (9.7)
Mouth ulceration	7 (22.6)
Nausea	3 (9.7)
Regurgitation	3 (9.7)
Stomatitis	5 (16.1)
General Disorders and Administration Site Conditions	13 (41.9)
Fatigue	7 (22.6)
Oedema	4 (12.9)
Pyrexia	4 (12.9)
Hepatobiliary disorders	6 (19.4)
Hepatic function abnormal	3 (9.7)
Liver injury	3 (9.7)
Investigations	20 (64.5)
Alanine aminotransferase increased	5 (16.1)
Aspartate aminotransferase increased	6 (19.4)
Blood bilirubin increased	3 (9.7)
Blood potassium decreased	3 (9.7)
Blood thyroid stimulating hormone increased	5 (16.1)
Blood urine present	3 (9.7)
Electrocardiogram T wave abnormal	3 (9.7)
Haemoglobin decreased	3 (9.7)
Neutrophil count decreased	5 (16.1)
Red blood cell count decreased	5 (16.1)
Weight decreased	7 (22.6)

Table 15. All-Causality Treatment-Emergent Adverse Events Experienced by ≥3 Patients by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; China Subgroup

System Organ Class Preferred Term	Total N = 31 n (%)
Weight increased	4 (12.9)
White blood cell count decreased	4 (12.9)
White blood cells urine positive	3 (9.7)
Metabolism and nutrition disorders	11 (35.5)
Decreased appetite	4 (12.9)
Hypocalcaemia	6 (19.4)
Hypokalaemia	5 (16.1)
Hypophosphataemia	3 (9.7)
Musculoskeletal Connective Tissue Disorders	11 (35.5)
Pain in extremity	4 (12.9)
Nervous system disorders	12 (38.7)
Dysgeusia	6 (19.4)
Headache	3 (9.7)
Hypogeusia	3 (9.7)
Renal and Urinary Disorders	9 (29.0)
Proteinuria	9 (29.0)
Respiratory, Thoracic and Mediastinal Disorders	7 (22.6)
Oropharyngeal pain	3 (9.7)
Skin and Subcutaneous Tissue Disorders	25 (80.6)
Alopecia	3 (9.7)
Hyperkeratosis	5 (16.1)
Nail discolouration	3 (9.7)
Palmar-plantar erythrodysaesthesia syndrome	6 (19.4)
Pigmentation disorder	5 (16.1)
Rash	5 (16.1)
Skin exfoliation	8 (25.8)
Vascular disorders	6 (19.4)
Hypertension	5 (16.1)

Source: Table 14.3.1.2.9.1.1
TEAEs were all AEs (serious and non-serious) that occurred for the first time on or after the first day of study drug and include data up to 9999 days after last dose of study drug. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
MedDRA (version 21.0) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients with at least 1 dose of study drug; TEAE = treatment-emergent adverse event.

Treatment-Related Treatment-Emergent Adverse Events

For the global population, a summary of treatment-related TEAEs is presented in Table 16. Of the total 1377 TEAEs reported (Table 12), 981 TEAEs were considered treatment-related. At least 1 treatment-related TEAE was reported in a total of 101 (95.3%) patients; 57 (93.4%) patients in the treatment-naïve cohort and 44 (97.8%) patients in the later-line cohort. Overall, 12 (11.3%) patients experienced a treatment-related SAE, with a higher proportion of patients in the treatment-naïve (14.8% patients) than the later-line cohort (6.7% patients). There were no Grade 5 treatment-related TEAEs reported. Grade 3 or 4 treatment-related TEAEs were reported in a higher proportion of patients in the treatment-naïve (37 [60.7%] patients) than the later-line (21 [46.7%] patients) cohort. A treatment-related TEAE resulted in the study drug being either permanently or temporarily discontinued in a total of 12.3% and 59.4% of the patients, respectively, with similar proportions of patients in the 2 cohorts for both categories. The study drug was reduced due to a treatment-related TEAE in a higher proportion of patients in the treatment-naïve (31.1% patients) than the later-line (13.3% patients) cohort.

