CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207793Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
NDA #	207793
Applicant	Merrimack Pharmaceuticals, Inc.
Date of Submission	24 Apr 2015 (submission of final portion of rolling NDA)
PDUFA Goal Date	24 Oct 2015
Proprietary Name / Established Name	Onivyde / Irinotecan liposome injection (MM-398)
Dosing Regimen*	The recommended dose of Onivyde is 80 mg/m^2 administered by intravenous infusion over 90 minutes every 2 weeks (in combination with 5-fluorouracil and irinotecan). The recommended starting dose of Onivyde in patients known to be homozygous for the UGT1A1*28 allele is 60 mg/m^2 administered by intravenous infusion over 90 minutes.
Proposed Indication(s)	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine
Recommended:	*Approval contingent upon reaching final agreement on product labeling*

*The dosing regimen in the table is the dosing regimen proposed in the original NDA based on the designation of strength by the hydrochloride salt rather than the freebase. Dosing in the final label may differ if the designation of strength is based on the freebase (refer to Section 3.0 below).

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1. Introduction

FDA received the complete New Drug Application (NDA) 207793 from Merrimack Pharmaceuticals, Inc. (Merrimack) on 24 Apr 2015 requesting marketing authorization (regular approval) for MM-398 (irinotecan liposome, proposed trade-name Onivyde) for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine. The application was received as a rolling submission. The first unit (nonclinical unit) was received on 29 Dec 2014.

Merrimack requested marketing authorization under the 505(b)(2) pathway. Merrimack's application relies, in part, on certain FDA findings for the listed drug Camptosar (irinotecan hydrochloride injection). In the application, Merrimack relied on prior FDA findings related to nonclinical genotoxicity, nonclinical carcinogenicity, and nonclinical reproductive and developmental toxicity. Merrimack also relied on certain clinical pharmacology findings from Camptosar (e.g., drug-drug interactions).

Important issues considered during the review of this NDA for MM-398 were whether the pivotal clinical trial (Study MM-398-07-03-01) isolated the effect of MM-398 based on differences in 5-fluorouracil dosing regimens between the treatment and control arm; whether the risk-benefit profile was favorable; and whether the single adequate and well controlled trial constituted substantial evidence of effectiveness. Additionally, FDA's Office of Clinical Pharmacology considered dosing issues pertaining to homozygosity for the UGT1A1*28 allele and bilirubin levels. To avoid redundancy, the risk-benefit discussion will be found at the end of this review and the discussion regarding dosing issues will be found in the Clinical Pharmacology section of this review.

Issue: Did the pivotal clinical trial isolate the effect of MM-398?

Study MM-398-07-03-01 was initially designed as a two arm (superiority) study that randomized patients to receive either MM-398 (120 mg/m^2 intravenously over 90 minutes every three weeks) or 5-fluorouracil (5FU) (2000 mg/m^2 intravenously over 24 hours) in combination with leucovorin (LV) weekly for four weeks followed by two weeks of rest. Merrimack stated that the regimen in the 5FU/LV control arm was based on the regimen administered to patients with pancreatic cancer in the CONKO3 study (see Section 2.1 below). FDA met with Merrimack to discuss the design of Study MM-398-07-03-01 in August of 2011 (and did not object to the 5FU/LV dosing regimen). *After* initiating the protocol, Merrimack amended the protocol (dated 14 Jun 2012) to add a third arm consisting of the following regimen: MM-398 80 mg/m^2 (initial dose of 60 mg/m^2 for patients homozygous for the UGT1A1*28 allele) every two weeks, 5-fluorouracil 2,400 mg/m^2 over 46 hours every two weeks, and leucovorin every 2 weeks.

In the protocol amendment, Merrimack provided a non-clinical rationale regarding why the combination of MM-398 and 5FU/LV may be effective. The protocol also provided summary data from a dose-finding trial (PEP0203) in patients with solid tumors that investigated MM-398 in combination with 5-fluorouracil and leucovorin. Sixteen patients were enrolled in this

trial; five had pancreatic cancer. The maximum tolerated dose (MTD) of MM-398 in this regimen was reported to be 80 mg/m^2 (in combination with 5-fluorouracil and leucovorin) with reported dose limiting toxicities occurring in two of five patients who received 100 mg/m^2 and two of two patients who received 120 mg m^2 MM-398 in combination with 5FU/LV.

Merrimack stated that the dose and schedule of 5FU and leucovorin (in the MM-398 combination arm) was designed to be similar to that in the FOLFIRI.3 regimen, which was being studied in patients with pancreatic cancer (this regimen allowed for biweekly dosing).

Additional data from this dose and schedule of MM-398 in combination with 5FU and leucovorin were available from the GERCOR PEPCOL study (Chibaudel et al., 2015 Gastrointestinal Cancers Symposium, Abstract 751). Merrimack provided summary data from the first 20 patients enrolled in the PEPCOL study in the NDA. Fifty-five patients with metastatic colorectal cancer (second-line) were randomized in this study to receive either MM-389 in combination with 5FU/LV or FOLFIRI (choice of FOLFIRI.1 or modified FOLFIRI.3) (bevacizumab was permitted in either arm). Merrimack elected not to change the dosing regimen of 5FU in the combination arm of Study MM-398-07-03-01 because of the safety experience with the regimen studied in PEPCOL and in PEP0203.

In the NDA, Merrimack provided the following rationale supporting their conclusion that the survival effect observed in Study MM-398-07-03-01 was due to the contribution of MM-398 (and not due to differences in the 5FU regimens).

- The planned 5-FU dose in the combination arm over six weeks was lower than that in the control arm (patients in the MM-398/5FU/LV arm received 7,200 mg/m^2 5FU over six weeks versus 8,000 mg/m^2 in the control arm). *Comment: this would theoretically bias results in favor of the control arm (unless the longer 5FU infusion impacts clinical effects).*
- The observed 5-FU dose in the MM-398/5FU/LV arm was lower than the observed 5FU dose in the 5FU/LV arm (6 week normalized dose intensity of 5,065.0 mg/m^2 versus 6,718 mg/m^2, respectively).
- Merrimack performed simulations of 5FU pharmacokinetics showing that the 6-week average AUC in the MM398/5FU/LV arm was 90% of that in the control arm.
- More patients in the MM-398 combination arm experienced adverse events that resulted in dose modification of 5FU (37% versus 4%), further reducing the amount of 5FU that patients in the combination arm received.
- Merrimack conducted a literature search (mostly based on *indirect* analyses in colorectal cancer) evaluating the clinical effects of different dosing regimens of 5FU and concluded that the different dosing regimens were unlikely to have resulted in differences in clinical outcomes. In their literature search, Merrimack found no study that *directly* compared the efficacy of the two different 5FU infusional regimens investigated in Study MM-398-07-03-01.

In summary, while there is some residual uncertainty regarding the magnitude of the effect contributed by MM-398 (especially in a single, relatively small study), this reviewer agrees that it is unlikely that differences in 5FU regimens alone would account for a statistically

significant 1.9 month improvement in overall survival (in patients with previously-treated pancreatic cancer). Patients in the control arm received a higher dose intensity of 5FU (normalized over 6 weeks). Additionally, the effects of 5FU as a single agent in patients with previously-treated pancreatic cancer are likely to be limited (see Section 2.1 below).

As such, this reviewer believes there is low regulatory risk that MM-398 is acting solely as a placebo in the regimen and that MM-398 at least contributes something to the clinical benefit of the combination. Nevertheless, this reviewer believes that it is risky for developers to make major changes to their pivotal studies (e.g., adding new arms) without first obtaining input in writing from FDA (or other stakeholders if approvals in other countries are sought).

DOP2 requested Special Government Employee (SGE) advice regarding the differences in 5FU dosing regimens in the control arm versus the combination arm. Two SGEs were cleared for this application including one SGE with extensive experience in the management of patients with pancreatic cancer and another SGE with extensive experience in regards to the effects of 5FU-based regimens. Separate telephone conferences were scheduled with each SGE. Each independent SGE agreed that the observed difference in overall survival between arms was unlikely to have been caused by the differences in 5-FU dosing regimens between arms.

Issue: Did the application contain substantial evidence of effectiveness from one adequate and well controlled trial?

FDA Guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998) states that reliance on a single adequate and well controlled study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and confirmation of the results in a second trial would be practically or ethically impossible.

Study MM-398-07-03-01 was a randomized (1:1:1), multicenter, multinational, controlled trial that enrolled patients with metastatic adenocarcinoma of the pancreas with disease progression following prior gemcitabine or gemcitabine-containing chemotherapy. The trial was initiated as a two arm trial of MM398 monotherapy versus 5-fluorouracil in combination with leucovorin (see Section 7 below for details regarding dosing and study design). After initiation, the trial was amended to add a third arm of MM-398 in combination with 5-fluorouracil plus leucovorin. The addition of the third arm was done with appropriate statistical adjustments for alpha (i.e., the Bonferroni-Holm adjustment) such that statistical significance for the overall survival analysis could be interpreted.

Table 1 summarizes the efficacy results from Study MM-398-07-03-01. These results were based on an updated analysis of OS submitted in the amended NDA that included additional death events (see Section 7.4.3 for details) from publically available information. The results demonstrated a statistically significant improvement in overall survival (i.e., at an alpha of 0.025). Although the study was small, the p value of 0.014 suggests robustness of the results. The results of the initial OS analyses that did not include these additional events were similar [HR of 0.67 (95% CI: 0.49, 0.92), p = 0.012] to the results of the updated analyses. The

updated analysis in the table partially addressed a weakness of the study in that there was an imbalance in the number of patients who withdrew consent among the three study arms (of 16 patients who withdrew consent, 11 were in the control arm and 4 were in the combination arm). The updated analysis included information from 8 of the 11 patients in the control arm and two of the four patients in the combination arm. Sensitivity analyses of OS provided in the NDA (e.g., stratified analyses per-protocol analyses, and analyses using imputed data) were consistent with the primary OS results.

Table 1 Summary of OS efficacy results (combination arm versus placebo comparison)

	MM398 + 5FU/LV N = 117	**5FU/LV N = 119**
# of events	77	86
Median (in mos.)	6.1	4.2
Stratified HR (95% CI)	0.68 (0.50, 0.93)	
p-value (two-sided)	0.014	

Merrimack provided an additional analysis of OS based on updated information in the 90-day safety update. After 86% of patients died in the updated analysis (MM-398 combination arm versus control), the HR for OS was 0.75 with a 95% CI of 0.57 to 0.99 and a *nominal* p value of 0.04. Median OS in the two arms were similar to the original analysis with a median survival duration in the combination arm of 6.2 months and a median survival duration in the 5FU/LV arm of 4.2 months. As such, these results are equivocal regarding the overall robustness of the results (noting that the pre-specified p value for the trial was less than 0.025).

In general, effects on tumor-based secondary endpoints were consistent with the results of the primary OS analysis with the nominal p value for PFS less than 0.001 favoring treatment with MM-398 in combination with 5-FU and leucovorin. In addition to supportive findings from tumor-based endpoints (see Section 7 for additional details), the point estimates for OS in most pre-planned subgroup analyses favored treatment in the MM-398 combination arm. For some of these analyses, the 95% CI crossed one; however, the small trial resulted in most of these subgroups being underpowered to show a (nominally) significant difference in OS. Three subgroups had HRs greater than one (ethnicity "others", prior irinotecan, and prior Whipple); however, these (especially the ethnicity "others" subgroup) were small subgroups so conclusions based on these analyses are limited.

In summary, although this application had several weaknesses (differences in 5FU regimens between arms and differences in numbers of patients who withdrew consent between arms), ultimately this reviewer agrees that the results from this single trial are acceptable in order to take action on the application. The patient population studied in this application has a particularly poor prognosis, and this reviewer believes that it would not be in the best interests of patients with pancreatic cancer to require another trial for MM-398.

2. Background

2.1 Disease and therapy related issues

Merrimack requested marketing authorization for MM-398 for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine. Because metastatic pancreatic cancer is incurable (and patients have a short median life-expectancy), the goal of treatment for these patients is to prolong life and/or improve quality of life.

As stated, metastatic pancreatic cancer has a poor prognosis. In the first-line setting, patients (who are good candidates) tend to receive either FOLFIRNOX (based on Conroy et al., French PRODIGE study published in the NEJM in 2011) or gemcitabine in combination with nab-paclitaxel (FDA approved nab-paclitaxel for pancreatic cancer on 6 Sep 2013). Gemcitabine (or gemcitabine-erlotinib) can also be administered to patients and the choice of therapy may depend on co-morbid conditions, biliary function, and the patient's functional status. Median overall survival with any of these regimens is generally less than one year.

