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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name Irinotecan liposome injection
Trade Name Onivyde
Therapeutic Class Topoisomerase I inhibitor
Applicant Merrimack Pharmaceuticals

Formulation(s) Liposomal solution
Dosing Regimen 80 mg/m² IV infusion over 90
minutes followed by leucovorin
400 mg/m² IV infusion followed
by 5-fluorouracil 2400 mg/m²
IV infusion, every 2 weeks
Indication(s) In combination with 5-
fluorouracil (5FU) and

leucovorin (LV) for the treatment of patients with metastatic adenocarcinoma of the pancreas with disease progression following gemcitabine-based therapy

Intended Population(s) Adults \geq 18 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval of new drug application (NDA) 207793 for irinotecan liposome injection (MM-398) for the treatment of patients with metastatic adenocarcinoma of the pancreas with disease progression following gemcitabine-based therapy.

The primary basis for this application is a single, randomized, open-label, three-arm, controlled trial in patients with metastatic pancreatic cancer, the NAPOLI-1 trial. The NAPOLI-1 trial enrolled 417 patients, utilized the MM-398/5FU/LV dosing regimen (same doses and schedule) proposed in this application, and consisted of the application's intended population. NAPOLI-1 was initially designed as a two-arm trial comparing arms A and B listed below. After enrollment of 63 patients, the applicant amended the trial to include arm C listed below, investigating the combination MM-398/5FU/LV. Under the revised protocol, patients were randomized (1:1:1) to the following treatment arms: A (MM-398): MM-398 120 mg/m², every 3 weeks; B (5FU/LV): 5FU 2000 mg/m² over 24 hours + LV 200 mg/m², weekly for 4 weeks of each 6 week cycle; or C (MM-398/5FU/LV): MM-398 80 mg/m² + 5FU 2400 mg/m² over 46 hours + LV 400 mg/m², every two weeks. Randomization was stratified by ethnicity (White vs. East Asian vs. other), KPS (70-80 vs. 90-100), and baseline albumin level (≥ 4 g/dL vs. 3.0-3.9 g/dL). With inclusion of arm C, the statistical plan was revised and the total sample size was increased from 270 to 405. The comparison between the MM-398/5FU/LV and 5FU/LV arms was limited to patients enrolled after the protocol was amended to add the third arm.

The primary endpoint of the NAPOLI-1 trial was overall survival (OS) assessed with two co-primary, pair-wise comparisons, one for each MM-398-containing arm (A or C) compared with the control arm (B). Secondary endpoints were progression free survival and objective response rate (investigator-assessed).

The assessment of benefit in this application is based on the primary endpoint of OS. This recommendation for approval is based on review of the clinical data, which support the conclusion that irinotecan liposome injection, in combination with 5-FU and leucovorin, prolongs OS in patients with pancreatic cancer who experienced disease progression following gemcitabine or gemcitabine-based therapy, compared to 5-FU/LV. A statistically significant, clinically meaningful prolongation in OS was observed in patients randomized to receive the MM-398/5FU/LV combination; the median OS was 6.1 months (95% CI: 4.8, 8.5) in the MM-398 combination arm compared to 4.2 months (95% CI: 3.3, 5.3) in the 5FU/LV arm with a hazard ratio of 0.68 (95% CI: 0.50, 0.93; p =

0.014). Treatment effect on OS in the MM-398-only arm compared to the 5FU/LV control was not demonstrated.

The secondary efficacy parameter of PFS was prolonged in the MM-398/5FU/LV arm, with a median PFS of 3.1 months (95% CI: 2.7, 4.2) compared to 1.5 months (95% CI: 1.4, 1.8) in the 5FU/LV arm. The estimated hazard ratio for PFS was 0.55 (95% CI: 0.41, 0.75) in favor of the MM-398 combination arm. The NAPOLI-1 trial also demonstrated an improvement in ORR in the MM-398/5FU/LV arm, with a ORR of 7.7% in the MM-398 combination arm compared to 1% in the 5FU/LV arm.

Overall, results from the NAPOLI-1 trial for the MM-398/5FU/LV arm demonstrate a consistent, robust treatment effect on OS. This reviewer concludes that this submission provides sufficient basis for approval, as set forth in the Guidance for Industry titled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." The guidance states that "reliance on only a single 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 potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible." NAPOLI-1 was a large multicenter trial that demonstrated a clinically meaningful improvement in overall survival that was consistent across subgroups, in a population of patients with advanced pancreatic cancer, in second line, who have limited treatment options.

1.2 Risk Benefit Assessment

The NAPOLI-1 trial included a total of 264 patients who received MM-398, including 117 patients who received MM-398 in combination with 5-FU and leucovorin at the dose and dosing schedule proposed in this application. The mean duration of treatment in the MM-398/5FU/LV arm was 93 days. The most common adverse events (AEs) that occurred in the MM-398/5-FU/LV arm (>10%) of NAPOLI-1, as described by PTs, were diarrhea, vomiting, nausea, decreased appetite, fatigue, anemia, neutropenia, pyrexia, abdominal pain, constipation, asthenia, weight decreased, neutrophil count decreased, white blood cell count decreased, alopecia, stomatitis, dizziness, back pain, hypokalemia, and peripheral edema.

The incidence of serious treatment-emergent adverse events (SAEs) was higher in the MM-398 combination arm compared to the 5FU/LV arm (48% vs. 45%). The most frequently reported treatment-emergent SAEs in the MM-398 combination arm were vomiting and diarrhea. Eleven percent of patients in the MM-398 combination arm experienced a treatment-emergent AE that resulted in permanent discontinuation of study drug, compared to 7% in the 5FU/LV arm. Thirty-three percent of patients in the MM-398 combination arm experienced treatment-emergent AE that resulted in dose

reduction of MM-398. A total of 62% of patients in the MM-398 combination arm experienced a treatment-emergent AE that resulted in dose delay.

The most common adverse events that led to dose reduction or dose delay were neutropenia and diarrhea.

The incidence of Grade 3 or higher neutropenia as described by a group of preferred terms including agranulocytosis, febrile neutropenia, neutropenia, and neutrophil count decreased) was 27% in the MM-398/5FU/LV arm, compared to 2% in the 5FU/LV arm. Two deaths due to sepsis following neutropenia occurred in MM-398-treated patients in the NAPOLI-trial.

Diarrhea occurred in 59% of patients in the MM-398/5FU/LV arm compared to 26% of patients in the 5FU/LV arm, with Grade 3-4 diarrhea occurring in 13% compared to 4%, respectively. Diarrhea occurred in one of two patterns, early onset or late onset (a patient may experience both forms within a treatment cycle), as also described in the Camptosar labeling. Early onset was defined as onset within 24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction. Late onset was defined as onset more than 24 hours following chemotherapy. Thirty percent of patients in the MM-398/5FU/LV arm experienced early onset diarrhea, compared to 15% in the 5FU/LV arm. Late onset diarrhea occurred in 43% of patients in the MM-398/5FU/LV arm compared to 17% of patients in the 5FU/LV arm.

In summary, after careful review of the safety and efficacy data submitted to NDA 207793, this reviewer concludes that MM-398 in combination with 5-FU and leucovorin has an acceptable-risk benefit profile for the second-line treatment of patients with metastatic pancreatic cancer, a life-threatening disease with limited treatment options. The 1.9 month improvement in overall survival demonstrated in the NAPOLI-1 trial is a reflection of safety as well as efficacy. In addition, the safety database demonstrates that the adverse events observed with MM-398 when used in combination with 5-FU/LV, at the dose and dosing schedule proposed in this application, are relatively manageable with prudent patient selection, monitoring, dose delays, and dose reductions.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None. The proposed USPI contains patient counseling information for prescribing physicians (oncologists).

1.4 Recommendations for Postmarket Requirements and Commitments

No specific new studies were recommended by the clinical team.

See the QT-IRT consult memoranda (dated 6-22-15 and 7-8-15) that were requested by the clinical pharmacology review team, and the Clinical Pharmacology review, regarding any postmarket requirements or commitments for QT assessment.

The application is exempt from the requirements under the Pediatric Research Equity Act (PREA) because this drug product has orphan drug designation for this indication (Orphan Drug Designation #11-3443 for the treatment of pancreatic cancer).

2 Introduction and Regulatory Background

The proposed trade name for irinotecan liposome injection is Onivyde.

Irinotecan liposome injection, referred to herein and in the application as MM-398, is a topoisomerase I inhibitor (described by the applicant as irinotecan in the form of a sucrosfate salt) encapsulated in a lipid bilayer vesicle, or liposome. Irinotecan is a camptothecin derivative. The application was submitted under the provisions of 505(b)(2) because the application relies upon information in the NDA for the reference drug Camptosar (Irinotecan Injection; NDA 20571).

The applicant seeks approval for Onivyde for the following proposed indication: “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.”

This review will describe the efficacy and safety data supporting approval and the recommendations of the clinical team.

2.1 Product Information

Table 1 Irinotecan Liposome Injection Product Information

Generic Name:	Irinotecan liposome injection
Trade Name:	Onivyde
Pharmacologic Category:	Topoisomerase I inhibitor
Drug Class:	Liposomal dispersion; cytotoxic
Route of Administration:	Intravenous infusion
Storage:	Refrigerate at 2°C to 8°C (36°F to 46°F)
Drug Product:	Single-dose vial containing (b) (4) mg irinotecan free base at a concentration of (b) (4) mg/mL
Dose and Regimen:	80 mg/m ² IV infusion over 90 minutes

	followed by leucovorin 400 mg/m ² IV infusion over 30 minutes followed by 5-fluorouracil 2400 mg/m ² IV infusion over 46 hours, every 2 weeks
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2.2 Tables of Currently Available Treatments for Proposed Indications

Despite recent advances in oncology, metastatic pancreatic cancer remains an incurable disease with a dismal prognosis. More than half of patients are diagnosed at a distant stage, with a 5-year survival of only 2%. With this context, approved treatments for metastatic pancreatic cancer have shown only a modest improvement in overall survival, and, in the past twenty years, only three drugs were approved by FDA for this disease.

In 2013, Abraxane was approved for use in combination with gemcitabine for first line treatment, based on an improvement in overall survival of 1.8 months compared to gemcitabine alone, observed in a trial of 861 patients. Prior to this approval of Abraxane, erlotinib was approved in 2005 for first line treatment of locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine, based on a modest improvement in overall survival which was less than one month. Prior to this, FDA approved gemcitabine in 1996 for the treatment of pancreatic cancer, both in first and second line (second line after treatment with 5-fluorouracil or 5-fluorouracil-containing regimen). “Clinical benefit response” (defined in the trial based on multiple parameters such as improvement in Karnofsky Performance Status, weight gain, or reduction in pain intensity or analgesic consumption) was the primary endpoint in the trial that supported the gemcitabine approval, though a beneficial effect on overall survival was also observed in the trial. Guidelines for the treatment of pancreatic cancer including the NCCN guidelines also include the FOLFIRINOX regimen as a category 1 recommendation in first line treatment. This recommendation is based on the results of a trial which demonstrated median overall survival of 11.1 months in the FOLFIRINOX arm compared to 6.8 months in patients randomized to receive gemcitabine. Significant toxicity was observed with the FOLFIRINOX regimen, with 45% of patients experiencing Grade 3-4 neutropenia and higher rates of thrombocytopenia and diarrhea.

For second-line treatment of patients who experience disease progression after treatment with gemcitabine or a gemcitabine-containing regimen, there is no single preferred regimen. In the second-line setting, NCCN guidelines describe clinical trial participation as preferred, and describe that second-line therapy is “best reserved for patients who maintain a good performance status.” These guidelines suggest that this may consist of fluoropyrimidine-based chemotherapy if patients were previously treated with gemcitabine-based therapy.

5-fluorouracil (5-FU) is a fluoropyrimidine, approved by FDA more than 30 years ago, indicated for use in the treatment of patients with pancreatic cancer. 5-FU has long been used in the treatment of this disease and was the comparator in the above-described trial which served as the basis for the approval of gemcitabine, and the comparator (with leucovorin) in the more recent CONKO-003 trial in patients whose disease progressed on gemcitabine (the trial was revised to add 5-FU/LV as the active comparator in place of best supportive care, which was the control in the initial CONKO-003 trial design; *refer to the analysis of the NAPOLI-1 trial design in section 5.3 of this review for further information regarding the CONKO-003 trial*).

The following table lists agents approved for use in the treatment of metastatic pancreatic cancer.

Table 2 Agents Approved for Use in the Treatment of Metastatic Pancreatic Cancer

First line	Abraxane (nab-paclitaxel) ¹
	Gemcitabine
	Erlotinib ²
Second-line	Gemcitabine ³
5-fluorouracil (line of therapy not specified)	

¹In combination with gemcitabine

²In combination with gemcitabine

³In patients previously treated with 5-FU

2.3 Availability of Proposed Active Ingredient in the United States

Irinotecan liposome injection is not currently marketed in the United States. The current application was submitted under the 505(b)(2) regulatory pathway; the reference drug Irinotecan Injection is marketed in the United States as Camptosar.

2.4 Important Safety Issues With Consideration to Related Drugs

Camptosar is the reference drug for this 505(b)(2) application.

The package insert for Camptosar contains a boxed warning for risks of early diarrhea (which can be accompanied by other cholinergic symptoms) and late diarrhea and for risk of severe myelosuppression. The package insert for Camptosar also includes the following potentially serious adverse events in warnings and precautions: diarrhea and cholinergic reactions, myelosuppression, neutropenia in patients with reduced UGT1A1 activity, hypersensitivity, renal impairment/renal failure (described as “usually in patients who become volume depleted from severe vomiting and/or diarrhea”), pulmonary toxicity, and use in patients with hepatic impairment. The warning regarding use in

patients with hepatic impairment describes that “patients with modestly elevated serum total bilirubin levels (1.0-1.0) mg/dL) had a significantly greater likelihood of experiencing first-cycle, grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/226]; $p < 0.001$).” The most common adverse reactions ($\geq 30\%$) are nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, body weight decreasing, and alopecia.

The package insert for Doxil, which is doxorubicin HCL encapsulated in liposomes, contains a boxed warning regarding acute infusion reactions which describe that serious, life-threatening, and fatal infusion reactions were reported. It has been described in the literature that infusion reactions to liposome-encapsulated formulations may involve a mechanism directed against the liposomes (may convey new or greater risk compared to the non-liposomal formulation).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- On October 15, 2011, FDA received new IND 102799 for MM-398 (previously referred to as PEP02), containing a clinical protocol titled “A Phase II Study of PEP02 as a Second Line Therapy for Patients with Metastatic Pancreatic Cancer” (PEP0208). *Refer to section 5.3 of this review where the PEP0208 study is further described.*
- On August 19, 2011, an End-of-Phase 2 (EOP2) meeting between FDA and Merrimack took place regarding results from the then ongoing PEP0208 study and Merrimack’s plans to conduct a Phase 3 trial of MM-398 in patients with pancreatic cancer who previously received gemcitabine-containing therapy.
 - FDA agreed with OS as the primary endpoint for the planned Phase 3 trial.
 - FDA did not object to Merrimack’s choice of 5-FU/LV as the control arm for the proposed patient population with previously treated metastatic pancreatic cancer.
 - FDA recommended that Merrimack consider a reduced initial MM-398 dose for patients homozygous for the UGT1A1*28 allele.
 - FDA agreed that the development program could qualify, upon application by the IND sponsor (Merrimack), for Fast Track designation.

- FDA encouraged Merrimack to identify which potential data from the Camptosar NDA Merrimack intends to rely on, in order to determine whether a 505(b)(2) application would be required.
- FDA recommended collecting baseline germline DNA from all patients in MM-398 clinical trials to allow for pharmacogenetic safety analysis.
- On October 21, 2011, FDA received the MM-398-07-03-01 (NAPOLI-1) protocol, titled “A randomized, open-label, phase 3 study of MM-398 versus 5-FU and leucovorin in patients with metastatic pancreatic cancer.”
- During development, FDA granted Orphan Drug Designation for the indication proposed in this application (Orphan Drug Designation #11-3443 for the treatment of pancreatic cancer).
- On July 28, 2014, Merrimack communicated plans to submit the then proposed NDA under the 505(b)(2) pathway.
- On August 1, 2014, a Type C meeting between FDA and Merrimack took place regarding Merrimack’s plans for an NDA submission based on results from the NAPOLI-1 trial.
 -  (b) (4)
 - FDA recommended against Merrimack submitting a request for Breakthrough Therapy, and stated that Merrimack could consider submission of a Fast Track designation request.
 - FDA discussed concerns regarding the different 5-FU dosing regimens used between arms in the trial. FDA requested that Merrimack include information in the NDA to support the conclusion of lack of potential impact on efficacy of the different 5-FU regimens employed in arms B and C of the trial.
- On November 17, 2014, FDA designated as a Fast Track development program the investigation of MM-398 in combination with 5-FU and LV for the treatment of metastatic pancreatic adenocarcinoma of the pancreas, in patients previously treated with gemcitabine, to demonstrate an improvement in overall survival (OS).

- On December 2, 2014, a Type B pre-NDA meeting between Merrimack and FDA took place regarding the then planned NDA submission for MM-398 for the pancreatic cancer indication proposed in this application and listed above.
 - FDA agreed that Merrimack could submit cumulative dosing and PK data from NAPOLI-1 and literature in the NDA submission regarding the issue discussed at the August 1, 2014 meeting relating to the different 5-FU dosing regimens used between arms B and C in the NAPOLI-1 trial and any potential impact on efficacy.
 - FDA conveyed that FDA preferred for the safety update to the NDA occur at 90 days rather than 120 days if possible.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Electronic datasets were submitted in CDISC format. Adverse events (AEs) from a random subset of approximately 10% of the case report forms for the NAPOLI-1 trial were reviewed and compared to the datasets in order to confirm accuracy of the data transfer. Verbatim terms for all AEs of Grade ≥ 3 (by NCI CTCAE v4.0) in the NAPOLI-1 trial were compared to the corresponding MedDRA lower level terms and AE coding was deemed adequate.

The NDA submission was of adequate quality to allow for review of the clinical trial pertaining to the proposed indication.

3.2 Compliance with Good Clinical Practices

The submission contained a statement [in the NAPOLI-1 complete study report (CSR) in module 5] that the NAPOLI-1 trial was performed according to the principles of the ICH Good Clinical Practice (GCP) Guideline. The submission also contained such a statement within the PEP0208 CSR regarding the PEP0208 study. Refer to section 5 for further information regarding the NAPOLI-1 trial and PEP0208 study.

An OSI consult was requested for the clinical inspection of 5 NAPOLI-1 trial sites. Sites were selected based upon analysis of site-specific efficacy and safety data, protocol violations, patient enrollment per site, prior inspection history, and investigator financial conflict of interest disclosures.

Table 3 OSI Clinical Site Inspections

Site Number	PI / Site	Number of Patients
366	Gyorgy Bodoky Budapest HUNGARY	23
881	Li-Tzong Chen Tainan TAIWAN	35
617	Andrew Dean Western Australia AUSTRALIA	18
120	Gayle Jameson Arizona USA	15
882	Chung-Pin Li Taipei TAIWAN	31

Final clinical site inspection results were pending at the time of completion of this review, however OSI provided preliminary information at the September 16, 2015 team meeting that no issues have been identified that would preclude recommendation of approval for the application and that one site may receive a VAI classification.

3.3 Financial Disclosures

The submission included a Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) completed by the Applicant. All financial disclosure materials in section 1.3.4 (Financial Disclosure) and those that were submitted to section 1.3.3 were reviewed.

One sub-investigator for the NAPOLI-1 trial, Dr. (b) (6) at (b) (6) was listed as holding disclosable financial interest. A Form 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) completed by the Applicant and disclosing a potential conflict of interest for Dr. (b) (6) was included in the application. A Statement of Actions to Minimize Bias, which was not

included with the initial submission of the Form 3455 for Dr. (b) (6), was later submitted. The Applicant submitted justification describing that the primary endpoint of the NAPOLI-1 trial (and primary basis for the assessment of benefit-risk in this application) was overall survival (OS), not a subjective endpoint open to investigator bias.

Reviewer comment: This reviewer notes that the number of patients enrolled at Site (b) (6) constituted less than 10% of patients enrolled in the trial. Based on the number of patients enrolled at the site and based on the overall OS results in the NAPOLI-1 trial, it is unlikely that the disclosed interest significantly impacted the overall trial results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

This section summarizes issues relating to the safety and efficacy of irinotecan liposome injection / MM-398 identified by other review disciplines as of September 24, 2015. Some portions were excerpted all or in part from the respective discipline reviews. This summary should be considered partial and preliminary; please refer to the respective discipline reviews for a full description of issues identified during the NDA review.

4.1 Chemistry Manufacturing and Controls

Irinotecan hydrochloride trihydrate is the hydrate of the hydrochloric acid salt of the free base irinotecan. The manufacturer of the drug substance (as described in Module 2 of the CMC portion of the NDA submission) is (b) (4), and a letter of authorization for the DMF was provided. This entity is responsible for manufacture of the drug substance (DS) and manufacture, release, and stability testing. In addition Merrimack tests incoming drug substance; according to Module 2, release testing is executed by Merrimack Pharmaceuticals in accordance with Official USP Monograph "Irinotecan Hydrochloride." Merrimack stated that the specifications for irinotecan hydrochloride trihydrate are in accordance with USP specifications detailed in the Official USP Monograph "Irinotecan Hydrochloride," and that irinotecan hydrochloride trihydrate is manufactured to meet the specifications detailed in the Official USP Monograph "Irinotecan Hydrochloride." Merrimack stated that stability testing of the DS is carried out by the manufacturer, and that detailed stability information is included in Drug Master File (DMF) # (b) (4), filed with FDA by (b) (4) and for which a letter of authorization was provided as above.

Merrimack stated that the drug product (DP) liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state, as a sucrosfate salt.

Merrimack stated that (b) (4)

(b) (4) Merrimack (in Module 2) reported that stability data from Phase 1 and Phase 2 clinical study batches demonstrate that the ingredients of the DP are compatible and stable for at least (b) (4) months, and primary stability batch studies demonstrate that the ingredients of the DP are compatible for at least 21 months.

Merrimack stated that each mL of the drug product contains 5 mg of irinotecan drug substance reported on the hydrochloride trihydrate basis, which is equivalent to 4.3 mg/mL irinotecan anhydrous base.

Reviewer comment: It was ultimately decided during the review cycle (though communicated prior to Merrimack as well; refer to the pre-NDA meeting minutes) that the DP should be labeled based on the free base. Merrimack replied that changing the labeled strength and concentration of Onivyde is more likely to lead to dispensing errors. This clinical team agreed that the 'uneven' (not round) numbers may lead to dosing errors and it was decided that the product will be labeled based on the free base but that the numbers (including different dose levels described in the PI) will be rounded, to help avoid dosing errors.

Merrimack described that the manufacture of the (b) (4) drug product is performed at Merrimack Pharmaceuticals and consists of (b) (4)

(b) (4) The DP is a liposomal dispersion for intravenous infusion.

As of the NDA 207793 wrap-up meeting, the CMC team communicated that there were no longer CMC issues identified or pending that would preclude approvability of the NDA.

4.2 Clinical Microbiology

Clinical microbiology is not applicable to this NDA.

As of the NDA 207793 wrap-up meeting, the CMC team communicated that there were no longer any CMC microbiology issues identified or pending that would preclude approvability of the NDA.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical pharmacology, pharmacokinetic, and toxicology studies were submitted to support the approval of liposomal irinotecan for the proposed indication. The 6-cycle (18 week) repeat-dose rat and dog toxicology studies were previously reviewed under IND 102799.

The liposomal formulation of irinotecan resulted in longer exposure of both irinotecan and SN-38 compared to free irinotecan in all species tested. The activity of irinotecan liposome was evaluated in several xenograft tumor models, including pancreatic tumor models. Irinotecan liposome exhibited improved tumor growth inhibition compared to equivalent doses of free irinotecan. The presence of irinotecan liposome also resulted in improved anti-tumor activity when used in combination with 5-FU compared to the activity of the single agents alone.

Irinotecan liposome was evaluated in 4-week and 6-cycle toxicology studies in rats and dogs. In general, toxicities were similar following dosing of irinotecan liposome or free irinotecan.

Following 4 weeks of dosing, irinotecan liposome was lethal at 260 mg/kg in rats, with toxicities including bone marrow hypocellularity, renal tubular hypertrophy and thymic atrophy, as well as histiocytosis of multiple organs.

Additional findings following 6 cycles of dosing with 30, 75, or 190 mg/kg irinotecan liposome in rats included hepatic necrosis and hematopoiesis of the spleen. Since histiocytosis was observed in control animals, the finding was considered by the applicant to possibly be vehicle-related. Since a saline control was not included in either study, verification of this conclusion was not possible; however, similar findings of increased histiocytosis have occurred following treatment of animals with other liposomal drug formulations. Infusion site toxicities included inflammation, necrosis, and thrombosis. Body weights were consistently depressed in the 6-cycle study at irinotecan liposome doses of 75 and 190 mg/kg. The incidence of dental loss/damage and neurological findings (tremors, uncoordinated gait/walking on toes) was reduced with irinotecan liposome compared to irinotecan hydrochloride, although a comparative increase in aggressiveness was observed with the liposome.

Weekly administration of irinotecan liposome for 4 weeks was lethal at 16 mg/kg in dogs. Primary target sites in dogs administered 8 and 16 mg/kg irinotecan liposome included the gastrointestinal tract, bone marrow, Peyer's patch, and spleen. No cardiovascular changes were observed in the 4-week study and there were no cardiovascular effects observed in dogs administered single doses of up to 21 mg/kg

irinotecan liposome in a safety pharmacology study.

Irinotecan liposome doses of 36 mg/kg every 3 weeks were lethal to dogs administered the drug in a 6-cycle repeat dose study. The primary target organs of animals administered irinotecan liposome at doses of 15 and 21 mg/kg during this study were the gastrointestinal tract, lymphatic and hematopoietic tissues (lymphoid atrophy/epithelial necrosis of GI, lymphoid atrophy of spleen, histiocytosis of spleen and liver and uterine atrophy). In general, histopathological findings were similar for irinotecan liposome and irinotecan hydrochloride with the exception of gastrointestinal epithelial necrosis which was not observed with irinotecan hydrochloride. A greater degree of platelet and WBC depletion was observed following administration of irinotecan liposome compared to irinotecan hydrochloride. Increased exposure and prolonged half-life of irinotecan and SN-38 occurred following irinotecan liposome administration compared to irinotecan HCl in both rats and dogs, with increased clearance observed with irinotecan HCl. Irinotecan liposome exhibited an exposure up to 70-fold higher by AUC when compared to irinotecan HCl.

Reproductive toxicity studies with irinotecan liposome were not conducted. Instead, the applicant relied on FDA's previous findings for the effects of irinotecan hydrochloride, the reference drug for this 505(b)(2) application, on reproductive and developmental toxicity to support the application for irinotecan liposome. Intravenous administration of irinotecan HCl at a dose of 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose resulted in an irinotecan exposure of approximately 0.002 times the exposure of irinotecan based on AUC in patients administered Onivyde at the 80 mg/m² dose. Structural abnormalities and growth delays were observed in rats at doses greater than 1.2 mg/kg/day (approximately 0.0002 times the clinical exposure to irinotecan from 80 mg/m² Onivyde based on the clinical AUC of 1364 µg•h/mL) and in rabbits at 72 mg/m²/day. Teratogenic effects included external, visceral, and skeletal abnormalities. Irinotecan HCl administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. Irinotecan HCl crosses the placenta of rats following intravenous administration at 10 mg/kg. Finally, atrophy of male and female reproductive organs was observed in dogs administered ≥ 9 mg/kg liposomal irinotecan once every 3 weeks for 6 cycles, suggesting potential effects on fertility. The nonclinical team recommended that a warning for embryofetal risk is warranted in the label along with warnings for females and males to use effective contraception during treatment with irinotecan liposome and for 1 and 4 months, respectively, following the final dose.

