1. TITLE PAGE

Study Title:	Phase II Randomized Study of BAX2398 in Combination with 5-Fluorouracil and Calcium Levofolinate in Japanese Patients with Metastatic Pancreatic Cancer, Which Progressed or Recurred After Prior Gemcitabine-Based Therapy
Investigational Product:	BAX2398 (Irinotecan hydrochloride encapsulated in liposomal particles)
Protocol Identifier:	331501
Clinical Condition/ Indication Studied:	Metastatic pancreatic cancer which progressed or recurred after prior gemcitabine-based therapy
Summary:	The study was conducted in 2 parts. In Part 1, the safety of BAX2398 in combination with 5-fluorouracil/leucovorin (5-FU/LV) was assessed to confirm the tolerability of the same dosing regimen as in pivotal NAPOLI-1 trial, and the pharmacokinetics (PK) of BAX2398 in combination with 5-FU/LV was characterized in Japanese patients. After the Independent Data Monitoring Committee (IDMC) had reviewed all safety data, Part 2 was opened to further assess the safety of the combination, the PK of BAX2398, and to compare the efficacy of BAX2398 in combination with 5 FU/LV versus 5 FU/LV. Patients in Part 1 continued in the study until progressive disease (radiologic or symptomatic deterioration) or the occurrence of unacceptable toxicity. All efficacy and safety data reported up to the primary analysis cut-off date of 2017 MAY 04 are reported in the clinical study report (CSR) (dated 2017 DEC 15). At that cut-off date, 70 of 79 randomised patients in Part 2 of the study had discontinued treatment (BAX2398+5-FU/LV: 35/40 patients, 87.5%; 5-FU/LV: 35/39 patients, 89.7%), 38 patients remained on study, either still on treatment or in follow-up (BAX2398+5-FU/LV: 16/40 patients, 40.0%; 5-FU/LV: 22/39 patients, 56.4%). Of these 38 patients, 5 patients receiving BAX2398+5-FU/LV and 4 patients receiving 5-FU/LV remained on treatment. Results of the primary analysis, including PFS, ORR (unconfirmed), DCR (unconfirmed), OS and PK, safety data up to the cut-off date of 2017 May 04 are covered in the CSR dated 2017 DEC 15. This addendum to the CSR provides final, confirmed ORR and DCR data, as well as updated OS and safety data up to the final cut-off date of 2018 AUG 28. The study had two types of ‘discontinuation’ dispositions: treatment discontinuation (relevant for the additional 9 patients included in the data for this addendum) and study discontinuation (relevant to all patients who were either still on study drug or still being followed up for overall survival (OS) at the primary analysis cut-off date). Following the primary analysis, there was 1 additional protocol amendment. amendment 04, dated 2017 OCT 12, which increased the

	expected duration of the study from 22-24 months to 34-36 months, with a revised completion date falling during Q4 2018. This amendment had no impact on the study conduct and data integrity.
CSR Addendum Date:	2018 DEC 13 (data cut-off date: 2018 AUG 08)
Full CSR Date:	2017 DEC 15 (primary analysis data cut-off date: 2017 MAY 04)

2. TABLE OF CONTENTS

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
CA-19-9	cancer antigen 19-9
CI	confidence interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut off (final DCO 08 AUG 2018)
DCR	disease control rate
ECG	electrocardiogram
5-FU	5-fluorouracil
FAS	full analysis set
G-CSF	granulocyte colony-stimulating factor
IDMC	Independent Data Monitoring Committee
IP	investigational product
ITT	intent-to-treat
IV	intravenous
LV	leucovorin
OR	overall response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	per-protocol
PR	partial response
PT	preferred term
QTcF	Fridericia corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1

Abbreviation	Definition
UGT1A1*6	uridine diphosphate glucuronosyltransferase 1A1 (type *6 variant)
UGT1A1*28	uridine diphosphate glucuronosyltransferase 1A1 (type *28 variant)

4. STUDY PATIENTS

4.1 Disposition of Patients

The disposition of patients of this study is summarized in Table 14.1.1.

By-patient disposition of all patients enrolled is provided in Listing 16.2.3.

4.1.1 Treatment Discontinuation

All enrolled patients discontinued treatment by the time of the final data cut-off (DCO). The most common reason for treatment termination was progressive disease based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (84.5%), followed by adverse events (AEs) (8.3%) and clinical deterioration (3.6%). Patient disposition at the time of the final DCO was consistent with that which was reported from the primary analysis in the CSR.

Discontinuation of treatment is summarized in Table 14.1.1.