Limited evidence is available to guide the selection of treatment beyond the first-line setting. Fluoropyrimidine therapy is often administered to patients who received gemcitabine in the first-line setting; however, the evidence for the efficacy of 5FU or 5FU/LV in the metastatic setting is limited. In one study (Crown et al., JCO, 1991), 5-FU 370 mg/m^2/day for five days (in each 28 day cycle) in combination with leucovorin was administered to 22 patients with pancreatic cancer (18 previously untreated). No patient (out of 20 response-assessable patients) in the trial experienced a complete or partial response and median survival was 10 weeks. Median reported survival was longer (6.2 months) in a different study (DeCaprio et al., JCO, 1991) of forty-two patients who received weekly 5FU (600 mg/m^2 plus leucovorin) for six weeks followed by 2 weeks rest; however, the ORR was less than 10%. A third study (Van Rijswijk, Eur J Cancer, 2004) of 5FU (2.6 mg/m^2) administered as a 24 hour infusion in combination with leucovorin (weekly for six weeks followed by 2 weeks rest) also demonstrated an ORR of less than 10% with a median survival of 19 weeks.

These three studies showed that limited evidence exists to support the use of 5FU (or 5FU/LV) in the first-line setting. *Less* evidence is available to demonstrate that 5FU (or 5FU/LV) is effective in the second-line setting.

The German CONKO-study group attempted to investigate the effects of 5-FU in combination with oxaliplatin (OFF regimen) versus best supportive care in patients who previously progressed on gemcitabine therapy (Pelzer et al., Eur J Cancer, 2011). Patients received folinic acid 200 mg/m^2 followed by 5-fluorouracil 2 g/m^2 over 24 hours on days 1, 8, 15, and 22 and oxaliplatin 85 mg/m^2 on days 8 and 22. After a rest period, the next cycle was initiated on day 43. This study terminated early after enrollment of 46 out of 165 patients and the report by Pelzer stated that the study closed due to low recruitment due to the diminishing acceptance of receiving best supportive care alone. The analysis of survival by the authors stated that median OS was 4.82 months for patients randomized to the OFF regimen versus 2.3 months for BSC with a HR = 0.45 (95% CI: 0.24, 0.83).

After the CONKO study was closed prematurely, the CONKO investigators initiated a second study (CONKO-003) investigating the effects of the OFF regimen versus folinic acid and fluorouracil (same dose and schedule as OFF regimen without the oxaliplatin). This study (published by Oettle et al., JCO, 2014) randomized 168 patients with previously treated metastatic pancreatic cancer. The analysis of the study, however, was conducted on data from 160 patients such that the analysis was not an ITT analysis. Additionally, the report indicated that the target number of deaths was 110 whereas the final analysis was conducted based on data from 155 deaths. The report stated that OFF improved median survival with a median survival duration of 5.9 months for OFF versus 3.3 months with fluorouracil plus folinic acid alone [HR = 0.66 (95% CI: 0.48 to 0.91), p = 0.01].

Finally, Gill et al., at the ASCO 2014 meeting (abstract 4022), reported on the results of the PANCREOX study that randomized 108 patients who previously received gemcitabine to receive either mFOLFOX6 or infusional 5FU plus leucovorin. The abstract stated that OS was inferior in patients randomized to receive mFOLFOX6 (median OS of 6.1 months versus 9.0 months with the reported p value of 0.02). More patients in the 5FU/LV arm received post-progression therapy.

In summary, the data appear inconclusive regarding the effects of both fluorouracil and oxaliplatin in the second-line setting. Fluorouracil alone exhibited limited activity even in the first-line metastatic setting. The studies investigating the use of oxaliplatin regimens were contradictory and all were small. Although beneficial effects of the OFF regimen were reported in two studies, one was terminated early and the second had analysis issues (e.g., difficult to interpret p value based on the non-ITT analysis that was conducted substantially after the pre-specified number of events occured). Also, the CONKO-003 study was not published until 2014 which was after Study MM-398-07-03-01 was initiated. Based on these considerations, this reviewer did not object to the use of the 5-FU alone control arm (notwithstanding the differences in 5FU regimens as described above) although it is not clear that 5FU (or 5FU/LV)-alone actually provides benefit to patients.

Irinotecan-based regimens

Clinicians administer FOLFIRINOX in the first-line setting based on the results of the Conroy study. Other irinotecan-based regimens have also been investigated for the treatment of patients with pancreatic cancer. Neuzillet et al., (2012) published a report of 63 patients with previously-treated pancreatic cancer who received either FOLFIRI.1 (n=55) or FOFLIRI.3 (n=8) (irinotecan 100 mg/m^2 on day 1 and leucovorin 400 mg/m^2, then 5-FU 2400 mg/m^2 as a 46-h infusion and irinotecan 100 mg/m^2 repeated on day 3, biweekly) at one of two institutions. A partial response was reported in 5 patients (8%).

An earlier published report (Taieb et al., 2007) of an uncontrolled study of an irinotecan-based regimen described a 37.5% response rate in 40 patients with previously untreated metastatic or locally advanced pancreatic cancer. The response rates in the Taieb study were not replicated in the second-line setting (with a slightly lower irinotecan dose) in a study published by Yoo et al (2009). The Yoo study randomized 61 patients to either mFOLFIRI.3 (n=31) or mFOLFOX (n=30). No responses were reported among patients randomized to FOLFIRI.3 versus two responses in patients randomized to mFOLFOX.

An additional study (Zaniboni et al, 2012) of 50 patients with previously-treated pancreatic cancer who received a modified FOLFIRI regimen (without irinotecan fractionation) reported an 8% response rate with the authors concluding that FOLFIRI exhibited modest clinical activity.

In summary, there were insufficient data to recommend an irinotecan-based regimen as the control arm in the second-line setting. Nevertheless, because the study subject to this application used a 5-fluorouracil/leucovorin arm, it is unknown whether MM-398 is superior to a standard irinotecan-based regimen.

2.2 U.S. regulatory history

The following summarizes the pertinent regulatory history and meetings held in relation to this NDA. (b) (4) .

18 Sep 2008 (pre-IND meeting): FDA and PharmaEngine (prior sponsor) met during a pre-IND meeting to discuss the sponsor's plans to initiate a clinical trial that would enroll patients with previously-treated pancreatic cancer. FDA stated that, new non-clinical studies did not appear necessary to support the proposed clinical trial based on the results of the completed non-clinical studies and a clinical trial conducted in Taiwan. FDA informed PharmaEngine that an embryo-fetal developmental toxicity study was not needed because irinotecan was a known teratogen. FDA provided general advice regarding development plans (b) (4) and in regards to the plan to evaluate the pharmacokinetics of liposomal irinotecan.

19 Aug 2011 (Type B, End of Phase 2 meeting): FDA and Merrimack met to discuss the preliminary results from the then ongoing trial of MM-398 as a second-line treatment in pancreatic cancer and to discuss the development plans for MM-398 including a proposed randomized clinical trial to be conducted in patients with pancreatic cancer. During the meeting, FDA stated that the overall survival results from the single-arm trial (with a response rate of less than 10%) were not interpretable and recommended that Merrimack conduct the randomized trial before submitting the NDA.

FDA informed Merrimack that for a single trial to support an NDA, the trial must be well designed, well conducted, internally consistent, and provide statistically and clinically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. As such, FDA expressed concerns regarding a proposed minimization plan and the proposed interim analysis plan given the small size of the study. FDA stated that stratification could be performed instead of the minimization procedure.

FDA did not object to the use of 5-FU and folinic acid in the control arm; however, FDA stated that the choice of control arm was Merrimack's decision and should be discussed with the study investigators.

FDA stated that the Agency could not evaluate the impact of MM-398 dosing in patients homozygous for the UGT1A1*28 allele based on the information provided in the briefing package. However, FDA recommended that Merrimack consider a reduced initial MM-398 dose for patients homozygous for UGT1A1*28.

Merrimack asked whether filing a future NDA through the provisions of 505(b)(2) was appropriate and acceptable. FDA stated that the Agency was unable to provide a response because Merrimack did not describe what information they intended to rely upon for which a right of reference did not exist.

1 Aug 2014 (Type C meeting): Merrimack requested this Type C meeting to obtain general FDA guidance on regulatory, nonclinical, clinical pharmacology, and statistical contents of a planned NDA.

FDA stated that Merrimack could request Fast Track designation for MM-398 in order to request a rolling NDA submission; however, FDA informed Merrimack that the PDUFA review clock would start when the application was complete.

(b) (4)

FDA provided advice regarding potential plans for expanded access and that consideration for expanded access (e.g., the type of expanded access) should be dictated by the demand for access.

FDA agreed based on the limited information provided in the briefing package, that a Risk Evaluation and Mitigation Strategy was not necessary in order to file the NDA.

FDA stated that the nonclinical studies listed for MM-389 in the briefing package appeared sufficient to support the NDA. FDA also provided clinical pharmacology comments including a post-meeting recommendation to investigate the *in vivo* stability of the liposome in a single-dose study in humans.

FDA informed Merrimack that the major issue regarding the approvability of an NDA using data from Study MM-398-07-03-01 (as a single-trial) related to the differences in the 5FU dosing regimens in the MM-398 combination arm versus the control arm. FDA stated that Merrimack will have to provide a scientific argument as to why the differences between the control and MM-398 combination arms are attributable to the addition of MM-398 rather than differences in 5FU dosing between arms.

18 Sep 2014 (Type B CMC pre-NDA meeting): FDA and Merrimack met to discuss CMC components of their planned NDA. FDA provided advice on validation of manufacturing processes, *in vitro* release methodology, and issues related to manufacturing process modifications. FDA also provided advice regarding characterization/specification of MM-398

as well as advice regarding stability data. FDA stated that the use of two drug substance (DS) suppliers can be acceptable provided that both suppliers produce the same DS and that materials from both suppliers meet the proposed specifications without significant differences.

2 Dec 2014 (Type B pre-NDA meeting): FDA and Merrimack held this meeting to discuss the contents of the NDA submission. FDA stated that the preferred method of submission of the NDA was via the FDA Electronic Submissions Gateway (ESG). Merrimack confirmed that they would submit data in SDTM and ADaM formats.

Merrimack asked about a proposed approach to provide justification for the lack of an impact on efficacy of different 5FU dosing regimens (between arms) in the MM-398-07-03-01 trial. FDA did not object to Merrimack's proposed approach that included analyses of literature, data intended to demonstrate that the planned cumulative doses of 5FU in the 5-FU/LV control arm were higher than in the MM-398 combination arm over a six week cycle, and PK simulation results showing that the 5FU area under the curve was higher in the control arm. FDA stated that the adequacy of the approach would be determined during the review of the NDA.

FDA agreed with Merrimack's proposed approach to the submission of the Integrated Summary of Safety. FDA stated whether the database is adequate to characterize the toxicity profile of MM-398 for the proposed use, i.e., in combination with 5FU and leucovorin, would depend on the incidence of serious or irreversible morbidity observed across the clinical trial experience with MM-398.

To facilitate the review, FDA requested that Merrimack submit a 90 day safety update in lieu of a 120 day update.

Merrimack proposed using PK data from Study PEP0201 (which measured both total and encapsulated irinotecan) to support the *in vivo* stability of the liposome. FDA did not object to the proposal under the condition that Merrimack provide justification in the NDA for not being able to develop the bioanalytical method to distinguish encapsulated and unencapsulated irinotecan.

FDA did not agree (b) (4) and informed Merrimack that all components of the NDA should be provided in the NDA with only minor components submitted up to day 30 after filing.

2.3 Application history

The following table summarizes the contents of amendments submitted to the NDA.

Table 2 Amendments to NDA 207793 (as of the date of the completion of this review)

Date of Receipt	Purpose of Submission
29 Dec 2014	Submission of nonclinical sections of the NDA.
31 Mar 2015	Submission of the full Chemistry, Manufacturing, and Controls (CMC) sections of the NDA.
24 Apr 2015	Submission of the full clinical portion of the NDA (designating the NDA to be complete and therefore used to determine the PDUFA goal date).

Date of Receipt	Purpose of Submission
29 Apr 2015	Inclusion of a patent certification in Module 1.3.5.2.
4 May 2015	Request for a proprietary name review for Onivyde. Also submitted the debarment certificate in Module 1.3.3 and moved the Financial Certification Form to the correct location in Module 1.3.4.
14 May 2015	Revised request for proprietary name review and a change in the contact agent.
29 May 2015	Response to clinical pharmacology information requests from FDA related to PK data and analyses, inclusion of DSMB minutes from Study MM-398-07-03-01, and a discussion for why the futility analysis was not conducted.
4 Jun 2015	Response to CMC information request dated 20 May 2015 and updated Sections of Module 3 (pertinent to Batch Analysis and Stability Data).
30 Jun 2015	Merrimack submitted additional CMC data, a replacement nonclinical report to update tabular information, and new art work for the vial label.
14 Jul 2015	Merrimack submitted a revised package insert in response to comments received by the Agency. Merrimack also submitted an updated Form 3455 from an investigator in Study MM-398-07-03-01.
16 Jul 2015	Merrimack submitted information in response to comments in the Filing letter (to support the updated package insert that was also included in this submission). The response included information regarding infusion reactions, diarrhea, early onset diarrhea, most common serious adverse drug reactions, and adverse events of special importance.
21 Jul 2015	Merrimack provided dates of death [when available (e.g., from public registries)] for patients who withdrew consent from the pivotal study. Merrimack provided this information following an FDA information request based on an imbalance in the number of patients who withdrew consent between arms. Merrimack also provided a re-analysis of OS based on this information.
23 Jul 2015	Submission of the 90-day safety update report based on a data cut-off date of 19 Jun 2015.
30 Jul 2015	Submission of the final two (Section) 3.2.P.5.3 validation summaries containing additional information (solution stability and robustness) and the corresponding validation reports.
31 Jul 2015	Response to FDA information request dated 7 Jul 2015 pertaining to CMC portions of the NDA.
3 Aug 2015	Resubmission of information described above (in the 21 Jul 2015 amendment) providing an updated analysis of OS and data also pertaining to the updated analysis of PFS (based on the additional OS information). Merrimack also provided new datasets.
11 Aug 2015	Merrimack submitted updated population pharmacokinetics and exposure-response analyses in response to an FDA information request dated 27 Jul 2015.
24 Aug 2015	Merrimack provided additional exposure-safety analyses and datasets to support the analyses.
25 Aug 2015	In response to an 11 Aug 2015 information request, Merrimack submitted certain updated CMC sections in Module 3 of the application.
15 Sep 2015	Merrimack provided revised product labels as well as a discussion pertaining to the expression of strength and dose as irinotecan free base in product labeling.
22 Sep 2015	Submission of a response to an FDA information request pertaining to CMC portions of the NDA.
24 Sep 2015	Submission of updated CMC sections of the NDA pertaining to the description and composition of the drug product and batch formula.