No studies have been performed to assess the potential of liposomal irinotecan to cause genetic toxicity. Irinotecan HCl, the reference drug, was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus

test in mice). Consistent with these genotoxic effects, when irinotecan HCl was administered to rats once weekly for 13 weeks followed by a 91 week recovery period, a significant linear trend between irinotecan HCl dosage and the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas was observed. Neither irinotecan HCl nor its active metabolite, SN-38, was mutagenic in the *in vitro* Ames assay.

The nonclinical team recommended that from the nonclinical perspective, liposomal irinotecan is approvable in combination with 5-FU and leucovorin for the proposed intended use.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Irinotecan liposome injection is a topoisomerase 1 inhibitor encapsulated in a lipid bilayer vesicle or liposome. Inhibition of topoisomerase 1 relieves torsional strain in DNA by inducing single-strand breaks. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase 1-DNA complex and prevent re-ligation of these single-strand breaks resulting in cell death.

4.4.2 Pharmacodynamics

The major efficacy outcome measure in the trial submitted to support clinical efficacy (the NAPOLI-1 trial) was overall survival (OS) with two pair-wise comparisons: Onivyde vs. fluorouracil/leucovorin and Onivyde plus fluorouracil/leucovorin vs. fluorouracil/leucovorin. Additional efficacy outcome measures included progression-free survival (PFS) and objective response rate (ORR).

4.4.3 Pharmacokinetics

The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received ONIVYDE, as a single agent or as part of combination chemotherapy, at doses between 60 and 180 mg/m² and 353 patients with cancer using population pharmacokinetic analysis.

Over the dose range of 60 to 180 mg/m², the C_{max} and AUC of total irinotecan increases with dose. Additionally, the C_{max} of total SN-38 increases proportionally with dose; however, the AUC of total SN-38 increases less than proportionally with dose.

In the population pharmacokinetic analysis using the results of a subset with UGT1A1*28 genotypic testing, in which the analysis adjusted for the lower dose

administered to patients homozygous for the UGT1A1*28 allele, patients homozygous (N=14) and non-homozygous (N=244) for this allele had similar total SN-38 average steady-state concentrations.

In a population pharmacokinetic analysis, mild-to-moderate renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. There was insufficient data in patients with severe renal impairment ($CL_{Cr} < 30$ mL/min) to assess its effect on pharmacokinetics.

The population pharmacokinetic analysis suggest that Asians (East Asians) have 50% lower total irinotecan average steady state concentration and higher total SN-38 average steady state concentration than Whites.

The pharmacokinetics of irinotecan liposome have not been studied in patients with hepatic impairment. In a population pharmacokinetic analysis, patients with baseline bilirubin concentrations of 1-2 mg/dL (n=19) had average steady state concentrations for total SN-38 that were increased by 24% compared to patients with baseline bilirubin concentrations of <1 mg/dL (n=329); however, there was no effect of elevated ALT/AST concentrations on total SN-38 concentrations. No data are available in patients with bilirubin >2 mg/dL.

In a population pharmacokinetic analysis, the pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin. Following administration of irinotecan HCl, dexamethasone, a moderate CYP3A4 inducer, does not alter the pharmacokinetics of irinotecan. In vitro studies indicate that irinotecan, SN-38, and another metabolite, aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes.

Pharmacogenomics

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from irinotecan HCl. In NAPOLI-1, patients homozygous for the UGT1A1*28 allele (n=7) received a reduced starting dose of Onivyde of 60 mg/m² in combination with 5-FU and leucovorin. The frequency of Grade 3 or 4 neutropenia in these patients [2 of 7 (28.6%)] was similar to the frequency in patients not homozygous for the UGT1A1*28 allele who received a starting dose of Onivyde of 80 mg/m² [30 of 110 (27.3%)].

As of the NDA 207793 wrap-up meeting, the clinical pharmacology team had not reported any issues that would preclude approvability of the NDA.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4 Studies/Clinical Trials in the NDA*

Type of Study	Study Identifier	Diagnosis of Population Studied	Number of Subjects
Bioanalytic Methods	Analysis across multiple studies	n/a	n/a
PK	PEP02; human plasma protein binding	n/a	n/a
	Pop PK and E-R Analysis; across multiple studies	Cancer	355 subjects
PK / Safety	PEP0201	Solid tumors	11 subjects
Feasibility / Safety	PEP0202	Metastatic cervical cancer	6 subjects
	PEP0203	Solid tumors	16 subjects
	PIST-CRC	Metastatic colorectal Cancer	18 subjects
	CITS (MM-398-01-01-01)	Solid tumors	13 subjects
Efficacy / Safety	NAPOLI-1 (MM-398-07-03-01)	Metastatic pancreatic cancer	417 subjects
	PEP0206	Gastric and GEJ cancer	132 subjects
	PEP0208	Metastatic pancreatic cancer	40 subjects
	PEPCOL	Metastatic colorectal cancer	55 subjects

*Reflects number of subjects enrolled as of October 24, 2014

5.2 Review Strategy

Safety and efficacy data including the clinical study report (CSR), case report forms (CRFs), and electronic datasets for the NAPOLI-1 trial were reviewed. NAPOLI-1 was a single, multicenter, three-arm, randomized, controlled, open-label trial that enrolled

patients with metastatic adenocarcinoma of the pancreas with disease progression following gemcitabine or gemcitabine-based therapy, and formed the basis of this NDA. Other studies submitted to the NDA included relatively few patients, or studied populations or dosing regimens different than those proposed in this application. PEP0208 was a single arm study that enrolled 40 patients with metastatic pancreatic cancer and investigated MM-398 as a single agent and at a dose and schedule different than that proposed in this application. PEPCOL is an investigator-sponsored trial in patients with metastatic colorectal cancer which tested MM-398 at the same dose and schedule and in the same combination as proposed in this NDA; approximately halfway through enrollment PEPCOL was amended to include bevacizumab.

The NAPOLI-1 trial enrolled 417 patients, utilized the MM-398/5FU/LV dosing regimen (same doses and schedule) proposed in the application, and consisted of the application's intended population.

Section 5.3 contains a detailed description of the design of NAPOLI-1. Refer to sections 6.1.1 and 7.1, the Methods sections of the Efficacy and Safety portions of this clinical review, respectively, for efficacy-specific or safety-specific review methodologies.

5.3 Discussion of Individual Studies/Clinical Trials

NAPOLI-1 (MM-398-07-03-01)

NAPOLI-1 was an international, randomized, controlled, open-label trial in patients with metastatic adenocarcinoma of the pancreas with disease progression after gemcitabine or gemcitabine-containing therapy.

NAPOLI-1 was initially designed as a two-arm trial comparing arms A and B shown below. After enrollment of 63 patients, the applicant amended the trial to include arm C shown below, investigating the combination MM-398/5FU/LV. The amended trial was entitled as follows:

“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”

Under the revised protocol, patients were randomized (1:1:1) to the following treatment arms:

- A (MM-398): MM-398 120 mg/m², every 3 weeks

- B (5FU/LV): 5FU 2000 mg/m² over 24 hours + LV 200 mg/m², weekly for 4 weeks of each 6 week cycle
- C (MM-398/5FU/LV): MM-398 80 mg/m² + 5FU 2400 mg/m² over 46 hours + LV 400 mg/m², every two weeks

Reviewer comment:

CONKO-003 was a trial initially designed as a randomized Phase 3 trial comparing OFF (oxaliplatin, 5-FU, and leucovorin) to best supportive care (BSC) in patients who experienced disease progression on gemcitabine therapy. The trial was terminated after enrolling 46 of the initially planned 165 patients due to poor accrual, and was subsequently redesigned to use the same 5-FU and leucovorin regimen as a control against OFF and then completed. This was rationale provided by the applicant for choosing the 5FU/LV control arm for NAPOLI-1 and the dose and schedule employed as the control in CONKO-003 was the regimen assigned to the control arm of NAPOLI-1. In the end-of-phase 2 meeting (refer to section 2.5 of this review), FDA agreed that the proposed 5FU/LV control arm was acceptable for the intended population of patients with previously treated metastatic pancreatic cancer and this reviewer agrees with the assessment. Though it is reasonable to consider further therapy in this setting in patients with good performance status, there is no single preferred regimen. Refer to section 2.2 of this review for additional detail.

Studies of irinotecan and 5-FU in pancreatic cancer have suggested some activity for the combination: in one study of the FOLFIRI3 regimen which enrolled 40 chemotherapy-naïve patients, 73% of whom had metastatic disease, the response rate reported was 37.5%. Grade 3-4 neutropenia was reported as occurring in 35% of the patients, with fever in two patients, and Grade 3-4 diarrhea reported as occurring in 25%.

The combination of MM-398/5FU/LV was studied, prior to NAPOLI-1, in a 16-patient dose escalation study (a population consisting of patients with various tumor types) and the PEPCOL study, an investigator-initiated study in patients with metastatic colorectal cancer which is described in further detail later in this section.

MM-398 as a single agent was studied as second-line treatment after gemcitabine-based therapy in 40 patients with metastatic pancreatic cancer; refer to the description of study PEP0208 later in this section.

Overall, there was adequate rationale for the investigation undertaken in addition of the third arm to the NAPOLI-1 trial. Refer to '5-FU Dosing Regimens' at the end of this section for detail/comments regarding the difference in 5-FU dosing regimens employed in arms B and C of the trial.

Randomization was stratified by:

- Ethnicity (White vs. East Asian vs. other)
- KPS (70-80 vs. 90-100)
- Baseline albumin level (≥ 4 g/dL vs. 3.0-3.9 g/dL)

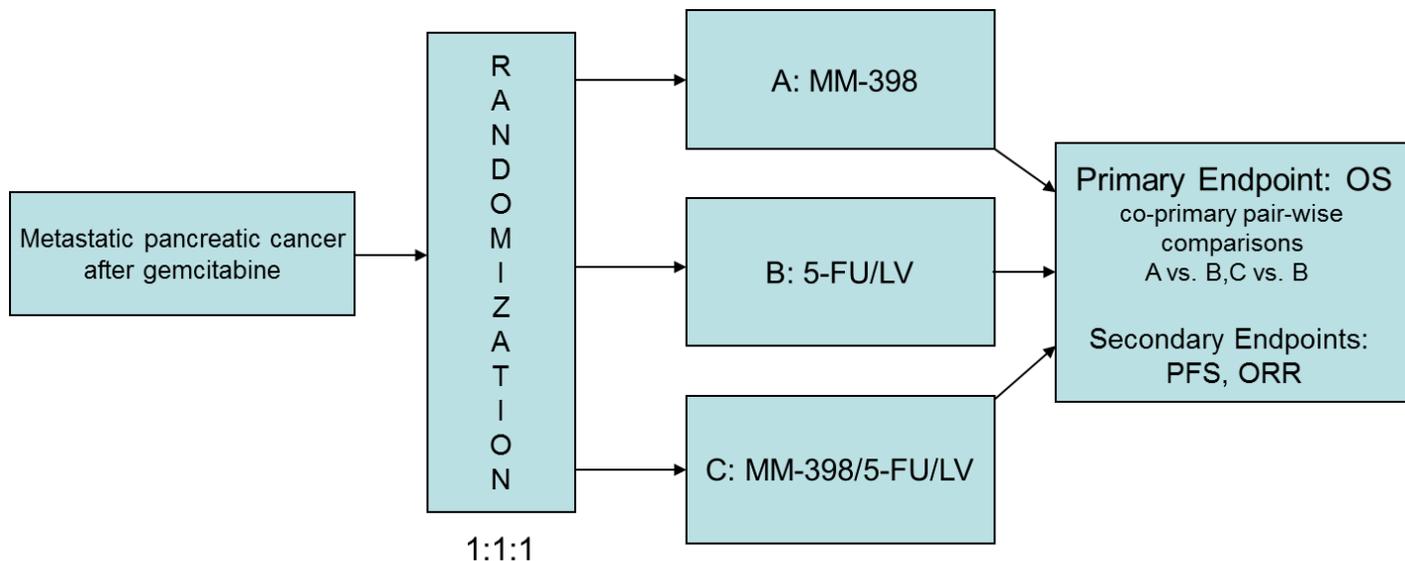
With inclusion of arm C, the statistical plan was revised and the total sample size was increased from 270 to 405.

Refer to Statistical Considerations later in this section and the statistical review for further information regarding the NAPOLI-1 statistical analysis plan.

Trial Endpoints:

- Primary: overall survival (OS)
 - Two co-primary, pair-wise comparisons, one for each MM-398-containing arm (A or C) compared with the control arm (B)
 - The amended statistical plan (submitted prior to the final analysis) specified the population for the comparison of arm C to arm B as only patients randomized following the addition of arm C. Comparisons of arm A to arm B would include patients randomized to either arm (A or B) under both versions of the protocol.
- Secondary:
 - Progression-free survival (PFS)
 - local determination; independent review was not required
 - Objective response rate (ORR)
- Exploratory: Exploratory endpoints included CA 19-9 analysis and patient reported outcome analysis.

Figure 1 NAPOLI-1 Trial Design



*After revision to include Arm C

Important enrollment criteria included:

- Metastatic pancreatic adenocarcinoma
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in the locally advanced or metastatic setting
- KPS \geq 70
- Age \geq 18 years
- Serum total bilirubin within institutional normal range (biliary drainage allowed for biliary obstruction)
- Albumin level \geq 3.0 g/dL

Reviewer comment: The criteria above would select for patients more likely to maintain good performance status and in whom it was reasonable to consider further therapy.

All patients were to be screened for UGT1A1*28 allele status. Patients homozygous for the UGT1A1*28 allele were to initiate MM-398 at a reduced dose [60 mg/m² with

5FU/LV (arm C); 80 mg/m² as a single agent (arm A)], with escalation as tolerated to the standard doses for the respective arms in increments of 20 mg/m².

*Reviewer comment: The reduced starting doses for patients homozygous for the UGT1A1*28 allele were reasonable based on data included in the Camptosar labeling regarding increased risk of neutropenia in these patients and based on safety/dose-finding data with MM-398.*

Leucovorin was to be administered prior to 5-FU, and MM-398 was to be administered prior to 5-FU and leucovorin. MM-398 was to be administered by IV infusion and over 90 minutes. For patients who experienced a grade 1 or 2 infusion reaction, the protocol stated that future infusions may be administered at a reduced rate (over 120 minutes) at the discretion of the investigator.

All patients were to be premedicated prior to MM-398 infusion with standard doses of dexamethasone and 5-HT₃ antagonist or other anti-emetics as per standard institutional practices for irinotecan administration (specific doses or agents other than dexamethasone were not protocol-specified). For patients who experienced early cholinergic symptoms during the previous cycle of MM-398, the protocol stated that prophylactic administration of atropine may be given at the discretion of the investigator.

Tumor assessments were to be conducted at baseline and every 6 weeks thereafter, using RECIST v1.1 guidelines.

Treatment was to continue until disease progression or unacceptable toxicity. Patients who were significantly noncompliant with study procedures per PI assessment were also to be discontinued from study treatment.

Adverse events were to be evaluated according to NCI CTCAE v4.0.

Dose Modification/Discontinuation for Adverse Events:

Prior to initiating a new cycle of therapy, patients were to have:

- ANC $\geq 1500/\text{mm}^3$
- Platelet count $\geq 100,000/\text{mm}^3$
- Diarrhea \leq Grade 1
- Other non-hematologic toxicities \leq Grade 1 or baseline

If a patient had febrile neutropenia, the ANC must have resolved to $\geq 1500/\text{mm}^3$ and the patient must have recovered from the infection.

The following dose modification tables for MM-398 are excerpted from the NDA submission.

Figure 2 NAPOLI-1 Dose Modification Tables for MM-398

Table 12: MM-398 Dose Modifications for Neutrophil Count

ANC: cells/mm ³ (Worst CTCAE grade)	MM-398 Dose for Next Cycle ^a		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 ^d Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28 ^d
≥ 1000 to 1999 (Grade 1 or 2)	100% of previous dose	100% of previous dose	100% of previous dose
< 1000 (Grade 3/4) or febrile neutropenia	Reduce dose by 20 mg/m ² to a minimum dose of 80 mg/m ² ^b	Reduce dose to 60 mg/m ² for the first occurrence and to 50mg/m ² for the second occurrence ^{c, d}	Reduce dose to 50 mg/m ² for the first occurrence and to 40 mg/m ² for the second occurrence ^{c, d}

^a All dose modifications should be based on the worst preceding toxicity

^b Patients who require a further dose reduction beyond 80 mg/m² must be withdrawn from the study

^c Patients who require a further dose reduction beyond 50 mg/m² must be withdrawn from the study

^d Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines provided above in [section 7.5.1](#).

^e Patients who require a further dose reduction beyond 40 mg/m² must be withdrawn from the study

Table 13: MM-398 Dose Modifications for Other Hematologic Toxicity

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle ^a		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 ^d Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28 ^d
≤ Grade 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3/4	Reduce dose by 20 mg/m ² to a minimum dose of 80 mg/m ² ^b	Reduce dose to 60 mg/m ² for the first occurrence and to 50mg/m ² for the second occurrence ^{c, d}	Reduce dose to 50 mg/m ² for the first occurrence and to 40 mg/m ² for the second occurrence ^{c, d}

^a All dose modifications should be based on the worst preceding toxicity

^b Patients who require a further dose reduction beyond 80 mg/m² must be withdrawn from the study

^c Patients who require a further dose reduction beyond 50 mg/m² must be withdrawn from the study

^d Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines provided above in [section 7.5.1](#).

^e Patients who require a further dose reduction beyond 40 mg/m² must be withdrawn from the study

Table 14: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle ^a		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 ^d Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28 ^d
Grade 1 or 2 (2-3 stools/day > pretreatment or 4-6 stools/day > pretreatment)	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 (7-9 stools/day > pretreatment) or Grade 4 (>10 stools/day > pretreatment)	Reduce dose by 20 mg/m ² to a minimum dose of 80 mg/m ² ^b	Reduce dose to 60 mg/m ² for the first occurrence and to 50 mg/m ² for the second occurrence ^{c, d}	Reduce dose to 50 mg/m ² for the first occurrence and to 40 mg/m ² for the second occurrence ^{c, d}

^a All dose modifications should be based on the worst preceding toxicity

^b Patients who require a further dose reduction beyond 80 mg/m² must be withdrawn from the study

^c Patients who require a further dose reduction beyond 50 mg/m² must be withdrawn from the study

^d Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines provided above in [section 7.5.1](#).

^e Patients who require a further dose reduction beyond 40 mg/m² must be withdrawn from the study

Table 15: MM-398 Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia^d

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle ^a		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 ^e Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28 ^e
Grade 1 or 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 or 4 (except nausea and vomiting)	Reduce dose by 20 mg/m ² to a minimum dose of 80 mg/m ² ^b	Reduce dose to 60 mg/m ² for the first occurrence and to 50mg/m ² for the second occurrence ^{c, e}	Reduce dose to 50 mg/m ² for the first occurrence and to 40 mg/m ² for the second occurrence ^{f, e}
Grade 3 or 4 nausea and or vomiting despite anti emetic therapy	Optimize anti-emetic therapy AND reduce dose by 20 mg/m ² to a minimum dose of 80 mg/m ² ^b	Optimize anti-emetic therapy AND reduce dose to 60 mg/m ² ; if the patient is already receiving 60 mg/m ² , reduce dose to 50 mg/m ² ^{c, e}	Optimize anti-emetic therapy AND reduce dose to 50 mg/m ² ; if the patient is already receiving 50 mg/m ² , reduce dose to 40 mg/m ² ^{f, e}

^a All dose modifications should be based on the worst preceding toxicity

^b Patients who require a further dose reduction beyond 80 mg/m² must be withdrawn from the study

^c Patients who require a further dose reduction beyond 50 mg/m² must be withdrawn from the study

^d Asthenia and Grade 3 Anorexia do not require dose modification

^e Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines provided above in section 7.5.1.

^f Patients who require a further dose reduction beyond 40 mg/m² must be withdrawn from the study

The following dose modification tables for 5-FU are excerpted from the NDA submission.

Figure 3 NAPOLI-1 Dose Modification Tables for 5-FU

Table 16: 5-FU Dose Modifications for Hematological Toxicities (Arm B & C)

ANC (cells/mm ³)		Platelets (cells/mm ³)	5-FU Dose for D8, D15, D22 ^a	5-FU Dose for Next Cycle ^a
≥ 1000	and	≥ 50,000	100% of previous dose	100% of previous dose
500 - 999	Or	<50,000 – 25,000	Hold; when resolved, reduce dose by 25% ^b	Reduce dose by 25% ^b
< 500 or febrile neutropenia	Or	< 25,000 or thrombocytopenia with bleeding	Hold dose; when resolved, reduce dose by 25% ^b	Reduce dose by 25% ^b

^a All dose modifications should be based on the worst preceding toxicity

^b Patients who require more than 2 dose reductions must be withdrawn from the study

Table 17: 5-FU Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia^c (Arm B & C)

Worst Toxicity CTCAE Grade	5-FU Dose for D8, D15, D22 ^a	5-FU Dose for Next Cycle ^a
Grade 1 or 2	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100% of previous dose, except for Grade 2 hand and foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity
Grade 2 hand foot syndrome	Reduce dose by 25% ^b	Reduce dose by 25% ^b
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	Discontinue therapy	Discontinue therapy
Grade 3 or 4	Hold; when resolved, reduce dose by 25% ^b , except for Grade 3 or 4 hand foot syndrome	Reduce dose by 25% ^b , except for Grade 3 or 4 hand foot syndrome
Grade 3 or 4 hand foot syndrome	Discontinue therapy	Discontinue therapy

^a All dose modifications should be based on the worst preceding toxicity

^b Patients who require more than 2 dose reductions must be withdrawn from the study

^c Asthenia and Grade 3 Anorexia do not require dose modification

The following excerpt from the protocol describes the dose modification instructions for MM-398 for patients in arm A or arm C who were homozygous for UGT1A1*28.

Patients randomized to Arm A and C, who are homozygous for UGT1A1*28 and have had their dose increased, should have their dose modified as follows:

- **Arm A**

Patients who have had their dose increased by both increments of 20 mg/m², to the maximum dose for the arm (120 mg/m²) should have their dose reduced in the same way as patients who are not homozygous for UGT1A1*28.

Patients who have had their dose increased by only one increment of 20 mg/m², to a final dose of 100 mg/m², should have their dose reduced to the starting dose (that is, 80 mg/m²) after the first instance of a toxicity that warrants a dose reduction. Future toxicities should be handled per guidelines for patients homozygous for UGT1A1*28.

- **Arm C**

Patients who have had their dose increased to the maximum dose for the arm (80 mg/m²) should have their dose reduced in the same way as patients who are not homozygous for UGT1A1*28.

If the dosing of either MM-398 or 5-FU/leucovorin needs to be withheld, then the other drug in the combination should not be administered either.

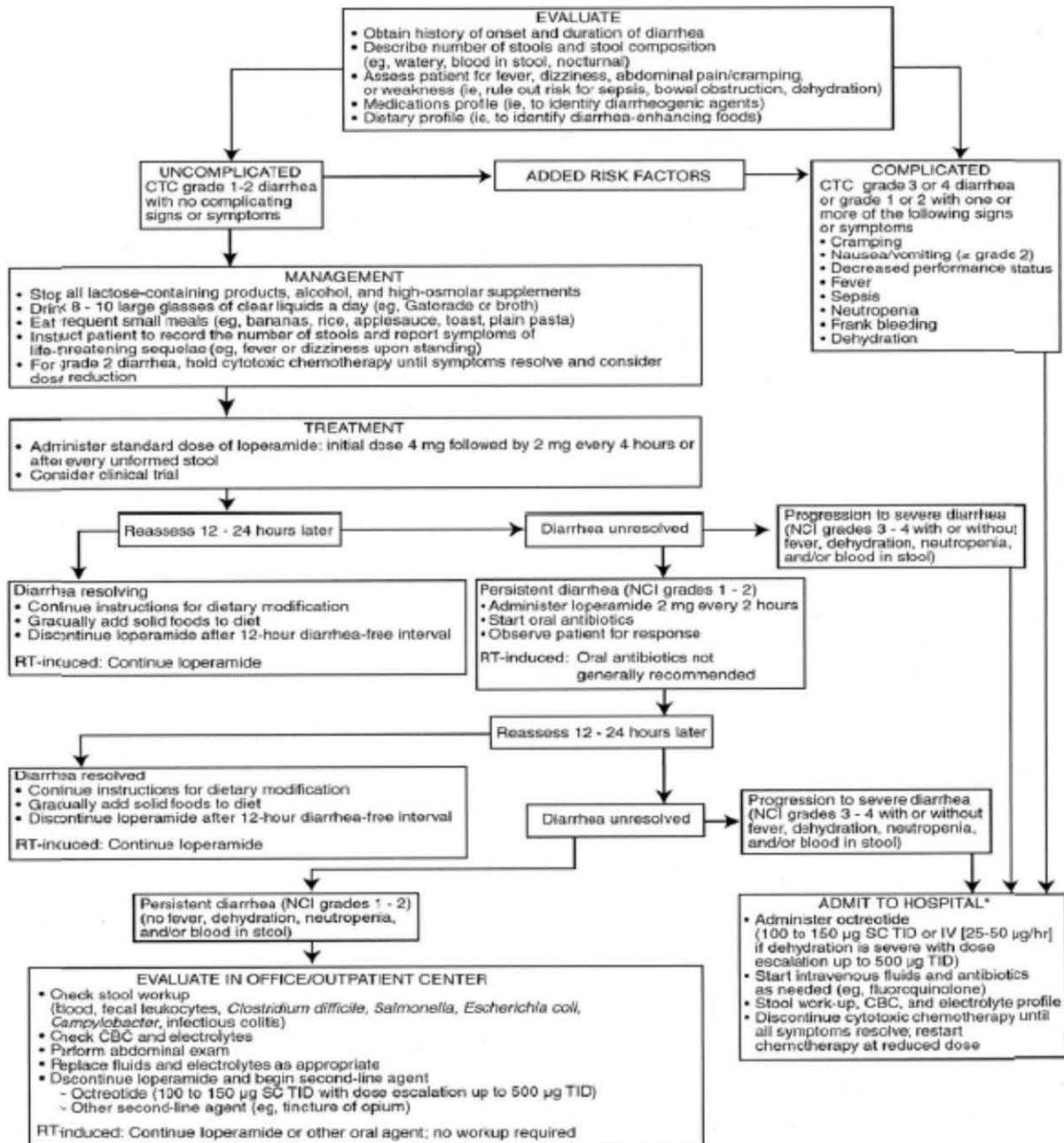
Once a patient's dose was reduced, re-escalation to an earlier dose was not permitted. Any patient who had two dose reductions and experienced an AE requiring a third dose reduction was to be discontinued from study treatment. If 5-FU dosing was held, then the leucovorin dosing was also to be held. For patients in arm C, if dosing of either MM-398 or 5FU/LV was held, then the other drug in the combination was not to be administered either.

