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APPLICATION NUMBER:

207793Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA	207793
Submission Date:	April 24, 2015
Brand Name:	Onivyde®
Generic Name:	Irinotecan Liposome Injection
Formulation:	Liposomal solution for injection
OCP Reviewer:	Sarah J. Schrieber, Pharm.D.
OCP Team Leader:	Gene M. Williams, Ph.D.
Pharmacometrics Reviewer:	Anshu Marathe, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
Pharmacogenomics Reviewer:	Anuradha Ramamoorthy, Ph.D.
Pharmacogenomics Team Leader:	Rosane Charlab Orbach, Ph.D.
OCP Division:	Division of Clinical Pharmacology V
OND Division:	Division of Drug Oncology Products
Applicant:	Merrimack
Submission Type; Code:	505(b)(2); SDN 3
Dosing regimen:	Onivyde 80 mg/m ² IV infusion over 90 minutes, every 2 weeks, with LV 400 mg/m ² infusion over 30 minutes followed by 5-FU 2400 mg/m ² infusion over 46 hours
Indication:	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5- fluorouracil (5-FU) and leucovorin (LV), in patients previously treated with gemcitabine

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1 EXECUTIVE SUMMARY

Merrimack Pharmaceuticals has submitted New Drug Application (NDA) 207793 for Onivyde (irinotecan liposome injection) in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas who have received a prior gemcitabine-containing regimen. Irinotecan is a topoisomerase 1 inhibitor. This NDA is a 505(b) (2) application relying on data from Camptosar, NDA 20571. An OCP Briefing was held on September 14, 2015.

The applicant supports this NDA submission with six clinical pharmacology studies.

The following are the major findings of the review:

- The exposure-response (E-R) relationship for efficacy and safety support the proposed Onivyde dose of 80 mg/m² IV infusion over 90 minutes, every 2 weeks.
 - Although there is an increase in overall survival (OS) with increase in SN-38 exposure, there is also an increase in grade 3 or 4 neutropenia and grade 3 or 4 diarrhea with increasing total SN-38 (an active metabolite that is the primary driver for efficacy) and total irinotecan exposure, respectively.
 - The safety profile was considered manageable at the proposed dose.
- A reduced starting dose of Onivyde for patients known to be homozygous for the UGT1A1*28 allele is acceptable.
 - In the randomized phase 3 trial, patients homozygous for the UGT1A1*28 allele received a lower starting dose (60 mg/m² rather than 80 mg/m²). Patients without drug related toxicities during the first cycle of therapy had their doses increased in to 80 mg/m² in Cycle 2.
 - The frequency of Grade 3 or 4 neutropenia in patients homozygous for the UGT1A1*28 allele (all of whom received the 60 mg/m² starting dose) was similar to the frequency in patients not homozygous for the UGT1A1*28 allele.
 - In the popPK analysis, adjusted for the lower dose administered to a subset of patients homozygous for the UGT1A1*28 allele, patients homozygous for this allele had only a slight increase (18%) in total SN-38 average steady-state concentration (C_{avg}) relative to patients non-homozygous for the allele.
- No dosing adjustment is recommended for any intrinsic or extrinsic factor.
 - Age, gender, or mild to moderate renal impairment had no clinically meaningful effect on the exposures of irinotecan and SN-38.
 - Asians (East Asians) were observed to have ~70% lower total irinotecan C_{avg} than Whites. However, there was minimal effect of ethnicity on SN-38 exposure (SN-38 C_{avg} and SN38 converted C_{avg}).
 - Patients with baseline bilirubin concentrations of 1-2 mg/dL had average steady state concentrations for total SN-38 that were increased by 45% compared to patients with

baseline bilirubin concentrations of <1 mg/dL. However in patients with elevated AST/ALT levels, 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.

- The pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 207793 and recommends approval of the application.

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Proposed Onivyde dose of 80 mg/m ² IV infusion over 90 minutes, every 2 weeks.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Refer to Sections 2.2.4, 2.2.5, and 2.2.9	Labeling Recommendation: The recommended dose of Onivyde is 80 mg/m ² IV infusion over 90 minutes, every 2 weeks
Proposed Onivyde starting dose of 60 mg/m ² IV infusion over 90 minutes for patients known to be homozygous for the UGT1A1*28 allele	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Refer to Section 2.2.7	Labeling Recommendation: The recommended starting dose of Onivyde in patients known to be homozygous for the UGT1A1*28 allele is 60 mg/m ² administered by IV infusion over 90 minutes
No dosing adjustment is recommended for any intrinsic or extrinsic factor	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Refer to Sections 2.2.6, 2.3.1, 2.4.7, and 2.4.8	Comment: No dose adjustment is recommended for ethnicity, age, gender, body surface area, mild to moderate renal impairment, hepatic impairment, or drug-drug interactions.

Labeling Recommendations

Refer to Section 3 DETAILED LABELING RECOMMENDATIONS.

1.2 Post-Marketing Requirements and Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

The doses of MM-398 described in this review are based on the protocol-administered doses. However, the product will be labeled based on the free base. Each single dose vial contains 43

mg irinotecan free base (equivalent to 50 mg irinotecan HCl), at a concentration of 4.3 mg/mL. Therefore, for example, the protocol-administered MM-398 dose of 80 mg/m² used in the phase 3 trial is equivalent to 68.8 mg/m² based on the free base.

Merrimack Pharmaceuticals has submitted New Drug Application (NDA) 207793 for Onivyde (irinotecan liposome injection) in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas who have received a prior gemcitabine-containing regimen. Irinotecan is a topoisomerase 1 inhibitor. The recommended clinical dose of Onivyde is 80 mg/m² administered as an intravenous infusion once every 2 weeks, followed by leucovorin 400 mg/m² and 5-fluorouracil 2400 mg/m². This NDA is a 505(b)(2) application relying on data from Camptosar, NDA 20571.

To support the efficacy in metastatic adenocarcinoma of the pancreas, the sponsor conducted one three-arm, randomized, open label trial in patients with metastatic pancreatic adenocarcinoma with documented disease progression after gemcitabine or gemcitabine-based therapy. Patients in the trial were randomized to receive Onivyde plus fluorouracil/leucovorin, Onivyde monotherapy, or fluorouracil/leucovorin. The major efficacy outcome measure was overall survival (OS) with two pair-wise comparisons: Onivyde vs. fluorouracil/leucovorin and Onivyde plus fluorouracil/leucovorin vs. fluorouracil/leucovorin. There was a statistically significant improvement in OS for the Onivyde plus fluorouracil/leucovorin arm over the fluorouracil/leucovorin arm (median OS=6.1 vs 4.2 months; HR (95% CI): 0.68 (0.50-0.93), p=0.014). There was no improvement in OS for the Onivyde arm over the fluorouracil/leucovorin arm (HR=0.99, p=0.94 (two-sided log-rank test)).

The safety profile of Onivyde was as anticipated based on the 5-FU/LV backbone and reference drug Camptosar. The most common adverse events (AEs) of the MM-398 (Onivyde API) + 5-FU/LV combination were neutropenia, diarrhea, nausea, vomiting, decreased appetite, fatigue, anemia, stomatitis, and pyrexia. AEs were generally manageable with dose delay and/or reduction with supportive care.

The applicant supports this NDA submission with six clinical pharmacology studies.

Pharmacokinetics

Distribution

- Direct measurement of irinotecan liposome showed that 95% of irinotecan remains liposome-encapsulated, and the ratios between total and encapsulated forms did not change with time from 0 to 169.5 hours post-dose.
- The mean volume of distribution of total irinotecan is approximately 4 L.
- Plasma protein binding is <0.44% of the total irinotecan in Onivyde.

Metabolism

- The metabolism of irinotecan liposome has not been evaluated. Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases, to form the active metabolite SN-38. UGT1A1 mediates glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to produce SN-38.

Excretion

- The disposition of Onivyde has not been elucidated in humans. Following administration of irinotecan HCl, the urinary excretion of irinotecan as parent drug is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%.
- The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide), over a period of 48 hours following administration of irinotecan HCl in two patients, ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

Population Pharmacokinetic Analysis

Population PK models were developed to describe MM-398 and SN-38 systemic exposure in patients and to determine if intrinsic factors influence systemic exposure.

Age, Gender, Renal Impairment, Ethnicity, Hepatic Impairment

- Age had no clinically meaningful effect on the exposure of irinotecan and SN-38.
- Gender had no clinically meaningful effect on exposure of irinotecan and SN-38 after adjusting for body surface area (BSA).
- Mild (CLcr 60 - 89 mL/min) -to-moderate (CLcr 30 - 59 mL/min) 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 (CLcr < 30 mL/min) to assess its effect on PK.
- Asians (East Asians) were observed to have ~70% lower total irinotecan C_{avg} than Whites. There was minimal effect of ethnicity on SN-38 exposure (SN-38 C_{avg} and SN-38 converted C_{avg}).
- Patients with baseline bilirubin concentrations of 1-2 mg/dL 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. 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.

Drug-Drug Interactions (DDI)

The pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin.

Pharmacogenomics

- In the randomized phase 3 trial, patients homozygous for the UGT1A1*28 allele received a lower starting dose 60 mg/m² rather than 80 mg/m²). 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 the unadjusted starting dose of Onivyde [30 of 110 (27.3%)].
- In the population pharmacokinetic analysis, adjusted for the lower dose administered to patients homozygous for the UGT1A1*28 allele, patients homozygous for this allele had 18% higher total SN-38 average steady-state concentrations (C_{avg}) relative to patients non-homozygous for the allele.

Signatures:

Reviewer: Sarah J. Schrieber, Pharm.D.
Division of Clinical Pharmacology 5
Reviewer: Anshu Marathe, Ph.D.
Division of Pharmacometrics
Reviewer: Anuradha Ramamoorthy,
Ph.D.
Division of Pharmacogenomics

Team Leader: Gene Williams, Ph.D.
Division of Clinical Pharmacology 5
Team Leader: Yaning Wang, Ph.D.
Division of Pharmacometrics
Team Leader: Rosane Charlab-Orbach, Ph.D.
Division of Pharmacogenomics

Cc: DDOP: CSO - D Varney; MTL - S Lemery; MO - S Pradhan
DCPV: Reviewers - S Schrieber (CP), A Marathe (PM) A Ramamoorthy (GG)
CP TL - G Williams , PM TL - Y Wang GG TL - R Charlab-Orbach
DDD - B Booth DD - A Rahman

2 QUESTION BASED REVIEW

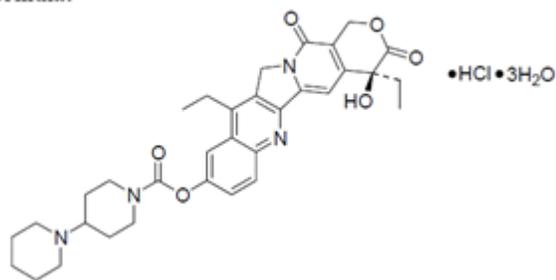
2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Onivyde injection is supplied as a sterile, white to slightly yellow, opaque, isotonic liposomal dispersion. Each single dose vial contains 43 mg irinotecan free base (equivalent to 50 mg irinotecan HCl), at a concentration of 4.3 mg/mL.

Figure 1. Structural formula of irinotecan hydrochloride trihydrate.

Structural formula:



Established names: Irinotecan hydrochloride, MM-398

Molecular Weight: 677.19 g/mol

Molecular Formula: $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$

Chemical Name: (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate.

The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelled or precipitated state as the

sucroseoctasulfate salt. The vesicle is composed of (b) (4)
distearoylphosphatidylcholine (DSPC; (b) (4) cholesterol (b) (4)
(polyethylene glycol) (b) (4) distearoylethanolamine (mPEG₂₀₀₀-DSPE) methoxy- (b) (4)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Irinotecan is a topoisomerase 1 inhibitor. The proposed Onivyde indication is for the treatment of metastatic adenocarcinoma of the pancreas, in combination with fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine-based therapy.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The doses of MM-398 described in this review are based on the protocol-administered doses. However, the product will be labeled based on the free base. Each single dose vial contains 43 mg irinotecan free base (equivalent to 50 mg irinotecan HCl), at a concentration of 4.3 mg/mL. Therefore, for example, the protocol-administered MM-398 dose of 80 mg/m² used in the phase 3 trial is equivalent to 68.8 mg/m² based on the free base.

The applicant proposes the following dosing regimen: Onivyde 80 mg/m² intravenous (IV) infusion over 90 minutes, every 2 weeks, followed by leucovorin 400 mg/m² infusion over 30 minutes followed by fluorouracil 2400 mg/m² infusion over 46 hours.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A single trial in patients with metastatic pancreatic adenocarcinoma with documented disease progression after gemcitabine or gemcitabine-based therapy was conducted to support the efficacy claim.

Efficacy Trial in Patients with Metastatic Pancreatic Adenocarcinoma

The efficacy trial MM-398-07-03-01 (NAPOLI-1) was a three-arm, randomized, open label trial in patients with metastatic pancreatic adenocarcinoma with documented disease progression after gemcitabine or gemcitabine-based therapy. Patients randomized to:

- Onivyde plus fluorouracil/leucovorin received Onivyde 80 mg/m² as an IV infusion over 90 minutes, followed by leucovorin 400 mg/m² IV over 30 minutes, followed by fluorouracil 2400 mg/m² IV over 46 hours, every 2 weeks.*
- Onivyde as a single agent received Onivyde 120 mg/m² as an IV infusion over 90 minutes every 3 weeks.*
- Fluorouracil/leucovorin received leucovorin 200 mg/m² IV over 30 minutes, followed by fluorouracil 2000 mg/m² IV over 24 hours, administered on Days 1, 8, 15 and 22 of a 6-week cycle.

*Patients homozygous for the UGT1A1*28 allele initiated Onivyde at a reduced dose (60 mg/m² Onivyde plus fluorouracil/leucovorin or 80 mg/m² Onivyde) with escalation to 80 mg/m² if the first dose was well tolerated.

Treatment continued until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS) with two pair-wise comparisons: Onivyde vs. fluorouracil/leucovorin and Onivyde plus fluorouracil/leucovorin vs. fluorouracil/leucovorin. Table 1 below shows a summary of the applicant’s results based on this primary outcome measure. There was no improvement in OS for the Onivyde arm over the fluorouracil/leucovorin arm (HR=0.99, p=0.94 (2-sided log-rank test)).

Table 1. Overall Survival (OS) in patients with metastatic pancreatic adenocarcinoma.		
	Onivyde+ 5-FU/LV (N=117)	5-FU/LV (N=119)
Median PFS in Months (95% CI)	6.1 (4.8, 8.5)	4.2 (3.3, 5.3)
p-value (long rank test)	< 0.014	
Hazard Ratio (95% CI)	0.68 (0.50 – 0.93)	

CI, confidence interval

Additional efficacy outcome measures included progression-free survival (PFS) and objective response rate (ORR).

A total of six studies were used to support the Clinical Pharmacology and Biopharmaceutics Section of the NDA (Table 2).

Cancer patient studies:

- Four Phase 1 studies – PEP201, PEP203, PIST-CRC-01, MM-398-01-01-02
- One Phase 2 study – PEP0206
- One Phase 3 study – MM-398-07-03-01

Clinical Pharmacology Reports of data from more than one study:

The plasma concentration data from several studies were used to develop a population pharmacokinetic (popPK) model to investigate the potential influence of covariates that contribute significantly to between-patient variability in pharmacokinetic parameters of irinotecan and the active metabolite, SN-38. The model was also used to characterize the exposure-safety relationships for select adverse events.

Table 2. Overview of Clinical Pharmacology Related Studies Submitted in NDA.			
Study Number	Study Description/Design	Subjects Evaluated Sex M/F Age (yr): Mean (SD) Race (W/B/His/As/Other/Unk)	Treatment Regimen/ Duration Route of Administration
Patient Pharmacokinetic Studies			
PEP0201	A Multi-Center, Open-Label Phase I Dose-Escalation Study of MM-398 Using a Once-Every-Three-Week Dosing Schedule in Advanced Solid Tumor Patients	Subjects: 11 Sex: 1 M / 10 F Age (yr): 47 (41-61) Race (As): 11	MM-398 doses of 60, 120, and 180 mg/m ² administered as a 90 min IV infusion.
PEP0203	A Multi-Center, Open-Label Phase I Dose-Escalation Study of MM-398 in Combination with 5-fluorouracil (5-FU) and Leucovorin (LV) in Advanced Solid Tumors	Subjects: 16 Sex: 7 M / 9 F Age (yr): 49.5 (30- 67) Race (As): 16	MM-398 dose level from 60 to 120 mg/m ² administered as a 90-minute IV infusion, followed by 5-FU 2,000 mg/m ² and LV 200 mg/m ² on Day 1 and Day 8.
PEP0206	A Randomized, Open-Label, Parallel Group, Phase II Study of MM-398, Camptosar® or Docetaxel as a Second Line Therapy in Patients with Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	Subjects: 132 Sex: 103 M / 29 F Age (yr): 58 (33-81) Race (W/As): 72 / 60	Arm 1: MM-398 120 mg/m ² as a single agent every 3 weeks. Arm 2: Camptosar® 300 mg/m ² as a single agent every 3 weeks. Arm 3: Docetaxel 75 mg/m ² as a single agent every 3 weeks
PIST-CRC-01	Phase I and Pharmacokinetic Study of Biweekly MM-398 in Patients with Metastatic Colorectal Cancer Refractory to First-line Oxaliplatin-based Chemotherapy	Subjects: 18 Sex: 9 M / 9 F Age (yr): 58 (45-85) Race (As): 18	MM-398 80, 90, and 100 mg/m ² administered as a 90-minute IV infusion once-every-two-weeks
MM-398-01-01-02 (ongoing)	Single Center, Open-Label, Pilot Study in Patients Treated with MM-398 to Determine Tumor Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumor Associated Macrophages	Subjects: 13 Sex: 4 M / 9 F Age (yr): 58 (28-80) Race (W/Other/Unknown): 12 / 1 / 1	MM-398 80 mg/m ² administered as a 90-minute IV infusion once-every-two-weeks
Efficacy and Safety Controlled Clinical Studies			
MM-398-07-03-01	NAPOLI-1: 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	Randomized: 417 Sex: 237 M / 180F Age (yr): 63 (31-87) Race (W/B/As/Other): 253 / 10 / 136 / 17	Arm A: MM-398 120mg/m ² Arm B: 5-FU/LV control arm Arm C: MM-398 80mg/m ² + 5-FU/LV

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The major efficacy outcome measure 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).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, all the submitted clinical pharmacology related studies analyzed plasma samples for total irinotecan (which includes encapsulated and unencapsulated irinotecan), its active metabolite SN-38 and its inactive glucuronidated form SN-38G.

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Exposure response analysis was conducted using data from the NAPOLI-1 trial (Study MM-398-07-03-01) in patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy. Analysis included data from 114 patients from a total of 117 patients in the combination therapy arm (MM-398 + 5-FU/LV). Based on Kaplan-Meier plots, a trend for increase in overall survival (OS) with total SN-38 exposures (C_{avg}) was identified within the exposures achieved when Onivyde is administered in combination with 5-FU/LV (Figure 2). C_{avg} was calculated for the first 2 or 3 weeks dose interval based on the actual dose. This represents C_{avg} at steady state.

The baseline patient and disease characteristics in total SN-38 exposure groups (grouped by quartiles: q1 – q4) are shown in Tables 3 and 4. To account for imbalances in these factors across exposure groups, a multivariate analysis was conducted, using only data from the MM-398 combination therapy arm, to adjust for these imbalances. Total SN-38 C_{avg} was also included in the analysis. The multivariate analysis showed that total SN-38 C_{avg} is a significant covariate for overall survival suggesting reduction in hazard with increase in exposure (Table 5). Similarly -38 converted C_{avg} was also identified as significant covariates for overall survival (Appendix 1). Converted SN-38 refers to the estimated amount that is converted from CPT-11 *in vivo* and excludes the contribution of (b) (4)

The details of the analysis and its limitations are provided in the Pharmacometrics review in Appendix 1.

Figure 2. Kaplan-Meier plots of overall survival for patients in various quartiles (q1, q2, q3 and q4) based on SN-38 total C_{avg} in the MM-398+5FU/LV arm. Total SN38 C_{avg} represents the steady state C_{avg} calculated for the first 2 or 3 weeks dose intervals based on the actual dose.

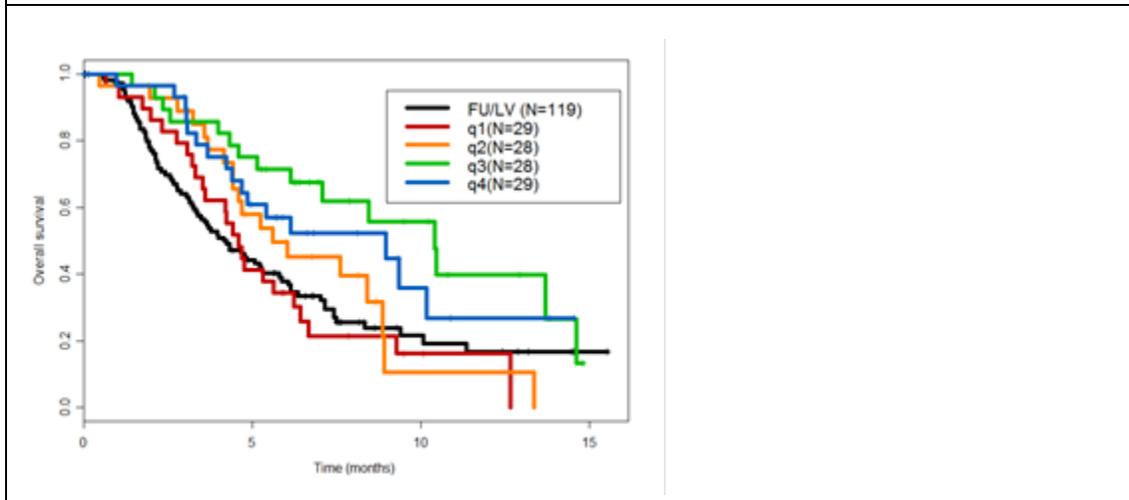


Table 3. Summary of continuous covariates by total SN-38 C_{avg} quartiles.

Group	N	Baseline KPS Levels	Baseline albumin (g/dL)	Age (years)	BMI (kg/m ²)	Time since diagnosis (year)	Time since metastatic diagnosis (year)
FU/LV	119	85.4	3.98	61.0	23.6	1.07	0.64
q1	29	84.5	3.90	63.3	22.8	1.09	0.79
q2	28	87.5	3.91	64.9	23.7	0.90	0.49
q3	28	89.6	4.14	61.5	23.3	1.11	0.62
q4	29	84.5	3.93	63.6	23.6	1.33	0.90

Table 4. Summary of categorical covariates by total SN-38 C_{avg} quartiles.

Group	N	Asian	Female	Not Stage IV	Prior 5 FU exposure	Prior Irinotecan Exposure	Prior Platinum Therapy	Prior Radio Therapy	Liver Metastases
FU/LV	119	30.3	43.7	47.9	43.7	14.3	34.5	22.7	70.6
q1	29	20.7	41.4	44.8	62.1	27.6	51.7	20.7	62.1
q2	28	35.7	25.0	60.7	10.7	3.6	14.3	14.3	67.9
q3	28	28.6	46.4	42.9	50.0	0.0	25.0	28.6	64.3
q4	29	31.0	55.2	44.8	44.8	10.3	37.9	17.2	62.1

The values for each covariate represent percentage (%)

Table 5. Parameter estimates from the multivariate analysis.

Analysis of Maximum Likelihood Estimates										
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label	
tsn38cavg	1	-2.29519	0.63306	13.1446	0.0003	0.101	0.029	0.348		
kps	1	-0.02749	0.01301	4.4685	0.0345	0.973	0.948	0.998		
alb	1	-0.65022	0.29758	4.7743	0.0289	0.522	0.291	0.935		
stage	0	1	0.65721	0.25110	6.8504	0.0089	1.179	3.156	stage 0	
livermfl	N	1	-0.75758	0.28084	7.2765	0.0070	0.469	0.270	0.813	livermfl N

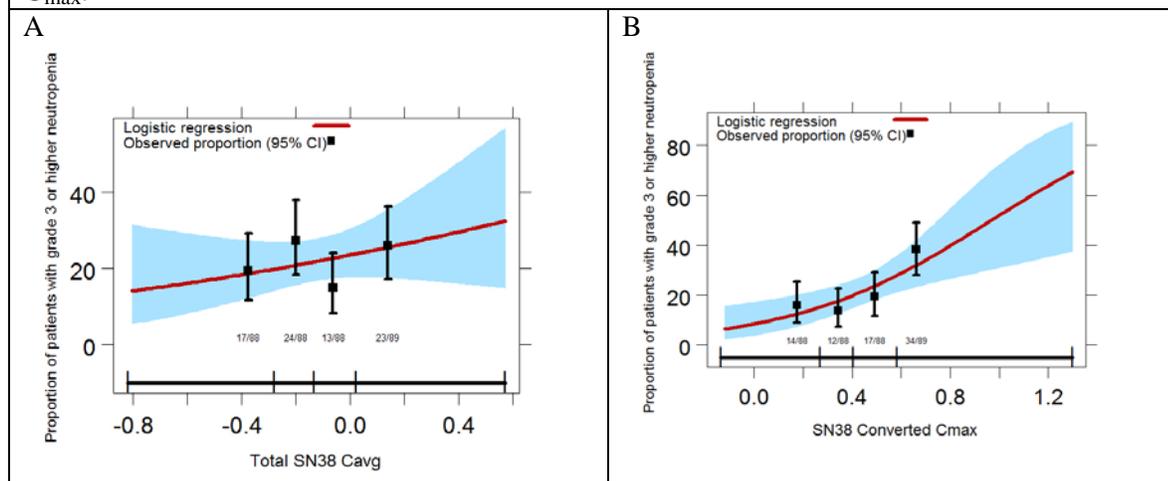
2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Exposure response analysis for safety was conducted using pooled data from various studies, including the NAPOLI-1 trial. Analysis included data from 353 patients that received MM-398 with or without 5FU/LV. For studies included in the exposure-safety analysis, see Pharmacometrics review in Appendix 1.

Neutropenia

There is a trend for increase in grade 3 or 4 neutropenia with increasing SN-38 exposure. Figure 3 shows an increase in the proportion of patients with grade 3 or 4 neutropenia with increasing total SN-38 C_{avg} or converted SN-38 C_{max} . Total SN-38 C_{avg} represents the steady state C_{avg} calculated for the first (2 or 3 weeks) dose interval based on the actual dose. Converted SN-38 C_{max} represents the maximum concentration of converted SN-38 for the first dose based on the actual dose. Converted SN38 refers to the estimated amount that is converted from irinotecan (CPT11) *in vivo* and excludes the contribution of (b) (4)

Figure 3. Exposure-response relationship for grade 3 or 4 neutropenia. Proportions of patients with grade 3 or 4 neutropenia by A) total SN-38 C_{avg} and B) converted SN-38 C_{max} .



Univariate analysis using total SN-38 C_{avg} as the exposure metric showed a trend for increase in grade 3 or 4 neutropenia with exposure. However, the relationship was not statistically significant (Table 6, top panel).

Multivariate analysis suggested that converted SN-38 C_{max} is a significant covariate for grade 3 or 4 neutropenia (Table 6, bottom panel). Race, baseline ANC and co-administration of 5-FU were also found to be significant covariates. Asian patients have a higher rate of grade 3 or 4 neutropenia compared to White patients. Co-administration of 5-FU increased the rate of grade 3 or 4 neutropenia. Higher ANC baseline is associated with lower rate of grade 3 or 4 neutropenia.

Table 6. Parameter estimates from univariate analysis using total SN3-8 C_{avg} (top panel) and multivariate (bottom panel) for grade 3 or 4 neutropenia analysis using converted SN-38 C_{max} as the exposure metrics.

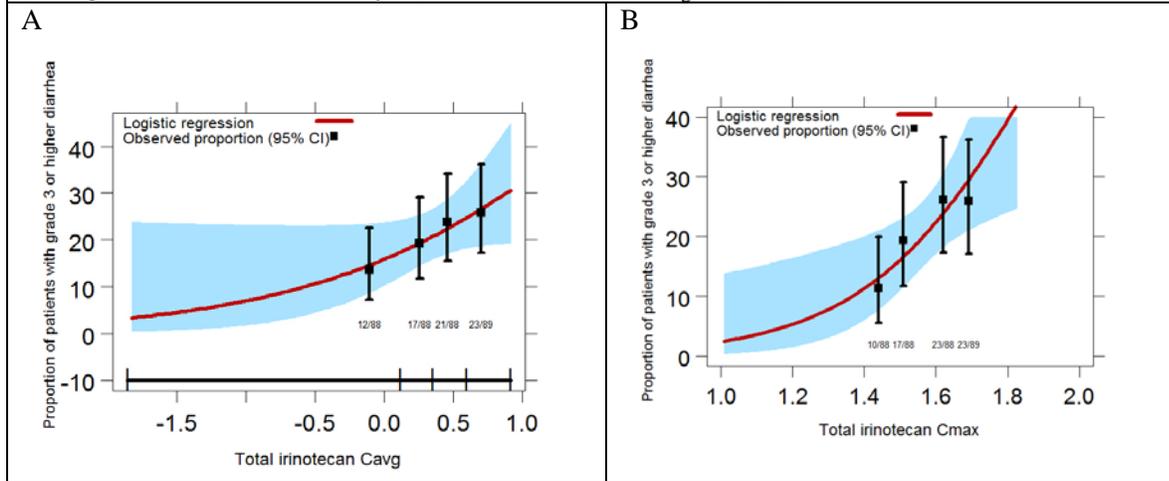
Univariate analysis based on total SN-38 C_{avg}						
Analysis of Maximum Likelihood Estimates						
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	
Intercept	1	-1.1836	0.1432	68.3673	<.0001	
SN38TOTA	1	0.7822	0.5728	1.8651	0.1720	

Multivariate analysis based on converted SN-38 C_{max}						
Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-0.8848	0.7161	1.5269	0.2166
SN38CON0		1	1.9912	0.8231	5.8520	0.0156
race	1 Asian	1	1.0999	0.3965	7.6938	0.0055
race	2 Others	1	-1.0463	0.7046	2.2050	0.1376
ANC		1	-2.5660	0.8096	10.0449	0.0015
fivefluflag	0 Ye	1	0.6911	0.1696	16.6026	<.0001

Diarrhea

There is a trend for increase in grade 3 or 4 diarrhea with increasing total irinotecan exposure. Figure 4 shows an increase in the proportion of patients with grade 3 or 4 diarrhea with increasing total irinotecan C_{avg} or total irinotecan C_{max} . Total irinotecan C_{avg} represents the steady state C_{avg} calculated for the first (2 or 3 week) dose interval based on the actual dose. Total irinotecan C_{max} represents the maximum concentration of irinotecan for the first dose based on the actual dose.

Figure 4. Exposure-response relationship for grade 3 or 4 diarrhea. Proportions of patients with grade 3 or 4 diarrhea by A) total irinotecan C_{avg} and B) total irinotecan C_{max} .



Univariate analysis using total irinotecan C_{avg} as the exposure metric showed an increase in grade 3 or 4 diarrhea with irinotecan C_{avg} (Table 7, top panel). However multivariate analysis did not identify total irinotecan C_{avg} as a covariate. Multivariate analysis suggested that total irinotecan C_{max} is a significant covariate for grade 3 or 4 diarrhea (Table 7, bottom panel). Ethnicity was also found to be a significant covariate. White patients have higher rate of grade 3 or 4 diarrhea compared to Asian patients.

Table 7. Parameter estimates from univariate analysis using total irinotecan C_{avg} (top panel) and multivariate analysis (bottom panel) for grade 3 or 4 diarrhea using total irinotecan C_{max} as the exposure metrics.

Univariate analysis based on total irinotecan C_{avg}						
Analysis of Maximum Likelihood Estimates						
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	
Intercept	1	-1.6695	0.2037	67.1717	<.0001	
CPT11_CA	1	0.9294	0.4012	5.3653	0.0205	

Multivariate analysis based on total irinotecan C_{max}						
Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-8.2603	2.0712	15.9060	<.0001
CPT11_CM		1	4.2095	1.2954	10.5600	0.0012
ETHNICC	1 Caucasian	1	0.6144	0.2861	4.6121	0.0317
ETHNICC	2 Others	1	-0.4729	0.5103	0.8588	0.3541

In summary, exposure-response analysis showed that there is a trend for increase in grade 3 or 4

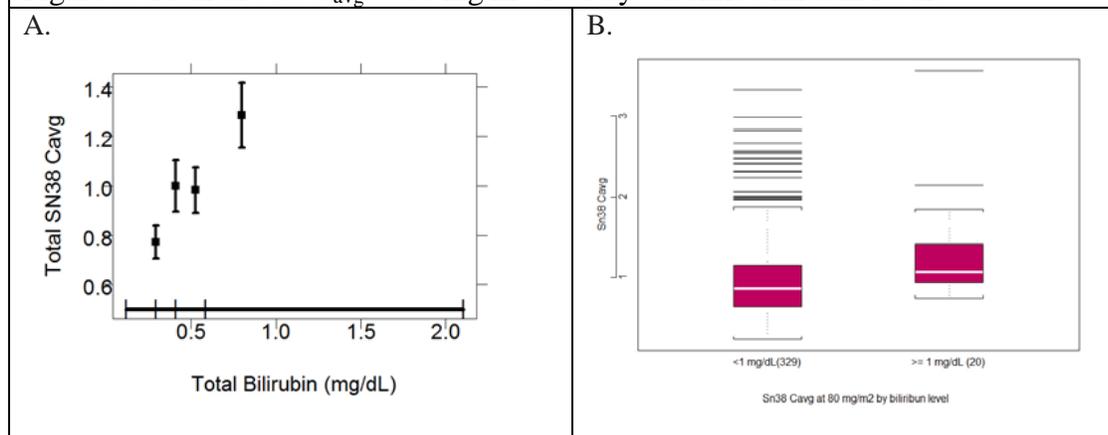
neutropenia with SN-38 exposure and grade 3 or 4 diarrhea with total irinotecan exposure. The details of the analysis and its limitations are provided in the Pharmacometrics review in Appendix 1.

2.2.6 Are the dosing guidelines appropriate for patients with bilirubin levels of 1-2 mg/dL?

(b) (4)

In this application, the number of patients with bilirubin \geq 1mg/dL was limited (only 6 patients in the MM-398+5-FU/LV arm, 9 patients in the MM-398 monotherapy arm and 13 patients in the 5-FU/LV control arm), so comprehensive comparison of safety in the MM-398 arms between those with a total bilirubin less than 1 mg/dL and those with 1 mg/dL or higher is difficult. There were no clinically relevant large differences in the frequency of the most common and most important adverse events based on levels of total bilirubin. Any grade neutropenia was reported in 44 of 109 (40.1%) patients with bilirubin less than 1 mg/dL in the MM-398+5-FU/LV combination arm and in 36 of 136 patients (26.5%) in the MM-398 monotherapy arm. For patients with total bilirubin of 1 mg/dL or higher, any grade neutropenia was reported for 2 of 6 (33.3%) in the MM-398+5-FU/LV arm, and 1 of 9 (11.1%) of patients in the MM-398 monotherapy arm. “There were too few patients treated in the NAPOLI-1 study with total bilirubin levels of more than 1 mg/dL to confidently assess whether higher bilirubin levels might be associated with a higher likelihood of neutropenia with MM-398 treatment” (Source: Applicant’s Integrated Safety Summary report). Based on exposure response analysis, there is a trend for increase in grade 3 or 4 neutropenia with increasing SN-38 exposure (see Section 2.2.4) and population PK analysis suggests a trend for increase in SN-38 exposure with increasing baseline bilirubin levels (Figure 5A). However, there is only 24% higher SN-38 exposure in patients with bilirubin levels \geq 1 mg/dL compared to patients with bilirubin levels $<$ 1 mg/dL at 80 mg/m² (Figure 5B). Thus, data in the current package seems insufficient to justify a reduced starting dose based on baseline bilirubin levels.

Figure 5. Total SN-38 C_{avg} at 80 mg/m² dose by baseline bilirubin level.



2.2.7 Are the dosing guidelines appropriate for patients known to be homozygous for the UGT1A1*28 allele?

The dosing and administration section of the label recommends (b) (4) a reduced starting dose of Onivyde of 60 mg/m² for patients known to be homozygous for the UGT1A1*28 allele. Patients without drug related toxicities during the first cycle of therapy may have their dose of Onivyde increased to 80 mg/m² in subsequent cycles based on individual patient tolerance. This is consistent with Camptosar label where a reduction in starting dose is recommended for patients known to be homozygous for the UGT1A1*28 allele. This recommendation for Camptosar was based on the association between UGT1A1*28 homozygosity and neutropenia.