Date of Receipt	Purpose of Submission
25 Sep 2015	Merrimack updated CTD Section 3.2.P.5.1 (Specifications) of the NDA based on an information request from FDA dated 25 Sep 2015.

3. CMC

The Quality Review team [Ray Frankewich (drug substance or DS), Mike Adams (drug product or DP), Sung Kim (process), Jaijing Hu (microbiology), Mike Shanks (facility), Banu Sizanli Zolnik (biopharmaceutics), Steven Kinsley (regulatory business process manager), Olen Stephens (application technical lead and environmental assessment reviewer), and Paul Perdue Jr. (ORA lead)] recommended approval of NDA 207793 and found the manufacturing and testing facilities to be acceptable.

In addition to the issues described below regarding the manufacture of DP, a review issue pertinent to this NDA involved the designation of strength by the freebase rather than the hydrochloride salt. This designation is based on the USP salt naming policy [i.e., as described in the June 2015 FDA Guidance (Naming of Drug Products Containing Salt Drug Substances)] and the policy that USP will base the strength of the product on the active moiety (the Guidance states that a drug product with labeling that contains a name that is inconsistent with the applicable monograph title risks being misbranded).

At this time, the strength designation has not been completed with the applicant; therefore, the OPQ review referenced strength in their review as either 50 mg of the irinotecan hydrochloride trihydrate or 43 mg irinotecan (e.g., as the base). Similarly, the strength of the solution is expressed as either 5 mg/mL irinotecan hydrochloride trihydrate or 4.3 mg/mL irinotecan (OPQ recommended labeling based on the freebase per the salt naming policy).

This review was written using the dose described in the protocol and in the original NDA based on the salt form (e.g. 80 mg/m^2). The 80 mg/m^2 dose is equivalent to 68.8 mg/m^2 based on the freebase. There was internal discussion during the review of the NDA regarding the potential for dosing errors based on the change (i.e., the trial was conducted using the dose based on the salt form and the results were presented at public meetings using this dose).

Despite these potential concerns, DMEPA recommended moving forward with the recommendation to label based on the freebase and that Merrimack could institute multiple strategies to reduce the risk of medications errors (e.g., involving labeling, etc.). Labeling based on freebase has been communicated with the applicant and the Division awaits the applicant's response to this issue.

3.1 Drug substance

The active ingredient of Onivyde consists of irinotecan hydrochloride trihydrate. Irinotecan hydrochloride trihydrate is manufactured by [redacted] (b) (4) and the information pertinent to the manufacture of irinotecan hydrochloride trihydrate was provided in a type II DMF [redacted] (b) (4).

3.2 Drug product

The DP is a liposomal product, and according to the OPQ review, the Onivyde liposome is a unilamellar lipid bilayer vesicle (refer to OPQ review for components of the lipid membrane), approximately 110 nm in diameter that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state as the sucroseoctasulfate salt. Furthermore, the review states that the DP liposomes are loaded with DS at a ratio of (b) (4) gm irinotecan/mole phospholipid.

From a lifecycle perspective, the OPQ team deemed Onivyde as a high risk product due to its liposomal formulation and method of manufacture. The following highlights some of the DP manufacturing steps:

- Manufacture, control, release and stability testing operations are conducted at Merrimack Pharmaceuticals, Inc., in Cambridge MA.
- Batches of bulk DP (b) (4) for filling into glass vials.
- Filled vials (b) (4) for labeling and packaging.

The OPQ review stated that the *in vitro* release method and acceptance criteria should be reviewed critically post-approval. Currently, the manufacturing process allows (b) (4) for the final fill operations. The OPQ review stated that Merrimack expressed understanding that a prior approval supplement would be required if Merrimack will propose (b) (4) in the final fill operations.

Although not recommended as a formal post-marketing commitment, Merrimack committed, as part of continual quality improvement for the manufacturing process, to develop and validate a method, and then submit the method description and validation studies as a prior approval supplement on or before December, 2016.

Merrimack also committed, as part of continual quality improvement for the manufacturing process, to perform a stability study (initiated on or before 31 Mar 2016) which incorporates a (b) (4) The stability study will incorporate both normal and worst case ambient light storage conditions to assess photostability.

The Quality team granted a 21 month shelf-life when Onivyde is stored at refrigerated storage conditions (2° to 8°C) with protection from light and freezing. This recommendation includes (b) (4)

4. Nonclinical Pharmacology/Toxicology

Dr. Margaret Brower, the primary nonclinical reviewer, concluded that from the nonclinical perspective, liposomal irinotecan can be approved in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas.

4.1 Nonclinical pharmacology

The nonclinical overview in the NDA stated that irinotecan liposome is a liposomal encapsulation of irinotecan hydrochloride, the active ingredient. Irinotecan and its active metabolite (SN-38) inhibit topoisomerase 1 and prevent re-ligation of single strand breaks leading to double-strand breaks and cell death. The nonclinical review stated that the liposomal formulation of irinotecan resulted in longer exposure of both irinotecan and SN-38 compared to free irinotecan in all species tested and that liposomal irinotecan demonstrated activity in several xenograft tumor models.

4.2 Nonclinical toxicology

Merrimack submitted toxicology studies conducted in both rats and dogs. Irinotecan liposome was lethal to rats following four weeks of weekly dosing at the 260 mg/kg dose. Toxicities observed in the four week study included bone marrow hypocellularity, renal tubular hypertrophy, thymic atrophy, and histiocytosis (however, histiocytosis was also observed in control animals). Hepatic necrosis and hematopoiesis of the spleen were observed in a long term rat study (liposome irinotecan administered once every three weeks for 6 doses). The non-clinical review also described decreased body weights at the 75 and 190 mg/kg doses in the 6 cycle rat study.

The nonclinical review found weekly administration of irinotecan liposome 16 mg/kg per week for four weeks to be lethal in dogs. Target organs affected by 8 or 16 mg/kg irinotecan liposome in dogs included the gastrointestinal tract, bone marrow, Peyer's patch, and spleen. In the 6 cycle (liposome irinotecan administered once every three weeks for 6 doses), repeat dose study, 36 mg/kg was the reported lethal dose in dogs. Target organs affected by the 15 and 21 mg/kg doses included the gastrointestinal tract, lymphatic tissues, and hematopoietic tissues.

Merrimack also submitted the results of a cardiovascular and respiratory safety pharmacology study in Beagle dogs. The nonclinical review found no drug-related changes in cardiovascular hemodynamic, electrocardiographic, or respiratory parameters following a single infusion of 9 to 21 mg/kg of irinotecan liposome.

The applicant did not conduct separate reproductive toxicology or genetic toxicity studies. In lieu of such studies, Merrimack relied on FDA's previous findings regarding irinotecan as part of the 505(b)(2) pathway. Based on the findings for irinotecan hydrochloride, the label for liposome irinotecan will carry a warning for embryofetal risk and recommendations for men and women to use effective contraception during and after treatment with irinotecan liposome (refer to nonclinical review for details).

The reference drug, irinotecan hydrochloride, was clastogenic in *in vitro* and *in vivo* studies; however, neither irinotecan HCL nor SN-38 were mutagenic in *in vitro* Ames assays. *Comment: this potential risk of genetic toxicity is considered acceptable for a drug intended for the second-line treatment of patients with pancreatic cancer.*

5. Clinical Pharmacology

5.1 General clinical pharmacology considerations

The Office of Clinical Pharmacology (OCP) review (Sarah Schrieber, primary reviewer; Gene Williams, team leader; Anshu Marathe, pharmacometrics; Yaning Wang, pharmacometrics team leader; Anuradha Ramamoorthy, pharmacogenomics; and Rosane Charlab Orbach, pharmacogenomics team leader) concluded that this NDA is acceptable from a clinical pharmacology perspective.

5.1.1 Dose selection

Prior to conducting MM-398-07-03-01, two studies were conducted that assessed the safety of MM-398 in combination with 5FU and leucovorin (PEPCOL and PEP0203).

Additionally, OCP conducted exposure-response analyses of available ER data in the NDA and found that the analyses supported the 80 mg/m^2 starting dose of MM-398 (when combined with 5FU and leucovorin). Although the OCP review found an association with SN-38 exposure and OS, there was also an association of severe neutropenia with SN-38 exposure (especially C_{max}) and severe diarrhea (especially C_{max}) with irinotecan exposure.

5.1.2 Pharmacokinetics

The applicant submitted results from Study PEP0206 that compared the pharmacokinetics of irinotecan and SN-38 in patients exposed to conventional irinotecan (300 mg/m^2) versus MM-398 (120 mg mg/m^2). The OCP review found MM-398 to result in higher exposure to total irinotecan (C_{max} 13.4-fold, t½ 2.0-fold, and $AUC_{0\text{-}inf}$ 46.2-fold). MM-398 also resulted in 3-fold higher SN-38 t½ and 1.4-fold $AUC_{0\text{-}inf}$; however, the SN-38 C_{max} was reduced compared to Camptosar (0.19-fold).

The pharmacokinetics of the 80 mg/m^2 dose both as a single agent and in combination with 5FU/LV were investigated in Studies PIST-CRC-01 (n=6) , MM-398-01-01-02 (n=13), and PEP0203 (n = 6). The summary PK statistics of MM-398 from these studies can be found in Table 9 of the OCP review. The C_{max} (SD) of irinotecan and SN-38 following a single dose of MM-398 were 37.2 µg/mL (8.8) and 5.4 ng/mL (3.4), respectively. The t½ of irinotecan and SN-38 following a single dose of MM-398 were 1.7 hours and 25 hours, respectively (refer to the OCP review for values for AUC, T_{max}, CL, and VD and the PK results of MM-398 from individual studies).

In regards to drug metabolism, Merrimack proposed to rely on information from the Camptosar package insert.

5.2 Drug-drug interactions

Merrimack relied on information in the Camptosar package insert to inform decisions on drug-drug interactions.

5.3 Demographic interactions/special populations

UGT1A1*28

Patients enrolled in Study MM-398-07-03-01 who were homozygous for the UGT1A1*28 allele received a lower starting dose (60 mg/m^2) of MM-398 when combined with 5FU/LV compared to patients who were non-homozygous for UGT1A1*28 (patients homozygous for UGT1A1*28 experience increased toxicity when exposed to Camptosar). The protocol allowed for such patients to increase the dose to 80 mg/m^2 if tolerated. Seven patients homozygous for UGT1A1*28 received MM-398 in combination with 5FU/LV in Study MM-398-07-03-01. Among these seven patients, two remained at the 60 mg/m^2 dose, three increased to 80 mg/m^2 without further reduction, one patient escalated to 80 mg/m^2 with a subsequent reduction to 60 mg/m^2, and one patient required dose reduction to 40 mg/m^2. One of these seven patients discontinued due to an adverse event and one discontinued due to patient's choice.

In summary, based on the limited numbers of patients homozygous for UGT1A1*28 enrolled in Study MM-398-07-03-01, there is residual uncertainty regarding the optimal dose for these patients. Nevertheless, the proposed lower starting dose appears acceptable based on experience with Camptosar, the allowance to increase the dose to 80 mg/m^2 if tolerated, and the OCP finding that the frequency of neutropenia in patients homozygous for the UGT1A1*28 allele (who received the lower dose) was similar to the frequency in non-homozygous patients who received the 80 mg/m^2 starting dose. Additionally, the OCP popPK analysis, adjusted for the lower dose of MM-398 administered to patients homozygous for the UGT1A1*28 allele, found that patients homozygous for this allele had only a slight increase (18%) in total SN-38 average steady state concentration relative to patients non-homozygous for this allele.

Bilirubin

The Camptosar label states that dosing of irinotecan for patients with bilirubin > 2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients. Furthermore, the Camptosar label states that patients with serum total bilirubin levels of 1 mg/dL or greater experienced an increased incidence rate of first-cycle Grade 3 or 4 neutropenia.