Table 16. Treatment-Related Treatment-Emergent Adverse Events – Safety Analysis Set; Global Population

	Treatment-Naïve Cohort N = 61	Later-Line Cohort N = 45	Total N = 106
Number of AEs	577	404	981
Patients, n (%)			
Patients with AEs	57 (93.4)	44 (97.8)	101 (95.3)
Patients with SAEs	9 (14.8)	3 (6.7)	12 (11.3)
Patients with Grade 3 or 4 AEs	37 (60.7)	21 (46.7)	58 (54.7)
Patients with Grade 5 AEs	0	0	0
Patients permanently discontinued due to AEs	8 (13.1)	5 (11.1)	13 (12.3)
Patients with dose reduced due to AEs	19 (31.1)	6 (13.3)	25 (23.6)
Patients with temporary discontinuation due to AEs	37 (60.7)	26 (57.8)	63 (59.4)

Source: Table 14.3.1.3.1
TEAEs were all AEs (serious and non-serious) that occurred for the first time on or after the first day of study drug and include data up to 9999 days after last dose of study drug. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
Patients are counted only once per cohort in each row.
SAEs - according to the investigator's assessment.
MedDRA (version 21) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

In the China subgroup, treatment-related TEAEs are summarized in Table 17. Of the total 414 TEAEs reported (Table 13), 344 TEAEs were considered treatment-related. There were no Grade 5 treatment-related TEAEs reported. Grade 3 or 4 treatment-related TEAEs were reported in 19 (61.3%) patients. A total of 5 (16.1%) patients experienced an SAE. A

treatment-related TEAE resulted in the study drug being temporarily discontinued in 17 (54.8%) patients, reduced in 6 (19.4%) patients, and permanently discontinued in 3 (9.7%) patients.

Table 17. Treatment-Related Treatment-Emergent Adverse Events – Safety Analysis Set; China Subgroup

	Total N = 31
Number of AEs	344
Patients, n (%)	
Patients with AEs	31 (100.0)
Patients with SAEs	5 (16.1)
Patients with Grade 3 or 4 AEs	19 (61.3)
Patients with Grade 5 AEs	0
Patients permanently discontinued due to AEs	3 (9.7)
Patients with dose reduced due to AEs	6 (19.4)
Patients with temporary discontinuation due to AEs	17 (54.8)

Source: Table 14.3.1.3.1.1
TEAEs were all AEs (serious and non-serious) that occurred for the first time on or after the first day of study drug and include data up to 9999 days after last dose of study drug. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
Patients are counted only once per cohort in each row.
SAEs - according to the investigator's assessment.
MedDRA (version 21.0) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

For the global population, treatment-related TEAEs by SOC and PT reported at a frequency of ≥5% in either cohort are presented in Table 18. Overall, the SOC with treatment-related TEAEs reported at the highest by patient frequency was Gastrointestinal disorders reported in 83 (78.3%) patients, followed by Blood and lymphatic system disorders in 68 (64.2%) patients, and Skin and subcutaneous tissue disorders in 64 (60.4%) patients. As reported in the primary CSR,[1] the 3 most commonly reported treatment-related TEAEs overall were neutropenia reported in 58 (54.7%) patients, followed by diarrhea in 50 (47.2%) patients, and leukopenia in 47 (44.3%) patients. Neutropenia and diarrhea were reported in a higher proportion of patients in the treatment-naïve cohort (59.0% and 49.2%, respectively) than in the later-line cohort (48.9% and 44.4%, respectively); and leukopenia in 42.6% and 46.7% patients in the 2 cohorts, respectively.

In general, the frequency pattern of the treatment-related TEAEs was similar to that described for all-causality TEAEs (Table 14).

Table 18. Treatment-Related Treatment-Emergent Adverse Events Experienced by ≥5% of Patients in Either Cohort by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; Global Population

