

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207793Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 207793

SUPPL #

HFD # 107

Trade Name ONIVYDE

Generic Name Irinotecan Liposome Injection

Applicant Name Merrimack Pharmaceuticals, Inc.

Approval Date, If Known 10/23/2015

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	20571	Camptosar
ANDA#	79068	Irinotecan HCl
ANDA#	78589	Irinotecan HCl
ANDA#	90726	Irinotecan HCl
ANDA#	78753	Irinotecan HCl
ANDA#	77219	Irinotecan HCl
ANDA#	78953	Irinotecan HCl
ANDA#	90137	Irinotecan HCl
ANDA#	200771	Irinotecan HCl
ANDA#	78188	Irinotecan HCl
ANDA#	77776	Irinotecan HCl
ANDA#	91032	Irinotecan HCl
ANDA#	90016	Irinotecan HCl
ANDA#	77915	Irinotecan HCl
ANDA#	78796	Irinotecan HCl
ANDA#	90675	Irinotecan HCl
ANDA#	90393	Irinotecan HCl
ANDA#	78122	Irinotecan HCl
ANDA#	78805	Irinotecan HCl
ANDA#	90101	Irinotecan HCl

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not

essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study MM-398-07-03-01: 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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study MM-398-07-03-01: 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

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 102799      YES       ! NO   
! Explain:

Investigation #2  
IND #              YES       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Deanne Varney  
Title: Senior Regulatory Project Manager  
Date: September 15, 2015

Name of Office/Division Director signing form: Patricia Keegan  
Title: Director, DOP2

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEANNE R VARNEY  
10/20/2015

PATRICIA KEEGAN  
10/22/2015



**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
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Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed):
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):						
		minimum	maximum		Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	wk. mo.	wk. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed):

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population		minimum	maximum				
<input type="checkbox"/>	Neonate	wk. mo.	wk. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy):							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):							
Population		minimum		maximum		PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	wk.	mo.	wk.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.		Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum		maximum	
<input type="checkbox"/>	Neonate	wk.	mo.	wk.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.	

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.**

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:							
Population		minimum		maximum		Extrapolated from:	
						Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	wk.	mo.	wk.	mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.		<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications.*

*Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:****Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed):
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

 Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):						
		minimum	maximum		Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	wk. mo.	wk. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed):

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population		minimum	maximum				
<input type="checkbox"/>	Neonate	wk. mo.	wk. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy):							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):							
Population		minimum		maximum		PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	wk.	mo.	wk.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.		Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum		maximum	
<input type="checkbox"/>	Neonate	wk.	mo.	wk.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	Other	yr.	mo.	yr.	mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.	

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	wk. mo.	wk. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEANNE R VARNEY  
09/24/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 207793 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Onivyde Established/Proper Name: Irinotecan Liposome Injection Dosage Form: Injection		Applicant: Merrimack Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Deanne Varney		Division: DOP2
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: 7/22/2015</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>October 24, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): New formulation  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Fast Track              | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review          | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation   |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval, 10/22/2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	Granted Letter (7/19/2015 and 10/20/2015)) Review (7/17/2015 and 10/20/2015)
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 7/2/2015 DMEPA: 10/21/2015 10/13/2015 7/27/2015 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: 10/13/2015 and 10/8/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: Pediatric and Maternal Health: 9/23/2015
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM Filing Review: 7/2/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	505(b)(2) Assessment: 9/21/2015 (DARRTS 10/20/2015)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included 10/22/2015

<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan designation, exempt from PREA</u></li> </ul> </li> </ul>	9/24/2015 (Pediatric Page)
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	10/21/2015 10/19/2015 10/9/2015 10/2/2015 9/25/2015 (Panorama) 9/23/2015 9/21/2015 (Panorama) 8/20/2015 (Panorama) 8/13/2015 8/11/2015 (Panorama) 7/27/2015 (2) 7/19/2015 7/9/2015 7/7/2015 (Panorama 8/11/2015) 6/23/2015 5/20/2015 (Panorama 8/11/2015) 5/14/2015 4/30/2015 (2) 1/14/2015
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	10/22/2015 9/23/2015 9/16/2015 (DARRTS 9/17/2015) 7/14/2015 (DARRTS 7/27/2015) [2] 7/20/2015 7/15/2015 7/9/2015 (2) 6/24/2015 5/12/2015 (DARRTS 5/13/2015)
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 12/2/2014
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 8/19/2011
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	9/18/2014 8/1/2014

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/22/2015
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/6/2015
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	9/30/2015 5/11/2015 (filing)
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	9/18/2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> ) • REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> ) • Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 10/2/2015
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/29/2015 5/21/2015 (filing)

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/30/2015 7/8/2015 (QT-IRT) 6/22/2015 (QT-IRT) 5/21/2015 (filing)
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 10/8/2015
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/28/2015 5/21/2015 (filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/16/2015 (memo) 9/30/2015 6/29/2015 (filing)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None Microbiology: 9/30/2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	9/30/2015 (page 157 of integrated quality assessment)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change))</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<b>23</b> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEANNE R VARNEY  
10/28/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

Memorandum

**DATE:** June 23, 2015  
**FROM:** Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
**SUBJECT:** NDA Review Designation  
Sponsor: Merrimack Pharmaceuticals, Inc.  
Product: Irinotecan Liposome Injection  
Indication: Metastatic adenocarcinoma of the pancreas  
**TO:** NDA 207793

The review status of this file is designated to be:

Standard (10 mon.)

Priority (6 mon.)

**Summary of Applicant's Request for Priority Designation**

This NDA relies on FDA's finding of safety and/or effectiveness for listed drug CAMPTOSAR® (irinotecan hydrochloride injection, 20mg/mL) intravenous infusion. (Pfizer; NDA 20-571). Merrimack is seeking approval for a new indication and not for the indications approved for the listed drug on which Merrimack relies.

This new indication is supported by the results of a single, randomized, three-arm clinical trial, Protocol MM-398-07-03-1, titled "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." The primary objective of this trial was demonstration of superior overall survival for MM-398 alone or for MM-398 in combination with 5-fluorouracil and leucovorin as compared to 5-fluorouracil and leucovorin.

A total of 417 patients were randomized to receive

- Arm A: MM-398 120 mg/m<sup>2</sup> Q3W
- Arm B: 5-fluorouracil 2000mg/m<sup>2</sup> QW (weeks 1-4) of each 6-week cycle and leucovorin
- Arm C: MM-398 80 mg/m<sup>2</sup> Q2W, 5-fluorouracil 2400mg/m<sup>2</sup> Q2W, and leucovorin

Merrimack states that the NAPOLI trial demonstrated a statistically significant improvement in overall survival [HR 0.67 (95% confidence interval 0.49, 0.92); p=0.012] and progression-free survival [HR 0.56 (95% CI: 0.41, 0.75); p<0.001] for patients randomized to Arm C as compared to Arm B. The median survival was 6.1 months vs 4.2 months and the median progression-free survival was 3.1 months vs. 1.5 months in Arms C and B, respectively. There was no statistically significant improvement for patients randomized to Arm A as compared to Arm B.

(b) (4) patients randomized to Arm C of the NAPOLI trial experienced a higher incidence of the following Grade 3-5 adverse reactions as compared to Arm B: neutropenia (27% vs. 2%), fatigue (14% vs. 4%) diarrhea (13% vs. 5%), vomiting (11% vs. 3%), anemia (9% vs. 7%), nausea (8% vs. 3%), dehydration (4% vs. 2%), stomatitis (4% vs. 1%), sepsis (3% vs. 1%), neutropenic fever/sepsis (3% vs. 0), gastroenteritis (3% vs 0) and thrombocytopenia

(3% vs. 0). There was no increase in the incidence of deaths within 30 days of last dose of protocol-specified therapy for Arm C vs. Arm B although a higher percentage of patients discontinued treatment in Arm C (11.1%) compared with Arm B (7.5%) due to adverse events.

### **Indicated population and Available Therapy**

Based on the Surveillance and Epidemiology and End Results (SEER) epidemiologic data, an estimated 48,960 new cases and 40,560 deaths due to pancreatic adenocarcinoma are anticipated in the U.S. in 2015.<sup>1</sup> Approximately half (53%) of new cases are metastatic at diagnosis; the 5-year survival rates for patients with metastatic disease is 2.4%.

There are five drugs which are currently FDA-approved for the treatment of pancreatic cancer:

Gemcitabine was approved on May 15, 1996 for “as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.” Approval was based on improvement in “clinical benefit” response rate, survival, and time-to-progression in a randomized trial comparing gemcitabine with 5-fluorouracil (5-FU) in patients who had received no prior chemotherapy.

Erlotinib was approved on November 2, 2005, for use “in combination with gemcitabine, for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.” Approval was based on demonstration of improved survival in a randomized, trial comparing erlotinib plus gemcitabine to gemcitabine alone.

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) was approved on September 6, 2013 for “the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.” Approval was based on the results of a randomized trial demonstrating improvement in overall survival, progression-free survival, and overall response for those randomized to paclitaxel protein-bound particles with gemcitabine compared with those randomized to gemcitabine alone.

Fluorouracil was approved in 1962 as a DESI product. The indications and usage section of labeling states “Fluorouracil is effective in the palliative management of carcinoma of the pancreas. The basis for approval is not described in product labeling.

Mitomycin is no longer marketed in the U.S. It was approved for the following indication “Mitomycin is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.”

In addition to the FDA-approved drugs discussed above, the combination chemotherapy regimen of FOLFIRINOX is recommended by the NCCN for the treatment of good performance status patients with metastatic pancreatic cancer, based on the published results by Conroy, et al.<sup>2</sup> In this trial, 342 patients with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group performance status score of 0 or 1 were randomized to receive FOLFIRINOX (oxaliplatin, 85 mg<sup>2</sup> body-surface area; irinotecan, 180 mg<sup>2</sup>; leucovorin, 400 mg<sup>2</sup>; and

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1 <http://seer.cancer.gov/statfacts/html/pancreas.html>

2 Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. NEJM. 2011 364(19):1817-25.

fluorouracil, 400 mg<sup>2</sup> given as a bolus followed by 2400 mg<sup>2</sup> given as a 46-hour continuous infusion, every 2 weeks) or gemcitabine at the approved dose and schedule for pancreatic cancer. As reported by Conroy, the trial demonstrated a statistically significant improvement in the primary endpoint of overall survival [HR 0.57 (95% CI 0.45, 0.73); p<0.001] with median survival times of 11.1 months in the FOLFIRINOX arm and 6.8 months in the gemcitabine arm. The trial also demonstrated a significant improvement in progression-free survival (HR 0.47 (95% CI: 0.37, 0.59); p<0.001) with median PFS times of 6.4 months and 3.3 months in the FOLFIRINOX and gemcitabine arms, respectively and a significant improvement in overall response rate (31.6% vs. 9.4%) for FOLFIRINOX.

The NCCN practice guidelines recommend combination chemotherapy with gemcitabine plus Abraxane or with FOLFIRINOX combination chemotherapy based on demonstration of a survival advantage gemcitabine alone as the initial treatment for unresectable disease. Additional regimens include which are considered reasonable include gemcitabine alone or in combination with erlotinib, capecitabine, infusional 5-fluorouracil, or a fluoropyrimidine in combination with oxaliplatin are acceptable first-line regimens. For patients receiving second-line chemotherapy following treatment with gemcitabine (the population studied in the NAPOLI trial), NCCN guidelines recommends enrollment in a clinical trial or treatment with fluoropyrimidine-based chemotherapy.

#### **Review Designation:**

I am designating this application as a priority review based on demonstration of a survival advantage over an accepted regimen for second-line treatment of metastatic adenocarcinoma of the pancreas, which meets meet the criteria specified in FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014) and for the reasons discussed below.

An application will be given priority review designation if it meets any of the following criteria:

- An application (original or efficacy supplement) for a drug that treats a serious condition **AND**, if approved, would provide a significant improvement in safety or effectiveness
- Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A
- An application for a drug that has been designated as a qualified infectious disease product
- Any application or supplement for a drug submitted with a priority review voucher

The NDA submitted by AstraZeneca meets the criteria under bullet 1 but not under bullets 2-4 above. As described in the Guidance, examples of significant improvement include

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

The application is for a drug (MM-398), which is intended to treat a serious condition (metastatic adenocarcinoma of the pancreas in patients whose disease has progressed <sup>(b) (4)</sup> following treatment with gemcitabine) and the results of the NAPOLI trial, which are reported to have demonstrated a statistically significant improvement in overall survival [HR 0.67 (95% confidence interval 0.49, 0.92); p=0.012] and in progression-free survival [HR 0.56 (95% CI: 0.41, 0.75); p<0.001] for the addition of MM-398 to 5-fluorouracil and leucovorin as compared

to 5-fluorouracil and leucovorin alone, support a conclusion that if approved, MM-398 would provide a significant improvement in efficacy over available therapy, i.e., a fluoropyrimidine-based, second-line chemotherapy regimen.

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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PATRICIA KEEGAN  
10/22/2015

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Wednesday, October 21, 2015 11:23 AM  
**To:** 'Michael Slater'  
**Subject:** RE: NDA 207793 / Onivyde (irinotecan liposome injection) ---- FDA Labeling Edits (Round 4)  
**Attachments:** 10 MM-398 USPI Tracked\_20OCT2015\_FDA Edits.docx

Hi Michael,

As discussed earlier today please find attached round 4 of proposed edits to the Onivyde (irinotecan liposome injection) package insert. Please review our proposed edits and comments to the labeling. Please accept all edits you are in agreement with, make any additional edits (if needed) in tracked-changes, and submit your updated labeling to me via email no later than **3PM today** (the earlier the better though) and follow with a formal submission to your NDA by **COB today** if possible. If you agree with all proposed edits and comments to the PI, please submit a clean version incorporating all edits.

**Please confirm receipt** and let me know should you have any questions.

Thank you,  
Deanne

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**From:** Michael Slater [<mailto:MSlater@merrimack.com>]  
**Sent:** Tuesday, October 20, 2015 3:15 PM  
**To:** Varney, Deanne  
**Subject:** RE: NDA 207793 / Onivyde (irinotecan liposome injection) ---- FDA Labeling Edits (Round 3)  
**Importance:** High

Hello Deanne,

Here is the latest set of edits as tracked and clean versions, together with the revised vial label. These will be filed to the NDA shortly.

Please do not hesitate to contact me if you have any questions.

Best regards,

Michael

MICHAEL SLATER  
Regulatory Affairs  
D 617.441.7498 M (b) (6)

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**From:** Varney, Deanne [<mailto:Deanne.Varney@fda.hhs.gov>]  
**Sent:** Monday, October 19, 2015 4:50 PM  
**To:** Michael Slater  
**Subject:** NDA 207793 / Onivyde (irinotecan liposome injection) ---- FDA Labeling Edits (Round 3)

Hello Mr. Slater,

Please find attached our third round of proposed edits to the Onivyde (irinotecan liposome injection) package insert.

We also have the following comment on your carton and container labeling:

The concentration statement should have a space between the numeral (4.3) and the unit (mg). Please change the concentration per mL statement to include a space. For example: change 4.3mg/mL to 4.3 mg/mL.

Please review our proposed edits and comments to the labeling. Please accept all edits you are in agreement with, make any additional edits (if needed) in tracked-changes, and submit your updated labeling to your NDA by **COB tomorrow, Tuesday, October 20, 2015**, with a courtesy copy to me via email. If you agree with all proposed edits and comments to the PI, please submit a clean version incorporating all edits and include the Revision date in Highlights as 10/2015.

**Please confirm receipt** and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Lead Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

Email secured by Check Point

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DEANNE R VARNEY  
10/21/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 207793

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Merrimack Pharmaceuticals, Inc.  
One Kendall Square  
Suite B7201  
Cambridge, MA 02139-1670

ATTENTION: Michael Slater  
Vice President of Regulatory Affairs

Dear Mr. Slater

Please refer to your New Drug Application (NDA) dated and received April 24, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Irinotecan Liposome Injection, 4.3 mg/mL.

We also refer to your correspondence, dated and received October 19, 2015, requesting review of your proposed proprietary name, Onivyde.

We have completed our review of the proposed proprietary name, Onivyde, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 19, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4901. For any other information regarding this application, contact Deanne Varney, Regulatory Project Manager in the Office of New Drugs, at 301-796-0297.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
10/20/2015

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Monday, October 19, 2015 4:51 PM  
**To:** Michael Slater (MSlater@merrimack.com)  
**Subject:** NDA 207793 / Onivyde (irinotecan liposome injection) ---- FDA Labeling Edits (Round 3)  
**Attachments:** MM-398 USPI Tracked\_V2\_FDA edits.docx

Hello Mr. Slater,

Please find attached our third round of proposed edits to the Onivyde (irinotecan liposome injection) package insert.

We also have the following comment on your carton and container labeling:

The concentration statement should have a space between the numeral (4.3) and the unit (mg). Please change the concentration per mL statement to include a space. For example: change 4.3mg/mL to 4.3 mg/mL.

Please review our proposed edits and comments to the labeling. Please accept all edits you are in agreement with, make any additional edits (if needed) in tracked-changes, and submit your updated labeling to your NDA by **COB tomorrow, Tuesday, October 20, 2015**, with a courtesy copy to me via email. If you agree with all proposed edits and comments to the PI, please submit a clean version incorporating all edits and include the Revision date in Highlights as 10/2015.

**Please confirm receipt** and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Lead Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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DEANNE R VARNEY  
10/19/2015

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Tuesday, October 13, 2015 1:46 PM  
**To:** Michael Slater (MSlater@merrimack.com)  
**Subject:** NDA 207793 / Onivyde (irinotecan liposome injection) ---- FDA Labeling Edits (Round 2)  
**Attachments:** 20151013\_MM-398 USPI Tracked\_FDA edits.docx

Hello Mr. Slater,

Please find attached our second round of proposed edits to the Onivyde (irinotecan liposome injection) package insert.

**We also have the following comments on your carton and container labeling:**

### Container:

1. The Principal Display Panel (PDP), as currently presented, appears crowded without adequate white space. Additionally, the (b) (4) is not essential information to promote the safe use of this drug product that crowds the PDP and still competes in prominence with proprietary and established names.
  - i. Per 21 CFR 201.10(g)(2), ensure that the established name is at least onehalf the height of the proprietary name.
  - ii. Delete (b) (4) .
2. Unbold the font used for the National Drug Code (NDC) and "Rx Only" statement.
3. Relocate the (b) (4) and (b) (4) statements from the side panel to the PDP and revise to read "For Intravenous Infusion After Dilution ".
4. Change the strength statement so that the total product strength per total volume is bolded. For example:  
**43 mg/10 mL**  
(4.3 mg/mL)  
Please note the strength, 43 mg/10 mL, is bolded; and the concentration, 4.3 mg/mL, is not bolded.
5. Unbold the statement, "Store ONIVYDE™ in original carton to protect from light."

### Carton:

6. Change the strength statement so that the total product strength per total volume is bolded. For example:  
**43 mg/10 mL**  
(4.3 mg/mL)  
Please note the strength, 43 mg/10 mL, is bolded; and the concentration, 4.3 mg/mL, is not bolded.
7. On the PDP and back panel, revise the (b) (4) and (b) (4) statements to read "For Intravenous Infusion After Dilution" and relocate it so that it is immediately below the product strength statement (see example below):  
**43 mg/10 mL**  
(4.3 mg/mL)

## For Intravenous Infusion After Dilution

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Please review our proposed edits and comments to the labeling. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit your updated labeling along with any supporting data required to your NDA by **COB on Thursday, October 15, 2015**, with a courtesy copy to me via email.