A dose of MM-398 in patients with bilirubin levels above normal cannot be recommended because Study MM-398-07-03-01 did not enroll patients with elevated bilirubin levels. The OCP review stated that only data from six patients with bilirubin levels ≥ 1.0 mg/dL who received MM-398 in combination with 5FU/LV were submitted in the application. The OCP review found that there were insufficient information to recommend a reduced starting dose in patients who had a bilirubin level ≥ 1.0 mg/dL but less than the upper limit of normal.

Ethnicity

The OCP review found the covariate with the strongest association to irinotecan and SN-38 following exposure to MM-398 was ethnicity. The OCP review found Asian patients to have approximately 70% lower total irinotecan C_{ave} compared to White patients (there were few patients of other ethnic backgrounds enrolled). The OCP review found minimal effect of ethnicity on SN38 C_{ave} (however, the applicant's report noted a higher SN-38 C_{max} in Asian patients). *Comment: This reduced exposure of irinotecan in Asian patients may account for the decreased rate of diarrhea; likewise the higher C_{max} in Asian patients could account for the*

higher reported rate of neutropenia in Asian patients. Ultimately, this information will be presented in the label to inform patients and physicians that the risk profile of MM-398 may be influenced by ethnicity.

5.4 Thorough QT study or other QT assessment

The applicant did not submit the results of a formal QTc evaluation based on the lack of evidence of cardiac toxicity in nonclinical studies and because the listed drug, Camptosar, does not contain labeling information that Camptosar increases QTc despite marketing approval since 1996. Although the QT-IRT consult recommended requesting a PMR to assess QTc according to ICH E14 guidance (partially based on differences in PKs between MM-398 and Camptosar), OCP did not agree with this recommendation that a PMR should be requested at this time based on the known information regarding the listed drug, non-clinical results, and the patient population for which MM-398 would be indicated (second-line pancreatic cancer). OCP recommended that Merrimack investigate the effects of MM-398 on QTc if Merrimack intends to develop MM-398 in other cancer indications.

This reviewer agrees with OCP that the risk (based solely on a drug-induced QTc effect through cardiac channels and not an effect of electrolyte wasting via diarrhea) of QTc prolongation is likely to be low based on the known experience with irinotecan and that the residual uncertainty regarding an effect on QTc is acceptable for this application that would involve the approval of MM-398 (a drug with an effect on OS) for patients with previously treated pancreatic cancer (a disease with a short estimated life expectancy).

6. Clinical Microbiology

This section is not applicable to this review.

7. Clinical/Statistical-Efficacy

The clinical reviewer (Dr. Shan Pradhan) recommended approval of this application based on the improvement in overall survival demonstrated in the MM-398-07-03-01 clinical trial.

The statistical reviewer (Dr. Hui Zhang) concluded that MM-398-07-03-01 showed that MM-398 + 5-FU/LV demonstrated a statistically significant improvement in the primary endpoint of OS compared with 5-FU/LV.

This section of the CDTL review will focus on the demonstration of safety and efficacy in the adequate and well controlled trial and will not focus on trials in other indications (e.g., that provided safety data) or on trials that supported the dose of MM-398 (refer to Clinical Pharmacology Section above).

7.1 Background of clinical program

The initial protocol for the pivotal trial (MM-398-07-03-01 also known as NAPOLI-1) was dated 6 Oct 2011 and contained the following title: A Randomized, Open-Label Phase 3 Study of MM-398 versus 5-Fluorouracil and Leucovorin in Patients with Metastatic Pancreatic Cancer.

The protocol was initially designed as a two arm trial of MM-398 as monotherapy (120 mg/m^2 intravenously over 90 minute every three weeks) versus 5-fluorouracil in combination with leucovorin.

Merrimack subsequently amended the protocol (see details below) to add the third arm of MM-389 in combination with 5FU and leucovorin. The amended protocol was dated 14 Jul 2012. The development plan for this NDA was primarily based on the results of a single adequate and well controlled trial (MM-398-07-03-01).

7.2 Design of MM-398-0703-01

7.2.1 Primary endpoint

The primary endpoint of MM-398-07-03-01 was overall survival (OS), defined as the time from randomization to the date of death from any cause. *Comment: As stated in the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.*

7.2.2 Secondary endpoints

The protocol listed progression free survival (PFS) defined as the number of months from the date of randomization to the date of death or progression; time to treatment failure (TTF) defined as time from randomization to either disease progression, death or study discontinuation due to toxicity; and objective response rate determined using RECIST as secondary efficacy analyses. The protocol also indicated patients would be assessed for "clinical benefit response" (i.e., with variables described in the gemcitabine label). Patients also completed EORTC-QLQ-C30 questionnaires for quality-of-life assessments.

The use of investigator assessments for progression (and response) was acceptable because the primary endpoint was overall survival (i.e., the PFS and ORR endpoints are considered supportive of the overall survival results). As stated in the May 2007 Guidance, TTF is not recommended as a regulatory endpoint for drug approval as it does not clearly distinguish the efficacy of the drug from toxicity or patient intolerance. Finally, although clinical benefit response is listed in the gemcitabine label, this endpoint can be problematic for multiple reasons, e.g., it utilizes physician-determined ECOG PS as a variable in an unblinded study and there is the potential for missing data regarding components of the endpoint.

7.2.3 Major eligibility criteria

The trial enrolled patients with histologically or cytologically confirmed metastatic adenocarcinoma of the exocrine pancreas with disease progression following prior gemcitabine or gemcitabine-containing chemotherapy (in the locally advanced or metastatic setting). The protocol allowed for the administration of gemcitabine in the adjuvant setting if disease recurrence occurred within 6 months of completion of adjuvant therapy. Other protocol requirements included Karnofsky performance status ≥ 70; neutrophil count > 1,500/mcL

without growth factors; platelet count > 100,000/mcL; hemoglobin > 9 g/dL; albumin ≥ 3 g/dL; normal bilirubin; serum creatinine ≤ 1.5 times the institutional upper limit of normal; normal ECG or ECG without clinically significant findings; and age ≥ 18 years.

The initial protocol excluded patients with the following: prior irinotecan; active CNS metastases; Grade 2 or greater diarrhea (or other clinically significant gastrointestinal disorders); severe arterial thrombotic event in prior 6 months; NYHA class III or IV heart failure or uncontrolled blood pressure; and active infection or unexplained fever that could compromise the patient's participation in the clinical trial.

Comment: (b) (4) *These patients were not evaluated in the MM-398-07-03-01 clinical trial, and therefore, the results of MM-398-07-03-01 cannot be extrapolated to patients with elevated bilirubin levels. Additionally, the results of the trial cannot be extrapolated to patients with poor performance status or albumin levels less than 3 g/dL.*

7.2.4 General study design/treatment plan

- The trial was initiated as an open-label, multi-national, randomized trial (1:1) that compared MM-398 to 5-fluorouracil and leucovorin. Randomization occurred via an Interactive Web Response System (IWRS). *Refer to Amendment 1 below for description of the third arm.*
- MM-398-07-03-01 randomized patients to receive either MM-398 (120 mg/m^2 intravenously over 90 minute every three weeks) or 5-fluorouracil (2000 mg/m^2 intravenously over 24 hours) in combination with leucovorin (200 mg/m^2 intravenously) weekly for four weeks followed by two weeks of rest. The protocol stipulated screening all patients for the UGT1A1*28 allele at baseline and a reduced *initial* dose of MM-398 (80 mg/m^2) for patients homozygous for the UGT1A1*28 allele.
- The protocol specified one interim analysis for safety and futility once 60 patients were enrolled and received at least one dose of investigational drug.
- The protocol stated that no established standard of care existed for patients in the control arm of the trial; however, the protocol stated that 5FU/LV has been used as a control arm in others trials in pancreatic cancer.

  At the time that MM-398-07-03-01 was initiated, one report (Pelzer et al., Eur J Cancer, 2011) described an improvement in overall survival of oxaliplatin, folinic acid and 5-fluorouracil (OFF regimen) compared to *best supportive care* in the second-line setting; however, the trial was terminated prematurely (due to inability to enroll patients with BSC in the control arm) after inclusion of only 46 patients (thus diminishing confidence in the reproducibility of the findings). More recently, (Oettle et al, JCO, 2014) a report compared the OFF regimen to 5-fluoruracil plus leucovorin (see Background Section of this review). The CONKO-3 report described improved OS in the OFF group compared to the 5-fluorouracil group (HR 0.66, log rank p = 0.01: median survival 5.9 versus 3.3 months). *Comment: Although OFF may have been a better performing control arm, lack of*

published results from the trial until 2014 would have made it difficult to stipulate OFF as a control arm in study MM-398*-07-03-01 at the time that the study was initiated.*

- Patients received treatment until disease progression (RECIST v1.1), symptomatic deterioration, intolerable toxicity, non-compliance with study procedures, or following patient or physician request.
- To prevent nausea or vomiting, the protocol required premedication with dexamethasone and a 5-HT3 antagonist (or other anti-emetics per institutional standard practices for irinotecan) prior to administration of MM-398. Prior to treatment with 5-FU and leucovorin, the protocol required premedication with dexamethasone, prochlorperazine or equivalent anti-emetics.
- In regards to MM-398, the protocol contained management instructions for infusion reactions (including permanent discontinuation for Grade 3 or 4 events); hematological toxicities; and non-hematological toxicities including diarrhea (including interruption and dose reductions). The protocol also contained management instructions for toxicities caused by 5-FU. The protocol allowed colony stimulating factors only in patients with ≥ Grade 3 neutropenia or neutropenic fever.
- The protocol stipulated atropine to treat cholinergic-syndrome-related diarrhea caused by irinotecan. The protocol also contained additional recommendations for the management of chemotherapy-induced diarrhea including loperamide, fluoroquinolones, hospitalization, intravenous fluids, and octreotide.
- Patients underwent assessments for tumor size in both arms every 6 weeks using CT or MRI and any other radiographic procedures deemed appropriate by the investigator. Survival status was to be collected during the treatment period and every one month from the date of the 30 day follow-up visit. CA 19-9 levels were also assessed every 6 weeks in both arms.
- The schedule of visits differed slightly between arms given the different schedules of treatment in both arms. *Given the primary endpoint, this is unlikely to have had a large influence on the trial results.*

7.2.5 Statistical design and analysis issues

Randomization/Stratification Factors
The original protocol specified the following three stratification factors: baseline albumin level (≥ 4 g/dL versus ≤ 4 g/dL), Karnofsky performance status (70 and 80 versus ≥ 90), and ethnicity (Caucasian versus East Asian versus all others).

Determination of Sample Size
The original protocol proposed randomizing 270 patients (1:1) to receive either MM-398 or 5-FU and leucovorin. The applicant designed the protocol with at least 85% power to detect a median 1.5 month difference in overall survival (with a 3 month estimate in control arm) with a two sided alpha of 0.05. The planned number of events for the final analysis was 220.
Comment: Protocol Amendment 1 introduced a change to the overall design of the trial and a new sample size (see below).

Analyses
The protocol stated that the primary efficacy analysis for overall survival would be tested using an un-stratified log rank test in the intent-to-treat population (including all randomized patients who provided informed consent). The *initial* protocol did not propose a plan to control Type 1 error in regards to testing for secondary endpoints.

7.2.6 Protocol amendments

Amendment 1 (Version 2.1), dated 14 Jun 2012

The following list describes major changes contained in Amendment 1.

- Changed the title to reflect the addition of a third arm: NAPOLI1: A Randomized, Open Label Phase 3 Study of MM-398 with or without 5-Fluorouracil and Leucovorin, *versus* 5-Fluorouracil and Leucovorin, in Patients with Metastatic Pancreatic Cancer Who have failed Prior Gemcitabine-based Therapy.
- This amendment added the third arm consisting of the following regimen: MM-398 80 mg/m^2 (initial dose of 60 mg/m^2 for patients homozygous for the UGT1A1*28 allele) every two weeks, 5-fluorouracil 2,400 mg/m^2 over 46 hours every two weeks, and leucovorin 200 mg/m^2 every 2 weeks. *Comment: This third arm was not discussed during the EOP2 meeting held with Merrimack and complicated the ability to interpret the results of the study given that the dose and schedule of 5FU differed between the experimental and control arms. Refer to Section 1 of this review for discussion of the different 5FU/LV dosing regimens.*
- The protocol now allowed patients to have received prior irinotecan.
- Amended the statistical analysis plan to (1) power the study based on 305 events; (2) increase the sample size to 405 patients; (3) allow for two null hypotheses (both arms compared separately with the 5-FU/LV control arm) with alpha controlled at the two-sided 0.05 level using the Bonferroni-Holm adjustment; (4) allow for 99% power to detect a survival effect (HR 0.5) in the new arm compared to the control arm assuming a median OS of 6 months in the new arm and 3 months in the control arm, and to (5) allow for 85% power to detect the survival effect (HR 0.67) in the MM-398 arm versus the control arm. As mentioned, the protocol stipulated two pair-wise comparisons in the ITT population using the un-stratified log rank test.
- The amendment updated the dose modification requirements based on the inclusion of the combination arm (for brevity, this review will limit the discussion of dose modification to actions in the combination arm).
    - Required a neutrophil count ≥ 1500/mcL and a platelet count ≥ 100,000/mcL prior to each cycle of therapy of MM-398.
    - Patients who experienced Grade 3 or 4 neutropenia, neutropenic fever, or other Grade 3 or 4 hematologic toxicity would undergo MM-398 dose reduction (60 mg/m^2 for the first occurrence and 50 mg/m^2 for the second occurrence). These patients also underwent a 25% dose reduction of 5FU.
    - Patients who experienced ≥ Grade 3 diarrhea or other non-hematological toxicities other than asthenia or Grade 3 anorexia underwent dose reduction of MM-398 (60

mg/m^2 for the first occurrence and 50 mg/m^2 for the second occurrence). The protocol also required dose reduction of 5FU for Grade 3 or 4 non-hematological toxicities (except asthenia and Grade 3 anorexia) and for Grade 2 hand foot syndrome. The protocol required discontinuation of 5FU for Grade 3 or 4 hand foot syndrome or ≥ Grade 2 neurocerebellar or cardiac toxicity.