The protocol stated that "late diarrhea should be treated promptly with loperamide" and that "neutropenic complications should be managed promptly with antibiotic support," and provided guidelines for management of hypersensitivity reactions. Use of G-CSF to treat patients with neutropenia or neutropenic fever was permitted. The protocol stated that cholinergic syndrome "will be treated with atropine" and that atropine should be considered in patients experiencing cholinergic symptoms on study.

The following regarding management of diarrhea was included as an appendix to the protocol:

Figure 4 Algorithm for Diarrhea Management (copied from the NAPOLI-1 protocol)

APPENDIX 6: Proposed Algorithm for Diarrhea Management



Proposed algorithm for the assessment and management of treatment-induced diarrhea. *For radiation-induced cases and select patients with CID, consider intensive outpatient management, unless the patient has sepsis, fever, or neutropenia. CTC, Common Toxicity Criteria; NCI, National Cancer Institute; RT, radiotherapy; SC, subcutaneous; tid, three times per day; IV, intravenous; CBC, complete blood count; CID, chemotherapy-induced diarrhea [24].

Schedule of Assessments:

Shown below is the Schedule of Assessments, excerpted from the NDA submission.

Figure 5 NAPOLI-1 Schedule of Assessments

Table 19: Arm A (MM-398)

Procedure	Screening Visit	Cycle 1			Even Numbered Cycles			Odd Numbered Cycles (Cycle 3 and beyond)			Every 6 weeks ⁵	30 Day Follow Up ¹²	Post Study F-Up (every 1 month) ¹²
		D1	D8 ¹⁰	D15 ¹⁰	D1	D8 ^{10,16}	D15	D1	D8 ^{10,16}	D15 ^{10,16}			
Informed consent	X ¹												
Medical history	X ¹												
Demographics	X ¹												
Physical exam	X ²				X			X				X	
Vital signs	X ²	X	X	X	X	X		X	X	X		X	
KPS	X ²	X	X	X	X	X		X	X	X		X	
Pain assessment & analgesic use diary ³	X ²	X	X	X	X	X	X	X	X	X		X	
EORTC-QLQ-C30	X ²							X ¹³				X	
CBC with differential ⁴	X ²		X	X	X	X		X	X	X		X	
Serum chemistry ^{4,5}	X ²		X	X	X	X		X	X	X		X	
Pregnancy test ⁷	X ²											X	
CA 19-9 ⁸	X ²										X ⁶	X ⁸	
UGT1A1*28 status	X ¹												
Randomization	X ²												
ECG ⁷	X ²											X	
Tumor assessment ⁹	X ¹										X ⁶	X ⁸	
Plasma sample for PK ¹⁴		X ⁸	X ⁹										
Concomitant medications	X ¹	X	X	X	X	X		X	X	X		X	
Concomitant procedures	X ¹	X	X	X	X	X		X	X	X		X	
Administration of MM-398 ¹⁰		X			X			X					
Adverse event reporting		X	X	X	X	X		X	X	X		X	
Overall survival reporting													X

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Table 20: Arm B (5-FU and Leucovorin)

Procedure	Screening Visit	Cycle 1						Additional Cycles						Every 6 weeks ⁶	30 Day Follow Up ¹²	Post Study F-Up (every 1 month) ¹²
		D1	D8	D15	D22	D29 ₁₁	D36	D1	D8	D15	D22	D29 _{11,16}	D36			
Informed consent	X ¹															
Medical history	X ¹															
Demographics	X ¹															
Physical exam	X ²				X			X			X				X	
Vital signs	X ²	X	X	X	X			X	X	X	X				X	
KPS	X ²	X	X	X	X			X	X	X	X				X	
Pain assessment and analgesic use diary ³	X ²	X	X	X	X	X	X	X	X	X	X	X	X		X	
EORTC-QLQ-C30	X ²							X ¹³							X	
CBC with differential ⁴	X ²		X	X	X	X		X	X	X	X	X			X	
Serum chemistry ^{4,5}	X ²		X	X	X	X		X	X	X	X	X			X	
Pregnancy Test ⁷	X ²														X	
CA 19-9 ⁶	X ²													X ⁶	X ⁶	
UGT1A1*28 status	X ¹															
Randomization	X ²															
ECG ⁷	X ²														X	
Tumor assessment ⁶	X ¹													X ⁶	X ⁶	
Sample for PK		X ⁶														
Concomitant medications	X ¹	X	X	X	X	X		X	X	X	X	X			X	
Concomitant procedures	X ¹	X	X	X	X	X		X	X	X	X	X			X	
Administration of 5-FU and Leucovorin ¹¹		X	X	X	X			X	X	X	X					
Adverse event reporting		X	X	X	X	X		X	X	X	X	X			X	
Overall survival reporting																X

Table 21: Arm C (MM-398 plus 5-FU and Leucovorin)

Procedure	Screening Visit	Cycle 1		Cycle 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17		Cycle 3, 6, 9, 12, 15, 18	Cycle 4, 7, 10, 13, 16	Every 6 weeks ⁶	30 Day Follow Up ¹²	Post Study F-Up (every 1 month) ¹²
		D1	D8 ¹⁵	D1	D8 ^{15,16}	D1	D1			
Informed consent	X ¹									
Medical history	X ¹									
Demographics	X ¹									
Physical exam	X ²			X		X			X	
Vital signs	X ²	X	X	X	X	X			X	
KPS	X ²	X	X	X	X	X			X	
Pain assessment & analgesic use diary ³	X ²	X	X	X	X	X			X	
EORTC-QLQ-C30	X ²						X ¹³		X	
CBC with differential ⁴	X ²		X	X	X	X			X	
Serum chemistry ^{4,5}	X ²		X	X	X	X			X	
Pregnancy test ⁷	X ²								X	
CA 19-9 ⁶	X ²							X ⁶	X ⁶	
UGT1A1*28 status	X ¹									
Randomization	X ²									
ECG ⁷	X ²								X	
Tumor assessment ⁶	X ¹							X ⁶	X ⁶	
Plasma sample for PK ¹⁴		X ⁸	X ⁹							
Concomitant medications	X ¹	X	X	X	X	X			X	
Concomitant procedures	X ¹	X	X	X	X	X			X	
Administration of MM-398 and 5-FU/LV ¹⁵		X		X		X				
Adverse event reporting		X	X	X	X	X			X	
Overall survival reporting										X

Footnotes:

1. Within 28 days of C1D1
2. Within 7 days of C1 D1
3. To be completed daily while the patient is on study
4. Day 1: within ≤ 3 days prior to Day 1 infusion
Day 8, Day 15, Day 22 and Day 29: within ≤ 1 day prior to infusion or due date for the visit, as applicable
Investigators must document their review of each laboratory report.
5. A chemistry sample must be sent to the central lab; chemistry may be done locally as well, and local lab results may be used for enrollment and dosing decisions if central lab results are not available.
6. To be assessed every 6 weeks after randomization (+/- 1 week), even if dose is delayed or interrupted.
In the event the patient discontinues study treatment for reasons other than disease progression, a tumor assessment should be completed as soon as possible relative to the date of study termination, unless performed within the prior 4 weeks, to ensure disease progression is not present and to assess overall disease status. In such patients, tumor assessment should occur no later than the date of the 30 day follow up visit and future assessments should continue to take place every 6 weeks during the follow-up period till objective disease progression or commencement of new anti-neoplastic therapy (in accordance with RECIST v1.1).
CA 19-9 assessments should follow the same schedule as tumor assessments.
7. To be repeated as clinically indicated during the study
8. Arm A- PK samples should be collected at the following time points: just prior to start of infusion, during infusion (at 80 to 90 minutes after start of infusion), between 2 and a half and four hours after the start of infusion
Arm B- PK sample should be collected at the end of cycle 1 week 1 infusion of 5-FU
Arm C- PK samples should be collected at the following time points: just prior to start of MM-398 infusion, during MM-398 infusion (at 80 to 90 minutes after start of infusion), between 2 and a half and four hours after the start of MM-398 infusion, and end of 5-FU infusion
9. One sample to be collected
10. Arm A: After Cycle 1 Day 1, subsequent cycles should be given every 21 days (+/- 3 days)
Day 8 and Day 15 visit: +/- 1 day
11. Arm B: After Cycle 1 Day 1, subsequent cycles should be given every 42 days (+/- 3 days)
Day 8, Day 15 and Day 22 infusion: +/- 1 day
Day 29 visit: +/- 1 day
12. Follow-up visits should occur every 1 month (+/- 1 week; this window period applies to the 30 day follow-up visit as well)
13. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration
14. A PK sample will be collected in C1, any time between 8 and 72 hours following administration of MM-398, from patients who provide an additional consent for collection of this sample.
15. Arm C: After Cycle 1 Day 1, subsequent cycles should be given every 14 days (+/- 3 days)
Day 8 visit: +/- 1 day
For patients who continue post Cycle 18, a schedule similar to the one outlined in Table 21, should be followed for all subsequent cycles
16. After completion of 3 months of therapy, patients are required to undergo these visits, and the corresponding assessments/investigations, only once every 6 weeks (within up to 3 days prior), except for the completion of the pain assessment and analgesic use diary, which is to be completed daily. Visits may be performed sooner at the discretion of the investigator.

corresponding assessments/investigations, only once every 6 weeks (within up to 3 days prior), except for the completion of the pain assessment and analgesic use diary, which is to be completed daily. Visits may be performed sooner at the discretion of the investigator.

Reviewer comment: It is unclear why the frequency of CBC monitoring for arm C was to be different (only Day 1 rather than Days 1 and 8) every third cycle compared to other cycles.

Disease Progression

Assessment of disease progression for discontinuation of patients from study treatment was to be based on RECIST v1.1 criteria. The protocol also described discontinuation of patients due to symptomatic deterioration that was not more specifically defined.

Reviewer comment: A criterion for patient discontinuation due to symptomatic deterioration that is subjective could lead to bias in outcome assessment. Refer to section 6.1.3 for further information regarding patient disposition in the NAPOLI-1 trial.

DSMB:

During the course of the trial, regular review of safety data was to be conducted by an independent data safety monitoring board (DSMB). The DSMB was to monitor safety in NAPOLI-1 by reviewing data at scheduled time points and also on an ad hoc basis as needed. The DSMB was comprised of three members, two oncologists and one biostatistician. The DSMB charter outlining the purpose and function of the NAPOLI-1 DSMB and procedures for data review by the DSMB was reviewed. The charter submitted included signatures of the members certifying that they do not have any serious conflict of interest that would bias their review of the trial data. As agreed at the May 21, 2015 technical walkthrough meeting between FDA and Merrimack, DSMB recommendations and comments, signed by the DSMB chair, for each DSMB meeting were submitted to the NDA. These documents were reviewed and no concerns were identified. The DSMB met on four dates for data review, beginning October 22, 2012. At each meeting the DSMB recommended continuing the NAPOLI-1 trial. After one meeting the DSMB requested additional information regarding supportive care for nausea and vomiting because rates of these events were higher than would have been expected.

Important Protocol Amendments:

- June 14, 2012
 - Arm C was added to the previously two-arm trial, to investigate the MM-398/5FU/LV combination.

- The sample size was increased to 405 (405 patients total, enrolled under any version of the protocol).
 - Requirement for additional safety review performed by the DSMB of the first 15 patients enrolled in each arm was added.
 - Dose modifications for toxicities tables were modified to include dose modifications for patients in arm C based upon UGT1A1*28 allele status.
 - Confirmation of PR or CR was no longer required.
- October 19, 2012
 - Clarified that comparisons between arms A and B would include patients randomized under all versions of the protocol and that comparisons between arms C and B would include only patients randomized after the addition of arm C to the trial.

Statistical Considerations:

The design of NAPOLI-1 (subsequent to the addition of arm C to the trial) was based on two pair-wise comparisons, assuming a two-sided type I error rate of 0.05 and median OS in the control arm of 3 months (and using the Bonferroni-Holm procedure to control overall type I error) with:

- At least 85% power to detect an improvement in OS at a hazard ratio of 0.67 (median OS 3 to 4.5 months) for arm A vs. B, and
- At least 95% power to detect an improvement in OS at a hazard ratio of 0.5 (median OS 3 to 6 months) for arm C vs. B.

Based on the assumptions, a total of 405 patients were planned, to observe a total of 305 death events among the three arms for the primary analysis. The primary analysis was to be conducted using unstratified log-rank tests.

This design did not include a plan for interim analysis of OS.

Multiplicity adjustment was specified for secondary endpoints PFS and ORR. A sequential testing procedure was specified to control the overall false positive rate at 0.05 (one-sided 0.025 level) for the primary and secondary endpoints, with the order of testing as follows: OS, PFS, ORR. A pairwise treatment comparison for a secondary endpoint was to be carried out if the prior pairwise comparisons in the hierarchy were significant. The pairwise comparison for OS and PFS was to be carried out using unstratified log-rank tests and the pairwise comparison for ORR was to be carried out using Fisher's exact test.

Difference in 5-FU Dosing Regimens:

The 5FU/LV dosing regimen assigned to the control arm of NAPOLI-1 (arm B) was the 5-FU dose and schedule that was employed as the control in the CONKO-003 trial. The MM-398/5FU/LV dosing regimen assigned to arm C of NAPOLI-1 was the same regimen (same dose and schedule) tested in the PEPCOL study, a French cooperative group study of the same combination of MM-398/5FU/LV in patients with metastatic colorectal cancer, from which safety data had become available (prior to the amendment of NAPOLI-1 which added arm C to the trial).

As agreed by FDA at the December 2, 2014 Pre-NDA meeting, to support the conclusion of lack of potential impact on efficacy of the different 5-FU dosing regimens employed in arm B vs. arm C of NAPOLI-1, the applicant included the following in the NDA submission:

- Data showing that the planned (and observed) cumulative doses of 5-FU in arm B (control arm; 5FU/LV) were higher than in arm C (MM-398/5FU/LV) over a six-week cycle,
- Summaries of literature/studies to support the conclusion that the 5-FU dose intensities and regimens did not have an effect on OS, and
- Pharmacokinetics (PK) simulation results showing that the 5-FU area under the curve (AUC) in arm B (control arm) was higher than in arm C (MM-398/5FU/LV).

The planned cumulative dose of 5-FU in the 5FU/LV control arm (arm B) was higher than in the MM-398/5FU/LV arm (arm C): 8000 versus 7200 mg/m² over a six-week cycle, equivalent to a dose intensity of 1333 versus 1200 mg/m²/week. Merrimack showed that the comparison of observed cumulative doses between arms B and C was consistent with the comparison of planned cumulative doses between arms B and C, with six-week average dose intensities of 6718 and 5065 mg/m² (or 1119.7 and 844.2 mg/m²/week) respectively, and that at any week except for the first week, the planned and observed cumulative 5-FU doses were higher in the control arm than in the MM-398/5FU/LV arm.

Merrimack further presented PK simulation results, describing that the six-week average 5-FU AUC in the MM-398/5FU/LV arm was 90% of that in the control arm.

Finally, Merrimack presented results from a literature search conducted to evaluate 5-FU dose intensity and infusion duration with respect to impact on efficacy endpoints:

In the pancreatic cancer indication, clinical studies reported in English were searched using PubMed. The strategy used a panel of keywords (listed in the NDA) involving 5-FU and pancreatic cancer. The search was further filtered for trials from January 1980

through December 2014, containing more than 10 patients per arm, and in patients with pancreatic cancer with locally advanced or metastatic disease eligible for any line of therapy. References from the search publications were included. One study dated 1974 was included as Merrimack deemed the study relevant. Combinations with agents other than LV were included only if the study included more than one 5-FU dose and regimen. Combinations with radiation therapy were excluded. Merrimack acknowledged that the list may not be exhaustive.

In the colorectal cancer indication, where the impact of different 5-FU dose regimens has been more extensively studied, Merrimack used three methods to conduct the search: references of review papers or other papers, direct PubMed search, and recommendations from individuals referenced by Merrimack as being “key opinion leaders.” Cited studies were limited to those that directly compared 5-FU dose regimens and contained at least 80 patients per arm (except for one publication that compared three different 5-FU dose schedules and consisted of approximately 30 patients per arm). Four studies were reviewed in a published meta-analysis (The meta-analysis group in cancer, 1998). One study (Leichman et al., 2005) was identified by PubMed recommendation when evaluating an earlier publication by the same author. Merrimack acknowledged that this list, too, may not be exhaustive.

Publications directly comparing the efficacy of the two 5-FU infusional regimens used in arms B and C of NAPOLI-1 were not found.

Reviewer comment: Review of the published data (most of which is indirect evidence from colorectal cancer trials) did not appear to indicate that the different dosing regimens in the two NAPOLI-1 arms (B and C) would result in improved clinical outcomes in the MM-398/5FU/LV test arm due solely to the differences in 5-FU doses between arms. Also, of particular note, the higher 5-FU cumulative dose per six-week cycle was administered to patients in the control arm (i.e., if any bias were introduced as a result of the difference in 5-FU doses, this would likely bias against the test arm).

A summary of the NDA including summary of the NAPOLI-1 trial and the above-described data and information regarding the difference in 5-FU dose between arms B and C in the trial, including excerpts from the applicant’s submission which included the applicant’s PK simulation methods, analyses, and results and the above-described literature references, were sent to two GI oncology disease area experts for consultation, seeking their review and conclusions with regard to the following question: “Based upon your review of the summary information provided, do you agree that the observed improvement in OS in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms?”

Both consultants specifically noted the higher planned cumulative 5-FU dose per six-week cycle for the control arm compared to the MM-398/5-FU/LV arm and agreed that

the difference in 5-FU dosing regimen between the two arms in NAPOLI-1 is highly unlikely to have contributed to the observed difference in overall survival between the arms. One stated that the difference between the two NAPOLI-1 arms in 5-FU dose delivered as observed via dose intensity was very small, and stated that overall, differences in 5-FU dosing schedules have not been observed in studies to result in different efficacy outcomes. The second expert stated that historically, differing 5-FU dosing schedules have not resulted in differences in efficacy outcomes, and stated that it is highly unlikely that the difference in 5-FU dosing regimens contributed to the observed difference in overall survival between the two arms in the NAPOLI-1 trial. The second consultant also noted the higher cumulative 5-FU doses administered in the control arm as compared to the MM-398/5FU/LV test arm.

PEP0208

PEP0208 was an open-label, single arm, multicenter study that evaluated MM-398 120 mg/m² administered every 3 weeks in patients with metastatic pancreatic cancer refractory to gemcitabine-based therapy. Forty patients were enrolled, to receive MM-398 as a single agent, as above, until disease progression. At the investigator's discretion, patients considered at high risk for toxicity could receive 100 mg/m² as the initial dose in cycle 1, with escalation to the higher dose in cycle 2 if no toxicities occurred. Adverse events were graded using NCI CTCAE v3.0. Patients who did not experience treatment-related toxicities worse than Grade 1 after the first administration of MM-398 could receive 150 mg/m². Enrollment criteria included KPS ≥ 70. The primary endpoint was 3-month survival and other endpoints included objective tumor response according to RECIST v1.0 and duration of response.

PEPCOL

PEPCOL is an investigator-initiated, open-label, randomized, multicenter study of MM-398/5-FU/LV or 5-FU/LV/ irinotecan (bevacizumab was added to the study approximately halfway through enrollment) in 55 patients with metastatic colorectal cancer. Patients in the irinotecan-containing arm could receive FOLFIRI1 or modified FOLFIRI3. Patients in the MM-398-containing arm received MM-398 80 mg/m², leucovorin 400 mg/m², and 5-FU 2400 mg/m² by 46-hour continuous IV infusion, every 14 days, the same dose and schedule proposed in this application and studied in the NAPOLI-1 trial. Approximately halfway through enrollment, the study was amended to include bevacizumab 5 mg/kg in both arms.

6 Review of Efficacy

Efficacy Summary

The primary basis for this application is a single, randomized, open-label, three-arm, controlled trial in patients with metastatic pancreatic cancer, the NAPOLI-1 trial. The NAPOLI-1 trial enrolled 417 patients, utilized the MM-398/5FU/LV dosing regimen (same doses and schedule) proposed in this application, and consisted of the application's intended population. NAPOLI-1 was initially designed as a two-arm trial comparing arms A and B listed below. After enrollment of 63 patients, the applicant amended the trial to include arm C listed below, investigating the combination MM-398/5FU/LV. Under the revised protocol, patients were randomized (1:1:1) to the following treatment arms: A (MM-398): MM-398 120 mg/m², every 3 weeks; B (5FU/LV): 5FU 2000 mg/m² over 24 hours + LV 200 mg/m², weekly for 4 weeks of each 6 week cycle; or C (MM-398/5FU/LV): MM-398 80 mg/m² + 5FU 2400 mg/m² over 46 hours + LV 400 mg/m², every two weeks. Randomization was stratified by ethnicity (White vs. East Asian vs. other), KPS (70-80 vs. 90-100), and baseline albumin level (≥ 4 g/dL vs. 3.0-3.9 g/dL). With inclusion of arm C, the statistical plan was revised and the total sample size was increased from 270 to 405. The comparison between the MM-398/5FU/LV and 5FU/LV arms was limited to patients enrolled after the protocol was amended to add the third arm.

The primary endpoint of the NAPOLI-1 trial was overall survival (OS) assessed with two co-primary, pair-wise comparisons, one for each MM-398-containing arm (A or C) compared with the control arm (B). Secondary endpoints were progression free survival and objective response rate (investigator-assessed).

The assessment of benefit in this application is based on the primary endpoint of OS. A statistically significant, clinically meaningful prolongation in OS was observed in patients randomized to receive the MM-398/5FU/LV combination; the median OS was 6.1 months (95% Ci: 4.8, 8.5) in the MM-398 combination arm compared to 4.2 months (95% Ci: 3.3, 5.3) in the 5FU/LV arm with a hazard ratio of 0.68 (95% Ci: 0.50, 0.93; p = 0.014). Treatment effect on OS in the MM-398-only arm compared to the 5FU/LV control was not demonstrated.

The secondary efficacy parameter of PFS was prolonged in the MM-398/5FU/LV arm, with a median PFS of 3.1 months (95% Ci: 2.7, 4.2) compared to 1.5 months (95% Ci: 1.4, 1.8) in the 5FU/LV arm. The estimated hazard ratio for PFS was 0.55 (95% Ci: 0.41, 0.75) in favor of the MM-398 combination arm. The NAPOLI-1 trial also demonstrated an improvement in ORR in the MM-398/5FU/LV arm, with a ORR of 7.7% in the MM-398 combination arm compared to 1% in the 5FU/LV arm.

Results of subgroup analyses were generally consistent and supportive of the primary analysis of OS in the trial.

6.1 Indication

Merrimack seeks approval in this NDA for the following proposed indication 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.”

Reviewer comment: For clarity and accuracy with regard to the intended patient population, the descriptor “with disease progression following gemcitabine-based therapy” (as this was required for enrollment in the NAPOLI-1 trial) was added to the indication statement. Also, a Limitation of Use statement was added regarding use of MM-398 as a single agent for the proposed indication, based on results in the MM-398-only arm of NAPOLI-1 (refer to section 6.1.4 Analysis of Primary Endpoint below).

6.1.1 Methods

This efficacy review focuses on results from the single, randomized, controlled, three-arm, global, open-label trial, NAPOLI-1; refer to section 5.3 Discussion of Individual Studies/Clinical Trials for further description of the NAPOLI-1 trial design. The trial enrolled 417 patients, Arm C utilized the MM-398/5FU/LV dosing regimen proposed in the application, and the trial consisted of the application’s intended population (this review team recommended some modification of the Indication statement in the product labeling as above, see section 6.1 Indication). The efficacy results presented in the application were from the planned analysis for efficacy defined in the protocol (see section 5.3 of this review under Statistical Considerations), with a data cutoff date of February 14, 2014. The primary analysis of OS was performed when at least 305 deaths had occurred. The trial was considered to be complete once all patients were off study treatment and at least 90% of possible events occurred; updated OS results constituting at least 90% of events were submitted to the NDA July 23, 2015 with the 90-Day Safety Update.

NAPOLI-1 was initially designed as a two-arm trial comparing arms A and B shown in section 5.3 of this review; after enrollment of 63 patients, the applicant amended the trial to include arm C. With inclusion of arm C, the statistical plan was revised and the total sample size was increased from 270 to 405.

Randomization was stratified by ethnicity (White vs. East Asian vs. other), KPS (70-80 vs. 90-100), and baseline albumin level (≥ 4 g/dL vs. 3.0-3.9 g/dL).

Efficacy data including the clinical study report, CRFs, and electronic datasets for the NAPOLI-1 trial were reviewed. Refer to section 5.3 Discussion of Individual Studies/Clinical Trials and the statistical review of this application by Dr. Hui Zhang (under separate cover) for description of the statistical methodologies.

Note that analyses presented in these sections were performed by Dr. Hui Zhang, the FDA statistical reviewer for this application; see Dr. Zhang’s review under separate cover.