**Please confirm receipt** and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Lead Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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/s/  
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DEANNE R VARNEY  
10/13/2015

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Friday, October 09, 2015 1:14 PM  
**To:** 'Michael Slater'  
**Cc:** Marion Scocca  
**Subject:** RE: NDA 207793 / Onivyde ---- Information Request - Response Requested by COB Today

**Importance:** High

Hello Michael,

Please provide a response to the below IR by COB today (Friday the 9<sup>th</sup>):

**Provide the dose conversion calculation you are using for changing the originally proposed dose of Onivyde (e.g., the original proposed dose of 80 mg /m<sup>2</sup>) to the free base expression. In your response, please clarify if the original proposed dose of Onivyde 80 mg/m<sup>2</sup> was expressed as the irinotecan hydrochloride trihydrate.**

Please confirm receipt and let me know should you have any questions.

Thank you,  
Deanne

---

**From:** Michael Slater [mailto:MSlater@merrimack.com]  
**Sent:** Wednesday, October 07, 2015 5:10 PM  
**To:** Varney, Deanne  
**Cc:** Marion Scocca  
**Subject:** RE: NDA 207793 / Onivyde ---- Proposed Labeling  
**Importance:** High

Dear Deanne,

I am enclosing the revised package insert, with updated table and figure numbers and Table of Contents. I also enclose attachments which explain in detail our consideration for some of the edits where you had requested further information or discussion.

We are providing a commitment to revise the release specification criteria and analytical methods to report irinotecan amounts based on free base instead of the HCl salt, as requested previously in the Information Request dated September 21, 2015, Merrimack will submit the relevant CMC sections to the NDA no later than October 9, 2015. Please refer to the Agency's request below.

### *Item 1*

#### *Agency Request:*

*Revise the calculations and criteria in the release specification tests involving irinotecan to reflect the decision to revise the labeled dose as based on irinotecan free base.* (b) (4)

*These revised documents may be submitted no later than October 9, 2015 pending resolution of FDA's internal labeling discussion.*

With reference to your comments on the carton and container labeling:

1. *Decrease the size and prominence of the green logo, and consider relocating to a location that does not compete in prominence. Critical product information, such as the proprietary name, should be the most prominent information on the principal display panel (PDP). Other information on the PDP such as manufacturer logo should not compete in size and prominence with important product information [see Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.]*
2. *To strengthen the cautionary statement, “(b) (4),” change the statement to read, “LIPOSOMAL FORMULATION DO NOT SUBSTITUTE FOR IRINOTECAN HYDROCHLORIDE.” Consider using sentence case or only capitalizing the first letter because words written in all-capital letters are less legible than words written in mixed case letters.*
3. *To emphasize the action required from the user, use bold font for the statement, “Refrigerate at 2°C to 8°C (36°F to 36°F).” In addition, remove bold font for the statement, “Do not freeze.”*
4. *Remove (b) (4).*
5. *Per 21CFR201.100(b)(5)(iii), the quantitative composition of all parenteral ingredients (except for pH adjusters) are required to be included on labeling. Include on the side panels the quantitative composition information; if there is not room on the vial label to include this information, it is acceptable for this composition information to appear only on the carton.*
6. *Replace the phrase (b) (4) to ‘single dose vial’.*

We have made these changes (see Attachment 3)

Regarding your comments on the container label:

7. *The proposed container label lacks a linear barcode. Please add a barcode as described in 21 CFR 201.25.*

We have made these changes (see Attachment 4)

These changes and updated labeling along with supporting data are being submitted to the NDA.

With kind regards,

Michael

Michael Slater  
Vice President of Regulatory Affairs  
Merrimack Pharmaceuticals, Inc.  
One Kendall Square, Suite B7201  
Cambridge, MA 02139-1670  
Tel: 617 441 7498  
Cell: (b) (6)  
Fax: 617 902 2540  
[www.merrimack.com](http://www.merrimack.com)

---

**From:** Varney, Deanne [<mailto:Deanne.Varney@fda.hhs.gov>]  
**Sent:** Friday, October 02, 2015 9:02 AM  
**To:** Michael Slater

**Cc:** Marion Scocca  
**Subject:** NDA 207793 / Onivyde ---- Proposed Labeling  
**Importance:** High

Hello Mr. Slater,

Please find attached our proposed edits to the Onivyde (irinotecan liposome injection) package insert. In addition to reviewing and incorporating these edits, please update all table and figure numbers as needed and correct formatting where required. The Table of Contents will need to be updated as well.

Please note that we have concluded that the drug product labels and labeling should be revised to be based on irinotecan free base. We request that you provide a commitment to revise the release specification criteria and analytical methods to report irinotecan amounts based on free base instead of the HCl salt. Please note that an approval action cannot be taken until all CMC issues are resolved.

**We also have the following comments on your carton and container labeling:**

1. Decrease the size and prominence of the green logo, and consider relocating to a location that does not compete in prominence. Critical product information, such as the proprietary name, should be the most prominent information on the principal display panel (PDP). Other information on the PDP such as manufacturer logo should not compete in size and prominence with important product information [see *Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance)*. April 2013.]
2. To strengthen the cautionary statement, “(b) (4) change the statement to read, “LIPOSOMAL FORMULATION DO NOT SUBSTITUTE FOR IRINOTECAN HYDROCHLORIDE.” Consider using sentence case or only capitalizing the first letter because words written in all-capital letters are less legible than words written in mixed case letters.
3. To emphasize the action required from the user, use bold font for the statement, “Refrigerate at 2°C to 8°C (36°F to 36°F).” In addition, remove bold font for the statement, “Do not freeze.”
4. Remove (b) (4).
5. Per 21CFR201.100(b)(5)(iii), the quantitative composition of all parenteral ingredients (except for pH adjusters) are required to be included on labeling. Include on the side panels the quantitative composition information; if there is not room on the vial label to include this information, it is acceptable for this composition information to appear only on the carton.
6. Replace the phrase ‘single use vial’ to ‘single dose vial’.

**We have the following comment on your container label:**

7. The proposed container label lacks a linear barcode. Please add a barcode as described in 21 CFR 201.25.

Please review our proposed edits and comments to the labeling. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit your updated labeling along with any supporting data required to your NDA by **COB on Wednesday, October 7, 2015**, with a courtesy copy to me via email.

Please confirm receipt of this communication and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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/s/  
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DEANNE R VARNEY  
10/09/2015

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Friday, October 02, 2015 9:03 AM  
**To:** MSlater@merrimackpharma.com  
**Cc:** Marion Scocca (MScocca@merrimackpharma.com)  
**Subject:** NDA 207793 / Onivyde ---- Proposed Labeling  
**Attachments:** 20151002\_USPI clean NDA 207793\_FDA Edits.docx

**Importance:** High

Hello Mr. Slater,

Please find attached our proposed edits to the Onivyde (irinotecan liposome injection) package insert. In addition to reviewing and incorporating these edits, please update all table and figure numbers as needed and correct formatting where required. The Table of Contents will need to be updated as well.

Please note that we have concluded that the drug product labels and labeling should be revised to be based on irinotecan free base. We request that you provide a commitment to revise the release specification criteria and analytical methods to report irinotecan amounts based on free base instead of the HCl salt. Please note that an approval action cannot be taken until all CMC issues are resolved.

### **We also have the following comments on your carton and container labeling:**

1. Decrease the size and prominence of the green logo, and consider relocating to a location that does not compete in prominence. Critical product information, such as the proprietary name, should be the most prominent information on the principal display panel (PDP). Other information on the PDP such as manufacturer logo should not compete in size and prominence with important product information [see *Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance)*. April 2013.]
2. To strengthen the cautionary statement, “ (b) (4) change the statement to read, “LIPOSOMAL FORMULATION DO NOT SUBSTITUTE FOR IRINOTECAN HYDROCHLORIDE.” Consider using sentence case or only capitalizing the first letter because words written in all-capital letters are less legible than words written in mixed case letters.
3. To emphasize the action required from the user, use bold font for the statement, “Refrigerate at 2°C to 8°C (36°F to 36°F).” In addition, remove bold font for the statement, “Do not freeze.”
4. Remove (b) (4)
5. Per 21CFR201.100(b)(5)(iii), the quantitative composition of all parenteral ingredients (except for pH adjusters) are required to be included on labeling. Include on the side panels the quantitative composition information; if there is not room on the vial label to include this information, it is acceptable for this composition information to appear only on the carton.
6. Replace the phrase (b) (4) to ‘single dose vial’.

### **We have the following comment on your container label:**

7. The proposed container label lacks a linear barcode. Please add a barcode as described in 21 CFR 201.25.

Please review our proposed edits and comments to the labeling. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit your updated labeling along with any supporting data required to your NDA by **COB on Wednesday, October 7, 2015**, with a courtesy copy to me via email.

Please confirm receipt of this communication and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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

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/s/  
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DEANNE R VARNEY  
10/02/2015

# WRAP-UP MEETING MINUTES

## September 23, 2015

New 505(b)(2) NDA 207793  
Irinotecan Liposome Injection  
Merrimack Pharmaceuticals, Inc.

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**Submission Date:** April 24, 2015 (final portion of rolling submission)  
**Received Date:** April 24, 2015  
**PDUFA:** October 24, 2015

**Proposed Indication:** Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine

### Core Review Team:

Patricia Keegan, Director DOP2  
Deanne Varney, RPM  
Shan Pradhan, Medical Officer  
Steven Lemery, Medical Officer Team Leader  
Hui Zhang, Statistics  
Kun He, Statistics Team Leader  
Sarah Schrieber, Clinical Pharmacology  
Gene Williams, Clinical Pharmacology Team Leader  
Anshu Marathe, Pharmacometrics Reviewer  
Margot Brower, Non-Clinical  
Whitney Helms, Non-Clinical Team Leader  
Mike Adams, CMC  
Olen Stephens, CMC (Branch Chief)  
Steven Kinsley, CMC RPM  
Anuradha Ramamoorthy, Genomics Reviewer  
Rosane Charlab Orbach, Genomics Team Leader  
Banu Zolnik, Biopharmaceutics Reviewer  
Okpo Eradiri, Biopharmaceutics Team Leader

### Consults:

Carole Broadnax, OPDP / Jessica Cleck Dereneck, OPDP TL  
Margaret Rand, DPV / Tracy Salaam, DPV TL  
Naomi Redd, DRISK / Doris Auth, DRISK TL  
Otto Townsend, DMEPA / Alice Tu, DMEPA TL  
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL  
Lauren Iacono-Connors, OSI / Susan Thompson, OSI TL  
Miriam Dinatale, PMHS / Tamara Johnson, TL /Denise Pica-Branco

**Application Details:**

- Priority Review requested (6 month review – not in the Program)
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of irinotecan liposome has been conducted under IND 102799

**Reminder of Milestone Dates for 6-Month Priority Review Clock:**

<b>Milestone</b>	<b>6 month review</b>
<b>Acknowledgment Letter</b>	<i>Issued April 30, 2015</i>
<b>Priority Review Determination OR Filing Issues Identified/Not Identified Letter</b>	June 23, 2015 <i>Issued June 23, 2015</i>
<b>Filing Issues Identified (74 Day Letter) — if not sent in Day 60 letter</b>	July 7, 2015
<b>Mid-Cycle Meeting</b>	July 20, 2015
<b>Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)</b>	October 3, 2015
<b>Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant</b>	October 10, 2015
<b>Advisory Committee Target Date</b>	Month 4-5 (August –September)
<b>Review Target Due Dates:</b> <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i>	<b>September 30, 2015</b> October 3, 2015 October 10, 2015 October 23, 2015
<b>Wrap-Up Meeting w/ Safety discussion</b>	September 26, 2015 <i>Scheduled September 23, 2015</i>
<b>Compile and circulate Action Letter and Action Package</b>	October 10, 2015
<b>FINAL Action Letter Due</b>	<b>October 23, 2015</b>

**Discussion:**

- Primary reviews are due **Wednesday, September 30, 2015**
- Target Action Date: **Friday, October 23, 2015**
- The team will consider taking an early action as there is another application with same action date

**Discuss Remaining Outstanding Pre-Action Items:**

1. **Target Action Date:** Friday, October 23, 2015

2. **Labeling:**

- Currently undergoing internal review. Will target to send to Merrimack by 9/30/2015.
- Meetings scheduled for 10/8 and 10/14 to review applicant edits
- Labeling based on free base vs. trihydrate

*Discussion:* The clinical team has concerns regarding dosing errors due to the 80 mg/m<sup>2</sup> dose becoming a 68.8 mg/m<sup>2</sup> dose if labeled based on free base. The clinical team will be more comfortable if the dose in the label can be rounded to 70 mg/m<sup>2</sup>. The other dose (60 mg/m<sup>2</sup>) will become 51.6 mg/m<sup>2</sup> which can be rounded to 50 mg/m<sup>2</sup>.

50 mg/m<sup>2</sup> becomes 43 mg/m<sup>2</sup> which can be rounded to 40 or 45 mg/m<sup>2</sup>.

40 mg/m<sup>2</sup> becomes 34.4 mg/m<sup>2</sup> which can be rounded to 35 mg/m<sup>2</sup>.

The team will review the calculated free base doses off-line, will come to a final decision, and update the doses throughout the PI accordingly.

The team does not need to update their reviews to reflect the new calculations; instead, include a note that calculations in the review are based on the protocol-given doses but the product will be labeled based on the free base.

(b) (4)

For Section 12, clinical pharmacology reviewed the internal request to update (b) (4)

(b) (4)

Clinical pharmacology therefore recommends leaving the category as “Whites”. The team concurred, and Section 5 will be reverted to the previous numbers based on “Whites” instead of (b) (4)

3. **Pending Issues:**

- **CMC:** Release acceptance criteria – [REDACTED] (b) (4)  
[REDACTED] The justification is pending CMC team review.

A comment will be included when labeling is sent to Merrimack that an approval action cannot be taken until CMC issues are resolved.

4. **Signed Review Status:**

- Primary Reviews: Nonclinical review complete, remainder pending
- Secondary Reviews: Nonclinical complete, remainder pending
- Consult Reviews: QT-IRT and DMEPA complete, remainder pending
- CDTL: Pending
- Division Director: Pending

5. **PMCs and PMRs:** Clinical pharmacology will review the available exposure data for “non-Asians” to determine if a PMC or PMR is necessary.

6. **Postmarket Safety Surveillance:** What adverse events should DPV look for once ONIVYDE is on the market?

*Discussion:* Interstitial lung disease and [REDACTED] (b) (4) due to the fact that they were included in the label only based on events seen with Camptosar and not seen with ONIVYDE.

7. **Press Release/ASCO Burst/Information Advisory:** PR has been reviewed by clinical team, pending DD review. IA pending.

*Discussion:* DD will review draft PR.

8. **Approval Letter:** Pending, RPM will draft w/c 9/28/15

*Discussion:* None.

9. **Inspections:**

- Clinical Site Inspections:** All inspections complete with no issues with exception of Hungary site 366 that will have a VAI for issues that will not affect overall study outcome.
- Manufacturing Site Inspections:** Complete, recommend approval from facility perspective.

*Discussion:* None.

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/s/  
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DEANNE R VARNEY  
09/23/2015

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Wednesday, September 23, 2015 2:44 PM  
**To:** MSlater@merrimackpharma.com  
**Subject:** NDA 207793 / Onivdye - CMC/Labeling Information Request (Urgent)

**Importance:** High

Hello Michael,

Please provide a written response to the below information request by **4PM today** to me via email. The formal response to your NDA can follow at a later date, but we do need quick resolution of the issues noted below.

“The revised labels expressing the strength of the product on the basis of irinotecan free base indicate that the product is formulated with irinotecan hydrochloride salt trihydrate. [REDACTED] (b) (4)

[REDACTED] Confirm which species is used to formulate the product, confirm that the expression of strength of the free base truly is 4.3 mg/mL, and amend the appropriate NDA sections to be consistent with the label.”

**Please confirm receipt** and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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/s/  
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DEANNE R VARNEY  
09/23/2015



NDA 207793

**INFORMATION REQUEST**

Merrimack Pharmaceuticals, Inc.  
Attention: James Williams, Sr. Director Regulatory Affairs  
One Kendall Square  
Suite B7201  
Cambridge, MA 02139-1670

Dear Dr. Williams,

Please refer to your original New Drug Application received April 24, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onivyde (Irinotecan Liposome) Injection, 5mg/mL.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, September 22, 2015.

- 1. Revise the calculations and criteria in the release specification tests involving irinotecan to reflect the decision to revise the labeled dose as based on irinotecan free base.** (b) (4)

[Redacted]

**These revised documents may be submitted no later than October 9, 2015 pending resolution of FDA's internal labeling discussion.**

- 2. Revise the calculation for percent unspecified impurity** (b) (4)

[Redacted]



3. The proposed criterion for (b) (4) (NMT (b) (4)%) is acceptable. This test and criterion should be added to the proposed release specifications for bulk drug product and drug product. Additionally, revise the acceptance criterion for irinotecan assay to NLT (b) (4)%.
4. Develop an analytical method and acceptance criterion for (b) (4) by December, 2016. Provide a stated agreement to file this specification change by December, 2016. The submission should include a method description; a complete method validation study; a proposed criterion with justification based on product quality; an appropriately characterized reference standard; and test results showing that bulk drug product and drug product consistently meet the proposed specification.
5. Specify whether any test value reported for the release of drug product is taken from the certificate of analysis for bulk drug product.
6. Revise the proposed release specification for bulk drug product to include testing for (b) (4). These tests reflect the quality of each batch of bulk drug product.
7. Specify what information is provided in the certificate of compliance which is part of the acceptance specification for filled vials at the packaging site. Provide a representative Certificate of Compliance issued to the packaging site.
8. The procedure for the manufacture of finished drug product which includes (b) (4) should be filed as a prior approval supplement.

Include an amendment to NDA Section 3.2.P.3.3 to explicitly state that (b) (4).

9. Revise the proposal to perform a stability study which incorporates (b) (4) before sending to the final packaging site. Provide a written commitment in the NDA amendment with a proposed date for initiating and completing of the study. The stability study should also evaluate the photostability of the bulk drug product as mentioned in the amendment of



8/25/15. Use of part of a commercial batch for this stability study would be acceptable.

10. The proposed dissolution acceptance criteria are not supported by the data in the Application. Based on the in vitro performance of the PPQ, aged Phase 3, and clinical stability batches, FDA recommends the following in-vitro release acceptance criteria:

2 hrs: (b) (4) %  
4 hrs: (b) (4) %  
16 hrs: NLT (b) (4) %

Note that the recommended acceptance criteria (b) (4) that were used to investigate the discriminating power of the dissolution method.

Consider amending the acceptance criteria to allow level 2 testing to be used in calculation for in vitro release.

If you have any questions, please contact Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,  
Steven  
Kinsley -S

Steven Kinsley, Ph.D.  
Regulatory Business Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Digitally signed by Steven Kinsley -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley -  
S, 0.9.2342.19200300.100.1.1=2001720189  
Date: 2015.09.21 16:27:07 -0400

# TEAM MEETING MINUTES

## September 16, 2015

New 505(b)(2) NDA 207793  
Irinotecan Liposome Injection  
Merrimack Pharmaceuticals, Inc.