- Stipulated that patients have been off steroids for CNS metastases for at least 28 days to be eligible for enrollment (patients with active CNS metastases indicated by clinical symptoms, cerebral edema, steroids, or progressive disease were still excluded from enrollment).
- Removed requirement of the formal interim analysis for safety and futility. Instead, the DSMB would perform an intensive safety review of the first 15 subjects enrolled in each arm.
- Stipulated that assessments for progressive disease would stop prior to progression if the patient received another anti-neoplastic therapy.
- Stipulated that per RECIST 1.1, because the primary endpoint was OS and not ORR, that confirmation of PR or CR was no longer required.

Amendment 2 (Version 2.2), dated 19 Oct 2012

The following list describes major changes contained in Version 2.2 of the protocol:

- Clarified dosing of leucovorin (i.e., when using racemic versus isomeric leucovorin).
- Clarified that all patients (irrespective of version) will count toward the overall enrollment of 405 patients and that the final analysis will take place once 305 events occurred.
- Clarified that in Arm C, if either one of the drugs was withheld, that neither drug could be administered.
- Clarified that the efficacy comparison between MM-398 alone and fluorouracil would include all patients randomized to either arm, under all versions of the protocol, whereas the efficacy comparison between the combination arm versus fluorouracil would only include patients randomized under Version 2.0 or later.

Additional comment regarding MM-398-07-03-01: Prior to the final analysis, the formal statistical analysis plan (dated 16 Apr 2014) designated a sequential testing procedure to control the Type 1 error for primary and secondary endpoints (with the specified sequence being OS followed by PFS followed by ORR).

7.3 Efficacy results

The first patient was enrolled into Study MM-398-07-03-01 on 11 Jan 2012 and the last patient's event for the final analysis occurred on 14 Feb 2014. Approximately 405 patients were planned for enrollment into the study following Amendment 1. According to the CSR, investigators screened 577 patients for inclusion into the study and 417 patients were randomized and included in the ITT population. A total of 63 patients were enrolled into Version 1 of the study prior to the amendment allowing for the third arm. Therefore, the majority of patients were enrolled into Version 2 (three arm study) or later. The study data

cut-off date was 14 Feb 2014, and 313 patients died across all three arms on or prior to the date of data cut-off.

As specified in the updated protocol, there were two sets of ITT analyses conducted in Study MM-398-07-03-01 (with adjustment for alpha). The first involved the comparison of MM-398 alone versus 5FU and leucovorin. This analysis included 151 patients in the MM-398 arm versus 149 patients in the 5FU/LV arm (and included all patients enrolled in the protocol). The second set of ITT analyses included comparisons between MM-398 in combination with 5FU/LV versus 5FU and leucovorin. The ITT population for these analyses included 117 patients in the MM-398 combination arm versus 119 patients in the 5FU/LV arm and only included patients enrolled in Version 2.0 or later. The review below (unless otherwise specified) will primarily focus on comparisons of the MM-398 combination arm versus 5FU/LV.

7.3.1 Demographics

The demographic data below are the data from all patients in the MM-398 combination and 5FU/LV arms who were randomized under Protocol Version 2 or later. This group of patients constituted the population of patients subject to the efficacy analysis that demonstrated statistical significance for OS.

Refer to the statistical and clinical reviews for demographic information from patients in the MM-398 monotherapy arm and all patients randomized to the 5FU/LV arm (starting from the first patient enrolled).

Median age of the 119 patients randomized to the MM-398 combination arm was 63 years (range 41 to 81) versus 62 years (range 34 to 80) in the 5FU/LV arm. Although the median age of patients in both arms were similar, there were more patients older than 65 years in the MM-398 combination arm.

Table 3 (data from Dr. Zhang's review) shows that the gender and ethnic background of patients enrolled into Study MM-398-07-03-01 were similar between arms.

Table 3 Demographics

	MM-398 + 5FU/LV N=117 (%)	5FU/LV N=119 (%)
Age		
> 65 years	44	32
Female		
Yes	41	44
Race		
White	62	64
Black	3	3
Asian	29	30
Other	6	3
Geographic Region		

	MM-398 + 5FU/LV N=117 (%)	5FU/LV N=119 (%)
North America	16	16
Asia	29	29
Europe	40	41
Other	15	13

In general, demographic characteristics of patients were balanced in the two arms. The 5FU/LV arm had fewer patients with KPS 90 and more with KPS 80 compared to the MM-398 combination arm. It is difficult to determine the significance of this as patients with both KPS 80 and 90 are able to carry on normal activity and work (the difference being "minor" symptoms versus "some" symptoms). A similar number of patients in both arms had a previous attempt at curative surgery (34% in the MM-398 combination arm versus 36% in the 5FU/LV control arm) with 25% of patients in the MM-398 combination arm versus 28% of patients in the 5FU/LV control arm having undergone a Whipple procedure. More patients in the MM-398 combination arm had a prior biliary stent (13% versus 7%).

Table 4 Disease characteristics at baseline

	MM-398 + 5FU/LV N=117 (%)	5FU/LV N=119 (%)
Baseline KPS		
50	1	0
60	2	0
70	6	9
80	33	43
90	44	34
100	15	14
Prior gemcitabine combination		
Yes	55	54
Baseline albumin		
< 4 g/dL	55	55
Metastases		
1 measurable site	16	18
2 measurable sites	42	49
3 measurable sites	19	13
≥ 3 measurable sites	6	7
Peritoneal	24	27
Lung	31	30
Liver	64	70

7.3.2 Disposition

A total of 417 patients were randomized out of 577 patients who were screened. The study data cut-off date was 14 Feb 2014, and 313 patients died across all three arms on or prior to the date of data cut-off (this number was close to the projected 305 event cut-off specified in

the protocol). Two patients in the MM-398 combination arm did not receive investigational therapy. One patient became ineligible after randomization and one was due to investigator decision. Fourteen patients (of 149 patients starting with Version 1.0) in the 5FU/LV arm were not treated (11 due to subject decision, one due to investigator's decision, and two due to other reasons). Additionally, one patient in the 5FU/LV arm received MM-398 in combination with 5FU/LV.

Table 5 (data from Table 3 in the statistical review which was copied from the Applicant's CSR) shows that the most common reasons for treatment termination were progressive disease per RECIST or clinical deterioration. More patients discontinued treatment due to adverse events in the MM-398 combination arm and more withdrew due to RECIST-defined progression in the 5FU/LV control arm. The proportion of patients who withdrew due to clinical deterioration or investigator's decision was similar in the two arms.

Table 5 Reason for treatment determination

	MM-398 + 5FU/LV N=117 (%)	5FU/LV N=119 (%)
Progressive disease	48.7	53.8
Clinical deterioration	11.1	10.1
Adverse event	9.4	5.9
Death	1.7	4.2
Investigator's decision	3.4	3.4
Sponsor's decision	0.9	0
Subject's decision	12	16

The investigators (and applicant) appeared to adequately follow patients for survival [outside of the imbalance between arms regarding the number of subjects who withdrew consent (see OS analyses below]; there was one patient in each arm (MM-398 combination arm and 5FU/LV arm) who was lost to follow-up.

7.3.3 OS analyses

Table 6, data obtained from the statistical review, summarizes the efficacy results from Study MM-398-07-03-01. These results were based on an updated analysis of OS submitted in the amended NDA (amendment received on 21 Jul 2015) that included additional death events from publically available information. The results demonstrated a statistically significant improvement in overall survival (i.e., at a two-sided alpha of 0.025). The updated analysis in the table partially addressed a weakness of the study in that there was an imbalance in the number of patients who withdrew consent among the three study arms (of 16 patients who withdrew consent, 11 were in the control arm and 4 were in the MM-398 combination arm). The updated analysis included information from 8 of 11 patients in the control arm and two of four patients in the MM-398 combination arm.

The results of the initial OS analyses submitted in the NDA that did not include these additional death events were similar [HR of 0.67 (95% CI: 0.49, 0.92), p = 0.012]. Imputation analyses of OS conducted by Merrimack were also supportive of the original results based on

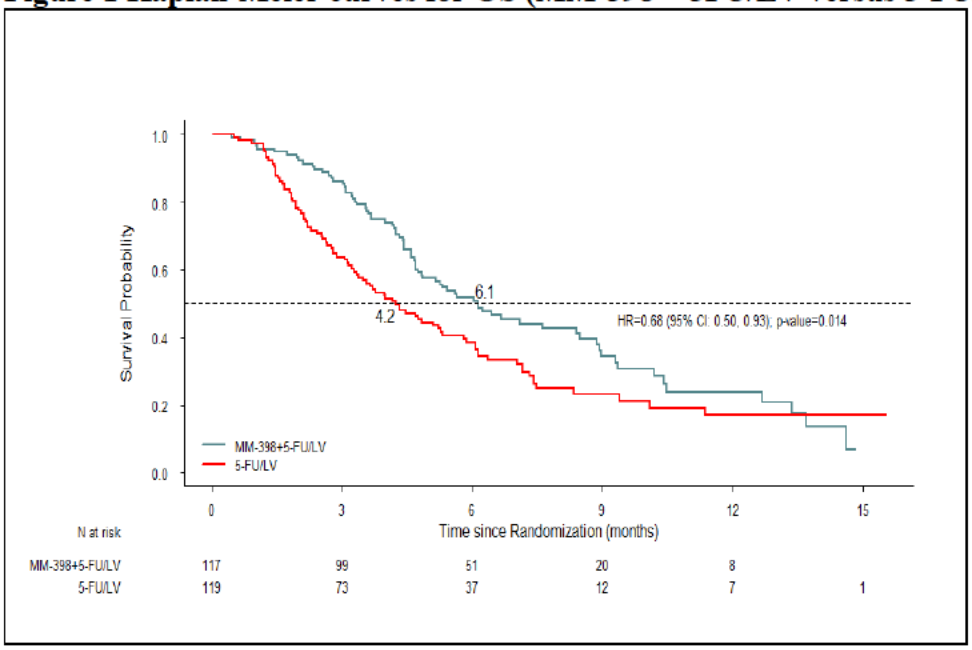
the ITT analysis. Additional sensitivity analyses of OS provided in the NDA (e.g., stratified analysis and per-protocol analyses) were consistent with the primary OS results.

Table 6 Summary of OS efficacy results (combination arm versus placebo comparison)

	MM398 + 5FU/LV N = 117	5FU/LV N = 119
# of deaths, n (%)	77 (66%)	86 (72%)
Median (in mos.)	6.1	4.2
95% CI	(4.8, 8.5)	(3.3, 5.3)
Stratified HR (95% CI)	0.68 (0.50, 0.93)	
p-value (two-sided)	0.014	

Figure 1, copied from Dr. Zhang's review, shows separation of the two survival curves prior to the three month time-point. Ultimately, the median difference in OS was 1.9 months between arms. The two curves converge at the tails after 12 months; however, this reflects the poor prognosis of patients with pancreatic cancer (even in those who receive a treatment that can prolong survival).

Figure 1 Kaplan-Meier curves for OS (MM-398 + 5FU/LV versus 5-FU/LV)



Merrimack provided an exploratory analysis of OS based on updated information in the 90-day safety update. After 86% (i.e., a more mature analysis) of patients died in the analysis of the MM-398 combination arm versus control, the HR for OS was 0.75 with a 95% CI of 0.57 to 0.99 and a *nominal* p value of 0.043. Median OS in the two arms were similar to the original analysis with a median survival duration in the combination arm of 6.2 months and a median survival duration in the 5FU/LV arm of 4.2 months.

It appeared unlikely that the improvement in survival in the MM-398 combination arm could have been attributed to differences in post-progression chemotherapy. In an analysis of

patients enrolled after the initiation of Version 2 of the protocol, 31% of patients in the MM-398 combination arm received post-progression chemotherapy versus 38% in the 5FU/LV arm.