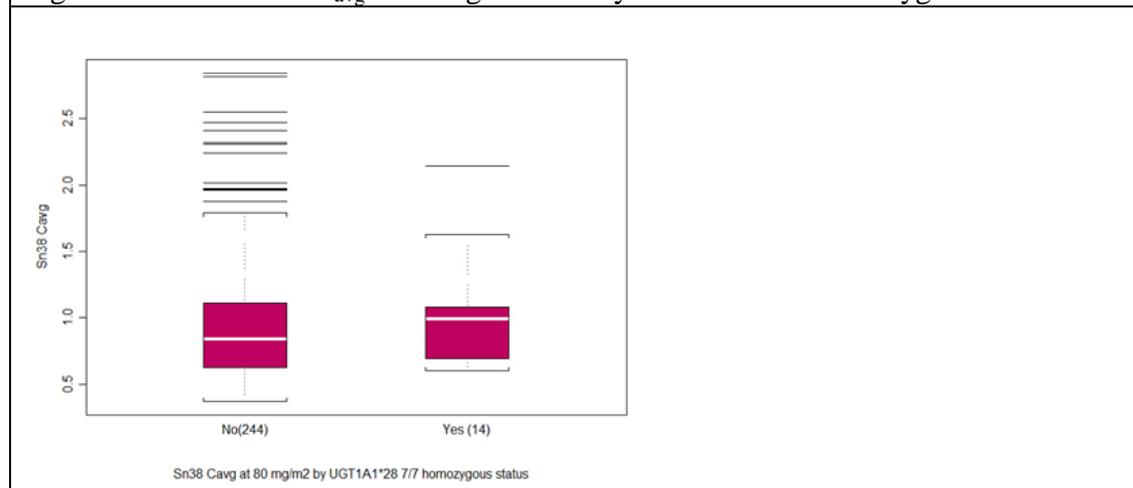
The sponsor's proposed dosing scheme was implemented in the NAPOLI-1 study. In the combination arm of the NAPOLI-1 study, there were 7 patients who were homozygous for the UGT1A1*28 allele. These patients started at the 60 mg/m² dose. Among these, 2 patients remained at the starting dose of 60 mg/m², 3 were escalated to 80 mg/m², 1 patient's dose was initially escalated to 80 mg/m² but later reduced to 60 mg/m² and 1 patient's dose was reduced to 40 mg/m² (Table 8). With this dosing scheme in the NAPOLI-1 trial, similar rates of neutropenia were observed in patients homozygous for UGT1A1*28 and non-homozygous patients. Grade 3 or 4 neutropenia in patients homozygous for UGT1A1*28 allele was 28.6% (2 out of 7 patients) and was 27.3% (30 of 110 patients) in non-homozygous patients. The results presented here should be viewed with caution as there were only 7 homozygous patients in the combination arm in the trial. Population PK analysis showed only 18% higher SN-38 exposure in homozygous patients compared to non-homozygous patients after adjusting for differences in dose but without adjusting for other covariates identified in the population PK model (Figure 6, includes data outside the NAPOLI-1 trial). After adjusting for all other covariates, the CL for SN-38 exposure in homozygous patients is essentially the same as that in non-homozygous patients (see Table 9 in Appendix 4.1). It is unclear why the association between SN-38 exposure and UGT1A1*28 homozygosity was not identified. The correlation between UGT1A1 status and other covariates could be inherent. Therefore, quantifying the "pure" UGT1A1 effect after adjusting for all other covariates may not be clinically relevant. Regardless, the UGT1A1 effect (unadjusted or adjusted) observed after administration of irinotecan liposome injection is not clinically meaningful to justify a dose reduction for UGT1A1*28 homozygous patients. Since a

prospective dose reduction strategy was implemented in the NAPOLI-1 trial and the dose could be increased based on the patients' response, the studied regimen is considered appropriate and acceptable for patients known to be homozygous for the UGT1A1*28 allele. For further details regarding this recommendation please see Appendix 4.2.

Table 8. Distribution of dose in patients homozygous for UGT1A1*28 status in NAPOLI-1 trial.

Treatment arm	Remained at the starting dose of 60 mg/m ²	Dose was escalated to 80 mg/m ²	Dose was initially escalated but reduced to 60 mg/m ² later in the trial	Dose was reduced to 40 mg/m ²
MM398 + 5-FU/LV	2	3	1	1

Figure 6. Total SN-38 C_{avg} at 80 mg/m² dose by UGT1A1*28 homozygous status.



2.2.8 Does this drug prolong the QT or QTc interval?

No formal QTc evaluation study was conducted during MM-398 clinical development because of 1) the lack of evidence of cardiac toxicity in pre-clinical studies with MM-398 and 2) because Camptosar, since its initial FDA approval in 1996, has not been known to cause QTc prolongation.

In the PEP0206 study, PK profiles of MM-398 (120 mg/m² q3w) and Camptosar (300 mg/m² q3w) were compared in patients treated for advanced gastric cancers. Following the administration of MM-398 compared to Camptosar, there was a slightly higher total SN-38 AUC_{0-inf} (1.4-fold) and a reduced C_{max} (0.19-fold). However, higher exposures of total irinotecan were observed for both C_{max} (13.4-fold) and AUC_{0-inf} (46.2-fold).

The higher total irinotecan exposures observed following MM-398 compared to Camptosar may not translate into a clinically meaningful different risk. Given that the indication being sought in this application is for a high-risk cancer patient population, the sponsor will be requested to

2.2.9 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The following support the selection of the MM-398 dose:

- The efficacy (i.e., OS benefit) was demonstrated in the phase 3 trial (MM-398-07-03-01).
- The safety profile was considered manageable at the 80 mg/m² every two week dose level.
- The exposure response relationship for efficacy and safety supports the MM-398 proposed dose of 80 mg/m². Although there is an increase in OS with increase in SN-38 exposure (see Section 2.2.4), there is also an increase in grade 3 or 4 neutropenia and grade 3 or 4 diarrhea with increasing SN-38 and irinotecan exposure (see Section 2.2.5).

2.2.10 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.10.1 What are the single dose PK parameters?

A non-compartmental analysis was completed using data from 25 patients who received MM-398 80 mg/m² as monotherapy (Study PIST-CRC-01 (n=6) and Study MM-398-01-01-02 (n=13)), and in combination with 5-FU/LV (Study PEP0203 (n=6)). The single dose PK parameters for total irinotecan and total SN-38 are summarized below in Table 9.

Mean (SD) PK Parameter	MM-398 80 mg/m ²			
	N	Total Irinotecan	N	Total SN-38
C _{max} (µg/mL, or ng/mL) ¹	25	37.2 (8.8)	25	5.4 (3.4)
AUC _{0-inf} (µg/mL*h or ng/mL*h) ^{1, 2}	23	1364 (1048)	13	620 (329)
T _{max} (h)*	25	1.7 (1.4-3.2)	25	10.5 (1.0-75.2)
T _{1/2} (h) ²	23	25.8 (15.7)	13	67.8 (44.5)
CL (mL/h) ²	23	0.20 (0.17)	13	0.26 (0.11)
Vd (L) ²	23	4.1 (1.5)	NA	NA

*median (range)

¹C_{max} are in µg/mL for total irinotecan and ng/mL for SN-38; AUC are in µg/mL*h for total irinotecan and ng/mL*h for SN-38.

²Parameter was calculated for a subset of patients due to insufficient number of samples in the terminal phase.

NA= not available.

The following is a summary of the single dose PK data from two individual studies where doses ranged from 60 – 120 mg/m². Study PEP201 was a MM-398 monotherapy study. In study PEP203, MM-398 was studied in combination with 5-FU/LV.

Study PEP201: MM-398 doses of 60, 120 and 180 mg/m² IV over 90 minutes were administered as the first cycle treatment to 1, 6, and 4 subjects, respectively. Tables 10 and 11 describe the PK parameters of the total irinotecan, and total SN-38 after the first dose.

	Dose	60 mg/m ² (N=1)	120 mg/m ² (N=6)	180 mg/m ² (N=4)
PK Parameter Mean (SD)	C _{max} (µg/mL)	31.8 (-)	79.4 (13.9)	102.0 (17.6)
	AUC _{0-inf} (µg/mL*h)	223 (-)	2963 (1947)	1963 (1035)
	T _{max} (h)	1.5 (-)	2.5 (1.1)	1.8 (0.5)
	T _{1/2} (h)	28.7 (-)	29.5 (17.2)	22.3 (11.5)
	CL (mL/h/m ²)	269 (-)	59.1 (36.7)	119 (70.3)
	Vd (L/m ²)	3.6 (-)	1.8 (0.8)	2.0 (0.3)

	Dose	60 mg/m ² (N=1)	120 mg/m ² (N=6)	180 mg/m ² (N=4)
PK Parameter Mean (SD)	C _{max} (ng/mL)	2.6 (-)	9.2 (3.5)	14.3 (6.2)
	AUC _{0-inf} (ng/mL*h)	-	997 (680)	1425 (1134)
	T _{max} (h)	3.6 (-)	21.9 (26.3)	21. (9.0)
	T _{1/2} (h)	-	75.4 (43.8)	58.0 (32.8)

Study PEP203: MM-398 doses of 60, 80, 100, and 120 mg/m² IV over 90 minutes followed by 5-FU/LV were administered as the first cycle treatment to 3, 6, 5, and 2 subjects, respectively. Tables 12 – 14 describe the PK parameters of the total irinotecan, total SN-38, and total SN-38G after the first dose. Note that the purity of the reference standard of SN-38G was not good enough to provide accurate quantification of SN-38G in plasma samples, so these data should not be highly regarded.

	Dose	60 mg/m ² (N=3)	80 mg/m ² (N=6)	100 mg/m ² (N=5)	120 mg/m ² (N=2)
PK Parameter Mean (SD)	C _{max} (µg/mL)	28.9 (15.8)	29.2 (5.2)	44.1 (7.7)	47.9 (16.2)
	AUC _{0-inf} (µg/mL*h)	1114 (1270)	1212 (925)	2473 (1262)	1262 (500)
	T _{max} (h)*	2.7 (1.6-2.9)	2.1 (1.4-2.8)	2.8 (1.5-10.7)	2.3 (1.6-2.9)
	T _{1/2} (h)	24.0 (16.8)	32.1 (18.2)	48.1 (17.4)	30.7 (5.3)
	CL (mL/h/m ²)	125 (106)	116 (95)	55 (36)	103 (41)
	Vd (L/m ²)	2.6 (1.4)	2.9 (0.6)	2.6 (0.5)	3.1 (0.4)

*median (range)

	Dose	60 mg/m ² (N=3)	80 mg/m ² (N=6)	100 mg/m ² (N=5)	120 mg/m ² (N=2)
PK Parameter Mean (SD)	C _{max} (ng/mL)	7.0 (5.6)	8.0 (4.4)	7.4 (1.7)	16.6 (9.4)
	AUC _{0-inf} (ng/mL*h)	1373 (1120)	502 (154)	844 (445)	474 (210)
	T _{max} (h)*	10.9 (2.7-25.6)	7.5 (1.6-49.8)	5.0 (1.9-25.7)	25.8 (1.6-49.9)
	T _{1/2} (h)	183.8 (172.3)	53.8 (15.6)	73.4 (18.3)	26.2 (6.5)

*median (range)

	Dose	60 mg/m ² (N=3)	80 mg/m ² (N=6)	100 mg/m ² (N=5)	120 mg/m ² (N=2)
PK Parameter Mean (SD)	C _{max} (ng/mL)	848 (1052)	307 (203)	524 (669)	790 (756)
	AUC _{0-inf} (ng/mL*h)	69401 (90016)	31038 (11878)	68414 (87179)	56630 (46061)
	T _{max} (h)*	25.8 (25.8-49.7)	49.4 (25.6-73.3)	50.0 (49.4-73.7)	37.8 (25.6-49.9)
	T _{1/2} (h)	31.4 (6.0)	54.0 (35.0)	62.4 (27.8)	38.7 (8.8)

*median (range)

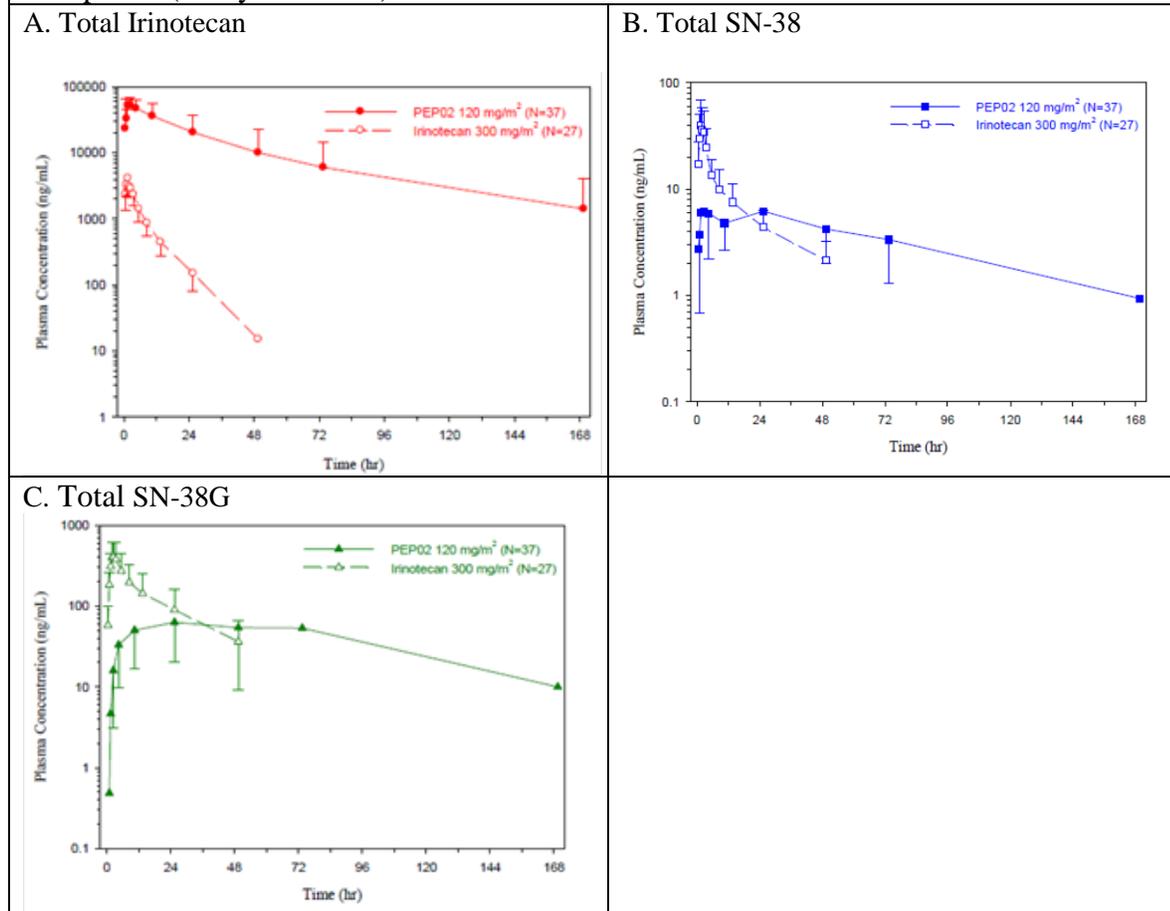
2.2.10.2 How do the single dose PK parameters between MM-398 and Camptosar compare?

The direct comparison of the PK of irinotecan and SN-38 in patients administered with MM-398 120 mg/m² q3w versus conventional irinotecan (Camptosar) 300 mg/m² q3w was evaluated in Study PEP0206. Compared to the administration of Camptosar, administration of MM-398 resulted in higher exposure of total irinotecan (C_{max} 13.4-fold, t_{1/2} 2.0-fold, and AUC_{0-inf} 46.2-fold; all comparison values were not dose-normalized), higher SN-38 t_{1/2} and AUC_{0-inf} (t_{1/2} 3.0-fold, and AUC_{0-inf} 1.4 fold), however, SN-38 C_{max} was reduced (0.19-fold) (Table 15). Figure 7 depicts the mean time vs. concentration profile for each analyte. The formation of SN-38 from irinotecan and SN-38G from SN-38 after infusion of MM-398 was less than that after infusion of Camptosar. The conversion ratios from irinotecan to SN-38 were 0.000289 and 0.0150 and from SN-38 to SN-38G were 11.5 and 16.4 after infusion of MM-398 and Camptosar, respectively. A scientifically plausible explanation for this observation is that most of the irinotecan remained in the liposomal form after infusion of MM-398, limiting the conversion from MM-398 to SN-38.

Table 15. PK Analysis Summary Statistics in Study PEP0206.

Analyte	Parameter	Unit	Geometric Mean (95% CI)		
			MM-398 120 mg/m ²	Camptosar® 300 mg/m ²	Ratio (MM-398: Camptosar®)
Total irinotecan	C _{max}	µg/ml	55.2 (48.2-63.3)	4.1 (3.7-4.6)	13.4 (11.2-16.1)
Total irinotecan	AUC _{0-∞}	h·µg/mL	1140.9 (799.6-1628.0)	24.7 (21.5-28.4)	46.2 (30.1-70.8)
Total irinotecan	t _{1/2}	h	14.0 (10.3-19.2)	7.1 (6.2-8.2)	2.0 (1.3-2.9)
Total irinotecan	T _{max}	h	1.9 (1.7-2.2)	1.5 (1.3-1.7)	1.3 (1.0-1.6)
SN-38	C _{max}	ng/ml	7.1 (5.9-8.6)	37.5 (30.0-46.9)	0.19 (0.14-0.25)
SN-38	AUC _{0-∞}	h·ng/mL	591.2 (465.8-750.3)	409.1 (348.5-480.1)	1.4 (1.1-2.0)
SN-38	t _{1/2}	h	63.7 (50.3-80.5)	20.8 (17.7-24.5)	3.0 (2.3-4.1)
SN-38	T _{max}	h	5.1 (3.4-7.7)	2.0 (1.7-2.2)	2.6 (1.6-4.2)
SN-38G	C _{max}	ng/ml	56.3 (44.4-71.4)	379.7 (303.2-475.5)	0.15 (0.11-0.21)
SN-38G	AUC _{0-∞}	h·ng/mL	5,843 (4,471-7,635)	5,837 (4,597-7,412)	1.0 (0.7-1.4)
SN-38G	t _{1/2}	h	57.0 (45.1-72.1)	18.0 (16.3-20.0)	3.2 (2.4-4.1)
SN-38G	T _{max}	h	29.7 (24.8-35.5)	2.4 (2.2-2.6)	12.4 (9.9-15.5)

Figure 7. Mean concentrations of total irinotecan (Panel A in red), SN-38 (Panel B in blue) and SN-38G (Panel C in green) after the administration of either MM-398 or Camptosar (Study PEP0206).



2.2.11 What are the characteristics of drug absorption?

MM-398 was given exclusively intravenously and is labeled for exclusively intravenous use.

2.2.12 What are the characteristics of drug distribution?

The total irinotecan volume of distribution (Vd) estimate in patients administered MM-398 80 mg/m² is approximately 4 L, which is similar to plasma volume, supporting that MM-398 may be largely confined within the plasma compartment. Also see section 2.2.10.

Distribution (Measurement in Tumor Lesion Biopsies)

In Study MM-398-01-01-02, penetration into tumor was evaluated by measuring concentrations of total irinotecan and SN-38 in tumor biopsies in 13 patients with advanced solid tumors administered MM-398 at a dose of 80 mg/m². Concentrations in tumor biopsies were collected at 72h post infusion. A higher concentration of SN-38 was observed in tumor lesions than in plasma (9.61 ng/g and 2.31 ng/ml, respectively) (Table 16). The ratio of tumor:plasma SN-38 concentration was 3.93. The ratio of SN-38:total irinotecan was 8-fold higher in tumor than in plasma (2,015 vs. 247); this suggests that conversion of irinotecan to SN-38 in patients

administered MM-398 may be higher in tumor than in plasma.

Table 16. Concentrations of Total Irinotecan and SN-38 in Plasma and Tumor at 72h after the Administration of 80 mg/m² MM-398 in Patients with Advanced Solid Tumors (Study MM-398-01-01-02).

	Total Irinotecan			SN-38			Total Irinotecan to SN-38 Ratio	
	Plasma (ng/ml)	Tumor (ng/g)	Tumor to Plasma Ratio ¹	Plasma (ng/ml)	Tumor (ng/g)	Tumor to Plasma Ratio ¹	Plasma	Tumor
N	13	31*	31 ^{**}	13 [†]	31*	31 ^{**†}	13 [†]	31 ^{**†}
Geometric Mean	4,647	2,372	0.47	2.31	9.61	3.93	2,015	247
Lower 90% CI	2,386	1,689	0.34	1.72	7.21	2.79	1,171	164
Upper 90% CI	9,049	3,332	0.63	3.10	12.82	5.53	3,466	370

^{*}Multiple biopsy samples were collected per patient.

[†]One patient with below-quantifiable SN-38 level in plasma was imputed with 0.6ng/ml (SN-38 LLOQ).

¹Tumor tissue density of 1 g/ml was assumed because the major component of the tissue is water.

Plasma Protein Binding

Protein binding analysis was conducted for plasma samples obtained from study PEP206. Protein binding was very low. For both liposomal separation methods used (gel chromatography and PEG capture), <0.44% of MM-398 was protein bound (<2.2 µg total protein per µmol of liposome phospholipid, or <4.36 µg of protein per mg of the irinotecan active pharmaceutical ingredient (API)).

2.2.13 Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not conducted. Excretion results are discussed in section 2.2.13.

2.2.14 What are the characteristics of drug metabolism?

No studies of the metabolism of MM-398 have been performed. The sponsor is relying on information from the Camptosar package insert:

- Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38.

No studies have been conducted in either animals or humans to determine the metabolism of the lipid components of MM-398. Phosphatidylcholine and cholesterol are constituents of normal body tissues and the applicant assumes that by injecting them they enter the normal metabolic pathways for these lipids.

2.2.15 What are the characteristics of drug excretion?

Elimination

The disposition of irinotecan has not been fully elucidated in humans. The sponsor is relying on information from the Camptosar package insert:

- The urinary excretion of irinotecan (i.e., Camptosar) is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of non-liposomal irinotecan and its metabolites (SN-38 and SN-38 glucuronide), over a period of 48 hours following administration of irinotecan in two patients, ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

2.2.16 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Data from healthy volunteers were not included in this submission.

2.2.17 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Using data from 95 patients (79 patients received 60, 80, 90, 100, 120 or 180 mg/m² MM-398 monotherapy (Studies PEP0201, PEP0206, PIST-CRC-01 and MM-398-01-01-02), and 16 patients received 60, 80, 100 or 120 mg/m² MM-398 in combination with 5-FU/LV (Study PEP0203)), a power model was applied to test dose proportionality for both total irinotecan and total SN-38. The results of this pooled analysis are provided in Figure 8. The slope for the power model on logarithmic scale is:

- 0.88 for total irinotecan AUC_{0-inf} with a 95% CI (0.06, 1.70)
- 1.13 for total irinotecan C_{max} with a 95% CI of (0.85, 1.42)
- 0.25 for total SN-38 AUC_{0-inf} with a 95% CI of (-0.40 0.89)
- 1.01 for total SN-38 C_{max} with a 95% CI of (0.55 1.46)

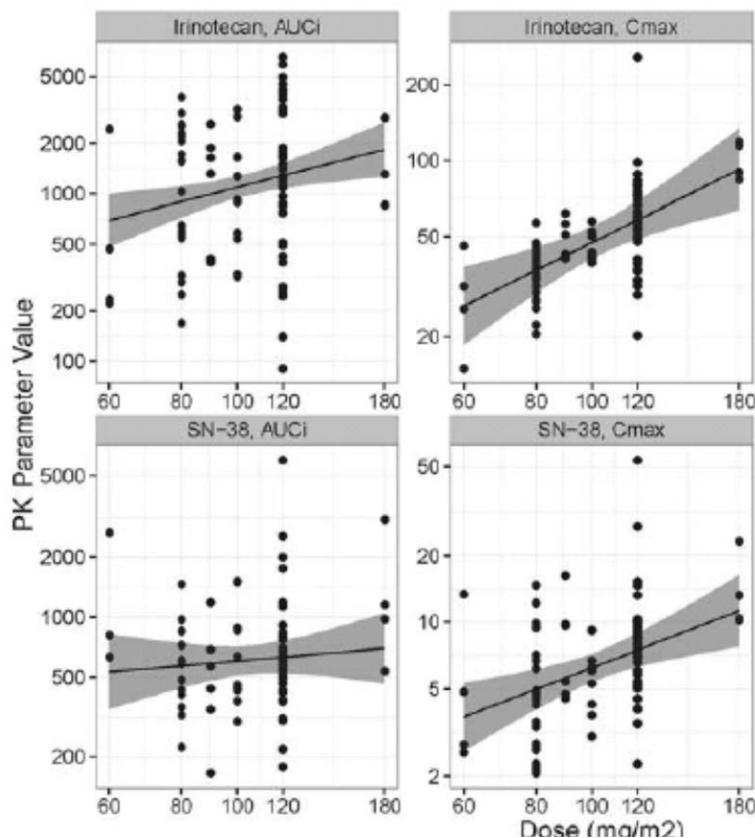
The AUC_{0-inf} and C_{max} of total irinotecan appear to increase with increasing dose. While the dose proportionality for the AUC_{0-inf} of total SN-38 appears to be relatively flat, total SN-38 C_{max} appears to increase with increasing dose.

Figure 8. Single Dose Total Irinotecan and Total SN-38 Exposure (Log AUC_{0-inf} and Log C_{max}) vs. Log of MM-398 Dose Across Multiple Studies in the Dose Range of 60 to 180 mg/m^2 .

The solid line represents the linear regression line and the shaded area represents the 95% confidence interval of the slope.

C_{max} : Total irinotecan in $\mu g/ml$, SN-38 in ng/ml

$AUC_i=AUC_{0-inf}$, Total irinotecan in $\mu g/mL*h$, SN-38 in $ng/mL*h$.



2.2.18 How do the PK parameters change with time following chronic dosing?

PK for multiple doses of MM-398 was not evaluated. The pre-dose levels of total irinotecan and total SN-38 before the second dose of MM-398 (in both q2w and q3w dosing schedules) were below limits of quantification.

2.2.19 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Total irinotecan pharmacokinetic parameters following Onivyde 80 mg/m^2 administration were highly variable. Unexplained inter-individual variability (CV%) were 77% and 88% for AUC_{0-inf} and CL, respectively (see Table 9 and section 2.2.10).

Based on the population PK modeling, between-subject variability for total irinotecan CL and Vd were approximately 89% and 49%, respectively, after adjusting for significant covariates.

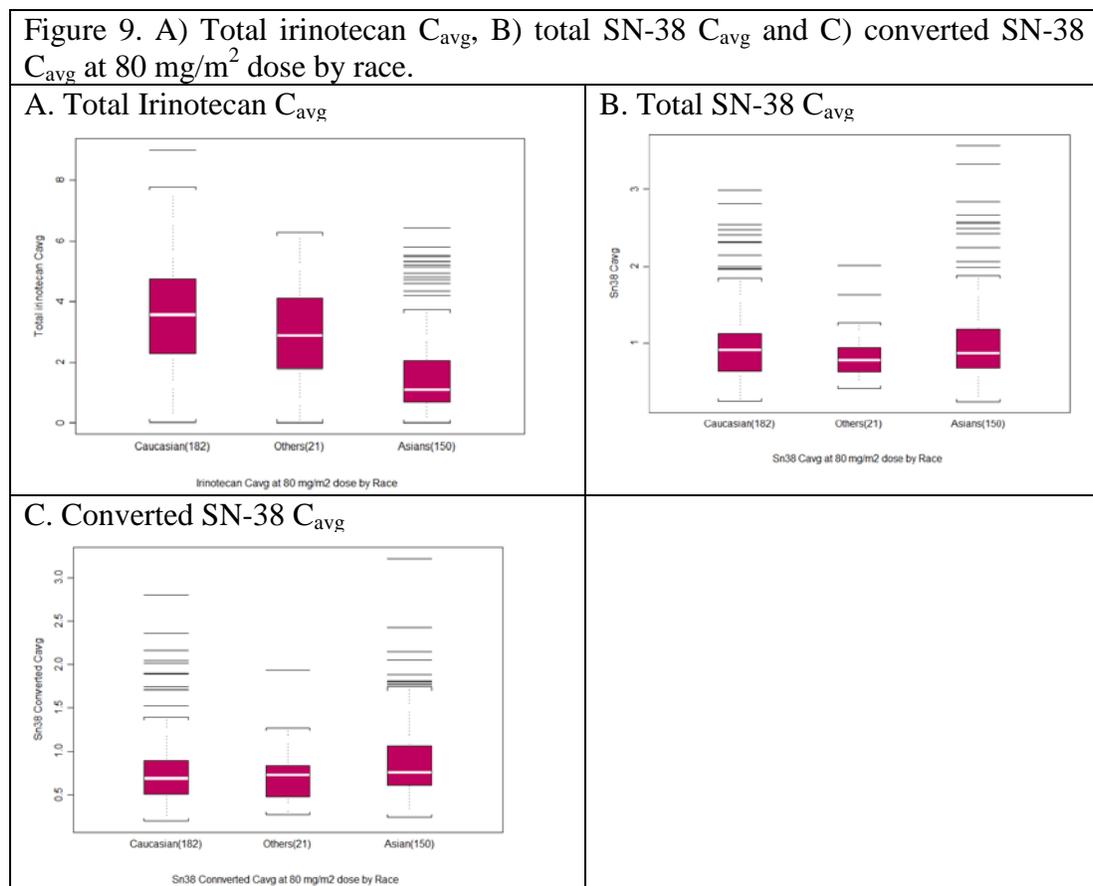
2.3 INTRINSIC FACTORS

2.3.1 Do intrinsic factors (race, gender, age, body weight, tumor type, genetic polymorphisms, renal function, and hepatic function) influence the PK of MM-398 and are dose adjustments needed based on these intrinsic factors?

No formal studies have been conducted to assess the effect of ethnicity, gender, age, body weight, genetic polymorphisms, and renal or hepatic function on the pharmacokinetics of MM-398.

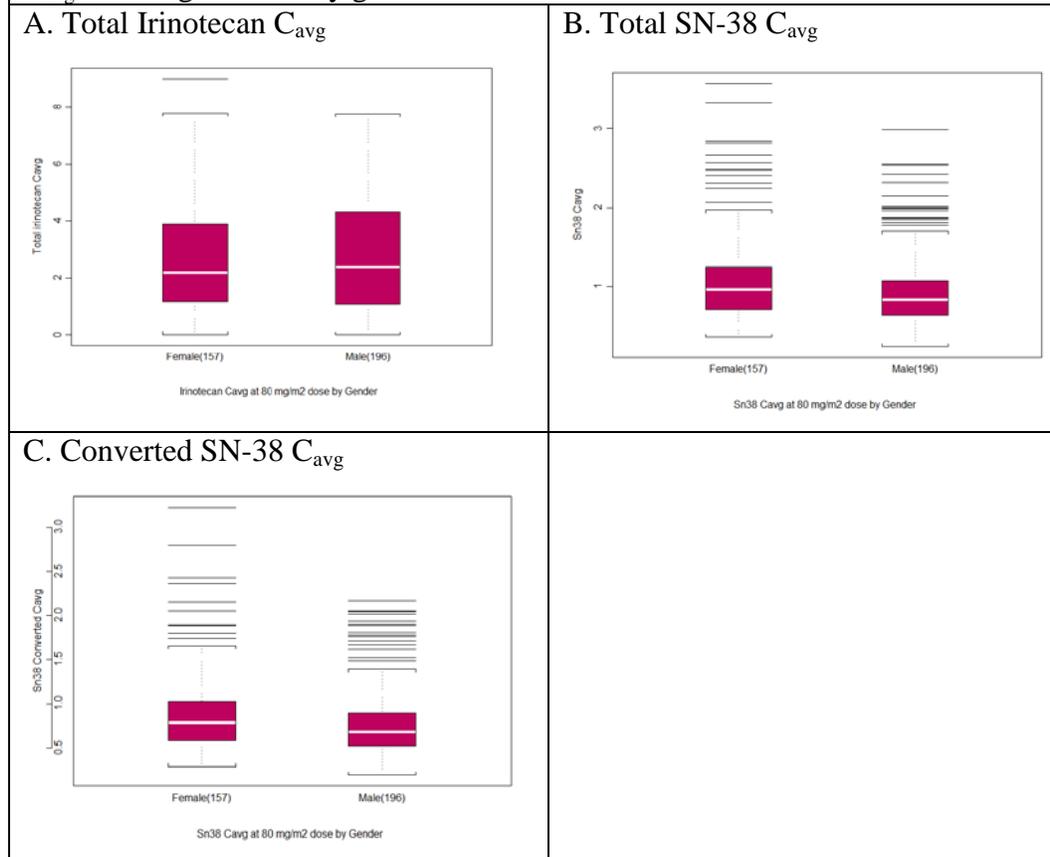
Using population PK, the effect of intrinsic factors was assessed on total irinotecan, total SN-38, and converted SN-38 exposures. The exposure metric selected for this assessment was steady state C_{avg} .

Ethnicity: The covariate with strongest association to irinotecan (CPT11) and SN-38 was ethnicity. Asians (N=150) were observed to have ~70% lower total CPT11 C_{avg} than Whites (N=182) as shown Figure 9. There was minimal effect of race on SN-38 exposure (SN-38 C_{avg} and SN38 converted C_{avg}).



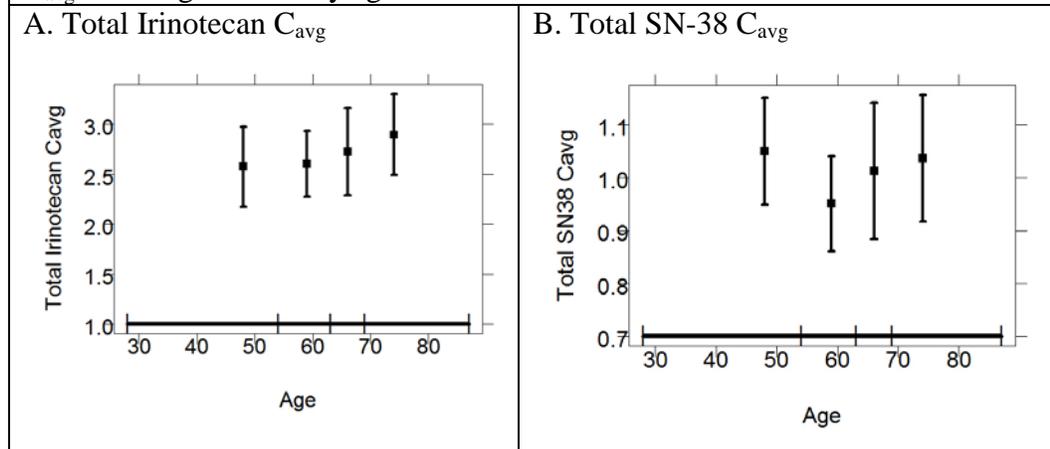
Gender: There is no clinically meaningful effect of gender on the exposure of total irinotecan, total SN-38 or converted SN-38 (Figure 10).

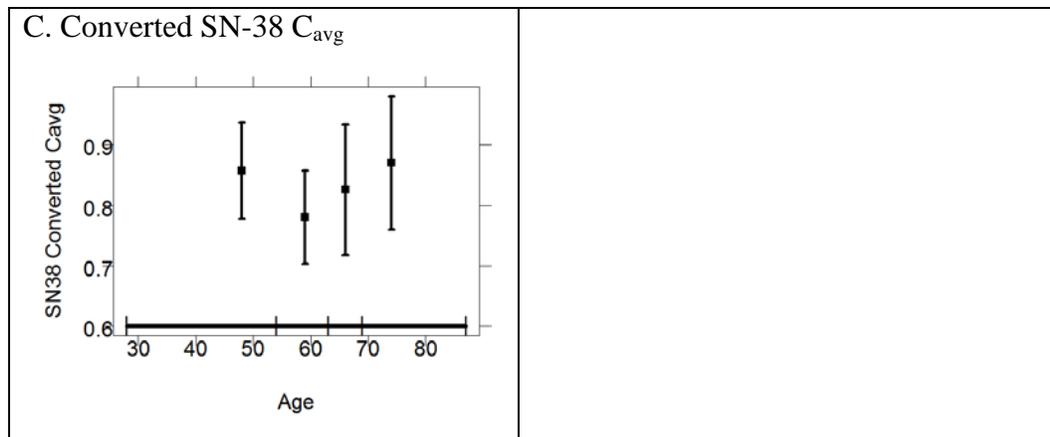
Figure 10. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by gender.



Age: There is no clinically meaningful effect of age on the exposure of total irinotecan, total SN-38 or converted SN-38 (Figure 11).

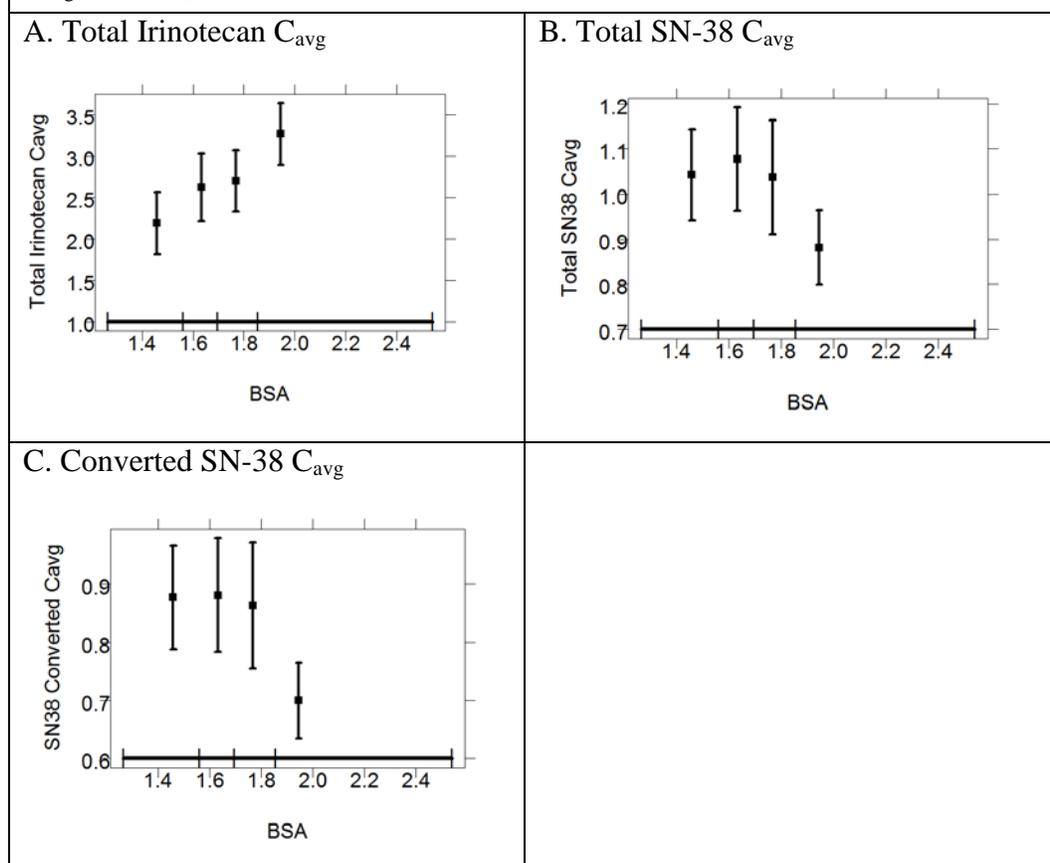
Figure 11. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by age.