System Organ Class Preferred Term	Treatment-Naïve Cohort N = 61 n (%)	Later-Line Cohort N = 45 n (%)	Total N = 106 n (%)
Any AE	57 (93.4)	44 (97.8)	101 (95.3)
Blood and Lymphatic System Disorders	37 (60.7)	31 (68.9)	68 (64.2)
Anaemia	8 (13.1)	9 (20.0)	17 (16.0)
Leukopenia	26 (42.6)	21 (46.7)	47 (44.3)
Lymphopenia	4 (6.6)	3 (6.7)	7 (6.6)
Neutropenia	36 (59.0)	22 (48.9)	58 (54.7)
Thrombocytopenia	18 (29.5)	15 (33.3)	33 (31.1)
Endocrine Disorders	5 (8.2)	4 (8.9)	9 (8.5)
Hypothyroidism	5 (8.2)	3 (6.7)	8 (7.5)
Eye disorders	7 (11.5)	2 (4.4)	9 (8.5)
Lacrimation increased	3 (4.9)	0	3 (2.8)
Gastrointestinal disorders	48 (78.7)	35 (77.8)	83 (78.3)
Abdominal distension	3 (4.9)	3 (6.7)	6 (5.7)
Abdominal pain	7 (11.5)	2 (4.4)	9 (8.5)
Abdominal pain upper	3 (4.9)	5 (11.1)	8 (7.5)
Constipation	0	4 (8.9)	4 (3.8)
Diarrhoea	30 (49.2)	20 (44.4)	50 (47.2)
Dyspepsia	6 (9.8)	11 (24.4)	17 (16.0)
Flatulence	3 (4.9)	0	3 (2.8)
Gastrooesophageal reflux disease	4 (6.6)	4 (8.9)	8 (7.5)
Mouth ulceration	4 (6.6)	5 (11.1)	9 (8.5)
Nausea	11 (18.0)	13 (28.9)	24 (22.6)
Oral Pain	1 (1.6)	3 (6.7)	4 (3.8)
Regurgitation	3 (4.9)	0	3 (2.8)
Stomatitis	14 (23.0)	6 (13.3)	20 (18.9)
Vomiting	5 (8.2)	4 (8.9)	9 (8.5)
General disorders and administration site conditions	29 (47.5)	19 (42.2)	48 (45.3)
Asthenia	7 (11.5)	5 (11.1)	12 (11.3)
Fatigue	18 (29.5)	9 (20.0)	27 (25.5)
Mucosal inflammation	5 (8.2)	4 (8.9)	9 (8.5)
Oedema	5 (8.2)	2 (4.4)	7 (6.6)
Oedema peripheral	5 (8.2)	0	5 (4.7)
Pyrexia	2 (3.3)	3 (6.7)	5 (4.7)
Hepatobiliary Disorders	10 (16.4)	1 (2.2)	11 (10.4)
Hepatic function abnormal	3 (4.9)	0	3 (2.8)
Liver injury	3 (4.9)	0	3 (2.8)

Table 18. Treatment-Related Treatment-Emergent Adverse Events Experienced by ≥5% of Patients in Either Cohort by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; Global Population

System Organ Class Preferred Term	Treatment-Naïve Cohort N = 61 n (%)	Later-Line Cohort N = 45 n (%)	Total N = 106 n (%)
Infections and Infestations	14 (23.0)	9 (20.0)	23 (21.7)
Nasopharyngitis	3 (4.9)	0	3 (2.8)
Investigations	23 (37.7)	15 (33.3)	38 (35.8)
Alanine aminotransferase increased	3 (4.9)	5 (11.1)	8 (7.5)
Aspartate aminotransferase increased	5 (8.2)	5 (11.1)	10 (9.4)
Blood bilirubin increased	1 (1.6)	3 (6.7)	4 (3.8)
Blood potassium decreased	3 (4.9)	0	3 (2.8)
Blood thyroid stimulating hormone increased	5 (8.2)	2 (4.4)	7 (6.6)
Blood urine present	3 (4.9)	0	3 (2.8)
Haemoglobin decreased	4 (6.6)	2 (4.4)	6 (5.7)
Neutrophil count decreased	5 (8.2)	3 (6.7)	8 (7.5)
Protein urine present	1 (1.6)	3 (6.7)	4 (3.8)
Red blood cell count decreased	2 (3.3)	3 (6.7)	5 (4.7)
Weight decreased	3 (4.9)	3 (6.7)	6 (5.7)
White blood cell count decreased	6 (9.8)	1 (2.2)	7 (6.6)
Metabolism and Nutrition Disorders	16 (26.2)	12 (26.7)	28 (26.4)
Decreased appetite	7 (11.5)	3 (6.7)	10 (9.4)
Hypocalcaemia		6 (13.3)	8 (7.5)
Hypokalaemia	5 (8.2)	1 (2.2)	6 (5.7)
Hypomagnesaemia	4 (6.6)	2 (4.4)	6 (5.7)
Hypophosphataemia	1 (1.6)	5 (11.1)	6 (5.7)
Musculoskeletal and Connective Tissue Disorders	11 (18.0)	13 (28.9)	24 (22.6)
Arthralgia	3 (4.9)	2 (4.4)	5 (4.7)
Back Pain	1 (1.6)	4 (8.9)	5 (4.7)
Muscle spasms	3 (4.9)	2 (4.4)	5 (4.7)
Myalgia	0	7 (15.6)	7 (6.6)
Pain in extremity	5 (8.2)	1 (2.2)	6 (5.7)
Nervous System Disorders	24 (39.3)	17 (37.8)	41 (38.7)
Dizziness	2 (3.3)	5 (11.1)	7 (6.6)
Dysgeusia	13 (21.3)	11 (24.4)	24 (22.6)
Headache	7 (11.5)	6 (13.3)	13 (12.3)
Paraesthesia	3 (4.9)	0	3 (2.8)
Renal and Urinary Disorders	6 (9.8)	7 (15.6)	13 (12.3)
Proteinuria	4 (6.6)	5 (11.1)	9 (8.5)
Respiratory, Thoracic and Mediastinal Disorders	14 (23.0)	11 (24.4)	25 (23.6)
Dyspnoea	1 (1.6)	3 (6.7)	4 (3.8)