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**Submission Date:** April 24, 2015 (final portion of rolling submission)  
**Received Date:** April 24, 2015  
**PDUFA:** October 24, 2015

**Proposed Indication:** Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine

### Core Review Team:

Patricia Keegan, Director DOP2  
Deanne Varney, RPM  
Shan Pradhan, Medical Officer  
Steven Lemery, Medical Officer Team Leader  
Hui Zhang, Statistics  
Kun He, Statistics Team Leader  
Sarah Schrieber, Clinical Pharmacology  
Gene Williams, Clinical Pharmacology Team Leader  
Anshu Marathe, Pharmacometrics Reviewer  
Margot Brower, Non-Clinical  
Whitney Helms, Non-Clinical Team Leader  
Mike Adams, CMC  
Olen Stephens, CMC (Branch Chief)  
Steven Kinsley, CMC RPM  
Anuradha Ramamoorthy, Genomics Reviewer  
Rosane Charlab Orbach, Genomics Team Leader  
Banu Zolnik, Biopharmaceutics Reviewer  
Okpo Eradiri, Biopharmaceutics Team Leader

### Consults:

Carole Broadnax, OPDP / Jessica Cleck Dereneck, OPDP TL  
Margaret Rand, DPV / Tracy Salaam, DPV TL  
Naomi Redd, DRISK / Doris Auth, DRISK TL  
Otto Townsend, DMEPA / Alice Tu, DMEPA TL  
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL  
Lauren Iacono-Connors, OSI / Susan Thompson, OSI TL  
Miriam Dinatale, PMHS / Tamara Johnson, TL /Denise Pica-Branco

## Application Details:

- Priority Review requested (6 month review – not in the Program)
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of irinotecan liposome has been conducted under IND 102799

## AGENDA ITEMS

### 1. Reminder of Milestone Dates for 6-Month Priority Review Clock:

Milestone	6 month review
Acknowledgment Letter	<i>Issued April 30, 2015</i>
Priority Review Determination OR Filing Issues Identified/Not Identified Letter	June 23, 2015 <i>Issued June 23, 2015</i>
Filing Issues Identified (74 Day Letter) — if not sent in Day 60 letter	July 7, 2015
Mid-Cycle Meeting	July 20, 2015
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	October 3, 2015
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	October 10, 2015
Advisory Committee Target Date	Month 4-5 (August–September)
Review Target Due Dates: <i>Primary Review Due</i>	<b>September 30, 2015</b>
<i>Secondary Review Due</i>	October 3, 2015
<i>CDTL Review Due</i>	October 10, 2015
<i>Division Director Review Due</i>	October 24, 2015
Wrap-Up Meeting w/ Safety discussion	September 23, 2015
Compile and circulate Action Letter and Action Package	October 10, 2015
FINAL Action Letter Due	<b>October 24, 2015</b>

### Discussion:

- Primary reviews are due Wednesday, September 30, 2015.
- Press Release: Comments requested by COB Monday, September 21<sup>st</sup>. The clinical team will provide comments to OMA with the caveat that there might be some changes after the label is finalized.
- Target Action Date: **Friday, October 23, 2015**

2. **SGE's**: Teleconferences were held with two SGE's on July 14, 2015. Both SGE's agreed that the observed improvement in overall survival in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms.
3. **ODAC**: An ODAC will not be held.
4. **Labeling**: Refer to Item 7 below for remaining schedule. The goal is to complete labeling meetings by Tuesday, September 22<sup>nd</sup> and have labeling ready to send to Merrimack by Thursday, September 24<sup>th</sup>. We will request a one-week turnaround time for them, with their counter-proposal due on October 1<sup>st</sup>. We have a meeting scheduled on October 8<sup>th</sup> to review their edits as well as OPDP and PLT edits.
5. **Review Issues**:

Discussion: The team confirmed that there are not currently any planned PMRs/PMCs

- a. **Clinical**: No issues.
- b. **Statistics**: No issues.
- c. **Clinical Pharmacology**: No issues.
- d. **Pharmacometrics**: No issues.
- e. **Genomics**: No issues.
- f. **Nonclinical**: Primary review signed in DARRTS
- i. **CMC**:
  - Label based on free base or trihydrate: DMEPA will provide feedback regarding medication error risks
  - CMC team and Dr. Keegan will have a teleconference with Merrimack on 9/18/15:
    - Microbiology DMF – the DMF holder has not responded to the information request despite two reminders. The response is anticipated to include a significant amount of

information and will take at least one week to review.  
CMC will finish their primary application review and will later add an addendum for the review of the DMF.  
Alternatively, it could trigger a major amendment.

*Post-Meeting Note: Response received 9/16/15*

- Stability during shipping
- Dissolution acceptance criteria

**g. Biopharmaceutics:** No issues.

**i. Regulatory:** 505(b)(2) assessment is with the committee and exclusivity summary is with CPMS

**6. Inspections:**

**a. Clinical Site Inspections:**

**Discussion:** All inspections complete with no issues with exception of Hungary site 366 that will have a VAI for issues that will not affect overall study outcome.

Sites 881 and 882 in Taiwan.

Site 366 in Hungary.

Site 617 in Australia.

Site 120 in US.

**b. Manufacturing Site Inspections:** Application is recommended for approval from facility review perspective.

**Discussion:** None.

**7. Internal Team Meetings:**

• **Mid-Cycle Meeting:** July 20, 2015

• **Labeling Meetings:** Updated labeling received from Merrimack on 7/14/15 and will be placed on SharePoint for review.

• Order of labeling meetings is outlined below:

**a. July 23, 2015:** Clinical and Statistics – Sections 1 and 14 (1 hour)

**b. July 28, 2015:** CMC, DMEPA, Clinical – Sections 3, 11, 16 (1 hour)

- c. July 29, 2015: Clinical – Sections 4, 5, 6, 17 (1.5 hours)
- d. August 18, 2015: Clinical, Maternal Health, Nonclinical – Sections 5.1, 8.1, 8.3, 8.4, 12.1, 13 (1.5 hours)
- e. August 19, 2015: Continuation of CMC (1 hour)
- f. August 20, 2015: Clin Pharm, Clinical and DMEPA – Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3 (1.5 hours)
- g. September 9, 2015: Continuation of Clinical Sections 4, 5, 2.2, Boxed Warning (1.5 hours)
- h. September 15, 2015: Continuation of Clinical Sections 6, 17 (1.5 hours)
- i. September 21, 2015: Continuation of Clin Pharm, Clinical and DMEPA – Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3 (1 hour)
- j. September 22, 2015: Highlights, Remaining issues (1 hour)
- k. October 8, 2015: Review of applicant and consult edits (1.5 hours)

- **Monthly Team Meetings:**

- a. June – June 24, 2015
- b. July – July 15, 2015
- c. August – August 19, 2015
- d. September – September 16, 2015
- e. October – October 14, 2015

- **Wrap- Up Meeting:** September 23, 2015

**8. Additional Items or Issues:**

**Discussion:**

- RPM will follow-up with Yana regarding free base vs. trihydrate

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/s/  
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DEANNE R VARNEY  
09/17/2015



NDA 207793

INFORMATION REQUEST

Merrimack Pharmaceuticals, Inc.  
Attention: James Williams, Sr. Director Regulatory Affairs  
One Kendall Square  
Suite B7201  
Cambridge, MA 02139-1670

Dear Mr. Williams,

Please refer to your original New Drug Application received Friday, April 24, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onivyde (Irinotecan Liposome Injection). Also refer to our CMC information request letter sent 11-Aug-2015 and to the proposed package insert. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Thursday, September 03, 2015.

**Based on patient safety concerns and the current salt nomenclature guidance, it has been determined that the strength and dose of Irinotecan Liposome Injection should be based on irinotecan free base, not on the hydrochloride salt. Strength and dose for the listed product, Camptosar, is labeled as the hydrochloride salt. However, Camptosar is a solution for injection and the labeling prescribes a very different dosing regimen compared to Onivyde. It is our concern that healthcare workers would see each product labeled based on the hydrochloride salt and not adjust for the different dosing regimens. In addition, labeling Onivyde based on free base would be one more indication to the healthcare provider to consult the package insert for the correct dose. We also noted that the package insert is ambiguous at several points regarding strength and dose expressed as the free base or hydrochloride salt.**

**Submit an amendment to NDA 207793 containing a revised package insert and product labels expressing the strength and dose as irinotecan free base in all sections. Regarding item 2(a) of the CMC information request letter, please submit the revised analytical methods, specifications, and analysis results to reflect irinotecan as the free base.**

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

Sincerely,

Olen Stephens -S

Digitally signed by Olen Stephens -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Olen Stephens -S,  
0.9.2342.19200300.100.1.1=2000558826  
Date: 2015.08.20 07:38:12 -04'00'

Olen Stephens, Ph.D.  
Branch Chief, Branch II  
Office of New Drug Products  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

## Varney, Deanne

---

**From:** Varney, Deanne  
**Sent:** Thursday, August 13, 2015 3:57 PM  
**To:** MSlater@merrimackpharma.com  
**Subject:** NDA 207793 / Clinical Pharmacology Information Request

Hello Michael,

Please refer to the below clinical pharmacology information request:

Reference is made to your Population PK Analysis report titled, "Population Pharmacokinetics and Exposure-Response Analysis of MM-398 ". We have the following information request specifically for the exposure-response analysis for safety. If the information is already submitted under the NDA 207793, please direct us to the correct location. **Please submit response to item 3 by COB August 17, 2015 and response to items 1-2 by August 20, 2015.**

1. Based on Table 11-1 of the report, the ER Safety dataset comprised of 353 subjects from 6 studies. For each study provide the proportion and number of subjects who experienced Neutropenia  $\geq 1$ , Neutropenia  $\geq 3$ , Diarrhea  $\geq 1$ , Diarrhea  $\geq 3$ , Anemia  $\geq 1$  and Anemia  $\geq 3$ .
2. Your exposure response analysis suggested association between SN-38 Converted Cmax and neutropenia, CPT-11 Cmax and diarrhea and SN-38 Converted Cmax and anemia. Please clarify if these findings are based on univariate analysis or multivariate analysis. If the results are based on univariate analysis, conduct multivariate analysis to adjust for confounding factors by including all likely factors such as ethnicity, age, gender, baseline kidney function, known risk factors for AEs (baseline neutrophil count) etc. Please submit any associated data set (.xpt format) and code.
3. Please provide the pooled dataset from 353 subjects for ER analysis for safety with the following variables. There should be one record for each unique ID.
  - a. Unique subject ID
  - b. Study ID
  - c. Treatment
  - d. PK metric (CPT11 Cavg, CPT11 Cmax, SN38 Cavg, SN38 Cmax, SN38 Converted Cavg, SN38 Converted Cmax [one column for each PK metric])
  - e. Neutropenia  $\geq 1$  (Yes/No and 1/0)
  - f. Neutropenia  $\geq 3$  (Yes/No and 1/0)
  - g. Diarrhea  $\geq 1$  (Yes/No and 1/0)
  - h. Diarrhea  $\geq 3$  (Yes/No and 1/0)
  - i. Anemia  $\geq 1$  (Yes/No and 1/0)
  - j. Anemia  $\geq 3$  (Yes/No and 1/0)
  - k. All likely covariates [one variable per column] such as race, age, gender, body weight, BSA, creatinine clearance, known risk factors for AEs (baseline neutrophil count) etc.

Please confirm receipt and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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/s/  
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DEANNE R VARNEY  
08/13/2015



NDA 207793

INFORMATION REQUEST

Merrimack Pharmaceuticals, Inc.  
Attention: Michael Slater, Vice President, Regulatory Affairs  
One Kendall Square  
Suite B7201  
Cambridge, MA 02139-1670

Dear Mr. Slater,

Please refer to your original New Drug Application received Friday, April 24, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onivyde (Irinotecan Liposome Injection) 5mg/mL.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, August 25, 2015.

1. Provide acceptance specifications for the drug product excipients HEPES, (b) (4), and sodium chloride. These specifications should include at least identity, purity and an acceptable certificate of analysis from the supplier for each material.
2. Regarding the proposed drug product specification (NDA section 3.2.P.5.1):
  - (a) Establish release specification criteria for (b) (4). Provide a justification for the proposed values.
  - (b) The composition statement (NDA section 3.2.P.1) and the package insert indicate that the label claim and dose are based on (b) (4). Revise the release specification criteria and analytical method calculations for bulk drug product and filled drug product vials (b) (4).
  - (c) Revise the calculations for individual and total irinotecan impurities (b) (4).
  - (d) Specify whether the drug substance reference standard is corrected for organic impurities and residual solvents.

**3. Regarding the proposed analytical methods (NDA sections 3.2.P.5.2 and 3.2.P.5.3):**

- (a)  (b) (4)
- (b) 
- (c) 

**4. For each reference standard proposed in NDA section 3.2.P.6, establish an acceptable retest period and an acceptance specification for use at initial acceptance and upon retesting. These specifications should include at least identity, purity and assay.**

**5. Specify whether the operations performed at  include   Describe the operations performed and specify  for the vials.**

**6. The stability data submitted to the NDA and proposed post approval stability protocol imply  (b) (4)**



**Therefore, the drug application should be revised as follows:**

- (a)  (b) (4)

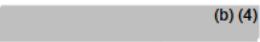
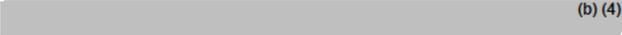
(b)

(b) (4)

(c)

(d)

(e)

7. Provide data on executed manufacturing scale batches for the bulk drug product and fill finish lots for the process performance qualification batches. Provide percent yield of each unit operation for the primary stability and process performance qualification (PPQ) batches and establish acceptable yield criteria for each unit operation accordingly to ensure robustness of the commercial manufacturing process.
8. Describe what controls are used to monitor completion of the steps such as  (b) (4)
9. Provide data and discuss the control strategy used to ensure consistent batch-to-batch quality of  (b) (4) manufactured during the development of the commercial manufacturing process for the drug product.
10. The application states that a  (b) (4)  Clarify what the  (b) (4) and provide information on  (b) (4) for the sample.
11. Provide information on the  (b) (4)  (b) (4)

12. It is noted that (b) (4)

(b) (4) Provide justification for the change and clarify whether the (b) (4) for the PPQ batches was within the proposed (b) (4) for the commercial production.

13. Executed batch records show that total amounts of drug to be used in the (b) (4) was calculated based on (b) (4)

(b) (4) Establish in-process acceptable limits for the (b) (4) to ensure consistent manufacturing of the (b) (4) or justify the absence of these limits.

14. Development studies indicate that (b) (4)

(b) (4) Provide information on controls in place to prevent (b) (4) during the manufacturing (b) (4) of your product.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -  
S

Digitally signed by Olen Stephens -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Olen Stephens -S,  
0.9.2342.19200300.100.1.1=2000558826  
Date: 2015.08.11 13:24:06 -04'00'

Olen Stephens, Ph.D.  
Branch Chief, Branch II  
Office of New Drug Products  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

## Varney, Deanne

---

**From:** Varney, Deanne  
**Sent:** Monday, July 27, 2015 9:31 AM  
**To:** MSlater@merrimackpharma.com  
**Subject:** NDA 207793 / Onivyde / Merrimack - Statistical Information Request

Hi Michael,

Please see the below statistical information request for NDA 207793. Please provide a response via email by July 31, 2015, followed by a formal submission to your NDA.

**Please refer to the Response to FDA's Information Request (SN0011, submitted on July 21, 2015).**

- 1. In Tables 1 and 2, the updated OS (months) should be computed as:  
*time in months = (date2-date1+1)/(365.25/12);***
- 2. Table 2 shows the OS results with updated death dates on patients who withdrew consent. Submit efficacy analysis dataset used to generate this table.**
- 3. Conduct analyses of PFS (ITT comparisons) using new number of PFS events with updated death dates. Submit efficacy analysis dataset and analysis results.**

Please confirm receipt and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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/s/  
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DEANNE R VARNEY  
07/27/2015

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Monday, July 27, 2015 9:47 AM  
**To:** MSlater@merrimackpharma.com  
**Subject:** NDA 207793 / Onivyde / Merrimack - Clinical Pharmacology Information Request

Hi Michael,

Please see the below clinical pharmacology/pharmacometrics information request. Please submit the responses by **August 7, 2015**. If the information is already submitted under the NDA 207793, please direct us the correct location.

Reference is made to your Population PK Analysis report entitled, "Population Pharmacokinetics and Exposure-Response Analysis of MM-398".

1. Based on the forest plot (Figure 9-3 in the report) the CPT11 Cavg is 3-fold higher in Caucasians compared to Asians; however the parameter estimates in Table 4-1 shows that the CL in Asians is only slightly higher compared to Caucasians. It is likely that the differences observed between the two races in Figure 9-3 are driven by other factors that are correlated with race. Please address the discrepancy and explain what drives this apparent difference in exposure between Asians and Caucasians. Provide a reasonable estimate of the exposure difference between the two races when other factors are the same.
2. Based on the population PK model, patients homozygous and non-homozygous for the UGT1A1\*28 allele have similar SN-38 exposure. This is not consistent with what is known for Camptosar® where the association of UGT1A1\*28 polymorphism with SN-38 exposure in Caucasians is well documented. Is it likely that the inclusion of data from significant number of Asians during the model development masked the association between SN-38 exposure and UGT1A1\*28? Please provide justification and consider developing the model separately for Caucasians and Asians. Additionally your analysis classifies patients who were heterozygous as non-homozygous. Please provide justification that this is not likely to influence your analysis in determining the association of UGT1A1\*28 with SN-38 exposure.

Please confirm receipt and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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/s/  
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DEANNE R VARNEY  
07/27/2015



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF INTERNAL MEETING MINUTES**

**Meeting Date and Time:** July 14, 2015  
**Meeting Location:** Teleconference  
**Application Number:** NDA 207793  
**Product Name:** Irinotecan Liposome Injection  
**Indication:** Metastatic adenocarcinoma of the pancreas  
**Applicant Name:** Merrimack Pharmaceuticals  
**Type of Meeting:** Teleconference with Special Government Employee (SGE), Dr. Carmen Allegra, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM)

**FDA ATTENDEES**

Steven Lemery, Cross Discipline Team Leader  
Shan Pradhan, Clinical Reviewer  
Deanne Varney, Regulatory Project Manager

**EXTERNAL CONSTITUENT ATTENDEES**

Dr. Carmen Allegra

**BACKGROUND:** Dr. Carmen Allegra agreed to serve and was cleared as an SGE for this NDA. Prior to this teleconference, background materials were provided to Dr. Allegra, along with one question to address during this teleconference.

**DISCUSSION POINTS:** In this application, Merrimack seeks the approval of Onivyde (irinotecan liposome injection) for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.

**FDA Questions for Discussion During Teleconference:**

1. Based upon your review of the summary information provided, do you agree that the observed improvement in overall survival (OS) in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms?

**Discussion:** Dr. Allegra stated that historically, differing 5-FU dosing schedules have not resulted in differences in efficacy outcomes. Dr. Allegra stated that it is highly unlikely that the difference in 5-FU dosing regimens contributed to the observed difference in overall survival between the arms in the NAPOLI-1 trial, and also noted the higher

July 14, 2015  
NDA 207793: Teleconference with SGE, Dr. Allegra

cumulative 5-FU doses administered in the control arm as compared to the MM-398/5-FU/LV test arm.