Discontinuation due to AEs is summarized in Table 14.3.1.1.

Patients who discontinued and the reason for discontinuation is provided in Listing 16.2.1.

4.1.2 Study Terminations

All enrolled patients discontinued from the study by the time of the final DCO. The most common reason for study termination in Part 2 of the study was death (BAX2398+5-FU/LV: 36/40 patients, 90.0%; 5-FU/LV: 35/39 patients, 89.7%). Four patients (10.0%) in the BAX2398+5-FU/LV group and 3 patients (7.7%) were still in the study at the time that the study was terminated by the sponsor.

Termination of study is described in Table 14.1.1.

4.2 Protocol Deviations

A total of 3 major protocol deviations were reported in 3 patients during the study (Table 14.1.12); 2 of the major protocol deviations were previously reported in the CSR, and both were associated with not following protocol-specified electrocardiogram (ECG) procedures at a single timepoint in each case. In addition, 1 subject in the 5-FU/LV group was reported with a major protocol deviation during the reporting period of this addendum, and was related to laboratory assessment criteria (ECG measurement was performed only once at Cycle 1 [pre-dose, post-dose 0-3hours], but the protocol required triplicate measurements). Medical review had determined that the three deviation events

were clinically non-significant to warrant excluding a patient from the per protocol analysis set.

Major protocol deviations are summarized in Table 14.1.12.

For details on all protocol deviations recorded during the study, refer to Listing 16.2.2.

5. EFFICACY EVALUATION

5.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics were previously reported in the CSR.

5.1.1 Demographic Characteristics

Not applicable.

5.1.2 Baseline Disease Characteristics

Not applicable.

5.1.3 Medical History

Prior medical and treatment history was previously reported in the CSR. A listing of medical history is provided in Listing 16.2.9.

5.1.4 Prior, Post Study, and Concomitant Medication

Prior anticancer, prior lines and post treatment anticancer therapy classification by medical review is summarized in Table 14.1.8.4.

A similar number of patients in both groups had at least 1 post treatment anticancer therapy (5-FU/LV: 29/39 patients, 74.4%; BAX2398+5-FU/LV: 27/40 patients, 67.5%). More patients in the BAX2398+5-FU/LV group received S-1 containing post treatment anticancer therapy (BAX2398+5-FU/LV: 15/40 patients, 37.5%; 5-FU/LV: 10/39 patients, 25.6%), whereas more patients in the 5-FU/LV group received post treatment anticancer therapies containing:

- gemcitabine (5-FU/LV: 11/39 patients, 28.2%; BAX2398+5-FU/LV: 8/40 patients, 20.0%)
- 5-FU (5-FU/LV: 25/39 patients, 64.1%; BAX2398+5-FU/LV: 19/40 patients, 47.5%)
- oxaliplatin (5-FU/LV: 26/39 patients, 66.7%; BAX2398+5-FU/LV: 19/40 patients, 47.5%),
- irinotecan (5-FU/LV: 20/39 patients, 51.3%; BAX2398+5-FU/LV: 9/40 patients, 22.5%), and
- “other” (5-FU/LV: 9/39 patients, 23.1%; BAX2398+5-FU/LV: 6/40 patients, 15.0%).

Concomitant medications are summarized in Table 14.1.9.1, concomitant procedures are summarized in Table 14.1.9.2, concomitant non-drug therapies are summarized in Table 14.1.9.3, with concomitant medications by ATC level 2 presented in Table 14.1.10. A summary of post treatment anticancer therapy is presented in Table 14.1.11. Concomitant medications and non-drug therapies administered through to the final DCO were consistent with what was previously reported in the CSR.

Concomitant medications by patient are provided in Listing 16.2.11.1. A listing of prior anticancer therapy is provided in Listing 16.2.10.2. A listing of prior medications and prior procedures are provided in Listing 16.2.10.4. A listing of patients who had granulocyte colony-stimulating factors is provided in Listing 16.2.12.1. A listing of patients receiving antineoplastic agents is provided in Listing 16.2.6.6. A listing of post treatment anticancer therapy is provided in Listing 16.2.12.2.

5.2 Efficacy Results and Tabulations of Individual Patient Data

5.2.1 Analysis of Efficacy

5.2.1.1 Primary Efficacy Outcome Measure - Progression-Free Survival

Results of the primary efficacy outcomes measure – progression-free survival (PFS) – are reported in the CSR. There are no further updates to PFS based on the final analysis.