6.1.2 Demographics

The following tables show baseline demographics and disease characteristics of patients enrolled in the NAPOLI-1 trial. A summary of stratification factors at baseline is also shown below. A total of 417 patients were randomized and constituted the intent-to-treat (ITT) population. Approximately one-third were enrolled in Asia; *enrollment between arms was well-balanced with respect to patients enrolled in Asia. There appeared to be a higher proportion of patients 65 or younger in the control arm. The arms were well-balanced with respect to other demographic variables including race. More patients had received gemcitabine in combination than had received gemcitabine alone. Most patients had liver involvement of their pancreatic cancer at the time of enrollment.*

Table 5 Baseline Demographics (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398 N = 151	5-FU/LV N = 149	MM-398 + 5-FU/LV N = 117	5-FU/LV N = 119
Age (years)				
Mean (SD)	63.6 (10.1)	61.8 (9.7)	63.2 (9.1)	61.0 (9.5)
Median (min – max)	65 (31 – 87)	63 (34 – 83)	63 (41 – 81)	62 (34 – 80)
Age group				
≤ 65	82 (54%)	94 (63%)	65 (56%)	81 (68%)
> 65	69 (46%)	55 (37%)	52 (44%)	38 (32%)
Race				
White	89 (59%)	92 (62%)	72 (62%)	76 (64%)
Black or African American	3 (2%)	3 (2%)	4 (3%)	3 (3%)

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Asian	52 (34%)	50 (34%)	34 (29%)	36 (30%)
Other	7 (5%)	4 (3%)	7 (6%)	4 (3%)
Gender				
Female	64 (42%)	68 (46%)	48 (41%)	52 (44%)
Male	87 (58%)	81 (54%)	69 (59%)	67 (56%)
Height				
Mean (SD)	166.6 (10.7)	166.2 (10.1)	167.5 (9.6)	166.7 (10.1)
	167	166	168	166
Median (min-max)	(144 – 193)	(145 – 193)	(142 – 189)	(147 – 193)
Weight				
Mean (SD)	64.7 (14.2)	65.6 (17.7)	65.9 (14.9)	66.1 (18.3)
	64 (38 –		64 (40 –	63 (37 –
Median (min-max)	118)	63 (37 – 151)	123)	151)
Region				
North America	25 (17%)	26 (17%)	19 (16%)	19 (16%)
Asia	48 (32%)	50 (33%)	34 (29%)	35 (29%)
Europe	55 (37%)	54 (36%)	47 (40%)	49 (41%)
Other	21 (14%)	21 (14%)	17 (15%)	16 (13%)

Table 6 Baseline Characteristics (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398 N = 151	5-FU/LV N = 149	MM-398 + 5-FU/LV N = 117	5-FU/LV N = 119
Measurable lesions at baseline	144 (95%)	144 (97%)	113 (97%)	114 (96%)
Measurable metastatic lesions at baseline	128 (85%)	129 (87%)	97 (83%)	103 (87%)
Prior Gemcitabine therapy				
Gemcitabine only	67 (44%)	66 (44%)	53 (45%)	55 (46%)
Gemcitabine in combination	84 (56%)	83 (56%)	64 (55%)	64 (54%)
Anatomical location of lesion at baseline				
Distant lymph node	44 (29%)	40 (27%)	32 (27%)	31 (26%)
Liver	101 (67%)	108 (73%)	75 (64%)	83 (70%)
Lung	49 (32%)	44 (30%)	36 (31%)	36 (30%)
Pancreas	99 (66%)	97 (65%)	75 (64%)	72 (61%)
Peritoneal	48 (32%)	39 (26%)	28 (24%)	32 (27%)
Regional lymph node	19 (13%)	20 (13%)	13 (11%)	14 (12%)
Other	38 (25%)	48 (32%)	27 (23%)	39 (33%)
Prior lines of treatment				
Neoadjuvant/adjuvant therapy only	17 (11%)	19 (13%)	15 (13%)	15 (13%)
Neoadjuvant/adjuvant + 1 line in advanced/metastatic setting	18 (12%)	16 (11%)	13 (11%)	14 (12%)
Neoadjuvant/adjuvant + 2 or more lines in advanced/metastatic setting	12 (8%)	4 (3%)	8 (7%)	4 (3%)
1 line in advanced/metastatic setting only	68 (45%)	70 (47%)	49 (42%)	53 (45%)
2 or more lines in advanced/metastatic setting only	36 (24%)	40 (27%)	32 (27%)	33 (28%)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398 N = 151	5-FU/LV N = 149	MM-398 + 5-FU/LV N = 117	5-FU/LV N = 119
setting only				
Number of measurable metastatic lesion				
0	23 (15%)	20 (13%)	20 (17%)	16 (13%)
1	36 (24%)	26 (17%)	19 (16%)	22 (18%)
2	63 (42%)	72 (48%)	49 (42%)	58 (49%)
3	22 (15%)	21 (14%)	22 (19%)	15 (13%)
4	6 (4%)	9 (6%)	7 (6%)	8 (7%)
5	1 (1%)	1 (1%)	0	0
Baseline KPS	n = 151	n = 148	n = 117	n = 118
50	0	0	1 (0.9%)	0
60	0	0	2 (1.7%)	0
70	15 (9.9%)	11 (7.4%)	7 (6.0%)	10 (8.5%)
80	50 (33.1%)	61 (41.2%)	38 (32.5%)	51 (43.2%)
90	64 (42.4%)	54 (36.5%)	51 (43.6%)	40 (33.9%)
100	22 (14.6%)	22 (14.9%)	18 (15.4%)	17 (14.4%)
Baseline albumin (g/dL)	n = 149	n = 146	n = 114	n = 116
Mean (SD)	4.0 (0.4)	4.0 (0.5)	4.0 (0.5)	4.0 (0.5)
Median (min – max)	4.0 (2.9 – 4.8)	4.0 (2.4 – 5.1)	4.1 (2.6 – 5.1)	4.0 (2.4 – 5.0)

Table 7 Summary of Stratification Factors at Randomization (ITT Population)

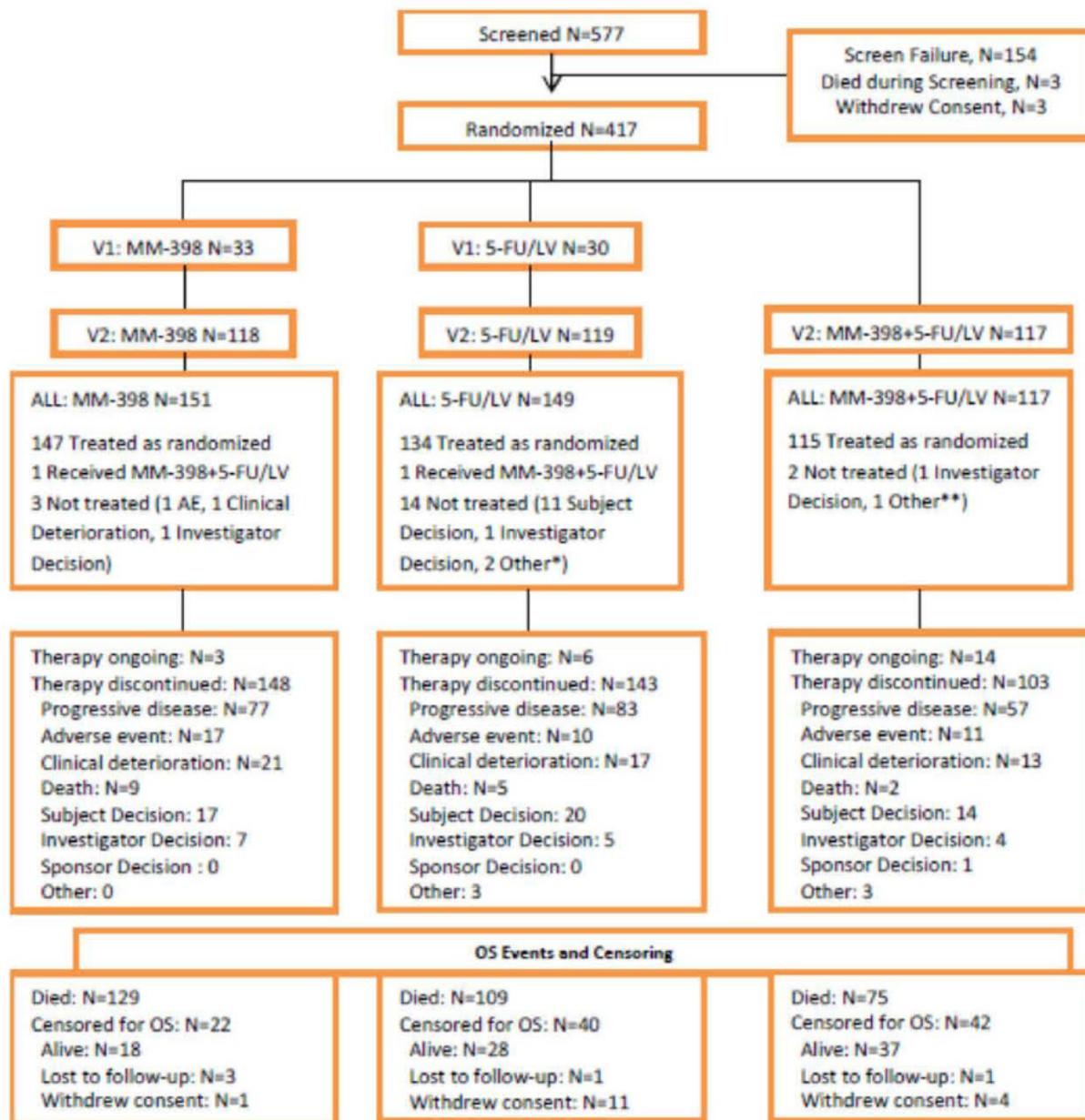
	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398 N = 151	5-FU/LV N = 149	MM-398 + 5-FU/LV N = 117	5-FU/LV N = 119
Baseline albumin levels				
< 4.0 g/dL	88 (58%)	83 (56%)	64 (55%)	65 (55%)
≥ 4.0 g/dL	63 (42%)	66 (44%)	53 (45%)	54 (45%)
KPS				
70 and 80	66 (44%)	65 (44%)	51 (44%)	52 (44%)
≥ 90	85 (56%)	84 (56%)	66 (56%)	67 (56%)
Ethnicity				
Caucasian	90 (60%)	90 (60%)	75 (64%)	75 (63%)
East Asian	53 (35%)	50 (34%)	34 (29%)	36 (30%)
All others	8 (5%)	9 (6%)	8 (7%)	8 (7%)

6.1.3 Subject Disposition

In the NAPOLI-1 trial there were 417 patients randomized who constituted the Intent-to-Treat (ITT) population, with a total of 151 patients who were randomized to receive MM-398 as a single agent, a total of 149 patients who were randomized to receive 5FU/LV, and 117 patients who were randomized to receive MM-398/5FU/LV. The following figure copied from the NDA submission shows patient enrollment and disposition by arm for the NAPOLI-1 trial (*this reviewer conducted analyses of the datasets that verified the numbers within the diagram that are listed above 'OS Events and Censoring'*).

Two patients in the MM-398/5FU/LV arm were not treated, and one patient in each of the other two arms inadvertently received MM-398/5FU/LV. Upon case review of patients reported as discontinued due to clinical deterioration it was noted that patients who discontinued due to disease progression were reported in the clinical deterioration category as were some patients who discontinued due to AE. By the date of data cutoff, most patients had discontinued study treatment.

Figure 6 Applicant's Analysis of Patient Disposition (copied from the NDA submission)



V1=Version 1 of the protocol; V2=Version 2 of protocol

*: 1 patient became ineligible post-randomization, 1 patient had AE that delayed dosing > 7 days from randomization.

** : 1 patient became ineligible post-randomization.

6.1.4 Analysis of Primary Endpoint(s)

Overall survival (OS) was the primary endpoint in the NAPOLI-1 trial. Overall survival was defined as the time from date of patient randomization to date of death or the date last known alive. Patients who were not known to have died as of the data cutoff date were censored at the date of last contact prior to the data cutoff date. Refer to section 5.3 of this review regarding followup that was to occur in the NAPOLI-1 trial.

Refer to section 5.3 of this review under Statistical Considerations and the FDA statistical review regarding the pairwise comparisons for OS for the three arms that was specified in the statistical analysis plan, populations specified for the comparisons, and rules specified for analysis of secondary endpoints.

Results for OS are shown in the tables and Kaplan-Meier (K-M) curves below. The second table shows results for OS based on updated data provided by the applicant for patients who had been censored due to withdrawal of consent. The first figure shows the K-M curves for the comparison between the MM-398 and 5FU/LV arms, while the second figure shows the K-M curves for the comparison between the MM-398/5FU/LV and 5FU/LV arms.

Table 8 Applicant’s Original Overall Survival Results (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398	5-FU/LV	MM-398 + 5-FU/LV	5-FU/LV
Subjects randomized	151	149	117	119
Death	129 (85.4%)	109 (73.2%)	75 (64.1%)	80 (67.2%)
Censored	22 (14.6%)	40 (26.8%)	42 (35.9%)	39 (32.8%)
Overall survival (months)				
Median (95% CI)	4.9 (4.2, 5.6)	4.2 (3.6, 4.9)	6.1 (4.8, 8.9)	4.2 (3.3, 5.3)
p-value ^a	0.942		0.012	
Hazard ratio (95% CI) ^b	0.99 (0.77, 1.28)		0.67 (0.49, 0.92)	

^a p-value is from an unstratified log-rank test.

^b Hazard ratio is from an unstratified Cox proportional hazards model.

Table 9 Applicant's Updated Overall Survival Results (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398	5-FU/LV	MM-398 + 5-FU/LV	5-FU/LV
Subjects randomized	151	149	117	119
Death	129 (85.4%)	115 (77.2%)	77 (65.8%)	86 (72.3%)
Censored	22 (14.6%)	34 (22.8%)	40 (34.2%)	33 (27.7%)
Overall survival (months)				
Median (95% CI)	4.9 (4.2, 5.6)	4.2 (3.6, 4.9)	6.1 (4.8, 8.5)	4.2 (3.3, 5.3)
p-value ^a	0.971		0.014	
Hazard ratio (95% CI) ^b	1.00 (0.77, 1.28)		0.68 (0.50, 0.93)	

^a p-value is from an unstratified log-rank test.

^b Hazard ratio is from an unstratified Cox proportional hazards model.

Figure 7 Kaplan-Meier Survival Curves for Overall Survival (ITT Population, MM-398 vs. 5-FU/LV)

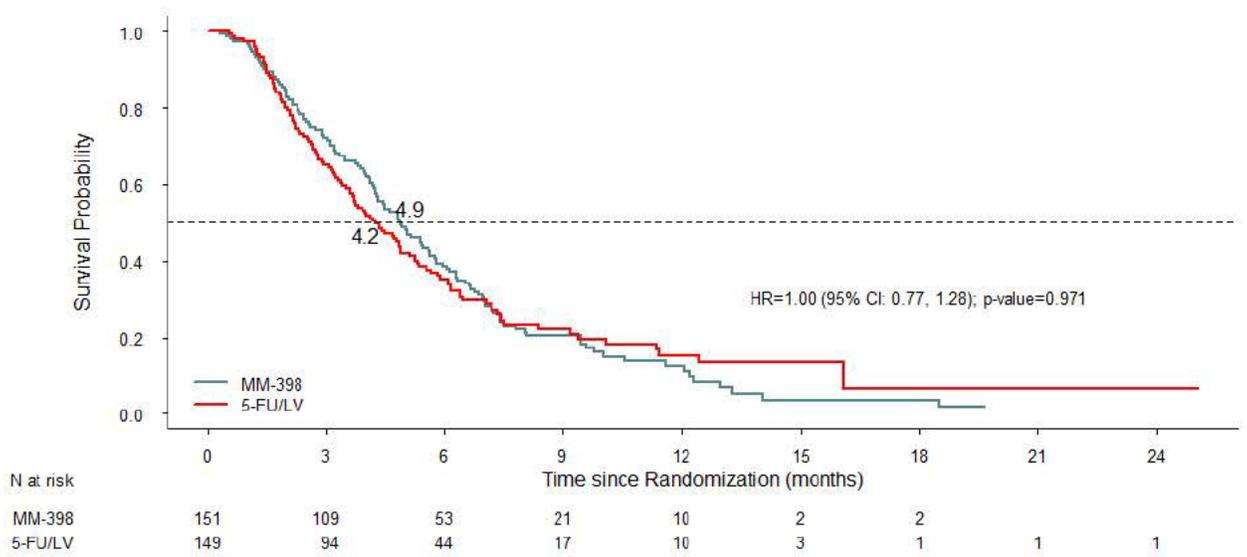
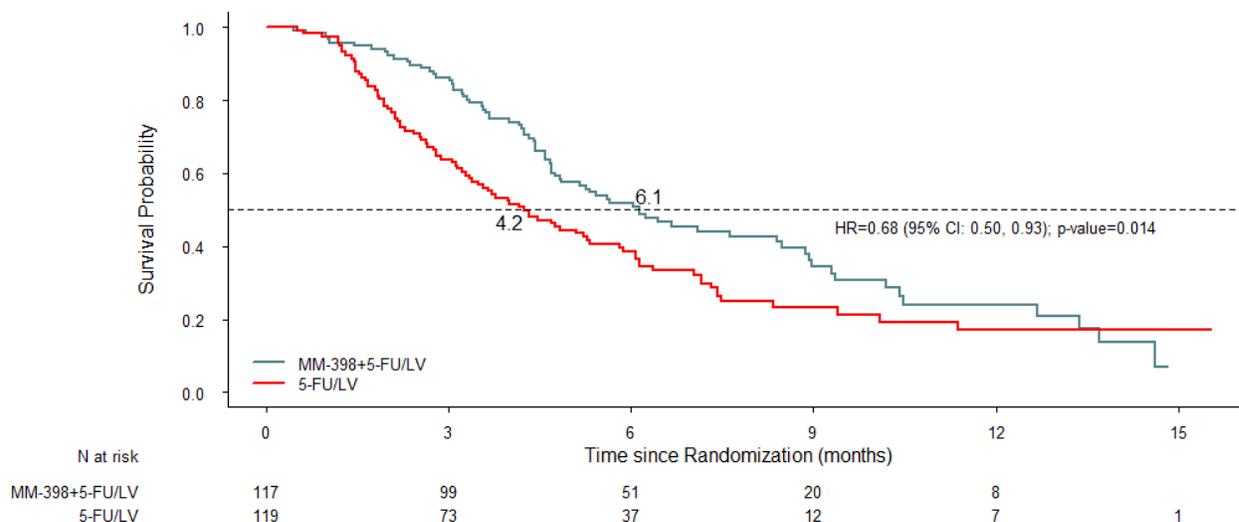


Figure 8 Kaplan-Meier Survival Curves for Overall Survival (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)



Reviewer comment: The median overall survival observed in the MM-398/5FU/LV arm of 6.1 months was statistically significant and represents a clinically meaningful improvement over that observed in the 5FU/LV control arm, 4.2 months. The median overall survival observed in the 5FU/LV arm was similar to that observed in previous studies. Results for OS were robust and consistent across subgroups; refer to section 6.1.7 Subpopulations and the FDA statistical review. Treatment effect on OS in the MM-398-only arm compared to the 5FU/LV control was not demonstrated.

6.1.5 Analysis of Secondary Endpoints(s)

Progression Free Survival

Progression free survival (PFS) was a secondary endpoint in the NAPOLI-1 trial, to be tested if the prior pairwise comparisons in the hierarchy were significant; refer to section 5.3 of this review under Statistical Considerations. PFS results are shown in the table and Kaplan-Meier curves for PFS below.

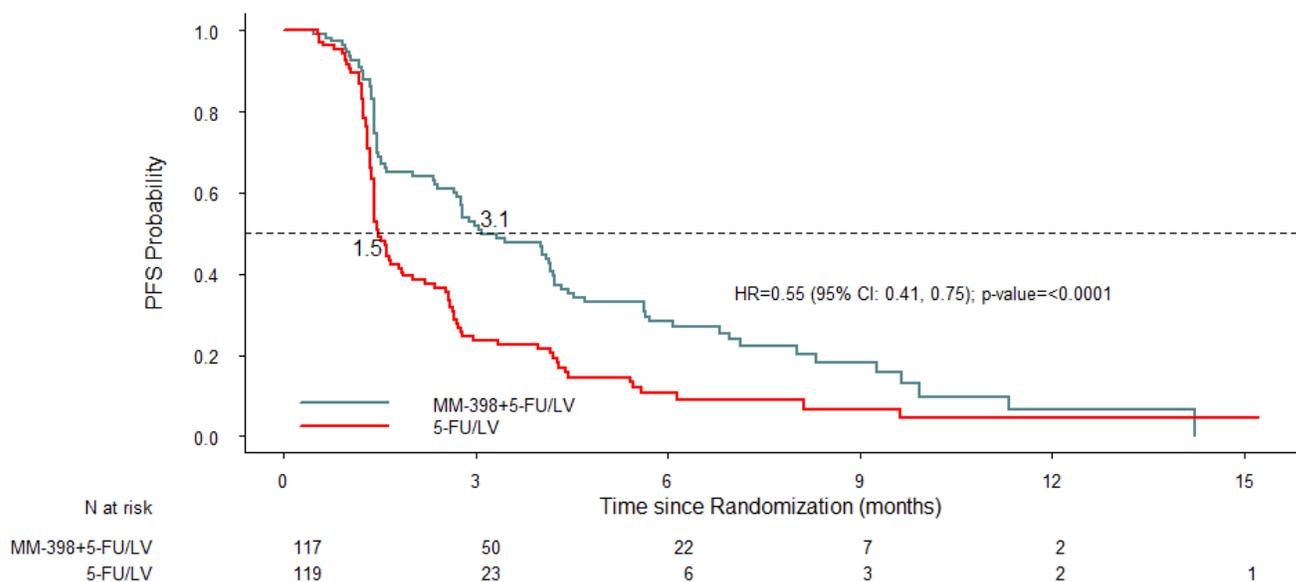
Table 10 Progression-Free Survival Results (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)

	MM-398 + 5-FU/LV	5-FU/LV
Subjects randomized	117	119
PD or Death	83 (70.9%)	94 (79.0%)
Censored	34 (29.1%)	25 (21.0%)
PFS (months)		
Median (95% CI)	3.1 (2.7, 4.2)	1.5 (1.4, 1.8)
p-value ^a	< 0.0001	
Hazard ratio (95% CI) ^b	0.55 (0.41, 0.75)	

^a p-value is from an unstratified log-rank test. This p-value is nominal.

^b Hazard ratio is from an unstratified Cox proportional hazards model.

Figure 9 Kaplan-Meier Survival Curves for Progression-Free Survival (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)



Objective Response Rate

Objective response rate (ORR) was a secondary efficacy endpoint in the NAPOLI-1 trial and was defined by percentage of patients with confirmed CR or PR, assessed by the investigator according to RECIST v1.1. The NAPOLI-1 statistical analysis plan specified that responses were to be confirmed. ORR results are shown in the table below.

There were 10 patients in the MM-398/5FU/LV arm who had unconfirmed PR. Among these 10 patients, 6 had PR but later scan showed no PR, and 4 patients did not have followup scans after PR.

Table 11 ORR Results (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)

	MM-398 + 5-FU/LV (N=117)	5-FU/LV (N=119)
Overall Response	9 (7.7%)	1 (0.8%)
Complete Response (CR)	0	0
Partial Response (PR)	9 (7.7%)	1 (0.8%)
Fisher's Exact Test p-value ^a		0.010

^a This p-value is nominal.

Reviewer comment: The PFS benefit observed in the MM-398/5FU/LV arm was modest with a median PFS of 3.1 months (95% CI: 2.7, 4.2) compared to 1.5 months (95% CI: 1.4, 1.8) with a hazard ratio of 0.55 (95% CI: 0.41, 0.75; p<0.0001, nominal). The overall response rate was modest consisting of 9 patients (7.7%) in the MM-398/5FU/LV arm and 1 patient (0.8%) in the 5FU/LV arm.

6.1.6 Other Endpoints

There were no additional efficacy endpoints considered for regulatory decision making from the NAPOLI-1 trial.

6.1.7 Subpopulations

Exploratory subgroup analyses of overall survival were performed by Dr. Hui Zhang, the statistical reviewer for this application; refer to Dr. Zhang's review under separate cover. Results of these analyses are shown in the following table and forest plot below and overall, were consistent with the results of the primary analysis for the NAPOLI-1 trial (refer to section 6.1.4 Analysis of the Primary Endpoint).

Table 12 OS Subgroup Analyses by Demographics (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)

	Event/Total (TRT: CTL)	HR (95% CI)^a
Age		
≤ 65	41/65 : 53/81	0.61 (0.40, 0.92)
> 65	36/52 : 33/38	0.78 (0.49, 1.26)
Sex		
Male	46/69 : 49/67	0.64 (0.43, 0.96)
Female	31/48 : 37/52	0.72 (0.44, 1.17)
Race		
White	45/72 : 58/76	0.66 (0.45, 0.97)
Black or African American	3/4 : 1/3	— ^b
Asian	23/34 : 24/36	0.54 (0.29, 0.98)
Other	6/7 : 3/4	— ^b
Region		
North America	14/19 : 14/19	0.75 (0.35, 1.57)
Europe	30/47 : 37/49	0.74 (0.46, 1.20)
Asia	23/34 : 24/35	0.51 (0.28, 0.93)
Other	10/17 : 11/16	0.58 (0.25, 1.38)

a HRs were estimated using unstratified Cox regression model

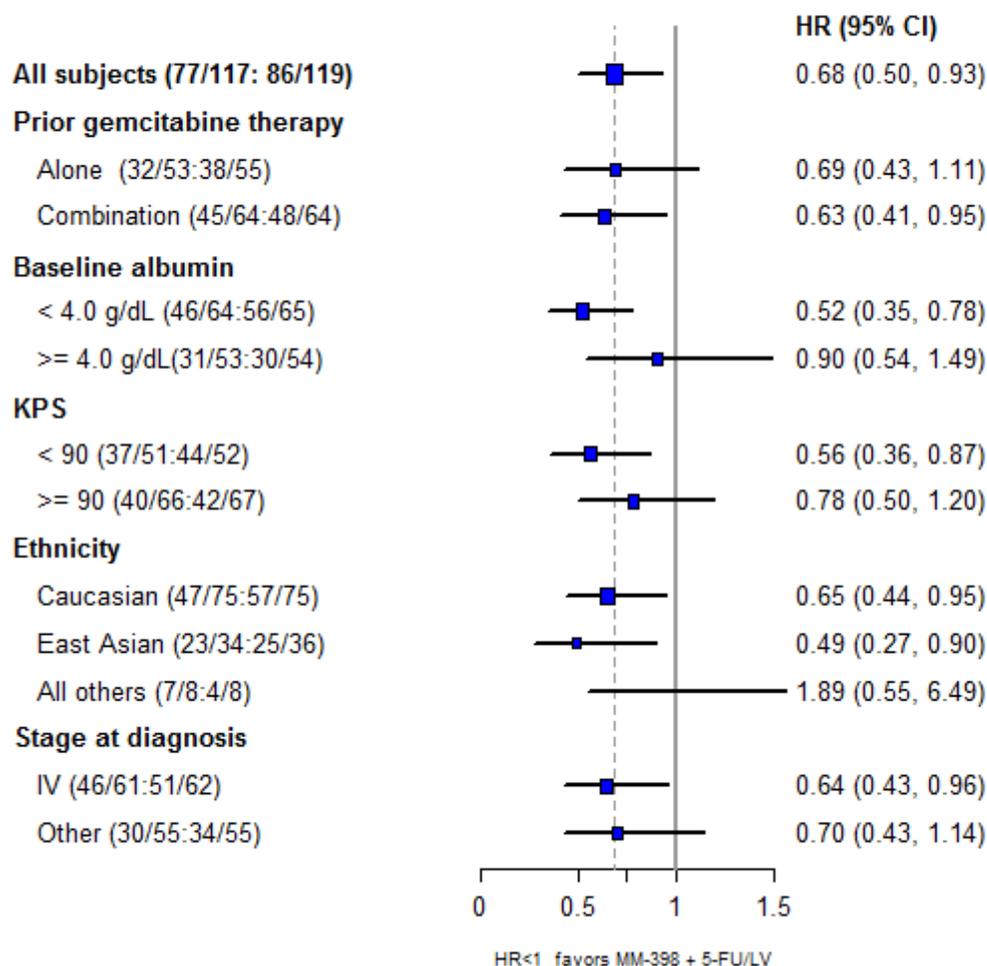
b Analysis was not performed due to the small number of patients

TRT: MM-398 + 5-FU/LV

CTL: 5-FU/LV

Reviewer comment: The above table depicts subgroup analyses by age group, gender, race, and geographic region. All hazard ratios estimates were less than one, indicative of favorable treatment effect in the subgroups analyzed. The HR estimate was smaller for patients 65 years of age or younger compared to those above 65, for Asian patients compared to White patients, and for Asia compared to North America and Europe; however, these numbers should be interpreted with caution given the smaller sample sizes and non-randomized groups.

Figure 10 Forest Plot of Subgroup Analyses of OS (ITT Population)



Reviewer comment: The HR estimates for OS for the subgroup with baseline albumin of 4 g/dL or higher and the subgroup with KPS 90 or above were higher in comparison to others, but should be interpreted with caution due to the smaller sample sizes. Also note that the 'all others' group for ethnicity contained very few patients (8 per arm). The HR estimates for patients who received prior gemcitabine alone and for patients who received prior gemcitabine in combination were similar, and similar to that using the ITT population.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In a dose finding study of MM-398 using a once every three weeks schedule in patients with advanced solid tumors (study *PEP0201*; refer to section 5.3 of this review), the MM-398 dose was escalated beyond 120 mg/m² (the regimen administered in arm A of the NAPOLI-1 trial) to 180 mg/m² (administered every three weeks). Dose limiting toxicities (Grade 3 febrile neutropenia, Grade 3 diarrhea, and Grade 4 leukopenia/neutropenia lasting longer than 3 days) occurred in 2 patients among the 4 treated at the 180 mg/m² dose level during the first cycle of treatment. In study *PEP0201*, 120 mg/m² was the maximum tolerated dose (MTD) of MM-398 when administered on a once every three weeks schedule.