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/s/  
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DEANNE R VARNEY  
07/27/2015



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF INTERNAL MEETING MINUTES**

**Meeting Date and Time:** July 14, 2015  
**Meeting Location:** Teleconference  
**Application Number:** NDA 207793  
**Product Name:** Irinotecan Liposome Injection  
**Indication:** Metastatic adenocarcinoma of the pancreas  
**Applicant Name:** Merrimack Pharmaceuticals  
**Type of Meeting:** Teleconference with Special Government Employee (SGE), Dr. David Kelsen, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM)

**FDA ATTENDEES**

Steven Lemery, Cross Discipline Team Leader  
Shan Pradhan, Clinical Reviewer  
Deanne Varney, Regulatory Project Manager

**EXTERNAL CONSTITUENT ATTENDEES**

Dr. David Kelsen

**BACKGROUND:** Dr. David Kelsen agreed to serve and was cleared as an SGE for this NDA. Prior to this teleconference, background materials were provided to Dr. Kelsen, along with one question to address during this teleconference.

**DISCUSSION POINTS:** In this application, Merrimack seeks the approval of Onivyde (irinotecan liposome injection) for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.

**FDA Questions for Discussion During Teleconference:**

1. Based upon your review of the summary information provided, do you agree that the observed improvement in overall survival in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms?

**Discussion:** Dr. Kelsen stated that firstly the difference between the NAPOLI-1 arms in 5-FU dose delivered as observed via dose intensity was very small. Dr. Kelsen stated that differences in 5-FU dosing schedules have not been observed in studies to result in different efficacy outcomes. Dr. Kelsen stated that the difference in 5-FU dosing regimen

July 14, 2015

NDA 207793: Teleconference with SGE, Dr. Kelsen

between arms in NAPOLI-1 is highly unlikely to have contributed to the observed difference in overall survival between the two arms, and also noted the higher cumulative 5-FU doses administered in the control arm as compared to the MM-398/5-FU/LV arm.

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/s/  
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DEANNE R VARNEY  
07/27/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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Memorandum

**Date:** July 20, 2015  
**From:** Deanne Varney, DOP2/OHOP/CDER  
**Subject:** Midcycle Meeting Minutes: Onivyde NDA 207793

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**NME Application:** NDA 207793

**Product:** Onivyde (irinotecan liposome injection)

**Received Date:** April 24, 2015

**PDUFA Date:** October 24, 2015

**Sponsor:** Merrimack Pharmaceuticals, Inc.

**Proposed Indication:** Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5 fluorouracil and leucovorin, in patients who have been previously treated with gemcitabineSupplied

This midcycle meeting for NDA 207793 was a face-to-face internal FDA meeting.

Attendees included: Richard Pazdur, Patricia Keegan, Steven Lemery, Shan Pradhan, Hui Zhang, Kun He, Sarah Schrieber, Gene Williams, Anshu Marathe, Anuradha Ramamoorthy, Margot Brower, Whitney Helms, Mike Adams, Liang Zhou, Olen Stephens, Rosane Orbach Charlab, , Jeff Summers, Monica Hughes, Jennie Chang, Miriam Dinatale, Otto Townsend, Carole Broadnax

**Discussion Items:**

Slides were presented by (in order):

- RPM Regulatory
- Clinical and Statistical, Efficacy & Safety
- Clinical Pharmacology
- Non-Clinical
- CMC

**Benefit-Risk Overview (summarized from Clinical):**

- OS of 6.1 months vs. 4.2 months; PFS of 3.1 months vs. 1.5 months; statistically significant benefit in OS
- Safety profile is acceptable

**Additional Issues:**

- Will consider including [REDACTED] <sup>(b) (4)</sup> in the Clinical Studies section of the label
- QTc: Will send a general comment under the IND to evaluate QTc if product is further studied in a lower risk population
- Quality team will review the ratio of [REDACTED] <sup>(b) (4)</sup> over the stability testing period

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/s/  
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DEANNE R VARNEY  
07/20/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 207793

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Merrimack Pharmaceuticals, Inc.  
One Kendall Square  
Suite B7201  
Cambridge, MA 02139-1670

ATTENTION: Michael Slater  
Vice President of Regulatory Affairs

Dear Mr. Slater

Please refer to your New Drug Application (NDA) dated and received December 29, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Irinotecan Liposome Injection, 5 mg/mL.

We also refer to:

- your correspondence, dated and received May 04, 2015, requesting review of your proposed proprietary name, Onivyde
- your amendment, dated and received May 14, 2015, to your request for name review

We have completed our review of the proposed proprietary name, Onivyde, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your May 4, 2015, or May 14, 2015, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4901. For any other information regarding this application, contact Deanne Varney, Regulatory Project Manager in the Office of New Drugs, at 301-796-0297.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
07/19/2015

# TEAM MEETING MINUTES

## July 15, 2015

New 505(b)(2) NDA 207793  
Irinotecan Liposome Injection  
Merrimack Pharmaceuticals, Inc.

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**Submission Date:** April 24, 2015 (final portion of rolling submission)  
**Received Date:** April 24, 2015  
**PDUFA:** October 24, 2015

**Proposed Indication:** Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine

### Core Review Team:

Patricia Keegan, Director DOP2  
Deanne Varney, RPM  
Shan Pradhan, Medical Officer  
Steven Lemery, Medical Officer Team Leader  
Hui Zhang, Statistics  
Kun He, Statistics Team Leader  
Sarah Schrieber, Clinical Pharmacology  
Gene Williams, Clinical Pharmacology Team Leader  
Anshu Marathe, Pharmacometrics Reviewer  
Margot Brower, Non-Clinical  
Whitney Helms, Non-Clinical Team Leader  
Mike Adams, CMC  
Liang Zhou, CMC Team Leader  
Olen Stephens, CMC (Branch Chief)  
Rabiya Laiq, CMC RPM  
Anuradha Ramamoorthy, Genomics Reviewer  
Rosane Charlab Orbach, Genomics Team Leader  
Banu Zolnik, Biopharmaceutics Reviewer  
Okpo Eradiri, Biopharmaceutics Team Leader

### Consults:

Carole Broadnax, OPDP / Jessica Cleck Dereneck, OPDP TL  
Margaret Rand, DPV / Tracy Salaam, DPV TL  
Naomi Redd, DRISK / Doris Auth, DRISK TL  
Otto Townsend, DMEPA / Alice Tu, DMEPA TL  
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL  
Lauren Iacono-Connors, OSI / Susan Thompson, OSI TL  
Miriam Dinatale, PMHS / Tamara Johnson, TL /Denise Pica-Branco

**Agenda Items:**

**1. Review Status:**

- Priority Review requested (6 month review – not in the Program)
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of irinotecan liposome has been conducted under IND 102799

**2. Milestone Dates for 6-Month Priority Review Clock:**

<b>Milestone</b>	<b>6 month review</b>
<b>Acknowledgment Letter</b>	<i>Issued April 30, 2015</i>
<b>Priority Review Determination OR Filing Issues Identified/Not Identified Letter</b>	June 23, 2015 <i>Issued June 23, 2015</i>
<b>Filing Issues Identified (74 Day Letter) — if not sent in Day 60 letter</b>	<i>July 7, 2015</i>
<b>Mid-Cycle Meeting</b>	July 20, 2015
<b>Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)</b>	October 3, 2015
<b>Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant</b>	October 10, 2015
<b>Advisory Committee Target Date</b>	Month 4-5 (August –September)
<b>Review Target Due Dates:</b> <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i>	September 30, 2015 October 3, 2015 October 10, 2015 October 24, 2015
<b>Wrap-Up Meeting w/ Safety discussion</b>	September 26, 2015
<b>Compile and circulate Action Letter and Action Package</b>	October 10, 2015
<b>FINAL Action Letter Due</b>	<b>October 24, 2015</b>

3. **Midcycle Preparation:** Midcycle will be held July 20<sup>th</sup>.

Discussion points are outlined below:

- Discipline Specific Reviews of Application
  - Applicable studies/information submitted
  - Status of your review of the data
  - Discussion of findings so far
    - a. Are there issues requiring resolution? Discuss in presentations or state no issues have been identified.
    - b. Are there any major labeling issues? Discuss in presentation or state there are no issues identified.
    - c. Are there PMC and Risk Management Plan Issues? Discuss during presentation or state that there are no plans/need for PMC/PMRs/REMS.
  - Identification of need for additional input from review team or through additional consults
  - Information requests to be sent to sponsor
  - Presentations
    - a. Regulatory/Introduction (Deanne Varney)=less than 5 minutes
    - b. Clinical/Statistical (Shan Pradhan/Hui Zhang)=30 minutes
    - c. Clinical Pharmacology (Sarah Schreiber)=10 minutes
    - d. Non-Clinical (Margot Brower)=10 minutes
    - e. CMC (Mike Adams)& Biopharmaceutics (Banu Zolnik) = 10 minutes
- Pending Inspections
  - OSI Inspections: Status Update
  - OMPQ Inspection: Status Update

**Discussion:** The team confirmed that the time allotments are adequate, and the RPM will follow-up with OSI and OMPQ regarding inspection status.

4. **SGE's:** Teleconferences were held with two SGE's on July 14, 2015. Both SGE's agreed that the observed improvement in overall survival in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms.

**Discussion:** None.

5. **ODAC:** An ODAC will not be held.

**Discussion:** None.

6. **Review Issues:**

- a. **Clinical:** No issues.
- b. **Statistics:** No issues. Response to pending IR due 7/20/15.
- c. **Clinical Pharmacology / Clinical:** QT-IRT determined that there is not an adequate assessment of irinotecan on QT prolongation. A PMR might be required. QT-IRT completed the review of the CITS protocol, and has determined that “”

The clinical pharmacology team does not think a dedicated QT study is needed and requested that the clinical team review the cardiac data to determine if they think additional QT data needs to be requested under a PMR. This issue will be discussed further during the midcycle meeting.

Clinical pharmacology will draft an IR requesting rationale for why a dedicated QT study is not needed.

Clinical pharmacology will confirm that the QT standard comments were previously sent to applicant.

- d. **Pharmacometrics:** Potential information requests regarding the labeling language for the population PK analysis.
- e. **Genomics:** One potential IR to clarify genotyping methods.
- f. **Nonclinical:** No issues.
- i. **CMC:** DMF not adequate to support review of application. IR sent to DMF holder on 7/7/15. Will discuss further at midcycle. Need to clarify and further define manufacturing process with applicant.
- g. **Biopharmaceutics:** No issues.
- h. **Regulatory:** No issues.

7. **Inspections:**

- a. **Clinical Site Inspections:**

**Discussion:** RPM will follow-up with OSI.

Sites 881 and 882 in Taiwan.

Site 366 in Hungary.

Site 617 in Australia.

Site 120 in US.

- b. Manufacturing Site Inspections:** Drug product manufacturing facilities to be inspected. Any updates on scheduled inspections?

**Discussion:** RPM will follow-up with assigned facility inspector.

**8. Internal Team Meetings:**

- **Mid-Cycle Meeting:** July 20, 2015
- **Labeling Meetings:** Updated labeling received from Merrimack on 7/14/15 and will be placed on SharePoint for review.
- Order of labeling meetings is outlined below:
  - a. July 23, 2015: Clinical and Statistics – Sections 1 and 14
  - b. July 28, 2015: CMC, DMEPA, Clinical – Sections 3, 11, 16
  - c. July 29, 2015: Clinical – Sections 4, 5, 6, 17
  - d. August 18, 2015: Clinical, Maternal Health, Nonclinical – Sections 5.1, 8.1, 8.3, 8.4, 12.1, 13
  - e. August 20, 2015: Clin Pharm, Clinical and DMEPA – Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3
  - f. September 15, 2015: Highlights, Remaining issues
  - g. October 8, 2015: Review of applicant and consult edits
- **Monthly Team Meetings:**
  - a. June – June 24, 2015
  - b. July – July 15, 2015
  - c. August – August 19, 2015
  - d. September – September 16, 2015
  - e. October – October 14, 2015

- **Wrap- Up Meeting:** September 23, 2015

**9. Additional Items or Issues:**

**Discussion:** None.

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/s/  
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DEANNE R VARNEY  
07/15/2015



Dr. Carmen Allegra  
Sent via email communication

Dear Dr. Allegra:

We corresponded several weeks ago regarding the possibility of your assistance in the review of a New Drug Application (NDA) 207793, submitted by Merrimack Pharmaceuticals (Merrimack). In this application, Merrimack seeks approval of irinotecan liposome injection for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine. Please note that information concerning this application is confidential.

I received notification from the CDER Division of Advisory Committee and Consultant Management (DACCM) that you are cleared to serve as a Special Government Employee (SGE) for the review of this NDA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for 11:00AM ET on July 14, 2015. The questions we would like to discuss during this teleconference are listed below.

Following our teleconference, please return the completed Timekeeper Payroll Record (enclosed) indicating the amount of time you worked on this review via one of the following methods:

- EMAIL: [Deanne.Varney@fda.hhs.gov](mailto:Deanne.Varney@fda.hhs.gov)
- FedEx or UPS overnight delivery to:  
Deanne Varney  
Division of Oncology Products 2  
Food and Drug Administration  
WO22-2326  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

Enclosed is a summary of the pivotal trial submitted with this application as well as excerpts from the NDA submission.

**FDA Question for Discussion During Teleconference:**

Based upon your review of the summary information provided, do you agree that the observed improvement in overall survival in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms?

If you have questions, please contact me at 301-796-0297.

Sincerely,

Deanne Varney  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosures:

1. NDA 207793 Summary Information
2. Timekeeper Payroll Record



**Proposed Indication:** “Onivyde (irinotecan liposome injection) is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.”

**Applicant:** Merrimack Pharmaceuticals, Inc.

**Information from NDA 207793:**

Irinotecan liposome injection (MM-398) is irinotecan in the form of a sucrosulfate salt, encapsulated in liposomes for intravenous infusion.

Merrimack submitted the NDA as a 505(b)(2) application for which Camptosar (irinotecan) is the reference drug, as Merrimack’s application relies on certain information (e.g., nonclinical, drug interactions, and other clinical pharmacology information) contained in the physician’s package insert for Camptosar.

To support the efficacy of MM-398 for the above-listed proposed indication, Merrimack submitted clinical data from single trial NAPOLI-1, which was an open-label, three-arm, randomized, international, multicenter trial.

NAPOLI-1 was initially designed as a two-arm trial comparing the safety and efficacy of MM-398 at a dose of 120 mg/m<sup>2</sup> every three weeks with 5-fluorouracil 2000 mg/m<sup>2</sup> (with leucovorin) every week for four weeks in a six week cycle (Arms A and B below). After enrollment of 63 patients, Merrimack amended the trial to include a third arm (Arm C) investigating the combination of MM-398, 5-fluorouracil (5-FU), and leucovorin (LV) at the doses shown below. The amended trial was entitled as follows.

**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 (MM-398-07-03-01)”

Under the revised protocol, patients were randomized (1:1:1) to Arms A, B, or C (shown below). Randomization was stratified by albumin level, Karnofsky Performance Score (KPS), and ethnicity.

- **Arm A:** MM-398 at a dose of 120 mg/m<sup>2</sup> every three weeks
- **Arm B:** 5-FU 2000 mg/m<sup>2</sup> over 24 hours and LV 200 mg/m<sup>2</sup> once weekly for 4 weeks of each 6 week cycle

- **Arm C:** MM-398 at a dose of 80 mg/m<sup>2</sup> every two weeks in combination with 5-FU 2400 mg/m<sup>2</sup> over 46 hours and LV 400 mg/m<sup>2</sup> every two weeks

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

The primary endpoint was overall survival (OS) with two co-primary, pair-wise comparisons, one for each MM-398-containing arm compared with the control arm (Arm B; 5-FU/LV), with Type I error controlled using the Bonferroni-Holm approach. The specified population (in the amended statistical plan submitted prior to the final analysis) for the comparison of Arm C to Arm B was limited to patients randomized following the addition of the third arm (Arm C). Secondary endpoints included progression-free survival (PFS) and objective response rate (ORR).

A total of 151 patients were randomized to Arm A, 149 to Arm B, and 117 to Arm C. For the comparison of Arm C vs. Arm B, the trial demonstrated a statistically significant difference in OS [HR=0.67 (95% CI 0.49-0.92); p=0.012]. There was no significant difference in OS for Arm A vs. Arm B [HR 0.99; p=0.9]. Median OS times for the two MM-398-containing arms were 6.1 months for Arm C and 4.9 months for Arm A. Median OS time for the control arm (Arm B) was 4.2 months. The comparison of PFS for Arm C vs. Arm B demonstrated a statistically significant improvement [HR 0.56 (95% CI 0.41-0.75); p=0.0001] with a median PFS of 3.1 months in Arm C and 1.5 months in Arm B.

### **5-FU Dosing Regimens**

The 5-FU/LV dosing regimen assigned to the control arm of NAPOLI-1 was the 5-FU dose and schedule that was employed as the control in the CONKO-003 trial (Pelzer et al., 2011). The MM-398/5-FU/LV dosing regimen assigned to Arm C of NAPOLI-1 was the same regimen (same doses and schedule) tested in the PEPCOL study, a French cooperative group study in patients with metastatic colorectal cancer, from which safety data had become available.

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

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

- Pharmacokinetics (PK) simulation results showing that the 5-FU area under the curve (AUC) in Arm B (control arm) was higher than in Arm C (MM-398/5-FU/LV).

The planned cumulative dose of 5-FU in the 5-FU/LV control arm (Arm B) was higher than in the MM-398/5-FU/LV arm (Arm C): 8000 versus 7200 mg/m<sup>2</sup> over a six-week cycle, equivalent to a dose intensity of 1333 versus 1200 mg/m<sup>2</sup>/week. Merrimack showed that the comparison of observed cumulative doses between Arms B and C was consistent with the comparison of planned cumulative doses between Arms B and C, with six-week average dose intensities of 6718 and 5065 mg/m<sup>2</sup> (or 1119.7 and 844.2 mg/m<sup>2</sup>/week) respectively, and that at any week except for the first week, the planned and observed cumulative 5-FU doses were higher in the control arm than in the MM-398/5-FU/LV arm.

Merrimack further presented PK simulation results showing that the six-week average 5-FU AUC in the MM-398/5-FU/LV arm was 90% of that in the control arm; see Appendix 1 which contains an excerpt from Merrimack's NDA submission describing Merrimack's methods, analyses, and results.

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

In the pancreatic cancer indication, clinical studies reported in English were searched using PubMed. The strategy used a panel of keywords (listed in the NDA) involving 5-FU and pancreatic cancer. The search was further filtered for trials from January 1980 through December 2014, containing more than 10 patients per arm, and in patients with pancreatic cancer with locally advanced or metastatic disease eligible for any line of therapy. References from the search publications were included. One study dated 1974 was included as Merrimack deemed the study relevant. Combinations with agents other than LV were included only if the study included more than one 5-FU dose and regimen. Combinations with radiation therapy were excluded. Merrimack acknowledged that the list may not be exhaustive.

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



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

See Appendix 2 which contains Merrimack's tables and Merrimack's summaries of the published studies identified above.