Body surface area (BSA): There is a trend for increase in total irinotecan exposure with increase in BSA (Figure 12). The total irinotecan C_{avg} increases by 49% from the first quartile (1.26 – 1.56 kg/m²) to the fourth quartile (1.85 – 2.54 kg/m²). There is a slight trend for decrease (~20%) in SN-38 exposure with increase in BSA.

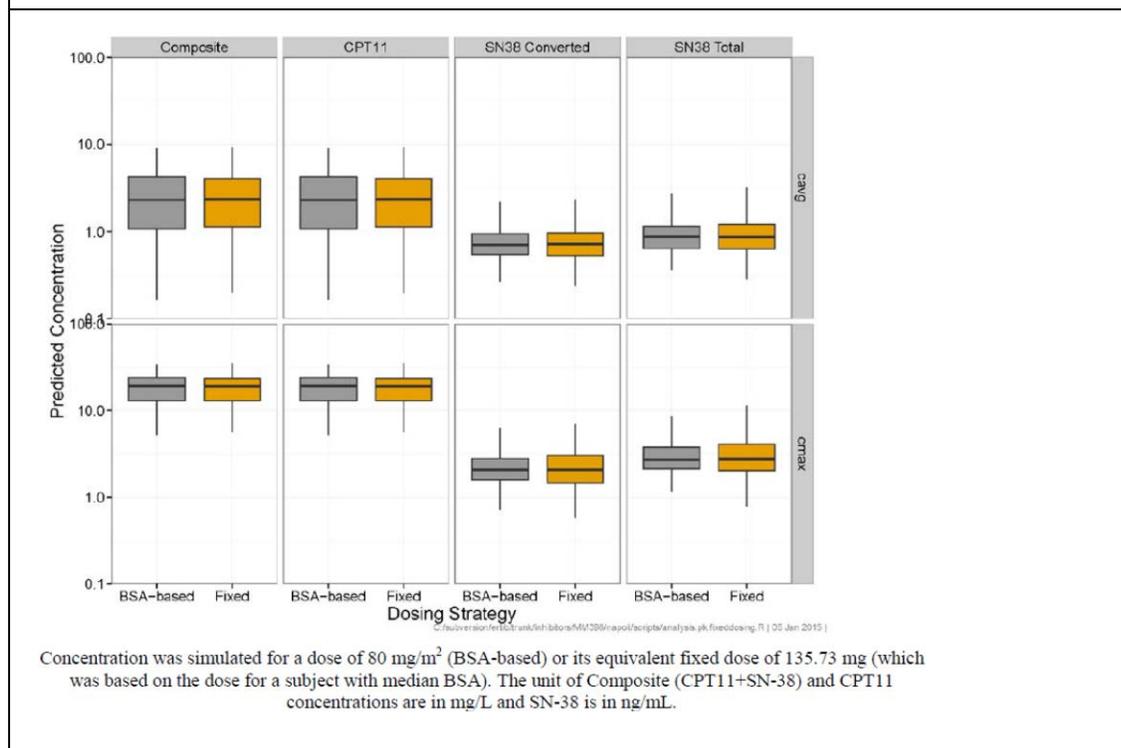
Figure 12. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by baseline BSA levels.



The applicant conducted simulations to compare the BSA-based dosing strategy versus fixed dosing strategy. Based on sponsor's simulation (Figure 13), it appears that fixed dosing strategy

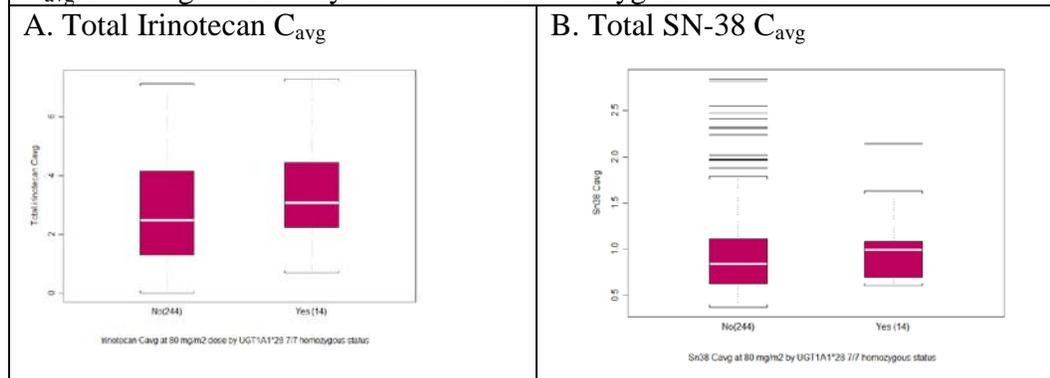
does not provide any advantage over the BSA-based dosing strategy for the population as the both dosing strategies show similar distribution of exposure in terms total irinotecan C_{avg} and total SN-38 C_{avg} .

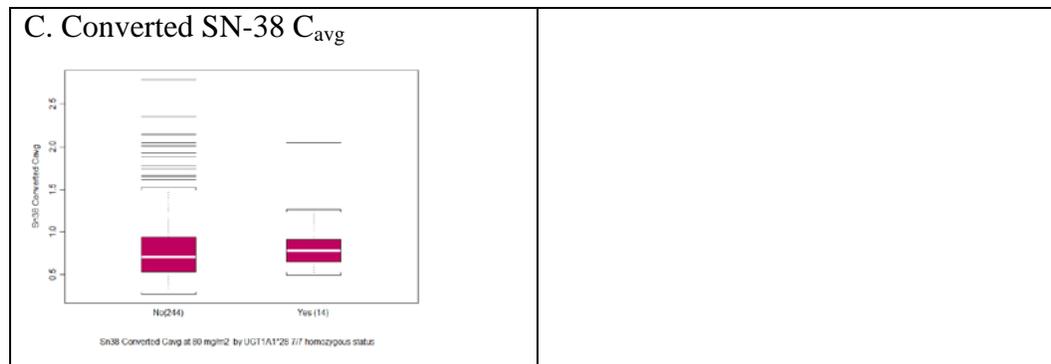
Figure 13. Simulated total irinotecan and total SN-38 concentration for BSA-based and Fixed dosing strategy.



UGT1A1*28 homozygous status: The exposure of total irinotecan and total SN38 are 24% and 18% higher in UGT1A1*28 homozygous patients (N=14) compared to non-homozygous patients (N=244) as shown in Figure 14. For dosing considerations based on UGT1A1*28 status, see section 2.2.7.

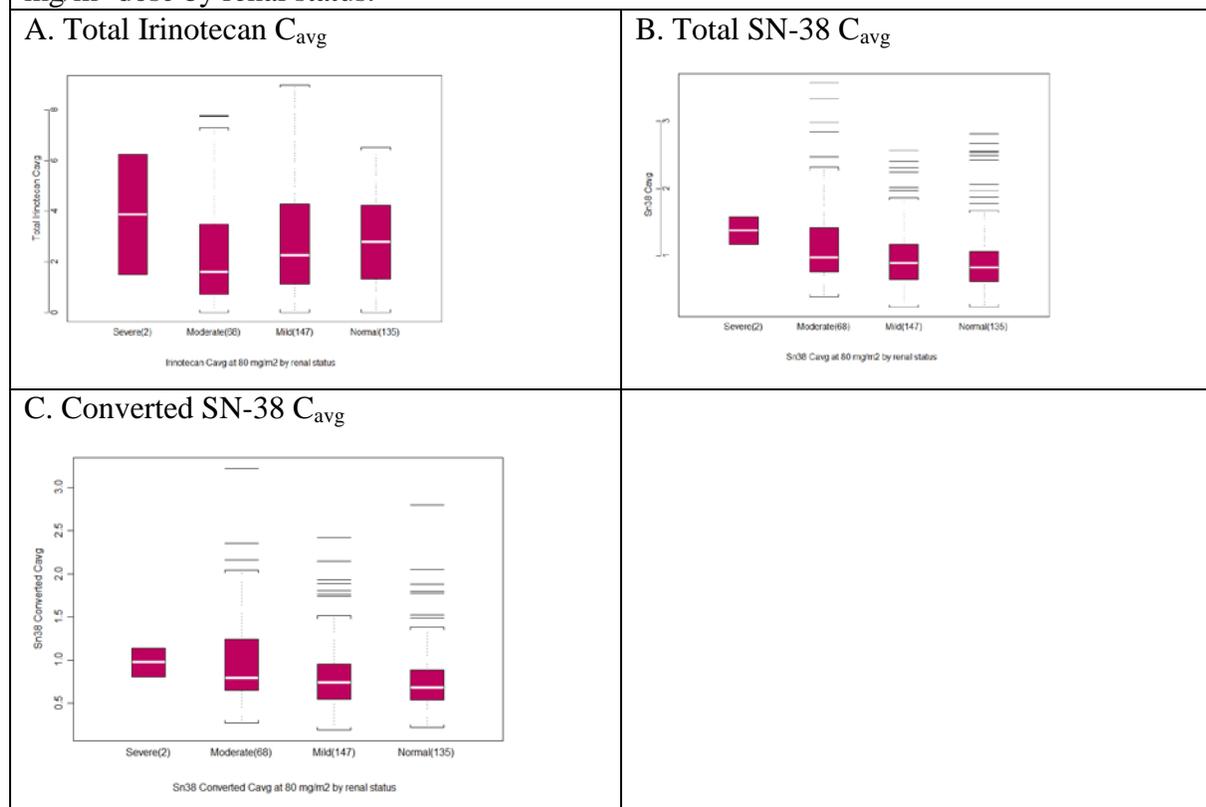
Figure 14. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by UGT1A1*28 homozygous status.





Renal status: There is no clinically meaningful effect of mild or moderate renal function on the exposure of total SN-38 (Figure 15). The exposure of total SN-38 in moderate patients (N=68) is 18% higher than normal patients (N=135). There were only two patients in the severe renal impairment category. The exposure of total SN-38 was 66% higher in those severe patients compared to normal patients. This should be viewed with caution as data are limited to only two patients.

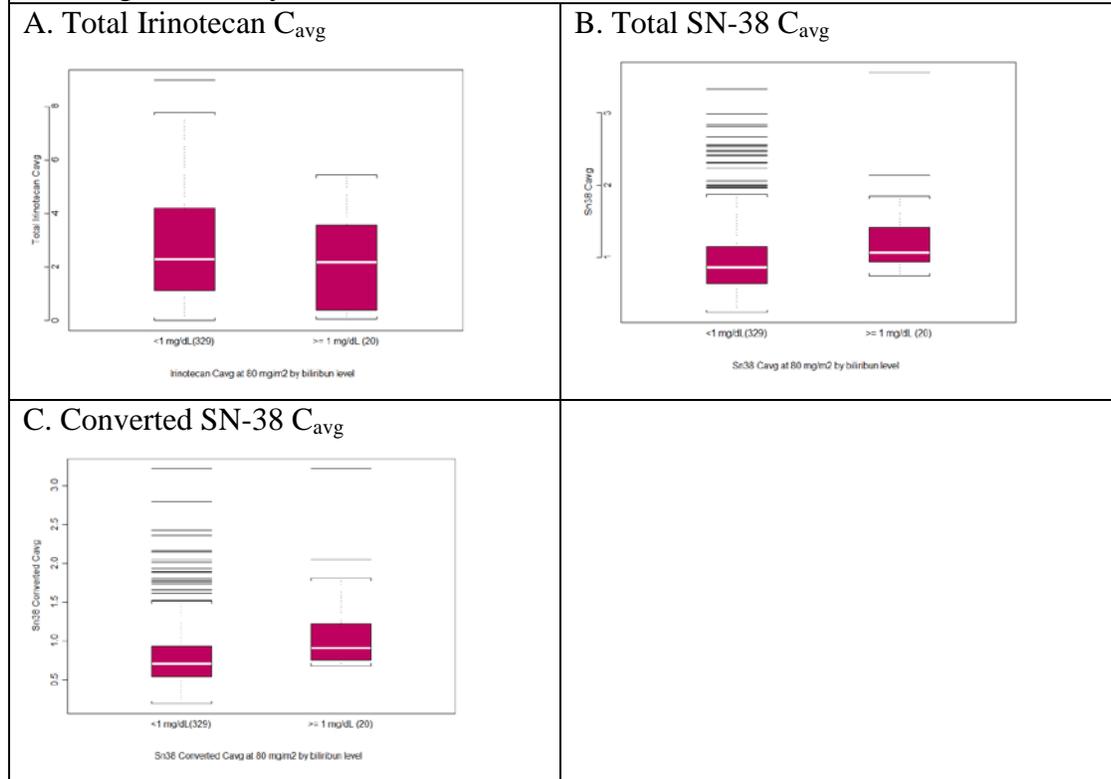
Figure 15. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by renal status.



Hepatic Enzymes:

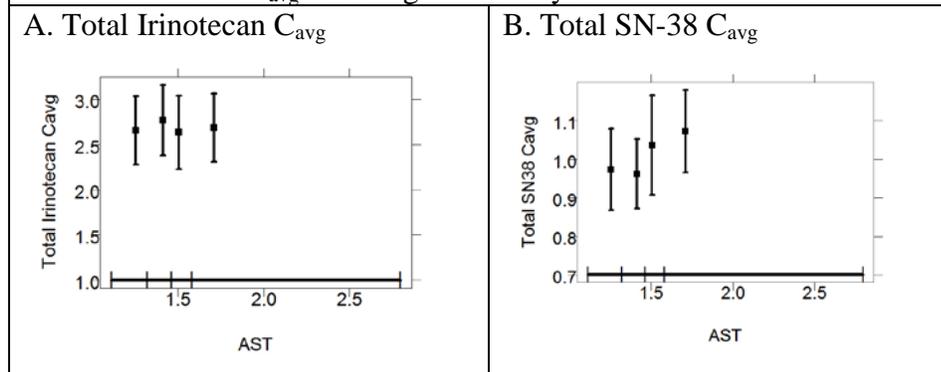
- **Bilirubin:** There is a trend for increase in total SN-38 exposure with increase in baseline bilirubin levels (Figure 16). However, this is unlikely to be clinically relevant as the total SN-38 C_{avg} is only 24% higher in patients with baseline bilirubin levels ≥ 1 mg/dL (N=20) compared to patients with bilirubin levels < 1 mg/dL (N=329). Also see section 2.2.6.

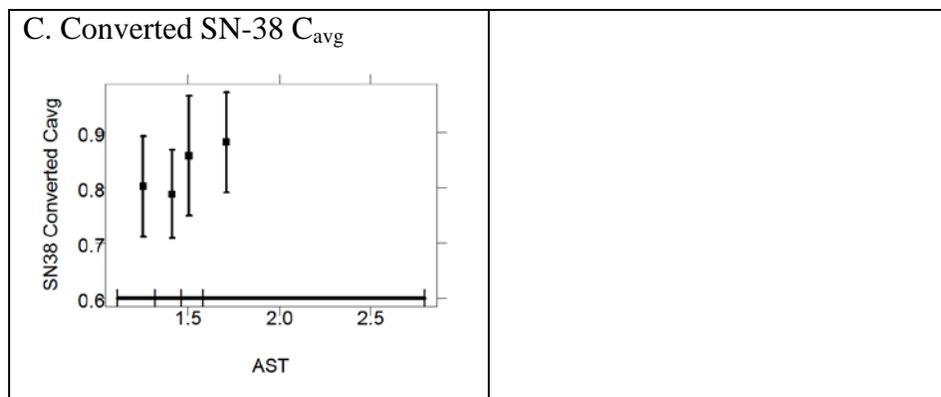
Figure 16. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by baseline bilirubin levels.



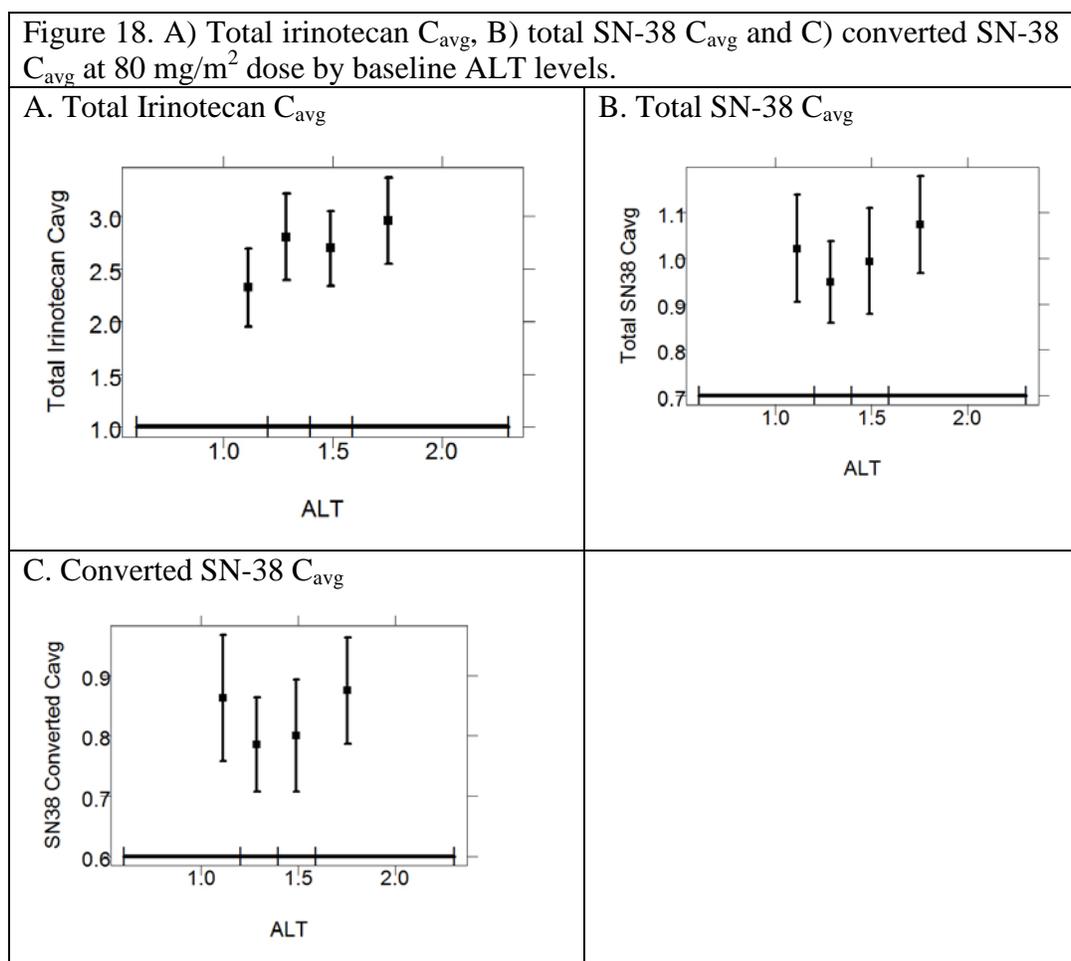
- **Aspartate aminotransferase (AST):** There is no clinically relevant effect of AST on SN-38 exposure. There is only ~10% increase in total SN-38 C_{avg} from first quartile to fourth quartile (Figure 17).

Figure 17. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by baseline AST levels.



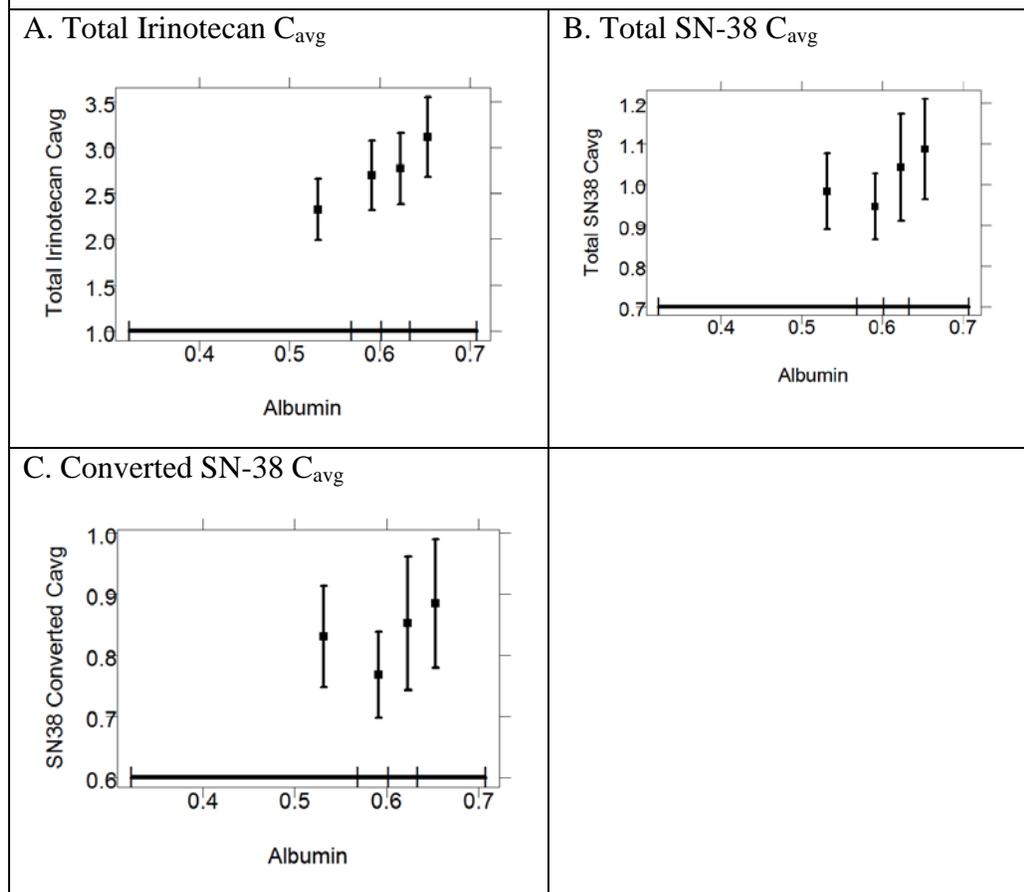


- Alanine Aminotransferase (ALT): There is no clinically relevant effect of ALT on SN-38 exposure (Figure 18). There is a slight increase in total irinotecan exposure with ALT. However there is only 27% increase from first quartile to fourth quartile.



- Albumin: There is no clinically relevant effect of albumin on total irinotecan and total SN-38 exposure (Figure 19). There is 34% increase in irinotecan exposure from first quartile to fourth quartile.

Figure 19. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by baseline albumin levels.



2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

- **Renal:** The influence of renal impairment on the PK of MM-398 (irinotecan) or SN-38 has not been evaluated. However, based on the popPK analysis, there is no clinically meaningful effect of mild or moderate renal function on the exposure of total SN-38. There were only two subjects in the severe renal impairment category. See section 2.3.1
- **Hepatic:** The influence of hepatic impairment on the PK of MM-398 (irinotecan) or SN-38 has not been evaluated. However, based on the popPK analysis, there is no clinically relevant effect of AST, ALT, or albumin on SN-38 exposure. There is a trend for increase in total SN-38 exposure with increase in baseline bilirubin levels. However, this is unlikely to be clinically relevant as the total SN-38 C_{avg} is only 24% higher in patients with baseline bilirubin levels ≥ 1 mg/dL (N=20) compared to patients with bilirubin levels < 1 mg/dL (N=329). There is no recommended dose for patients with serum bilirubin above the upper limit of normal because such patients were excluded from NAPOLI-1. See sections 2.2.6 and 2.3.1.

- Pediatric patients: The safety and effectiveness of Onivyde has not been established in pediatric patients and no data in pediatric patients were submitted.

2.3.3 What pregnancy and lactation use information is there in the application?

The safety and effectiveness of MM-398 have not been established in pregnancy and in lactating women and no data in pregnant or lactating women were submitted.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, diet, and alcohol use on the dose-exposure and/or dose-response for MM-398 have not been assessed.

Drug-drug interactions

Of note, the sponsor is relying on information from the Camptosar package insert; the information in the sections that follow is extracted from that label.

2.4.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. *In vitro* studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*.

2.4.3 Is the drug a substrate of CYP enzymes?

Yes, irinotecan is metabolized by CYP3A4; see section 2.4.2 above.

2.4.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro studies indicate that neither irinotecan, SN-38, nor another metabolite, aminopentane carboxylic acid (APC), inhibit cytochrome P-450 isozymes.

The Camptosar label does not describe irinotecan or SN-38 as inducers of CYP enzymes; no such data was submitted in the NDA.

2.4.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes?

The Camptosar label does not describe irinotecan or SN-38 as substrates and/or inhibitors of P-

gp; no such data was submitted in the NDA.

2.4.6 Are other metabolic/transporter pathways important?

Yes, SN-38 is metabolized by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1).

2.4.7 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes, MM-398 will be co-administered with 5-FU/LV. Specifically, Onivyde 80 mg/m² IV infusion over 90 minutes, every 2 weeks, with LV 400 mg/m² infusion over 30 minutes followed by 5-FU 2400 mg/m² infusion over 46 hours.

In the phase 3 study MM-398-07-03-01 (NAPOLI-1), the PK of MM-398 and 5-FU were evaluated. The data from that study support that there is no clinically relevant effect of co-administration of 5-FU on the total irinotecan and total SN3-8 exposure. Onivyde PK samples were collected following the first dose in Cycle 1 at end of infusion, 2.5-4 h after start of infusion, 8-72 h post-infusion (optional), and Week 1 (one sample on Days 5-8). 5-FU PK samples were collected the end of the first dose in Cycle 1.

- The PK of total irinotecan, total SN-38, and SN-38G were consistent with the PK observed in previous studies that evaluated different MM-398 dose regimens (e.g., 80 mg/m² q2w for MM-398+5-FU/LV and 120 mg/m² q3w for MM-398 monotherapy).
 - Total irinotecan C_{max} was higher in the 120 mg/m² q3w arm than in the 80 mg/m² q2w arm (37.6 and 26.1 mg/L, respectively).
 - Week 1 SN-38 concentration was 0.72 and 0.98 ng/mL in the MM-398 80 mg/m² q2w +5-FU/LV and MM-398 120 mg/m² q3w monotherapy, respectively.
- The pharmacokinetics of 5-FU were consistent with the differences in the 5-FU dose regimens between the combination of MM-398 with 5-FU/LV and the 5-FU/LV control arms, with the observed geometric mean ratio of 0.63 (95% CI: 0.28-1.39) (Table 17). This ratio was consistent with the theoretical ratio obtained from the difference in the infusion rate between the two treatment arms, these differences would result in a ratio of steady-state concentrations of 0.626.

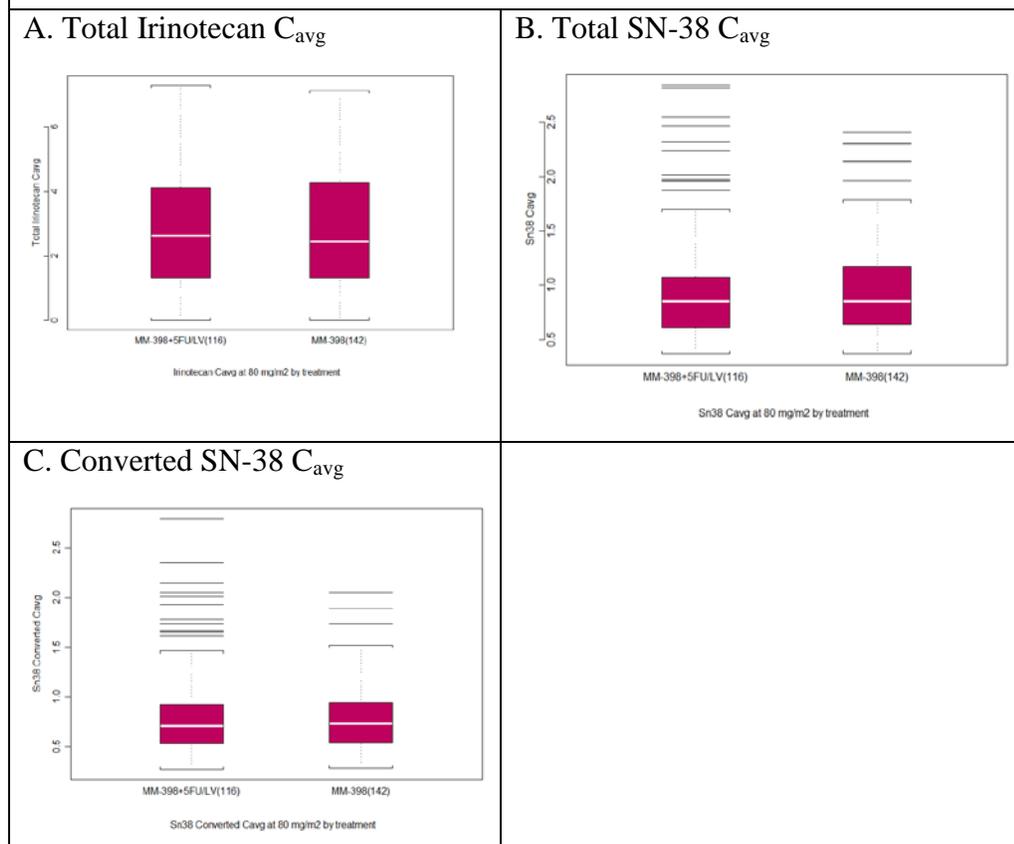
Table 17. Summary Statistics of PK of 5-FU by Treatment (Study NAPOLI-1)

Analyte	Treatment	N	Concentration					Geometric Mean Ratio (MM-398+5FU/LV:5-FU/LV) Point [95% CI]	
			Unit	Geometric Mean	% CV	Median	Inter-Quartile Dispersion		% <LLOQ
5-FU	5FU/LV	80	mg/L	0.22	384%	0.30	330%	13%	0.63 [0.28 - 1.39]
5-FU	MM-398 + 5FU/LV	84	mg/L	0.14	400%	0.22	390%	25%	

Abbreviations: 5-FU=5-fluorouracil; 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval; CV=coefficient of variance; L=liter; LLOQ=lower limit of quantification; mg=milligram

- Population PK analyses also confirm that there is no clinically meaningful effect of co-administration of 5-FU on the total irinotecan and total SN-38 exposure (Figure 20).

Figure 20. A) Total irinotecan C_{avg} , B) total SN-38 C_{avg} and C) converted SN-38 C_{avg} at 80 mg/m² dose by with/without administration of 5FU/LV.



The Camptosar package insert states that the disposition of irinotecan was not substantially altered when 5-FU/LV were co-administered which also supports the current lack of PK-based DDI between irinotecan and 5-FU/LV.

2.4.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No such data was submitted in the NDA. The sponsor is relying on information from the Camptosar package labeling as follows:

- **Moderate CYP3A4 Inducer:** Dexamethasone, a moderate CYP3A4 inducer, does not appear to alter the PK of irinotecan.
- **Strong CYP3A4 Inducers:** 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.
- **Strong CYP3A4 or UGT1A1 Inhibitors:** Patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

BCS classification is not an issue for this parenteral formulation.

2.5.2 What is the composition of the to-be-marketed formulation?

Onivyde is a sterile, white to slightly yellow opaque isotonic liposomal dispersion. Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelled or precipitated state as the sucroseoctasulfate salt. The vesicle is composed the (b) (4) distearoylphosphatidylcholine (DSPC; (b) (4) cholesterol (b) (4) methoxy-(polyethylene glycol)-derivatized distearoylethanolamine (mPEG2000-DSPE) (b) (4)

2.5.3 What moieties should be assessed in bioequivalence studies?

Bioequivalence is not an issue, as the to-be-marketed formulation was studied in the safety and efficacy study.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food is not an issue for parenteral formulations.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

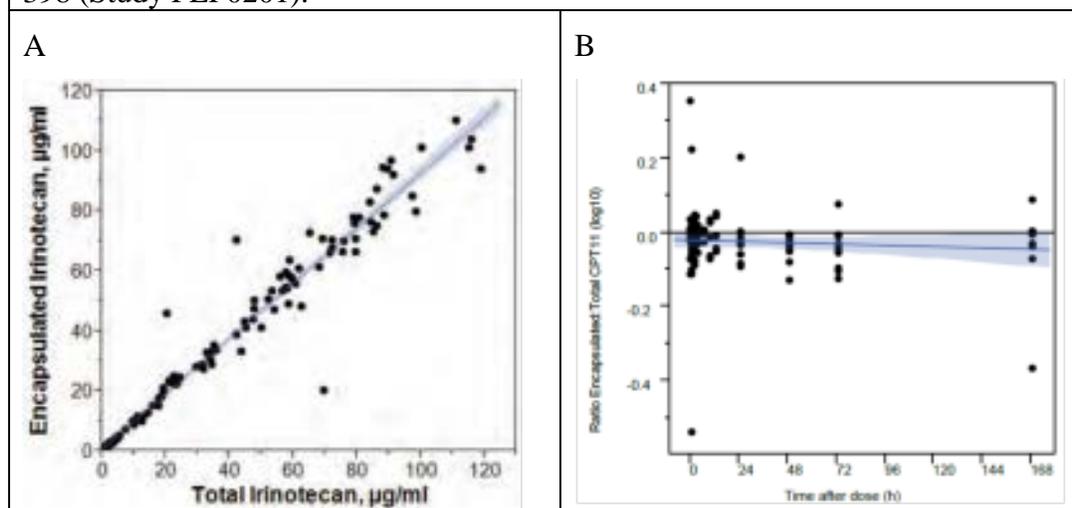
There are no unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE.

2.5.6 What is the *in-vivo* stability of MM-398?

In Study PEP0201, the *in vivo* stability of Onivyde (irinotecan liposomal formulation) was evaluated by comparing the total and encapsulated forms of irinotecan in 11 patients dosed with MM-398 (60, 120 or 180 mg/m²). The results are as follows:

- Total and encapsulated forms were indistinguishable (n= 112 matched PK samples; Pearson correlation= 0.996, ratio=0.95 [95% CI= 0.7-1.6]; RMSE=0.08) (Figure 21, Panel A).
- The ratios between total and encapsulated did not appear to change over time, with a slope of log₁₀(ratios) by time of -0.000026 h⁻¹ (SE=0.00017) (Figure 21, Panel B).

Figure 21. Total and encapsulated irinotecan concentrations (Panel A) and Ratio of encapsulated:total irinotecan by time (Panel B) after administration of MM-398 (Study PEP0201).



2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, all the submitted clinical pharmacology related studies analyzed plasma samples for total irinotecan (which includes encapsulated and unencapsulated irinotecan), its active metabolite SN-38 and its inactive glucuronidated form SN-38G. See sections 2.2.3 and 2.2.8.

2.6.2 Which metabolites have been selected for analysis and why?

Irinotecan's active metabolite SN-38 and its inactive glucuronidated form SN-38G were analyzed. See section 2.2.3.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Encapsulated irinotecan (PEP02) was measured in Study PEP0201. The results showed that encapsulated (PEP02) and total irinotecan (CPT-11) was indistinguishable (see section 2.5.6). Un-encapsulated irinotecan was not measured because of this finding and SN-38 was used as the surrogate to measure the un-encapsulated (released) form of irinotecan. The measurement of total concentrations in clinical trials is acceptable.

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>)

The bioanalytical methods used to measure encapsulated irinotecan (PEP02), total irinotecan (CPT-11), SN-38, SN-38G, and 5-FU concentrations in human plasma or tissue pharmacokinetic samples were developed and validated. A summary of the clinical studies and the associated assay report numbers is provided in Table 18.

- A LC/MS/MS assay for the determination of liposome-encapsulated irinotecan concentration in human potassium oxalate/sodium fluoride human plasma was validated.
- A LC/MS/MS assay for the detection and quantitation of total irinotecan (CPT-11), its metabolite SN-38, and SN-38G in human potassium oxalate/sodium fluoride human plasma was validated.
- A LC/MS/MS assay for detection and quantitation of total irinotecan (CPT-11), its metabolite SN-38, and SN-38G in tumor biopsies was validated.
- A LC/MS/MS assay for the detection and quantitation of 5-FU in K₂EDTA human plasma was fully validated using K₂EDTA human plasma and then partially validated using sodium heparin human plasma as the matrix.

Details of each method are described in the respective validation reports.