The applicant described that from a population PK analysis, compared to MM-398 120 mg/m² every 3 weeks, a dose of 80 mg/m² every two weeks resulted in similar average concentration, 1.5-fold lower C_{max} of both total irinotecan and SN-38, and 7-fold higher SN-38 converted C_{min}.

The proposed dosing regimen in this application is MM-398 80 mg/m² every two weeks administered in combination with 5FU/LV. The applicant described that based on the population PK results described above, with 80 mg/m² every two weeks providing lower C_{max} of total irinotecan and of SN-38 compared to 120 mg/m² every 3 weeks, the 80 mg/m² every two weeks was expected to result in reduced incidence of toxicity including neutropenia.

The PEPCOL study (refer to section 5.3 of this review for details regarding this investigator-initiated study of MM-398 that was sponsored by a French cooperative group) investigated the 80 mg/m² every two weeks dose and schedule; patients in the MM-398-containing arm of the PEPCOL study received MM-398 80 mg/m², leucovorin 400 mg/m², and 5-FU 2400 mg/m² by 46-hour continuous IV infusion, every 14 days (the same dose and schedule proposed in this application and studied in the NAPOLI-1 trial). The doses and schedule selected for the added arm C of the NAPOLI-1 trial (and those proposed in this application) were based on experience in the PEPCOL study.

Refer to section 5.3 and the clinical pharmacology/pharmacogenomics review regarding the reduced starting dose of MM-398 received by patients homozygous for the UGT1A1*28 allele and which is recommended for this subgroup in the proposed labeling.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to the analyses of OS, PFS, and duration of response in sections 6.1.4 and 6.1.5 regarding persistence of efficacy effects.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable; refer to section 5.3 of this review for discussion of the difference in 5-FU dosing regimens between arms B and C of the NAPOLI-1 trial.

7 Review of Safety

Safety Summary

The NAPOLI-1 trial included a total of 264 patients who received MM-398, including 117 patients who received MM-398 in combination with 5-FU and leucovorin at the dose and dosing schedule proposed in this application. The mean duration of treatment in the MM-398/5FU/LV arm was 93 days. The most common adverse events (AEs) that occurred in the MM-398/5-FU/LV arm (>10%) of NAPOLI-1, as described by PTs, were diarrhea, vomiting, nausea, decreased appetite, fatigue, anemia, neutropenia, pyrexia, abdominal pain, constipation, asthenia, weight decreased, neutrophil count decreased, white blood cell count decreased, alopecia, stomatitis, dizziness, back pain, hypokalemia, and peripheral edema.

The incidence of serious treatment-emergent adverse events (SAEs) was higher in the MM-398 combination arm compared to the 5FU/LV arm (48% vs. 45%). The most frequently reported treatment-emergent SAEs in the MM-398 combination arm were vomiting and diarrhea. Eleven percent of patients in the MM-398 combination arm experienced a treatment-emergent AE that resulted in permanent discontinuation of study drug, compared to 7% in the 5FU/LV arm. Thirty-three percent of patients in the MM-398 combination arm experienced treatment-emergent AE that resulted in dose reduction of MM-398. A total of 62% of patients in the MM-398 combination arm experienced a treatment-emergent AE that resulted in dose delay.

The most common adverse events that led to dose reduction or dose delay were neutropenia and diarrhea.

The incidence of Grade 3 or higher neutropenia as described by a group of preferred terms including agranulocytosis, febrile neutropenia, neutropenia, and neutrophil count decreased) was 27% in the MM-398/5FU/LV arm, compared to 2% in the 5FU/LV arm. Two deaths due to sepsis following neutropenia occurred in MM-398-treated patients in the NAPOLI-trial.

Diarrhea occurred in 59% of patients in the MM-398/5FU/LV arm compared to 26% of patients in the 5FU/LV arm, with Grade 3-4 diarrhea occurring in 13% compared to 4%,

respectively. Diarrhea occurred in one of two patterns, early onset or late onset (a patient may experience both forms within a treatment cycle), as also described in the Camptosar labeling. Early onset was defined as onset within 24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction. Late onset was defined as onset more than 24 hours following chemotherapy. Thirty percent of patients in the MM-398/5FU/LV arm experienced early onset diarrhea, compared to 15% in the 5FU/LV arm. Late onset diarrhea occurred in 43% of patients in the MM-398/5FU/LV arm compared to 17% of patients in the 5FU/LV arm.

In general, the safety data submitted to NDA 207793 showed that MM-398 in combination with 5-FU and leucovorin, at the dose and dosing schedule proposed in this application, has an acceptable safety profile in the second-line treatment of patients with metastatic pancreatic cancer, a life-threatening disease with limited treatment options; the risks were balanced by the robustness of the improvement in OS observed in the NAPOLI-1 trial and can be managed with prudent patient selection and monitoring and dose delays and reductions.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety analyses were conducted using data from the NAPOLI-1 trial; refer to section 5.3 of this review regarding the design elements of the NAPOLI-1 trial. The safety analysis population in NAPOLI-1 consisted of 398 patients who received at least one dose of study drug and included 264 patients who received at least one dose of MM-398. Patients were grouped according to study treatment actually received.

Other studies that contributed to the overall evaluation of safety included 7 early-phase studies in which 148 additional patients with advanced malignancy received at least one dose of MM-398; including the 264 patients who received MM-398 in NAPOLI-1, this provided an MM-398 exposure of 412 patients in the data submitted to the NDA.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were coded in the NAPOLI-1 trial using version 14.1 of the MedDRA dictionary. For other studies of MM-398 included in the applicant's Integrated Summary of Safety, AEs were re-coded using MedDRA version 14.1.

Toxicity grading of AEs was based on the NCI CTCAE v4.0.

Treatment-emergent adverse events (TEAEs) were defined as events that occurred or worsened on or after the day of the first dose of study drug and within 30 days after last administration of study drug.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary analysis of safety was performed using the electronic datasets, including the adverse event and laboratory results datasets, from the NAPOLI-1 trial in which 398 patients were treated. In general, other studies submitted to the NDA included relatively few patients, studied populations or dosing regimens different than those proposed in this application, and lacked the control arm for assessment of the background incidence of adverse events.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

NAPOLI-1 trial enrollment was limited to patients with KPS \geq 70, serum total bilirubin within institutional normal range, albumin level \geq 3.0 g/dL, and adequate bone marrow, renal, and hepatic function.

Reviewer comment: Given the improvement in overall survival demonstrated in this trial of second-line therapy in a population of patients with incurable malignancy and a poor prognosis, the safety results from NAPOLI-1 along with supportive data submitted from the additional studies described in sections 7.1 and 5.3 above encompassed an adequate number of patients for consideration for approval.

The following table summarizes study drug exposure for the NAPOLI-1 trial. The dose intensity is described as a 6-week normalized figure based upon the schedule of study drug administration in each arm of the trial (3 week cycle vs. 6 week cycle vs. 2 week cycle; refer to section 5 of this review for details of the regimen administered in each arm).

Table 13 NAPOLI-1 Exposure Summary

	MM-398 N=147	5FU/LV N=134	MM-398/5FU/LV N=117
Mean duration of treatment (days)	64	59	93
Mean 6-week normalized dose intensity (mg/m²/6 weeks) (mean, SD)			
MM-398	188.0 (44.8)		167.5 (52.0)
5-FU		6718.0 (1770.2)	5065.0 (1539.1)
LV		676.7 (176.8)	810.8 (284.0)

The applicant reported mean relative dose intensities (described as based on total dose received and time frame of exposure, expressed as percentage of planned drug in the protocol-specified schedule) as follows, by arm:

- MM-398: MM-398 90.2%
- 5FU/LV: 5-FU 95.6%, LV 96.3%
- MM-398/5FU/LV: MM-398 83.2%, 5-FU 83.9%, LV 78.9%

There were no significant differences in demographic characteristics between the NAPOLI-1 safety analysis population and the efficacy analysis population described in section 6 of this review. Refer to section 7.5.3 (Drug-Demographic Interactions) of this review for safety analysis by age, sex, and race. Analyses by race with the exception of analyses of the subgroup of Asian patients were limited by small numbers of patients in other non-White subgroups.

7.2.2 Explorations for Dose Response

NAPOLI-1, the randomized, international, multicenter trial that forms the basis of this application was conducted with two dose levels of MM-398, however one of these dose levels (120 mg/m²) was MM-398 administered as a single agent and on an every-three-week schedule, and the other (the dosing regimen proposed in this application) was MM-398 administered in combination with other chemotherapy (5-FU and LV) and on an every-two-week schedule. The 7 patients who began at the protocol-specified reduced starting dose of MM-398 in the MM-398/5FU/LV arm were homozygous for the UGT1A1*28 allele (confounding any comparison based on dose level).

In a dose escalation study of MM-398 using a once every three weeks schedule in patients with advanced solid tumors (study *PEP0201*; refer to section 5.3 of this review), the MM-398 dose was escalated beyond 120 mg/m² (the regimen administered in arm A of the NAPOLI-1 trial) to 180 mg/m² (administered every three weeks). Dose limiting toxicities (Grade 3 febrile neutropenia, Grade 3 diarrhea, and Grade 4 leukopenia/neutropenia lasting longer than 3 days) occurred in 2 patients among the 4

treated at this dose level, during the first cycle of treatment. In study PEP0201, 120 mg/m² was the maximum tolerated dose (MTD) of MM-398 when administered on a once every three weeks schedule.

Refer to the clinical pharmacology review regarding exploration of plasma drug and metabolite levels and toxicity.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the Toxicology review; this reviewer is not aware of any outstanding issues from a toxicology standpoint that would preclude recommendation of approval for this drug.

7.2.4 Routine Clinical Testing

Overall, routine clinical and laboratory evaluations were adequate to assess the safety of MM-398 in the NAPOLI-1 trial. Refer to Section 5.3 that describes the laboratory schedule of assessments and Section 7.4.2 for details of hematology, chemistry, and other monitoring.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the clinical pharmacology review and sections 7.5.4 and 7.5.5 of this review.

No specific drug-disease interaction studies were conducted. The pharmacokinetics (PK) of irinotecan liposome have not been studied in patients with hepatic impairment, and patients with serum bilirubin above the upper limit of normal were to be excluded from the NAPOLI-1 trial. In a population PK analysis (refer to the clinical pharmacology review), patients with baseline serum bilirubin concentration of 1-2 mg/dL (n=19) had increased average steady-state concentrations of total SN-38 compared to patients with baseline bilirubin concentrations < 1 mg/dL (n=329); however, there was no effect of elevated AST/ALT concentrations on total SN-38 concentrations. Regarding patients with baseline serum bilirubin values of 1-2 mg/dL, note that for all patients in the NAPOLI-1 safety population the institutional reference range upper limit of normal value was 1.2 mg/dL, and that small numbers of patients within the above-specified range of values limited meaningful comparison with respect to safety data; refer to exposure-response information in the clinical pharmacology review. No PK data are available in patients with bilirubin > 2 mg/dL. In a population PK analysis, mild to moderate renal impairment had no effect on exposure of total SN-38 after adjusting for BSA, and there was insufficient data in patients with severe renal impairment (CrCl < 30 mL/min) to assess effect on PK of MM-398.

In a population PK analysis, the PK of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin. Following administration of non-

liposomal irinotecan (i.e., irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital, carbamazepine, or St. John's wort. Following administration of irinotecan HCl, dexamethasone, a moderate CYP3A4 inducer, does not alter the pharmacokinetics of irinotecan. Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. In vitro studies indicate that irinotecan, SN-38 and another metabolite, aminopentane carboxylic acid, do not inhibit cytochrome P-450 isozymes.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Refer to section 2.4 Important Safety Issues With Consideration to Related Drugs and section 7.3.5 Submission Specific Primary Safety Concerns.

7.3 Major Safety Results

7.3.1 Deaths

In the NAPOLI-1 trial, overall survival data was to be collected every 1 month after a patient completes the 30 day followup visit (see section 5.3 of this review and the NAPOLI-1 Schedule of Assessments). All patients were to be followed until death or study closure. Regarding AE reporting, all AEs that started after first administration of study drug through 30 days following the last dose of study drug were to be recorded.

Of the NAPOLI-1 safety population which consisted of 398 patients, there were 304 deaths reported through the date of data cutoff. The majority of these deaths were associated with progressive disease. Three patients in the 5FU/LV arm and 1 patient in the MM-398 arm were reported as having an unknown reason for death. For those with a reason for death other than progressive disease, the numbers of patients in most adverse event categories were small (one patient each), limiting meaningful comparison between treatment arms with respect to cause of death.

Of the 304 patient deaths in the safety population that were reported prior to data cutoff, most occurred more than 30 days after the last dose of study drug. For most of these patients the reason for death was reported as progression of disease.

Of the 304 deaths, 47 (12% of the safety analysis population) occurred within 30 days of the last dose of study drug. For these patients, narratives provided by the applicant and AE and other datasets, including laboratory results and exposure datasets, were

reviewed. Of the deaths with corresponding events in the AE datasets of Grade 5/fatal outcome, 10 occurred in the 5FU/LV arm, 15 occurred in the MM-398 arm, and 2 occurred in the MM-398/5FU/LV arm; fewer in each arm had AE listed as the reported reason for death (versus progressive disease) than had corresponding Grade 5/fatal outcome AE dataset events. One patient died of unknown cause.

Analysis of TEAEs of Grade 5/fatal outcome in the MM-398-containing arms in NAPOLI-1 is shown in the following table.

Table 14 Reviewer Analysis of TEAEs of Grade 5 / Fatal Outcome in NAPOLI-1 MM-398-containing Arms

Arm	Age/Sex	PT	Reviewer Comments
MM-398/5FU/LV	47/F	Dyspnea	Progressive Disease
MM-398/5FU/LV	80/M	Septic shock	Severe neutropenia, septic shock
MM-398	73/M	Suppurative cholangitis	Progressive Disease
MM-398	69/M	Respiratory failure	Dyspnea, leukocytosis, pleural effusion; taken home by family and passed away at home.
MM-398	66/M	Infectious enterocolitis	Abdominal pain, watery diarrhea, vomiting that began 17 days post last dose; not noted to be neutropenic
MM-398	53/M	Hyperkalemia	Hyperkalemia 31 days post first and only dose, multiple medical comorbidities
MM-398	79/M	General physical health deterioration	Progressive disease
MM-398	64/F	Pulmonary embolism, DIC	11 days post first and only dose; discharged from hospital the day prior after prolonged complicated course that began approximately 1 week prior to Cycle 1 Day 1
MM-398	70/F	Septic shock	Neutropenia, sepsis
MM-398	65/M	Metastases to lung	Progressive disease
MM-398	76/M	Gastrointestinal hemorrhage	GI bleed, pneumonia; 27 days post last dose
MM-398	48/M	Liver abscess, brain abscesses, meningitis, coma, sepsis	Abscesses noted to be related to separate abscess patient had prior to Cycle 1 Day1, which was 20 days prior to liver abscess and 36 days prior to brain abscess; seizures; not neutropenic
MM-398	66/M	Cerebrovascular accident	CVA/stroke
MM-398	76/F	Pneumoperitoneum	3 days post last dose, 25 days post first dose; minimal information available; abdominal pain; not noted to be neutropenic; history of tumor

			infiltration noted as causing gastroparesis; TPN; suspect progressive disease
MM-398	69/M	Acute prerenal failure	Progressive disease
MM-398	60/F	Respiratory failure	Progressive disease
MM-398	76/M	Gastrointestinal toxicity	Aspiration; 28 days post last dose; not neutropenic 5 days prior to death

Reviewer comment: Most deaths in the NAPOLI-1 trial, both overall deaths reported prior to data cutoff and those that occurred within 30 days of last dose of study drug, were attributed to progressive disease. Nonetheless, MM-398 can cause severe and life-threatening toxicity including neutropenia, and two deaths due to sepsis following neutropenia, one in each MM-398-containing arm, are highlighted in the above table; this information should be included (b) (4) in labeling, both in the Warnings and Precautions section and in the Boxed Warning.

7.3.2 Nonfatal Serious Adverse Events

In the NAPOLI-1 protocol, a serious adverse event (SAE) was defined (*in accordance with the ICH Good Clinical Practice Guideline*) as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient if may require intervention to prevent one of the other outcomes listed above

Per patient incidence of treatment-emergent SAEs across the arms of the NAPOLI-1 trial is shown in the table below.

Table 15 Treatment-Emergent Serious Adverse Events (per patient incidence)

	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
TEAEs	60 (45%)	90 (61%)	56 (48%)

The following table depicts the per patient incidence of treatment-emergent SAEs in either MM-398-containing arm, by MedDRA SOC.

Table 16 Treatment-Emergent SAEs by SOC

SOC	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (2%)	12 (8%)	7 (6%)
CARDIAC DISORDERS	1 (1%)	1 (1%)	0 (0%)
EAR AND LABYRINTH DISORDERS	1 (1%)	0 (0%)	0 (0%)
GASTROINTESTINAL DISORDERS	21 (16%)	45 (31%)	26 (22%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (6%)	11 (7%)	6 (5%)
HEPATOBIILIARY DISORDERS	7 (5%)	8 (5%)	4 (3%)
INFECTIONS AND INFESTATIONS	15 (11%)	22 (15%)	20 (17%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (1%)	0 (0%)	4 (3%)
INVESTIGATIONS	0 (0%)	1 (1%)	0 (0%)
METABOLISM AND NUTRITION DISORDERS	4 (3%)	14 (10%)	8 (7%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (2%)	0 (0%)	0 (0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (3%)	3 (2%)	0 (0%)
NERVOUS SYSTEM DISORDERS	3 (2%)	7 (5%)	3 (3%)
PSYCHIATRIC DISORDERS	0 (0%)	1 (1%)	0 (0%)
RENAL AND URINARY DISORDERS	4 (3%)	4 (3%)	2 (2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (4%)	8 (5%)	1 (1%)
VASCULAR DISORDERS	7 (5%)	2 (1%)	1 (1%)

Reviewer comment: There were higher rates of SAEs in the Gastrointestinal Disorders, Infections and Infestations, and Metabolism and Nutrition Disorders SOCs in the MM-398-containing arms, with the Metabolism and Nutrition Disorders events consisting primarily of the PTs decreased appetite and dehydration and PTs reflecting electrolyte derangements, likely resulting from diarrhea/dehydration.

The following table depicts the incidence of treatment-emergent SAEs with a per patient incidence >1% in either MM-398-containing arm, by MedDRA preferred term.

Table 17 Treatment-Emergent SAEs by PT (per patient incidence >1% in either MM-398-containing arm)

PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
DIARRHEA	2 (1%)	19 (13%)	7 (6%)
VOMITING	2 (1%)	14 (10%)	11 (9%)
ABDOMINAL PAIN	6 (4%)	6 (4%)	5 (4%)
PYREXIA	2 (1%)	5 (3%)	3 (3%)
NAUSEA	1 (1%)	5 (3%)	4 (3%)
FEBRILE NEUTROPENIA	1 (1%)	6 (4%)	2 (2%)
DEHYDRATION	2 (1%)	3 (2%)	3 (3%)
SEPSIS	1 (1%)	3 (2%)	4 (3%)
DECREASED APPETITE	1 (1%)	6 (4%)	1 (1%)
ABDOMINAL PAIN UPPER	1 (1%)	4 (3%)	1 (1%)
BILE DUCT OBSTRUCTION	2 (1%)	2 (1%)	2 (2%)
SEPTIC SHOCK	1 (1%)	3 (2%)	2 (2%)
ASTHENIA	1 (1%)	2 (1%)	2 (2%)
BILIARY TRACT INFECTION	2 (1%)	1 (1%)	2 (2%)
PNEUMONIA	1 (1%)	1 (1%)	3 (3%)
DEVICE RELATED INFECTION	0 (0%)	1 (1%)	3 (3%)
GASTROENTERITIS	0 (0%)	2 (1%)	2 (2%)
GENERAL PHYSICAL HEALTH DETERIORATION	1 (1%)	3 (2%)	0 (0%)
PULMONARY EMBOLISM	1 (1%)	3 (2%)	0 (0%)
GASTROINTESTINAL HEMORRHAGE	1 (1%)	1 (1%)	2 (2%)
ACUTE PRERENAL FAILURE	0 (0%)	1 (1%)	2 (2%)
SMALL INTESTINAL OBSTRUCTION	0 (0%)	3 (2%)	0 (0%)
PANCYTOPENIA	0 (0%)	0 (0%)	2 (2%)
DUODENAL ULCER	0 (0%)	0 (0%)	2 (2%)

Reviewer comment: The most frequently reported SAEs in the MM-398-containing arms as shown in the above table included diarrhea, vomiting, nausea, pyrexia, and febrile neutropenia; for each of these terms other than febrile neutropenia, a ≥2% difference in incidence was observed between the MM-398/5FU/LV arm and the 5FU/LV control arm. While this reviewer for this review elected to present rates of TESAEs by individual arm in the above table, the most common serious adverse reactions in MM-398-treated patients as a group are reflected in the proposed labeling, which adequately conveys the risks.

7.3.3 Dropouts and/or Discontinuations

The exposure dataset was used to analyze reported reasons for discontinuing study treatment; the results of this analysis are shown in the table below.

Table 18 Reasons for Study Treatment Discontinuation

	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
Progressive disease based on RECIST v1.1 criteria	83 (62%)	76 (52%)	58 (50%)
(missing) ¹	5 (4%)	3 (2%)	15 (13%)
Subject decision	9 (7%)	17 (12%)	13 (11%)
Clinical deterioration	17 (13%)	20 (14%)	13 (11%)
Adverse event	10 (7%)	16 (11%)	11 (9%)
Investigator decision	4 (3%)	6 (4%)	4 (3%)
Deceased	5 (4%)	9 (6%)	2 (2%)
Sponsor decision	0 (0%)	0 (0%)	1 (1%)
Other	1 (1%)	0 (0%)	0 (0%)

¹ Patients who were receiving study drug at the time of data cutoff

Reviewer comment: Most patients in each arm were reported as discontinuing study treatment due to disease progression; a higher proportion is noted in the 5FU/LV arm. Both in above table and based on analysis of the AE datasets, higher proportions of patients in the MM-398-containing arms discontinued study treatment due to adverse events.

Per patient incidence of treatment-emergent AEs that resulted in permanent discontinuation of study drug is shown in the table below across the arms of the NAPOLI-1 trial, and incidence by PT is shown in the table further below (for events with per patient incidence >1% in the MM-398/5FU/LV arm).

Table 19 Treatment-Emergent AEs Resulting in Permanent Discontinuation of Study Drug (per patient incidence)

	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
TEAEs	10 (7%)	17 (12%)	13 (11%)

Table 20 Treatment-Emergent AEs Resulting in Permanent Discontinuation of Study Drug, by PT (per patient incidence ≥1% in the MM-398/5FU/LV arm)

PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
ASCITES	0 (0%)	0 (0%)	2 (2%)
VOMITING	1 (1%)	3 (2%)	2 (2%)
DIARRHEA	0 (0%)	3 (2%)	2 (2%)
SEPSIS	1 (1%)	1 (1%)	2 (2%)
DEHYDRATION	1 (1%)	0 (0%)	1 (1%)
GRANULOCYTOPENIA	0 (0%)	0 (0%)	1 (1%)
GANGRENE	0 (0%)	0 (0%)	1 (1%)
DECREASED APPETITE	0 (0%)	0 (0%)	1 (1%)
BILIARY TRACT INFECTION	0 (0%)	0 (0%)	1 (1%)
CEREBROVASCULAR ACCIDENT	1 (1%)	1 (1%)	1 (1%)
ACUTE PRERENAL FAILURE	0 (0%)	0 (0%)	1 (1%)
ABDOMINAL PAIN	0 (0%)	0 (0%)	1 (1%)
NEUTROPENIA	0 (0%)	1 (1%)	1 (1%)
LEUKOPENIA	0 (0%)	1 (1%)	1 (1%)
PNEUMONIA	0 (0%)	0 (0%)	1 (1%)
INFECTIOUS PERITONITIS	0 (0%)	0 (0%)	1 (1%)
PELVIC FRACTURE	0 (0%)	0 (0%)	1 (1%)
SEPTIC SHOCK	0 (0%)	0 (0%)	1 (1%)

Reviewer comment: Both cases involving ascites leading to drug discontinuation in the MM-398/5FU/LV arm were reviewed; in both cases ascites was likely due to the patients' pancreatic cancer. While this reviewer for this review elected to present rates of TEAEs resulting in permanent discontinuation of study drug by individual arm in the above table, the most common adverse reactions that led to permanent discontinuation in MM-398-treated patients as a group are reflected in the proposed labeling, which adequately conveys the risks.

Per patient incidence of treatment-emergent AEs that led to dose reduction is shown in the table below across the arms of the NAPOLI-1 trial, and incidence by PT is shown in the table further below (for events with per patient incidence >1% in the MM-398/5FU/LV arm).

Table 21 Treatment-Emergent AEs Leading to Dose Reduction (per patient incidence)

	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
TEAEs	5 (4%)	46 (31%)	39 (33%)

Table 22 Treatment-Emergent AEs Leading to Dose Reduction, by PT (per patient incidence >1% in the MM-398/5FU/LV arm)

PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
NEUTROPENIA	0 (0%)	3 (2%)	10 (9%)
NEUTROPHIL COUNT DECREASED	0 (0%)	7 (5%)	8 (7%)
DIARRHEA	0 (0%)	17 (12%)	7 (6%)
WHITE BLOOD CELL COUNT DECREASED	0 (0%)	3 (2%)	6 (5%)
ANEMIA	0 (0%)	6 (4%)	4 (3%)
NAUSEA	0 (0%)	4 (3%)	4 (3%)
VOMITING	0 (0%)	9 (6%)	2 (2%)
FATIGUE	1 (1%)	1 (1%)	2 (2%)

The following table depicts the number of patients who underwent each of one or two dose reductions of MM-398, by treatment arm, based on analysis of NAPOLI-1 exposure datasets.

Table 23 Per Patient Incidence of Each of One or Two Dose Reductions of MM-398

Number of MM-398 Dose Reductions	MM-398 N=147	MM-398/5FU/LV N=117
1	51 (35%)	45 (38%)
2	15 (10%)	8 (7%)

Per patient incidence of treatment-emergent AEs that led to dose delay is shown in the table below across the arms of the NAPOLI-1 trial, and incidence by PT is shown in the table further below (for events with per patient incidence >1% in the MM-398/5FU/LV arm).