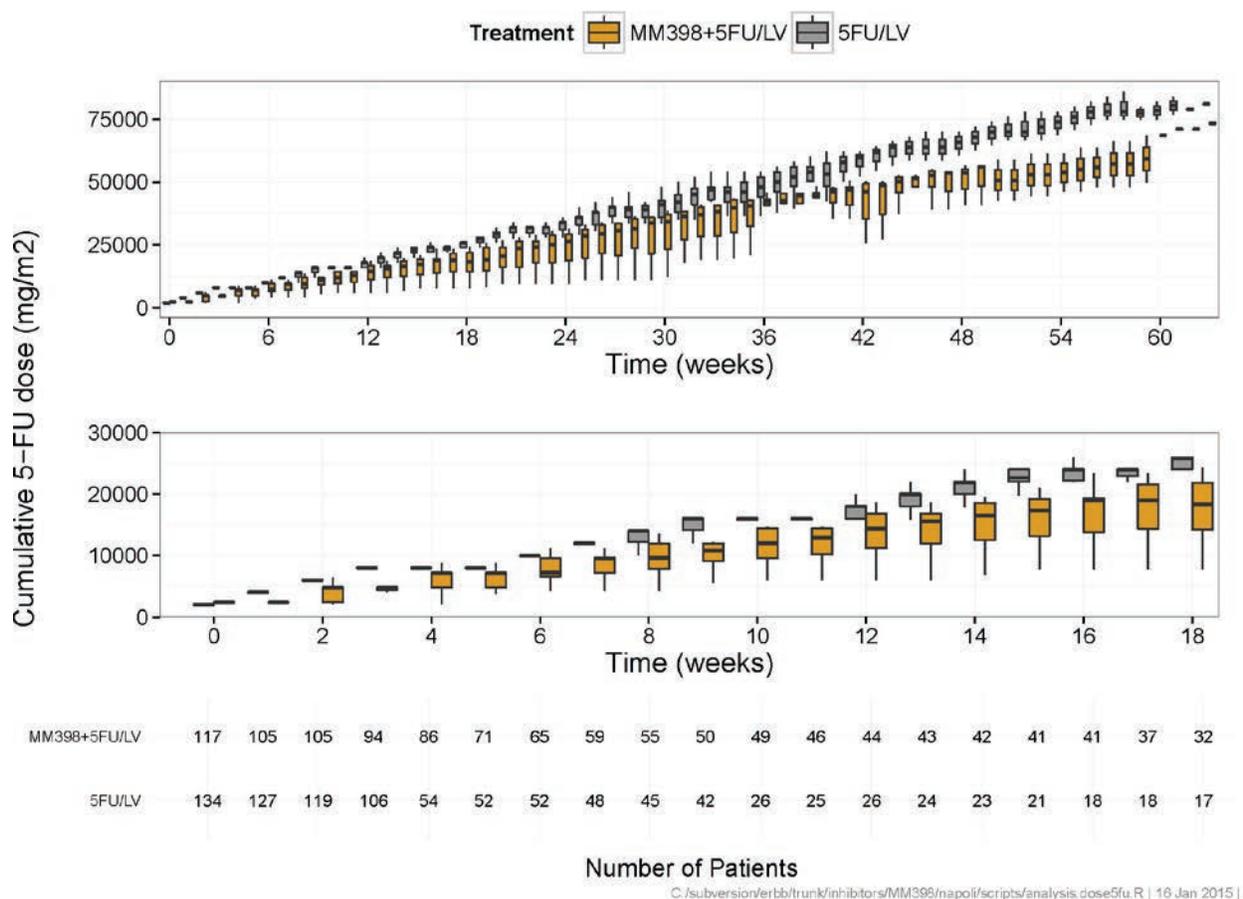
The review of the published data (most of which is indirect evidence from colorectal cancer trials) does not appear to indicate that the different dosing regimens in the two NAPOLI-1 arms (B vs. C) would result in improved clinical outcomes in the MM-398/5-FU/LV arm solely due to the differences in 5-FU doses between arms (noting that the higher 5-FU cumulative dose per six-week cycle was administered to patients in the control arm).

***FDA QUESTION FOR DISCUSSION DURING TELECONFERENCE:***

*Based upon your review of the summary information provided, do you agree that the observed improvement in OS in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms?*



**APPENDIX 1 (excerpt from Merrimack's NDA submission)**



**Figure 2-1** Observed 5-FU Doses by Treatment Regimen over Time in the NAPOLI-1 Study

Each box plot includes patients with reported dosing at the respective week. Number of patients in the bottom corresponds to the lower figure in the first 18 weeks.

Source: dose5fu.pdf

## 2.A.2 Clinical Pharmacology of 5-FU

### 2.A.2.1 Literature review: 5-FU therapeutic target AUC of 20-25 h mg/L

Compared to administered dose levels, the pharmacokinetic parameters of 5-FU, specifically the AUC, have been shown to provide a better prediction of efficacy and safety (Saif, Choma, Salamone, & Chu, 2009). A consistent target range of AUC for all infusion based regimens has been established as 20-25 mg h/L, and a therapeutic dose monitoring based on 5-FU AUC has been shown to improve efficacy and safety (Gamelin et al., 2008). **Table 2-2 Literature Review of Target 5-FU AUC** shows that the target AUC of approximately 20 h mg/L is consistent for continuous infusion for a wide range of infusion durations (8h – 96h). Therefore, the time-average (6-week) AUC can be used as a metric to compare the different 5-FU doses of the two arms in NAPOLI-1 study.

**Table 2-2 Literature Review of Target 5-FU AUC**

reference	Indication Cancer Type	N	Type	Dose	Interval	Infusion duration (h)	Target AUC (h mg/L)
Fety1998	head neck	122	continuous infusion	4g/m <sup>2</sup> /cycle AUC-adjusted	every 2 weeks	96	Dose reduced if AUC <sub>48</sub> >20
Gamelin2008	colorectal	208	continuous infusion	1500mg/m <sup>2</sup> /week AUC-adjusted (mean=1790mg/m <sup>2</sup> /week)	every 1 week	8	AUC <sub>8</sub> 20-24
Ychou2003	colorectal	53	continuous infusion	400mg/m <sup>2</sup> (bolus)+ 600mg/m <sup>2</sup> /day	2 days every 2 weeks	22	AUC <sub>46</sub> 20
DiPaolo2008	colorectal	115	Bolus	370mg/m <sup>2</sup> /day	5 days every 4 weeks	2 m	AUC <sub>bolus</sub> 8.4

### 2.A.2.2 Comparison of 5-FU pharmacokinetics in the NAPOLI-1 Study

MM-398 and 5-FU have different metabolic pathways and therefore are unlikely to have drug-drug interactions. The disposition of irinotecan was not altered when 5-FU was co-administered (Camptosar package insert). The metabolism of 5-FU is via catabolism by dihydropyrimidine dehydrogenase (DPD), while the active ingredient of MM-398 is irinotecan, for which conversion to the active metabolite, SN-38, is mediated by carboxylesterase enzymes. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite (irinotecan USPI).

Simulation of 5-FU pharmacokinetic parameters was performed for the two 5-FU regimens of NAPOLI-1 (**Figure 2-2 Simulated 6-Week Average 5-FU AUC for 5-FU Dose Regimens of NAPOLI-1**) using three published 5-FU pharmacokinetic parameters (listed in **Table 2-3 Simulated and Observed 5-FU Pharmacokinetics by Dose Regimens**). Two simulation approaches were evaluated: 1) to simulate based on Monte-Carlo random parameters generated based on the previously published parameters, without using 5-FU samples in NAPOLI-1; or 2) to estimate the pharmacokinetic parameters based on the 5-FU samples in NAPOLI-1 using Empirical Bayesian Estimation, with priors from the previously published parameters. The 6-week average AUCs were used as the primary comparison, because of the findings that total exposure AUC appears to be the 5-FU pharmacokinetic driver of efficacy (Saif et al., 2009); and a 6-week duration provides a common duration for both the 5-FU/LV and MM-398+5-FU/LV arms of NAPOLI-1. Details of the simulation methods and results are provided in **Section 6**.

The simulation results from approach 1, which was based on previously published parameters without using 5-FU samples in NAPOLI-1, showed that the 5-FU 6-week average AUC in the MM-398+5-FU/LV arm was 90% of the AUC in the 5-FU/LV control arm (**Table 2-3 Simulated and Observed 5-FU Pharmacokinetics by Dose Regimens**). Moreover, the percentage of patients with a 6-week average 5-FU AUC greater than the target AUC (of 20 mg h/L) was 2%-7% lower in the MM-398+5-FU/LV arm compared to that in the 5-FU/LV arm.

The simulation results from approach 2, which was on the 5-FU samples in NAPOLI-1 using Empirical Bayesian Estimation, with priors from the previously published parameters, showed a similar result as those obtained without using the measured NAPOLI-1 5-FU samples (rows 1 and 3 of **Table 2-3**). It was noted that evaluation of the estimation results showed some bias in the goodness of fit, see **Section 6D**.

The observed 5-FU concentrations for both 5-FU containing treatment arms in NAPOLI-1 were lower than the predicted steady-state concentrations; this is likely due to the fact that the majority (75%) of pharmacokinetic samples in NAPOLI-1 were collected after the end of infusion and during the time of rapid clearance of 5-FU, which, with a known a half-life of 16 minutes ((b) (4)) would result in lower concentrations that are not representative of steady-state levels. The predicted steady-state concentration ratio of the MM-398+5-FU/LV arm to the 5-FU/LV arm was 0.626, similar to the observed concentration ratio of 0.63 [95%CI 0.28-1.39] (of note, the 5-FU concentrations measured in NAPOLI-1 were a mixture of steady-state and post-infusion).

**Table 2-3 Simulated and Observed 5-FU Pharmacokinetics by Dose Regimens**

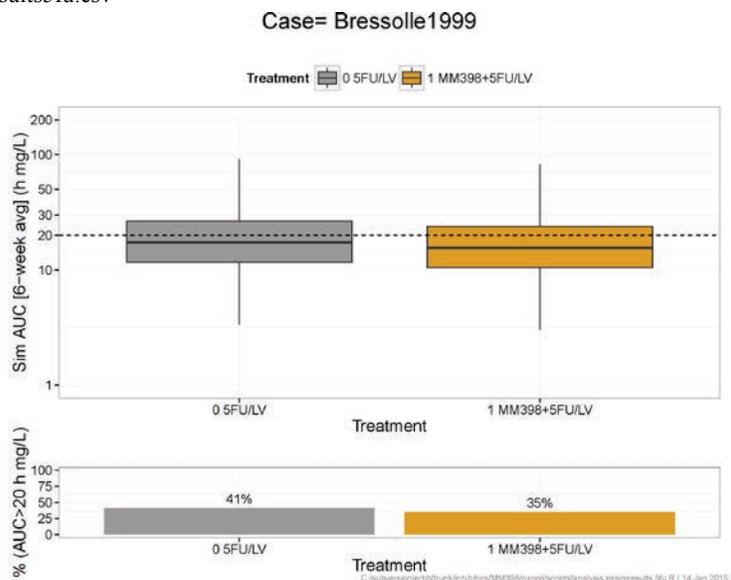
Reference for 5-FU PK Parameters	Steady-state Conc (mg/L)			Predicted 6-week Average AUC					
	GLS Mean		Ratio <sup>2</sup> Mean [95%CI]	AUC (h mg/L)			% AUC>20 h mg/L		
	5-FU/LV	MM-398 +5-FU/LV		5-FU/LV	MM-398 + 5-FU/LV	Ratio <sup>2</sup>	5-FU/LV	MM-398 + 5-FU/LV	Diff <sup>3</sup>
Bressolle1999	1.091	0.683	0.626	17.456	15.710	0.9	41%	35%	-6%
Mueller2013	0.901	0.564	0.626	14.418	12.976	0.9	10%	4%	-6%
Bressolle1999+ NAPOLI-1 5-FU concentration	1.212	0.759	0.626	19.392	17.453	0.9	49%	42%	-7%
Woloch2012	2.771	1.735	0.626	44.329	39.896	0.9	96%	94%	-2%
NAPOLI-1 observed 5-FU concentration <sup>1</sup>	0.22	0.14	0.63 [0.28-1.39]						

<sup>1</sup> The majority (75%) of the 5-FU concentrations were collected after the end of infusion, therefore, the observed concentration is lower than steady-state concentration (5-FU was cleared rapidly after the end of infusion with the estimated half-life of 8-14 minutes).

<sup>2</sup> Ratio is defined as concentration or AUC ratio of MM-398+5-FU/LV relative to 5-FU/LV

<sup>3</sup> Difference is defined as percentage of MM-398+5-FU/LV minus percentage for 5-FU/LV

Source: summary.pksimresults5fu.csv



**Figure 2-2 Simulated 6-Week Average 5-FU AUC for 5-FU Dose Regimens of NAPOLI-1**

Simulation was performed using 5-FU pharmacokinetic parameters in (Bressolle et al., 1999).

Source: pk5fu.pdf

## 6 APPENDIX: DETAILED PHARMACOKINETICS ANALYSES OF 5-FU TO EVALUATE DIFFERENT 5-FU DOSES IN STUDY MM-398-07-03-01 (NAPOLI1)

### A. OBJECTIVES

1. To compare the 5-FU pharmacokinetic difference that arises from the difference in the 5-FU dose regimens of the control and investigational treatment arms in NAPOLI-1 Study

### B. METHODS

#### 6.B.1 Study design

Subjects in NAPOLI-1 Study MM-398-07- randomized to the two 5-FU/LV containing arms, MM-398+5-FU/LV and 5-FU/LV, were to receive the following planned dose regimens:

- MM-398+5-FU/LV arm: MM-398 80 mg/m<sup>2</sup> IV and 5-FU 2400 mg/m<sup>2</sup> IV over 46 hours and LV 400 mg/m<sup>2</sup> IV over 30 minutes, every 2 weeks
- 5-FU/LV arm: 5-FU 2000 mg/m<sup>2</sup> IV over 24 hours and LV 200 mg/m<sup>2</sup> IV over 30 minutes, administered weekly for the first 4 weeks, followed by 2 weeks of rest, in a 6 weekly cycle

#### 6.B.2 Dataset

Pharmacokinetic samples of 5-FU from both arms were collected at the end of 5-FU infusion (Cycle 1 Day 2). A total of 163 samples from 129 subjects were collected, and 75% (122/163) of the samples were collected after the end of infusion.

#### 6.B.3 Models

Pharmacokinetics of 5-FU is described as a one-compartmental model, based on the previously published studies (Bressolle et al., 1999; Mueller et al., 2013; Woloch et al., 2012). The published effects of covariates to 5-FU pharmacokinetics were not implemented because some of the covariates were not collected in the NAPOLI-1 Study. Fixed and random effect parameter estimates from the literature are summarized in Table 6-1.

**Table 6-1 Pharmacokinetic Models of 5-FU from Literature that are Used in the Simulation Study**

reference	N	Clearance (L/week)		Volume (L)	
		<i>Fixed effect</i>	<i>Random effect</i>	<i>Fixed effect</i>	<i>Random effect</i>
Bressolle1999	85	21504	56%	18.4	114%
Woloch2012	127	8568	43%	22.0	50%
Mueller2013	32	26544	22%	54.9	18.5%

Source: (Bressolle et al., 1999; Mueller et al., 2013; Woloch et al., 2012)

Pharmacokinetic analyses were conducted using 2 approaches:

1. To estimate the pharmacokinetic parameters based on the 5-FU samples in NAPOLI-1 using Empirical Bayesian Estimation, with priors from the previously published parameters
2. To simulate based on Monte-Carlo random parameters generated based on the previously published parameters, without using 5-FU samples in NAPOLI-1

In the first approach, measured concentrations below limit of quantification (BQL) were modeled by the mixed continuous and categorical method (M3 method, (Bergstrand & Karlsson, 2009)). The M3 method was implemented using log-transformed values of concentration and the LAPLACIAN estimation method.

#### 6.B.4 Simulation Methods

Simulation was conducted by comparison of the 5-FU pharmacokinetic simulations in both 5-FU regimens (in the control and the investigational arms of NAPOLI-1). The PK parameters were either obtained from Empirical Bayesian Estimate from the NAPOLI-1 study or obtained by sampling, 1000 times, the random clearance and volume estimates from the distribution as specified in Table 6-1. Planned 5-FU doses as specified in Section 6.B.1 were used, which represent the optimistic boundary for the analysis because of the higher percentage of 5-FU dose reductions in the MM-398+5FU/LV arm than in the 5FU/LV alone arm. As the doses were BSA-based, the distribution of BSA follows those observed in the NAPOLI-1 study.

Compared to the weekly dose intensity, pharmacokinetic parameters of 5-FU have been shown to provide a better prediction of efficacy and safety (reviewed in (Saif et al., 2009)). A consistent target range of AUC for all infusion based regimens has been established as 20-24 mg h/L (Gamelin et al., 2008). A therapeutic dose monitoring based on 5-FU AUC has been shown to improve efficacy and safety (Gamelin et al., 2008). Table 6-2 showed that the target AUC is consistent for continuous infusion with varying infusion durations (8h – 96h). Therefore, time-average (6-week) AUC is used as a metric to compare the different 5-FU doses of the two arms in NAPOLI-1 study.

From the simulation results, 6-week average AUC of 5-FU were compared by treatment arms. Moreover, the percentage of patients who have 6-week AUC greater than target AUC of 20 mg h/L was evaluated.

**Table 6-2 Literature review of target 5-FU AUC**

reference	Indication	N	Type	Dose	Interval	Infusion duration (h)	Target AUC (h mg/L)
Fety1998	head neck	122	continuous infusion	4g/m2/cycle AUC-adjusted	every 2 weeks	96	Dose reduced if AUC <sub>48</sub> >20
Gamelin2008	colorectal	208	continuous infusion	1500mg/m2/week AUC-adjusted (mean=1790 mg/m2/wk)	every 1 week	8	AUC <sub>8</sub> 20-24
Ychou2003	colorectal	53	continuous infusion	400mg/m2 (bolus)+ 600mg/m2/day	2 days every 2 weeks	22	AUC <sub>46</sub> 20
DiPaolo2008	colorectal	115	bolus	370mg/m2/day	5 days every 4 weeks	2 min	AUC <sub>bolus</sub> 8.4

#### 6.B.5 Software

All data preparation and presentation was performed using SAS® Version 9.3 or later (SAS Institute) and R Version 3.0.2. PK modeling used NONMEM version 7.3, with default setting to be FOCEI with the Laplacian method. Package Perl Speaks NONMEM (PSN) was used for interface to NONMEM. Package Xpose4 was used for model diagnostics.

**C. SIMULATION RESULTS: COMPARISON OF THE 5-FU PHARMACOKINETICS BY DIFFERENT 5-FU DOSE REGIMENS**

To evaluate the contribution of different 5-FU regimens, a simulation study was conducted to compare different 5-FU doses. Details of the simulation are provided in Section 6.B.4. The 6-week average AUC was used as the primary comparison because of the findings that time-average AUC appears to be the 5-FU pharmacokinetic driver of efficacy and safety (Saif et al., 2009).

The simulation results are summarized in Table 6-3. The 6-week average AUC of the MM-398+5-FU/LV arm is predicted to be 90% of the AUC of 5-FU/LV control regimen. The percentage of patients with 6-week average AUC greater than the target AUC (of 20 h mg/L) is 2%-7% lower in the MM-398+5-FU/LV arm compared to those in the 5-FU/LV control arm. The simulation results from the Bayesian estimates were comparable to the results without using 5-FU concentration samples collected in the NAPOLI-1 Study (it is noted that evaluation of the estimation results showed some bias in the goodness of fit, see Section D). Because of sparsity of the samples and the bias in the goodness of fit, exposure-efficacy and exposure-safety analyses were not conducted.