Table 18. Assays Used to Quantify Analytes in Clinical Studies

Clinical studies	Sample Analytical Report #	Assay Validation Report #	Analyte	Location of Assay Development and Validation	
PEP0201	T125-0402 and T125-0404	T125-0403, T125-0403addendum, T125-0403addendum1_frozen T125-0403addendum1_stocksolution	Encapsulated irinotecan	(b) (4)	
		T125-0401, T125-0401addendum1 T125-0401addendum	CPT-11, SN-38 CPT-11		
		J5CP11HV01 J5CP11HV02	CPT-11, SN-38		
PEP0206	T125-0804	T125-0901 VAR-090323, T125-0401, T125-0401addendum, T125-0401addendum1, T125-0801amendment1	CPT-11, SN-38 CPT-11 CPT-11, SN-38 CPT-11		
		T125-0803 T125-0803amendment1	SN-38		
		T125-0802	SN-38G		
		T125-0401, T125-0401addendum, T125-0401addendum1, T125-0801amendment1	CPT-11, SN-38 CPT-11 CPT-11, SN-38 CPT-11		
PIST-CRC-01	T377-0901	T125-0803 T125-0803amendment1	SN-38		
		T125-0802	SN-38G		
		379-1201A 379-1201B 379-1201C 379-1201D	379-1301amendment2 379-1102 379-1103amendment1 42-1211 42-1211amendment1		CPT-11 SN-38 SN-38G 5-FU
MM-398-07-03-01 (NAPOLI-1)	379-1201A 379-1201B 379-1201C 379-1201D	379-1303A 379-1303B 379-1303C	379-1301 379-1102 379-1103amendment1		CPT-11 SN-38 SN-38G
		MN1011	CPT-11, SN-38, SN-38G		

CPT-11= total irinotecan

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The validated LC-MS/MS methods for plasma irinotecan analyte pharmacokinetics analyses were used in the Clinical Pharmacology studies submitted in this NDA.

Results for irinotecan analytes were calculated using peak area ratios of analyte to internal standard and calibration curves were generated using a weighted ($1/x$ or $1/x^2$) linear least-squares regression. For the inter- and intra-assay evaluations, a mean %bias of $\leq \pm 15\%$ from theoretical was considered acceptable for each calibration standard, except at the lowest calibration

standard, where a mean %bias of $\leq \pm 20\%$ from the theoretical was considered acceptable. The methods were appropriate for analyses of analyte plasma concentrations in all the trials.

- Assays used to measure encapsulated irinotecan in plasma were designed to measure concentration in the low (2-300 ng/mL) and high (2-300 $\mu\text{g/mL}$) range of concentrations (Table 19).

Table 19. Comparison of Encapsulated Irinotecan (PEP02) Assays and Assay Performance Summaries.

Study Number	(b) (4) T125-0403
Analyte Name	Liposome-encapsulated irinotecan
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein precipitation
Sample Volume	200 μL
QC Concentrations	2, 6, 100, and 1800 ng/mL
Standard Curve Concentrations	2, 6, 20, 100, 500, 1000, 1500 and 2000 ng/mL
Lower Limit Of Quantitation	2 ng/mL
Upper Limit Of Quantitation	2000 ng/mL
Average Recovery of Drug (%)	74.9
Average Recovery of IS (%)	105.8
QC Intraday Precision Range (%CV)	1.2 to 6.7
QC Intraday Accuracy Range (%RE)	-1.2 to 5.3
QC Interday Precision Range (%CV)	1.8 to 6.0
QC Interday Accuracy Range (%RE)	-2.6 to 1.3
Stock Solution Solvent	100% DMSO
Benchtop Stability in Plasma	19 Hours at Room Temperature
Autosampler Stability (Stability in Processed Samples)	60 hours at Room Temperature
Freeze/Thaw Stability in Plasma	3 Cycles at -70°C
Dilution Integrity	20000 ng/mL, diluted 10-fold
Selectivity	$\leq 20.0\%$ LLOQ for analyte; $\leq 5.0\%$ for IS

Study Numbers	(b) (4) T125-0403 addendum T125-0403 addendum1_stocksolution T125-0403 addendum1_frozen
Analyte Name	PEP02
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein precipitation
Sample Volume	100 μL
QC Concentrations	0.3, 0.6, 30, and 270 $\mu\text{g/mL}$
Standard Curve Concentrations	0.3, 0.6, 3, 20, 60, 100, 200, and 300 $\mu\text{g/mL}$
Lower Limit Of Quantitation	0.3 $\mu\text{g/mL}$
Upper Limit Of Quantitation	300 $\mu\text{g/mL}$
Average Recovery of Drug (%)	47.4
Average Recovery of Internal Standard (%)	84.1
QC Intraday Precision Range (%CV)	1.9 to 5.7
QC Intraday Accuracy Range (%RE)	-3.3 to 1
QC Interday Precision Range (%CV)	3.0 to 4.8
QC Interday Accuracy Range (%RE)	-2.6 to 3.3
Master Stock Solution Stability in solvent	91 Days at 4°C
Master Stock Solution Stability in water	8 Hours at Room Temperature
Benchtop Stability in Plasma	19 Hours at Room Temperature
Freeze/Thaw Stability in Plasma	3 Cycles at -70°C
Long-term Frozen Stability in Plasma	147 Days at -70°C
Dilution Integrity	1000 $\mu\text{g/mL}$, diluted 10-fold
Selectivity	$\leq 20.0\%$ LLOQ for analyte; $\leq 5.0\%$ for IS

*PEP02=liposomal encapsulated irinotecan

- Assays used to measure total irinotecan in plasma were designed to measure concentration in the low and high range of concentrations (Table 20).

Table 20. Comparison of Total Irinotecan (CPT-11) Assays.

Study Number	T125-0401	T125-0401addendum and T125-0401addendumI	T125-0801	J5CP11HV01, J5CP11HV02 ¹	379-1301
Analyte Name	CPT-11	CPT-11	CPT-11	CPT-11	CPT-11
Internal Standard (IS)	(b) (4)				
Sample Volume	100 µL	50 µL	100 µL	200 µL	50 µL
QC Concentrations	2, 6, 100, and 1800 ng/mL	0.3, 0.6, 30, and 270 µg/mL	60, 180, 700, and 5000 ng/mL	High: 0.2, 0.6, 6, 80 µg/mL Low: 1, 3, 40, 400 ng/mL	0.14, 0.42, 5.6, 35, and 56 µg/mL
Standard Curve Concentrations	2, 6, 20, 100, 500, 1000, 1500, and 2000 ng/mL	0.3, 0.6, 3, 20, 60, 100, 200, and 300 µg/mL	60, 100, 200, 500, 1000, 2000, 4000, and 6000 ng/mL	High: 0, 0.2, 0.5, 1, 2, 5, 10, 20, 50, 100 µg/mL Low: 0, 1, 2, 5, 20, 50, 100, 200, 500 ng/mL	0.14, 0.28, 1.4, 2.8, 7, 28, 60, and 70 µg/mL
Lower Limit Of Quantitation	2 ng/mL	0.3 µg/mL	60 ng/mL	High: 200 ng/mL Low: 1 ng/mL	0.14 µg/mL
Upper Limit Of Quantitation	2000g/mL	300 µg/mL	6000ng/mL	High: 100µg/mL Low: 0.5µg/mL	70 µg/mL
Stability in Plasma		210 days at -70°C	567 days at -70°C	415 days at -80°C	96 days at -20°C and -70°C 657 days at -70°C
Weighting of Regression Analysis	1/X	1/X ²	1/X	1/X	1/X ²

¹Two assays were developed to measure low (1-500 ng/mL, J5CP11HV02) and high concentration (0.2-100 µg/mL, J5CP11HV01) of irinotecan

Tables 21-25 contain the validation summaries for the total irinotecan assays described in Table 18 above.

Table 21. (b) (4) T125-0401 and Addendum Assay Performance.

Assay	Assay Range	Intraday Precision (CV%)	Intraday Accuracy (%Diff)	Interday Precision (%CV)	Interday Accuracy (%Diff)
T125-0401	2-2000 ng/mL	1.0 to 8.1	-7.0 to 6.7	3.8 to 4.3	-7.2 to 3.0
T125-0401 Addendum	0.3-300 µg/mL	2.4 to 13.4	-5.9 to 5.7	2.0 to 6.8	-5.9 to 4.0

Table 22. (b) (4) T125-0801 Assay Validation Summary.

Report Title	Partial Validation of a Method for the Determination of Irinotecan Hydrochloride Trihydrate in Potassium Oxalate/NaF Human Plasma by LC-MS/MS
Report Number	(b) (4) T125-0801
Analyte Name	Irinotecan Hydrochloride Trihydrate
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein Precipitation Extraction
QC Concentrations	60, 180, 700 and 5000 ng/mL
Standard Curve Concentrations	60, 100, 200, 500, 1000, 2000, 4000 and 6000 ng/mL
Lower Limit Of Quantitation	60 ng/mL
Upper Limit Of Quantitation	6000 ng/mL
QC Intraday Precision Range (%CV)	1.6 to 3.4
QC Intraday Accuracy Range (%RE)	-4.4 to 10.1
Frozen Master Stock Solution Stability in 100% DMSO	253 Days at -70°C
Master Stock Solution Stability in 100% DMSO	17 Hours at Room Temperature
Freeze/Thaw Stability in Potassium Oxalate/NaF Human Plasma	9 Cycles at -70°C
Long-term Storage Stability in Potassium Oxalate/NaF Human Plasma	567 Days at -70°C

Table 23. J5CP11HVO1 Assay Validation Summary.

Irinotecan

- Standard curve linear range:** 200 ng/mL ~ 100000 ng/mL.
Precision: 1.3% ~ 4.9%.
Accuracy: -3.7% ~ 4.7%.
- Selectivity:** Yes.
Response variability at concentration 200 ng/mL (LLOQ).
 - Peak area (CV %): 4.5%.
- Within run precision and accuracy of quality control samples**
Precision: 4.0% ~ 9.0% at 600 ng/mL, 1.7% ~ 4.9% at 6000 ng/mL, 1.9% ~ 4.0% at 80000 ng/mL and 9.9% ~ 13.4% at 150000 ng/mL, respectively.
Accuracy: -3.5% ~ 2.7% at 600 ng/mL, -2.5% ~ 4.3% at 6000 ng/mL, 0.8% ~ 4.0% at 80000 ng/mL and -1.2% ~ 6.6% at 150000 ng/mL, respectively.
- Between run precision and accuracy of quality control samples**
Precision: 6.1% at 600 ng/mL, 4.3% at 6000 ng/mL, 3.3% at 80000 ng/mL and 10.9% at 150000 ng/mL, respectively.
Accuracy: 1.0% at 600 ng/mL, 1.6% at 6000 ng/mL, 2.4% at 80000 ng/mL and 2.5% at 150000 ng/mL, respectively.

- Lower limit of quantification:** 200 ng/mL.
 - Within run precision and accuracy**
Precision: 2.7% ~ 12.4%.
Accuracy: -4.5% ~ 12.3%.
 - Between run precision and accuracy**
Precision: 8.4%.
Accuracy: 2.0%.
- Recovery:** 94.9% for irinotecan and 93.9% for internal standard.
- Short-term stability:** at least 23 hours at room temperature.
- Post-preparative stability:** at least 73 hours at room temperature and a 4°C refrigerator.
- Long-term stability:** at least 415 days at a -80°C freezer.

Table 24. J5CP11HVO2 Assay Validation Summary.

Irinotecan

- Standard curve linear range:** 1 ng/mL ~ 500 ng/mL.
Precision: 2.2% ~ 9.0%.
Accuracy: -6.2% ~ 9.4%.
- Selectivity:** Yes.
Response variability at concentration 1 ng/mL (LLOQ).
 - Peak area (CV %): 8.3%.
- Within run precision and accuracy of quality control samples**
Precision: 4.8% ~ 13.5% at 3 ng/mL, 4.3% ~ 10.3% at 40 ng/mL and 3.4% ~ 8.0% at 400 ng/mL, respectively.
Accuracy: -7.1% ~ 1.6% at 3 ng/mL, -6.5% ~ 6.9% at 40 ng/mL and -4.4% ~ 10.0% at 400 ng/mL, respectively.
- Between run precision and accuracy of quality control samples**
Precision: 8.8% at 3 ng/mL, 8.3% at 40 ng/mL and 8.3% at 400 ng/mL, respectively.
Accuracy: -3.4% at 3 ng/mL, -2.2% at 6000 ng/mL and 2.9% at 400 ng/mL, respectively.
- Lower limit of quantification:** 1 ng/mL.
 - Within run precision and accuracy**
Precision: 7.7% ~ 14.6%.
Accuracy: -1.7% ~ 7.5%.
 - Between run precision and accuracy**
Precision: 10.7%.
Accuracy: 1.7%.
- Recovery:** 81.8% for irinotecan and 81.3% for internal standard.
- Short-term stability:** at least 23 hours at room temperature.
- Post-preparative stability:** at least 24 hours at room temperature and a 4°C refrigerator.
- Long-term stability:** at least 431 days at a -80°C freezer.

Table 25. (b) (4) 379-1301 Assay Validation Summary.

Report Title	Validation of a Method for the Quantitation of Total Irinotecan in Potassium Oxalate/Sodium Fluoride Human Plasma by LC-MS/MS
Study Number	(b) (4) 379-1301
Analyte Name	Irinotecan
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein precipitation
Sample Volume	50 µL
QC Concentrations	0.14, 0.42, 5.6, 35, and 56 µg/mL
Standard Curve Concentrations	0.14, 0.28, 1.4, 2.8, 7, 28, 60, and 70 µg/mL
Lower Limit Of Quantitation	0.14 µg/mL
Upper Limit Of Quantitation	70 µg/mL
Average Recovery of Drug (%)	105.2
Average Recovery of Internal Standard (%)	NA*
QC Intraday Precision Range (%CV)	0.9 to 6.5
QC Intraday Accuracy Range (%RE)	-12.9 to 1.0
QC Interday Precision Range (%CV)	1.4 to 4.1
QC Interday Accuracy Range (%RE)	-12.9 to 0.0
Stock Solution Solvent	17 mM HEPES 144 mM NaCl pH=7.25
Master Stock Solution Stability in 17 mM HEPES 144 mM NaCl pH=7.25	6 Hours at Ambient Temperature
Processed Sample Stability	170 Hours at 4°C
Benchtop Stability in KOx/NaF Human Plasma	24 Hours at Room Temperature
Freeze/Thaw Stability in KOx/NaF Human Plasma	3 Cycles at -20°C 5 Cycles at -70°C
Benchtop Stability in Whole Blood	2 Hours at Room Temperature
Long-term Storage Stability in KOx/NaF Human Plasma	96 Days at -20°C and -70°C To Be Determined at 14 Months at -70°C
Dilution Integrity	200 µg/mL diluted 10-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS

* Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

- Assays to measure SN-38 in plasma had LLOQ values of 0.6-1 ng/mL and ULOQ values of 120-1000 ng/mL (Table 26).

Table 26. Comparison of SN-38 Assays.

Study Number	T125-0401 T125-0401 addendum 1	T125-0803 Amendment 1	379-1102	J5CP11HV02
Analyte Name	SN-38	SN-38	SN-38	SN-38
Internal Standard (IS)	(b) (4)			
QC Concentrations	1, 3, 50, and 900 ng/mL	0.6, 1.8, 10, and 100 ng/mL	0.6, 1.8, 10, and 100 ng/mL	1, 3, 40, and 400 ng/mL
Standard Curve Concentrations	1, 3, 10, 50, 250, 500, 750, and 1000 ng/mL	0.6, 1, 2, 5, 20, 50, 90, and 120 ng/mL	0.6, 1, 2, 5, 20, 50, 90, and 120 ng/mL	0, 1, 2, 5, 20, 50, 100, 200 and 500 ng/mL
Lower Limit Of Quantitation	1 ng/mL	0.6 ng/mL	0.6 ng/mL	1 ng/mL
Upper Limit Of Quantitation	1000 ng/mL	120 ng/mL	120 ng/mL	0.5 µg/mL
Stability in matrix (human Plasma)	210 days at -70°C	566 days at -70°C	113 days at -20°C 566 days at -70°C	415 days at -80°C
Dilution Integrity	10000 ng/mL diluted 10-fold	1000 ng/mL diluted 10-fold	600 ng/mL diluted 10-fold	
Weighting of Regression Analysis	1/X	1/X	1/X ²	1/X

Tables 27-30 contain the validation summaries for SN-38 for the total SN-38 assays described in Table 26 above.

Table 27. (b) (4) T125-0401 Assay Performance.

Analyte	Assay Range (ng/mL)	Intraday Precision (%CV)	Intraday Accuracy (%Diff)	Interday Precision (%CV)	Interday Accuracy (%Diff)
SN-38	1 to 1000	1.4 to 15.5	-6.0 to 3.7	2.2 to 9.6	-0.2 to 2.0

Table 28. (b) (4) T125-0803 Assay Validation Summary.

Report Title	Partial Validation of a Method for the Determination of SN-38 in Potassium Oxalate/NaF Human Plasma by LC-MS/MS
Report Number	(b) (4) T125-0803
Analyte Name	SN-38
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein Precipitation Extraction
QC Concentrations	0.6, 1.8, 10 and 100 ng/mL
Standard Curve Concentrations	0.6, 1, 2, 5, 20, 50, 90 and 120 ng/mL
Lower Limit Of Quantitation	0.6 ng/mL
Upper Limit Of Quantitation	120 ng/mL
Average Recovery of Drug (%)	89.0 %
Average Recovery of Internal Standard (%)	87.1 %
QC Intraday Precision Range (%CV)	2.3 to 16.7
QC Intraday Accuracy Range (%RE)	-10.3 to -2.6
Reinjection Reproducibility in Processed Samples	70 Hours at Room Temperature
Benchmark Stability in Potassium Oxalate/NaF Human Plasma	17 Hours at Room Temperature
Freeze/Thaw Stability in Potassium Oxalate/NaF Human Plasma	9 Cycles at -70°C
Frozen Master Stock Solution Stability in 100% Dimethyl Sulfoxide	266 Days at -70°C
Master Stock Solution Stability in 100% Dimethyl Sulfoxide	17 Hours at Room Temperature
Long-term Storage Stability in Potassium Oxalate/NaF Human Plasma	566 Days at -70°C
Dilution Integrity	1000 ng/mL diluted 10-fold
Selectivity	≤ 20.0% LLOQ for SN-38; ≤ 5.0% for (S)-(+)-Camptothecin

Table 29. (b) (4) 379-1102 Assay Validation Summary.

Report Title	Validation of a Method for the Quantitation of SN-38 in Potassium Oxalate/NaF Human Plasma by LC-MS/MS
Study Number	(b) (4) 379-1102
Analyte Name	SN-38
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein precipitation
Sample Volume	50 µL
QC Concentrations	0.6, 1.8, 10, and 100 ng/mL
Standard Curve Concentrations	0.6, 1, 2, 5, 20, 50, 90, and 120 ng/mL
Lower Limit Of Quantitation	0.6 ng/mL
Upper Limit Of Quantitation	120 ng/mL
Average Recovery of Drug (%)	118.2
Average Recovery of Internal Standard (%)	NA ^a
QC Intraday Precision Range (%CV)	1.4 to 8.2
QC Intraday Accuracy Range (%RE)	-6.8 to 0.3
QC Interday Precision Range (%CV)	2.4 to 6.9
QC Interday Accuracy Range (%RE)	-3.3 to -2.1
Stock Solution Solvent	DMSO ^b
Master Stock Solution Stability in DMSO	266 Days at -70°C ^b
Master Stock Solution Stability in DMSO	17 Hours at Room Temperature ^b
Reinjection Reproducibility in Processed Samples	145 Hours at 4°C
Benchmark Stability in Plasma	17 Hours at Room Temperature ^b
Freeze/Thaw Stability in Plasma	9 Cycles at -70°C ^b
Long-term Storage Stability in Plasma	113 Days at -20°C 566 Days at -70°C ^b
Dilution Integrity	600 ng/mL diluted 10-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS

^a Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

^b Refer to (b) (4) Report T125-0803 Amendment 1

Table 30. J5CP11HVO2 Assay Validation Summary.
SN38

1. **Standard curve linear range:** 1 ng/mL ~ 500 ng/mL.
Precision: 2.3% ~ 9.2%.
Accuracy: -8.5% ~ 12.8%.
2. **Selectivity:** Yes.
Response variability at concentration 1 ng/mL (LLOQ).
 - Peak area (CV %): 14.2%.
3. **Within run precision and accuracy of quality control samples**
Precision: 4.9% ~ 9.8% at 3 ng/mL, 4.2% ~ 8.7% at 40 ng/mL and 1.8% ~ 9.3% at 400 ng/mL, respectively.
Accuracy: -8.2% ~ -1.7% at 3 ng/mL, -10.0% ~ -2.5% at 40 ng/mL and -0.7% ~ 8.3% at 400 ng/mL, respectively.
4. **Between run precision and accuracy of quality control samples**
Precision: 7.7% at 3 ng/mL, 6.2% at 40 ng/mL and 6.5% at 400 ng/mL, respectively.
Accuracy: -6.3% at 3 ng/mL, -4.7% at 40 ng/mL and 4.7% at 400 ng/mL, respectively.
5. **Lower limit of quantification:** 1 ng/mL.
 - **Within run precision and accuracy**
Precision: 5.1% ~ 18.1%.
Accuracy: 3.2% ~ 18.3%.
 - **Between run precision and accuracy**
Precision: 11.7%.
Accuracy: 10.5%.
6. **Recovery:** 83.2% for SN-38 and 81.3% for internal standard.
7. **Short-term stability:** at least 23 hours at room temperature.
8. **Post-preparative stability:** at least 24 hours at room temperature and a 4°C refrigerator.
9. **Long-term stability:** at least 431 days at a -80°C freezer.

- Assays to measure SN-38G in plasma had LLOQ values of 2.5 ng/mL and ULOQ values of 500 ng/mL (Table 31).

Table 31. Comparison of SN-38G Assays

Study Number	(b) (4) T125-0802	(b) (4) 379-1103
Analyte Name	SN-38G	SN-38G
Internal Standard (IS)	(b) (4)	(b) (4)
QC Concentrations	2.5, 7.5, 30 and 400 ng/mL	2.5, 7.5, 80, and 400 ng/mL
Standard Curve Concentrations	2.5, 5, 10, 20, 50, 100, 300, and 500 ng/mL	2.5, 5, 10, 20, 50, 100, 450, and 500 ng/mL
Lower Limit of Quantification	2.5 ng/mL	2.5 ng/mL
Upper Limit of Quantification	500 ng/mL	500 ng/mL
Dilution Integrity	4000 ng/mL diluted 10-fold	800 ng/mL diluted 10-fold
Weighting of Regression Analysis	1/X	1/X ²

Tables 32-33 contain the validation summaries for the SN-38G for assays described in Table 31 above.

Table 32. (b) (4) T125-0802 Assay Validation Summary.

Report Title	Validation of a Method for the Determination of SN-38G in Potassium Oxalate/NaF Human Plasma by LC-MS/MS
Report Number	(b) (4) T125-0802
Analyte Name	SN-38G
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein Precipitation Extraction
QC Concentrations	2.5, 7.5, 30 and 400 ng/mL
Standard Curve Concentrations	2.5, 5, 10, 20, 50, 100, 300 and 500 ng/mL
Lower Limit Of Quantitation	2.5 ng/mL
Upper Limit Of Quantitation	500 ng/mL
Average Recovery of Drug (%)	74.2 %
Average Recovery of Internal Standard (%)	70.7 %
QC Intra-run Precision Range (%CV)	1.8 to 11.5
QC Intra-run Accuracy Range (%RE)	-5.6 to 11.7
QC Inter-run Precision Range (%CV)	3.8 to 10.6
QC Inter-run Accuracy Range (%RE)	-2.1 to 3.4
Stock Solution Solvent	100% Dimethyl Sulfoxide
Master Stock Solution Stability in 100% Dimethyl Sulfoxide	294 Days at -70°C
Master Stock Solution Stability in 100% Dimethyl Sulfoxide	6 Hours at Room Temperature
Reinjection Reproducibility in Processed Samples	89 Hours at Room Temperature
Benchtop Stability in Potassium Oxalate/NaF Human Plasma	21.5 Hours at Room Temperature
Freeze/Thaw Stability in Potassium Oxalate/NaF Human Plasma	9 Cycles at -70°C
Long-term Storage Stability in Potassium Oxalate/NaF Human Plasma	539 Days at -70°C
Dilution Integrity	4000 ng/mL, diluted 10-fold
Selectivity	≤ 20.0% LLOQ for SN-38G; ≤ 5.0% for Diclofenac

Table 33. (b) (4) 379-1103 Assay Validation Summary.

Report Title	Validation of a Method for the Quantitation of SN-38G in Potassium Oxalate/NaF Human Plasma by LC-MS/MS
Study Number	(b) (4) 379-1103
Analyte Name	SN-38G
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein precipitation
Sample Volume	50 µL
QC Concentrations	2.5, 7.5, 80, and 400 ng/mL
Standard Curve Concentrations	2.5, 5, 10, 20, 50, 100, 450, and 500 ng/mL
Lower Limit Of Quantitation	2.5 ng/mL
Upper Limit Of Quantitation	500 ng/mL
Average Recovery of Drug (%)	74.8%
Average Recovery of Internal Standard (%)	NA ^a
QC Intraday Precision Range (%CV)	0.7 to 8.5
QC Intraday Accuracy Range (%RE)	-7.8 to 7.4
QC Interday Precision Range (%CV)	1.9 to 8.9
QC Interday Accuracy Range (%RE)	-1.2 to 2.5
Stock Solution Solvent	Dimethyl Sulfoxide (DMSO)
Master Stock Solution Stability in DMSO	294 Days at -70°C ^b
Master Stock Solution Stability in DMSO	6 Hours at Room Temperature ^b
Reinjection Reproducibility in Processed Samples ^c	163 Hours at 4°C
Benchtop Stability in Potassium Oxalate/NaF Human Plasma	21.5 Hours at Room Temperature ^b
Freeze/Thaw Stability in Potassium Oxalate/NaF Human Plasma	9 Cycles at -70°C ^b
Long-term Storage Stability in Potassium Oxalate/NaF Human Plasma	61 Days at -20°C 539 Days at -70°C ^b
Dilution Integrity	800 ng/mL, diluted 10-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS

^a Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

^b Refer to (b) (4), report T125-0802

^c Also referred to as Post-Preparative Reinjection Reproducibility (PPRR)

- An assay to measure total irinotecan (CPT-11), its metabolite SN-38, and SN-38G in needle tumor biopsies had an LLOQ value of 0.05 ng/mL and ULOQ value of 50 ng/mL. The method was validated for linearity, precision and accuracy (report MN1011) at (b) (4). Needle biopsies were homogenized, extracted using methanol and analyzed by LC/MS/MS. The assay and its performance are summarized in Tables 34 and 35, respectively.

Table 34. MN1011 Assay Summary.

Study Number	MN1011 (b) (4)
Analyte Name	CPT-11, SN-38, SN-38G
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC/MS/MS
Extraction Method	Protein precipitation
QC Concentrations	0.3, 3, 30 ng/mL
Standard Curve Concentrations	0, 0.05, 0.1, 0.2, 0.25, 0.5, 1, 5, 10, 50 ng/mL
Lower Limit Of Quantitation	0.05 ng/mL
Upper Limit Of Quantitation	50 ng/mL
Average Recovery of Analyte (%)	100%
Average Recovery of Internal Standard (%)	102%, 101%, 97.8%

Table 35. MN1011 Assay Performance Summary.

Assay Parameters		Analytical Results (CPT-11; SN-38; SN-38G)
Linearity	Calibration Range	0.050 - 50 ng/mL
	Lower Limit of Quantitation	0.050 ng/mL
Accuracy	Calibration Samples	100% AR; 100% AR; 100% AR
	Quality Control Samples: Overall *	102% AR; 101% AR; 97.8% AR
Precision	Calibration Samples	5.99% RSD; 6.77% RSD; 7.86% RSD
	Quality Control Samples: Overall *	7.52% RSD; 7.67% RSD; 10.1% RSD

* Data not include QCs for SN-38G-502

- An assay to measure 5-FU in plasma was validated over the concentration range of 5 to 3000 ng 5-FU/mL of human plasma using a 100-µL sample (Report (b) (4) 42-1211). Calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression. The concentration range in the calibration curve using diluted samples was in the appropriate range for analysis of 5-FU concentrations. Table 36 is a validation summary for 5-FU.

Table 36. (b) (4) 42-1211 Validation and Partial Validation Summary.

Study Number	(b) (4) 42-1211 (4) 42-1211 Amendment 1
Analyte Name	5-Fluorouracil
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Protein precipitation
Sample Volume	100 µL
QC Concentrations	5, 15, 240, and 2400 ng/mL
Standard Curve Concentrations	5, 10, 30, 100, 300, 1000, 2700 and 3000 ng/mL
Lower Limit Of Quantitation	5 ng/mL
Upper Limit Of Quantitation	3000 ng/mL
Average Recovery of Analyte (%)	116.8
Average Recovery of Internal Standard (%)	NA ^a
LLOQ QC Intraday Precision Range (%CV)	3.4 to 4.9 (full validation) 3.9 (partial validation)
LLOQ QC Intraday Accuracy Range (%RE)	2.5 to 2.9 (full validation) 6.6 (partial validation)
Analytical QC Intraday Precision Range (%CV)	0.5 to 3.0 (full validation) 0.7 to 1.7 (partial validation)
Analytical QC Intraday Accuracy Range (%RE)	-0.4 to 4.6 (full validation) 3.0 to 6.5 (partial validation)
LLOQ QC Interday Precision (%CV)	4.0
LLOQ QC Interday Accuracy (%RE)	2.7
Analytical QC Interday Precision Range (%CV)	1.2 to 2.9
Analytical QC Interday Accuracy Range (%RE)	1.2 to 3.4
Stock Solution Stability in Methanol	574 Days at -20°C ^b 16.5 Hours at Room Temperature
Processed Sample Stability	286 Hours at 4°C
Benchmark Stability in K ₂ EDTA Human Plasma	16.5 Hours at Room Temperature
Benchmark Stability in Sodium Heparin Human Plasma	19 Hours at Room Temperature
Freeze/Thaw Stability in K ₂ EDTA Human Plasma	5 Cycles at -20°C and -70°C (full validation)
Freeze/Thaw Stability in Sodium Heparin Human Plasma	5 Cycles at -20°C and -70°C (partial validation)
Benchmark Stability in K ₂ EDTA Whole Blood	2 Hours at 4°C (full validation)
Benchmark Stability in Sodium Heparin Whole Blood	2 Hours at 4°C (partial validation)
Long-term Storage Stability in K ₂ EDTA Human Plasma	To Be Determined at -20°C and -70°C
Long-term Storage Stability in Sodium Heparin Human Plasma	574 Days at -20°C To Be Determined at -70°C
Dilution Integrity	10000 ng/mL diluted 10-fold
Selectivity	< 20.0% LLOQ for analyte; < 5.0% for IS

^a Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

^b Partially validated to change the anti-coagulant from K₂EDTA to Sodium Heparin

2.6.6 What is the QC sample plan?

- Encapsulated irinotecan (PEP02), total irinotecan (CPT-11), SN-38, and SN-38G in plasma: QC standards at six replicates in three separate runs of each analyte at 4 concentrations were included in each analytical run. For a run to be acceptable, a minimum of 2/3 of the total number of QCs could not deviate by more than $\pm 15.0\%$ ($\pm 20.0\%$ at LLOQ QC) from their nominal values.
- Total irinotecan (CPT-11), SN-38, and SN-38G in tissue: QC standards at 3 concentrations (0.3, 3, and 30 ng/mL) were processed in quadruplicate in the first run (S01) and triplicate in the second run (S02). For a run to be acceptable, all concentrations are to be within the range of the nominal concentration $\pm 15\%$ and all relative standard deviations to be $\leq 15\%$.
- 5-FU in plasma: QC standards at 4 concentrations (5, 15, 240, and 2400 ng/mL) were included in each analytical run. For a run to be acceptable, a minimum of 2/3 of the total number of QCs could not deviate by more than $\pm 15.0\%$ ($\pm 20.0\%$ at LLOQ QC) from their nominal values, and at least half of the QC samples at each concentration had to be within $100 \pm 15.0\%$ ($\pm 20.0\%$ at the LLOQ QC) of their nominal values.

3 DETAILED LABELING RECOMMENDATIONS

Clinical pharmacology related sections of the applicant's proposed package insert, together with FDA's most current revisions (as tracked changes), begin on the following pages of this review. FDA's edits may undergo further revision, as they have not been conveyed to and negotiated with the applicant.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
PHARMACOMETRIC REVIEW

Application Number	NDA 207793
Submission Date	April 24, 2015
Compound	Irinotecan liposome injection
Dosing regimen/route of administration	80 mg/m ² intravenous infusion over 90 minutes, every 2 weeks, with LV 400 mg/m ² infusion over 30 minutes followed by 5-FU 2400 mg/m ² infusion over 46 hours.
Indication	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.
Clinical Division	Division of Drug Oncology Products
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there an exposure-response relationship for effectiveness?

Exposure response analysis was conducted using data from the NAPOLI trial (Study MM-398-07-03-01) in patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy. Analysis included data from 114 patients from a total of 117 patients in the combination therapy arm (MM-398+5FU/LV). Based on Kaplan-Meier plots, a trend for increase in overall survival with total SN38 exposures (Cavg) was observed within the exposures achieved when Onivyde is administered in combination with FU/LV (Figure 1). However, such a trend is confounded by the imbalances in other risk factors (Table 1 and Table 2). Cavg was calculated for the first 2 or 3 weeks dose intervals based on the actual dose. This represents Cavg at steady state. The baseline patient and disease characteristics in various total SN38 exposure groups are shown in Table 1 and Table 2. To account for imbalances in these factors across exposure groups, a multivariate analysis was conducted to adjust for these imbalances. Total SN38 Cavg was also included in the analysis. The multivariate analysis showed that total SN38 Cavg is a significant covariate for overall survival suggesting reduction in hazard with increase in exposure (Table 3). Multivariate analysis was conducted utilizing data from the combination therapy arm. One assumption in the multivariate analysis is that there is no interaction between the exposure effect and any other covariate. Even though interaction terms could be included in Cox model, it is often challenging to test for significant interactions among various risk factors and the exposure effect. When more than one risk factor (in addition to the exposure effect) is included in the Cox model, higher order interaction than the typical two-way interaction becomes possible and the number of possible interactions makes it impractical to test and identify significant interactions. Similarly SN38 Converted Cavg was also identified as a significant covariate for overall survival (data not shown). Converted SN38 refers to the amount that is converted from CPT11 *in vivo* and excludes the contribution of (b) (4)

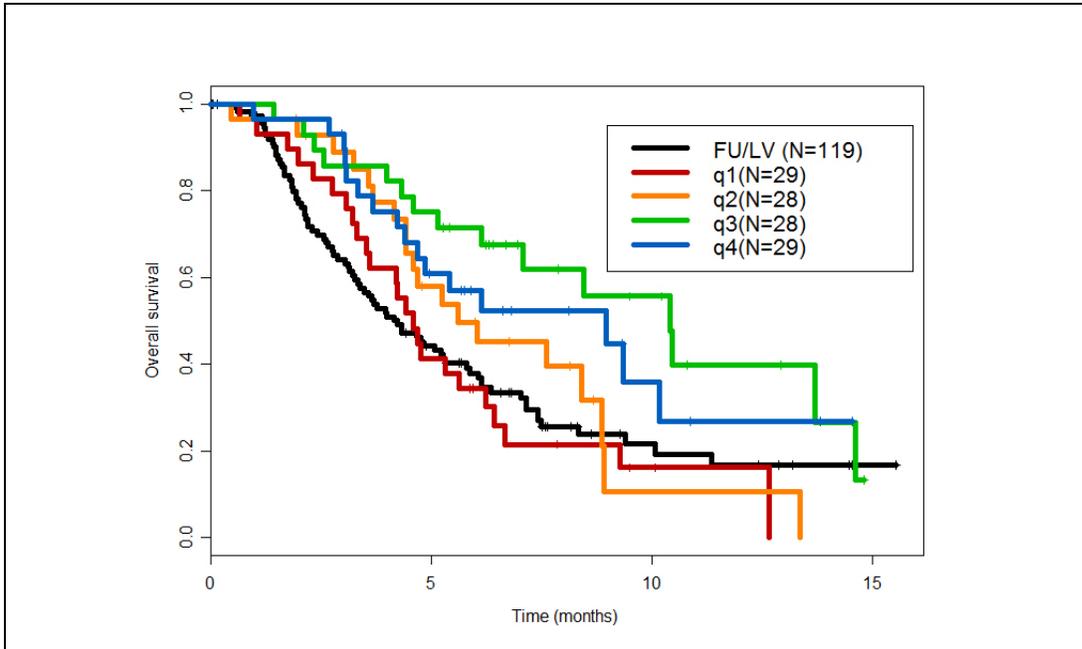


Figure 1: Kaplan-Meier plots of overall survival for patients in various quartiles (q1, q2, q3 and q4) based on SN38 total Cavg in the MM-398+5FU/LV arm. Total SN38 Cavg represents the steady state Cavg calculated for the first 2 or 3 weeks dose intervals based on the actual dose. Source: Reviewer’s analysis.