5.2.1.2 Secondary Efficacy Outcome Measures

Previously pending, confirmed objective response rate (ORR), and disease control rate (DCR), as well as updated overall survival (OS) data (cut-off 2018 AUG 08) for the secondary outcome measures are described below.

5.2.1.2.1 Objective Response Rate in Part 2 (Confirmed)

The ORR is defined as the percentage of patients in the study population with a best overall response of complete response (CR) or partial response (PR) by independent and investigator assessments. The best overall response is defined as the best response per RECIST (version 1.1) since from randomization until progression or end of study.

Confirmed ORR in Part 2 based on independent assessment in the intent-to-treat (ITT) analysis set was observed in 4 patients (10%) in the BAX2398+5-FU/LV group and no patients in the 5-FU/LV group.

Three patients in the BAX2398+5-FU/LV group who were previously reported in the CSR as having had CR or PR (unconfirmed) at the time of the primary analysis were since determined to instead have confirmed stable disease (SD) and are therefore no

longer considered to have achieved objective response. Therefore, 17 patients (42.5%) in the BAX2398+5-FU/LV group had SD at the time of the final DCO; the number of patients with SD in the 5-FU/LV group was unchanged (10 patients, 25.6%).

A summary of ORR in Part 2 by independent assessment for the ITT analysis set is presented in Table 14.2.6.1.1. A summary of ORR in Part 2 by independent assessment is presented for the per-protocol (PP) analysis set in Table 14.2.6.2.1. A summary of ORR in Part 2 by independent assessment is presented for the Evaluable Patient analysis set in Table 14.2.6.3.1. The results of ORR in Part 2 by independent assessment for the PP and Evaluable Patient analysis sets were consistent with the ITT analysis.

A presentations of the sensitivity analyses for ORR by independent assessment in Part 2 is provided in Table 14.2.12.10.1.1 for the full analysis set (FAS). The sensitivity analysis was in alignment with the primary DCR analysis.

5.2.1.2.2 **Disease Control Rate in Part 2 (Confirmed)**

The DCR is defined as patients with a best overall response of CR, PR, or stable disease lasting ≥24 weeks following the first study drug administration.

The confirmed DCR at the time of the final DCO was the same as was reported in the CSR for the primary analysis (BAX2398+5-FU/LV: 8/40 patients, 20.0%; 5-FU/LV: 2/39 patients, 5.1%).

A summary of confirmed DCR in Part 2 by independent assessment is presented for the ITT analysis set in Table 14.2.7.1.1. A summary of DCR in Part 2 by independent assessment is presented for the PP analysis set in Table 14.2.7.2.1. A summary of DCR in Part 2 by independent assessment is presented for the Evaluable Patient analysis set in Table 14.2.7.3.1. The results of DCR in Part 2 by independent assessment for the PP and Evaluable Patient analysis sets were consistent with the ITT analysis.

A presentations of the sensitivity analyses for ORR by independent assessment in Part 2 is provided in Table 14.2.12.11.1.1 for the FAS. The sensitivity analysis was in alignment with the primary DCR analysis.

5.2.1.2.3 **Overall Survival in Part 1**

At the time of the final DCO, 5/6 patients (83.3%) in Part 1 of the study had died and 1 subject (16.7%) was censored after having discontinued from the study.

A summary of OS in Part 1for the safety analysis set is presented in Table 14.2.3.

5.2.1.2.4 **Overall Survival in Part 2**

In the ITT analysis set of Part 2 of the study, approximately 90% of patients in each group had died and 10% in each group were censored due to study discontinuation at the time of final DCO. Median OS time was 6.3 months (95% CI: 5.22, 8.94) in the BAX2398+5-FU/LV group and 9.1 months (95% CI: 6.05, 11.37) in the 5-FU/LV group (hazard ratio: 1.24 [95% CI: 0.775, 1.973]; p=0.371). The OS analysis in Part 2 for the ITT analysis set is summarized in Table 1 and is presented graphically in Figure 1.