**Table 6-3 Summary statistics of simulated and observed 5-FU pharmacokinetics from multiple reference pharmacokinetic models**

reference for 5-FU PK Parameters	Steady-state Conc (mg/L)			Predicted 6-week Average AUC					
	GLS Mean		Ratio <sup>2</sup> Mean [95%CI]	AUC (h mg/L)			% AUC>20 h mg/L		
	5-FU/LV	MM-398 +5-FU/LV		5-FU/LV	MM-398 + 5-FU/LV	Ratio <sup>2</sup>	5-FU/LV	MM-398 + 5-FU/LV	Diff <sup>3</sup>
Bressolle1999	1.091	0.683	0.626	17.456	15.71	0.9	41%	35%	-6%
Mueller2013	0.901	0.564	0.626	14.418	12.976	0.9	10%	4%	-6%
NAPOLI1+Bressolle1999	1.212	0.759	0.626	19.392	17.453	0.9	49%	42%	-7%
Woloch2012	2.771	1.735	0.626	44.329	39.896	0.9	96%	94%	-2%
NAPOLI-1 observed 5-FU concentration <sup>1</sup>	0.22	0.14	0.63 [0.28-1.39]						

<sup>1</sup> The majority (75%) of the 5-FU concentrations were collected after the end of infusion, therefore, the observed concentration is lower than steady-state concentration (5-FU was cleared rapidly after the end of infusion with the estimated half-life of 8-14 minutes).

<sup>2</sup> Ratio is defined as concentration or AUC ratio of MM-398+5-FU/LV relative to 5-FU/LV

<sup>3</sup> Difference is defined as percentage of MM-398+5-FU/LV minus percentage for 5-FU/LV

Source: [summary.pksimresults5fu.csv](#)



**APPENDIX 2 (excerpt from Merrimack's NDA submission)**

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**Table 2-6 Published Studies in Pancreatic Cancer Containing 5-FU alone or 5-FU/LV Dose Regimens**

PubMed ID:	Author, Year	5-FU administration					Line of treatment	N	Median Overall Survival (mo)
		Adm	Dose (mg/m <sup>2</sup> ) [duration]	Schedule	Cycle	Dose intensity (mg/m <sup>2</sup> /wk)			
24982456	Oettle, 2014	CI	2000 [24h]	d1, d8, d15, d22	q6w	1333	2nd	84	3.3 (95% CI: 2.7-4.0)
NA	Gill, 2014 (1)	CI	2400 [46h]		q2w	1200	2 <sup>nd</sup>	54	9.9 (95%CI: 6.7-16.9)
NA	Von Hoff, 2014 (NAPOLI-1)	CI	2000 [24h]	W1-4+2w rest	q6w	1333	2 <sup>nd</sup>	119	4.24 (95%CI 3.29-5.32)
		CI + MM-398	2400 [46h]		q2w	1200	2 <sup>nd</sup>	117	6.14 (95%CI 4.76-8.87)
8052479	Takada, 1994	BL	310	d1-d5 w1 and w3	q6w	517	≥1st	36	6.0 (95% CI: 5.8-10.1)
1960554	DeCaprio, 1991	BL	600	d1, d8, d15, d22, d29, d36	q8w	450	1st	42	6.2 (range: 0.2-33)
11128566	Figer, 2000	BL	900	d1	q2w	450	≥1st	22	9
		BL	370	d1-d5	q4w	463		25	5
10955877	Choi, 2000	BL	375	d1-d5	q4w	469	≥1st	23	6
2189551	Cullinan, 1990	BL	500	d1-d5	q5w	500	≥1st	64	3.5
4812773	Kovach, 1974	BL	506*	d1-d5	q5w	506	1st	31	7.4
9196156	Burris, 1997	BL	600	d1	q1w	600	1st	63	4.4
2579257	Cullinan, 1985	BL	500	d1-d5	q4w	625	≥1st	50	5.1 mo (22 wk)-
12181240	Ducreux, 2002	BL	500	d1-d5	q4w	625	≥1st	103	3.4 (102 d)
15341982	Van Rijswijk, 2004	CI	2600 [24h]	d1, d8, d15, d22, d29, d36	q8w	1950	1st	33	4.4 mo (19 wk, 95% CI: 12-35)

BL= bolus; CI= continuous infusion;

\* Drug Conversion: based on assumption that weight is 60 kg and body surface area is 1.6m<sup>2</sup>

(1) OS was noted by the authors to have a potential bias because of imbalances in subsequent treatments (23% received subsequent therapies) and disease characteristics within the younger patient subgroup

**Table 2-7 Published Studies in Metastatic Colorectal Cancer Comparing 5-FU Doses**

reference	Study Name	Cohort	Drug Regimens	5-FU Dose Regimen			N	Overall Survival					Response Rate (%)
				Dose (mg/m <sup>2</sup> or mg/m <sup>2</sup> /d) [infusion duration in h]	Adm	Dose Intensity (mg/m <sup>2</sup> /w)		HR	P	Median (m)	Rate 3 y	Rate 5 y	
Kohne 2013	PETACC-2	Metastatic	5FU+LV	370-425mg/m <sup>2</sup> /d for 5d q4w	BL	463-531	804	0.96	0.74	nrd	85%	79%	NR
Kohne 2013	PETACC-2	Metastatic	5FU+LV	(1) 3500mg/m <sup>2</sup> [48h] q1w (2) 2600mg/m <sup>2</sup> [24h] q1w (3) 400mg/m <sup>2</sup> BL +600mg/m <sup>2</sup> [22h] for 2 d q2w	CI	3500 2600 800	797	ref		nrd	85%	79%	nr
Leichman 2005	NA	Metastatic	5FU	300mg/m <sup>2</sup> /d [28d] q5w	CI	1680	347	nr	0.70	13	nr	nr	nr
Leichman 2005	NA	Metastatic	5FU	2600mg/m <sup>2</sup> [24h] q1w	BL	2600	361	ref		13	nr	nr	nr
Andre 2007	GERCOR C96.1	Metastatic	5FU+LV	400mg/m <sup>2</sup> for 5d q4w	BL	500	453	1.02	0.91	nrd	nr	78% <sup>1</sup>	nr
Andre 2007	GERCOR C96.1	Metastatic	5FU+LV	400mg/m <sup>2</sup> BL + 600mg/m <sup>2</sup> [22h] for 2 d q2w	CI	800	452	ref		nrd	nr	76% <sup>1</sup>	nr
Shah 1985	NA	Metastatic	5FU	30mg/kg/d [48h] q1w	CI	2400 <sup>2</sup>	30	ref		14	nr	nr	30%
Shah 1985	NA	Metastatic	5FU	30mg/kg/d [72h] q2w	CI	1800 <sup>2</sup>	31	nr	nr	9.5	nr	nr	16%
Shah 1985	NA	Metastatic	5FU	30mg/kg/d [72h] q3w	CI	1200 <sup>2</sup>	33	nr	.09	9	nr	nr	0%
Weinerman 1992	NCIC	Metastatic	5FU	350mg/m <sup>2</sup> /d [2w] q4w	CI	1225	94	nr	0.21	nr	nr	nr	13%
Weinerman 1992	NCIC	Metastatic	5FU	400-450mg/m <sup>2</sup> /d for 5d q4w	BL	500-562	90	ref		nr	nr	nr	7%
Hansen 1996	ECOG	Metastatic	5FU	300mg/m <sup>2</sup> /d	CI	2100	159	nr	0.22	13	nr	nr	28%
Hansen 1996	ECOG	Metastatic	5FU	500mg/m <sup>2</sup> for 5d, then 600mg/m <sup>2</sup> /d q1w	BL	600	153	ref		10.4	nr	nr	18%
Leichman 1995	SWOG	Metastatic	5FU	500mg/m <sup>2</sup> for 5d q5w	BL	500	60	ref	nr	14	nr	nr	29%
Leichman 1995	SWOG	Metastatic	5FU+LV	425mg/m <sup>2</sup> for 5d q4w twice, then q5w	BL	425-531	61	0.97	nr	14	nr	nr	27%
Leichman 1995	SWOG	Metastatic	5FU+LV	600mg/m <sup>2</sup> q1w 6 times over 8 weeks	BL	450	60	1.04	nr	13	nr	nr	21%
Leichman 1995	SWOG	Metastatic	5FU	300mg/m <sup>2</sup> for 28d q5w	CI	1680	61	0.85	nr	15	nr	nr	29%
Leichman 1995	SWOG	Metastatic	5FU+LV	200mg/m <sup>2</sup> for 28d q5w	CI	1120	58	0.93	nr	14	nr	nr	26%
Leichman 1995	SWOG	Metastatic	5FU	2600mg/m <sup>2</sup> /d q1w	CI	2600	63	0.85	nr	15	nr	nr	25%
Leichman 1995	SWOG	Metastatic	5FU+PALA	2600mg/m <sup>2</sup> /d q1w	CI	2600	63	1.33	nr	11	nr	nr	15%
Lokich 1989	MAOP	Metastatic	5FU	300mg/m <sup>2</sup> /d	CI	2100	87	nr	0.38	10.3	nr	nr	30%
Lokich 1989	MAOP	Metastatic	5FU	500mg/m <sup>2</sup> for 5d q5w	BL	500	87	ref		11.2	nr	nr	7%
Poplin 2005	INT0153	Adjuvant	5FU+LV +levamisole	250mg/m <sup>2</sup> /d for 56d q9w	CI	1556	475	1.16	0.18	nrd	nr	69%	nr
Poplin 2005	INT0153	Adjuvant	5FU+LV +levamisole	425mg/m <sup>2</sup> /d for 5d q4w twice, then q5w	BL	455	464	ref		nrd	nr	70%	nr
Goldberg 2004	N9741	Metastatic	5FU+LV +oxaliplatin	400mg/m <sup>2</sup> BL +600mg/m <sup>2</sup> [22h] for 2 d q2w	CI	800	267	0.66	0.0001	19.5	nr	nr	45%
Goldberg 2004	N9741	Metastatic	5FU+LV +irinotecan	500mg/m <sup>2</sup> weeks 1,2,3,4 q6w	BL	333	264	ref		15.0	nr	nr	31%

ref= reference; nr= not reported; NA= not available. nrd= not reached. HR= hazard ratio. qXw= every X weeks (X is a number). d= day. h=hour. w=week, m=month; y= year. Adm= dose administration type (CI= continuous infusion; BL= bolus). <sup>1</sup>OS rate at 6 years <sup>2</sup>Dose was converted from per weight to per BSA using a conversion factor of 40 kg/m<sup>2</sup>

## **7 APPENDIX: SUMMARY OF PUBLICATIONS INCLUDED IN THE LITERATURE REVIEW**

### **A. PUBLICATIONS IN PANCREATIC CANCER**

#### **7.A.1 Oettle2014**

##### **Authors and Title**

Oettle et al. Second-Line Oxaliplatin, Folinic Acid, and Fluorouracil Versus Folinic Acid and Fluorouracil Alone for Gemcitabine-Refractory Pancreatic Cancer: Outcomes From the CONKO-003 Trial. *J Clin Oncol* 32(23):2423-2429, 2014.

##### **Purpose**

To assess the efficacy of a second-line regimen of oxaliplatin and folinic acid–modulated fluorouracil in patients with advanced pancreatic cancer who have experienced progression while receiving gemcitabine monotherapy.

##### **Patients and Methods**

A total of 168 patients who experienced disease progression during first-line gemcitabine therapy were randomized to folinic acid and fluorouracil (FF) (n=84) or oxaliplatin and FF (OFF) (n=76). FF comprised IV folinic acid 200 mg/m<sup>2</sup> followed by a continuous IV infusion of fluorouracil 2,000 mg/m<sup>2</sup> over 24 hours on days 1, 8, 15, and 22. OFF comprised FF and oxaliplatin 85 mg/m<sup>2</sup> IV administered before FF on days 8 and 22.

##### **Results**

The median overall survival in the OFF group (5.9 months; 95% CI, 4.1 to 7.4) versus the FF group (3.3 months; 95% CI, 2.7 to 4.0) was significantly improved (HR, 0.66; 95% CI, 0.48 to 0.91; log-rank p = .010). Time to progression with OFF (2.9 months; 95% CI, 2.4 to 3.2) versus FF (2.0 months; 95% CI, 1.6 to 2.3) was significantly extended also (HR, 0.68; 95% CI, 0.50 to 0.94; log-rank p = .019).

##### **Relevance to 5-FU dose comparisons**

As the two arms of this study had the same 5-FU regimen (24 hour continuous infusion), no conclusions can be drawn about the 5-FU dose. The dose and schedule for the FF was used for the control arm of NAPOLI-1.

## 7.A.2 Gill2014

### Authors and Title

Gill et al. PANCREOX: A randomized phase 3 study of 5-FU/LV with or without oxaliplatin for 2nd line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. 2014 ASCO Annual Meeting, BC Cancer Agency, Canada. Abstract 4022.

### Purpose

To compare 5-FU/LV with and without oxaliplatin for 2nd line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy

### Patients and Methods

One hundred eight patients with advanced pancreatic cancer previously treated with gemcitabine were randomized to either the 5-FU/LV treatment group (5-FU/LV without oxaliplatin) as in the FF regimen published by Oettle, et al, 2013, IV folinic acid 200 mg/m<sup>2</sup> followed by a continuous IV infusion of fluorouracil 2,000 mg/m<sup>2</sup> over 24 hours on days 1, 8, 15, and 22 (n=54) or the mFOLFOX6 treatment group (5-FU/LV with oxaliplatin), oxaliplatin 85 mg/m<sup>2</sup> IV over two hours on days 1 and 15, leucovorin 400 mg/m<sup>2</sup> IV over two hours concurrent with oxaliplatin, fluorouracil 400 mg/m<sup>2</sup> IV bolus, followed by fluorouracil 2400 mg/m<sup>2</sup> IV over 46 hours (n=54)

### Results

The median progression free-survival was 3.1 months with 5-FU/LV and 2.9 months with mFOLFOX6 (HR=1.00 [95% CI: 0.66-1.53], p value = 0.989). The overall response rate was 8.5% in the 5-FU/LV group and 13.2% in the mFOLFOX6, p = 0.361, no p value, CI, or Odds Ratios reported. The complete response was 0% in both treatment groups. The median duration of overall survival was 9.9 months (95% CI: 6.7 – 16.9) with 5-FU/LV and 6.1 months (95% CI: 3.2 – 8.0) with mFOLFOX6 (HR=1.78 [95% CI: 1.08 – 2.93], p value = 0.024). OS was noted by the authors to have a potential bias because of imbalances in subsequent treatments (23% received subsequent therapies) and disease characteristics within the younger patient subgroup

### Relevance to 5-FU dose comparisons

In contrast to the results presented by Oettle et al. for CONKO-003, overall survival was better in the cohort without oxaliplatin in this study in second-line disease, and is much longer than previously published results with this treatment.

### **7.A.3 Takada1994**

#### **Authors and Title**

Takada et al. Comparison of 5-Fluorouracil, Doxorubicin and Mitomycin C with 5-Fluorouracil Alone in Treatment of Pancreatic-Biliary Carcinomas. *Oncology* 51:396-400, 1994.

#### **Purpose**

To compare the safety and efficacy of a modified FAM regimen (5-FU, doxorubicin, and mitomycin C [MMC]) to 5-FU alone in the treatment of patients with nonresectable carcinomas of the pancreas or biliary tract.

#### **Patients and Methods**

Seventy-one patients with previously treated nonresectable cancers of the pancreas or biliary tract were randomized to two chemotherapy regimens: Arm A (n=35), 5-FU, doxorubicin, and MMC or Arm B (n=36), 5-FU alone. Arm A consisted of MMC 6 mg/m<sup>2</sup> administered intravenously on day 1; 5-FU 310 mg/m<sup>2</sup>/day IV was administered by bolus injections for 5 days in week 1 and week 3; ADR 12 mg/m<sup>2</sup>/day IV was administered in week 2. Each drug administration was repeated every 6 weeks. Arm B consisted of 5-FU alone, administered in the same manner as Arm A.

#### **Results**

PR was achieved in 1 patient (4%) in Arm A. No change and PD were observed in 10 (40%) and 14 (56%) in Arm A, and 12 (46%) and 14 (54%) in Arm B, respectively. Median time to PD was 3.1 months (95% CI: 6.9-3.3 months) in Arm A and 2.5 months (95% CI: 4.9-2.5 months) in Arm B, with no significant differences between the two arms (log rank test, p=0.18). Median overall survival was 6.2 months (CI: 10.8-6.6 months) in Arm A and 6.0 months (CI: 10.1-5.8 months) in Arm B, with no significant differences between the two (log rank, p=0.67). One year survival rate was 14.3% (CI: 4.8-30.3%) in Arm A, and 25% (CI: 12.2-42.2%) in Arm B, no p value or CI reported.

#### **Relevance to 5-FU dose comparisons**

As the two arms of this study had the same 5-FU regimen (bolus injection for d1-5 of week one and three, repeated every six weeks), no conclusions can be drawn about the impact of different 5-FU dose and schedule on patients with previously treated nonresectable pancreatic cancer. Time to progression and overall survival were similar to what has been seen in other studies of pancreatic cancer.

#### **7.A.4 DeCaprio1991**

##### **Authors and Title**

DeCaprio et al. Fluorouracil and High-Dose Leucovorin in Previously Untreated Patients With Advanced Adenocarcinoma of the Pancreas: Results of a Phase II Trial. *J Clin Oncol* 1991; 9:2128-2133.

##### **Purpose**

To evaluate the safety and efficacy of 5-FU and leucovorin in previously untreated patients with histologically proven locally un-resectable or metastatic adenocarcinoma of the pancreas and measurable lesions.

##### **Patients and Methods**

Forty-two previously untreated patients with advanced, measurable adenocarcinoma of the pancreas were treated with weekly IV fluorouracil (5-FU; 600 mg/m<sup>2</sup> IV bolus) and leucovorin 500 mg/m<sup>2</sup> IV for 6 weeks followed by a 2-week rest. The median total dose of 5-FU delivered was 6,400 mg/m<sup>2</sup> (range, 600 to 38,500 mg/m<sup>2</sup>). A median of 11 (range, one to 76) doses was given. A median of two courses was given (range, 0.2 to 13). The main end points were response as measured by shrinkage of the primary and metastatic tumor and survival.

##### **Results**

There were three partial responses (three of 42 [7%]; 95% CI, 1 % to 19%) and no complete responses. Median survival was 6.2 months (range, 0.2 to 33 months), with seven patients surviving longer than 12 months. No HRs were reported.

##### **Relevance to 5-FU dose comparisons**

Patients with untreated advanced pancreatic adenocarcinoma were treated with weekly IV fluorouracil (5 FU; 600 mg/m<sup>2</sup> IV) and leucovorin 500 mg/m<sup>2</sup> IV for 6 weeks followed by a 2-week rest. Survival and response rates are similar to what has been seen with other 5-FU regimens used prior to 1991.

### **7.A.5 Figer2000**

#### **Authors and Title**

Figer et al. A Comparison of Two Dose Regimens in Pancreatic Cancer. *J Chemother.* 2000; 12(5):442-445.

#### **Purpose**

To evaluate the safety and efficacy of 5-FU and leucovorin (LCV), comparing standard and dose intense schedules in patients with histologically proven pancreatic cancer

#### **Patients and Methods**

Forty-seven consecutive patients on two hospital campuses with histologically proven pancreatic cancer were treated with a standard or dose intense 5-FU regimen, based on their treatment center. The dose intense schedule was a regimen of 5-FU 900 mg/m<sup>2</sup> IV preceded by LCV 200 mg/m<sup>2</sup>, both as rapid IV infusion every 2 weeks. The standard regimen schedule was: LCV 20 mg/m<sup>2</sup> followed by 5-FU 370 mg/m<sup>2</sup> IV bolus for 5 consecutive days every 28 days. The median duration of treatment was 4.3 months (5.1 for the dose intense and 3.6 for the standard schedule).