Table 24 Treatment-Emergent AEs Leading to Dose Delay (per patient incidence)

	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
TEAEs	43 (32%)	49 (33%)	73 (62%)

Table 25 Treatment-Emergent AEs Leading to Dose Delay, by PT (per patient incidence >1% in the MM-398/5FU/LV arm)

PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
NEUTROPENIA	3 (2%)	6 (4%)	17 (15%)
WHITE BLOOD CELL COUNT DECREASED	1 (1%)	1 (1%)	14 (12%)
NEUTROPHIL COUNT DECREASED	2 (1%)	6 (4%)	11 (9%)
DIARRHEA	4 (3%)	9 (6%)	9 (8%)
FATIGUE	1 (1%)	4 (3%)	8 (7%)
VOMITING	3 (2%)	4 (3%)	7 (6%)
LEUKOPENIA	1 (1%)	1 (1%)	7 (6%)
PLATELET COUNT DECREASED	1 (1%)	1 (1%)	6 (5%)
ASTHENIA	3 (2%)	4 (3%)	5 (4%)
ANEMIA	0 (0%)	1 (1%)	3 (3%)
NAUSEA	3 (2%)	1 (1%)	3 (3%)
FEBRILE NEUTROPENIA	0 (0%)	2 (1%)	3 (3%)
SEPSIS	0 (0%)	0 (0%)	2 (2%)
INFUSION RELATED REACTION	0 (0%)	0 (0%)	2 (2%)
THROMBOCYTOPENIA	0 (0%)	1 (1%)	2 (2%)
PYREXIA	4 (3%)	1 (1%)	2 (2%)
DUODENAL ULCER	0 (0%)	0 (0%)	2 (2%)
DEVICE RELATED INFECTION	0 (0%)	1 (1%)	2 (2%)
ABDOMINAL PAIN	2 (1%)	3 (2%)	2 (2%)
HYPOKALEMIA	1 (1%)	3 (2%)	2 (2%)

7.3.4 Significant Adverse Events

The ICH E3 Guidance considers potentially important abnormalities that do not meet the criteria of a serious adverse event (*refer to section 7.3.2 of this review*) to be potentially significant. The following is an analysis of ≥ Grade 3 (by CTCAE) adverse events, using

the MedDRA hierarchy of event terms. Further below is an analysis using Standardized MedDRA Queries (SMQs), conducted to assess for additional safety signals not identified through analyses using MedDRA hierarchy terms alone.

Refer to section 7.4.2 of this review for analysis of laboratory abnormalities.

Per patient incidence in the NAPOLI-1 trial of TEAEs \geq Grade 3 is shown in table below across the arms of the NAPOLI-1 trial, and incidence by PT is shown in the table further below (for events with a 2% or higher increased incidence in either MM-398-containing arm compared to the 5FU/LV arm).

Table 26 Treatment-Emergent AEs \geq Grade 3 (per patient incidence)

	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
TEAEs	75 (56%)	112 (76%)	90 (77%)

Table 27 Treatment-Emergent AEs \geq Grade 3, by PT (2% or greater increased incidence in either MM-398-containing arm compared to 5FU/LV)

PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
NEUTROPENIA	1 (1%)	8 (5%)	17 (15%)
FATIGUE	5 (4%)	9 (6%)	16 (14%)
DIARRHEA	6 (4%)	31 (21%)	15 (13%)
VOMITING	4 (3%)	20 (14%)	13 (11%)
NEUTROPHIL COUNT DECREASED	1 (1%)	12 (8%)	12 (10%)
ANEMIA	9 (7%)	16 (11%)	11 (9%)
NAUSEA	4 (3%)	8 (5%)	9 (8%)
WHITE BLOOD CELL COUNT DECREASED	0 (0%)	4 (3%)	9 (8%)
ABDOMINAL PAIN	8 (6%)	12 (8%)	8 (7%)
DECREASED APPETITE	3 (2%)	13 (9%)	5 (4%)
DEHYDRATION	2 (1%)	5 (3%)	5 (4%)
HYPOKALEMIA	3 (2%)	17 (12%)	4 (3%)
SEPSIS	1 (1%)	3 (2%)	4 (3%)
HYPONATREMIA	2 (1%)	9 (6%)	3 (3%)
DEVICE RELATED INFECTION	0 (0%)	2 (1%)	3 (3%)
STOMATITIS	1 (1%)	0 (0%)	3 (3%)
BILIARY TRACT INFECTION	2 (1%)	1 (1%)	3 (3%)
GASTROENTERITIS	0 (0%)	1 (1%)	3 (3%)

PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
FEBRILE NEUTROPENIA	0 (0%)	6 (4%)	2 (2%)
HYPOTENSION	0 (0%)	1 (1%)	2 (2%)
MUCOSAL INFLAMMATION	0 (0%)	0 (0%)	2 (2%)
LYMPHOPENIA	0 (0%)	2 (1%)	2 (2%)
WEIGHT DECREASED	0 (0%)	2 (1%)	2 (2%)
ASCITES	2 (1%)	5 (3%)	2 (2%)
GAMMA- GLUTAMYLTRANSFERASE INCREASED	2 (1%)	4 (3%)	2 (2%)
PANCYTOPENIA	0 (0%)	0 (0%)	2 (2%)
DIABETES MELLITUS	0 (0%)	0 (0%)	2 (2%)
HYPERGLYCEMIA	3 (2%)	8 (5%)	1 (1%)
LEUKOPENIA	0 (0%)	4 (3%)	1 (1%)
HYPOALBUMINEMIA	0 (0%)	4 (3%)	1 (1%)
BLOOD BILIRUBIN INCREASED	0 (0%)	3 (2%)	1 (1%)
ABDOMINAL PAIN UPPER	0 (0%)	3 (2%)	0 (0%)
GENERAL PHYSICAL HEALTH DETERIORATION	0 (0%)	5 (3%)	0 (0%)
HYPOGLYCEMIA	0 (0%)	4 (3%)	0 (0%)
INTERNATIONAL NORMALIZED RATIO INCREASED	0 (0%)	3 (2%)	0 (0%)
RENAL FAILURE ACUTE	0 (0%)	3 (2%)	0 (0%)
HYPOMAGNESEMIA	1 (1%)	4 (3%)	0 (0%)

Reviewer comment:

Grade 3 or higher adverse events with a 2% or higher increased incidence in the MM-398/5FU/LV arm compared to the 5FU/LV control were recommended for inclusion in the labeling, also noting that the MM-398/5FU/LV regimen is that which is proposed in this application. Terms reflecting laboratory abnormalities better described using laboratory test results were recommended for inclusion based on laboratory-detected rates. The preferred terms fatigue and asthenia (asthenia was not shown in the table above as the specified criteria for inclusion in the table were not met) were pooled for inclusion in the label. The applicant chose to include incidence rates for neutropenia that were based on a composite analysis combining several preferred terms. This analysis of neutropenia was acceptable; refer to section 7.3.5 of this review for further detail regarding neutropenia and the applicant's analysis. Similarly the applicant chose to include in adverse reactions in the product labeling a composite term 'neutropenic fever/neutropenic sepsis,' also an acceptable analysis and in which the preferred terms

febrile neutropenia and neutropenic sepsis were combined, and a composite for stomatitis consisting of several preferred terms such as mucosal inflammation and stomatitis, also acceptable. For diarrhea, total incidence rates above were included in the labeling and separate incidence rates for early and for late diarrhea were also included, as can be seen in the Camptosar package insert and as is consistent with the distinct mechanisms involved in the two forms of diarrhea observed with MM-398 (and commonly described with Camptosar); refer to section 7.5.3 of this review for further detail regarding diarrhea.

Narrow-scope MedDRA SMQs (NSMQs) were analyzed for the NAPOLI-1 trial, comparing the MM-398/5FU/LV arm to the 5FU/LV control. The following table shows results with an odds ratio greater than 1.0 and p-value less than 0.04; p-values in this section are used for ranking purposes only and are not a measure of statistical significance.

Table 28 Per Patient Incidence of AEs by Narrow-Scope SMQ (MM-398/5FU/LV vs. 5FU/LV; NAPOLI-1)

NSMQ	MM-398/5FU/LV		5FU/LV		OR	p-value
	N=117	%	N=134	%		
(2) Hematopoietic leukopenia	52	44.44	11	8.21	8.945	3E-11
(1) Hematopoietic cytopenias	57	48.72	19	14.18	5.75	0.000000004
(1) Oropharyngeal disorders *	39	33.33	20	14.93	2.85	0.00093
(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic *	32	27.35	15	11.19	2.987	0.001
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	107	91.45	104	77.61	3.087	0.003
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	107	91.45	105	78.36	2.955	0.005
(1) Agranulocytosis	7	5.98	1	0.75	8.464	0.027

* After SMQ name indicates SMQ with narrow terms only. Broad search will yield the same results.

Reviewer comment:

The NSMQ terms ‘hematopoietic leukopenia,’ ‘hematopoietic cytopenias,’ and ‘agranulocytosis’ encompass the adverse reaction neutropenia which is described above and below in section 7.3.5 of this review; the proposed labeling includes severe neutropenia as a warning and boxed warning. The NSMQ agranulocytosis includes the PTs agranulocytosis, febrile neutropenia, neutropenic sepsis, pancytopenia, sepsis, and septic shock; these terms are included in the composite analysis for neutropenia that is

included in the labeling in section 6 (with laboratory abnormalities for this adverse reaction also included in a separate table), with the exception of the PT septic shock for which there was one Grade 3-4 event in the MM-398/5FU/LV arm compared to no Grade 3-4 events in the 5FU/LV arm. There was one Grade 5 event in the MM-398/5FU/LV arm (the fatal event of neutropenic sepsis specifically described in the warning regarding neutropenia) and one Grade 5 event in the 5FU/LV arm. The majority of 'oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic' is comprised of the PTs stomatitis and mouth ulceration (21% of patients in the MM398/5FU/LV arm compared to 8% in the 5FU/LV arm), which are PTs that were included in the composite analysis used to describe stomatitis in section 6 of the proposed labeling, which was acceptable. Other PTs under the nonspecific SMQ were disparate, for example 'geographic tongue.' 'Gastrointestinal nonspecific symptoms and therapeutic procedures' is nonspecific and included diarrhea, nausea, and vomiting.

7.3.5 Submission Specific Primary Safety Concerns

The applicant defined adverse events of special interest based on the known profile of MM-398 to date and on the Camptosar labeling. The applicant described that some analyses were based on groupings of MedDRA PTs used in the Camptosar label.

Neutropenia and neutropenic fever/neutropenic sepsis

The applicant analyzed neutropenia using a "product-specific" query, or grouping of MedDRA PTs, that was a subset of the myelosuppression SMQ.

Reviewer comment: This analysis was acceptable and used the PTs agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, neutrophil count decreased, and pancytopenia. This reviewer additionally recommended the inclusion of the laboratory-detected rates of neutropenia in NAPOLI-1 to provide more complete information regarding neutropenia.

The applicant reported that for the MM-398/5FU/LV arm, mean absolute neutrophil count reached its lowest level on Day 15 of a cycle and remained below baseline in almost all subsequent assessments.

The applicant also analyzed neutropenic fever and neutropenic sepsis together, which this reviewer deemed acceptable and encompassing of a single concept (though recommended revision (b) (4) to state the two separate PTs fully, though together). Additionally, the applicant analyzed a group of PTs the applicant stated were medically consistent with sepsis or bacteremia and occurred in at least one patient in either arm (the terms for this analysis were bacteremia, biliary sepsis, Campylobacter sepsis, Escherichia bacteremia, Escherichia sepsis, neutropenic sepsis, Pseudomonas sepsis, sepsis, septic shock, and urosepsis). The applicant reported that 7.7% of patients in the MM-398/5FU/LV arm experienced

such events compared to 6 % of patients in the 5FU/LV arm (with the rates for ≥ Grade 3 events being 6% compared to 4.5%, respectively).

This reviewer conducted an analysis of Grade 4 events within the Infections and Infestations SOC to further analyze sepsis or cases potentially meeting criteria for sepsis; this analysis is depicted in the table below.

Table 29 Grade 4 Events Within the Infections and Infestations SOC (per patient incidence)

SOC	PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
INFECTIONS AND INFESTATIONS	CHOLANGITIS SUPPURATIVE	1 (1%)	0 (0%)	0 (0%)
	ESCHERICHIA SEPSIS	1 (1%)	0 (0%)	0 (0%)
	PSEUDOMONAL SEPSIS	1 (1%)	0 (0%)	0 (0%)
	SEPSIS	0 (0%)	1 (1%)	1 (1%)

Reviewer comment: The three events other than covered by the term sepsis occurred in the 5FU/LV arm, not an MM-398-containing arm.

In the NAPOLI-1 trial, the use of G-CSF to treat patients with neutropenia or neutropenic fever was permitted. The following table depicts per patient incidence by arm of patients who received colony stimulating factors on study, based on analysis of the concomitant medications datasets. *Note the applicant reported in Module 2 that 11.6% of patients in the MM-398/5FU/LV arm received neutrophil growth factors, and in Module 5 reported 17%.*

Table 30 Per Patient Incidence of Colony Stimulating Factor Use

	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
Use of Colony Stimulating Factors	3 (2%)	17 (12%)	22 (19%)

Diarrhea

Diarrhea occurred in 59% of patients in the MM-398/5FU/LV arm compared to 26% of patients in the 5FU/LV arm, with Grade 3-4 diarrhea occurring in 13% compared to 4%,

respectively. Diarrhea is described in the proposed labeling as occurring in one of two patterns, early onset or late onset (a patient may experience both forms within a treatment cycle), as in the Camptosar labeling. Early onset was defined (as in the Camptosar labeling) as onset within 24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction. Late onset was defined as onset more than 24 hours following chemotherapy. Thirty percent of patients in the MM-398/5FU/LV arm experienced early onset diarrhea, compared to 15% in the 5FU/LV arm. Late onset diarrhea occurred in 43% of patients in the MM-398/5FU/LV arm compared to 17% of patients in the 5FU/LV arm. The applicant reported that more patients in the MM-398/5FU/LV arm experienced diarrhea, both total or early or late onset, in the first six weeks of treatment, compared to later. Of patients receiving MM-398/5FU/LV in NAPOLI-1, 34% received loperamide and 26% received atropine. Less than 3% received a fluoroquinolone (despite the diarrhea management guidelines included in the NAPOLI-1 protocol) and less than 3% received other systemic antibiotic (not a fluoroquinolone).

Reviewer comment: The language regarding (b) (4) in the proposed labeling was removed (b) (4)

Stomatitis

The applicant analyzed stomatitis using a query based on a grouping of MedDRA PTs which this reviewer identified as encompassed the HLT stomatitis and ulceration. This included the PTs aphthous stomatitis, mouth ulceration, mucosal inflammation, and stomatitis. This reviewer analyzed all PTs occurring in the trial and deemed this grouping of terms encompassing and appropriate to convey risk of stomatitis.

Reviewer comment: The results of this composite term analysis for stomatitis are included in the labeling (in the adverse reactions table) (b) (4) and it is recommended that this composite term analysis be retained.

Cholinergic events

The applicant analyzed cholinergic events as defined in the Camptosar label, which was acceptable. The Camptosar label describes that early diarrhea may be accompanied by other cholinergic symptoms and lists rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping, which is an adequate listing. Thus-defined cholinergic events excluding diarrhea occurred in 12 patients in the MM-398-containing arms of NAPOLI-1. The events were Grade 1-2 and included the PTs anxiety, cholinergic syndrome, flushing, and lethargy. Six of the 12 patients received atropine (as recommended in the protocol and the Camptosar label); in 5 of the 6 patients, the atropine was not administered for diarrhea.

Reviewer comment: This reviewer believes that given the nature of the events included above, such as miosis or lacrimation, and particularly if occurring with diarrhea, it is possible that these events may have occurred at higher incidence but were not reported, and they were not otherwise captured in the trial. This reviewer also believes it is likely that most such events would occur in conjunction with diarrhea, and that atropine should be considered even for non-severe events without diarrhea given the well-characterized cholinergic mechanism.

Acute renal failure

The applicant analyzed acute renal failure based on the acute renal failure SMQ. This SMQ is defined by the PTs acute prerenal failure, anuria, blood creatinine increased, proteinuria, renal failure acute, renal impairment, and urine output decreased. *This was an acceptable method of analysis.* There was an incidence of 5% in each of the MM-398/5FU/LV arm and the 5FU/LV arm, with one \geq Grade 3 event in the 5FU/LV arm (and none in the MM-398/5FU/LV arm).

Reviewer comment: While there is a warning in the Camptosar label regarding acute renal failure related to hypovolemia secondary to diarrhea/vomiting, the incidence rates are the same in the two relevant arms of the NAPOLI-1 trial, and diarrhea and vomiting are included in the labeling; therefore, acute renal failure does not meet criteria for inclusion in the current product labeling, based on this data at this time.

Infusion-associated reaction

The applicant analyzed this (b) (4) (infusion-associated reaction) based on a subset of infusion-associated reaction which occurred on the day of study drug administration, with infusion-associated reaction defined by the hypersensitivity SMQ. Preferred terms or verbatim terms (identified upon further case review) occurring in the MM-398-containing arms included infusion-related reaction, urticaria, periorbital edema, pruritus, allergic reaction, and rash, with an overall incidence of 3% in patients who received MM-398 in the NAPOLI-1 trial (both arms). All were reported as Grade 1-2 events.

Reviewer comment: Upon review of cases, this reviewer agrees with inclusion of this term in the labeling ((b) (4) to include specific events/symptoms observed). This reviewer did not agree (b) (4)

Based on literature reports, it is possible that liposomal drug formulations may convey risk of infusion-related reaction that could involve a mechanism directed against the liposome. The package insert for Doxil (which is a liposomal drug formulation) carries a boxed warning regarding acute infusion associated reaction. Also based on the Grade 1-2 hypersensitivity events observed in NAPOLI-1 with MM-398, the contraindication (b) (4) was revised to contraindicate MM-398 (b) (4) in the event of severe hypersensitivity (b) (4)

Interstitial lung disease (ILD)

The applicant analyzed for pulmonary toxicity based on the ILD SMQ. ILD-like events have been reported in patients receiving Camptosar. Two patients in the MM-398 arm had pneumonitis reported by PT; there were no other occurrences of the term in the trial.

Reviewer comment: Upon case review, neither was consistent with ILD or ILD-like event. One patient had symptomatic progression of multiple lung metastases and the other patient had pneumonitis pre-existing, or from prior to beginning on study.

Premedication

The applicant's proposed labeling included recommendations for premedication for MM-398 with a corticosteroid and (b) (4) antiemetic). Based on analysis of the concomitant medications datasets for NAPOLI-1, 68% of patients in the MM-398/5FU/LV arm received an antiemetic/antinauseant for prophylaxis, on the day of the first MM-398 dose, 50% similarly received dexamethasone, and 67% a 5HT3 antagonist.

Reviewer comment: While additional information as to first cycle incidence of nausea or vomiting in patients who received antiemetic/antinauseant compared to those who did not would be useful, this reviewer agrees with the recommendation proposed by the applicant based on the number of patients shown in the analysis above, who received the premedication in the MM-398/5FU/LV arm and the resulting rates of nausea/vomiting observed.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The safety database for the NAPOLI-1 trial was analyzed at each level of the MedDRA hierarchy for common adverse events. The following table shows per patient incidence of treatment-emergent AEs in the NAPOLI-1 trial, across treatment arms. Almost all patients in each treatment group experienced at least one TEAE.

Table 31 Per Patient Incidence of Treatment-Emergent AEs

	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
TEAEs	132 (99%)	145 (99%)	116 (99%)

The most common AEs that occurred in the MM-398/5-FU/LV arm (>10%), as described by PTs, were diarrhea, vomiting, nausea, decreased appetite, fatigue, anemia, neutropenia, pyrexia, abdominal pain, constipation, asthenia, weight decreased, neutrophil count decreased, white blood cell count decreased, alopecia, stomatitis, dizziness, back pain, hypokalemia, and peripheral edema.

The table below shows AEs reported at per patient incidence more than 5% in the MM-398/5FU/LV arm of the NAPOLI-1 trial, by PT.

Table 32 Treatment-Emergent AEs, by PT (per patient incidence >5% in MM-398/5FU/LV arm)

PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
DIARRHEA	35 (26%)	103 (70%)	69 (59%)
VOMITING	35 (26%)	80 (54%)	61 (52%)
NAUSEA	46 (34%)	89 (61%)	60 (51%)
DECREASED APPETITE	43 (32%)	72 (49%)	52 (44%)
FATIGUE	37 (28%)	54 (37%)	47 (40%)
ANEMIA	31 (23%)	48 (33%)	44 (38%)
NEUTROPENIA	4 (3%)	22 (15%)	27 (23%)
PYREXIA	15 (11%)	29 (20%)	27 (23%)
ABDOMINAL PAIN	42 (31%)	50 (34%)	27 (23%)
CONSTIPATION	32 (24%)	26 (18%)	26 (22%)
ASTHENIA	22 (16%)	35 (24%)	24 (21%)
WEIGHT DECREASED	9 (7%)	29 (20%)	20 (17%)
NEUTROPHIL COUNT DECREASED	2 (1%)	15 (10%)	17 (15%)
WHITE BLOOD CELL COUNT DECREASED	2 (1%)	10 (7%)	17 (15%)
ALOPECIA	6 (4%)	32 (22%)	16 (14%)
STOMATITIS	8 (6%)	5 (3%)	16 (14%)
DIZZINESS	13 (10%)	17 (12%)	15 (13%)
BACK PAIN	16 (12%)	12 (8%)	15 (13%)
HYPOKALEMIA	12 (9%)	32 (22%)	14 (12%)
EDEMA PERIPHERAL	20 (15%)	28 (19%)	13 (11%)
LEUKOPENIA	1 (1%)	6 (4%)	12 (10%)
PLATELET COUNT DECREASED	3 (2%)	3 (2%)	12 (10%)
MUCOSAL INFLAMMATION	5 (4%)	8 (5%)	12 (10%)
ABDOMINAL PAIN UPPER	10 (7%)	17 (12%)	11 (9%)
ABDOMINAL DISTENSION	8 (6%)	12 (8%)	10 (9%)
INSOMNIA	5 (4%)	12 (8%)	9 (8%)

PT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
DYSPNEA	6 (4%)	11 (7%)	9 (8%)
DEHYDRATION	9 (7%)	15 (10%)	9 (8%)
ALANINE AMINOTRANSFERASE INCREASED	2 (1%)	5 (3%)	8 (7%)
MOUTH ULCERATION	3 (2%)	6 (4%)	8 (7%)
HYPOTENSION	2 (1%)	6 (4%)	7 (6%)
HYPOMAGNESEMIA	5 (4%)	20 (14%)	7 (6%)
HYPOALBUMINEMIA	8 (6%)	19 (13%)	7 (6%)

Reviewer comment:

For all AEs, events occurring at 5% or greater increased incidence in the MM-398/5FU/LV arm compared to the 5FU/LV arm were recommended for inclusion in the label, also noting that the MM-398/5FU/LV regimen is that which is proposed in this application. Terms reflecting laboratory abnormalities better described using laboratory test results were recommended for inclusion based on laboratory-detected rates. The preferred terms fatigue and asthenia (asthenia was not shown in the table above as the specified criteria for inclusion in the table were not met) were pooled for inclusion in the label. The applicant chose to include incidence rates for neutropenia that were based on a composite analysis combining several preferred terms. This analysis of neutropenia was acceptable; refer to section 7.3.5 of this review for further detail regarding neutropenia and the applicant's analysis. Similarly the applicant chose to include in adverse reactions in the product labeling a composite term for stomatitis consisting of several preferred terms such as mucosal inflammation and stomatitis, also an acceptable analysis; this reviewer analyzed all preferred terms reported in the trial to verify that the applicant's analysis encompassed all terms that would be appropriate. For diarrhea, total incidence rates above were included in the labeling and separate incidence rates for early and for late diarrhea were also included, as can be seen in the Camptosar package insert and as is consistent with the distinct mechanisms involved in the two forms of diarrhea observed with MM-398 (and commonly described with Camptosar); refer to section 7.5.3 of this review for further detail regarding diarrhea. The adverse reactions table in the proposed labeling further organized events by MedDRA SOC.

The table below shows AEs reported at per patient incidence more than 10% in the MM-398/5FU/LV arm of the NAPOLI-1 trial, by MedDRA high level term (HLT).

Table 33 Treatment-Emergent AEs, by HLT (per patient incidence >10% in MM-398/5FU/LV arm)

HLT	5FU/LV N=134	MM-398 N=147	MM-398/5FU/LV N=117
NAUSEA AND VOMITING SYMPTOMS	59 (44%)	110 (75%)	86 (74%)
DIARRHEA (EXCL INFECTIVE)	35 (26%)	104 (71%)	69 (59%)
ASTHENIC CONDITIONS	67 (50%)	88 (60%)	68 (58%)
APPETITE DISORDERS	47 (35%)	74 (50%)	56 (48%)
ANEMIAS NEC	34 (25%)	54 (37%)	46 (39%)
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	57 (43%)	65 (44%)	40 (34%)
GASTROINTESTINAL ATONIC AND HYPOMOTILITY DISORDERS NEC	37 (28%)	32 (22%)	34 (29%)
FEBRILE DISORDERS	17 (13%)	32 (22%)	29 (25%)
NEUTROPENIAS	6 (4%)	26 (18%)	28 (24%)
STOMATITIS AND ULCERATION	11 (8%)	11 (7%)	26 (22%)
WHITE BLOOD CELL ANALYSES	7 (5%)	21 (14%)	24 (21%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE PAIN AND DISCOMFORT	33 (25%)	22 (15%)	22 (19%)
PHYSICAL EXAMINATION PROCEDURES	13 (10%)	30 (20%)	22 (19%)
ALOPECIAS	6 (4%)	34 (23%)	16 (14%)
EDEMA NEC	24 (18%)	34 (23%)	16 (14%)
POTASSIUM IMBALANCE	14 (10%)	34 (23%)	16 (14%)
LIVER FUNCTION ANALYSES	10 (7%)	16 (11%)	15 (13%)
NEUROLOGICAL SIGNS AND SYMPTOMS NEC	14 (10%)	18 (12%)	15 (13%)
LEUKOPENIAS NEC	1 (1%)	8 (5%)	14 (12%)

Reviewer comment: This reviewer analyzed further the HLTs in the above table that occurred at more than 5% increased incidence (highlighted rows) in the MM-398/5FU/LV arm compared to the 5FU/LV arm.

- **NAUSEA AND VOMITING SYMPTOMS:** This is the HLT that occurred with greatest incidence in the MM-398/5FU/LV arm. This HLT was comprised of the PTs nausea, vomiting, and regurgitation (regurgitation occurred in one patient, who was in the 5FU/LV arm). Nausea and vomiting are more specific and are included in the labeling.
- **DIARRHEA (EXCL INFECTIVE):** This HLT is consists of the PT diarrhea, which is included in the labeling.
- **ASTHENIC CONDITIONS:** This HLT is comprised of the PTs fatigue and asthenia, which were combined in the labeling (see reviewer comment above the table).
- **APPETITE DISORDERS:** This HLT is primarily the PT decreased appetite which is included in the labeling. The other PT in the HLT, hypophagia, was reported in 1% of patients in the trial.
- **ANEMIAS NEC:** This HLT consists primarily of the PT anemia, which is included in the labeling (see reviewer comment above the table; anemia was included as described by laboratory-detected rates). The other PT, hemorrhagic anemia, occurred in one patient in the trial.
- **FEBRILE DISORDERS:** This HLT consists of the PT pyrexia, which is more specific and is included in the labeling.
- **NEUTROPENIAS:** This HLT is comprised of the PTs agranulocytosis, febrile neutropenia, granulocytopenia, and neutropenia, which are included in the labeling based on composite analyses incorporating these terms more specifically, as described in the reviewer comment above the table and in section 7.3.5 of this review.
- **STOMATITIS AND ULCERATION:** This HLT is primarily comprised of the PTs stomatitis and mouth ulceration, which are included in the labeling using a composite term for stomatitis that includes both PTs and other PTs (see reviewer comment above the table). The other PT in the HLT, aphthous stomatitis, was reported in 2 patients in the trial.
- **WHITE BLOOD CELL ANALYSES:** This HLT is comprised of WBC count increased, eosinophil count decreased, lymphocyte count decreased, and (primarily) neutrophil count decreased and WBC count decreased; neutropenia is specifically described in the labeling using both a composite of PTs and using laboratory-detected rates (see reviewer comment above the table).