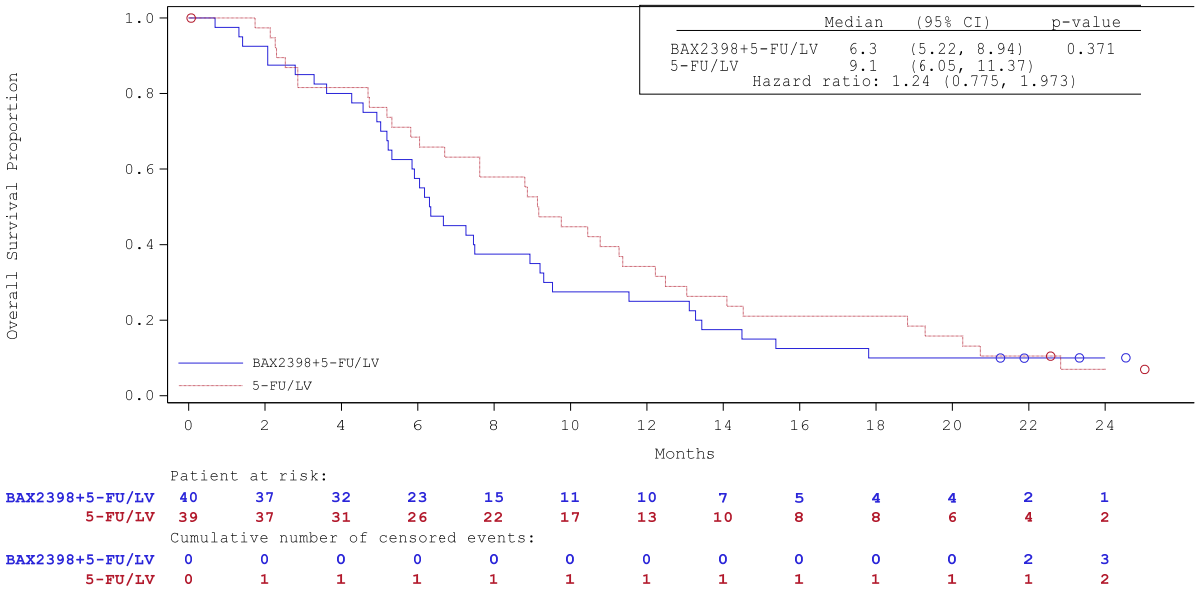
Results for OS were identical in both the ITT and PP analysis set, which was in alignment with the results of the primary analysis.

Table 1 Overall Survival in Part 2 Intent-to-Treat Analysis Set

	BAX2398+5-FU/LV (N=40)	5-FU/LV (N=39)	
Number of events (death), n(%)	36 (90.0)	35 (89.7)	
Number of censors, n(%)	4 (10.0)	4 (10.3)	
Reason for censoring, n(%)			
Alive on data cut-off date	0 (0.0)	0 (0.0)	
Alive at study completion	0 (0.0)	0 (0.0)	
Discontinued study	4 (10.0)	4 (10.3)	
Overall Survival (months)			
Median (95% CI)	6.3 (5.22, 8.94)	9.1 (6.05, 11.37)	
Two-sided p-value from log-rank test			0.371
Hazard ratio (95% CI)			1.24 (0.775, 1.973)

Note: Percentages are based on the number of patients in the analysis population.
Note: Median is Kaplan-Meier estimate of median overall survival time.
Note: Hazard ratio is computed from Cox proportional hazards modeling.
Source: Table 14.2.4.1

Figure 1: Kaplan-Meier Plot for Overall Survival in Part 2 Intent-to-Treat Analysis Set



Patient at risk:

BAX2398+5-FU/LV	40	37	32	23	15	11	10	7	5	4	4	2	1
5-FU/LV	39	37	31	26	22	17	13	10	8	8	6	4	2

Cumulative number of censored events:

BAX2398+5-FU/LV	0	0	0	0	0	0	0	0	0	0	0	2	3
5-FU/LV	0	1	1	1	1	1	1	1	1	1	1	1	2

Note: Median is Kaplan-Meier estimate of median overall survival time. Corresponding 95% CI and p-value are computed using unstratified log-rank test.
Note: Hazard ratio, corresponding 95% CI is computed from Cox proportional hazards modeling.
Source: Figure 14.2.4.1

A summary of OS in Part 2 for the ITT analysis set is presented in Table 14.2.4.1. A summary of OS in Part 2 for the PP analysis set is presented in Table 14.2.4.2. Results for the PP analysis set were in alignment with those of the ITT analysis set. A Kaplan-Meier plot for OS in Part 2 for the ITT analysis set is presented in Figure 14.2.4.1.

5.2.2 Statistical/Analytical Issues

For a detailed discussion of statistical and analytical issues, refer to the Statistical Analysis Plan version 2017 SEP 06.

5.2.2.1 Handling of Dropouts or Missing Data

Methods of handling missing, unused, or spurious data are described in detail in Section 5.1 of the SAP. Refer to the Statistical Analysis Plan version 2017 SEP 06.