Table 7 Exploratory updated analysis of OS in 90-day safety update

	MM398 + 5FU/LV N = 117	5FU/LV N = 119
# of deaths, n (%)	104 (89%)	99 (83%)
Median (in mos.)	6.2	4.2
95% CI	(4.8, 8.4)	(3.3, 5.3)
Stratified HR (95% CI)	0.75 (0.57, 0.99)	
p-value (two-sided)	0.043	

MM-398 when administered *as a single agent* did not improve the survival of patients with previously treated pancreatic cancer when compared to 5FU and leucovorin (Table 8). The denominators for these analyses differed from the OS analyses above because all patients from the initial version of the protocol were included (as specified in the SAP). The analyses in the table below reflect the results based on the statistical review of the data in the NDA as amended on 21 Jul 2015; however, the results of these analyses and the analyses in both the original NDA and the exploratory updated analyses of OS were similar. Based on these results, substantial evidence does not exist to support the use of MM-398 *as a single agent* to treat patients with metastatic pancreatic cancer.

Table 8 OS Analyses of MM-398 as a single agent versus 5FU/LV

	MM-398 alone N = 151	5FU/LV N = 149
# of deaths, n (%)	129 (85)	115 (77)
Median (in mos.)	4.9	4.2
95% CI	(4.2, 5.6)	(3.6, 4.9)
Stratified HR (95% CI)	1.0 (0.77, 1.28)	
p-value (two-sided)	0.97	

Table 14 and Figure 6 in the statistical review [Table 9 below presents some of the analyses (data copied from the statistical review)] shows that for almost all subgroups tested, that the HR (point estimate) was less than one. The HR for OS was greater than one for the "others" ethnicity subgroup; however, this group comprised only 9 events in 16 patients across both arms. The HR (point estimate) also was greater than one (1.25) for patients who received prior irinotecan; however this subgroup was also small comprising 20 events in 29 patients.

The 95% CIs crossed one for many of the analyses; however, the sample size in these subgroups was smaller than the overall patient population and thus these subgroups were not adequately powered to demonstrate a (nominally) statistically significant effect on OS.

Table 9 Subgroup analyses for OS (MM-398 + 5FU/LV versus 5FU/LV)

Subgroup	N*	HR (95% CI)
Race		
White	72/76	0.66 (0.45, 0.97)
Asian	34/36	0.54 (0.29, 98)
Gender		
Women	48/52	0.72 (0.44, 1.17)
Men	69/67	0.64 (0.43, 0.96)
Age in years		
≤ 65	65/81	0.61 (0.40, 0.92)
> 65	52/38	0.78 (0.49, 1.26)
Region		
North America	19/19	0.75 (0.35, 1.57)
Europe	47/49	0.74 (0.46, 1.20)
Asia	34/35	0.51 (0.28, 0.93)
Prior gemcitabine		
Alone	53/55	0.69 (0.43, 1.11)
In Combination	64/64	0.63 (0.41, 0.95)
Baseline albumin		
< 4 g/dL	64/65	0.52 (0.35, 0.78)
≥ 4 g/dL	53/54	0.90 (0.54, 1.49)

*MM-398 combination arm/5FU-LV control arm

7.3.4 Secondary endpoints

Progression Free Survival

Table 10 [data copied from the statistical review and based on the updated PFS information (see above)] shows that MM-398 in combination with 5FU/LV increased progression free survival compared to 5FU/LV. The effect at the median was modest (1.6 months). *Comment: the lack of early separation of the KM curves likely was influenced by the imaging schedule with the first CT scan obtained at week 6.*

Table 10 PFS analyses (ITT)

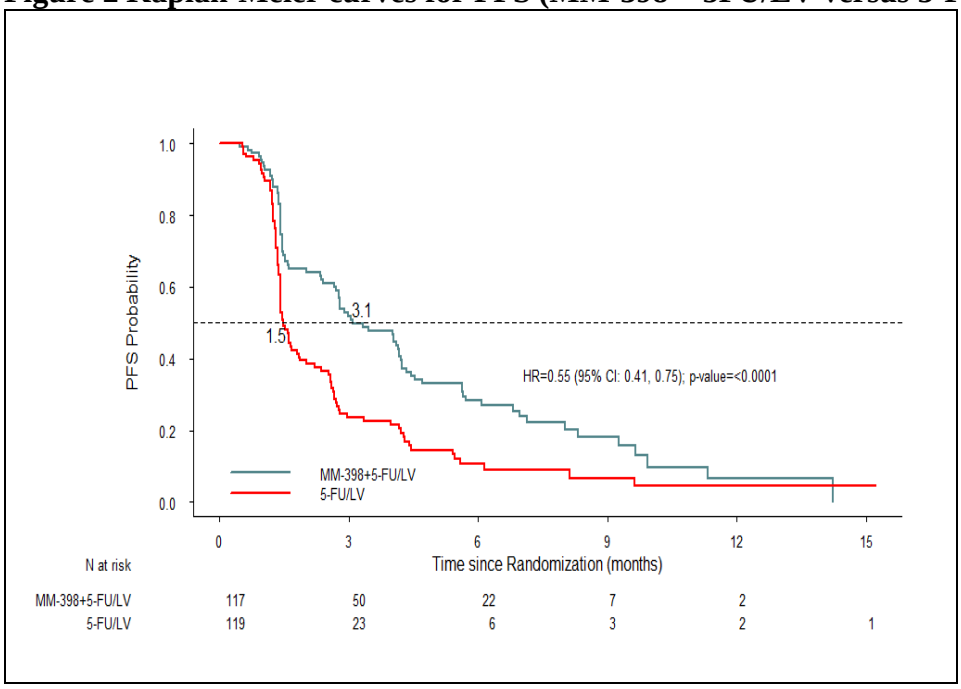
	MM398 + 5FU/LV N = 117	5FU/LV N = 119
Number of events, n (%)	83 (71%)	94 (79%)
Median PFS (months)	3.1	1.5
95% CI	(2.7, 4.2)	(1.4, 4.8)
HR (95% CI)	0.55 (0.41, 0.75)	
Unstratified *nominal* log-rank test p-value[a]	< 0.0001	

Objective Response Rate

There were 9 (7.7%) reported confirmed partial responses (based on investigator assessment) in the MM-398 + 5FU/LV arm compared with 1 (0.8%) reported confirmed partial response in the 5FU/LV arm.

Comment: Ultimately, the clinical benefit of MM-398 when combined with 5FU and leucovorin is based on the effect on overall survival rather than any modest effect on ORR or PFS.

Figure 2 Kaplan-Meier curves for PFS (MM-398 + 5FU/LV versus 5-FU/LV)



Clinical Benefit Response (CBE) Endpoint

CBR was a composite endpoint listed by the applicant as a secondary endpoint. To assess the endpoint, Merrimack collected data on pain (using a 100 mm visual analogue scale); opioid analgesic consumption; inanition and decreased performance status; and lack of appetite, decreased nutritional intake and significant weight loss. Merrimack stated that daily compliance with the diary was low, and therefore only 60% of the patients were evaluable for this endpoint. Merrimack stated that 14% of the 78 patients in the MM-398 combination arm experienced a CBR versus 12% of 60 patients in the 5FU/LV control arm. *Comment: limitations of the data preclude any conclusions related to this endpoint.*

Quality of Life

During the study, patients were asked to complete the EORTC QLQ-C30 questionnaire at baseline, every six weeks and at the 30 day follow-up visit. Again, the analyses of the PRO measures were affected by missing data or study discontinuation (e.g., due to progression) with 62% of the ITT study population being included in the PRO analysis population. Although conclusions based on such data should be taken with caution, Merrimack stated that median scores at Week 6 and Week 12 showed no appreciable changes from baseline and suggested that the effects of the treatments on Global Health Status and Functional Scale scores were negligible. *Comment: In situations without a high objective response rate, it could be difficult to demonstrate improvements in PRO measures without performing PRO assessments after progression occurs (because that is the time when cancer symptoms would be expected to worsen).*

8. Safety

8.1 Adequacy of database

Based on the treatment effect (overall survival improvement) observed in Study MM-398-07-03-01, this reviewer found the safety database to be adequate. Merrimack submitted datasets in CDISC (STDM and ADaM) format which facilitated the FDA analyses of data.

The clinical review primarily focused on data from Study MM-398-07-03-01 as this was the large controlled trial intended to support approval of MM-398 (in combination with 5-fluorouracil and leucovorin) for the indicated patient population.

The safety population of Study MM-398-07-03-01 included 264 patients with advanced pancreatic cancer who received MM-398 either a single agent or in combination with 5FU and leucovorin. Additionally, the NDA stated that 176 patients received MM-398 either as a single agent or in combination with other agents in phase 1 or 2 studies (including 44 patients who received MM-398 in combination with 5FU and leucovorin).

In Study MM-398-07-03-01, the safety population (consisting of patients who actually received investigational treatment) included 147 patients in the MM-398 single agent group, 134 patients in the 5FU/LV group, and 117 patients in the MM-398/5FU/LV group. This review will primarily focus on the comparison of the MM-398/5FU/LV combination group versus the 5FU/LV group in the randomized controlled trial (Study MM-398-07-03-01).

In Study MM-398-07-03-01, patients in the MM-398/5FU/LV group received a median exposure of 8.7 weeks and a mean (SD) exposure of 15.0 (13.73) weeks. Patients in the 5FU/LV group received a median exposure of 6 weeks and a mean (SD) exposure of 10.4 (11.30) weeks. *Comment: The short duration of therapy in both arms reflected the poor prognosis of patients with previously treated metastatic pancreatic cancer. Nevertheless, this reviewer agrees that it is appropriate to take action on this application despite the lack of long-term safety data based on the modest improvement in overall survival and the short life expectancy of patients with previously treated pancreatic cancer.*

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

The KM curves of OS in Section 7 of this review summarize the overall occurrence of deaths in Study MM-398-07-03-01. These curves provided some assurance of the relative safety of MM-398 (when administered at the 80 mg/m^2 dose in combination with 5FU/LV).

According to the applicant, there were 47 deaths (across all three arms) that occurred during the treatment period, defined as deaths occurring on or after the day of the first dose of study drug and within 30 days of the final administration of study medication. Thirty of the deaths were considered related to pancreatic cancer by the applicant. One death occurred due to an unknown cause and 16 were attributed to an adverse event. One patient died of septic shock in the MM-398 combination arm and two patients died of infectious etiology in the MM-398

single-agent arm. Nevertheless, fatal infectious events also occurred in patients randomized to receive 5FU/LV-alone.

The analysis of Grade 5 treatment-emergent adverse events using the ADAE (adverse event analysis dataset) differed somewhat from the above description (this can occur due to inconsistencies in reporting events in CRF pages). In the ADAE dataset, 27 patients experienced 34 treatment-emergent Grade 5 adverse events. Fifteen of these patients received MM-398 alone, 10 received 5FU/LV, and 2 received MM-398 in combination with 5FU/LV. One of the events in the combination arm was related to septic shock and one was coded as dyspnea (this patient had bilateral effusions requiring thoracentesis and bilateral nodular densities in the lungs on CT).

Again, the overall survival analyses provided some assurance of the *relative* safety of MM-398 (when administered at the 80 mg/m^2 dose in combination with 5FU and leucovorin). Few treatment emergent deaths occurred in patients in the combination arm (compared to the other two arms). Ultimately, attribution of events in these cases can be complicated due to the underlying pancreatic cancer. Nevertheless, the patient in the combination arm with septic shock (with *E. coli* found in a blood culture) had neutropenia at the time she was admitted with hypotension and therefore, therapy may have contributed to her death. Labeling will describe this risk and will instruct physicians to monitor blood counts.

8.2.2 SAEs

Merrimack's clinical study report defined (*non-verbatim definition*) a serious adverse event (SAE) as any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or caused prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; or was an important medical event that could jeopardize the patient or require intervention to prevent one of the other serious outcomes listed above.

The most important serious adverse events [in terms of differences between the MM-398 combination arm versus the 5FU/leucovorin control arm] were diarrhea (6.0% versus 1.5%), nausea (3.4% versus 0.7%), vomiting (9.4% versus 1.5%), and infections and infestations (MedDRA SOC) (17% versus 11%). SAEs of febrile neutropenia (preferred term analysis) occurred in 1.7% of patients in the MM-398 combination arm versus 0.7% of patients in the 5FU control arm. The rates of febrile neutropenia and diarrhea (as SAEs) were highest in the MM-398 *monotherapy* arm (4.1% and 12.9%, respectively).

Comment: The most important SAEs related to MM-398 (in combination with 5FU and leucovorin) appear to be those expected when treating patients with a camptothecin and a fluoropyrimidine (and cytotoxic chemotherapy in general). Oncologists understand these toxicities and standard practice is to obtain informed consent prior to administering chemotherapeutic drugs.

8.2.3 Drop-outs and discontinuations due to adverse events

According to the applicant, 11.1% (13/117) of patients in the MM-398/5FU/LV arm versus 7.5% (10/134) in the 5FU/LV arm discontinued study treatment due to an AE. In general, as

shown in Table 20 of the clinical review, most adverse events causing discontinuation were expected either based on the mechanism of action of the drugs (e.g., gastrointestinal toxicity or infection) or based on the underlying malignancy (e.g., ascities).

In regards to dose reduction, the applicant stated that 33.3% of patients experienced treatment emergent adverse events that required dose reduction. The most common reasons for dose reduction were hematologic (i.e., neutropenia) or diarrhea.