Table 18. Treatment-Related Treatment-Emergent Adverse Events Experienced by ≥5% of Patients in Either Cohort by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; Global Population

System Organ Class Preferred Term	Treatment-Naïve Cohort N = 61 n (%)	Later-Line Cohort N = 45 n (%)	Total N = 106 n (%)
Epistaxis	6 (9.8)	5 (11.1)	11 (10.4)
Skin and Subcutaneous Tissue Disorders	40 (65.6)	24 (53.3)	64 (60.4)
Alopecia	7 (11.5)	1 (2.2)	8 (7.5)
Dry skin	4 (6.6)	2 (4.4)	6 (5.7)
Erythema	0	3 (6.7)	3 (2.8)
Hair colour changes	0	6 (13.3)	6 (5.7)
Hyperkeratosis	5 (8.2)	1 (2.2)	6 (5.7)
Nail discolouration	3 (4.9)	0	3 (2.8)
Palmar-plantar erythrodysaesthesia syndrome	19 (31.1)	14 (31.1)	33 (31.1)
Pigmentation disorder	5 (8.2)	1 (2.2)	6 (5.7)
Rash	7 (11.5)	3 (6.7)	10 (9.4)
Skin exfoliation	8 (13.1)	1 (2.2)	9 (8.5)
Vascular disorders	16 (26.2)	10 (22.2)	26 (24.5)
Hypertension	14 (23.0)	9 (20.0)	23 (21.7)

Source: Table 14.3.1.3.9.1
Patients are only counted once per cohort for each row.
TEAEs were all AEs (serious and non-serious) that occurred for the first time on or after the first day of study drug and include data up to 9999 days after last dose of study drug. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
MedDRA (version 21.0) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria;
TEAE = treatment-emergent adverse event.

For the China subgroup, treatment-related TEAEs experienced by at least 3 patients overall are presented by SOC and PT in Table 19. Overall, the SOC with treatment-related TEAEs reported at the highest by patient frequency was Blood and lymphatic system disorders reported in 27 (87.1%) patients, followed by Skin and subcutaneous tissue disorders reported in 25 (80.6%) patients and Gastrointestinal disorders reported in 22 (71.0%) patients. All the reported all-causality TEAEs in the SOC Blood and lymphatic system disorders (Table 15) were considered treatment-related. Therefore, the 3 most commonly reported all-causality TEAEs were also the 3 most commonly reported treatment-related TEAEs and were all in the SOC Blood and lymphatic system disorders: leukopenia reported in 24 (77.4%) patients, followed by neutropenia in 23 (74.2%) patients, and thrombocytopenia in 15 (48.4%) patients. Diarrhea, which was one of the most commonly reported treatment-related TEAEs in the global cohort (Table 18) was reported in a high proportion of patients in the China subgroup as well (13 [41.9%] patients).

In general, most of the frequently reported TEAEs were treatment-related and the overall frequency pattern of TEAEs was similar to that reported in the primary CSRs.[1,2]

Table 19. Treatment-Related Treatment-Emergent Adverse Events Experienced by ≥3 Patients, by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; China Subgroup