5.2.3 Efficacy Conclusion

The final analyses of efficacy measures from Study 331501 in Japanese patients with metastatic pancreatic cancer which progressed or recurred after prior gemcitabine-based therapy were as follows:

- Primary Endpoint: PFS in Part 2 (BAX2398+5-FU/LV versus. 5-FU/LV)
  The primary endpoint was reported in the Study 331501 CSR.

- Secondary Endpoints in Part 1 (BAX2398+5-FU/LV):
  The secondary endpoint for Part 1 of the study (Best Overall Response) was reported in the Study 331501 CSR.

- Secondary Endpoints in Part 2 (BAX2398+5-FU/LV versus. 5-FU/LV):

  - ORR: Confirmed ORR in Part 2 based on independent assessment in the ITT analysis set was 4 patients (10%) in the BAX2398+5-FU/LV group and no patients in the 5-FU/LV group.

  - DCR: A total of 8/40 patients (20.0%) in the BAX2398+5-FU/LV treatment arm achieved confirmed disease control by independent assessment, versus 2/39 patients (5.1%) in the 5-FU/LV control arm, which was in alignment with the results of the primary analysis.

  - OS: Median OS was 6.3 months (95% CI: 5.22, 8.94) in the BAX2398+5-FU/LV group and 9.1 months (95% CI: 6.05, 11.37) in the 5-FU/LV group (hazard ratio: 1.24 [95% CI: 0.775, 1.973]; p=0.371).

    - The OS observed in the 5-FU/LV control arm may not be fully attributable to the 5-FU/LV regimen itself, as patients stayed on the 5 FU/LV control arm for a shorter duration than patients on the experimental BAX2398 + 5-FU/LV arm, and subsequently received other efficacious regimens after discontinuing from the trial.

      - The mean exposure for the 5-FU/LV control arm was 12.7 weeks, as compared with the mean exposure for BAX2398 + 5-FU/LV (17.1 weeks) (Table 14.1.13).

      - The number of patients with a duration of exposure greater than or equal to 12 weeks for the 5-FU/LV control arm was 9 of 38 patients (23.7%) compared to 19 of 46 patients (41.3%) for BAX2398 + 5-FU/LV arm (Post Hoc Analysis Table 6)

- Differences were also observed in the post study treatments received, which might have influenced the OS outcome. A higher number of patients received an irinotecan-containing regimen in the 5-FU/LV arm (20/39 patients, 51.3%) than in the BAX2398 + 5-FU/LV experimental arm (9/40 patients, 22.5%). Similarly, the number of patients receiving an oxaliplatin containing regimen was higher in the 5-FU/LV arm (26/39 patients, 66.7%) than in the BAX2398 + 5-FU/LV experimental arm (19/40 patients, 47.5%) (Table 14.1.8.4).

6. SAFETY EVALUATION

Safety measurements included occurrence of AEs and SAEs, seriousness, severity and causal relationship to investigational product (IP) exposure, changes in vital signs and in clinical laboratory parameters.

The Independent Data Monitoring Committee (IDMC) reviewed the safety data at pre-specified intervals throughout the study. In Part 1, safety and tolerability data from 6 patients treated with the BAX2398+5-FU/LV were evaluated by the IDMC and the recommendation was made to continue into Part 2 of the study as planned with this treatment regimen without any modification of the trial course. Subsequently in Part 2, IDMC evaluated safety data 3 additional times at prespecified intervals and recommended continuing the study without any change to the planned course.

6.1 Extent of Exposure

Treatment was administered in 2-week cycles. BAX2398 was administered prior to LV, which was to be administered prior to 5-FU.

A total of 84 patients (6 patients in Part 1 and 78 patients in Part 2) received at least 1 dose of study medication and are included in the safety analysis population. A summary of the extent of total calculated study treatment exposure to BAX2398, 5-FU, and LV is presented in Table 14.1.13. Patients receiving BAX2398+5-FU/LV treatment had drug administered by intravenous (IV) infusion over 90 minutes (±10) every 2 weeks and received, on average, a mean total dose of BAX2398 of 830.33 mg (SD 958.327) over a mean duration of 17.03 weeks (SD 17.472) of exposure by the time of the final DCO.

Mean total duration of 5-FU and LV exposure was 16.95 weeks (SD 17.534) in patients treated with BAX2398+5-FU/LV and 12.70 weeks (SD 19.135) in patients treated with 5-FU/LV.

In patients treated with BAX2398+5-FU/LV, the total mean calculated 5-FU dose was 24599.09 mg (SD 26378.033) and the total mean calculated LV dose was 2416.75 mg (SD 2651.587).