Table 1: Summary of continuous covariates by total SN38 Cavg quartiles

Group	N	Baseline KPS Levels	Baseline albumin (g/dL)	Age (years)	BMI (kg/m ²)	Time since diagnosis (year)	Time since metastatic diagnosis (year)
FU/LV	119	85.4	3.98	61.0	23.6	1.07	0.64
q1	29	84.5	3.90	63.3	22.8	1.09	0.79
q2	28	87.5	3.91	64.9	23.7	0.90	0.49
q3	28	89.6	4.14	61.5	23.3	1.11	0.62
q4	29	84.5	3.93	63.6	23.6	1.33	0.90

Source: Reviewer’s analysis

Table 2: Summary of categorical covariates by total SN38 Cavg quartiles

Group	N	Asian	Female	Not Stage IV	Prior 5 FU exposure	Prior Irinotecan Exposure	Prior Platinum Therapy	Prior Radio Therapy	Liver Metastases
FU/LV	119	30.3	43.7	47.9	43.7	14.3	34.5	22.7	70.6
q1	29	20.7	41.4	44.8	62.1	27.6	51.7	20.7	62.1
q2	28	35.7	25.0	60.7	10.7	3.6	14.3	14.3	67.9
q3	28	28.6	46.4	42.9	50.0	0.0	25.0	28.6	64.3
q4	29	31.0	55.2	44.8	44.8	10.3	37.9	17.2	62.1

The values for each covariate represent percentage (%)

Table 3: Parameter estimates from the multivariate analysis

Analysis of Maximum Likelihood Estimates										
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label	
tsn38cavg	1	-2.29519	0.63306	13.1446	0.0003	0.101	0.029	0.348		
kps	1	-0.02749	0.01301	4.4685	0.0345	0.973	0.948	0.998		
alb	1	-0.65022	0.29758	4.7743	0.0289	0.522	0.291	0.935		
stage	0	1	0.65721	0.25110	6.8504	0.0089	1.929	1.179	3.156	stage 0
livermfl	N	1	-0.75758	0.28084	7.2765	0.0070	0.469	0.270	0.813	livermfl N

Source: Reviewer's analysis

1.1.2 Is there exposure-response relationship for safety?

Exposure response analysis for safety was conducted using pooled data from various studies including the NAPOLI trial as listed in Table 7 in section 2.1. Analysis included data from 353 patients.

Neutropenia

There is a trend for increase in grade 3 or 4 neutropenia with increasing SN38 exposure. Figure 2 shows an increase in the proportion of patients with grade 3 or 4 neutropenia with increasing total SN38 Cavg or converted SN38 Cmax. Total SN38 Cavg represents the steady state Cavg calculated for the first 2 or 3 weeks dose intervals based on the actual dose. Converted SN38 Cmax represents the maximum concentration of converted SN38 for the first dose based on the actual dose. Converted SN38 refers to the amount that is converted from CPT11 *in vivo* and excludes the contribution of (b) (4)

Multivariate analysis suggested that converted SN38 Cmax is a significant covariate for grade 3 or 4 neutropenia (Table 4, bottom panel). Race, baseline ANC and co-administration of FU were also found to be

significant covariates. Asian patients have higher rate of grade 3 or 4 neutropenia compared to Caucasian patients. Similarly co-administration of FU increased the rates of grade 3 or 4 neutropenia. Higher ANC baseline is associated with lower rate of grade 3 or 4 neutropenia. Please see section 1.1.1 for the assumptions and limitations of multivariate analysis. Univariate analysis using total SN38 Cavg as the exposure metric showed a trend for increase in grade 3 or 4 neutropenia with exposure. However, the relationship was not statistically significant (Table 4, top panel).

Diarrhea

There is a trend for increase in grade 3 or 4 diarrhea with increasing total irinotecan exposure. Figure 3 shows an increase in the proportion of patients with grade 3 or 4 diarrhea with increasing total irinotecan Cavg or total irinotecan Cmax. Total irinotecan Cavg represents the steady state Cavg calculated for the first 2 or 3 weeks dose intervals based on the actual dose. Total irinotecan Cmax represents the maximum concentration of irinotecan for the first dose based on the actual dose. Multivariate analysis suggested that total irinotecan Cmax is a significant covariate for grade 3 or 4 diarrhea (Table 4, bottom panel). Race was also found to be a significant covariate. Caucasian patients have higher rate of grade 3 or 4 diarrhea compared to Asian patients. Please see section 1.1.1 for the assumptions and limitations of multivariate analysis.

Univariate analysis using total irinotecan Cavg as the exposure metric showed an increase in grade 3 or 4 diarrhea with irinotecan Cavg (Table 4, top panel). However multivariate analysis did not identify total irinotecan Cavg as a covariate.

In summary, exposure-response analysis showed that there is a trend for increase in grade 3 or 4 neutropenia with SN38 exposure and grade 3 or 4 diarrhea with total irinotecan exposure.

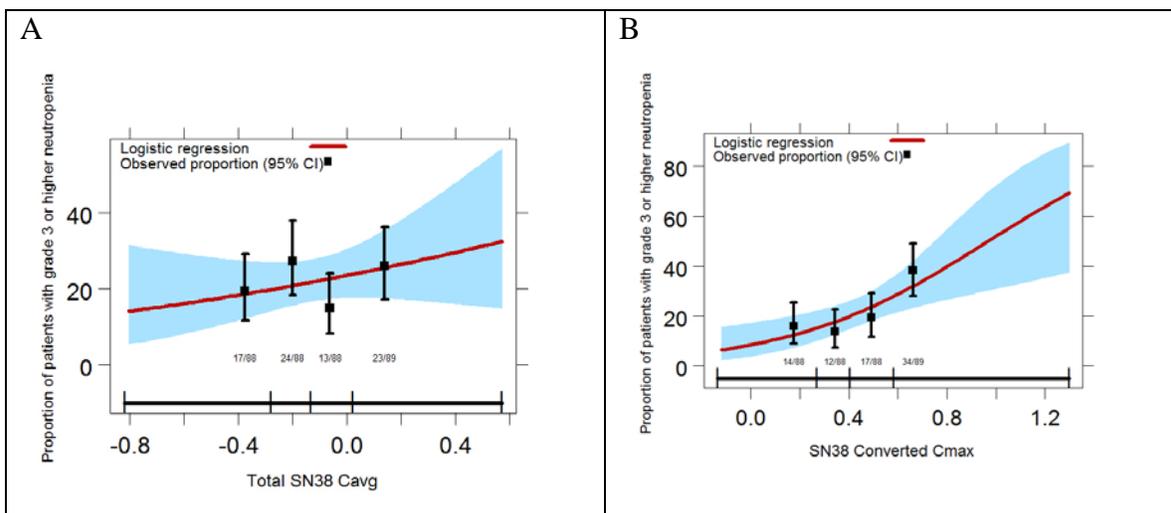


Figure 2: Exposure-response relationship for grade 3 or 4 neutropenia. Proportions of patients with grade 3 or 4 neutropenia by A) total SN38 Cavg and B) converted SN38 Cmax. Definitions of the exposure metrics are provided in the text in section 1.1.2. Source: Reviewer’s Analysis.

Table 4: Parameter estimates from univariate analysis using total SN38 Cavg (top panel) and multivariate (bottom panel) for grade 3 or 4 neutropenia analysis using converted SN38 Cmax as the exposure metrics

Univariate analysis based on total SN38 Cavg

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-1.1836	0.1432	68.3673	<.0001
SN38TOTA	1	0.7822	0.5728	1.8651	0.1720

Multivariate analysis based on converted SN38 Cmax

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-0.8848	0.7161	1.5269	0.2166
SN38CON0		1	1.9912	0.8231	5.8520	0.0156
race	1 Asian	1	1.0999	0.3965	7.6938	0.0055
race	2 Others	1	-1.0463	0.7046	2.2050	0.1376
ANC		1	-2.5660	0.8096	10.0449	0.0015
fiveflag	0 Ye	1	0.6911	0.1696	16.6026	<.0001

Source: Reviewer's analysis

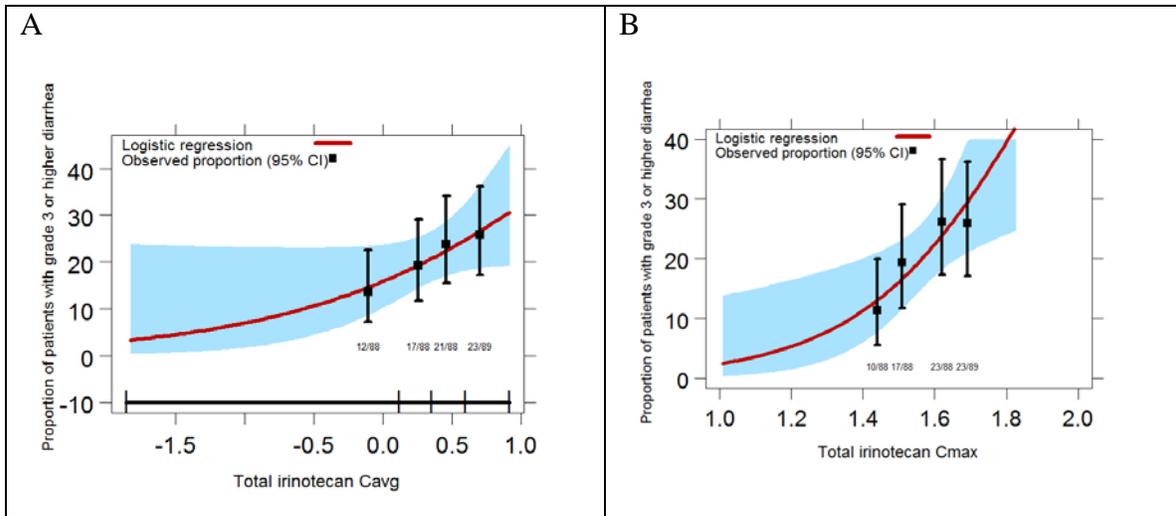


Figure 3: Exposure-response relationship for grade 3 or 4 diarrhea. Proportions of patients with grade 3 or 4 diarrhea by A) total irinotecan Cavg and B) total irinotecan Cmax. Source: Reviewer’s Analysis.

Table 5: Parameter estimates from univariate analysis using total irinotecan Cavg (top panel) and multivariate analysis (bottom panel) for grade 3 or 4 diarrhea using total irinotecan Cmax as the exposure metrics

Univariate analysis based on total irinotecan Cavg

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-1.6695	0.2037	67.1717	<.0001
CPT11_CA	1	0.9294	0.4012	5.3653	0.0205

Multivariate analysis based on total irinotecan Cmax

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-8.2603	2.0712	15.9060	<.0001
CPT11_CM		1	4.2095	1.2954	10.5600	0.0012
ETHNICC	1 Caucasian	1	0.6144	0.2861	4.6121	0.0317
ETHNICC	2 Others	1	-0.4729	0.5103	0.8588	0.3541

Source: Reviewer’s analysis

1.1.3 Does the E-R relationship of efficacy and safety support the starting dose of 80 mg/m² appropriate?

Yes, the exposure response relationship for efficacy and safety supports the proposed dose of 80 mg/m². Although there is an increase in overall survival with increase in SN38 exposure (section 1.1.1), there is also an increase in grade 3 or 4 neutropenia and grade 3 or 4 diarrhea with increasing SN38 and irinotecan exposure (section 1.1.2).

1.1.4 Is the dosing guidelines appropriate for patients with bilirubin levels of 1-2 mg/dL?

(b) (4)

In this application, the number of patients with bilirubin \geq 1mg/dL (only 6 patients in the MM-398+5-FU/LV arm, 9 patients in the MM-398 monotherapy arm and 13 patients in the 5-FU/LV control arm), so comprehensive comparison of safety in the MM-398 arms between those with a total bilirubin less than 1 mg/dL and those with 1 mg/dL or higher is difficult. There were no clinically relevant large differences in the frequency of the most common and most important adverse events based on levels of total bilirubin. Any grade neutropenia was reported in 44 of 109 (40.1%) patients with bilirubin less than 1 mg/dL in the MM-398+5-FU/LV combination arm and in 36 of 136 patients (26.5%) in the MM-398 monotherapy arm. For patients with total bilirubin of 1 mg/dL or higher, any grade neutropenia was reported for 2 of 6 (33.3%) in the MM-398+5-FU/LV arm, and 1 of 9 (11.1%) of patients in the MM-398 monotherapy arm. There were too few patients treated in the NAPOLI-1 study with total bilirubin levels of more than 1 mg/dL to confidently assess whether higher bilirubin levels might be associated with a higher likelihood of neutropenia with MM-398 treatment (Source: Sponsor's Integrated Safety Summary report). Based on exposure response analysis, there is a trend for increase in grade 3 or 4 neutropenia with increasing SN38 exposure (section 1.1.2) and population PK analysis suggests a trend for increase in SNr8 exposure with increasing baseline bilirubin levels (Figure 4). However, there is only 24% higher SN38 exposure in patients with bilirubin levels \geq 1 mg/dL compared to patients with bilirubin levels $<$ 1 mg/dL at 80 mg/m² (Figure 4). Thus data in the current package seems insufficient to justify a reduced starting dose based on baseline bilirubin levels.

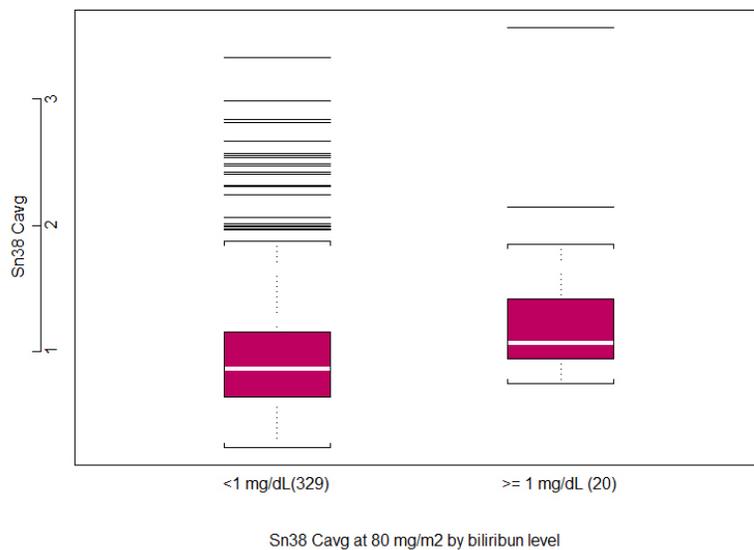
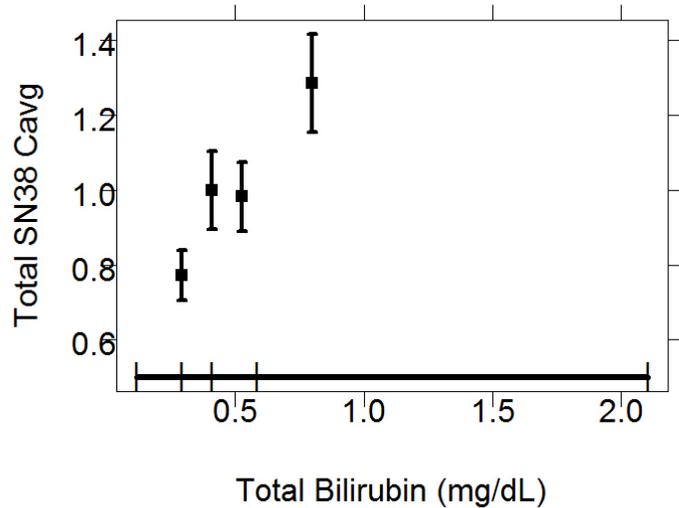


Figure 4: Total SN38 Cavg at 80 mg/m2 dose by baseline bilirubin level. Source: Reviewer's analysis.

1.1.5 Is the dosing guidelines appropriate for patients known to be homozygous for the UGT1A1*28 allele?

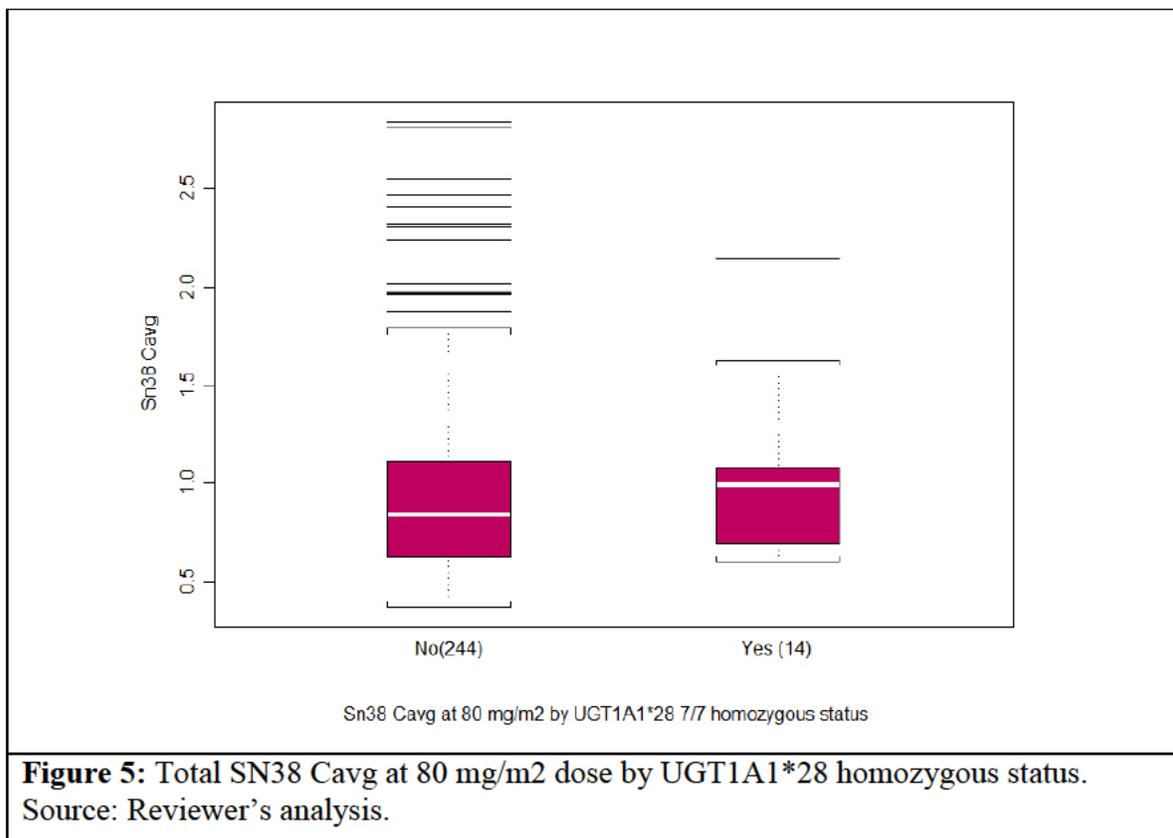
The dosing and administration section of the label states (b) (4) a reduced starting dose of ONIVYDE of 60 mg/m² for patients known to be homozygous for the UGT1A1*28 allele. Patients without drug related toxicities during the first cycle of therapy may have their dose of ONIVYDE increased to 80 mg/m² in subsequent cycles based on individual patient tolerance. This is consistent with Camptosar label where a reduction in starting dose is recommended for patients known to be homozygous for the UGT1A1*28 allele. This recommendation for Camptosar was based on the association between UGT1A1*28 homozygosity and neutropenia.

The sponsor's proposed dosing scheme was implemented in the NAPOLI study. In the combination arm of the NAPOLI study, there were 7 patients who were homozygous for the UGT1A1*28 allele. These patients started at the 60 mg/m² dose. Among these, 2 patients remained at the starting dose of 60 mg/m², 3 were escalated to 80 mg/m², 1 patient's dose was initially escalated to 80 but later reduced to 60 mg/m² and 1 patient's dose was reduced to 40 mg/m² (Table 6). With this dosing scheme in the NAPOLI trial, similar rates of neutropenia was observed in patients homozygous for UGT1A1*28 and non-homozygous patients. Grade 3 or 4 neutropenia in patients homozygous for UGT1A1*28 allele was 28.6% (2 out of 7 patients) and was 27.3% (30 of 110 patients) in non-homozygous patients. The results presented here should be viewed with caution as there were only 7 homozygous patients in the combination arm in the trial. Population PK analysis showed only 18% higher SN38 exposure in homozygous patients compared to non-homozygous patients after adjusting for differences in dose but without adjusting for other covariates identified in the population PK model (Figure 5). After adjusting for all other covariates, the clearance for SN38 exposure in homozygous patients is essentially the same as that in non-homozygous patients as shown in Table 9. It is unclear why the association between SN38 exposure and UGT1A1*28 homozygosity was not identified. The correlation between UGT1A1 status and other covariates could be inherent. Therefore, quantifying the "pure" UGT1A1 effect after adjusting for all other covariates may not be clinically relevant. Regardless, the UGT1A1 effect (unadjusted or adjusted) observed after administration of irinotecan liposome injection is not clinically meaningful to justify a dose reduction for UGT1A1*28 homozygous patients. Since a prospective dose reduction strategy was implemented in NAPOLI study and the dose could be increased based on the patients' response, the reviewer agrees that the studied regimen is appropriate for patients known to be homozygous for the UGT1A1*28 allele.

For further details regarding this recommendation please see Dr. Ramamoorthy's pharmacogenomics review.

Table 6: Distribution of dose in seven patients homozygous for UGT1A1*28 status in the NAPOLI trial

Treatment arm	Remained at the starting dose of 60 mg/m ²	Dose was escalated to 80 mg /m ²	Dose was initially escalated but reduced to 60 mg/m ² later in the trial	Dose was reduced to 40 mg/m ²
MM398 + FU/LV	2	3	1	1



1.1.6 Do intrinsic factors (body weight, gender, race, age, renal function, tumor type) and extrinsic factors affect the PK of irinotecan and SN38 and are dose adjustments needed based on these intrinsic factors?

The effect of intrinsic factors was assessed on total irinotecan, total SN38 and converted SN38 exposures. The exposure metric selected for this assessment was steady state C_{avg} .

Race: The covariate with strongest association to irinotecan (CPT11) and SN-38 was race. Asians (N=150) were observed with ~70% lower total CPT11 C_{avg} than Caucasians (N=182) as shown in Figure 6. There was minimal effect of race on SN38 exposure (SN38 C_{avg} and SN38 converted C_{avg}).

Gender: There is no clinically meaningful effect of gender on the exposure of total irinotecan, total SN38 or converted SN38 (Figure 7)

Age: There is no clinically meaningful effect of age on the exposure of total irinotecan, total SN38 or converted SN38 (Figure 8)

Body surface area (BSA): There is a trend for increase in total irinotecan exposure with increase in BSA (Figure 9). The total irinotecan C_{avg} increases by 49% from the first quartile (1.26 – 1.56 kg/m²) to the fourth quartile (1.85 – 2.54 kg/m²). There is a slight trend for decrease (~20%) in SN-38 exposure with increase in BSA. The applicant conducted simulations to compare the BSA-based dosing strategy versus fixed dosing strategy. Based on sponsor's simulation (Figure 10), it appears that fixed dosing strategy does not provide any advantage over the BSA-based dosing strategy for the population as the both dosing strategies show similar distribution of exposure in terms total irinotecal C_{avg} and total SN-38 C_{avg} .

UGT1A1*28 homozygous status: The exposure of total irinotecan and total SN38 are 24% and 18% higher in UGT1A1*28 homozygous patients (N=14) compared to non-homozygous patients (N=244) as shown in Figure 11. For dosing considerations based on UGT1A1*28 status, see section 1.1.5.

Renal status: There is no clinically meaningful effect of renal function on the exposure of total SN38 (Figure 12). The exposure of total SN38 in moderate subjects (N=68) is 18% higher than normal subjects (N=135). There were only 2 subjects in the severe renal impairment category. The exposure of total SN38 was 66% higher in those subjects compared to normal. This should be viewed with caution as data is limited to only 2 subjects.

Hepatic Enzymes:

Bilirubin- There is a trend for increase in total SN38 exposure with increase in baseline bilirubin levels (Figure 13). How this is unlikely to be clinically relevant as the total SN38 C_{avg} is only 24% higher in patients with baseline bilirubin levels \geq 1mg/dL (N=20) compared to patients with bilirubin levels $<$ 1 mg/dL (N=329).

Aspartate aminotransferase (AST)- There is no clinically relevant effect of AST on SN38 exposure. There is only ~10% increase in total SN38 C_{avg} from first quartile to fourth quartile (Figure 14)

Alanine Aminotransferase (ALT)-There is no clinically relevant effect of ALT on SN38 exposure (Figure 15). There is a slight increase in total irinotecan exposure with ALT. However there is only 27% increase from first quartile to fourth quartile.

Albumin: There is no clinically relevant effect of albumin of total SN38 and total irinotecan exposure (Figure 16). There is 34% increase in irinotecan exposure from first quartile to fourth quartile.

Co-administration of 5-FU: There is no clinically relevant effect of co-administration of 5-FU on the total SN38 and total irinotecan exposure (Figure 17).

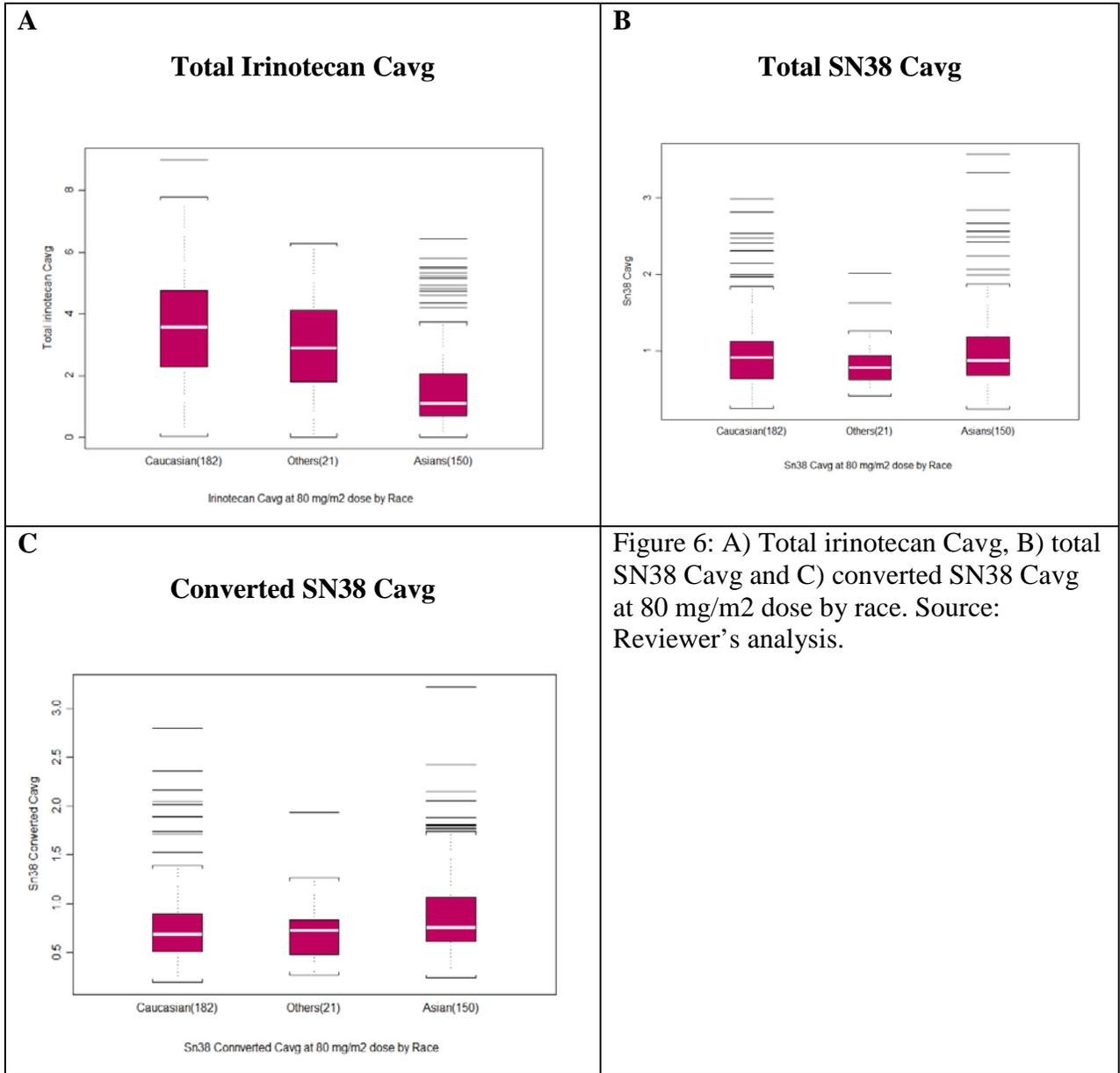


Figure 6: A) Total irinotecan Cavg, B) total SN38 Cavg and C) converted SN38 Cavg at 80 mg/m² dose by race. Source: Reviewer's analysis.

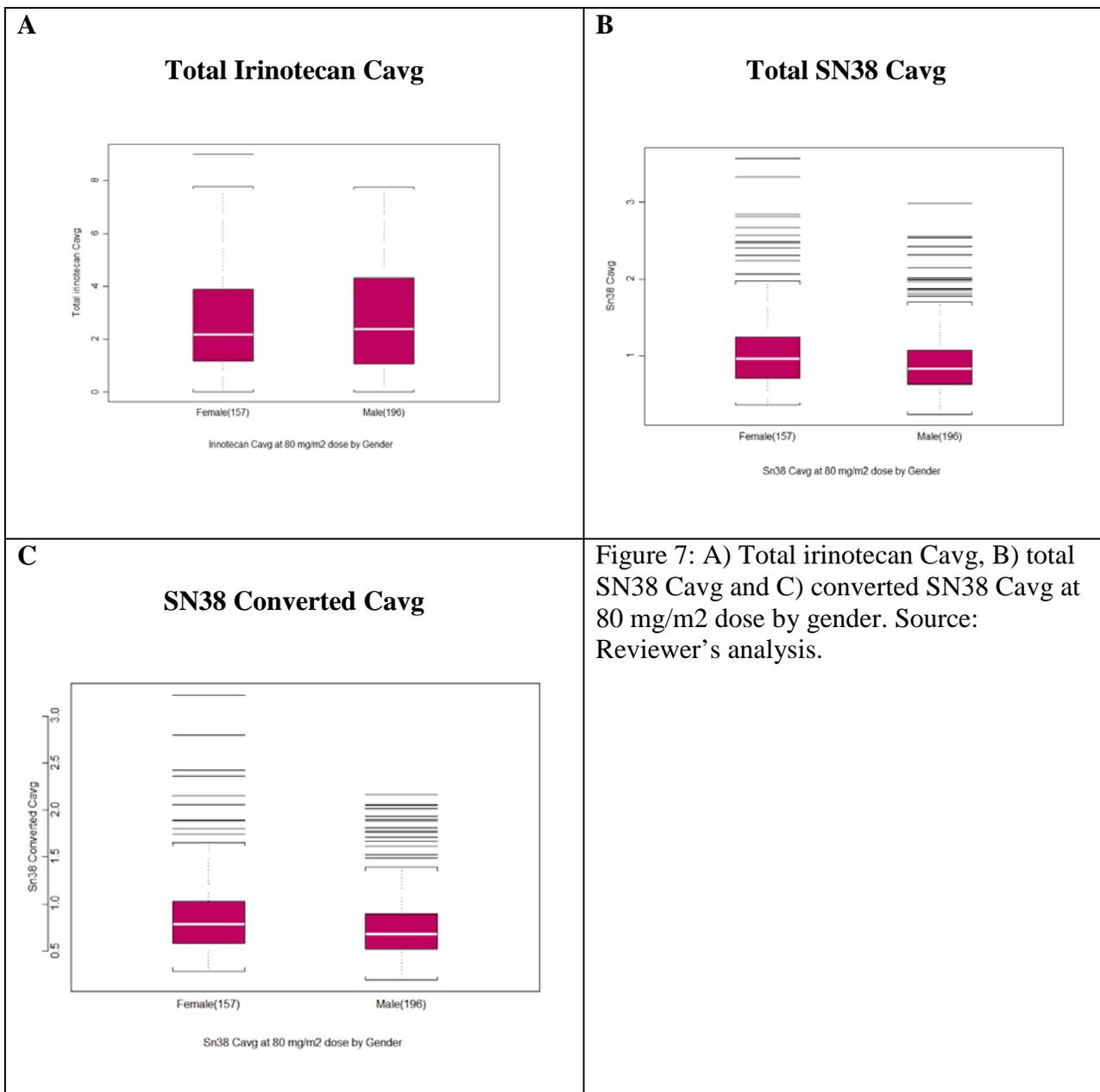
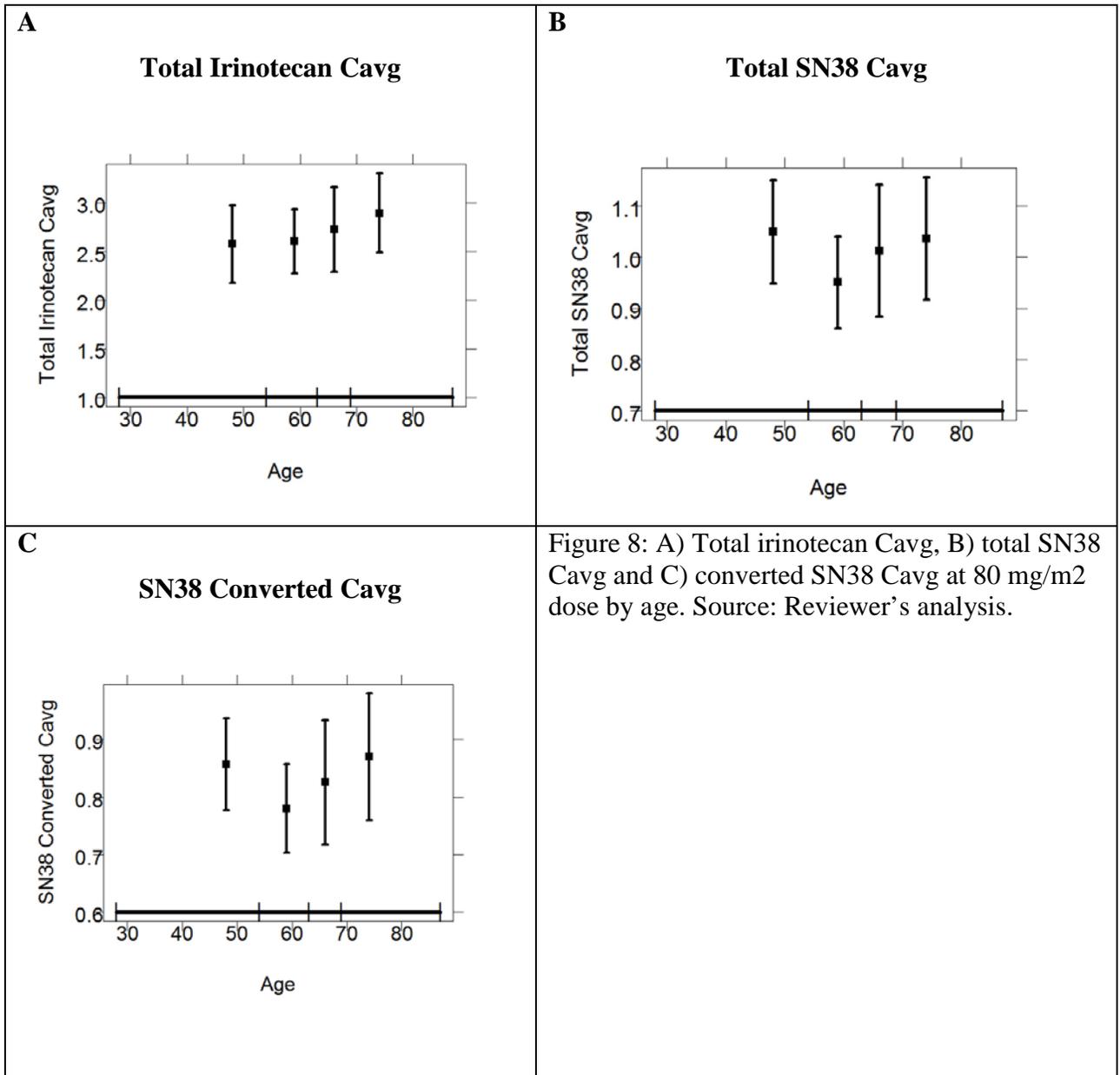
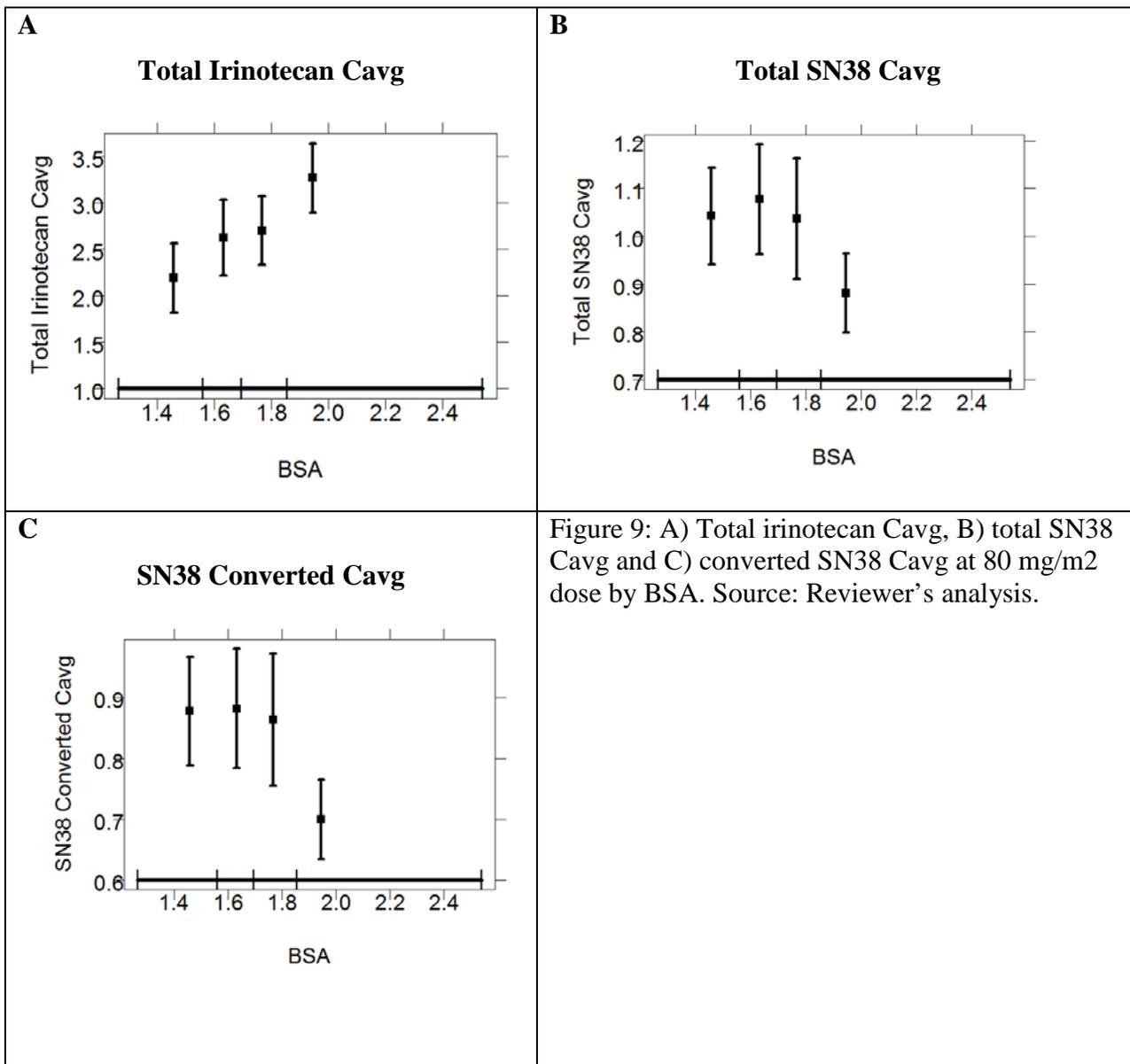
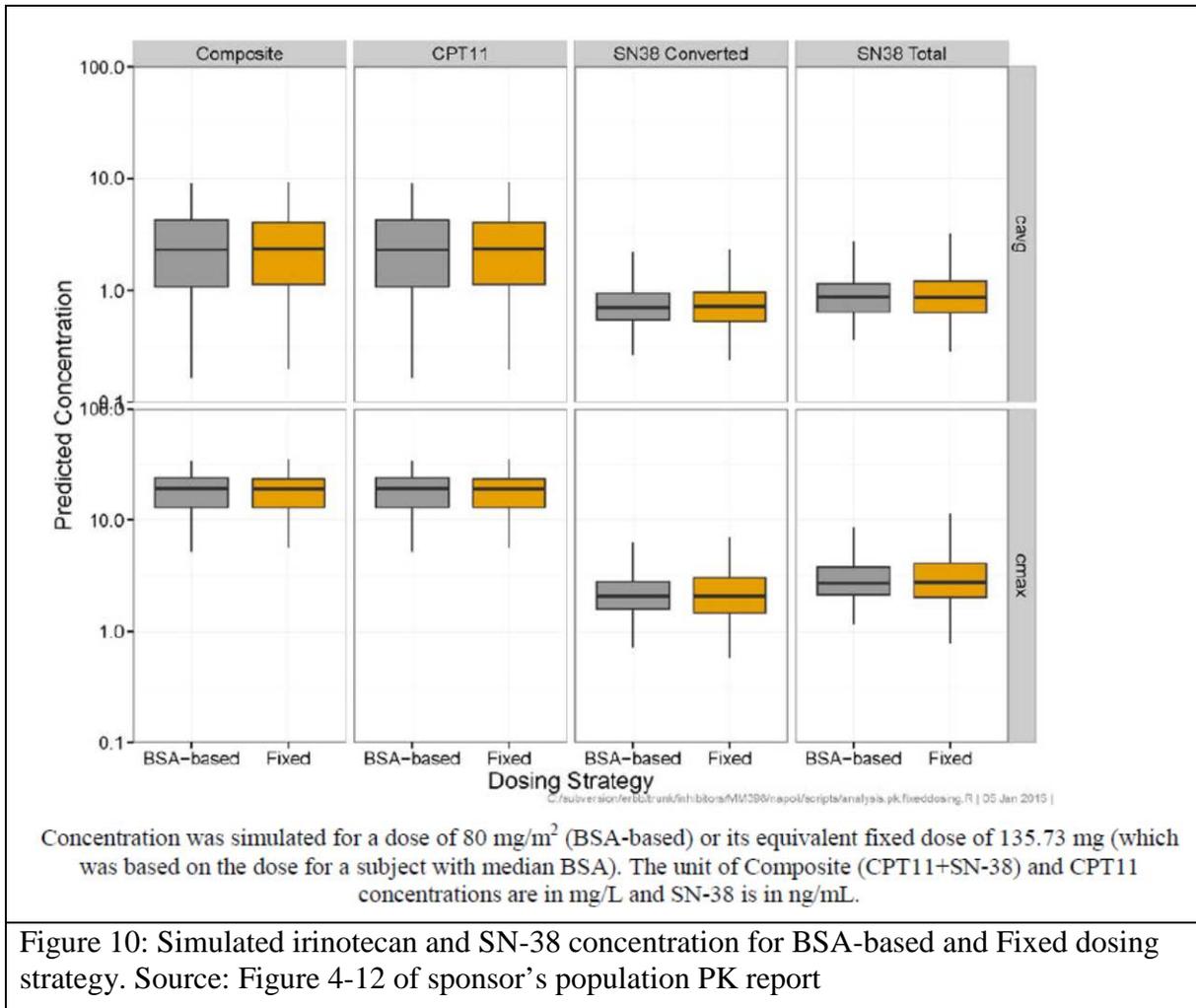