System Organ Class Preferred Term	Total N = 31 n (%)
Any AE	31 (100%)
Blood and Lymphatic System Disorders	27 (87.1)
Anaemia	4 (12.9)
Leukopenia	24 (77.4)
Neutropenia	23 (74.2)
Thrombocytopenia	15 (48.4)
Endocrine disorders	4 (12.9)
Hypothyroidism	3 (9.7)
Eye disorders	5 (16.1)
Eyelid oedema	3 (9.7)
Gastrointestinal Disorders	22 (71.0)
Abdominal distension	4 (12.9)
Abdominal pain	3 (9.7)
Abdominal pain upper	4 (12.9)
Diarrhoea	13 (41.9)
Gastrooesophageal reflux disease	3 (9.7)
Mouth ulceration	7 (22.6)
Regurgitation	3 (9.7)
Stomatitis	5 (16.1)
General Disorders and Administration Site Conditions	10 (32.3)
Fatigue	7 (22.6)
Oedema	4 (12.9)
Hepatobiliary disorders	5 (16.1)
Hepatic function abnormal	3 (9.7)
Liver injury	3 (9.7)
Investigations	18 (58.1)
Alanine aminotransferase increased	4 (12.9)
Aspartate aminotransferase increased	5 (16.1)
Blood bilirubin increased	3 (9.7)
Blood potassium decreased	3 (9.7)
Blood thyroid stimulating hormone increased	5 (16.1)
Blood urine present	3 (9.7)
Electrocardiogram T wave abnormal	3 (9.7)
Haemoglobin decreased	3 (9.7)
Neutrophil count decreased	5 (16.1)
Red blood cell count decreased	5 (16.1)
Weight decreased	3 (9.7)
White blood cell count decreased	4 (12.9)

Table 19. Treatment-Related Treatment-Emergent Adverse Events Experienced by ≥3 Patients, by System Organ Class and Preferred Term (All Cycles, All Grades) – Safety Analysis Set; China Subgroup

System Organ Class Preferred Term	Total N = 31 n (%)
Metabolism and nutrition disorders	9 (29.0)
Hypocalcaemia	6 (19.4)
Hypokalaemia	3 (9.7)
Musculoskeletal Connective Tissue Disorders	8 (25.8)
Pain in extremity	3 (9.7)
Nervous system disorders	10 (32.3)
Dysgeusia	6 (19.4)
Hypogeusia	3 (9.7)
Renal and Urinary Disorders	6 (19.4)
Proteinuria	6 (19.4)
Skin and Subcutaneous Tissue Disorders	25 (80.6)
Alopecia	3 (9.7)
Hyperkeratosis	5 (16.1)
Nail discolouration	3 (9.7)
Palmar-plantar erythrodysaesthesia syndrome	6 (19.4)
Pigmentation disorder	5 (16.1)
Rash	5 (16.1)
Skin exfoliation	8 (25.8)
Vascular disorders	5 (16.1)
Hypertension	4 (12.9)

Source: Table 14.3.1.3.9.1.1
TEAEs were all AEs (serious and non-serious) that occurred for the first time on or after the first day of study drug and include data up to 9999 days after last dose of study drug. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
MedDRA (version 21.0) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria;
TEAE = treatment-emergent adverse event.

Listing of Adverse Events by Patient

See Section 16.2.7.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths

For the global population, deaths are summarized in Table 20, individual listings of deaths are presented in Table 14.3.2.1 and notice of death listing is provided in Table 14.3.2.1.3. Of the 48 deaths reported in the overall population (45.3% of patients), the majority occurred during the follow-up period (44 [41.5%] patients): 18 (29.5%) patients in the treatment-naïve cohort and 26 (57.8%) patients in the later-line cohort. There were no deaths due to study treatment toxicity. All deaths that occurred during the treatment period (4 [3.8%] patients) and the majority of deaths during the follow-up period (38 [35.8%] patients) were considered to be related to the disease under study. In 4 (3.8%) patients, the reason for death was reported as "Other": pneumonia and multiple organ failure (both in 1 patient), liver failure, respiratory failure, and disease progression (in 1 patient each; 3 patients) (Table 14.3.2.1.3). In 2 patients (1.9%) the reason for death was unknown.

Table 20. Summary of Deaths – Safety Analysis Set; Global Population

	Treatment-Naïve Cohort N = 61 n (%)	Later-Line Cohort N = 45 n (%)	Total N = 106 n (%)
Deaths[a]	20 (32.8)	28 (62.2)	48 (45.3)
Patients who died while on-treatment[b]	2 (3.3)	2 (4.4)	4 (3.8)
Disease under study	2 (3.3)	2 (4.4)	4 (3.8)
Study treatment toxicity	0	0	0
Unknown	0	0	0
Other	0	0	0
Patients who died during follow-up[c]	18 (29.5)	26 (57.8)	44 (41.5)
Disease under study	14 (23.0)	24 (53.3)	38 (35.8)
Study treatment toxicity	0	0	0
Unknown	2 (3.3)	0	2 (1.9)
Other	2 (3.3)	2 (4.4)	4 (3.8)

Source: Table 14.3.2.1.2
[a]Investigator was notified of death of 1 patient enrolled in China in the treatment-naïve cohort after the patient discontinued from study.
[b] On-treatment deaths are those that occurred after the first dose of study drug and within 28 days of last dose.
[c] Follow-up deaths are those that occurred after 28 days of last dose.
Abbreviations: N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria.