8.2.4 Common adverse events

Table 11, shows the analysis of adverse events (rounded to the nearest integer and occurring with a per-patient incidence rate of ≥ 11% in the MM-398/LV/5FU arm). In general, the clinical reviewer's analysis matched the applicant's with minor apparent differences related to the how the numbers were rounded (i.e., based on the nearest integer versus at the decimal level). The label will differ from the table below because some of the analyses in the label used terms that were less granular (e.g., summarizing different but related neutropenia or fatigue related MedDRA terms).

The table below shows that the most common and most common severe adverse events were expected based on the known adverse event profile of irinotecan and 5FU/LV (refer to risk-benefit section of this review for discussion of these adverse events). The rate of severe diarrhea and vomiting were higher in patients who received MM-398 alone (21% and 14%, respectively).

Table 11 Common AEs

	MM398 + 5FU/LV N = 117		**5FU/LV N = 134**	
	All Grades (%)	≥ Grade 3 (%)	All Grades (%)	≥ Grade 3 (%)
Diarrhea	59	13	26	4
Vomiting	52	11	26	3
Nausea	51	8	34	4
Decreased appetite	44	4	32	2
Fatigue	40	14	28	4
Anemia	38	9	23	7
Neutropenia	23	15	3	1
Pyrexia	23	2	11	1
Abdominal pain	23	7	31	6
Constipation	22	0	24	1
Asthenia	21	8	16	7
Decreased weight	17	2	7	0
Decreased neutrophil count	15	10	1	1
Decreased white blood cell count	15	8	1	0
Alopecia	14	n/a	4	n/a
Stomatitis	14	3	6	1
Dizziness	13	<1%	10	0
Back pain	13	<1%	12	1%

	MM398 + 5FU/LV N = 117		5FU/LV N = 134	
	All Grades (%)	≥ Grade 3 (%)	All Grades (%)	≥ Grade 3 (%)
Hypokalemia	12	3	9	2
Peripheral edema	11	0	15	1

8.2.5 Laboratory tests

As described in the analysis of adverse events, MM-398 resulted in hematological toxicity, including severe neutropenia. MM-398 also resulted in patients having decreased levels of electrolytes (presumably through inducing diarrhea or dehydration). The incidence tables (34 and 35) in the clinical review confirmed the results described by the applicant in the MM-398-07-03-01 clinical study report. Fifty two percent of patients who received MM-398 in combination with 5FU and leucovorin developed neutropenia; Grade 4 neutropenia (< 500 mcL) occurred in 4%. Grade 4 thrombocytopenia was not reported; however, 2% of patients experienced Grade 3 thrombocytopenia (< 50,000/mcL) in the MM-398 combination arm. Anemia was common across each arm.

Electrolyte abnormalities, including hyponatremia, hypokalemia, hypocalcemia, and hypomagnesmia occurred more commonly in patients treated with MM-398 in combination with 5FU/LV compared to patients who received 5FU/LV. In most cases, these electrolyte abnormalities were Grade 1 or 2 in severity. More patients in the MM-398-combination arm experienced increased levels of alanine aminotransferase (50.5% versus 36.9%); however, abnormalities in aspartate aminotransferase, alkaline phosphatase, and bilirubin were similar between arms. More patients in the MM-398-combination arm experienced hypoalbuminemia (42.9% versus 30.4%).

8.3 Special safety concerns

8.3.1 Drug-demographic interactions

The clinical reviewer conducted analyses of adverse events by age range (≥ 65 years versus less than 65 years), sex, and race and concluded that there were no major differences in the incidence or patterns of adverse events in women versus men or in patients 65 years of age or older versus younger patients.

Comment: Overall, the analysis of adverse events in subgroups was limited by the numbers of patients in the various arms (and because the principles of randomization are lost in these subgroups). For example, although over 100 patients 65 years of age or older received MM-398 in Study MM-398-07-03-01, there were only 52 patients older than 65 years in the MM-398 plus 5FU/LV arm. In Merrimack's analysis, more patients who received MM-398 in combination with 5FU/LV experienced ≥ Grade 3 adverse events who were 65 years of age *or younger* (51% versus 39%); however, any overall conclusions are limited by the small sample size. Merrimack also found that vomiting (all grades) occurred more frequently in younger patients across all arms; however, the difference was greatest between age groups in the MM-398 combination arm (65% versus 37%). Overall, treatment emergent adverse events leading

to any dose modification were similar in older versus younger patients (72% versus 69% in Merrimack's analysis).

Merrimack also found the incidence of most treatment-emergent adverse events to be similar between men and women. Alopecia occurred more frequently among women in the combination arm (20% versus 9%). Diarrhea was also reported more frequently in women; however, this finding was observed across all arms.

The clinical review found differences in the per-patient incidence rate of neutropenia and diarrhea in Asian patients as compared to White patients who received MM-398 in combination with 5FU and leucovorin. Severe (≥ Grade 3) neutropenia was higher in Asian patients and severe diarrhea was higher in White patients. In Merrimack's analysis using a composite term for different neutropenia-related adverse events, Merrimack found the per-patient incidence rate of Grade 3 or higher neutropenia in Asians to be 55% in the MM-398 combination arm versus 18% in White patients.

Differences in the toxicity profile in Asian patients versus White patients could potentially be explained by differences in pharmacokinetics. Merrimack found that higher SN-38 exposures (C_{max}) occurred in Asian patients and this was correlated with neutropenia. Higher irinotecan exposure was found in White patients (potentially explaining the higher incidence rate of diarrhea). *Comment: Although differences in certain adverse events were observed between Asian patients and White patients, caution is indicated regarding the interpretation of the data because there were only 33 (East) Asian patients (from South Korea and Taiwan) who received MM-398 in combination with 5-FU and leucovorin.*

8.3.2 Additional in-depth analyses of specific events (as determined in Study MM-398-07-03-01)

Additional analyses were conducted for diarrhea, stomatitis, cholinergic events, acute renal failure, infusion-related reactions, intestinal lung disease, and nausea (specifically pre-medication for nausea). The clinical review found that 30% of patients in the MM-398 combination arm experienced early-onset diarrhea and 43% experienced late-onset diarrhea (refer to clinical review for discussion of the other specific events).

8.4 Discussion of primary reviewer's findings and conclusions

The clinical review stated that the safety results of NAPOLI-1 along with supportive data from additional studies was sufficient for approval consideration based on the improvement in overall survival demonstrated in Study MM-398-07-03-01.

The clinical review found that the most common adverse events in the MM-398-combination arm from Study MM-398-07-03-01 were diarrhea, vomiting, nausea, decreased appetite, fatigue, anemia, neutropenia, pyrexia, abdominal pain, constipation, asthenia, decreased weight, decreased neutrophil counts, decreased white blood cell counts, alopecia, stomatitis, dizziness, back pain, hypokalemia, and peripheral edema. The most frequently reported serious adverse events described in the clinical review in the MM-398-combination arm were vomiting and diarrhea. The most common adverse events leading to dose reduction or dose delay were neutropenia and diarrhea.

The clinical reviewer found that MM-398 when administered in combination with 5FU and leucovorin had an acceptable risk-benefit profile for the intended indication and that the adverse events are relatively manageable with prudent patient selection, monitoring, dose delays, and dose reduction.

9. Advisory Committee Meeting

The review team determined that an ODAC meeting was not necessary for this application involving a new formulation of irinotecan and an application with a survival advantage. Oncologists are familiar with the toxicites caused by irinotecan.

In lieu of an ODAC meeting, the Division independently cleared two Special Government Employees (SGEs) with expertise in gastrointestinal malignancies and with expertise in the use of 5FU. Each independent SGE agreed that the observed difference in overall survival between arms was unlikely to have been caused by the differences in 5-FU dosing regimens between arms. Because the SGEs independently agreed regarding the clinical effects of the different 5-FU dosing regimens, an ODAC meeting was determined not to be necessary.

10. Pediatrics

This NDA is exempt from the requirement to assess the safety and effectiveness of this product for the claimed indication in all pediatric age groups because FDA granted orphan-drug designation to irinotecan liposome injection (MM-398) for the treatment of pancreatic cancer (dated 21 Jul 2011).

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The NDA contained a statement signed by the Vice President, Regulatory Affairs from Merrimack that certified that Merrimack did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

All but one investigator reported that they did not enter into any financial arrangements whereby the value of compensation to the investigator would be expected to affect the outcome of the study as defined in 21 CFR 54.2(a). The applicant certified that the listed investigators referenced on Form 3454 did not disclose financial interests as defined in 21 CFR 54.2(b) or significant payments as described in 21 CFR 54.2(f).

Merrimack submitted one Form 3455 indicating that one clinical investigator involved in Study MM-398-07-03-01 reported a financial arrangement involving consulting services and an honorarium.

Comment: The investigator's site was one of 76 sites and the primary endpoint was overall survival, decreasing the chance that the study could have been influenced by a conflict (if such

bias theoretically existed). Additionally, the active ingredient (irinotecan) has an established safety profile such that it is unlikely that this conflict had a major impact on the study results. The updated Form 3455 stated that the investigator was not involved in patient enrollment at this site. (b) (6)

11.3 GCP issues

Merrimack provided 19 audit certificates from different investigators from Study MM-398-03-07-01. Merrimack included a statement in the MM-398-03-07-01 study report that the trial was not initiated until approval of the protocol and informed consent document from the local Institutional Review Board or Ethics Committee was obtained.

Merrimack also included a statement in the MM-398-03-07-01 clinical study report that the study was performed according to the principles of the Declaration of Helsinki, the International Conference of Harmonization (ICH) Guidance on Good Clinical Practice (GCP), and the requirements of the United States Food and Drug Administration and/or local regulatory authorities regarding the conduct of human clinical trials.

In general, as shown in Table 7 of the statistical review (that was copied from the CSR), the numbers of major protocol deviations were similar between arms. There were two eligibility criteria violations listed in the MM-398 combination arm and three in the control arm (out of 119 patients in the control arm).

There was one exception to the finding that the numbers of protocol violations were similar between arms. This exception involved protocol deviations related to investigational product (IP) compliance with 32.5% (n=38) of patients having a violation in the MM-398 plus 5FU/LV combination arm versus 14.3% (n = 17) in the 5FU/LV alone arm (ITT analysis of combination arm). Twenty three of the 38 patients who had IP violations in the MM-398/5FU/LV arm received a lower dose of racemic leucovorin (200 mg/m^2 instead of 400 mg/m^2). This finding was noted during the OSI inspection of the Hungary site (that received an interim classification of VAI); however, the applicant also identified these violations in the NDA.

Reviewer's comment: This difference between arms may have been related to the specific language for dosing of leucovorin in Arm C (MM-398 combination arm) on page 46 of Version 2.1 of the protocol, dated 14 Jun 2012. "Leucovorin will be administered at a dose of 200 mg/m^2 as an IV infusion over 30 minutes, every 2 weeks." ....Page 46 in Version 2.2 of the protocol dated 19 Oct 2012 was amended to read (for the dosing instruction of leucovorin in the MM-398 combination arm) "Leucovorin will be administered at a dose of 400 mg/m^2 of the l + d racemic form, or l form 200 mg/m^2, as an IV infusion over 30 minutes, every 2 weeks." Because LV underdosing was limited to Arm C, this reviewer would expect these protocol violations to bias the results of the study towards the null (e.g., no effect) and therefore did not compromise the integrity of the study. This imbalance between arms was documented by the sponsor and confirmed by FDA inspection of the Hungary site.

In general, most other protocol violations related to the administration of IP appeared to be isolated instances. For example, a single dose of 5FU may have been administered over a longer or shorter duration, or (for example) 5FU and LV were infused at the same time during one infusion. In general, this reviewer would not expect these isolated instances to affect the integrity of the study. A proportion of patients who were enrolled at two sites in Taiwan (10-20% according to the OSI review) missed doses of leucovorin in Arms B and C. These patients missed one or more doses of leucovorin due to leucovorin shortages at these sites and both arms appeared to be affected. It is unlikely (especially for the patients that missed a single dose of LV) that the missed dose would have markedly affected the outcomes (related to efficacy) for these patients (or the integrity of the trial). Importantly, the applicant disclosed these events in the application and they appeared limited to the two sites in Taiwan.

11.4 OSI audits

DOP2 requested FDA inspections of clinical sites because this application is the first for Onivyde. DOP2 and OSI selected five clinical sites based on site-specific efficacy results, protocol violations, conflicts of interest, or patient enrollment at each site. FDA inspected sites in Hungary, Taiwan, Australia, and Arizona. The site in Hungary received an interim classification of VAI (voluntary action indicated). The other sites received interim classifications of NAI (no action indicated). OSI found that based on the review of the inspectional findings, that the data from Study MM-398-03-07-01 appeared reliable and could be used in support of the application (refer to Section 11.3 above regarding findings pertaining to violations regarding leucovorin dosing).

11.5 Other discipline consults

11.5.1 OPDP

To facilitate action on this application, this review was completed prior to the completion of the OPDP review.

11.5.2 Drug name review (DMEPA)

During the review of this application, DMEPA sent a letter dated 19 Jul 2015 informing Merrimack that the proposed trade name of Onivyde was (conditionally) acceptable. The DMEPA review considered the name from a promotional perspective in consultation with DOP2 and OPDP. DMEPA also considered the name Onivyde from a safety perspective (i.e., performed assessments for look-alike and sound-alike drugs) and found the name acceptable.