Figure 7: A) Total irinotecan Cavg, B) total SN38 Cavg and C) converted SN38 Cavg at 80 mg/m² dose by gender. Source: Reviewer's analysis.







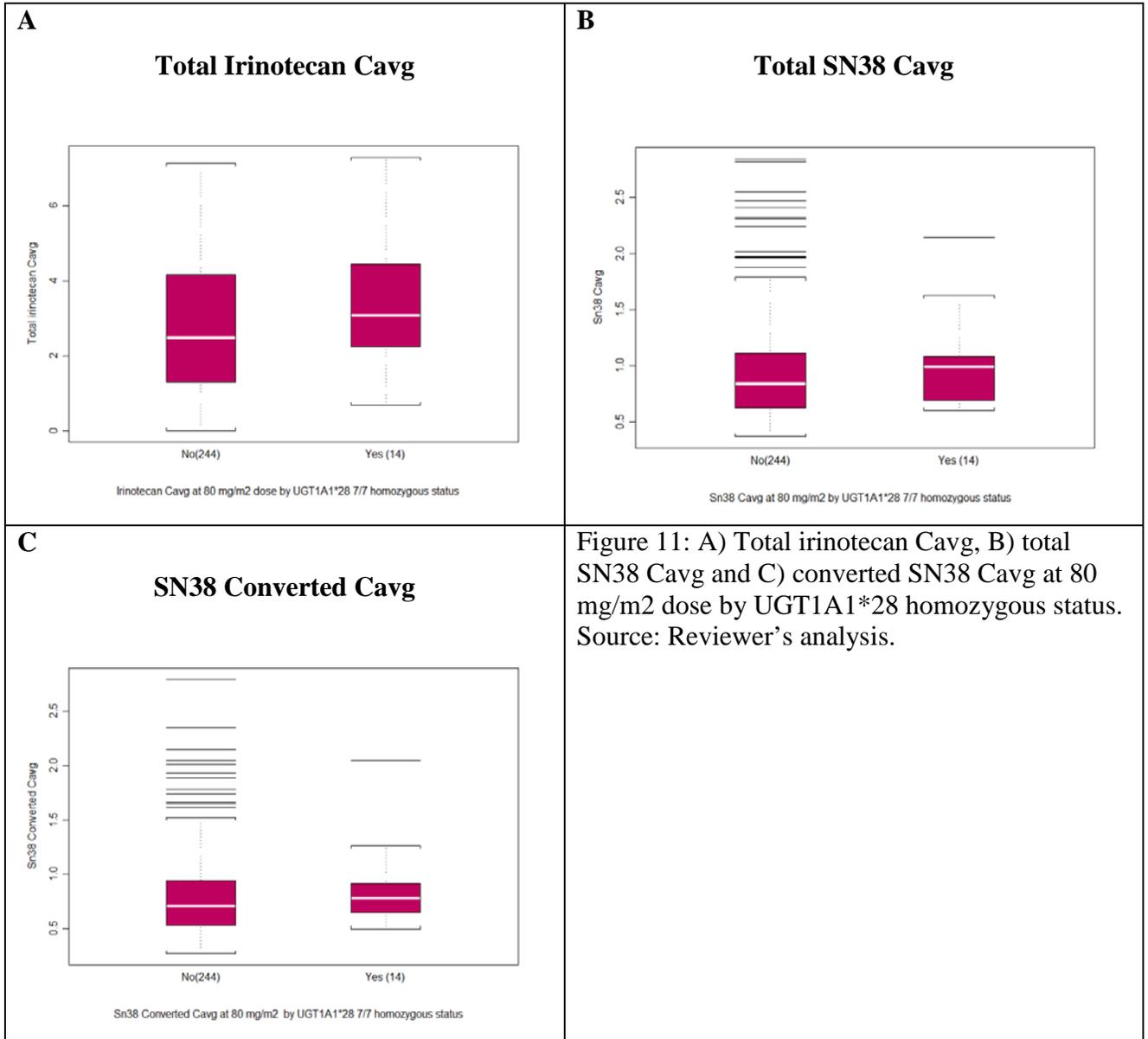


Figure 11: A) Total irinotecan Cavg, B) total SN38 Cavg and C) converted SN38 Cavg at 80 mg/m² dose by UGT1A1*28 homozygous status. Source: Reviewer's analysis.

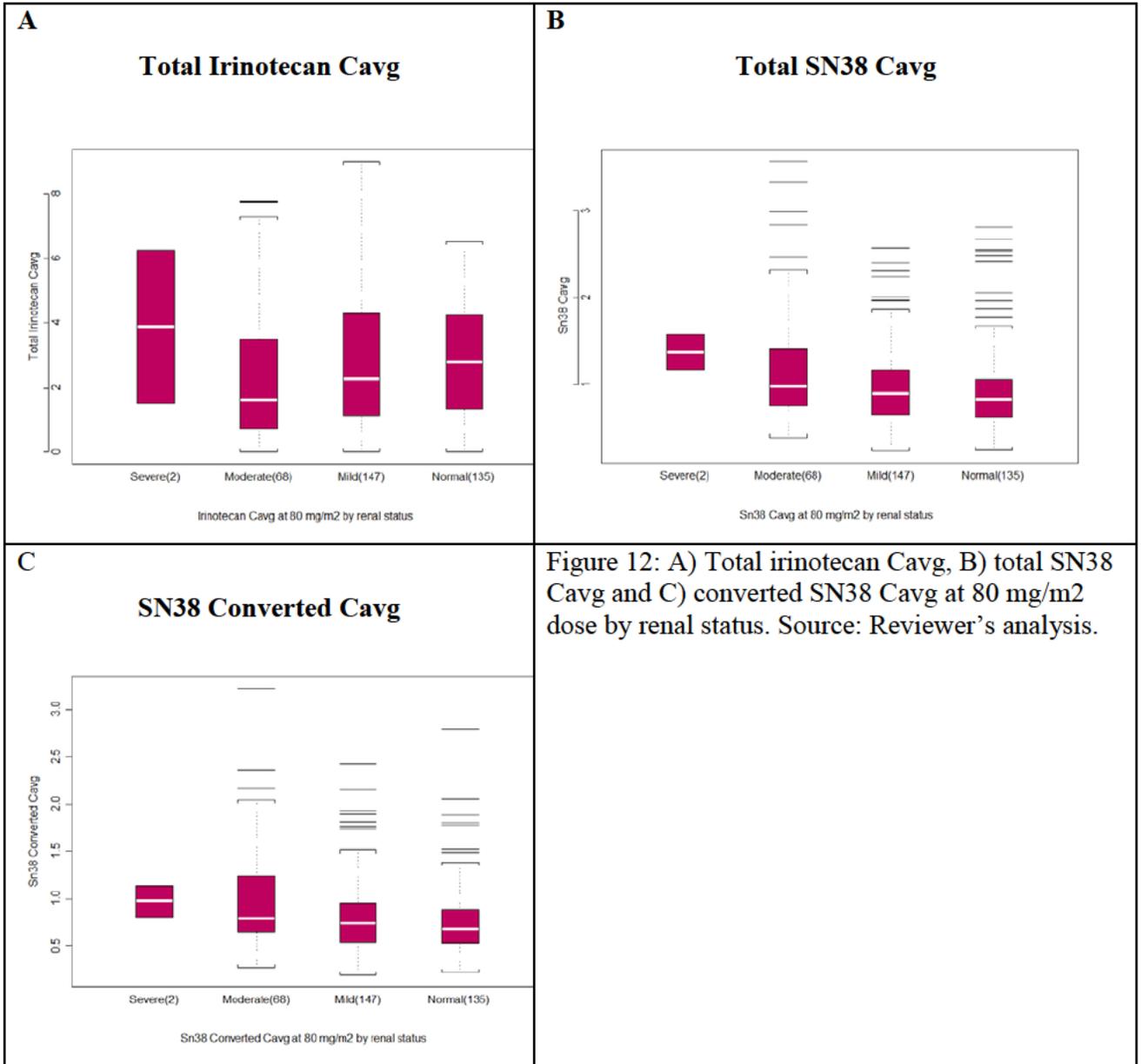


Figure 12: A) Total irinotecan Cavg, B) total SN38 Cavg and C) converted SN38 Cavg at 80 mg/m² dose by renal status. Source: Reviewer's analysis.

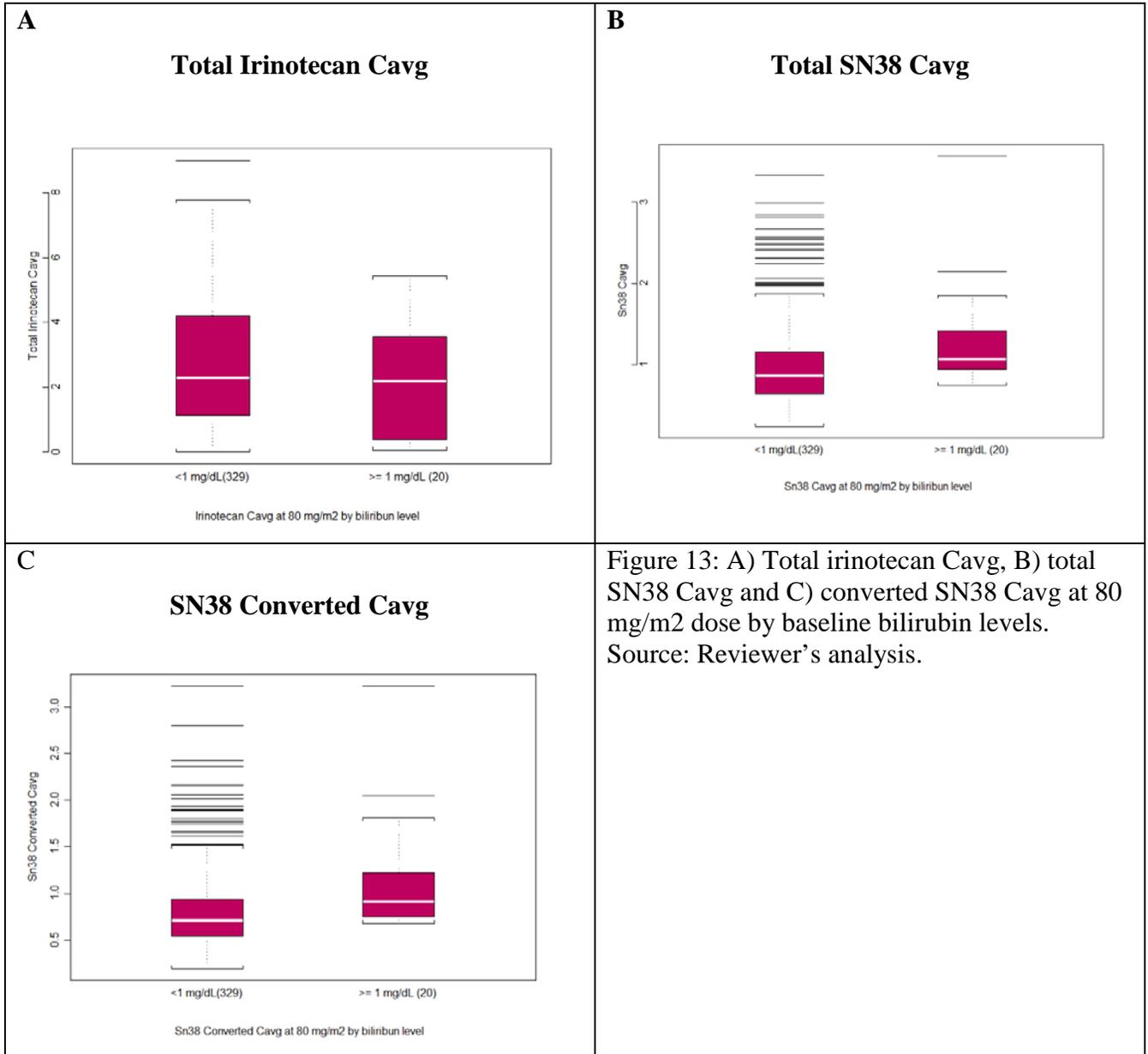
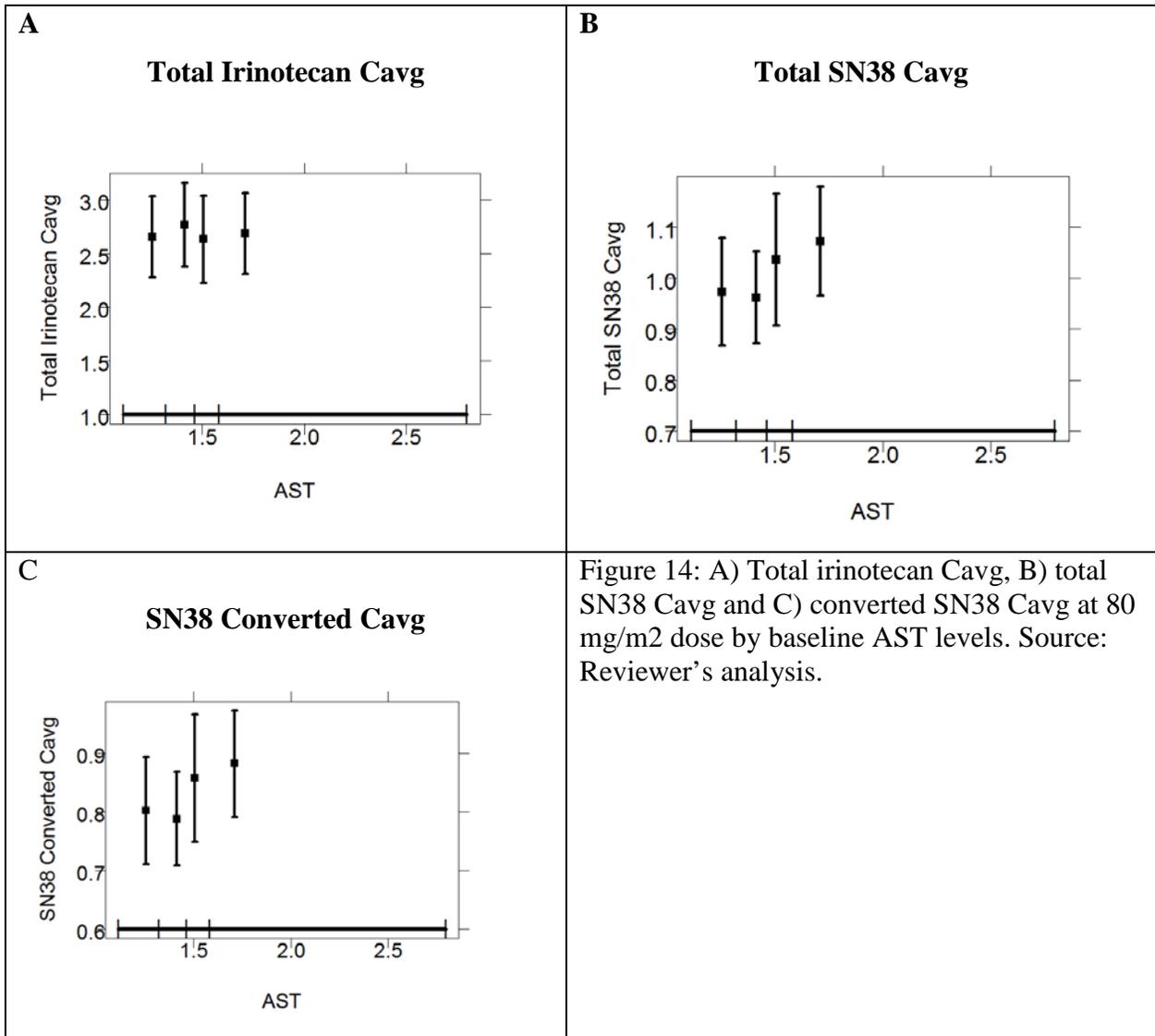


Figure 13: A) Total irinotecan Cavg, B) total SN38 Cavg and C) converted SN38 Cavg at 80 mg/m2 dose by baseline bilirubin levels. Source: Reviewer’s analysis.



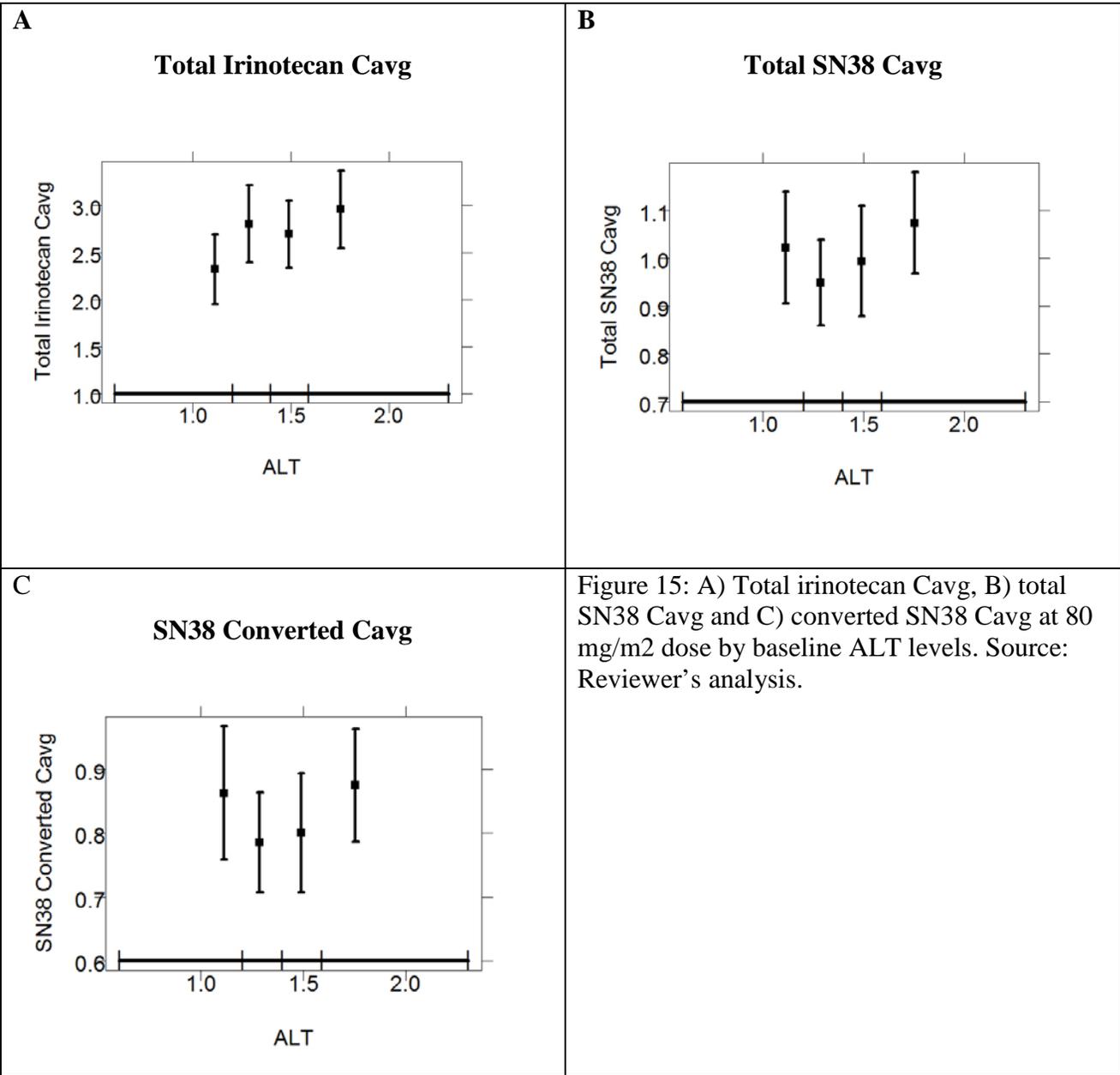
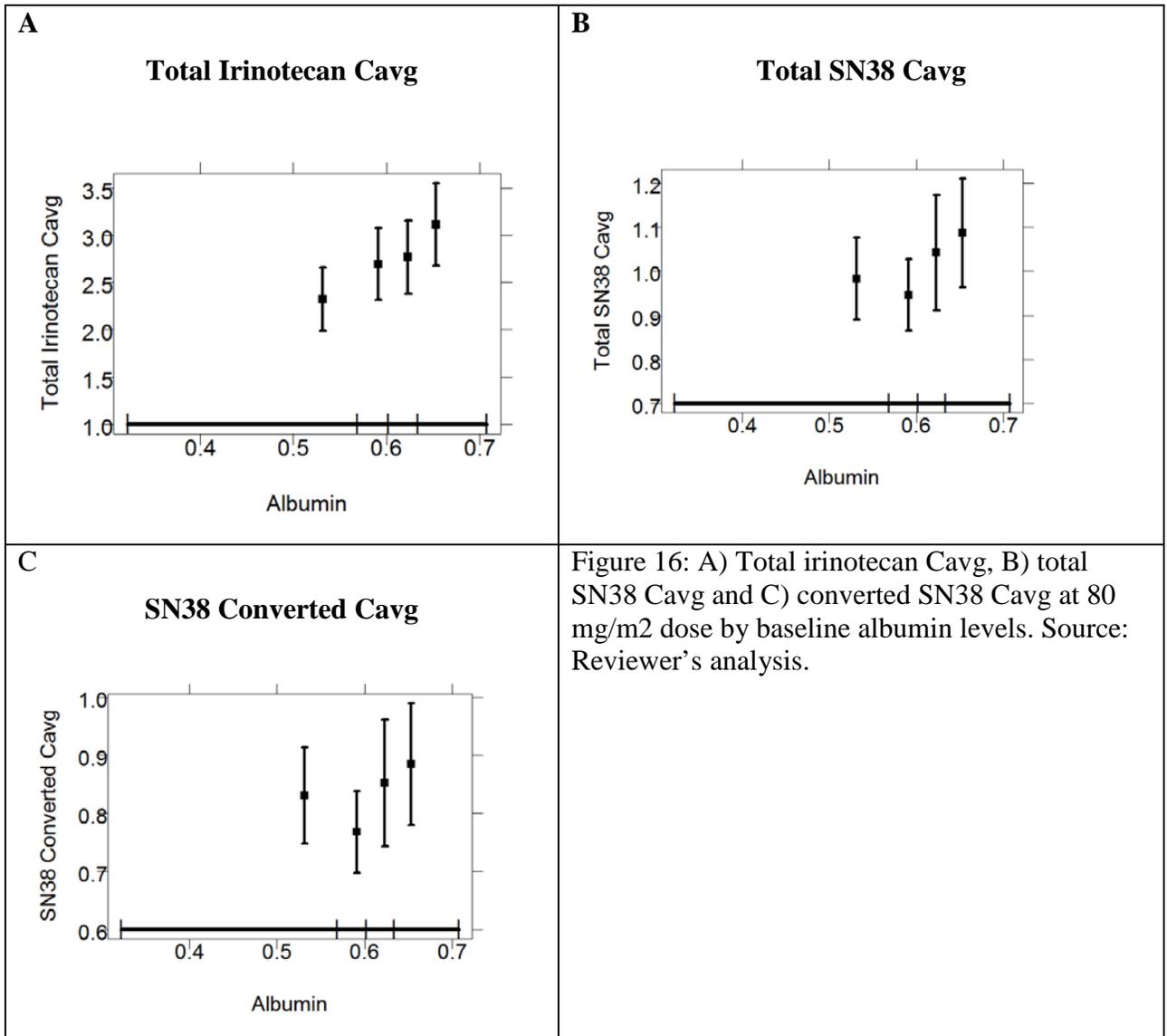


Figure 15: A) Total irinotecan Cavg, B) total SN38 Cavg and C) converted SN38 Cavg at 80 mg/m² dose by baseline ALT levels. Source: Reviewer’s analysis.



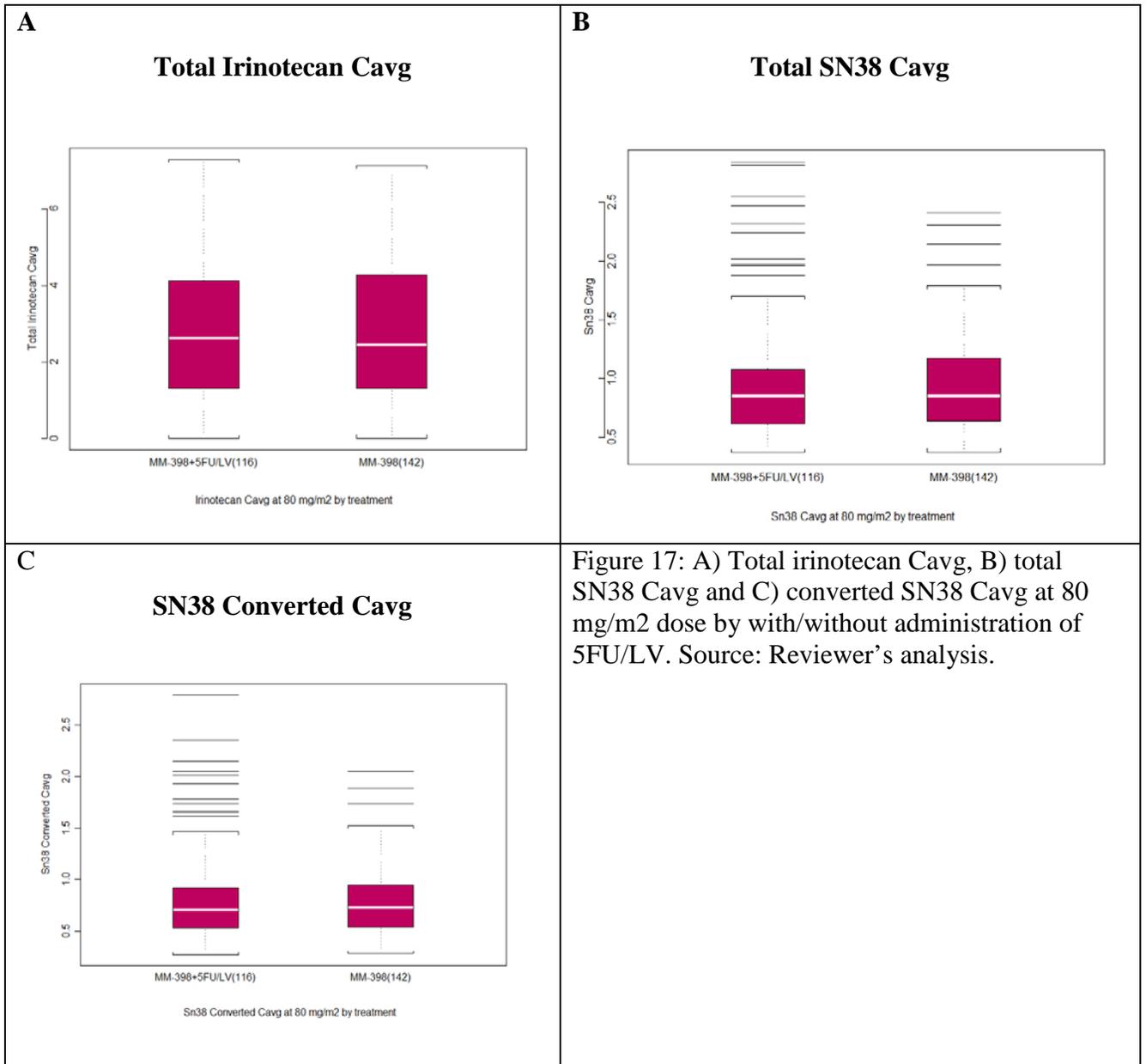


Figure 17: A) Total irinotecan Cavg, B) total SN38 Cavg and C) converted SN38 Cavg at 80 mg/m² dose by with/without administration of 5FU/LV. Source: Reviewer's analysis.

1.2 Recommendations

Division of Pharmacometrics finds NDA 207793 acceptable from a clinical pharmacology perspective provided an agreement regarding the label language can be reached between the sponsor and the Agency

1.3 Label Statements

See section 3 of the Clinical Pharmacology Review.

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

The objectives of sponsor's population PK analysis were:

- To describe the PK profiles for MM-398 (total Irinotecan and SN-38) in patients with advanced solid cancer;
- To evaluate the impact of intrinsic (body size, demographics, lab measurements of hepatic and renal functions, and UGT1A1*28 homozygosity) and extrinsic factors (co-administration with 5-FU, and manufacturing site) on the PK of MM-398;

2.1.1 Data

Data from six studies were used in the population pharmacokinetic analysis. The design of each study is provided in Table 7. The analytes measured in these studies include total (encapsulated and free) irinotecan (CPT11), its active metabolite SN-38, and inactive metabolite SN-38G. In Study PEP0201, the levels of encapsulated irinotecan were measured and the measured values were indistinguishable from total irinotecan; therefore, only total irinotecan levels were measured in the subsequent studies. SN-38G was not evaluated in the current analysis as described in the population pharmacokinetic analysis plan because preliminary analysis of a model that included SN-38G did not improve the SN-38 model performance (compared to a model without SN-38G) and because SN-38G is not an active metabolite.

Table 7: Summary of Studies included in Population PK Analysis

Study number	N	MM-398 dose regimen (mg/m ²)	Drugs in combination	PK sample collections	Analytes
PEP0201	11	60, 120 or 180 q3w	None (monotherapy)	Cycle 1: 0 (pre-dose), 0.5, 1.0, 1.5, 2.5, 3.5, 4.5, 7.5, 10.5, 13.5, 25.5, 49.5, 73.5 and 169.5 hr post drug infusion Cycle 2: 0 (pre-dose)	Total irinotecan, encapsulated irinotecan and SN-38
PEP0203	16	60, 80, 100 or 120 q3w	5-FU/LV	Cycle 1: 0 (pre-dose), 0.5, 1.0, 1.5, 2.5, 4.5, 10.5, 25.5, 49.5, 73.5 and 169.5 hr post drug infusion Cycle 2: 0 (pre-dose)	Total irinotecan and SN-38
PEP0206	37	120 q3w	None (monotherapy)	Cycle 1: 0 (pre-dose), 0.5, 1.0, 1.5, 2.5, 4.5, 10.5, 25.5, 49.5, 73.5 and 169.5 hr post drug infusion Cycle 2: 0 (pre-dose)	Total irinotecan, SN-38 and SN-38G
PIST-CRC-01	18	80, 90, 100 q2w	None (monotherapy)	Cycle 1: 0 (pre-dose), 0.5, 1.0, 1.5, 2.5, 4.5, 10.5, 25.5, 49.5, 73.5, 169.5 hr post drug infusion	Total irinotecan and SN-38
NAPOLI-1 (MM-398-07-03-01)	260	Arm 2: 120 q3w Arm 3: 80 q2w	Arm 2: None (monotherapy) Arm 3: 5-FU/LV	Cycle 1: 0 (pre-dose), 1.5, 2.5, 48 (Arm 3 only) and 168 hr	Total irinotecan, SN-38, SN-38G and 5-FU
CITS (MM-398-01-01-02)	13	80 q2w	None (monotherapy)	Cycle 1: 0 (pre-dose), 1.5, 3, 72 and 168 hr Cycle 2: 0 (pre-dose)	Total irinotecan, SN-38 and SN-38G

qXw= every X weeks (X is a number).

Source: Table 3-1 of sponsor's population PK and ER analysis of MM-398 report.

2.1.2 Results

The time-course of total irinotecan (CPT11) concentrations was described as a two-compartmental model. Final estimated parameters are listed in Table 8. The goodness of fit plots is shown in Figure 18. The time-course of SN-38 concentrations were modeled as a one-compartmental model with two input fluxes: (b) (4) and the *in vivo* conversion from un-encapsulated CPT11 released from MM-398. Final estimated parameters are listed in Table 9. The goodness of fit plots is shown in Figure 19. In the model, SN-38 were differentiated based on their origin: (b) (4) and 'SN-38 Converted' if originating from the *in vivo* conversion. The differentiation of the origins of SN-38 was supported by the observation in study PEP0206: cohorts with MM-398 administration had delayed appearance of SN-38G relative to the appearance of SN-38, but no delay was observed with Camptosar®. Moreover, comparison of models with and without consideration of (b) (4) showed that a model with the two source of SN-38 had significant improvements in the model fitting (objective functions of -2544.36 vs -456.67, for models with and without initial (b) (4) administration).