In patients treated with 5-FU/LV, the total mean calculated 5-FU dose was 21398.20 mg (SD 29309.935) and the total mean calculated LV dose was 1818.73 mg (SD 2462.599).

Across treatments, the majority of patients were exposed to treatment for 6 or more weeks (BAX2398+5-FU/LV: 76.1%; 5-FU/LV: 84.2%) (Post Hoc Analysis Table 6).

Patients receiving the BAX2398+5FU/LV treatment regimen were on treatment longer than patients treated with only 5-FU/LV. Patients receiving 5-FU/LV experienced fewer dose reductions than patients receiving BAX2398+5- FU/LV. Duration of treatment, the proportion of patients with 1 or more dose reductions, and the relative dose intensity by cycle were generally unchanged in the final analysis from what was previously reported in the CSR. A summary of the extent of total calculated study treatment exposure to BAX2398, 5-FU, and LV is presented by cycle in Table 14.1.13 and in Table 14.1.14.

BAX2398, LV, and 5-FU administration in each patient are provided in Listing 16.2.5.1.1, Listing 16.2.5.1.3, and Listing 16.2.5.1.2, respectively. Study drug exposure is presented by patient in Listing 16.2.5.2.

6.2 Adverse Events

6.2.1 Brief Summary of Adverse Events

An overview of TEAEs is presented in Table 14.3.1.1.

There were no substantive changes to the overall safety profile of BAX2398 combined with +5-FU/LV observed during the follow-up period.

6.2.2 Display of Adverse Events

Adverse events are listed by patient in tabular format in Listing 16.2.7.1 to Listing 16.2.7.6 (appendix: Adverse Event Listings). Adverse events are summarized as described below in Section 6.2.3.

6.2.3 Analysis of Adverse Events

6.2.3.1 Analysis of Adverse Events by Severity

There were no changes in the incidence of AEs by severity observed during the follow-up period from the data reported in the CSR.

A summary of patients with Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 treatment-emergent adverse events (TEAEs) by system organ class (SOC) and preferred term (PT) is presented in Table 14.3.1.6. A summary of patients with Grade 3 or 4 TEAEs by PT is presented in Table 14.3.1.13. A summary of patients with TEAEs by SOC, PT, and CTCAE Grade is presented in Table 14.3.1.14.

6.2.3.2 Analysis of Adverse Events by Causality

There were no changes in the incidence of AEs by causality observed during the follow-up period from the data reported in the CSR.

The most commonly reported treatment-related TEAEs across all patients were in the SOCs of Gastrointestinal Disorders, followed by Investigations, General Disorders, and Metabolism and Nutrition Disorders. In general, there were more patients with treatment-related TEAEs in the BAX2398+5-FU/LV group compared with the 5-FU/LV group (Table 14.3.1.1).

A summary of patients with study drug-related TEAEs by SOC and PT is presented in Table 14.3.1.2.

6.2.4 Listing of Adverse Events by Patient

Please refer to the following listings for recorded AEs:

- Listing 16.2.7.1 Adverse Events
- Listing 16.2.7.2 Serious Adverse Events
- Listing 16.2.7.3 Adverse Events Leading to Dose Reduction
- Listing 16.2.7.4 Adverse Events Leading to Dose Delay
- Listing 16.2.7.5 Adverse Events Leading to Withdrawal of Study Drug
- Listing 16.2.7.6 Adverse Events With a Fatal Outcome
- Listing 16.2.7.7 Adverse Events for Subjects Homozygous for uridine diphosphate glucuronosyltransferase 1A1 (type *28 variant) (UGT1A1*28) or uridine diphosphate glucuronosyltransferase 1A1 (type *6 variant) (UGT1A1*6) Alleles or Who Have UGT1A1*28 and UGT1A1*6 Alleles

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

6.3.1 Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

6.3.1.1 Deaths

There were no new deaths attributable to AEs during the follow-up period.

In total, 76 deaths were reported at the time of final analysis: 41 patients (89.1%) treated with BAX2398+5-FU/LV and 35 (92.1%) patients treated with 5-FU/LV died during the study or during the survival follow-up period. Of those, 3 (6.5%) patients treated with BAX2398+5-FU/LV and 1 (2.6%) patient treated with 5-FU/LV died during the active treatment period or within 30 days after the last dose of study medication; 37 (80.4%) patients treated with BAX2398+5-FU/LV and 33 (86.8%) patients treated with 5-FU/LV died more than 30 days after the last dose of study medication. The majority of deaths during the active treatment period (as described in the CSR) and all deaths during the survival period were attributed to progressive disease (Listing 16.2.1).