For the China subgroup, deaths are summarized in Table 21, individual listings of deaths are presented in Table 14.3.2.1.1 and notice of death listing is provided in Table 14.3.2.1.3.1. A total of 10 (32.3%) patients died in the China subgroup, all during the follow-up period, and in 6 (19.4%) patients, death was considered to be related to the disease under study. There were no deaths due to study treatment toxicity. In 3 (9.7%) patients, the reason for death was

reported as "Other": liver failure, respiratory failure, and disease progression (in 1 patient each) (Table 14.3.2.1.3.1). In 1 (3.2%) patient the reason for death was unknown.

Table 21. Summary of Deaths – Safety Analysis Set; China Subgroup

	Total N = 31 n (%)
Deaths[a]	10 (32.3)
Patients who died while on-treatment[b]	0
Patients who died during follow-up[c]	10 (32.3)
Disease under study	6 (19.4)
Study treatment toxicity	0
Unknown	1 (3.2)
Other	3 (9.7)

Source: Table 14.3.2.1.2.1
[a]Investigator was notified of death of 1 patient enrolled in China in the treatment-naïve cohort after the patient discontinued from study.
[b]On-treatment deaths are those that occurred after the first dose of study drug and within 28 days of last dose.
[c]Follow-up deaths are those that occurred after 28 days of last dose.
Abbreviations: N = number of patients with at least 1 dose of study drug; n = number of patients who met the criteria.

Council for International Organizations of Medical Sciences (CIOMS) reports for deaths that were reported are available in Section 14.3.3.

Other Serious Adverse Events

For the global population, SAEs were reported in a total of 29 (27.4%) patients, of which 17 (27.9%) patients were in the treatment-naïve cohort and 12 (26.7%) patients in the later-line cohort (Table 12). SAEs for the global population are presented by SOC, PT, severity grade and cohort in Table 14.3.2.2.2. Of the total SAEs reported, the severity was Grade 5 in 4 (3.8%) patients, Grade 4 in 9 (8.5%) patients, Grade 3 in 14 (13.2%) patients, and Grade 2 in 2 (1.9%) patients. The SOC with by far the most commonly reported SAEs was Gastrointestinal disorders (13 [12.3%] patients). The most commonly reported SAEs were abdominal pain (Grades 2 or 3) and disease progression (all Grade 5), both reported in 4 (3.8%) patients each. SAEs are detailed by the actual treatment group in Table 14.3.2.2.

For the China subgroup, SAEs were reported in a total of 8 (25.8%) patients, (Table 13). SAEs are detailed by the actual treatment group in Table 14.3.2.2.1.1. The data for the China subgroup on SAEs by SOC, PT, severity grade and cohort are part of the data for the global population presented in Table 14.3.2.2.2.

Other Significant Adverse Events

Thyroid Dysfunction

For the global population, all-causality TEAEs related to thyroid dysfunction were reported in a total of 10 (9.4%) patients: 6 (9.8%) patients in the treatment-naïve cohort and 4 (8.9%) patients in the later-line cohort (Table 14.3.1.2.9.5). All these TEAEs were of severity Grades 1 or 2. Overall, hypothyroidism was the single most commonly reported TEAE in this category, reported in 8 (7.5%) patients.

For the China subgroup, all-causality TEAEs related to thyroid dysfunction were reported in a total of 5 (16.1%) patients (Table 14.3.1.2.9.5.1). Similar to the global population, all such events were severity Grades 1 or 2; and hypothyroidism was the single most commonly reported TEAE in this category, reported in 3 (9.7%) patients.

All-causality TEAEs related to thyroid stimulating hormone (TSH) were reported in the global population in a total of 8 (7.5%) patients, all with severity Grades 1 or 2 (Table 14.3.1.2.9.6); and in the China subgroup in a total of 5 (16.1%) patients, all with severity Grade 1 (Table 14.3.1.2.9.6.1).