Covariate Analysis

The covariate model structure for CPT11 followed the pre-defined structure in the analysis plan and follows biological and pharmacological rationales, and included:

- body surface area (BSA) and volume of distribution (to evaluate the relationship between dose and body size)
- hepatic and renal functions (AST, ALT, albumin, liver metastasis status, bilirubin, UGT1A1*28, and creatinine clearance) to clearance (to evaluate potential differences in metabolism by liver and renal functions)
- demographics (sex, age, race) to clearance (to evaluate potential differences in metabolism by baseline demographics)
- external functions (co-administration with 5-FU and manufacturing site) to clearance (to evaluate potential drug interaction and differences in manufacturing)

During the development of the SN-38 model, it became apparent that the clearance of CPT11 is an important covariate to the input flux of SN-38, and therefore, the estimated clearance and volume of CPT11 were added as covariates to the SN-38 input flux. Mechanistically, an increased clearance of CPT11 was hypothesized to generate more released un-encapsulated irinotecan that would be available for *in vivo* conversion to SN-38. Manufacturing site was also evaluated as a potential covariate to the input flux of SN-38. The effect of the various covariates on CPT11 and SN38 exposure are shown in Figure 20, Figure 21 and Figure 22.

- The covariate with strongest association to CPT11 and SN-38 was race. Asians were observed with lower CPT11 exposure than Caucasians.
- Baseline bilirubin was also associated with SN-38: increasing bilirubin levels was associated with higher SN-38 exposure
- The incidence of UGT1A1*28 homozygosity was too few (N=2/129) in the Asian subgroup. In the Caucasian subgroup, no significant association was observed

- between UGT1A1*28 homozygosity and SN-38 exposure. Caucasians who were homozygous had numerically higher SN-38 Converted average concentrations, but these are not statistically significant (0.81 (95%CI: 0.72-0.92; n= 23) and 0.68 (95%CI: 0.65-0.72; n= 220) ng/mL; P=0.30; these concentration numbers were for a simulated dose of 80 mg/m² for both patients with and without UGT1A1*28 homozygosity; in Study MM-398-07-03-01, the actual dose in patients who were homozygous was lower than those in patients who were not homozygous).
- Body surface area (BSA) was associated with CPT11 and SN-38 with opposite directions: higher BSA was associated with higher CPT11 and with lower SN-38. Simulation study showed that, compared to BSA-based, fixed dosing would result in reduction in CPT11 variability but increased in SN-38 variability (interquartile range of CPT11 Cmax: 54% vs 58%, interquartile range of SN-38 Cmax: 74% vs 57%). This result implies a benefit of BSA-based dosing strategy, as compared to flat-dosing strategy, in reducing the variability of SN-38 exposure.
 - No association was found between SN-38 exposure and covariates measuring hepatic and renal functions, including AST, ALT, albumin, liver metastasis, and creatinine clearance. No association was found between CPT11 and these covariates, except for albumin: higher albumin was associated with higher CPT11. Because the direction of the association was opposite to that expected in patients with hepatic impairment, and that no association were found between albumin with SN-38, the implication of this association is unknown.
 - No association was found between CPT11 and SN-38 exposures and demographics variables including sex and age.
 - No difference in exposure were found by co-administration with 5-FU.

Table 8: Parameter estimates of the final population PK model for total irinotecan

Parameter	Estimated values (final model)	Estimated Values from Bootstrapping (N=497)		
		Median	2.5%	97.5%
Objective Function	-1196.3895	-1238.53	-2100.37	-506.661
Fixed effects				
Volume (V1)	4.498	4.498	4.1604	4.6668
Clearance (CL)	15.44	15.438	11.705	21.403
Q	0.05413	0.054	0.0254	0.6766
V2	0.06817	0.068	0.0524	43.9466
V1-BSA	0.3749	0.375	0.2004	0.534
CL-(race=Asian)	0.7172	0.715	0.5704	0.8842
CL-(treatment contains 5FU)	0.0331	0.029	-0.0982	0.1986
CL-(manufacturing site)	0.04327	0.037	-0.218	0.2572
CL-(liver metastasis)	-0.03806	-0.031	-0.228	0.1456
CL-(ALT)	-0.03428	-0.343	-0.6404	-0.0492
CL-(Albumin)	-1.731	-1.731	-3.5044	-0.5054
CL-(Bilirubin)	0.1716	0.172	-0.1128	0.5266
CL-(Creatinine Clearance)	0.002168	0.002	-0.001	0.004
Random effects				
Omega(V1)	0.2388	0.057	0.015	0.0966
Omega(CL)	0.7712	0.127	0.0474	0.2378
Omega(V1-CL)(off-diagonal)	0.6869	0.596	0.377	1.043
Residuals				
Standard deviation of residual error	0.3012	0.301	0.2008	0.3856

Source: Table 4-1 of sponsor's population PK and ER analysis of MM-398 report.

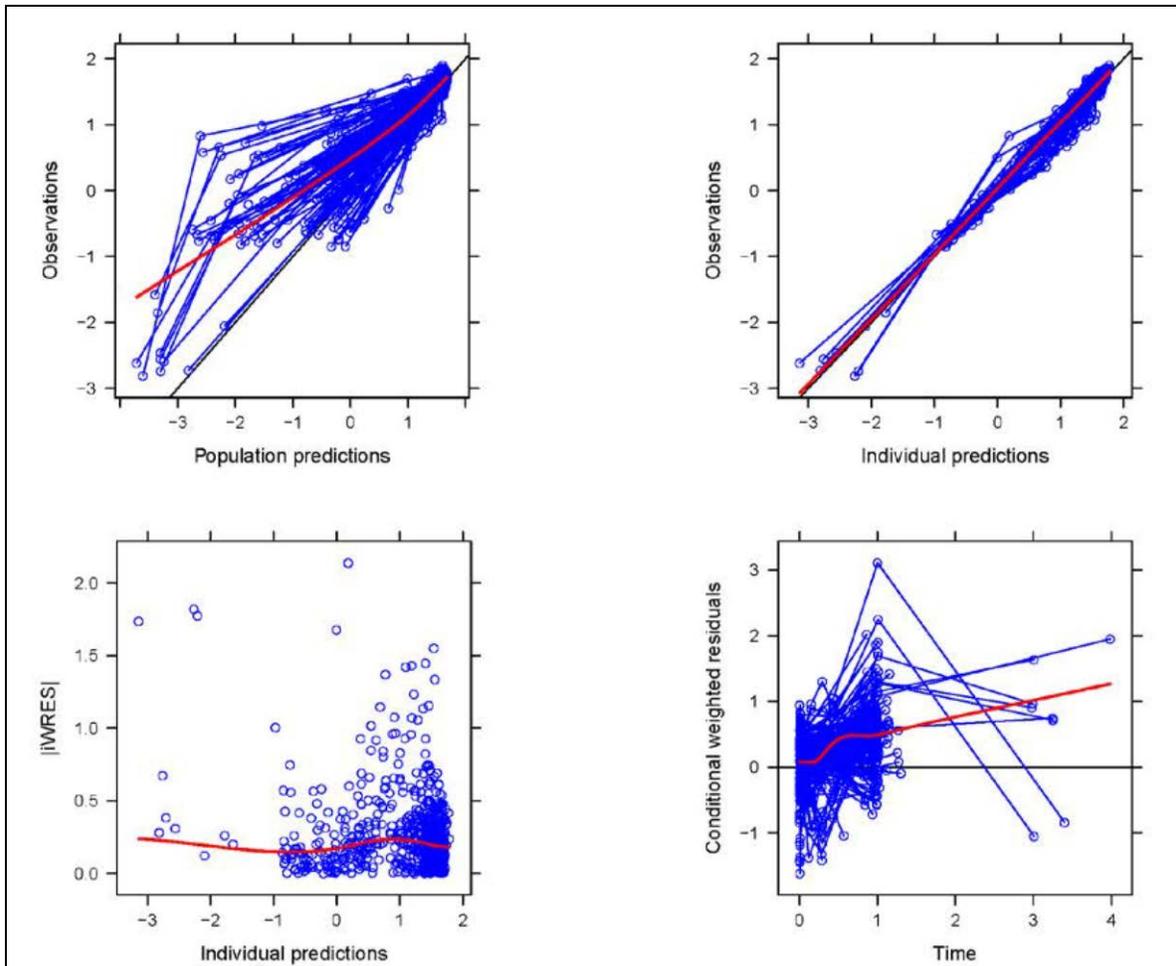


Figure 18: Goodness of fit plots from the final population PK model of total irinotecan. Source: Figure 7-3 of sponsor's population PK and ER analysis of MM-398 report.

Table 9: Parameter estimates of the final population PK model for total SN-38

Parameter Name	Estimated Values (Final Model)	Estimated Values from Bootstrap (n=499)		
		Median	2.5%	97.5%
Objective Function	-2863.2540	-2897.94	-3191.04	-2560.65
Fixed effects				
Clearance (CL)	13.3	13.27	12.0126	14.0213
K13 conversion flux from CPT11	0.0683	0.07	0.064	0.077
Impurity (IMP)				(b) (4)
CL-(race==Asian)	-0.0733	-0.071	-0.1312	-0.00835
CL-(UGT1A1*28==homozygote)	-0.00259	-0.002	-0.003	-0.002
CL-(treatment contains 5FU)	0.00272	0.003	0.001	0.005
K13-(manufacturing site)	0.000557	0.001	0.001	0.001
CL-(liver metastasis)	-0.00551	-0.004	-0.008	-0.00045
CL-(ALT)	-0.000124	0	0	0
CL-(Albumin)	-0.0403	-0.023	-0.046	0.001
CL-(Bilirubin)	-0.571	-0.545	-0.95955	-0.22785
CL-(Creatinine Clearance)	-0.145	-0.11	-0.21	-0.00625
K13-CPT11clearance	1.97	1.966	1.7518	2.20155
K13-CPT11volume	-0.0552	-0.042	-0.083	0.011
K13-BSA	-1.24	-1.195	-1.733	-0.70485
Random effects				
Omega(CL)	0.2993	0.092	0.076	0.107
Omega(CL-K13) (off diagonal)	-0.1974	-0.013	-0.021	0.01555
Omega(K13)	0.4637	0.224	0.18145	0.275
Omega(CL-impurity) (off diagonal)				(b) (4)
K13-impurity (off diagonal)				
Omega(Impurity)				
Residuals				
Standard deviation of residual error	0.156	0.157	0.139	0.17565

Source: Table 4-2 of sponsor's population PK and ER analysis of MM-398 report.

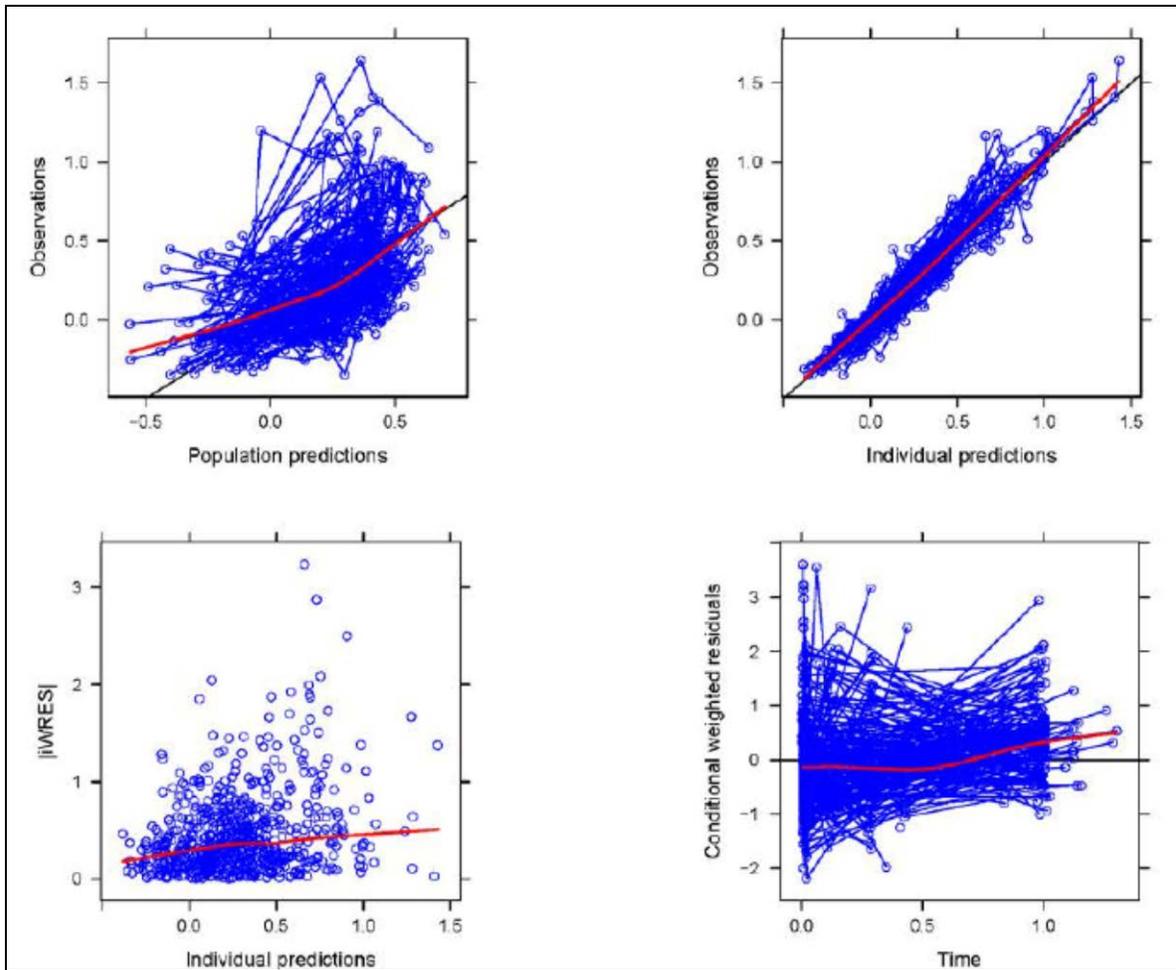


Figure 19: Goodness of fit plots from the final population PK model of SN-38. Source: Figure 8-3 of sponsor's population PK and ER analysis of MM-398 report.

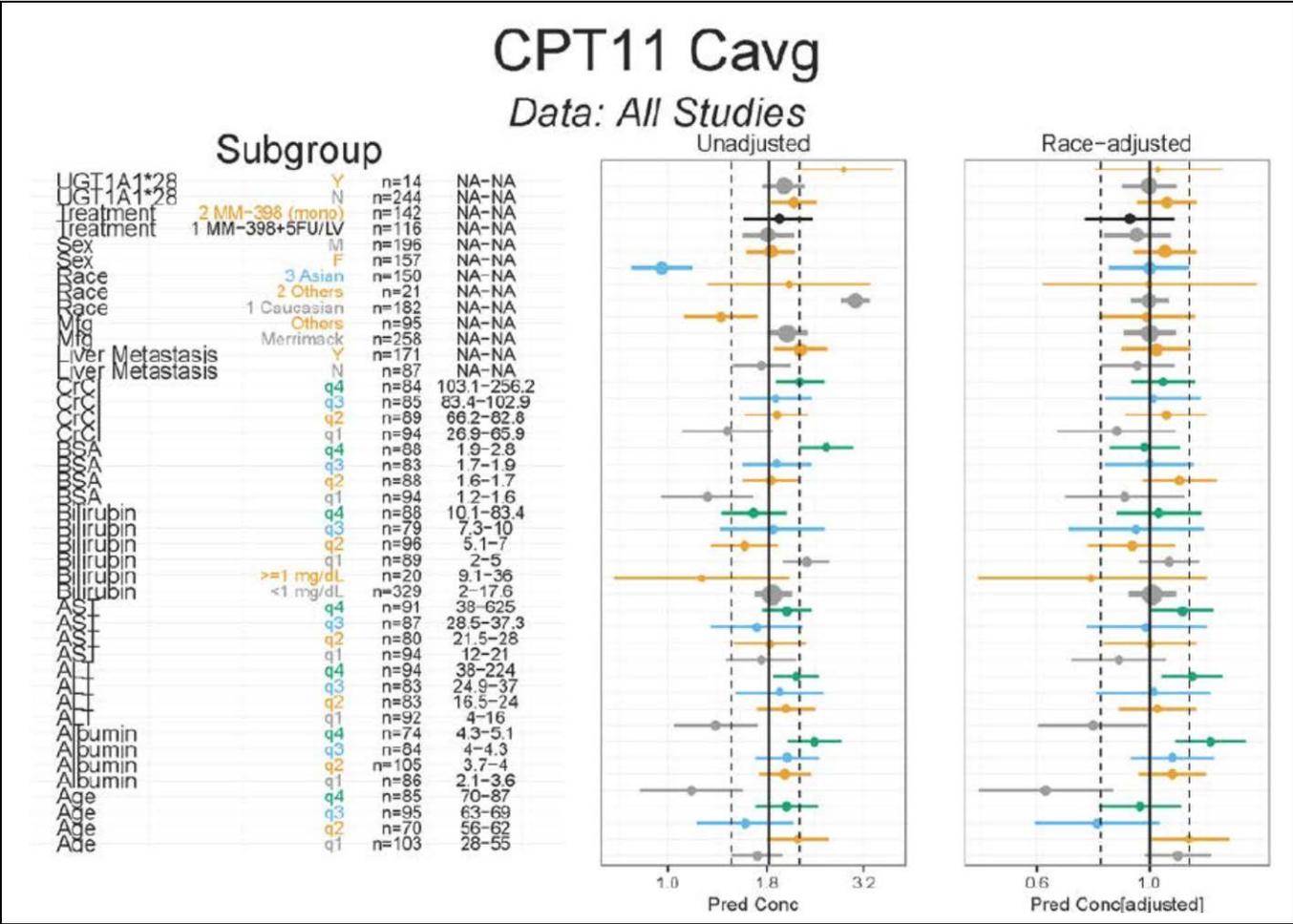


Figure 20: Forest Plot of CPT11 Average Concentration (C_{avg}) by Baseline Covariate Subgroup. Point=geometric means, whiskers= 95% confidence intervals. Pred Conc= predicted concentration. Pred Conc [adjusted] = Race-adjusted concentration ratio calculated as the concentration ratio of the observed and the expected from the race distribution in the corresponding subgroup (assuming race as the only important covariate). See text for details of the method. Solid vertical line= mean of the whole population; dotted vertical lines, 80% to 120% of the mean concentration of the whole population. Source: Figure 9-3 of sponsor's population PK and ER analysis of MM-398 report.

SN38 Total Cavg

Data: All Studies

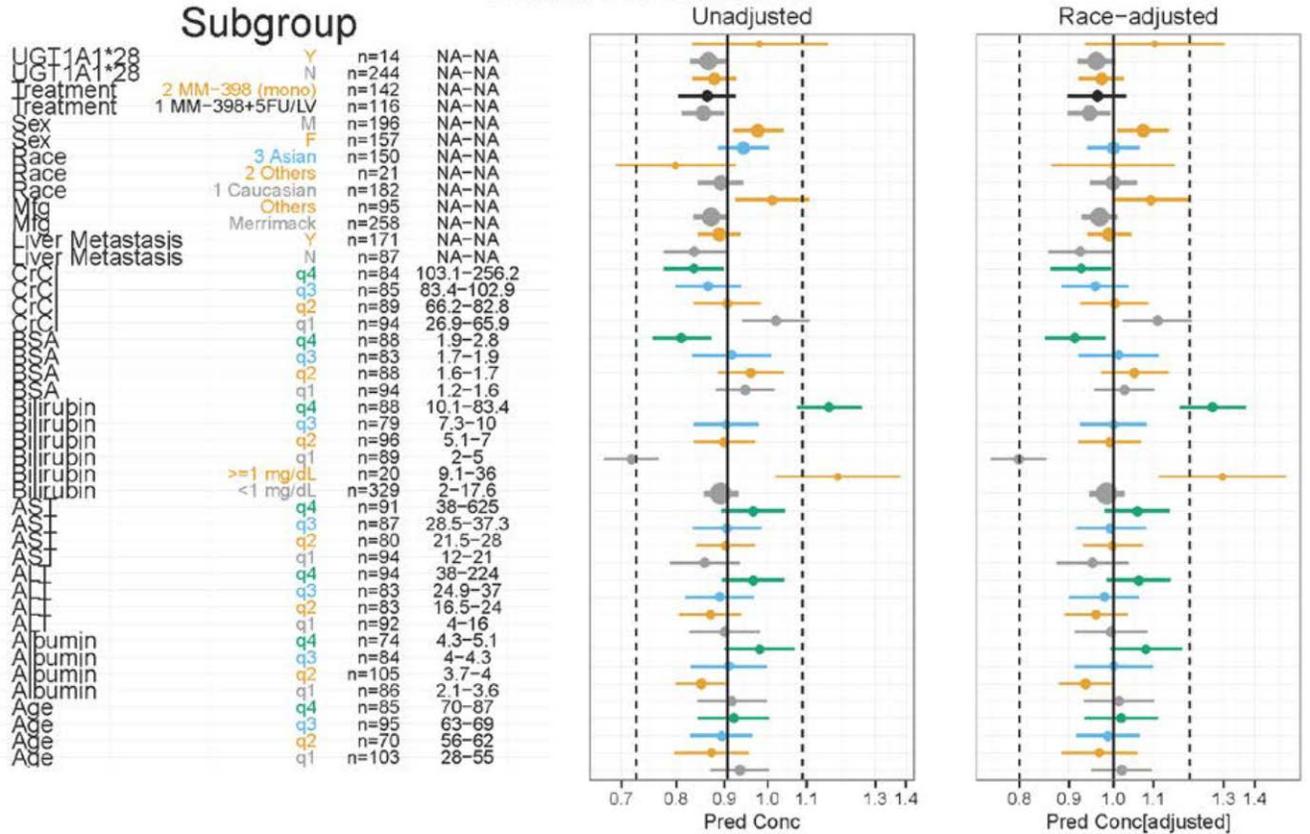


Figure 21: Forest Plot of SN38 Total Average Concentration (C_{avg}) by Baseline Covariate Subgroup. Point=geometric means, whiskers= 95% confidence intervals. Pred Conc= predicted concentration. Pred Conc [adjusted] = Race-adjusted concentration ratio calculated as the concentration ratio of the observed and the expected from the race distribution in the corresponding subgroup (assuming race as the only important covariate). See text for details of the method. Solid vertical line= mean of the whole population; dotted vertical lines, 80% to 120% of the mean concentration of the whole population. Source: Figure 9-5 of sponsor's population PK and ER analysis of MM-398 report.

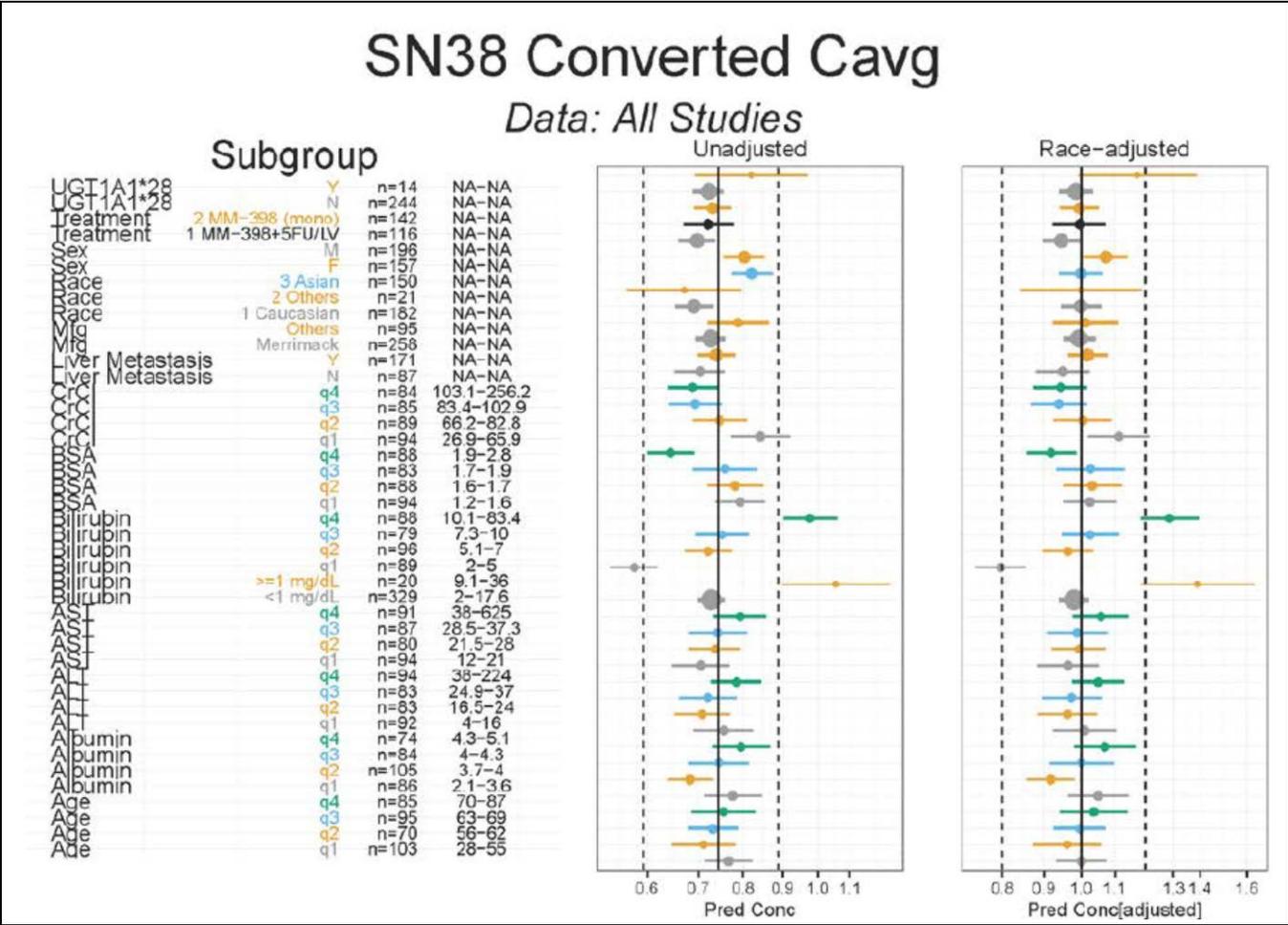


Figure 22: Forest Plot of SN38 Converted Average Concentration (C_{avg}) by Baseline Covariate Subgroup. Point= geometric means, whiskers= 95% confidence intervals. Pred Conc= predicted concentration. Pred Conc [adjusted] = Race-adjusted concentration ratio calculated as the concentration ratio of the observed and the expected from the race distribution in the corresponding subgroup (assuming race as the only important covariate). See text for details of the method. Solid vertical line= mean of the whole population; dotted vertical lines, 80% to 120% of the mean concentration of the whole population. Source: Figure 9-7 of sponsor's population PK and ER analysis of MM-398 report.

Reviewer's comments:

- Sponsor population PK model for total irinotecan and SN-38 is reasonable based on model diagnostics.
- The reviewer assessment of effect of covariate on total irinotecan and SN38 exposures are provided in section 1.1.6.

2.2 Exposure Response Analysis for Efficacy

The objectives of sponsor's exposure response analysis were:

- To evaluate the relationship between exposure and efficacy endpoints

2.2.1 Data

Exposure-efficacy analysis was conducted from the dataset of NAPOLI study only. A total of 258 patients who had PK measurements were included in the dataset.

2.2.2 Results

1. In this study, higher exposures of total irinotecan and its active metabolite, SN-38, in the MM-398+5-FU/LV treatment arm were associated with longer OS and PFS (and lower hazard ratios).
2. The strongest association with OS and PFS was observed for the average concentrations of SN-38 Total and SN-38 Converted (SN-38 Total referred to SN-38 both inside and outside the liposomes; SN-38 Converted referred to the SN-38 outside the liposomes originating from in vivo conversion of released irinotecan).
3. To visualize the association, each of the average concentration measures was separated into quartiles, and each quartile was compared against the 5-FU/LV control arm (Figure 24). The summary of the estimated OS hazard ratio (relative to 5-FU/LV control arm) and the SN-38 Converted average concentration is provided in Figure 23.
4. The summary of the estimated OS and PFS hazard ratio (relative to 5-FU/LV control arm) and various PK parameters are provided in Figure 25 for the MM-398+5-FU/LV treatment arm and Figure 26 for MM-398 monotherapy arm.

The impact of dose modification was evaluated by comparing the PK parameters with and without factoring the dose modification occurring during the length of the treatment.

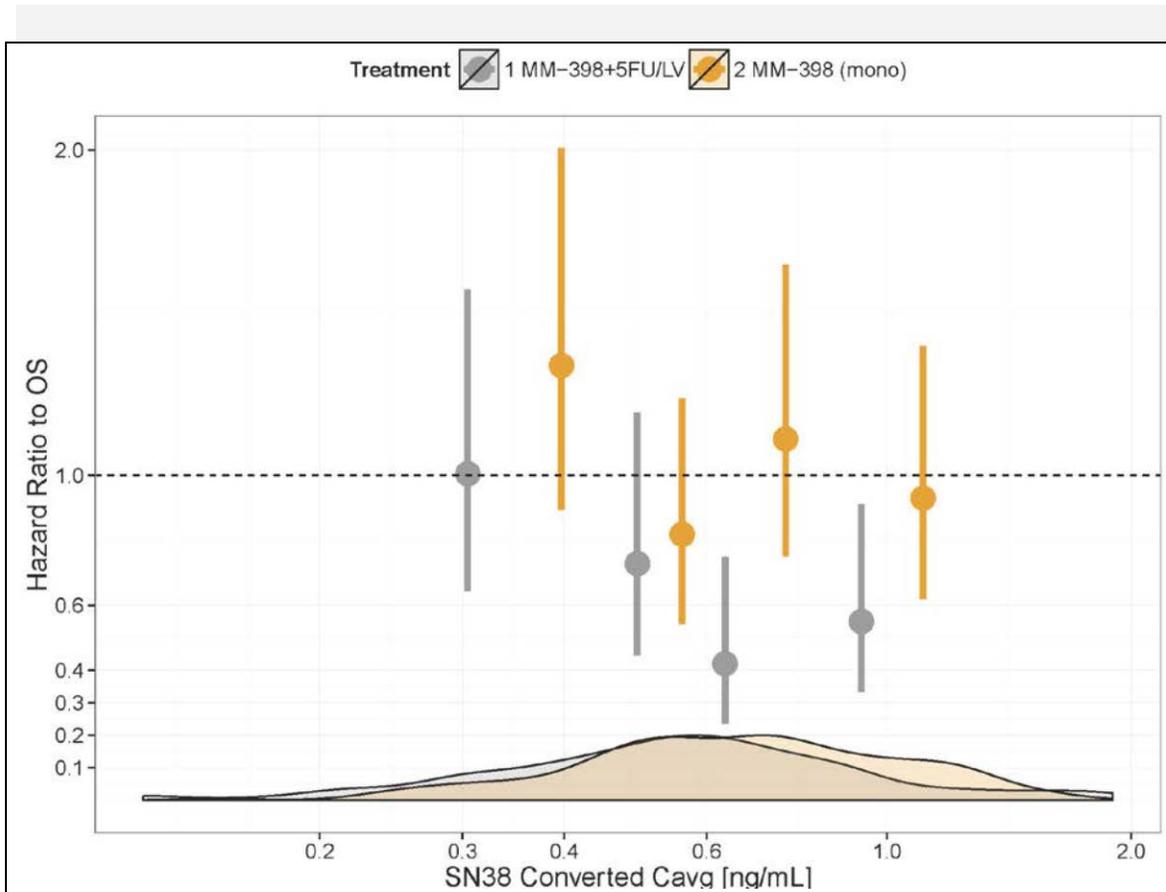


Figure 23: Hazard Ratio Estimates for OS by SN-38 Converted Cavq concentration in NAPOLI study. Hazard ratio was estimated for each quartile of SN-38 converted average concentration relative to the 5-FU/LV control arm using Cox proportional hazard model. Source: Figure 10-2 of sponsor's population PK and ER analysis of MM-398 report.

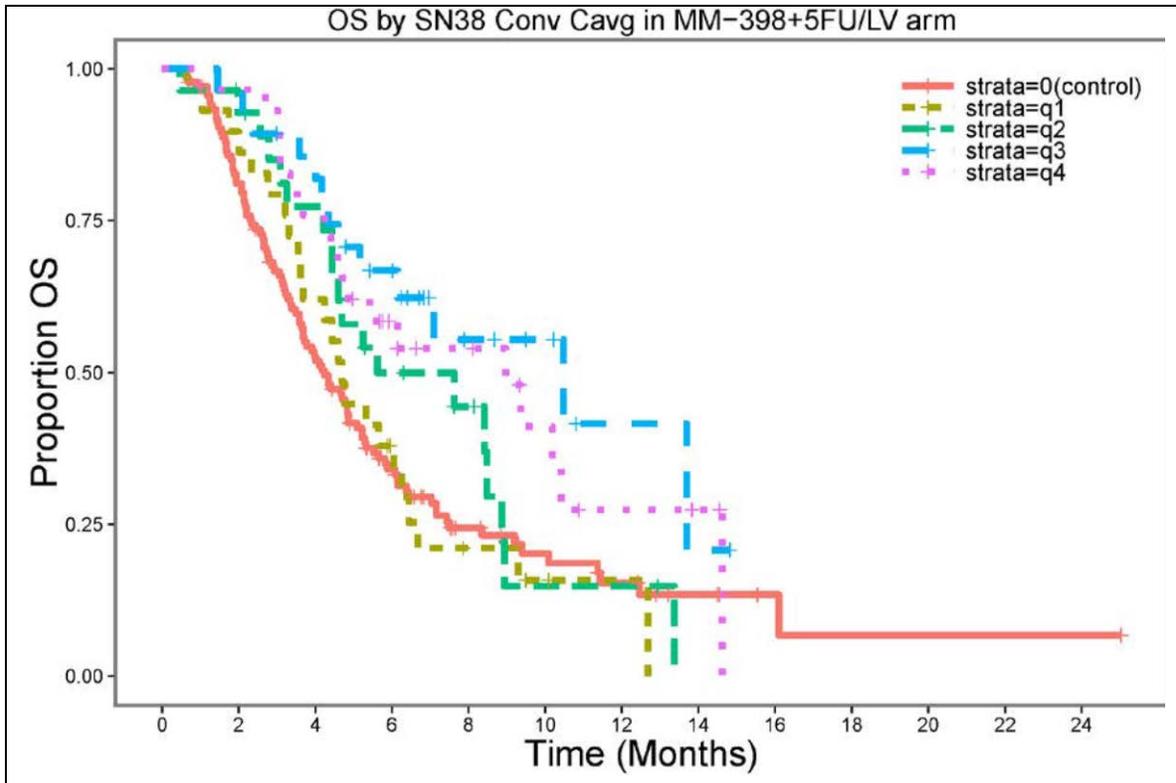


Figure 24: Kaplan-Meier Plot of OS by Quartiles of SN-38 Converted Cavg in MM-398+5FU/LV arm. Source: Figure 10-9 of sponsor's population PK and ER analysis of MM-398 report.

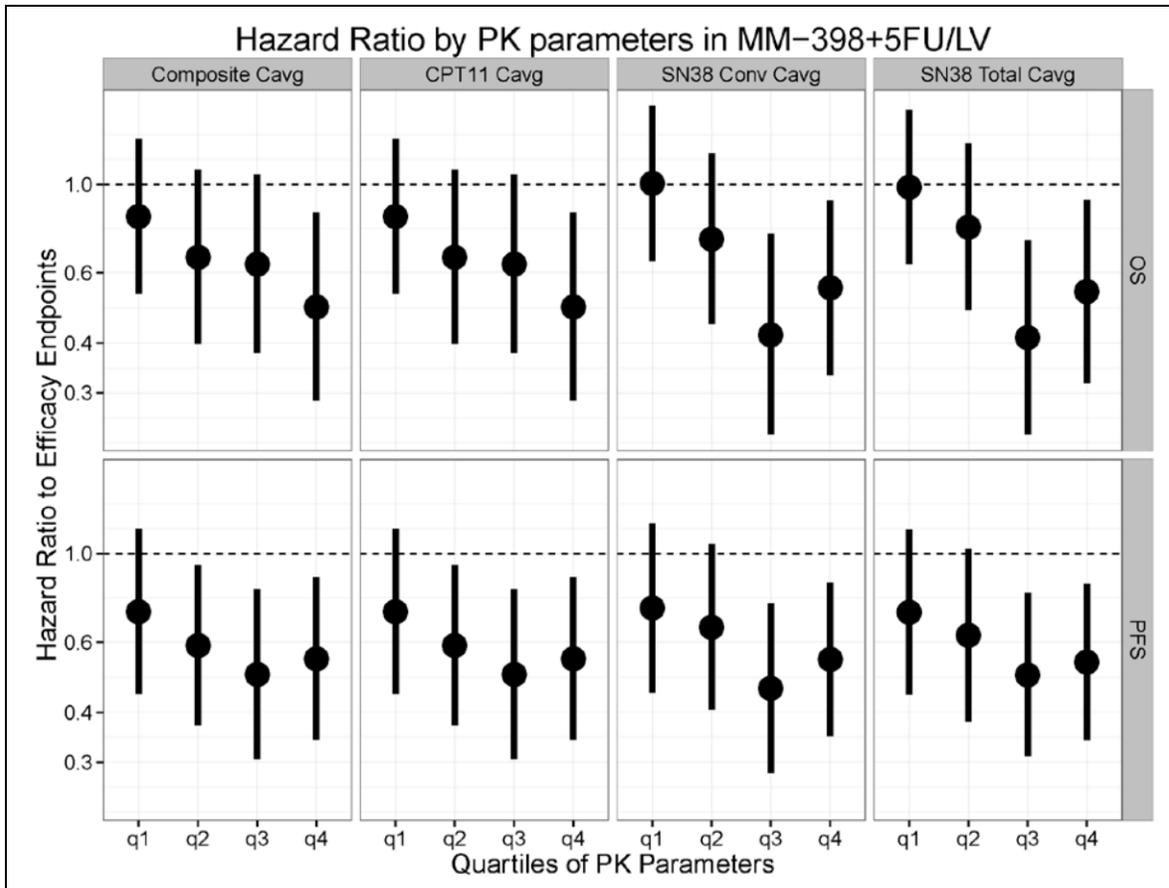


Figure 25: Hazard Ratio Estimates for OS (top) and PFS (bottom) by Quartiles of PK Parameters in MM-398+5FU/LV Arm in NAPOLI study. Hazard ratio was calculated using Cox proportional hazard model relative to the 5FU/LV control arm. Q1-q4: quartiles of PK parameter that are calculated separately for each treatment. Source: Figure 10-3 of sponsor's population PK and ER analysis of MM-398 report.