A summary of patients with AEs with a fatal outcome by SOC and PT is presented in Table 14.3.1.10. A summary of all deaths by epoch and attribution is presented in Table 14.3.1.15.

6.3.1.2 Other Serious Adverse Events

The incidence of SAEs at the time of final DCO was generally in alignment with what was reported in the primary analysis CSR. In patients treated with BAX2398+5-FU/LV, 23 (50.0%) patients experienced SAEs, and 6 (13.0%) patients experienced treatment-related SAEs. In patients treated with 5-FU/LV, 9 (23.7%) patients experienced SAEs and 1 (2.6%) patient experienced treatment-related SAEs.

One new SAE was observed during the follow-up period (BAX2398+5-FU/LV group, pleural effusion, onset date 2017 MAY 26 and ongoing at the time of DCO, not considered related to study treatment). Although this event was not reported in the primary clinical analysis as the onset occurred after the primary DCO, a safety narrative was included for this patient (Site 15, Patient 001) in Section 14.2 of the CSR as the patient safety narratives were compiled using the later data cut-off date of 2017 SEP 28.

A summary of patients with SAEs by SOC and PT is presented in Table 14.3.1.3.

A by-patient listing of SAEs is presented in Listing 16.2.7.2.

6.3.1.3 Other Significant Adverse Events

6.3.1.3.1 Adverse Events Leading to Dose Reduction

Among patients treated with BAX2398+5-FU/LV, 25 (54.3%) patients experienced TEAEs that required dose reductions by the time of the final DCO (increased from 50.0% at the time of the primary analysis). In patients treated with 5-FU/LV, 3 (7.9%) patients experienced TEAEs that required dose reductions, which was unchanged from primary analysis.

A summary of patients with TEAEs leading to dose reduction by SOC and PT is presented in Table 14.3.1.7.

6.3.1.3.2 Adverse Events Leading to Dose Delay

Among patients treated with BAX2398+5-FU/LV, 33 (71.7%) patients experienced TEAEs that led to dose delay by the time of the final DCO (increased from 32 [69.6%] at the time of the primary analysis). In patients treated with 5-FU/LV, 11 (28.9%) patients experienced TEAEs that led to dose delay, which was unchanged from primary analysis.

A summary of patients with TEAEs leading to dose delay by SOC and PT is presented in Table 14.3.1.8.

6.3.1.3.3 Adverse Events Leading to Withdrawal of Study Drug

There were no changes to AEs leading to withdrawal of study drug observed during the follow-up period.

A summary of patients with TEAEs leading to withdrawal of study drug by SOC and PT is presented in Table 14.3.1.9.

6.3.1.3.4 Adverse Events of Neutropenia and Diarrhea

There were no changes to the number of patients with AEs of neutropenia and diarrhea observed during the follow-up period.

A summary of granulocyte colony-stimulating factor (G-CSF) use, neutropenia and exposure is presented in Table 14.3.4.5.

A summary of patients with TEAEs of Neutropenia and Diarrhea is presented in Table 14.3.1.16.

6.3.1.3.5 Treatment Emergent Adverse Events – UGT1A1*28 Status

There were no changes to TEAEs by UGT1A1*28 status during the follow-up period.

A summary of all TEAEs by SOC and PT for patients homozygous for UGT1A1*28 or UGT1A1*6 alleles or who have UGT1A1*28 and UGT1A1*6 alleles is presented in Table 14.3.1.11. A summary of all Grade 3 or 4 TEAEs by SOC and PT for patients homozygous for UGT1A1*28 or UGT1A1*6 alleles or who have UGT1A1*28 and UGT1A1*6 alleles is presented in Table 14.3.1.12. Adverse events of each patient homozygous for UGT1A1*28 or UGT1A1*6 alleles or who have UGT1A1*28 and UGT1A1*6 alleles is presented in Listing 16.2.7.7.

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

Narratives of deaths, other serious adverse events, and certain other significant adverse events are presented in Section 8.2. No new events requiring a safety narrative occurred during the extension period. Narratives of deaths, other serious adverse events, and certain other significant adverse events occurring after the primary analysis DCO of 2017 MAY 04 but before 2017 SEP 28 were included with the CSR; narratives for events after that date are in Section 8.2 of this addendum.