Proteinuria

All-causality TEAEs related to proteinuria were of severity Grades 1, 2 or 3, reported in the global population in a total of 15 (14.2%) patients (Table 14.3.1.2.9.7); and in the China subgroup in a total of 10 (32.3%) patients (Table 14.3.1.2.9.7.1).

Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Death Narratives

CIOMS reports of patients who died during the treatment period or the 28-day post-treatment period were provided in the primary CSRs for the global population and the China subgroup. Deaths occurring in the survival follow-up period are not included in the safety narratives (Section 14.3.3.1), as per the Safety Narratives Plan.

Other Serious Adverse Event Narratives

CIOMS reports for patients who experienced any treatment-related SAEs or SAEs resulting in permanent discontinuation are provided in Sections 14.3.3.2.1 and 14.3.3.2.2, respectively.

Other Adverse Events Narratives

A prose narrative for a patient who experienced a non-serious AE that resulted in discontinuation is provided in Section 14.3.3.3.1.

Clinical Laboratory Evaluation

Abnormal values that the investigator determined to be clinically significant were reported as AEs.

Laboratory data are presented for the global population in Table 16.2.8.1.1 and Table 16.2.8.1.4, and by NCI-CTC grade in Table 16.2.8.1.1.1. Laboratory test abnormalities are listed by patient in Table 16.2.8.1.2 and by test in Table 16.2.8.1.3. Hematology and Chemistry test results of Grade ≥3 are listed in Table 16.2.8.1.5 and Table 16.2.8.1.6, respectively. China subgroup data were not separately analyzed for these safety measures. There were no notable clinical laboratory evaluations reported other than those described in the primary CSR.[1]

Vital Signs, Electrocardiogram, and Physical Findings

China subgroup data was part of the global subpopulation data and were not separately analyzed for these safety measures.

Vital Signs

Vital signs data for the SAS are provided in Table 16.2.8.2.1, vital signs change from baseline in Table 16.2.8.2.2, and vital signs in specific categories in Table 16.2.8.2.4. There were no notable vital signs observations reported other than those described in the primary CSR.[1]

Electrocardiogram Results

ECG data for the SAS are provided in Table 16.2.8.3.1, and ECG change from baseline data in Table 16.2.8.3.2. Changes in QTcB and QTcF interval within normal range at baseline to ≥30 msec post-baseline were observed in 18 and 15 patients, respectively. Overall, mean changes from baseline in QTcB and QTcF interval during and at the end of treatment were small. Clinically meaningful ECG abnormalities, all of severity Grade 1, were reported as AEs in the SOC Investigations in 5 (4.7%) patients (Table 14.3.1.3.9.1).

Physical Findings

Physical examinations data for the SAS for changes from screening are provided in Table 16.2.8.4.2.

CONCLUSIONS

Efficacy

As reported in the primary CSR, Study A6181202 met its primary objective of confirming sunitinib treatment effect on PFS per investigator assessment in patients with advanced metastatic, well-differentiated, unresectable pNETs per RECIST 1.0, with a median investigator-assessed PFS of 13.2 months (95% CI: 10.9, 16.7). As estimation of OS was one of the planned secondary endpoints of the study, patients were followed-up to collect survival data. OS data for the global population and the China subgroup presented in this sCSR are summarized as follows.

Global population:

- Of the 106 patients enrolled, 61 patients were in the treatment-naïve cohort and 45 patients in the later-line cohort; all were treated with sunitinib;

- At the end of the study, after a 3-year follow-up, 20 (32.8%) patients in the treatment-naïve cohort and 28 (62.2%) patients in the later-line cohort had died;

- Survival probability at Year 1 was 88.3% (95% CI: 80.3, 93.2) and at Year 2 was 75.0% (95% CI: 65.3, 82.4);

- Overall, the median OS for the global population was estimated to be 54.1 months (95% CI: 37.9, not reached). The median OS could not be determined for the treatment-naïve cohort as the data were still immature; and was 37.9 months (95% CI: 22.9, 56.1) for the later-line cohort;

- The median OS in this study was higher than the median OS reported in the pivotal study A6181111 (38.6 months; 95% CI: 25.6, 56.4) in the sunitinib group (both treatment-naïve and later-line patients);

- Like in the primary CSR, a combined analysis was done to compare treatment-naïve sunitinib-treated patients pooled from studies A6181202 and A6181111 (sunitinib arm) with placebo-treated patients from A6181111 study (placebo arm). However, the median OS could not be determined for either arm because a high proportion of the patients were censored: 80 (78.4%) patients and 29 (82.9%) patients, in the sunitinib and placebo arms, respectively;