- **PHYSICAL EXAMINATION PROCEDURES:** This HLT is primarily comprised of weight decreased, which is specifically described in the labeling. Other PTs were weight increased, skin turgor increased, and nutritional condition abnormal, unrelated terms, each of which occurred in 1% or fewer patients in the trial.
- **ALOPECIAS:** This HLT consists of the PT alopecia which is included in the labeling.
- **LIVER FUNCTION ANALYSES:** This HLT is primarily comprised of the PT ALT increased, which is included in the labeling as described by laboratory-detected rates. Other PTs occurred in 5 or fewer patients in the MM-398/5FU/LV arm and occurred at equal or higher incidence in the 5FU/LV arm (with the exception of 'hepatic enzyme increased' which was reported in one patient, who was in the MM-398/5FU/LV arm).
- **LEUKOPENIAS NEC:** This HLT is comprised primarily of the PT leukopenia, which is described more specifically in the label as the adverse reaction neutropenia.

Reviewer comment:

(b) (4)

7.4.2 Laboratory Findings

Serum chemistry and hematology parameters were measured in NAPOLI-1 according the Schedule of Assessments for each treatment arm; refer to section 5.3 of this review. For the 5FU/LV arm, measurements were to occur on Days 1, 8, 15, 22, and 29 of each (6-week) cycle. For the MM-398/5FU/LV arm, measurements were to occur on Days 1

and 8 of each (2-week) cycle, with the exception of every third cycle when measurements were to occur only on Day 1 (and not Day 8).

Laboratory-detected parameters were analyzed by worst grade experienced by a patient on the trial. Only patients with a baseline and at least one post-baseline measurement were included and percentages are expressed accordingly. The incidence of laboratory-detected abnormalities by worst grade is shown in the table below.

Reviewer comment: Laboratory abnormalities with 5% or higher increased incidence in the MM-398/5FU/LV arm compared to the 5FU/LV arm were recommended for inclusion in the labeling. Also including Grade 3-4 abnormalities with 5% or greater increased incidence in the MM-398/5FU/LV arm compared to the 5FU/LV arm did not result in the inclusion of additional terms. This reviewer for this review elected to present incidence per Grade per laboratory abnormality; in the labeling the incidence is presented for CTCAE Grades grouped, which is acceptable. Cytopenias are a result of the myelosuppression with MM-398 that is described elsewhere in the labeling, and electrolyte derangements were likely related to diarrhea and/or vomiting. Hepatic function parameters should be interpreted with caution in this population of patients with pancreatic cancer, due to frequent liver involvement and frequent biliary involvement/obstruction, due to the cancer, which can alter hepatic function. For the same reasons, due to the population of patients with pancreatic cancer studied in this trial, the graph further below depicting possible Hy's Law cases should similarly be interpreted with caution.

Table 34 Incidence of Hematologic Laboratory-detected Abnormalities by Worst Grade During Treatment

Laboratory Test	5FU/LV N=134 %	MM- 398/5FU/LV N=117 %
Decreased neutrophils		
N	133	114
Gr 1-4	6	52
Gr 1	3	11
Gr 2	1	20
Gr 3	2	16
Gr 4	0	4
Decreased platelets		
N	133	115
Gr 1-4	33	41
Gr 1	32	36
Gr 2	2	4
Gr 3	0	2
Gr 4	0	0
Decreased hemoglobin		
N	133	115
Gr 1-4	86	97
Gr 1	50	49
Gr 2	32	42
Gr 3	5	6
Gr 4	0	0
Decreased lymphocytes		
N	133	113
Gr 1-4	75	81
Gr 1	32	23
Gr 2	26	30
Gr 3	13	26
Gr 4	5	2

Table 35 Incidence of Non-Hematologic Laboratory-detected Abnormalities by Worst Grade During Treatment

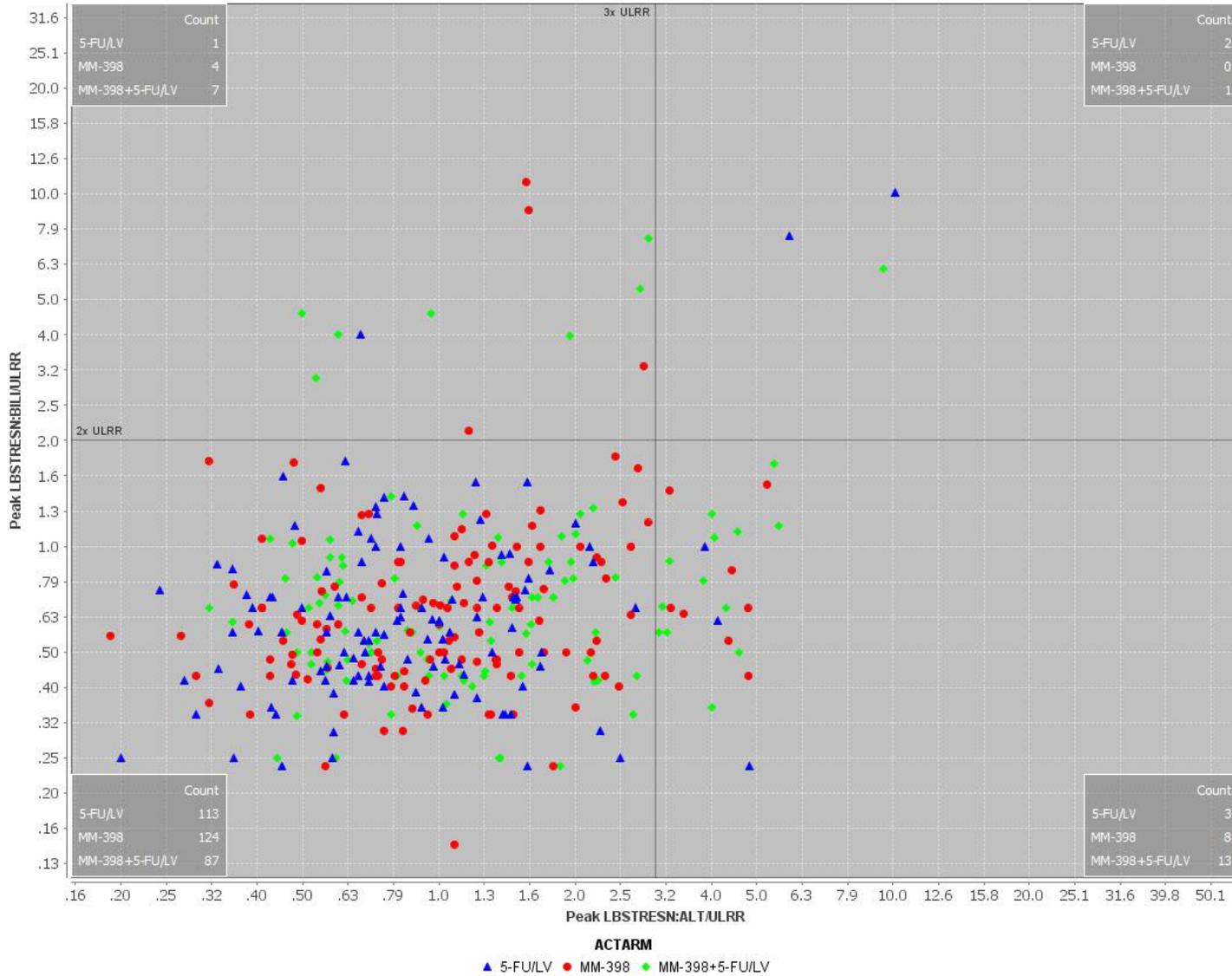
Laboratory Test	5FU/LV N=134 %	MM- 398/5FU/LV N=117 %
Decreased sodium		
N	125	112
Gr 1-4	12	27
Gr 1	9	22
Gr 2	0	0
Gr 3	3	5
Gr 4	0	0
Decreased potassium		
N	124	109
Gr 1-4	19	32
Gr 1	16	30
Gr 2	0	0
Gr 3	2	1
Gr 4	0	1
Decreased calcium		
N	125	112
Gr 1-4	20	32
Gr 1	19	27
Gr 2	1	5
Gr 3	0	0
Gr 4	0	1
Decreased albumin		
N	125	112
Gr 1-4	30	43
Gr 1	19	24
Gr 2	11	17
Gr 3	0	2
Gr 4	0	0
Decreased phosphate		
N	125	112
Gr 1-4	18	29
Gr 1	6	2
Gr 2	12	22
Gr 3	1	4
Gr 4	0	1
Decreased magnesium		

Laboratory Test	5FU/LV N=134 %	MM- 398/5FU/LV N=117 %
N	126	112
Gr 1-4	21	35
Gr 1	19	32
Gr 2	2	3
Gr 3	0	0
Gr 4	0	0
Increased ALT		
N	122	109
Gr 1-4	37	51
Gr 1	31	39
Gr 2	5	6
Gr 3	1	6
Gr 4	0	0
Increased AST		
N	122	108
Gr 1-4	38	39
Gr 1	32	31
Gr 2	4	6
Gr 3	2	3
Gr 4	0	0
Increased bilirubin		
N	124	112
Gr 1-4	20	16
Gr 1	12	10
Gr 2	7	3
Gr 3	1	4
Gr 4	1	0
Increased alkaline phosphatase		
N	125	112
Gr 1-4	66	70
Gr 1	38	43
Gr 2	21	18
Gr 3	7	9
Gr 4	0	0
Increased creatinine		
N	126	112
Gr 1-4	13	18
Gr 1	10	13

Laboratory Test	5FU/LV N=134 %	MM- 398/5FU/LV N=117 %
Gr 2	2	5
Gr 3	0	0
Gr 4	0	0
Increased urate		
N	125	112
Gr 1-4	6	8
Gr 1	4	8
Gr 2	0	0
Gr 3	2	0
Gr 4	0	0

Figure 11 Plot Depicting Possible Hy's Law Cases (ALT/bilirubin)

FDA.742.0501pBL Hys Law Plot: Post BL ALT/BILI/ALP Filter ^ - Subset of patients



Patient Selection Criteria: Exposure.Safety Population Flag =Y

Output Filter: LB*SAS*.Lab Test or Examination Short Name =ALP AND LB*SAS*.Numeric Result/Finding in Standard Units <LB*SAS*.Reference Range 2x Upper Limit-Std Units AND LB*SAS*.S

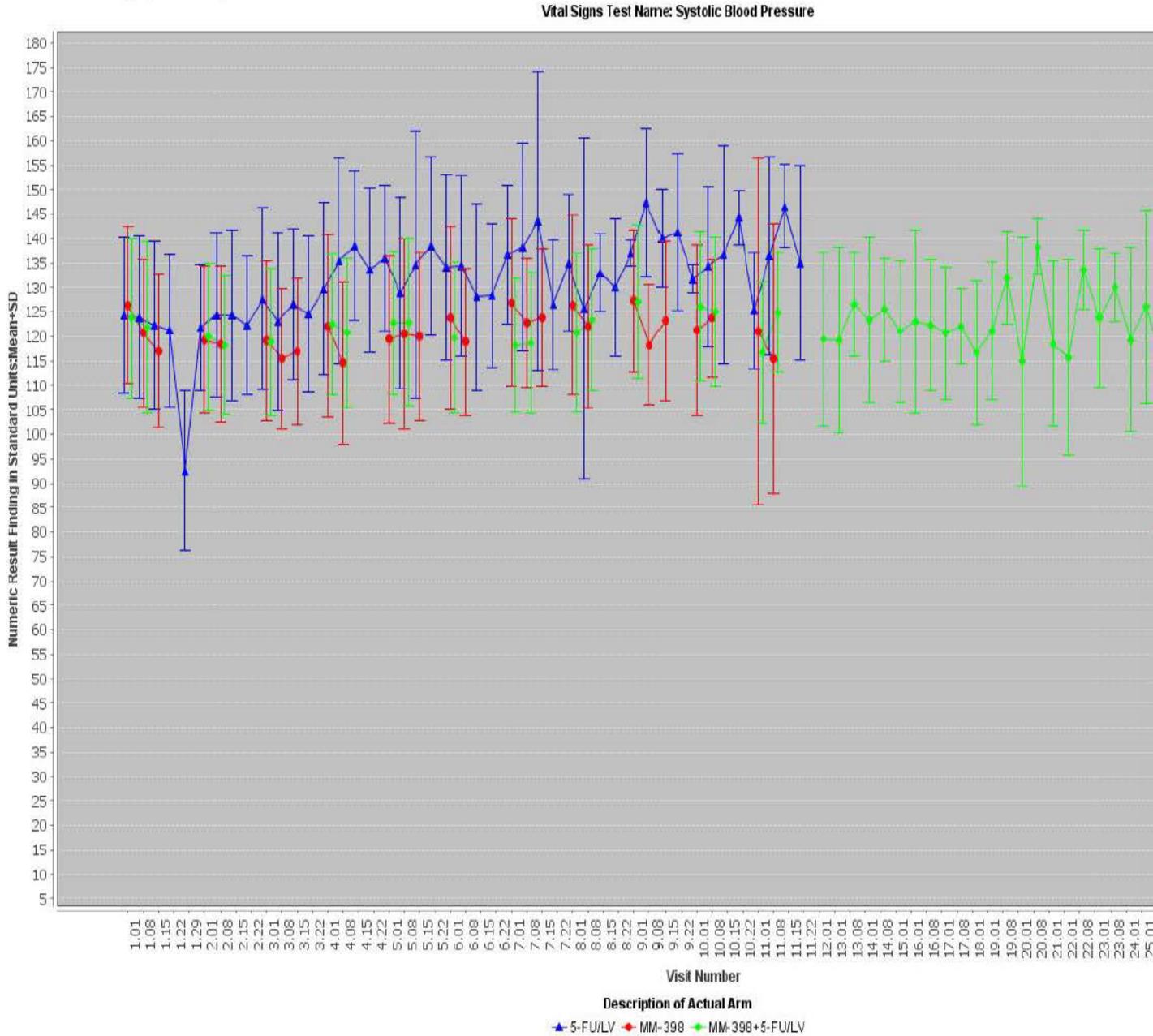
7.4.3 Vital Signs

In addition to at the screening and 30 day followup visits, vital signs were measured in the MM-398/5FU/LV arm of NAPOLI-1 on Days 1 and 8 of every cycle, other than every third cycle when vital signs were measured on Day 1. In the 5FU/LV arm of NAPOLI-1, in addition to at the screening and 30 day followup visits, vital signs were measured on Days 1, 8, 15, and 22 of every cycle (refer to the NAPOLI-1 Schedule of Assessments in section 5.3 of this review).

Reviewer comment: As shown below, there were no notable differences between the two groups or notable upward or downward trends over time in systolic or diastolic blood pressure, respiratory rate, heart rate, or body temperature. For body weight, separation over time is noted between the means in the 5FU/LV arm and means in both MM-398-containing arms, with the trend toward lower values in the MM-398-containing arms compared to the 5FU/LV arm. X-axis tickmarks in the graphs below represent consecutive visits. Blue represents the 5FU/LV arm, green represents the MM-398/5FU/LV arm, and red represents the MM-398 arm. Fewer patients were evaluated at later time points, and if more patients with higher baseline weights continued on study over time in the 5FU/LV arm compared to those with lower baseline weights, this would also affect interpretation of the results depicted in the graph. The applicant reported that a higher proportion of patients in the MM-398-containing arms compared to the 5-FU arm experienced a >5% decrease from baseline weight (25% in the 5FU/LV arm, 53% in the MM-398/5FU/LV arm, and 58% in the MM-398 arm). Weight decreased is an AE that was included in the labeling in the table of adverse reactions, based on incidence rate of the preferred term (refer to section 7.4.1 of this review).

Figure 12 Mean Systolic Blood Pressure

Mean + Std Dev vs Category - Subset of patients



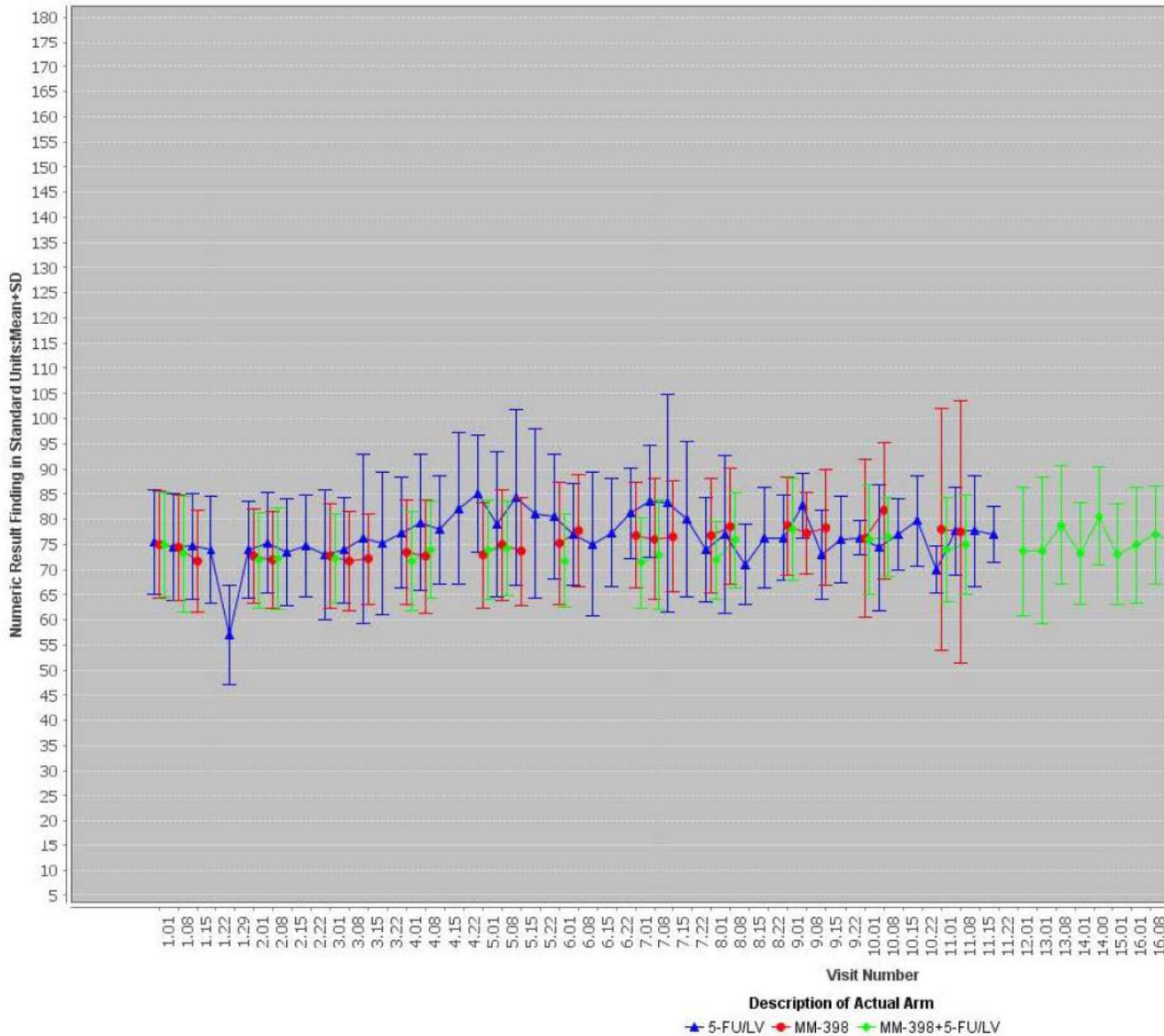
Patient Selection Criteria: Exposure.Safety Population Flag=Y

Output Filter: Vital Signs.Visit Number >0 AND Vital Signs.Visit Number <600 AND Vital Signs.Visit Number is not missing

Figure 13 Mean Diastolic Blood Pressure

Mean + Std Dev vs Category - Subset of patients

Vital Signs Test Name: Diastolic Blood Pressure



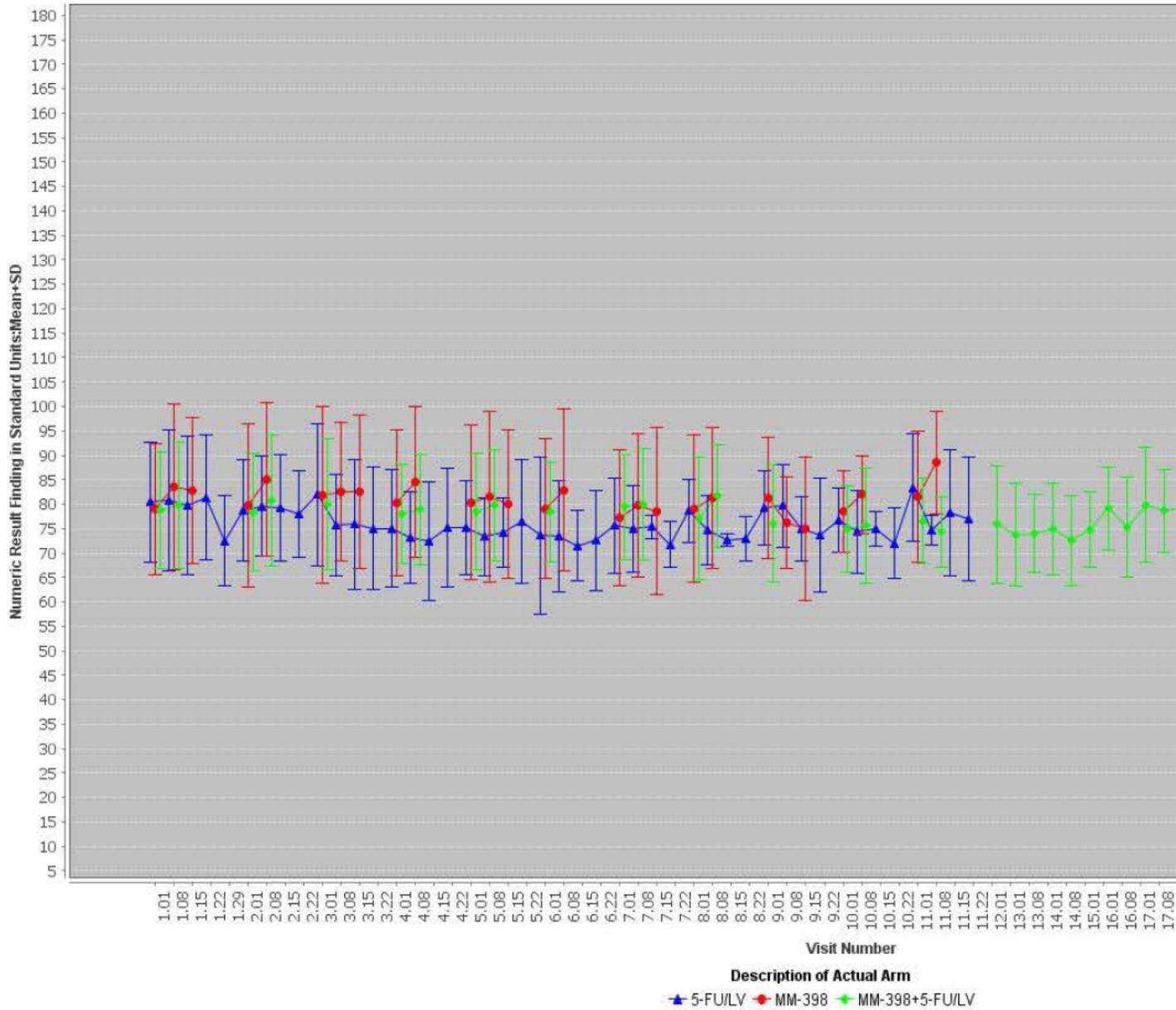
Patient Selection Criteria: Exposure.Safety Population Flag =Y

Output Filter: Vital Signs.Visit Number >0 AND Vital Signs.Visit Number <600 AND Vital Signs.Visit Number is not missing

Figure 14 Pulse Rate

Mean + Std Dev vs Category - Subset of patients

Vital Signs Test Name: Pulse Rate

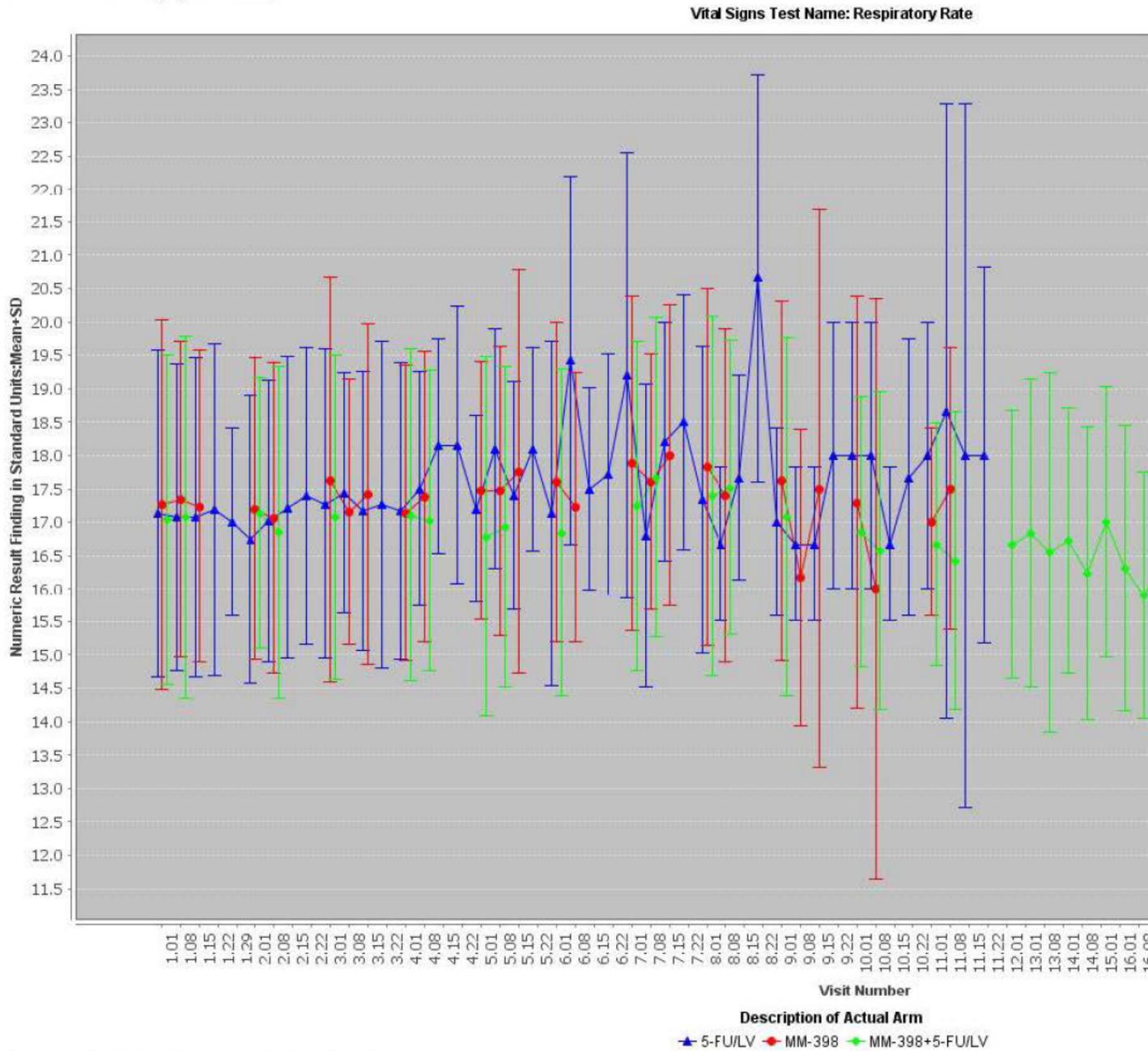


Patient Selection Criteria: Exposure.Safety Population Flag =Y

Output Filter: Vital Signs.Visit Number >0 AND Vital Signs.Visit Number <600 AND Vital Signs.Visit Number is not missing