#### **Results**

Partial response was observed in one standard dose regimen patient (4%). No change was observed in 4 (40%) standard dose regimen patients and 8 (53%) intense schedule regimen patients (total 12 patients [48%]). Progression of disease was observed in 5 (50%) standard dose regimen patients and 7 (47%) intense schedule regimen patients (total 12 patients [48%]). Clinical benefit, measured by symptomatic improvement, was observed in 3 (12%) standard dose regimen patients and 6 (27%) intense schedule regimen patients (total 9 patients [19%]). Median survival was 8 months for all the patients (5 months for standard dose regimen and 9 months for intense dose regimen). The 1 year survival rate was 32% (dose groups not reported). No p values, CIs, or HRs were reported. There was no survival benefit for the dose intense regimen.

#### **Relevance to 5-FU dose comparisons**

When comparing a dose intense 5-FU administration regimen to the standard 5-FU administration regimen in pancreatic cancer patients, it was determined that the study regimens give similar outcome results, with some improvement in quality of life for a small percentage of patients. Authors conclude that “the dose-intense schedule is of little benefit in treating pancreatic cancer”

### **7.A.6 Choi2000**

#### **Authors and Title**

Choi et al. Effects of 5-Fluorouracil and Leucovorin in the Treatment of Pancreatic-Biliary Tract Adenocarcinomas. *Am J Clin Oncol* 23(4): 425-428, 2000.

#### **Purpose**

To study the efficacy of 5-Fluorouracil (5-FU), modulated with leucovorin, in patients affected by advanced pancreatic and biliary tract cancer

#### **Patients and Methods**

Fifty-one patients with advanced adenocarcinoma of the pancreas (23 stage IV pancreatic cancer patients) or biliary tract (9 stage IV gallbladder cancer patients and 19 cholangiocarcinoma patients), previously untreated with chemotherapy, received chemotherapy consisting of leucovorin 25 mg/m<sup>2</sup>/day by 2-hour intravenous infusion, followed by 5-FU 375 mg/m<sup>2</sup>/day by bolus intravenous infusion, from day 1 to 5. The treatment was repeated every 4 weeks. Chemotherapy was continued until progression of disease or unacceptable toxicity ensued. Efficacy endpoints included: complete response (CR), partial response (PR), stable disease, and progressive disease.

#### **Results**

Of the 23 pancreatic adenocarcinoma patients, one patient showed CR with a survival duration of 13 months (response duration was 9 months). Three pancreatic adenocarcinoma patients had PRs with survival times of 6, 12, and 15 months. The overall response rate was 17.4% (95% CI, 7.2%-36.2%). The median time of overall survival was 6 months (95% CI not reported, range: 1-15 months). Of the 28 biliary tract cancer patients, CRs were observed in 2 patients (7.1%). Seven patients had PRs. The overall response rate was 32.1% (95% CI, 20.3%-57.5%). HRs were not reported.

#### **Relevance to 5-FU dose comparisons**

5-FU was dosed on a schedule of 375 mg/m<sup>2</sup>/day on day 1 to 5 every four weeks in combination with leucovorin in previously untreated patients with adenocarcinomas of the pancreas or biliary tract, resulted in a median survival of 6 months. Results in this small trial showed a slightly better response rate than the historical results for 5-FU monochemotherapy (15% in Mayo Clinic experience), but these response rates and overall survival are not superior to those using 5-FU monochemotherapy historical controls at that time.

### **7.A.7 Cullinan1990**

#### **Authors and Title**

Cullinan et al. A Phase III Trial on the Therapy of Advanced Pancreatic Carcinoma, Evaluations of the Mallinson Regimen and Combined 5-Fluorouracil, Doxorubicin, and Cisplatin. *Cancer*. 1990 May 15;65(10):2207-12.

#### **Purpose**

To compare the safety and efficacy of the following three chemotherapeutic regimens in the treatment of advanced pancreatic carcinoma: 5-fluorouracil (5-FU) versus Mallinson Regimen versus Combined 5-Fluorouracil, Doxorubicin, and Cisplatin (FAP)

#### **Patients and Methods**

One hundred eighty-four patients with previously untreated, histologically proven advanced pancreatic adenocarcinoma were randomly assigned to therapy with 5-fluorouracil alone (5-FU; n=64), to the Mallinson regimen (combined and sequential 5-FU, cyclophosphamide, methotrexate, vincristine, and mitomycin C; n=61), or to combined 5-FU, doxorubicin, and cisplatin (FAP; n=59). Patients with both measurable and nonmeasurable disease were included. The primary study end point was survival. 5-FU alone: 5-FU was given in undiluted form by rapid intravenous injection at a dosage of 500 mg/m<sup>2</sup>/d for 5 consecutive days. Courses were repeated every 5 weeks. Mallinson regimen: As an induction therapy 5-FU was given by rapid intravenous injection at a dosage of 270 mg/m<sup>2</sup>/d for 5 consecutive days. Cyclophosphamide was administered by rapid intravenous injection at a dose of 160 mg/m<sup>2</sup> on days 1 and 5, methotrexate was given by rapid intravenous injection at 11 mg/m<sup>2</sup> on days 1 and 4, and vincristine was given by rapid intravenous injection at 0.7 mg/m<sup>2</sup> on days 2 and 5. For maintenance therapy the patient was initiated on 5-FU (350 mg/m<sup>2</sup>) and mitomycin C (3.5 mg/m<sup>2</sup>) at 5 weeks, both given by rapid intravenous injection daily for 5 consecutive days and repeated every 6 weeks. FAP: 5-FU was given in undiluted form by rapid intravenous injection at a dosage of 300 mg/m<sup>2</sup>/d for 5 consecutive days. Doxorubicin was given by rapid intravenous injection on day 1 at a dose of 40 mg/m<sup>2</sup>. In jaundiced patients (total serum bilirubin level < 2 mg) the dose was reduced by 30%. The maximum total dose allowed was 500 mg/m<sup>2</sup>. Cisplatin was administered by 2-hour to 3-hour intravenous infusion in 1000 ml of 5% dextrose and 0.5 normal saline together with 25 g of mannitol. It was given at a dose of 60 mg/m<sup>2</sup> on the first day of each course of therapy and infusion was initiated immediately after administration of 5-FU and doxorubicin. Courses of this three-drug combination were repeated every 5 weeks.

#### **Results**

Only 41 patients had measurable disease, objective tumor responses were seen for one patient (7%) treated with 5-FU alone, three patients (21%) for the Mallinson regimen, and two patients (15%) treated with FAP. One hundred sixty-eight of the 184 evaluable patients were dead at the time of the report. The median interval to progression for each of the three regimens was 2.5 months. Survival curves intertwined with similar median survival times for patients treated with FAP and 5-FU (3.5 months) and those who received the Mallinson regimen (4.5 months). Neither combination regimen offers a survival advantage over 5-FU alone (both one-sided, P > 0.48, CI not reported).

#### **Relevance to 5-FU dose comparisons**

The dose and schedule of 5-FU treatment varied by regimen in this trial. Increased toxicity was seen in regimens using a combination of agents, without a benefit in overall survival.

### **7.A.8 Kovach1974**

#### **Authors and Title**

Kovach et al. A Controlled Study of Combined 1,3-BIS-(2-Chloroethyl)-1-nitrosourea and 5 fluorouracil Therapy for Advanced Gastric and Pancreatic Cancer. *Cancer* 33: 563-567, 1974.

#### **Purpose**

Treatment with the combination of 1, 3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) and 5-FU was compared to therapy with each drug used alone in a prospective randomized study of 167 patients with advanced adenocarcinoma of the stomach and pancreas.

#### **Patients and Methods**

A total of 167 patients with histologically proven unresectable adenocarcinoma of the stomach or pancreas were randomized to treatment with 5-FU, or BCNU, or a combination of BCNU and 5 FU according to the primary site of origin of the adenocarcinoma, the grade of anaplasia, and the site of the primary indicator lesion. All drugs were given intravenously by rapid injection according to the following schedules: 5-FU alone, 13.5 mg/kg/day x 5 days (n=59); BCNU alone, 50 mg/m<sup>2</sup>/day x 5 days (n=44); and 5-FU plus BCNU, 10 mg/kg/day x 5 days and 40 mg/m<sup>2</sup>/day x 5 days (n=64), respectively.

#### **Results**

Therapy with the combination of 5-FU and BCNU was associated with the highest rate of objective response, 41.3% in carcinoma of the stomach and 33.3% in carcinoma of the pancreas. Although these percentages are more favorable than those observed with 5-FU alone, the differences are not significant (gastric carcinoma,  $p \approx 0.3$ ; pancreatic carcinoma  $p \approx 0.15$ ). Therapy with the combination, 5-FU and BCNU, and with 5-FU alone was more effective ( $p < 0.05$ ) than BCNU alone in producing objective responses in both pancreatic and gastric adenocarcinoma. The corresponding rates of objective response with 5-FU alone were 28.6% and 16.1%, and with BCNU alone the rates were 17.4% and 0%. In pancreatic carcinoma, there was no discernible difference in survival among patients in each treatment arm. In gastric carcinoma, however, both 5-FU and the combination therapy produced an increase in survival when compared to BCNU alone, and the combination of 5-FU and BCNU produced an increase in long-term survival compared to 5-FU alone (5-FU, 7% surviving; 5-FU + BCNU, 26.5% surviving;  $p < .05$ ). CIs were not reported.

#### **Relevance to 5-FU dose comparisons**

In both pancreatic carcinoma and gastric carcinoma patients, the 30% difference in dose intensity of 5-FU, 13.5 mg/kg/day vs 10 mg/kg/day, did not significantly affect the efficacy measurements.

### **7.A.9 Burris1997**

#### **Authors and Title**

Burris et al. Improvements in Survival and Clinical Benefit With Gemcitabine as First Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial. *J Clin Oncol* 15:2403-2413, 1997.

#### **Purpose**

To compare the efficacy of gemcitabine in patients with newly diagnosed advanced pancreas cancer

#### **Patients and Methods**

One hundred twenty-six patients with previously untreated advanced symptomatic pancreas cancer were randomized to receive either gemcitabine (n= 63), or to single agent 5 FU (n= 63). Gemcitabine was given at 1,000 mg/m<sup>2</sup> weekly x 7 followed by 1 week of rest, then weekly x 3 every 4 weeks thereafter, and 5 FU given at 600 mg/m<sup>2</sup>, once weekly, by IV over 30 minutes, with a cycle defined as one 4-week period. Treatment with gemcitabine or 5-FU continued until disease progression or until there was significant clinical deterioration because of tumor-related symptoms.

#### **Results**

There was a clinical benefit response experienced by 23.8% of gemcitabine-treated patients versus 4.8% of 5-FU-treated patients (p = .0022). The median survival durations were 5.65 months (95% CI not reported) and 4.41 (95% CI not reported) months for gemcitabine-treated and 5-FU-treated patients, respectively (p = 0.0025, no CI reported). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients. The 5-week extension translates into a 28% relative improvement in median survival. In addition, the 6-, 9-, and 12-month survival rates were higher with gemcitabine (46%, 24%, and 18%, respectively) than with 5-FU (31 %, 6%, and 2%, respectively). Despite a modest tumor response rate of only 5.4% in the gemcitabine arm and 0% in the 5-FU arm, there was a statistically significant improvement in survival for patients who received gemcitabine. Other measures of efficacy included response rate, time to progressive disease, and survival. Only three (4.8%) 5-FU patients experienced clinical benefit (sustained [ $\geq$  4 weeks] improvement in at least one parameter without worsening in any others), as assessed by their primary measures (pain and Karnofsky performance status). The median time to achieve a clinical benefit response was 7 weeks for the gemcitabine-treated patients (n=15) and 3 weeks for the 5-FU-treated patients (n = 3). The mean duration of clinical benefit was 18 weeks and 13 weeks for gemcitabine-treated and 5-FU-treated patients. The median time to progressive disease for gemcitabine was 9 weeks compared with 4 weeks for the 5-FU arm (log-rank test, p = .0002, CI not reported). Among fifty seven 5-FU -treated patients with measurable disease, none (0%) achieved a complete or partial response. Eleven patients (19%) had stable disease. The difference in partial response rates was not statistically significant. HRs were not reported.

#### **Relevance to the comparison of 5-FU doses**

The high initial response rates reported for several multi-agent regimens, such as the Mallinson regimen (5-FU, methotrexate, vincristine, and cyclophosphamide induction followed by maintenance 5-FU and mitomycin), the 5-FU, doxorubicin, and mitomycin (FAM) regimen, the cisplatin, cytarabine, and caffeine (CAC) regimen, and the streptozotocin, mitomycin, and 5-FU (SMF) regimen appeared to herald advances in the treatment of patients with advanced pancreas cancer. When the present study was designed, single-agent 5-FU was selected as the control treatment, as it had been the previous standard and the dose would be approximately equitoxic to the dose of gemcitabine. The weekly schedule of 5-FU was selected to allow the trial to be conducted on a single-blind basis. The survival duration with this 5-FU regimen in this setting, previously untreated advanced pancreatic cancer, was consistent with previously reported data.

### **7.A.10 Cullinan1985**

#### **Authors and Title**

Cullinan et al. A Comparison of Three Chemotherapeutic Regimens in the Treatment of Advanced Pancreatic and Gastric Carcinoma: Fluorouracil vs Fluorouracil and Doxorubicin vs Fluorouracil, Doxorubicin, and Mitomycin. JAMA. 1985 Apr 12;253(14):2061-7.

#### **Purpose**

At the time of this study, conflicting literature existed as to the benefit of adding other chemotherapeutic agents to single agent 5-FU. This study was designed to compare the safety and efficacy of the following three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma: fluorouracil versus fluorouracil and doxorubicin (FA) versus fluorouracil, doxorubicin, and mitomycin (FAM).

#### **Patients and Methods**

Two hundred ninety-five patients with previously untreated un-resectable or metastatic gastric or pancreatic adenocarcinoma were stratified according to primary tumor (gastric or pancreatic), stage of disease (regionally un-resectable or distant metastasis), the presence of measurable disease, and performance status (Eastern Cooperative Oncology Group [ECOG] performance score). Patients were randomized to treatment with fluorouracil alone (n=101), FA (n=93), or FAM (n=101). The fluorouracil alone regimen was given by a five-day intensive course at a daily dose of 500 mg/m<sup>2</sup>. Courses were repeated at four weeks, eight weeks, and every five weeks thereafter. The FA combination was administered with fluorouracil given by a four-day course at a daily dose of 400 mg/m<sup>2</sup> and with 40 mg/m<sup>2</sup> of doxorubicin given on the first day of each course. Courses were repeated at four weeks, eight weeks, and every five weeks thereafter. The FAM combination was administered with fluorouracil given at 600 mg/ m<sup>2</sup> on days 1, 8, 29, and 36; doxorubicin at 30 mg/ m<sup>2</sup> on days 1 and 29; and mitomycin at 10 mg/ m<sup>2</sup> on day 1. All drugs were given by rapid intravenous injection. The primary end point of the study was survival. Other endpoints included disease progression, objective response rates, and palliative effects (improved performance, body weight, or symptoms).

#### **Results**

The median survival time for patients with pancreatic cancer was 22 weeks, and for patients with gastric carcinoma it was 29 weeks. There was no difference in survival between the three different regimens tested. The median interval to progression for all patients with pancreatic carcinoma was nine weeks, and for all with gastric carcinoma, 17 weeks. As with survival times, the distribution of progression times between the three treatment arms within each tumor type completely overlapped.

#### **Relevance to 5-FU dose comparisons:**

Because the FAM combination was becoming an increasingly employed therapy for gastric and pancreatic carcinoma, it was important that the therapeutic claims for this regimen be evaluated by randomized controlled comparison with the previously accepted standard, fluorouracil used alone. The two-drug combination of fluorouracil plus doxorubicin (FA) was evaluated because of a very small but randomized trial indicating a possible therapeutic advantage in gastric cancer for this regimen over fluorouracil as a single drug. The dosing regimens for 5-FU varied between the different arms to conform with concomitant medications and prior studies. In the 5 FU alone arm dosing was 5 days of 500 mg/m<sup>2</sup>, in the FA arm it was given as 4 days of 400 mg/m<sup>2</sup>, and in the FAM arm the dose was 600 mg/m<sup>2</sup> on days 1, 8, 29 and 36 of an 8-week cycle. While there were different combination medications, no differences in efficacy outcomes were apparent, and survivals were consistent with other reported outcomes for patients with previously untreated unresectable or metastatic pancreatic cancer with bolus 5-FU treatment.

### **7.A.11 Ducreux2002**

#### **Authors and Title**

Ducreux 2002. A randomized trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma. *Ann Oncol* (2002) 13 (8): 1185-1191.

#### **Purpose**

To compare the safety and efficacy of 5-FU versus 5-fluorouracil (5-FU) plus cisplatin (FUP) in pancreatic adenocarcinoma patients

#### **Patients and Methods**

Two hundred seven patients with untreated cytologically or histologically proven metastatic or locally advanced adenocarcinoma of the pancreas were randomized to one of two chemotherapy regimens. The two chemotherapy regimens consisted of a control FU arm (5 FU 500 mg/m<sup>2</sup>/day administered by rapid infusion for 5 days) (n=103) and the investigational FUP arm (continuous infusion 5-FU 1000 mg/m<sup>2</sup>/day for 5 days plus cisplatin 100 mg/m<sup>2</sup> on day 1 or day 2) (n=104). In both arms, chemotherapy was repeated at day 29. Among the 202 patients who received chemotherapy, the median total dose of 5-FU received was 5 g/m<sup>2</sup> in the FU arm and 10 g/m<sup>2</sup> in the FUP arm.

#### **Results**

The tumor response rate was 0% with FU and 10% with FUP (95% CI, 4-16%). Median survival was 102 days in the FU arm and 112 days in the FUP arm, and there was no difference in the relative risk of death between treatment arms (log-rank test 0.10). However, the percentage of survivors at 1 year was 17.3% in the FUP arm compared with 8.7% in the FU arm (p = 0.07, no CI reported). The median duration of progression free-survival was 59 days with FU and 73 days with FUP. At 6 months, 4% of patients in the FU arm and 19% in the FUP arm were free from progression. At 1 year, seven patients in the FUP arm were free from progression compared with none in the FU arm (p = 0.0001, log rank test, CI not reported). Survival was compared after adjusting for absence of metastases, ampulloma, the number of target lesions and eligibility, and the FUP regimen was not found to be superior to the FU regimen in terms of survival (p = 0.08, CI not reported). No HR was reported.

#### **Relevance to 5-FU dose comparisons**

Median survival was 102 days in the FU arm and 112 days in the FUP arm, within the range for bolus 5-FU treatment for untreated pancreatic cancer.

### **7.A.12 Van Rijswijk2004**

#### **Authors and Title**

Van Rijswijk et al. Weekly high-dose 5-fluorouracil and folinic acid in metastatic pancreatic carcinoma: a phase II study of the EORTC GastroIntestinal Tract Cancer Cooperative Group. *Eur J Cancer* 40: 2077–2081, 2004.

#### **Purpose**

The aim of the study was to assess the response rate and toxicity of high-dose 24 h infusion of 5 FU in metastatic adenocarcinoma of the pancreas.