- It should be noted that survival follow-up was shorter in Study A6181111 (data cutoff date, 15 April 2009; range for survival follow-up: 0.03 to 20.63 months) compared with Study A6181202 (data cutoff date, 26 July 2018; range of survival follow-up, 0.03 to 70.83 months) leading to an imbalance in the follow-up between sunitinib and placebo arms;

- The estimated HR was 0.303 (95% CI: 0.100, 0.921), indicating a 69.7% reduction in risk of death with sunitinib treatment compared with placebo; and the difference was statistically significant (p-value = 0.013).

China subgroup:

- A total of 31 patients were enrolled in China and treated with sunitinib;

- A high proportion of the patients were censored (21 [67.7%] patients), and the median OS could not be determined;

- Survival probability at Year 1 was 84.1% (95% CI: 66.0, 93.1) and at Year 2 was 77.7% (95% CI: 58.7, 88.7).

Safety

Global population:

- Altogether 98.1% of patients experienced at least 1 all-causality TEAE and 95.3% of the patients experienced at least 1 treatment-related TEAE;

- Of the total 1377 TEAEs reported, 981 TEAEs were considered treatment-related;
- SAEs were reported in a total of 29 (27.4%) patients and were of Grades 2 to 5;
- Grade 5 TEAEs were reported in 4 (3.8%) patients: in 2 patients each in the treatment-naïve (3.3%) and the later-line (4.4%) cohorts; and none of these was treatment-related;
- All-causality TEAEs resulted in the study drug being temporarily discontinued in 68 (64.2%) patients, reduced in 25 (23.6%) patients, and permanently discontinued in 22 (20.8%) patients;
- Treatment-related TEAEs resulted in the study drug being temporarily discontinued in 63 (59.4%) patients, reduced in 25 (23.6%) patients, and permanently discontinued in 13 (12.3%) patients;
- The 3 most commonly reported all-causality TEAEs were neutropenia reported in 60 (56.6%) patients, diarrhea in 55 (51.9%) patients, and leukopenia in 47 (44.3%) patients. This order was the same for treatment-related TEAEs: neutropenia in 58 (54.7%) patients, diarrhea in 50 (47.2%) patients, and leukopenia in 47 (44.3%) patients;
- There were no deaths due to study treatment toxicity. The majority of deaths occurred during the follow-up period and were due to the disease under study. Deaths that occurred during the treatment period (4 [3.8%] patients) were due to disease under study.

China subgroup:

- All patients experienced at least 1 all-causality TEAE and 1 treatment-related TEAE;
- Of the total 414 TEAEs reported, 344 TEAEs were considered treatment-related;
- SAEs were reported in a total of 8 (25.8%) patients;
- No Grade 5 TEAEs were reported;
- All-causality TEAEs resulted in the study drug being temporarily discontinued in 18 (58.1%) patients, reduced in 6 (19.4%) patients, and permanently discontinued in 5 (16.1%) patients;
- Treatment-related TEAEs resulted in the study drug being temporarily discontinued in 17 (54.8%) patients, reduced in 6 (19.4%) patients, and permanently discontinued in 3 (9.7%) patients;
- The 3 most commonly reported TEAEs were all in the SOC Blood and lymphatic disorders and were all considered treatment-related TEAEs: leukopenia reported in

24 (77.4%) patients, neutropenia in 23 (74.2%) patients, and thrombocytopenia in 15 (48.4%) patients;

- All the reported deaths (10 [32.3%] patients) occurred during the follow-up period and the majority were due to the disease under study (6 [19.4%] patients).

In general, the safety findings in the global population and the China subgroup were similar to those reported in the respective primary CSRs.

In summary, in Study A6181202, at the data cutoff date (26 July 2018), the median OS for the global population was estimated to be 54.1 months (95% CI: 37.9, not reached). The OS data were still immature to draw conclusions for the treatment-naïve cohort of the global population and China subgroup. Safety findings in the global population and the China subgroup were consistent with the known safety profile of sunitinib, and there were no unexpected findings.

In conclusion, the sunitinib treatment effect was confirmed in patients with advanced metastatic, well-differentiated, unresectable pNETs with an acceptable safety profile. The benefit-risk profile of sunitinib was confirmed to be favorable for this patient population.

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