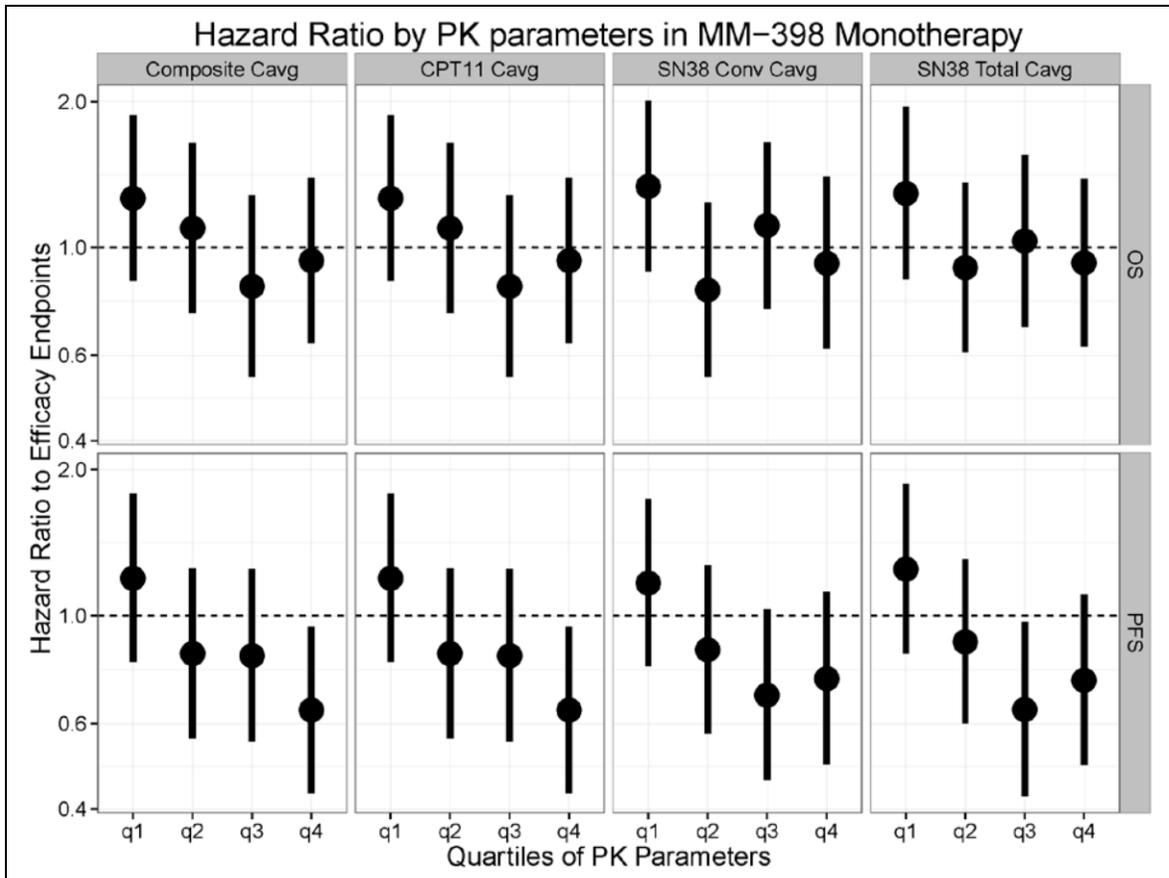


Figure 26: Hazard Ratio Estimates for OS (top) and PFS (bottom) by Quartiles of PK Parameters in MM-398 Monotherapy Arm in NAPOLI study. Hazard ratio was calculated using Cox proportional hazard model relative to the 5FU/LV control arm. Q1-q4: quartiles of PK parameter that are calculated separately for each treatment. Source: Figure 10-5 of sponsor's population PK and ER analysis of MM-398 report.

Reviewer's comments:

- Reviewer's multivariate analysis confirmed that there is increase in overall survival with increase in total SN38 Cavg (for details see section 1.1.1).

2.3 Exposure Response Analysis for Safety

The objectives of sponsor's exposure response analysis were:

- To evaluate the relationship between exposure and safety endpoints of interest of diarrhea, neutropenia, and anemia

2.3.1 Data

Three different dataset cases were used: all studies as described in Table 7, NAPOLI-1 combined both MM-398 treatment arms, and NAPOLI-1 separately for each MM-398 treatment arm.

2.3.2 Results

The association between common adverse events of interest (diarrhea and neutropenia) and multiple pharmacokinetic parameters were evaluated. The highlights of the safety findings are summarized below. The strongest association was observed for neutropenia followed by diarrhea.

Neutropenia

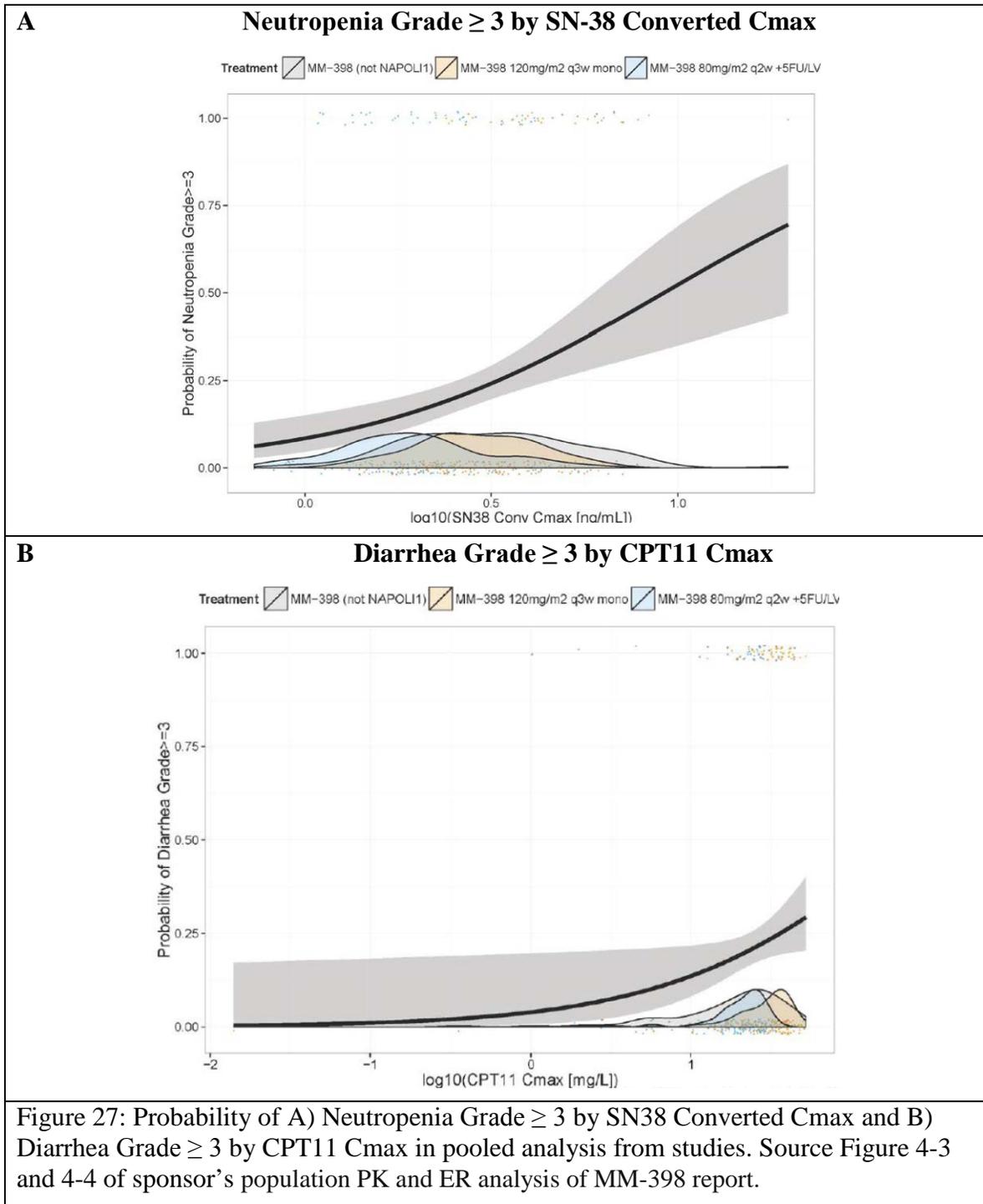
1. For the incidence of grade ≥ 3 neutropenia treatment-emergent adverse events (TEAEs) in data combined from three studies, the strongest association was observed with PK parameters related to SN-38 Converted C_{max} (**Error! Reference source not found.**).
2. The association to neutropenia was stronger for SN-38 Converted than for SN-38 Total (for example, the association p-values for the incidence of neutropenia grade ≥ 3 TEAEs and C_{max} were <0.001 and 0.031 for SN-38 Converted and for SN-38 Total, respectively)

Diarrhea

1. In combined dataset, higher CPT11 exposures, in particular C_{max} , were associated with a higher probability of incidence of diarrhea (grade ≥ 3) (Figure 27Figure 27).

Reviewer's comments:

- *The reviewer's assessment of exposures-response analysis is provided in section 1.1.2. Both univariate and multivariate analyses was conducted by the reviewer.*
- *Sponsor's conclusions were primarily based on univariate analysis. Thus an IR was sent to the sponsor to conduct multivariate analysis. Sponsor's multivariate analysis confirmed that the association between grade ≥ 3 neutropenia and converted SN38 C_{max} was retained after adjusting for other factors associated with neutropenia, including baseline ANC and 5-FU/LV administration. Similarly, multivariate analysis indicated an association of diarrhea (particularly grade ≥ 3) with CPT-11 C_{max} , after adjusting for other baseline factors that may be associated with diarrhea.*



3 RESULTS OF REVIEWER'S ANALYSIS

3.1 Exposure Response Analysis for Efficacy

See section 1.1.1 for reviewer's analysis.

3.2 Exposure Response Analysis for Safety

See section 1.1.2 for reviewer's analysis.

4.2 PHARMACOGEMOMICS REVIEW

Table 1: Clinical studies with UGT genotype data

Study identifier (Objectives)	Study design	N, Population studied ⁽⁺⁾	Test product(s); Dosage regimen; Route of administration	UGT alleles analyzed	DNA sample acquisition N (%)
MM-398-07-03-01; NAPOLI-1 (Efficacy and Safety)	Phase 3, randomized, open label, global trial of MM-398, with or without 5-FU/LV, vs. 5-FU/LV alone (active control)	417 patients with metastatic pancreatic cancer	Arm A: MM-398 120 mg/m ² q3w; Arm B: 5-FU/LV; Arm C: MM-398 80 mg/m ² in combination with 5-FU/LV. MM-398 starting dose was reduced in patients homozygous for UGT1A1*28.	UGT1A1*28	413/417 (99%)
PEP0202** (Safety and PK)	Phase 1/2; Phase 1: dose escalation; Phase 2: not performed	6 patients with metastatic cervical cancer	MM-398 in combination with cisplatin; MM-398: 60 and 80 mg/m ² q3w IV	UGT1A1*6, *28; UGT1A9*1b	6/6 (100%)
PEP0203 (Safety and PK)	Phase 1, open label, multi-center, dose escalation of MM-398 in combination with 5-FU/LV	16 patients with solid tumors	MM-398 in combination with 5-FU/LV; MM-398: 60, 80, 100, 120 mg/m ² q3w IV	UGT1A1*6, *27, *28, *60, *93; UGT1A9*1b	16/16 (100%)
PIST-CRC (Safety and PK)	Phase 1, open label, dose escalation	18 patients with colorectal cancer	MM-398: 80, 90 and 100 mg/m ² q2w IV	UGT1A1*6, *7, *27, *28, *29, *93; UGT1A9*1b	18/18 (100%)
PEP0206 (Efficacy and Safety)	Phase 2, open label, randomized	132 patients with gastric & GEJ cancer	Arm 1: MM-398 120 mg/m ² q3w IV; Arm 2: Irinotecan 300 mg/m ² q3w IV; Arm 3: docetaxel 75 mg/m ² q3w IV	UGT1A1*6, *27, *28, *60, *93; UGT1A9*1b	70/132 (53%)
PEP0208 (Efficacy and Safety)	Phase 2, open label, multicenter, single arm	40 patients with metastatic pancreatic cancer	MM-398 120 mg/m ² q3w IV	UGT1A1*6, *27, *28, *60, *93; UGT1A9*1b	28/40 (70%)

Source: Applicant's tabular listing of all clinical studies; PK: pharmacokinetic; GEJ: gastroesophageal junction; PEP0202 clinical study report included genotype information on UGT1A1*6, *28 and UGT1A9*1b alleles. Genotyping data for UGT1A1*27, *60 and *93 were submitted as a part of an information request (May 14, 2015); In PIST-CRC, UGT1A1 T-3279G is described as UGT1A1*7 and UGT1A1*93 is defined as "C/C". According to the UGT Alleles Nomenclature (<https://www.pharmgkb.org/haplotypeSet/PA166115840>), these correspond to UGT1A1*60 and -G3156A, respectively; ⁽⁺⁾ Number of patients enrolled in MM-398 studies as of October 24, 2014; DPYD (DPYD*2A) was also genotyped in studies PEP0203 and PEP0206 (not shown).

3. KEY QUESTIONS AND SUMMARY OF FINDINGS

3.1. Is the proposed MM-398 dosing appropriate for patients homozygous for the UGT1A1*28 allele?

The applicant's proposed dosing recommendation for patients known to be homozygous for the UGT1A1*28 allele appears appropriate. Although limited by the small number of patients homozygous for UGT1A1*28 in NAPOLI-1, the applicant's proposed reduced starting dose of MM-398 is supported by the following: (1) all patients homozygous for UGT1A1*28 randomized to the MM-398+5-FU/LV combination arm in NAPOLI-1 (n=7) received a reduced starting dose of 60 mg/m² of MM-398, as pre-specified in the trial protocol, (2) dose escalation of MM-398 to 80 mg/m² without further dose reduction was possible in approximately 43% (n=3/7) of UGT1A1*28 homozygous patients, and (3) the observed frequency of grade 3 or 4 neutropenia was similar between patients homozygous (28.6%; n=2/7) and non-homozygous (27.3%; n=30/110) for UGT1A1*28. A reduced starting dose for patients homozygous for the UGT1A1*28 allele is also supported by the well-established association between UGT1A1*28 and increased risk of neutropenia following irinotecan therapy.

3.1.1. Distribution of UGT1A1 gene polymorphisms across populations

UGT1A1*28, a promoter polymorphism that leads to reduced UGT1A1 transcription, is one of the most

commonly studied reduced function alleles in Whites due to its association with SN-38 toxicity, especially neutropenia. In addition, Gilbert's syndrome, characterized by mild hyperbilirubinemia due to the inability to conjugate bilirubin (a substrate of UGT1A1), is frequently associated with UGT1A1*28 in Whites. UGT1A1 reduced function alleles exhibit high racial/ethnic variability (Table 2). Asians have a relatively low prevalence of UGT1A1*28 homozygosity; approximately 10% of Whites and 20% of individuals of African origin are homozygous for UGT1A1*28, but less than 2-3% of East-Asians have this genotype. The UGT1A1*6 allele, present in 15-24% of Asians (while mostly absent in Whites), is considered the primary allele responsible for the severe irinotecan toxicity in this population, and this variant has been associated with Gilbert's syndrome in Asians [PMID: 17529881]. Compound heterozygotes for reduced function alleles such as UGT1A1*6/*28 may also be at an increased risk of developing irinotecan associated neutropenia [PMID: 17558305, 23303296].

Table 2: Selected UGT1A1 reduced function allele frequencies in different populations

UGT1A1 allele	Variant allele frequency (%)		
	European	Asian	African
*28	30-40	1.9-16	35-45
*60	42	23	74
*93	27	8.9	37
*6	0	21	0
*27	0	0.6	0
*7	1.4	ND	ND

Source: Modified from PMID: 20235794 and 12815363; Values reflect results of different studies and may vary within specific populations; ND - not determined.

Reviewer comment: Based on the racial/ethnic variation in the alleles underlying reduced UGT1A1 mediated metabolism, it is important to identify UGT1A variants relevant in individuals of different racial/ethnic groups in studies evaluating potentially significant genotype associations with pharmacokinetics (PK) or clinical outcome, which may not be found if relevant alleles are not genotyped [PMID: 20511137].

3.1.2. Clinical Studies: NAPOLI-1

NAPOLI-1 was a global, open-label, randomized, three-arm, Phase 3 trial in patients with metastatic pancreatic cancer previously treated with a gemcitabine-based therapy. It was originally designed with two treatment arms, comparing MM-398 monotherapy to a control of 5-FU/LV, and was later amended to add a third arm to investigate the combination treatment of MM-398 with 5-FU/LV (MM-398+5-FU/LV). Eligible patients were randomly assigned to these arms in 1:1:1 ratio, stratified by baseline albumin levels (≥ 4.0 g/dL vs. < 4.0 g/dL), KPS (Karnofsky performance score; 70 and 80 vs. > 90), and ethnicity/race (Whites vs. East Asians vs. All Others). Patients with serum total bilirubin above the normal range for the institution were excluded. The primary endpoint was overall survival (OS). The key secondary endpoints were progression-free survival (PFS), objective response rate (ORR), tumor marker response of CA (carbohydrate antigen) 19-9, and safety.

Patients non-homozygous for UGT1A1*28 received an initial dose of MM-398 of 80 mg/m² (MM-398+5-FU/LV arm) or 120 mg/m² (MM-398 monotherapy arm). The protocol specified a reduced starting dose of MM-398 for patients homozygous for UGT1A1*28 allele randomized to a MM-398 containing arm (60 mg/m² in the MM-398+5-FU/LV combination arm and 80 mg/m² in the MM-398 monotherapy arm). If patients did not experience any drug related toxicity after the MM-398 administration, from cycle 2 onward the dose of MM-398 could be increased to 80 mg/m² in the combination arm, and by 20 mg/m² increments up to 120 mg/m² in the monotherapy arm. For UGT1A1*28 genotyping, a whole blood sample was collected from all patients prior to treatment. Samples were to be processed by a central lab, although local lab results could be used if the central lab

results were not available at the time of randomization. Genotyping was performed by DNA sequencing.

A total of 417 patients were randomized in the trial, and are included in the Intent-to-Treat (ITT) population (151 to the MM-398 monotherapy arm, 117 to the MM-398+5-FU/LV combination arm, and 149 to the 5-FU/LV arm). The treatment groups were balanced in terms of demographic and disease characteristics. The majority of patients in the ITT were male (56.8%), and the most common race/ethnicity was White (60.7%) followed by Asian (32.6%).

Based on the applicant's analysis, the median OS was 6.1 months in the MM-398+5-FU/LV combination arm compared to 4.2 months in the 5-FU/LV control arm [HR (95% CI): 0.68 (0.50-0.93), p=0.014]. Serious TEAEs were reported with a similar frequency in the MM-398+5-FU/LV combination arm (47.9%) compared to the 5-FU/LV arm (44.8%). Within the MM-398+5-FU/LV combination arm, 39 patients (33.3%) experienced TEAEs that required dose reductions. Dose delays were primarily due to neutropenia and neutrophil count decrease (14.5% and 9.4%, respectively). The frequency of dose delays in the combination arm was higher than that observed in either the MM-398 monotherapy (4.5% and 0.7%) or the 5-FU/LV control (2.2% and 0.7%) arms.

3.1.2.1. UGT1A1*28 distribution in NAPOLI-1

There were 27 patients homozygous for UGT1A1*28 in the trial (7 in the MM-398+5-FU/LV arm, 7 in the MM-398 monotherapy arm, and 13 in the 5-FU/LV arm). The remaining patients were classified as non-homozygous (could be either wild-type or heterozygous for UGT1A1*28). Table 3 shows UGT1A1*28 genotype distribution by race/ethnicity in all patients receiving treatment (N=398) and in patients randomized to the MM-398+5-FU/LV combination arm (N=117).

Table 3: UGT1A1*28 genotype by race/ethnicity in NAPOLI-1

UGT1A1*28 genotype	Number (%) of patients					
	All patients receiving treatment (N=398) [¶]			MM-398+5-FU/LV combination arm (N=117)		
	Asian (N=129)	White (N=243)	All Other (N=26)	Asian (N=33)	White (N=73)	All Other (N=11)
UGT1A1*28 homozygous	2 (1.6)	23 (9.5)	2 (7.7)	1 (3)	6 (8.2)	0
UGT1A1*28 heterozygous [§]	21 (16.3)	110 (45.3)	13 (50) ^Δ	5 (15.2)	36 (49.3)	6 (54.5)
Wild-type for UGT1A1*28 [§]	104 (80.6)	110 (45.3)	10 (38.5)	27 (81.8)	31 (42.5)	5 (45.5)
Not available [#]	2 (1.6)	0	1 (3.8)	0	0	0

Source: Reviewer's analysis. [¶] Of 417 patients in the ITT, 19 patients were not treated; [§] Non-homozygous were broken down by the reviewer into UGT1A1*28 heterozygous and wild-type for UGT1A1*28; ^Δ Includes 1 patient with genotype TA(6)/TA(8); [#] Cases where genotype data was missing/not available were classified as UGT1A1*28 non-homozygous by the applicant.

There were no reported relevant differences in patient disposition when UGT1A1*28 status was considered.

*Reviewer comment: The lower frequency of homozygosity for UGT1A1*28 in Asians compared to Whites observed in NAPOLI-1 is expected based on reported UGT1A1*28 frequencies in the literature (2% in East Asians vs. 10% in Whites). Asian patients were not genotyped for the UGT1A1*6 allele which may introduce a null bias for genotype effects on SN-38 PK or MM-398 safety.*

3.1.2.2. Analysis of safety according with race/ethnicity and UGT1A1*28 genotype

With respect to race/ethnicity, in the MM-398+5-FU/LV combination arm, grade ≥ 3 drug related TEAEs were more frequent in Asians (72.7%) than Whites (45.2%), primarily due to an increased frequency of grade ≥ 3 neutropenia (per Neutropenia adverse events of special importance (AESI), product specific Merrimack MedDRA queries (PMMQ); 54.5% in Asians vs. 17.8% in White). Accordingly, more dose delays and dose reductions were necessary in Asians compared to Whites in the MM-398+5-FU/LV arm (84.8% and 48.5% vs. 54.8% and 24.7%), a pattern that was not observed in the 5-FU/LV control arm, although permanent discontinuation rates were similar. Diarrhea was more frequent and severe in Whites than Asians (grade ≥ 3 diarrhea 19.2% in Whites vs. 3% in Asians).

In the combination arm, the frequency of TEAEs leading to any dose modification (including dose delay, reduction, and discontinuation) was higher in non-homozygous patients (Table 4). The frequency of grade 3 or 4 neutropenia was similar between patients homozygous (28.6%; n=2/7) and non-homozygous (27.3%; n=30/110) for the UGT1A1*28 allele in the combination arm. Among non-homozygous patients, the frequency of grade 3 or 4 neutropenia was 31.7% (n=20/63) in patients wild-type and 21.3% (n=10/47) in patients heterozygous for the UGT1A1*28 allele. Grade 3 or 4 neutropenia by UGT1A1*28 genotype and race/ethnicity is described in Table 5.

Table 4: Frequency of serious treatment emergent adverse events (TEAEs) in the MM-398+5-FU/LV combination arm

UGT1A1*28 genotype	Number (%) of patients	
	All serious TEAEs	TEAEs leading to dose modification [¶]
UGT1A1*28 non-homozygous (N=110)	53 (48.2)	79 (71.8)
UGT1A1*28 homozygous (N=7)	3 (42.9)	4 (57.1)

Source: NAPOLI-1 clinical study report. TEAEs - treatment emergent adverse events; [¶] Dose modification includes dose delay, reduction, and discontinuation.

Table 5: Grade 3 or 4 neutropenia by UGT1A1*28 genotype and race/ethnicity in NAPOLI-1 MM-398+5-FU/LV arm

UGT1A1*28 genotype	Number (%) of patients		
	Asian (N=33)	White (N=73)	All Other (N=11)
UGT1A1*28 homozygous	1 (3)	1 (1.4)	0
UGT1A1*28 heterozygous [§]	1 (3)	8 (11)	1 (9.1)
UGT1A1*28 wild-type [§]	16 (48.5)	4 (5.5)	0

Source: Reviewer's exploratory analysis. [§] Non-homozygous (N=110) were broken down in UGT1A1*28 heterozygous (N=47) and UGT1A1*28 wild-type (N=63).

*Reviewer comment: The frequency of grade 3 or 4 neutropenia did not differ significantly between homozygous and non-homozygous patients perhaps as a result of the prospective dose adjustment strategy. Potential confounding factors include (1) the fact that 42.7% of patients classified as non-homozygous by the applicant were heterozygous for UGT1A1*28, and (2) other reduced function UGT1A1 alleles such as UGT1A1*6 associated with irinotecan toxicity in Asians were not taken into account.*

Elevated bilirubin may be an indicator of reduced conjugation capacity and reduced UGT1A1 function. In the combination arm, 6 patients had bilirubin ≥ 1 mg/dL. Of these, four were wild-type for UGT1A1*28, 1 was homozygous for UGT1A1*28, and 1 patient had no available genotype information. Per the applicant, the numbers were small to assess the association of bilirubin levels with neutropenia. Based on POP PK analysis, these patients had 24% higher SN-38 exposure than patients with bilirubin levels < 1 mg/dL, and a trend for increase in grade 3 or 4 neutropenia was observed with increasing SN-38

exposure (refer to Pharmacometrics review (Dr. Anshu Marathe) for a detailed analysis).

3.1.2.3. Summary of dose reductions and treatment discontinuation for patients homozygous for UGT1A1*28

Of the 7 patients homozygous for UGT1A1*28 receiving an initial dose of 60 mg/m² in the MM-398+5-FU/LV combination arm, 2 patients remained at the starting dose of 60 mg/m², 3 were escalated to 80 mg/m² without the need for further dose reduction, 1 was escalated but reduced to 60 mg/m², and 1 was dose reduced to 40 mg/m². At the time of cutoff, 2 patients were still on treatment, 3 discontinued due to progressive disease, 1 discontinued to an adverse event, and 1 patient discontinued due to patient's decision. Similarly, in the MM-398 monotherapy arm, of the 7 patients homozygous for UGT1A1*28 receiving an initial dose of 80 mg/m², 4 patients remained at the starting dose of 80 mg/m², 2 had MM-398 dose escalation (1 dose escalated to 100 mg/m², and the other to 120 mg/m²), and 1 patient had a dose reduction following the 80 mg/m² starting dose. No patient discontinued the drug due to adverse event, 4 discontinued due to progressive disease, 1 due to death, and 2 patients discontinued the drug due to patient's decision.

Most patients homozygous for UGT1A1*28 discontinued treatment either due to progressive disease and death. Dose escalation of MM-398 without further dose reduction was possible in 35.7% (n=5/14) of UGT1A1*28 homozygous patients randomly assigned to a MM-398-containing arm, and in 42.9% (n=3/7) when only the combination arm is considered.

3.1.2.4. Differences in SN-38 exposure and MM-398 associated neutropenia

Based on the applicant's analysis, higher SN-38 converted C_{max} was associated with a higher incidence of neutropenia. Patients homozygous for UGT1A1*28 had numerically higher, but not statistically significant SN-38 converted C_{max} when compared to non-homozygous patients. The POP PK analysis conducted by the pharmacometrics reviewer (Dr. Anshu Marathe) showed an 18% higher SN-38 exposure (Coverage) in patients homozygous compared to patients non-homozygous for UGT1A1*28, although there was a trend for increase in grade 3 or 4 neutropenia with increasing SN-38 exposure (refer to Pharmacometrics review for a detailed analysis).

3.1.3. Other reduced function UGT1A genetic polymorphisms

The applicant explored the role of polymorphisms in UGT1A1 (in addition to UGT1A1*28, also UGT1A1*6, UGT1A1*27, UGT1A1*60, and UGT1A1*93), UGT1A9 (UGT1A9*22 (*1b)) and DPYD (DPYD*2A) in 5 Phase 1 and 2 trials (Table 1). No conclusive results regarding correlations of genotype with clinical outcome or PK parameters were reported or identified in exploratory analyses by the reviewer (results not shown).

Reviewer comment: Potential limitations include small sample sizes, variable rates of DNA sample acquisition for genotyping, and differences in the alleles genotyped, trial design, patient population and MM-398 therapy (dosing, and monotherapy vs. combination therapy) in the various studies.

4. SUMMARY AND CONCLUSIONS

The association between UGT1A1*28 and increased risk of neutropenia following irinotecan therapy is well established. The labeling for irinotecan includes warnings about the risk for neutropenia in patients homozygous for UGT1A1*28, and recommends dose reductions in patients known to have this genotype.

All patients homozygous for UGT1A1*28 randomized to the MM-398+5-FU/LV combination arm in NAPOLI-1 (n=7) received a reduced starting dose of 60 mg/m² of MM-398 with subsequent dose

escalation based on tolerability. Dose escalation to 80 mg/m² of MM-398 without further dose reduction was possible in approximately 43% of the UGT1A1*28 homozygous patients. It appears that by using this strategy, the observed frequency of grade 3 or 4 neutropenia in the combination arm was similar between patients homozygous and non-homozygous for UGT1A1*28. Major differences in PK were not observed across the UGT1A1 genotype groups.

A significant proportion of the population was of Asian ancestry, and alleles relevant to that population were not tested (e.g., *6) in the pivotal NAPOLI-1 trial. Additionally, the primary comparisons for safety and PK were between UGT1A1*28 homozygous and non-homozygous patients, meaning that patients with reduced function (heterozygous for UGT1A1*28, as well as, patients with other reduced function UGT1A1 alleles) were classified as UGT1A1*28 non-homozygous and compared to the *28 homozygous group. Not factoring in the heterozygosity status and the presence of reduced function alleles in the non-homozygous population could introduce a null bias that may have limited detection of relevant differences in PK or safety. In addition, the number of patients homozygous for UGT1A1*28 was small to allow firm conclusions about differences in PK and safety.

(b) (4)
Although there were no reported significant PK differences between patients homozygous and non-homozygous for UGT1A1*28 receiving MM-398 after accounting for differences in the administered dose, it is still uncertain whether lack of an initial MM-398 dose adjustment based on genotype in NAPOLI-1 would have resulted in higher rates of neutropenia or dose reduction in patients homozygous for UGT1A1*28. Also, there is a relationship between SN-38 exposure and efficacy (i.e., greater efficacy in those with highest concentrations; see Pharmacometrics review) that needs to be acknowledged. Based on the limitations discussed above, and given the history of irinotecan and increased risk for neutropenia in patients homozygous for UGT1A1*28, the applicant's proposed dosing recommendation to (b) (4) reduced starting dose of MM-398 in patients known to be homozygous for UGT1A1*28 and increase based on tolerability is reasonable. The applicant's proposed language is consistent with the current labeling for non-liposomal irinotecan.

5. RECOMMENDATIONS

The submission is acceptable from a Genomics and Targeted Therapy Group perspective. The labeling should be modified to include the Pharmacogenomics section.

5.1. Post-marketing studies

No post-marketing commitments or requirements are recommended at this time.

5.2. Labeling recommendations

Please see integrated labeling recommendations in Section 3 of the Clinical Pharmacology review.

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

/s/

SARAH J SCHRIEBER
09/30/2015

ANURADHA RAMAMOORTHY
09/30/2015

ANSHU MARATHE
09/30/2015

ROSANE CHARLAB ORBACH
09/30/2015

YANING WANG
09/30/2015

GENE M WILLIAMS
09/30/2015

I concur with the recommendations

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	207793	SDN	3
Applicant	Merrimack	Submission Date	4/24/15
Generic Name	Irinotecan Liposome	Brand Name	Onivyde
Drug Class	camptothecin derivative / topoisomerase I inhibitor		
Indication	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in patients previously treated with gemcitabine		
Dosage Regimen	ONIVYDE 80 mg/m ² IV infusion over 90 minutes, every 2 weeks, with LV 400 mg/m ² infusion over 30 minutes followed by 5-FU 2400 mg/m ² infusion over 46 hours		
Dosage Form	50 mg/10 mL dispersion in a single use vial	Route of Administration	IV
OCP Division	DCPV	OND Division	DOP2
OCP Review Team	Primary Reviewer(s)		Secondary Reviewer/ Team Leader
Division	Sarah J. Schrieber		Gene Williams
Pharmacometrics	Jian Wang		Yaning Wang
Genomics	Anuradha Ramamoorthy		Rosane Charlab-Orbach
Review Classification	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	6/23/2015	74-Day Letter Date	7/7/2015
Review Due Date	9/30/2015	PDUFA Goal Date	10/24/2015

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

Yes

No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

Yes

No

If yes list comment(s):

1. Submit the PK analysis datasets and PK parameter datasets in .xpt format for the following studies: PEP0201, PEP0202, PEP0203, PIST-CRC, and PEP0206.
2. Provide the UGT genotyping method, and submit the pharmacogenetic datasets (UGT1A1 and UGT1A9 genotyping analysis) in .xpt format for the following studies: PEP0202, PEP0203, PIST-CRC and PEP0206.

Is there a need for clinical trial(s) inspection?

Yes

No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies Yes No Clinical Pharmacology Summary Yes No
 Bioanalytical and Analytical Methods Yes No Labeling Yes No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
<input type="checkbox"/> Metabolism Characterization		
<input type="checkbox"/> Transporter Characterization		
<input checked="" type="checkbox"/> Distribution	1	Human plasma protein binding report
<input type="checkbox"/> Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
<input type="checkbox"/> Absolute Bioavailability		
<input type="checkbox"/> Relative Bioavailability		
<input type="checkbox"/> Bioequivalence		
<input type="checkbox"/> Food Effect		
<input type="checkbox"/> Other		
Human Pharmacokinetics		
Healthy Subjects	<input type="checkbox"/> Single Dose	
	<input type="checkbox"/> Multiple Dose	
Patients	<input checked="" type="checkbox"/> Single Dose	4
	<input checked="" type="checkbox"/> Multiple Dose	
		PEP0201, PEP0202, PEP0203, PIST-CRC
		See single dose above (studies had multiple dose PK collected)
<input type="checkbox"/> Mass Balance Study		
<input type="checkbox"/> Other (e.g. dose proportionality)		
Intrinsic Factors		
<input type="checkbox"/> Race		
<input type="checkbox"/> Sex		
<input type="checkbox"/> Geriatrics		
<input type="checkbox"/> Pediatrics		
<input type="checkbox"/> Hepatic Impairment		
<input type="checkbox"/> Renal Impairment		
<input type="checkbox"/> Genetics		
Extrinsic Factors		
<input type="checkbox"/> Effects on Primary Drug		
<input type="checkbox"/> Effects of Primary Drug		
Pharmacodynamics		
<input type="checkbox"/> Healthy Subjects		
<input type="checkbox"/> Patients		
Pharmacokinetics/Pharmacodynamics		
<input type="checkbox"/> Healthy Subjects		
<input checked="" type="checkbox"/> Patients	3	MM-398-07-03-01 (NAPOLI 1), PEP0206, MM-398-01-01-02 (CITS) <i>GG data only: PEP0208</i>

<input type="checkbox"/> QT				
Pharmacometrics				
<input checked="" type="checkbox"/> Population Pharmacokinetics		popPK & E-R report		
<input checked="" type="checkbox"/> Exposure-Efficacy		popPK & E-R report		
<input checked="" type="checkbox"/> Exposure-Safety		popPK & E-R report		
Total Number of Studies		In Vitro	1	In Vivo
Total Number of Studies to be Reviewed		In Vitro	1	In Vivo
				8
				8

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	505b2 application with cross-reference to NDA 20-571 Camptosar® (irinotecan hydrochloride injection)
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Intravenous drug. Biopharm agreed that PK could be characterized within the clinical trial(s)
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Datasets in the proper format for the pivotal study MM-398-07-03-01 have been submitted. Need datasets in .xpt format: PEP0201, PEP0202, PEP0203, PIST-CRC, and PEP0206
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?		
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	See above regarding need for PK datasets to be submitted for the listed studies.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Datasets in the proper format for the pivotal study MM-398-07-03-01 have been submitted. Need datasets in .xpt format: PEP0201, PEP0202, PEP0203, PIST-CRC, and PEP0206
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?

Yes No N/A

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

/s/

SARAH J SCHRIEBER
05/21/2015

GENE M WILLIAMS
05/21/2015
I concur