12. Labeling

FDA sent draft labeling recommendations to Merrimack on 2 Oct 2015. Labeling recommendations described below should not be considered final as labeling negotiations are ongoing.

In general, DOP2 revised all sections of the label for brevity and clarity. The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Merrimack. Numbering below is consistent with the applicable sections in product labeling.

This review will not comment on all sections of the label (for example, if only minor edits were made to a section).

1. Indication and Usage: Based on the results in the MM-398 single agent arm in Study MM-398-03-07-01, DOP2 recommended a limitation of usage to inform prescribers that MM-398 is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

2. Dosage and Administration: Changes were made to simplify this section. For example, (b) (4) .

5. Warnings and Precautions: DOP2 revised the warning for (b) (4) to specify the most important and severe adverse reaction: severe neutropenia. Additional information regarding monitoring and management was provided. DOP2 separated (b) (4) severe diarrhea was an important (and potentially life-threatening) adverse reaction of irinotecan/MM-398. DOP2 removed (b) (4)

6. Adverse Reactions: DOP2 provided additional information regarding Study MM-398-03-07-01 including information on important enrollment characteristics of patients in the trial (i.e., serum bilirubin within the institutional normal rage, albumin $\geq$ 3 g/dL; and KPS $\geq$ 70).

(b) (4)

14. Clinical Studies: FDA revised this section to provide additional details regarding the design of Study MM-398-03-07-01. FDA also recommended providing additional details regarding the patients who were treated including the proportion of patients who previously received gemcitabine in combination with nab-paclitaxel. Statistical reviewers recommended removing (b) (4)

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This reviewer recommends regular approval of NDA 207793 based on substantial evidence from one adequate and well controlled trial (Study MM-398-07-03-01) establishing that MM-398 in combination with 5-fluoruracil and leucovorin can prolong the overall survival of patients with previously treated, metastatic pancreatic cancer. This approval recommendation is contingent upon reaching final agreement on labeling.

As stated above, although this application had several weaknesses [differences in 5FU regimens between the MM-398 and 5-FU combination arm and the control arm; potential financial conflict of interest (see above); and differences in withdrawal of consent between arms], ultimately this reviewer agrees that MM-398 should be approved. The patient population studied in this application has a particularly poor prognosis, and this reviewer believes that it would not be in the best interests of patients with pancreatic cancer to require another trial for MM-398 especially given the scarcity of treatment options available to this patient population.

13.2 Risk-benefit assessment

The recommendation for approval of this application is based on a statistically significant (but clinically modest) improvement on OS observed in Study MM-398-03-07-01. According to the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 23 Dec 2013), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.

Prior to discussing the risk-benefit assessment for this application in more detail, a discussion of the context of this application is important. Study MM-398-03-07-01 enrolled patients with metastatic pancreatic adenocarcinoma who previously received gemcitabine. Based on the control arm of Study MM-398-03-07-01 and based on data in the Abraxane label, patients with previously-treated metastatic pancreatic adenocarcinoma have an expected median overall survival of only 3-4 months. This median survival likely represents an *overestimate* given that patients enrolled in these trials were highly selected (e.g., normal bilirubin levels and acceptable performance status). It is in this context, and in the context of a paucity of beneficial therapies, that this application was submitted.

Section 2 of this review provided details regarding available therapies for patients who previously received gemcitabine to treat their metastatic pancreatic cancer. In summary, the data supporting the use of 5FU (or 5FU/LV)-based regimens were limited. One study (CONKO-003) reported improved survival for OFF (oxaliplatin, 5FU, and folinic acid) compared to folinic acid and fluorouracil; however, there was a large difference (45) between the target number of events and the analysis based on 155 events (see Section 2 for details) and a second study (PANCREOX) evaluating a different oxaliplatin regimen did not find a survival benefit for oxaliplatin when added to 5FU/LV.

In this context, i.e., a patient population with an extremely poor prognosis and limited data supporting any treatment options, Merrimack submitted NDA 207793 containing data from Study MM-398-03-07-01 demonstrating an estimated median 1.9 month overall survival advantage when MM-398 was added to 5FU/LV. Importantly, the study included a MM-398 monotherapy arm that did not demonstrate an improvement of OS when compared to 5FU/LV. Although 1.9 months is a modest effect, it may be important to some patients with metastatic pancreatic cancer.

This reviewer believes that there is some residual uncertainly regarding the magnitude of the estimated 1.9 month effect. Residual uncertainty based on differences in backbone 5FU/LV regimens between arms was discussed in other sections of this review. Uncertainty also exists because gemcitabine in combination with nab-paclitaxel has become standard of care for many patients with metastatic pancreatic cancer in the first-line setting. Study MM-398-03-07-01 enrolled only 13% of patients who received prior nab-paclitaxel in combination with gemcitabine and therefore there is insufficient data to determine whether the estimated 1.9 month effect is similar in these patients compared to all patients enrolled in Study MM-398-03-07-01. Finally, the hazard ratio for OS in patients enrolled in Asia was less than the hazard ratios for OS of patients enrolled in Europe or North America. While this reviewer agrees that chance in a (relatively small) single trial could explain these findings, there were differences in pharmacokinetics that could also have resulted in different treatment effects across populations.

Despite the uncertainties regarding the *magnitude* of the treatment effect, this reviewer believes that a statistically significant effect was observed in the trial, and given the context of this application, the application can be approved despite the residual uncertainties. Ultimately, it is difficult for this reviewer to determine what trade-offs a patient with metastatic pancreatic cancer would make regarding risk-benefit if the true treatment effect was less than 1.9 months.

The effect on OS in this application was supported by effects on PFS and ORR (see above). Unfortunately, the collection of PROs in Study MM-398-03-07-01 appeared insufficient to provide for an accurate assessment of how patients felt following treatment with MM-398 in combination with 5FU and leucovorin.

Adverse events observed in Study MM-398-03-07-01 were generally considered in-line with toxicities observed following the administration of a camptothecin and 5FU/LV. The most important toxicities were myelotoxicity (especially neutropenia) and gastrointestinal toxicity (especially diarrhea and sequelae of diarrhea). Although the 1.9 month effect on OS may be important for some patients, physicians and patients will need to carefully consider the adverse event profile of MM-398 in combination with 5FU and leucovorin. This adverse event profile included an estimated 13% per-patient incidence rate of ≥ Grade 3 diarrhea and 11% per-patient incidence rate of ≥ Grade 3 vomiting. Serious adverse events related to diarrhea and vomiting occurred in 6% and 9.4% of patients in the MM-398-combination arm, respectively. These estimated rates may differ in the community setting post-approval in situations where eligibility criteria (e.g., based on bilirubin) or management of toxicities (e.g., diarrhea) are not respected. Nevertheless, oncologists understand these toxicities and standard practice is to obtain informed consent prior to administering cytotoxic chemotherapeutic drugs.

In addition to gastrointestinal toxicity, MM-398 in combination with 5FU and leucovorin can cause life-threating neutropenia. One patient in the MM-398-combination arm died in the setting of neutropenia with *E. coli* sepsis. Serious infections were increased in the MM-398 combination arm (17% versus 11% for the 5FU/LV arm) despite only 4% of patients developing Grade 4 neutropenia. It is unclear to what extent the 11% serious infection rate in the control arm was caused by chemotherapy versus the increased risk in patients with pancreatic cancer (e.g., due to biliary sepsis).

Other important toxicities related to MM-398 include increased rate of fatigue (and severe fatigue) and decreased weight. Although toxicities were common (and potentially severe), toxicities caused by MM-398 are in line with toxicities that have been historically considered acceptable in the practice of oncology (provided that the drug confers benefit).

Importantly, the risk-benefit profile in Study MM-398-03-07-01 was studied in a patient population with KPS ≥ 70 and with a normal bilirubin level (for the institution). This reviewer cannot extrapolate the survival benefit observed in Study MM-398-03-07-01 to patients with KPS < 70 or with an abnormal bilirubin. The hazard for death is sufficiently high in these patients that the risk-benefit profile may differ compared to patients with less co-morbidity. As such, this reviewer recommends that the label describe the population studied in MM-398-03-07-01.

The patient population studied in this application has a particularly poor prognosis, and this reviewer believes that it would not be in the best interests of patients with pancreatic cancer to require another trial for MM-398. Nevertheless, this reviewer acknowledges that the 1.9 month improvement in median overall survival represents a modest effect and that based on this modest effect and based on the toxicity profile of MM-398 (also with the requirements for increased monitoring and the possibility for hospitalization due to SAEs), a reasonable person may decide whether or not to receive MM-398 in combination with 5FU/LV (e.g., versus no treatment, alternative treatment, or enrollment into a clinical trial). However, based on the effect on OS that was observed in Study MM-398-03-07-01, this reviewer believes that there is substantial evidence to support the claim that MM-398 *does* improve overall survival and that NDA 207793 can be approved.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review teams did not identify any REMS as necessary prior to a marketing authorization for MM-398. MM-398 will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious toxicities caused by anti-neoplastic drugs including hematological and gastrointestinal toxicites. Standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

Refer to Section 5.0 of this review for a discussion of a PMR related to QTc prolongation. No other PMCs and PMRs were recommended for this application.

14 References

Chibaudel B, F Maindrault-Goebel, T Andre, JB Bachet, C Louvet, et al., 2015, PEPCOL: A Randomized Noncomparative Phase II Study of PEP02 (MM-398) or Irinotecan in Combination with Leucovorin and 5-Fluorouracil as Second-line Therapy in Patients with Unresectable Metastatic Cancer—A GERCOR Study, JCO, 33 (suppl 3; abstr 751).

Conroy T, F Desseigne, M Ychou, O Bouche, R Guimbaud, et al., 2011, FOFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer, NEJM, 364: 1817-1825.

Crown J, ES Casper, J Botet, P Muray, and DP Kelsen, 1991, Lack of Efficacy of High-Dose Leucovorin and Fluorauracil in Patients with Advanced Pancreatic Cancer, JCO, 9: 1682-1686.

DeCaprio JA, RJ Mayer, R Gonin, and SG Arbuck, 1991, Fluorouracil and High-Dose Leucovorin in Previously Untreated Patients with Advanced Adenocarcinoma of the Pancreas: Results of a Phase II Trial, JCO, 9: 2128-2133.

Gill S, Y-J Ko, C Cripps, A Beaudoin, SK Dhesy-Thind, et al., 2014, PANCREOX: A Randomized Phase 3 Study of 5FU/LV with or without Oxaliplatin for Second-Line Advanced Pancreatic Cancer (APC) in Patients (pts) Who have Received Gemcitabine (GEM)-Based Chemotherapy, JCO, 32:5S (suppl; abstr 4022).

Neuzillet C, O Hentic, B Rousseau, V Rebours, L Bengrine-Fefevre, et al., 2012, FOLFIRI Regimen in Metastatic Pancreatic Adenocarcinoma Resistant to Gemcitabine and Platinum Salts, World J Gastroenterol, 18: 4533-4511.

Oettle H, H Riess, JM Stieler, G Heil, I Schwaner, et al., 2014, Second-Line Oxaliplatin, Folinic Acid, and Fluorouracil versus Folinic Acid and Fluorouracil Alone for Gemcitabine-Refractory Pancreatic Cancer: Outcomes from the CONKO-003 Trial, JCO, 32, 2423-2429.

Pelzer U, I Schwaner, J Stieler, M Adler, J Seraphin, et al., 2011, Best Supportive Care (BSC) versus Oxaliplatin, Folinic acid, and 5-Fluorouracil (OFF) plus BSC in Patients for Second-Line Advanced Pancreatic Cancer: A Phase III-Study from the German CONKO-Study Group, Eur J Cancer, 47, 1676-1681.

Taieb J, T Lecomte, T Aparicio, A Asnacios, T Mansourbakht et al., 2007, FOFIRI.3, A New Regimen Combining 5-Fluorouracil, Folinic Acid and Irinotecan, for Advanced Pancreatic Cancer: Results of an Association des Gastro-Enterologues Oncologues (Gastroenterologist Oncologist Association) Multicenter Phase II Study, Ann Oncol, 18: 498-503.

Van Rijswijk RE, K Jeziorski, DJ Wagener, JL Van Laethem, S Reuse, et al., 2004, Weekly High-Dose 5-Fluorouracil and Folinic Acid in Metastatic Pancreatic Carcinoma: A Phase II Study of the EORTC GastroIntestinal Tract Cancer Cooperative Group, Eur J Cancer, 40, 2077-2081.

Yoo C, JY Hwang, J-E Kim, TW Kim, JS Lee, et al., 2009, A Randomized Phase II Study of Modified FOLFIRI.3 vs Modified FOLFOX as Second-Line Therapy in Patients with Gemcitabine-Refractory Advanced Pancreatic Cancer, Br J Cancer, 17, 1658-1663.

Zaniboni A, E Aitini, S Barni, D Ferrari, S Cascinu, V Catalano, 2012, FOLFIRI as Second-Line Chemotherapy for Advanced Pancreatic Cancer: A GISCAD Multicenter Phase II Study, Cancer Chemother Pharmacol, 69, 1641-5.

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/s/

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10/06/2015