Figure 15 Respiratory Rate

Mean + Std Dev vs Category - Subset of patients

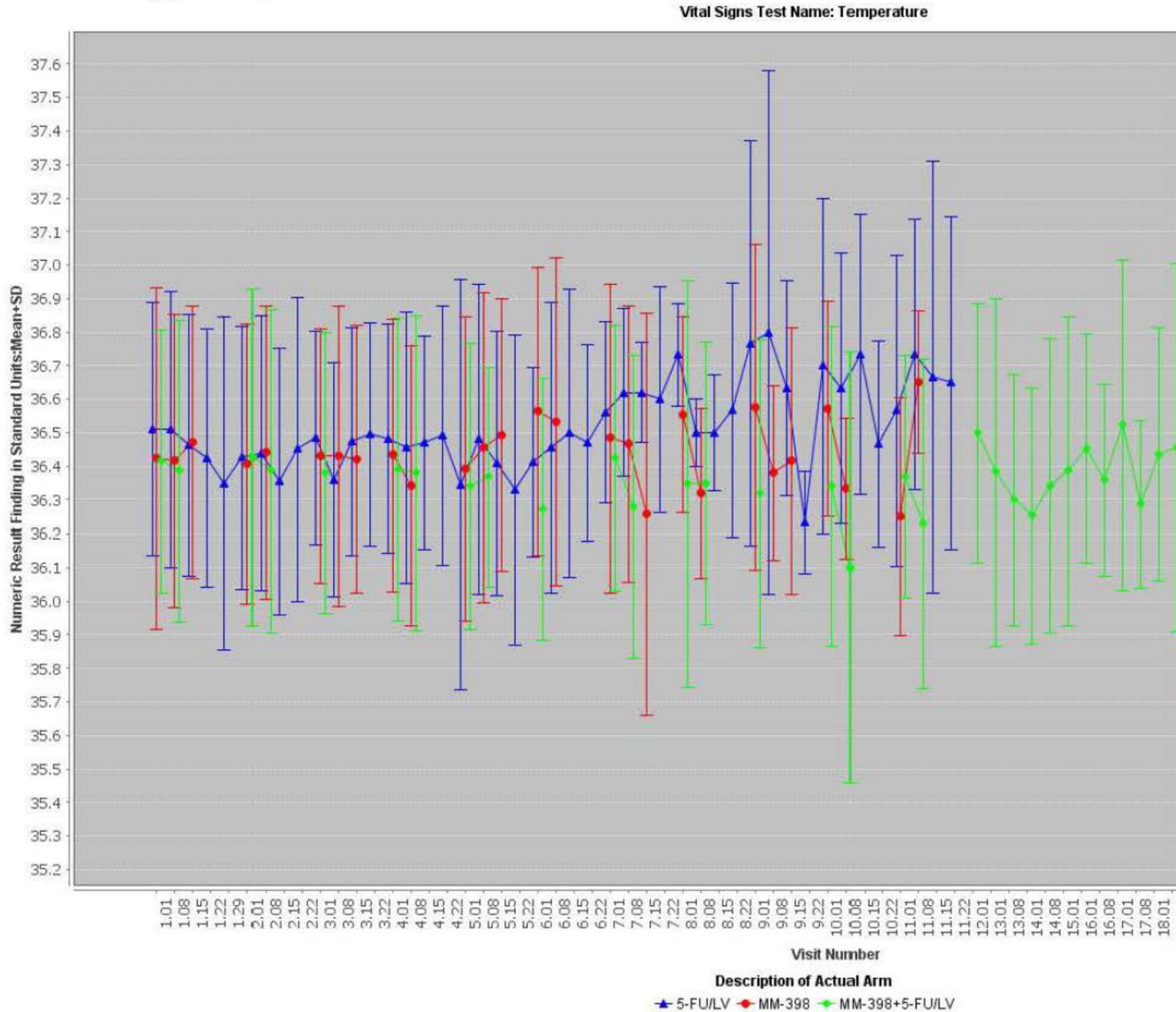


Patient Selection Criteria: Exposure.Safety Population Flag =Y

Output Filter: Vital Signs.Visit Number >0 AND Vital Signs.Visit Number <600 AND Vital Signs.Visit Number is not missing

Figure 16 Body Temperature

Mean + Std Dev vs Category - Subset of patients

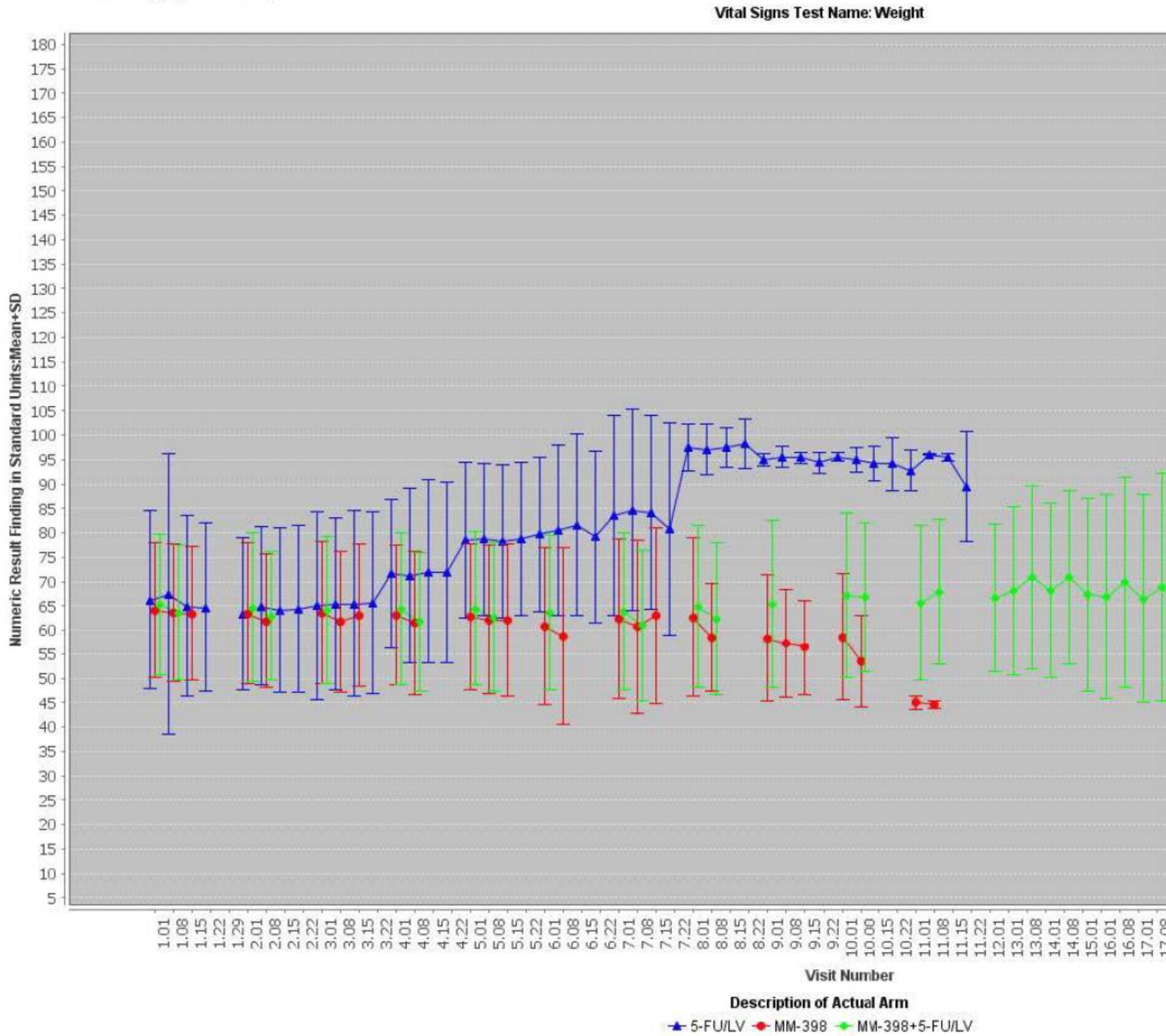


Patient Selection Criteria: Exposure.Safety Population Flag=Y

Output Filter: Vital Signs.Visit Number >0 AND Vital Signs.Visit Number <600 AND Vital Signs.Visit Number is not missing

Figure 17 Body Weight

Mean + Std Dev vs Category - Subset of patients



Patient Selection Criteria: Exposure.Safety Population Flag =Y

Output Filter: Vital Signs.Visit Number >0 AND Vital Signs.Visit Number <600 AND Vital Signs.Visit Number is not missing

7.4.4 Electrocardiograms (ECGs)

In the NAPOLI-1 trial, ECGs were to be obtained at baseline and at 30-day followup, and were to be repeated during the study as clinically indicated (*refer to the NAPOLI-1 Schedule of Assessments in section 5.3 of this review*). In the NAPOLI-1 clinical study report, the applicant stated “there were no clinically significant changes in ECG parameters during the course of the study” and “in addition, for those patients with QTc evaluations, there were no clinically significant changes in QTc interval during the course of the study.”

Upon review of the ECG datasets it was noted that two patients, one in each MM-398-containing arm, experienced >60 msec QTc change from baseline. Based on review of the AE and exposure datasets, it did not appear that either patient experienced corresponding clinical AEs.

See the QT-IRT consult memoranda (dated 6-22-15 and 7-8-15) that were requested by the clinical pharmacology review team, and the Clinical Pharmacology review, regarding any postmarket requirements or commitments for QT assessment.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted.

7.4.6 Immunogenicity

Immunogenicity information was not provided and not considered necessary for this cytotoxic chemotherapeutic drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

NAPOLI-1, the randomized, international, multicenter trial that forms the basis of this application, was conducted with two dose levels of MM-398, however one of these dose levels (120 mg/m²) was MM-398 administered as a single agent and on an every-three-week schedule, and the other (the dosing regimen proposed in this application) was MM-398 administered in combination with other chemotherapy (5-FU and LV) and on an every-two-week schedule. The 7 patients who began at the protocol-specified reduced starting dose of MM-398 in the MM-398/5FU/LV arm were homozygous for the UGT1A1*28 allele.

Refer to the clinical pharmacology review regarding exploration of plasma drug and metabolite levels and toxicity.

7.5.2 Time Dependency for Adverse Events

The table below shows incidence of TEAEs Grades 1-4 in the MM-398/FU/LV arm of NAPOLI-1 by cycle number of onset, for cycles 1-6.

Table 36 Incidence of TEAEs Grade 1-4 by Cycle of Onset

AE Onset (cycle number)	MM-398/5FU/LV n=117 %
1	99
2	87
3	68
4	48
5	43
6	40

The table below shows incidence of TEAEs Grades 3-4 in the MM-398/FU/LV arm of NAPOLI-1 by cycle number of onset, for cycles 1-6.

Table 37 Incidence of TEAEs Grades 3-4 by Cycle of Onset

AE Onset (cycle number)	MM-398/5FU/LV n=117 %
1	76
2	67
3	52
4	38
5	36
6	32

The incidence of AEs was higher in earlier cycles, however note that mean duration of treatment was 15 weeks in this treatment group.

Refer to section 7.3.5 regarding analyses of neutropenia and diarrhea.

7.5.3 Drug-Demographic Interactions

This reviewer conducted analyses of all adverse events and of adverse events Grade 3 or higher, by age and by race, of the 264 patients who received MM-398 (as a single agent or in combination with 5FU/LV) in the NAPOLI-1 trial.

Of the 264 patients 49% were ≥ 65 years old and 13% were ≥ 75 years old. In general there were no major differences in incidence or patterns of adverse events in patients who received MM-398 (as a single agent or in the combination arm) in NAPOLI-1 who were ≥ 65 years of age compared to those less than 65 years of age.

Of the 264 patients 43% were female. In general there were no major differences in incidence or patterns of adverse events in patients who received MM-398 (as a single agent or in the combination arm) in NAPOLI-1 who were females compared to those who were males.

Of the 264 patients 32% were Asian, 60% were White, 3% were Black or African American, 5% were identified as 'Other,' and 1 patient was American Indian or Alaska Native. Grade 3 or higher neutropenia occurred in 41% of Asian patients compared to 11% of White patients. Grade 3 or higher diarrhea occurred in 11% of Asian patients compared to 23% of White patients. In general there were no other major differences in incidence or patterns of adverse events between these two groups, and analysis of other race groups was limited by small numbers of patients in each group.

Reviewer comment:

Refer to the clinical pharmacology review and section 4.4.3 of this review; population PK analysis suggested that Asians have lower total irinotecan average steady state concentration and higher total SN-38 average steady state concentration than Whites [to which the increased incidence of Grade 3 or higher neutropenia observed in Asian patients who received MM-398 (alone or in combination), compared to White patients, may be related].

The increased rate of Grade 3-4 neutropenia in the Asian subgroup compared to White patients, for the MM-398/5FU/LV arm, was included in the proposed labeling and it is recommended that this information be retained. Note that the numbers in the labeling differ slightly from above due to the analyses above describing both MM-398-containing arms together. The numbers included in the labeling adequately convey the noted difference between the subgroups with respect to the combination arm (who received the regimen proposed in this application).

7.5.4 Drug-Disease Interactions

No specific drug-disease interaction studies were conducted.

All patients in the NAPOLI-1 trial that forms the basis of this application had life-threatening metastatic pancreatic cancer.

Refer to the clinical pharmacology review for further detail. The pharmacokinetics (PK) of irinotecan liposome have not been studied in patients with hepatic impairment, and patients with serum bilirubin above the upper limit of normal were to be excluded from the NAPOLI-1 trial. In a population PK analysis (refer to the clinical pharmacology review), patients with baseline serum bilirubin concentration of 1-2 mg/dL (n=19) had increased average steady-state concentrations for total SN-38 compared to patients with baseline bilirubin concentrations < 1 mg/dL (n=329); however there was no effect of elevated AST/ALT concentrations on total SN-38 concentrations. No PK data are available in patients with bilirubin > 2 mg/dL. In a population PK analysis, mild to moderate renal impairment had no effect on exposure of total SN-38 after adjusting for BSA, and there was insufficient data in patients with severe renal impairment (CrCl < 30 mL/min) to assess effect on PK of MM-398.

7.5.5 Drug-Drug Interactions

Refer to the clinical pharmacology review.

In a population PK analysis, the PK of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin.

Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital, carbamazepine, or St. John's wort.

Following administration of irinotecan HCl, dexamethasone, a moderate CYP3A4 inducer, does not alter the pharmacokinetics of irinotecan.

Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38.

In vitro studies indicate that irinotecan, SN-38 and another metabolite, aminopentane carboxylic acid, do not inhibit cytochrome P-450 isozymes.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant did not perform studies to assess the carcinogenic or genotoxic potential of MM-398. Irinotecan HCl was clastogenic in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice), as described in section 13.1 of the Camptosar labeling. Refer to the toxicology review for further detail. The labeling proposed for Onivyde includes this information and a statement that no studies assessing carcinogenic potential of MM-398 have been performed.

The proposed use of MM-398 in this application is for the treatment of patients with life-threatening malignancy, and also, for which patients received prior therapy.

7.6.2 Human Reproduction and Pregnancy Data

There are no available data in pregnant women. The applicant stated that no pregnancies were reported during the clinical investigation of MM-398, and that because the active ingredient of MM-398 is irinotecan, the previous findings with Camptosar regarding pregnancy are referenced (Camptosar labeling). The current version of the proposed labeling, which has not yet been finalized, states that based on animal data with irinotecan HCl and the mechanism of action of Onivyde, Onivyde can cause fetal harm when administered to a pregnant woman. Refer to toxicology and maternal health reviews for further information.

No animal studies were conducted to evaluate the effect of irinotecan liposome on reproduction and fetal development; however, studies were conducted with irinotecan HCl, which was observed to cross the placenta of rats following IV administration. Also, IV administration of irinotecan to rats and rabbits during organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. Teratogenic effects were identified in animal studies with irinotecan HCl and included external, visceral, and skeletal abnormalities.

Refer to the toxicology review for further information.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable to this application/intended population. Pancreatic cancer is rare in children, and the application is exempt from the requirements under the Pediatric Research Equity Act (PREA) because this drug product was granted orphan drug designation for the pancreatic cancer indication.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no events of overdose of MM-398 in the studies submitted.

One occurrence of the MedDRA preferred term 'overdose' was identified in the AE datasets in an MM-398-containing arm, and occurred in the MM-398/5FU/LV arm of NAPOLI-1; upon further case review, this was determined to be a report of 5-FU overdose.

Reviewer comment: The package insert for Camptosar contains the following statements: "There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhea." This reviewer recommends inclusion of this data regarding overdosage experience with irinotecan HCl in section 10 of the proposed Onivyde labeling.

There is no expected drug abuse potential for MM-398. The applicant did not report any evidence of drug abuse potential, withdrawal, or rebound.

7.7 Additional Submissions / Safety Issues

The applicant submitted the 90-day safety update on July 23, 2015. The amendment consisted of materials previously agreed upon by FDA including new and updated case narratives and CRFs through June 19, 2015. At the time of the primary analysis cutoff date, 23 patients were receiving study treatment, including 14 in the MM-398/5FU/LV arm. Also included was an updated OS analysis with 376 deaths, constituting 90% of total randomized patients. Datasets were not included (and were not part of the materials requested or agreed upon for the update during the pre-NDA meeting). All case narratives were reviewed.

Reviewer comment: Overall, the results from the safety update were consistent with the findings presented in the NDA submission and did not identify new information regarding the safety profile of MM-398.

8 Postmarket Experience

There is no postmarketing experience with MM-398 because MM-398 has not been approved.

Appears this way on original

9 Appendices

9.1 Literature Review/References

American Cancer Society, Cancer Facts and Figures 2015. Atlanta, American Cancer Society 2015.

Chanan-Khan et al, "Complement activation following first exposure to pegylated liposomal doxorubicin (Doxil): possible role in hypersensitivity reactions." *Annals of Oncology*, 2003; 14(9): 1430.

Conroy et al, "FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer." *New England Journal of Medicine*, 2011; 364: 1817-1825.

Moore et al, "Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group." *Journal of Clinical Oncology*, 2007; 25: 1960-1966.

NCCN Clinical Practice Guidelines in Oncology, Pancreatic Adenocarcinoma, v 2.2015, National Comprehensive Cancer Network, at nccn.org.

Oettle et al. "Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial." *Journal of Clinical Oncology*, 2014; 32: 2423-2429.

Pelzer et al. "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." *European Journal of Cancer*, 2011; 47: 1676-1681.

Product labeling for Camptosar, Abraxane, and Doxil, at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.

Rahma, et al. "Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials." *Annals of Oncology*, 2013; 24: 1972-1979.

Von Hoff et al, "Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine." *New England Journal of Medicine*, 2013; 369: 1691-1703.

Xiong et al, "Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer." *Cancer*, 2008; 113: 2046-2052.

9.2 Labeling Recommendations

At the time of completion of this review, text for the proposed labeling was not finalized and negotiations not complete. Therefore, the material below may not reflect the final changes agreed upon by FDA.

The following are high-level labeling recommendations and only clinically-relevant, substantive content changes are discussed. All sections of the package insert were revised for clarity, brevity, consistency, and active voice. Revisions were made throughout to ensure inclusion of information necessary for safe and effective prescribing and in accordance with FDA labeling guidances. Only clinically relevant, substantive content changes are included below.

Boxed Warning

- Heading revised to neutropenia (b) (4) as neutropenia is the specific risk described
- Heading and bullets reordered to neutropenia then diarrhea
- Summary information added regarding monitoring, withholding Onivyde, threshold for restarting, dose reduction, and treatment for early and for late diarrhea
- (b) (4) removed
- (b) (4)

Indications and Usage

- ‘... (b) (4) disease progression following ...’ added for clarity regarding intended population
- Limitation of use added regarding use as a single agent for the proposed indication, based on results in the MM-398-only arm of NAPOLI-1

Dosage and Administration

- Statement of recommended starting dose in patients homozygous for UGT1A1*28 added, (b) (4)
 - Revisions for clarity regarding increasing dose in subsequent cycles in these patients

- [REDACTED] (b) (4)
- Extensive reformatting of and other edits to Dose Modifications for Adverse Reactions section for brevity and clarity

[REDACTED] (b) (4)

Contraindications

- Revised to contraindicate only in patients who have experienced severe hypersensitivity, [REDACTED] (b) (4)

Warnings and Precautions

- [REDACTED] (b) (4) retitled to 'Severe Neutropenia' as severe neutropenia is the risk described
 - Incidence rates of severe neutropenia in NAPOLI-1 arms added
 - Incidence rate for Grade 3-4 neutropenic fever/neutropenic sepsis in the control arm added
 - Comparison of Grade 3-4 neutropenia rates and neutropenic fever/neutropenic sepsis rates in 'Asian' vs. 'White' patients changed to reflect rates in 'Asian' vs. non-'Asian' patients
 - Instructions for monitoring CBCs to mitigate risk added
 - Instructions regarding withholding Onivyde, criteria for restarting, and dose reduction/discontinuation modified for clarity
 - Statements [REDACTED] (b) (4) removed
 - [REDACTED] (b) (4)
- Diarrhea [REDACTED] (b) (4)
 - Overall incidence of diarrhea in NAPOLI-1 arms added (early vs. late) and statement that a given patient may experience one or both within a treatment cycle added
 - Definitions for early vs. late diarrhea revised for clarity
 - Incidence rates added for early vs. late diarrhea in the control arm
 - Percentage of patients who received loperamide and who received atropine added

- Statements (b) (4) removed
- Instructions regarding withholding Onivyde, criteria for restarting, and dose reduction/discontinuation modified for clarity
- Information regarding treatment of early and of late diarrhea and of cholinergic symptoms other than diarrhea revised for clarity and to provide recommendations
- Incidence rate of cholinergic symptoms added and percentage of patients who received atropine added
- (b) (4) removed (b) (4) which was incorporated in other sections of the labeling
- (b) (4) retitled to Interstitial Lung Disease to more specifically identify the risk
- (b) (4) removed (b) (4)
- Warning regarding Severe Hypersensitivity (b) (4) added based on data with irinotecan HCl and the contraindication described above

Adverse Reactions

- Additional information regarding NAPOLI-1 trial design added
- Replacement of adverse event table with table showing selected adverse reactions and based on FDA analysis
 - Terms better described by laboratory-derived incidence rates and terms not meeting selection criteria removed from table
- Listings of adverse reactions revised to reflect regulatory definition of adverse reaction
- Laboratory abnormality data revised to tabular presentation format
- (b) (4) removed (b) (4)
- Added information regarding infusion reaction revised to better reflect events observed in NAPOLI-1 known to be manifestations of infusion reaction and to include incidence

Use in Specific Populations

- Revision of geriatric use section to align with 21 CFR 210.57 requirements

Overdosage

- [REDACTED] (b) (4)
remove statements [REDACTED] (b) (4)

Clinical Pharmacology

- Inclusion of statement that in NAPOLI-1, patients in the study arm who were homozygous for UGT1A1*28 began Onivyde at a reduced dose, and that the incidence of Grade 3-4 neutropenia was similar in this group compared to patients in the study arm who were not homozygous

Clinical Studies

- [REDACTED] (b) (4)
- Inclusion of information regarding stratification factors applied at randomization
- Revision of efficacy results table [REDACTED] (b) (4) to include only confirmed response results (confirmed results were specified in the NAPOLI-1 statistical analysis plan)
- Inclusion of K-M curves [REDACTED] (b) (4) for OS (primary outcome measure)

Patient Counseling Information

- Information added regarding [REDACTED] (b) (4) severe hypersensitivity reactions

9.3 Advisory Committee Meeting

Due to robustness of the results demonstrating a clinically meaningful improvement in overall survival in patients randomized to MM-398/5FU/LV, and the overall favorable risk-benefit assessment in the intended population of patients with metastatic adenocarcinoma of the pancreas, an Advisory Committee Meeting was not deemed necessary in order to render a regulatory decision regarding the application.

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/s/

SHAN PRADHAN
09/30/2015

STEVEN J LEMERY
09/30/2015

Clinical Investigator Financial Disclosure
Review Template

Application Number: 207793

Submission Date(s): 4/24/15

Applicant: Merrimack Pharmaceuticals

Product: Onivyde (irinotecan liposome injection)

Reviewer: Shan Pradhan, MD

Date of Review: 9/18/15

Covered Clinical Study (Name and/or Number): NAPOLI-1

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 106 site PI's, plus subinvestigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator:</p> <p>Significant equity interest held by investigator in sponsor of covered study:</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: n/a	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Refer to section 3.3 of the Clinical Review. Disclosure of financial interests/arrangements was adequate. NAPOLI-1 was a large randomized trial with a primary efficacy endpoint of overall survival, a measure not subject to investigator bias. The single investigator with a disclosable interest was not the principal investigator at the site, and the number of patients enrolled at the site constituted less than 10% of patient enrollment to the trial. It is unlikely that the disclosed interest significantly impacted the overall trial results.

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/s/

SHAN PRADHAN
09/18/2015

STEVEN J LEMERY
09/18/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207793

Applicant: Merrimack

Stamp Date: 4/24/15

Drug Name: irinotecan liposome injection **NDA/BLA Type:** 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			While the overall design of the draft labeling appears on initial review to be in PLR format, the labeling is missing certain required components (e.g., ^(b) ₍₄₎ 
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			The ISE submission in Module 5 references Module 2 for the text portion.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(2)
505(b)(2) Applications					

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			As requested the applicant included detailed justification for the difference in 5-FU/LV dosing regimen between the MM-398/5-FU/LV and 5-FU/LV study arms.
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Though the application was not based solely on foreign data, such a section was not found and will be requested from the applicant.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			The applicant did not submit a QT study report, and instead made reference to limited ECG data collected for NAPOLI-1. A QT-IRT consult was sent to determine adequacy of the data submitted.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			The DMC meeting minutes for NAPOLI-1 were not found. These were requested from the applicant in the December 2, 2014 Pre-NDA meeting minutes and will be requested from the applicant again.
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Exempt from requirements, due to orphan drug designation.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Though the application was not based solely on foreign data, such a section was not found and will be requested from the applicant.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms	X			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	in a legible format (deaths, serious adverse events, and adverse dropouts)?				
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			A statement of steps taken to minimize bias was not found for the one investigator for whom the applicant submitted a Form 3455 (with a disclosable financial interest); this will be requested from the applicant.
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			The CSRs in Module 5 for NAPOLI-1, PEP0206, and PEP0208 contain a statement that the study was performed according to the principles of the ICH Guidance on GCP.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAN PRADHAN
05/11/2015

STEVEN J LEMERY
05/11/2015