6.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths:
The total number of deaths reported during this study was 41 in the BAX2398+5-FU/LV treatment arm and 35 in the 5-FU/LV treatment arm (Table 14.3.1.15). A total of 70 (BAX2398+5-FU/LV: 37; 5-FU/LV: 33) of the deaths reported occurred during the follow-up period covered by this report (Table 14.3.1.15). None of the deaths that occurred during follow-up were attributed to an AE and were due to underlying disease.

A summary of deaths is presented in Table 14.3.1.15.

Serious Adverse Events:
One new SAE (not related to BAX2398+5-FU/LV) was reported during the follow-up period covered by this report.

6.4 Clinical Laboratory Evaluation

6.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Listings of laboratory measurements (hematology and clinical chemistry) are provided in the appendix, Listing 16.2.8.1.1 (hematology), Listing 16.2.8.1.2 (clinical chemistry), Listing 16.2.8.2.1 (patient with abnormal hematology results), and Listing 16.2.8.2.2 (patient with abnormal clinical chemistry results).

6.4.2 Evaluation of Each Laboratory Parameter

6.4.2.1 Laboratory Values over Time

No unexpected trends over time or between the treatment groups were observed in any of the blood hematology or clinical chemistry laboratory variables (Table 14.3.4.1.1 and Table 14.3.4.1.2).

A boxplot for hematology results is presented in Figure 14.3.4.1.1. A boxplot for clinical chemistry results is presented in Figure 14.3.4.1.2.

6.4.2.2 Individual Patient Changes

A shift table of hematology results is presented in Table 14.3.4.2.1, and a shift table of clinical chemistry results is presented in Table 14.3.4.2.2. A shift table of CTCAE Grade from Baseline for hematology results is presented in Table 14.3.4.4.1, and a shift table of CTCAE Grade from Baseline for clinical chemistry results is presented in Table 14.3.4.4.2. A summary of CTCAE Grade for hematology results is presented in Table 14.3.4.3.1, and a summary of CTCAE Grade for clinical chemistry results is presented in Table 14.3.4.3.2.

6.4.2.3 Individual Clinically Significant Abnormalities

Laboratory values outside the normal range for individual patients are displayed in the appendix, Listing 16.2.8.2.1 for abnormal hematology results and in Listing 16.2.8.2.2 for abnormal serum chemistry results. Some inter-patient discrepancies were observed in the investigators' rating of clinical significance due to pre-existing diseases of abnormal parameters at baseline and post treatment.

There were no new clinically significant abnormal laboratory results that were considered to be an SAE or other significant AE.

6.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

6.5.1 Vital Signs

A summary of vital signs is presented in Table 14.3.4.11. A summary of worst on treatment vital signs is presented in Table 14.3.4.12. A listing of vital signs is provided in Listing 16.2.8.4.

6.5.2 Electrocardiograms

A summary of ECG results is presented in Table 14.3.4.6. A summary of ECG parameters is presented in Table 14.3.4.8. A summary of classification of ECG sinus

rhythm is presented in Table 14.3.4.9. A listing of ECG results is provided in Listing 16.2.8.3.

6.5.2.1 Individual Patient Changes

A shift table of ECG results between Baseline and 30-day follow-up is presented in Table 14.3.4.7.1. A shift table of ECG results between Baseline and worst on treatment is presented in Table 14.3.4.7.2. There was a single finding of QT prolongation reported as abnormal, clinically significant (ACS) in an elderly patient with a history of hypertension. No additional AEs or symptoms (e.g. syncope) of clinical significance were reported and/or associated with the event.

A summary of ECG prolongation of Fridericia corrected QT interval (QTcF) interval is presented in Table 14.3.4.9. A summary of ECG prolongation of worst on-treatment QTcF interval is presented in Table 14.3.4.10.

6.6 Safety Conclusions

The results of the updated analyses of key safety variables are consistent with the safety profile of BAX2398 described in the CSR dated 15 DEC 2017.

The BAX2398+5-FU/LV treatment regimen in Japanese patients is safe as assessed in this Study 331501 and evaluated by the IDMC. No new safety signal was identified in Japanese patients, and the observed safety profile in this study is consistent with the global NAPOLI-1 study.

There were no deaths associated with an AE during this study and 1 new SAEs occurred during the following up period covered by this report.

7. DISCUSSION AND OVERALL CONCLUSION

The data in this addendum further support the overall conclusion from the primary analysis (CSR dated 2017 DEC 15), that is, the safety, PK, and efficacy in a Japanese population demonstrates clinical benefit of BAX2398+5-FU/LV regimen in metastatic pancreatic cancer patients who have progressed after prior gemcitabine-based therapy.