#### **Patients and Methods**

Patients with measurable disease, performance status 0–2, and no prior chemotherapy were registered to receive cycles of leucovorin (LV) 500 mg/m<sup>2</sup> (or 1-LV 250 mg/m<sup>2</sup>) over 1 h followed by 5-FU 2600 mg/m<sup>2</sup> as a 24 h infusion, weekly for 6 weeks, followed by a 2-week rest.

#### **Results**

The number of enrolled was 37. Three patients (9%, 95% CI: 2-24) out of 33 patients with reportable activity outcome achieved a partial response, and another 7 (21%, CI not reported) patients had stable disease. The median time to progression was 7 weeks (95% CI: 6.4 11.7), and the median survival 19 weeks (95% CI: 12-35.2).

#### **Relevance to 5-FU dose comparisons**

The improved response rate of protracted infusion that exists in colorectal cancer is not evident in pancreatic cancer. This trial showed a low response rate of 9%, which was below the present level of interest (20%) of this schedule, and no clear prolongation of overall survival based on historical controls.

## B. PUBLICATIONS IN COLORECTAL CANCER

### 7.B.1 Andre2007

#### Authors and Title

Andre, et al. Phase III Study Comparing a Semimonthly With a Monthly Regimen of Fluorouracil and Leucovorin As Adjuvant Treatment for Stage II and III Colon Cancer Patients: Final Results of GERCOR C96.1. *J Clin Oncol* 25:3732-3738, 2007.

#### Purpose

To compare the efficacy and safety of a semimonthly regimen of fluorouracil and leucovorin (the LV5FU2 group) *versus* a monthly regimen of fluorouracil and leucovorin (the mFU/LV group) as adjuvant treatment of stage II and III colon cancer

#### Patients and Methods

Patients with stage II or III colon or high rectum cancer were randomly assigned to two adjuvant chemotherapy regimens (LV5FU2 or mFU/LV) and two treatment durations (24 or 36 weeks) using a 2x2 factorial design. Patients assigned to the LV5FU2 group received racemate (*dl*-)LV 200 mg/m<sup>2</sup> or levogyre (*l*-)LV 100 mg/m<sup>2</sup> (according to drug availability in each institution), as a 2-hour infusion, followed by bolus fluorouracil 400 mg/m<sup>2</sup> and a 22-hour infusion of fluorouracil 600 mg/m<sup>2</sup> for 2 consecutive days every 14 days. Patients in the mFU/LV group received an infusion of *dl*-LV 200 mg/m<sup>2</sup> (or *l*-LV 100 mg/m<sup>2</sup>) for 15 minutes, followed by a 15-minute bolus fluorouracil 400 mg/m<sup>2</sup> for 5 consecutive days every 28 days.

#### Results

A total of 905 patients with stage II (43%) and III (57%) colon cancer were enrolled. The median follow-up was 6 years. No statistically significant difference was observed between LV5FU2 (n=452) and mFU/LV (n=453) in terms of overall survival (OS; HR= 1.02; 95% CI= 0.77-1.34; *P* =.91) or Disease-Free Survival (DFS, hazard ratio [HR], 1.01; 95% CI, 0.81-1.27; *P* =.74). The median time to OS was not reached. The 6-year OS were 78% and 76% for mFU/LV and LV5FU2, respectively).

	LV5FU2	mFU/LV
<b>5FU dose intensity (mg/m2/week)</b>	800	500
<b>N</b>	452	453
<b>Median OS (months)</b>	Not reached	Not reached
<b>OS Hazard Ratio</b>	Reference	1.02 (95%CI: 0.77-1.34 <i>P</i> =.91)
<b>OS rate 6 year</b>	76%	78%
<b>DFS Hazard Ratio</b>	Reference	1.01 (95% CI: 0.81-1.27; <i>P</i> = .74).
<b>Response Rate (%)</b>	Not reported	Not reported

#### Relevance to the comparison of 5FU doses

This study demonstrates that a difference in 5-FU dose intensities of 500 and 800 mg/m<sup>2</sup>/week (mFU/LV and LV5FU2, respectively) and infusion durations of 15 min and 22 h in adjuvant therapy for patients with Stage 2 and 3 colon cancer did not have an impact to the OS and DFS.

## 7.B.2 Goldberg2004

### Authors and Title

Goldberg, et al. A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer.

### Purpose

To compare the activity and toxicity of two-drug combinations out of three drugs (fluorouracil, irinotecan, and oxaliplatin) in patients with metastatic colorectal cancer who had not been treated previously for advanced disease.

### Methods

Patients were concurrently randomly assigned to receive irinotecan and bolus fluorouracil plus leucovorin (IFL, control combination), oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX), or irinotecan and oxaliplatin (IROX). The primary end point was time to progression, with secondary end points of response rate, survival time, and toxicity. The regimens (doses in mg/m<sup>2</sup>) were as follows: IFL was irinotecan 125 and bolus FU 500 plus LV 20 on days 1, 8, 15, and 22 every 6 weeks; FOLFOX was oxaliplatin 85 on day 1 and bolus FU 400 plus LV 200 followed by FU 600 in 22-hour infusions on days 1 and 2 every 2 weeks; and IROX was oxaliplatin 85 and irinotecan 200 every 3 weeks.

### Results

A total of 795 patients were randomly assigned between May 1999 and April 2001. Median follow-up time is 20.4 months. A median time to progression of 8.7 months, response rate of 45%, and median survival time of 19.5 months were observed for FOLFOX. These results were significantly superior to those observed for IFL for all end points (6.9 months, 31%, and 15.0 months, respectively) or for IROX (6.5 months, 35%, and 17.4 months, respectively) for time to progression and response.

	<b>IFL</b>	<b>FOLFOX</b>	<b>IROX</b>
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	333	800	-
<b>N</b>	264	267	264
<b>Median OS (months)</b>	15.0	19.5	17.4
<b>OS Hazard Ratio (compared to IFL)</b>	Reference	0.66 (95%CI 0.54-0.82; P=.0001)	0.81 (95%CI 0.66-1.00; P=.04)
<b>Median TTP (months)</b>	6.9	8.7	6.5
<b>TTP Hazard Ratio (compared to IFL)</b>	Reference	0.74 (95% CI, 0.61 to 0.89; P=0.0014)	1.02 (95% CI 0.85-1.23; P > .50)
<b>Response Rate (%)</b>	31%	45% (P=.002)	35% (P=.03)

### Relevance to the comparison of 5FU doses

This study provides an example of a pivotal trial containing two different 5FU dose intensities (333 and 800 mg/m<sup>2</sup>/week for IFL and FOLFOX, respectively) in patients with untreated metastatic colorectal cancer. While the authors acknowledged that the study does not allow isolation of the relative independent contributions of oxaliplatin versus irinotecan and infused versus bolus FU, the authors recommended the use of FOLFOX a first-line standard of care for patients with advanced colorectal cancer, because the superiority the FOLFOX arm is most likely attribute-able to oxaliplatin (vs. irinotecan) rather than to the difference in the 5-FU dose regimen.

### 7.B.3 Hansen 1996

#### Authors and Title

Hansen, et al. Phase III Study of Bolus Versus Infusion Fluorouracil With or Without Cisplatin in Advanced Colorectal Cancer

#### Purpose

This phase 3 study in adults with metastatic colorectal cancer was planned as a comparison of objective response rates, toxicity, and survival in patients receiving bolus versus protracted-infusion 5-FU with or without cisplatin.

#### Methods

Previously untreated patients with advanced, measurable metastatic colorectal cancer were randomly assigned to receive one of 4 treatment arms:

- A (bolus 5-FU at 500 mg/m<sup>2</sup> for 5 days followed in 2 weeks by weekly bolus 5-FU at 600 mg/m<sup>2</sup>);
- B (bolus 5-FU at 500 mg/m<sup>2</sup> for 5 days followed in 2 weeks by weekly bolus 5-FU at 600 mg/m<sup>2</sup>, plus weekly cisplatin at 20 mg/m<sup>2</sup>);
- C (5-FU at 300 mg/m<sup>2</sup> per day by continuous infusion), or
- D (5-FU at 300 mg/m<sup>2</sup> per day by continuous infusion plus weekly cisplatin at 20 mg/m<sup>2</sup>).

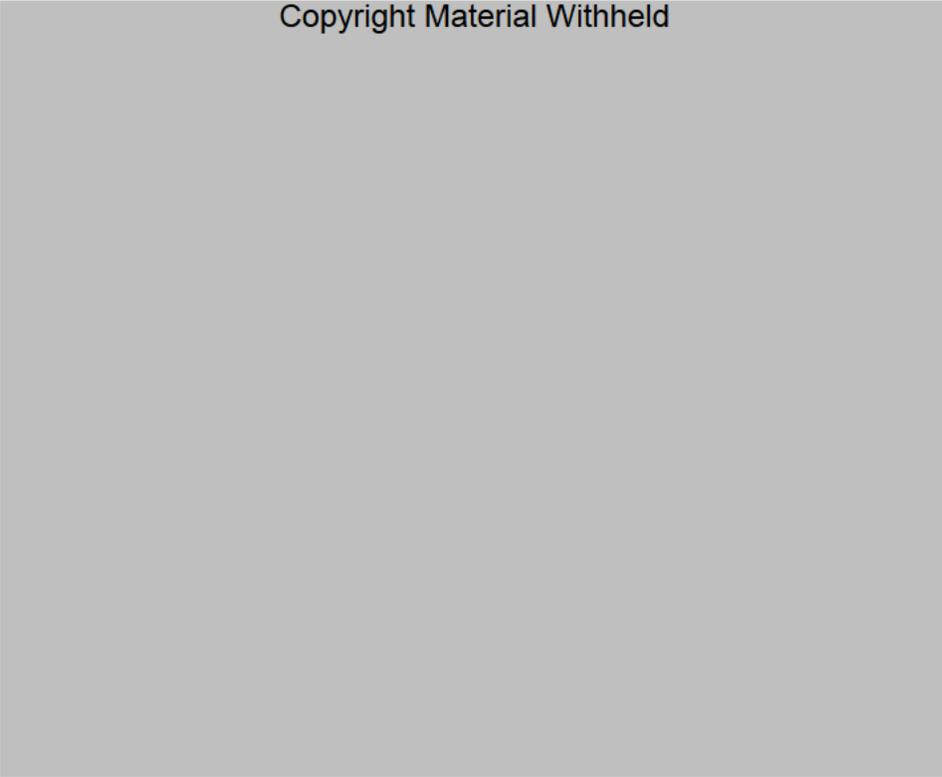
#### Results

A total of 497 (477 eligible) patients were assigned to A, B, C, or D. Because of excessive toxicity, treatment B was discontinued after only 12 patients had begun treatment. The median survival time was 10.4, 13.0, and 13.0 months for patients in A (bolus 5-FU), C (continuous-infusion 5-FU alone), and D (cisplatin added to continuous-infusion 5-FU); these differences were not statistically significant. Median time to disease progression was 5.1, 6.2, and 6.5 months for A, C, and D, respectively; these differences achieved statistical significance. Objective tumor response was observed in 28 (18%) of 153 patients receiving treatment A, in 45 (28%) of 159 patients receiving treatment C (C versus A; P = .045), and in 47 (31%) of 153 patients receiving treatment D (D versus A; P = .016).

	<b>A (bolus 5FU)</b>	<b>B (bolus 5FU+DDP)</b>	<b>C (CI 5FU)</b>	<b>D (CI5FU+DDP)</b>
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	600	600	2100	2100
<b>N</b>	153	12	159	154
<b>Median OS (months)</b>	10.4		13.0	13.0
<b>OS Hazard Ratio</b>	Reference		Not Reported P=.223	Not Reported P=.586
<b>OS rate 5 y</b>	Not reported			
<b>Median TTP (months)</b>	5.1		6.2 (C vs A, P=.007)	6.5 (D vs A, P=.017)
<b>TTP Hazard Ratio</b>	Not reported			
<b>Response Rate (%)</b>	18%		28% (C vs A, P=.045)	31% (D vs A, P=.016)

5FU= fluorouracil, DDP= cisplatin, CI= continuous infusion

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**Fig. 2. Overall survival: all patients with follow-up. FU = fluorouracil; DDP = cisplatin.**

**Relevance to the comparison of 5FU doses**

This study provides evidence that a difference in 5FU dose of 600 mg/m<sup>2</sup>/week bolus and 2100 mg/m<sup>2</sup>/week continuous infusion did not have a statistically significant impact to OS, with and without the addition of cisplatin, in patients with chemotherapy-naïve metastatic colorectal cancer. Higher 5FU dose intensity resulted in longer time to disease progression and higher response rate.

### 7.B.4 Kohne2013

#### Authors and Title

Kohne, et al. A randomised phase III intergroup trial comparing high-dose infusional 5-fluorouracil with or without folinic acid with standard bolus 5-fluorouracil/folinic acid in the adjuvant treatment of stage III colon cancer: the Pan-European Trial in Adjuvant Colon Cancer 2 study. Eur J Cancer. 2013 May;49(8):1868-75.

#### Purpose

To investigate whether infusional high-dose 5-fluorouracil (HD-FU) provides a significant improvement in recurrence-free survival (RFS) and overall survival (OS) compared with a standard bolus 5-FU regimen (MayoClinic) in patients with curatively resectable stage III colon cancer

#### Patients and Methods

Patients with UICC stage III, histologically confirmed adenocarcinoma or mucinous adenocarcinoma of the colon who had undergone curative radical resection within the 8 weeks prior to randomization were randomised to receive either the bolus 5-FU/FA regimen (Mayo Clinic) or one of the three HD-FU regimens as follows:

- Bolus 5-FU/FA (the Mayo-Clinic regimen): FU 370-425 mg/m<sup>2</sup>/day on day 1-5 every 4 weeks
- HD-FU: (1) the Spanish TTD regimen: HD-FU alone 3500 mg/m<sup>2</sup> [over 48h] q1w; (2) the German AIO regimen: day 1, FA, 500 mg/m<sup>2</sup> i.v. 2-h infusion, followed by 5-FU, 2600 mg/m<sup>2</sup> [over 24-h], given weekly during a 6-week cycle for 3-cycles; (3) the French de Gramont regimen LV5FU2: day 1–2 of a 2-week cycle, DL-FA, 200 mg/m<sup>2</sup> 2-h infusion, followed by 5-FU, 400 mg/m<sup>2</sup> i.v., bolus, followed by 5-FU, 600 mg/m<sup>2</sup> [over 22-h ], for 12-cycles

#### Results

A total of 1601 patients were randomised to receive a bolus 5-FU/FA or a HD- FU regimen. No differences in OS were observed between the two treatment arms (HR=0.96, 95%CI= 0.78-1.20; p = 0.74), with 3-year OS rate of 84.5% and 85.0% in bolus vs HDFU, respectively. A five-year OS rate of 78.9% was observed in both arms. No differences were observed in RFS (HR =0.997, 95%CI=0.84-1.18; p = 0.98); 3-year and 5-year RFS rates were also similar.

	<b>Bolus 5-FU/FA</b>	<b>HD-FU</b>
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	463-531	3500 2600 800
<b>N</b>	804	797
<b>Median OS (months)</b>	Not reached	Not reached
<b>OS Hazard Ratio</b>	Reference	0.96 (95%CI: 0.78-1.20 P=.74)
<b>OS rate 3 year</b>	84.5%	85.0%
<b>OS rate 5 year</b>	78.9%	78.9%
<b>Median RFS (months)</b>	Not reached	
<b>RFS Hazard Ratio</b>	Reference	0.997 (95%CI=0.84 1.18; P = .98)
<b>Response Rate (%)</b>	Not reported	

#### Relevance to the comparison of 5FU doses

This is the largest (1600 patients) and the most recent study that provides strong evidence that a difference in 5FU dose intensity of 463-531 mg/m<sup>2</sup>/week and 800-3500 mg/m<sup>2</sup>/week and in infusion duration of 15 min and 22-48 h did not have an impact on the OS and RFS in patients with stage 3 colon cancer after adjuvant therapy

### 7.B.5 Leichman 2005

#### Author and Title

Leichman, et al., Assessment of Infusional 5-Fluorouracil Schedule and Dose Intensity: A Southwest Oncology Group and Eastern Cooperative Oncology Group Study. *Clinical Colorectal Cancer*, Vol. 5, No. 2, 119-123, 2005.

#### Purpose

To compare low-dose continuous infusion (LDCI) of 5-fluorouracil (5-FU) versus intermittent high-dose infusion (HDI) of 5-FU in disseminated colorectal cancer (CRC) for evidence of survival advantage based on dose intensity

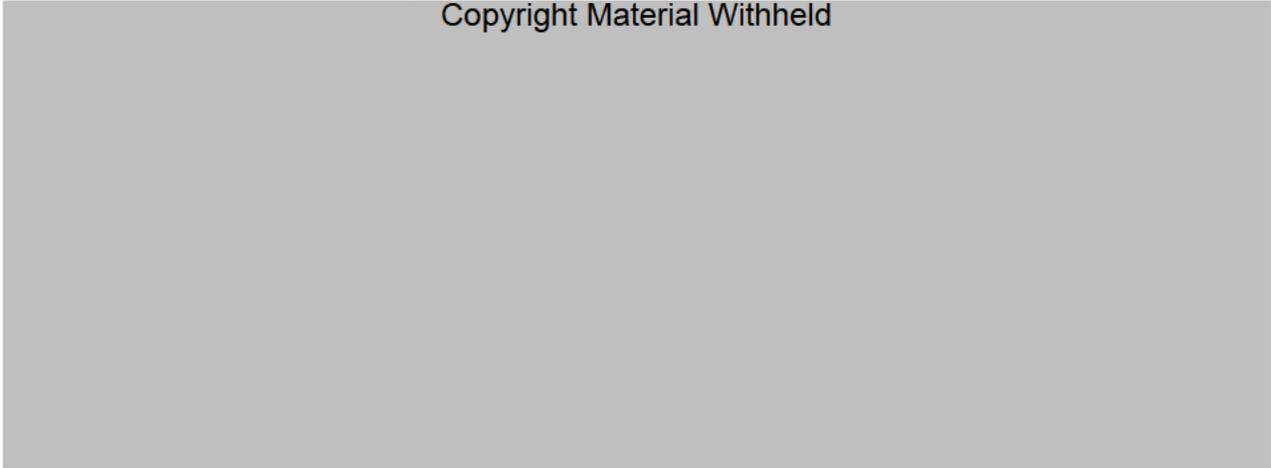
#### Methods

Eligibility included histologic diagnosis of disseminated CRC, measurable or evaluable disease, no previous therapy for metastatic disease, performance status of 0-2, and adequate renal, hepatic, cardiac, and hematologic function. Patients were randomized to receive (1) LDCI 5-FU 300 mg/m<sup>2</sup> per day continuous infusion for 28 days every 5 weeks or (2) HDI 5-FU 2600 mg/m<sup>2</sup> for 24 hours each week.

#### Results

Between April 1995 and May 1999, 730 patients were accrued (LDCI arm, n = 360; HDI arm, n = 370). Of these, 708 eligible patients were assessable for survival and 690 for toxicity. No significant survival difference was seen between the 2 treatment arms (P = 0.70). Hazard ratio was not reported. Median survival for both groups was 13 months. Kaplan Meyer plot was provided, but no OS rates were reported. Median progression-free survival times were 6 months for the LDCI arm and 5 months for the HDI arm; this difference was not statistically significant (P = 0.93).

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Source: Figure 1 of the reference.

#### Relevance to the comparison of 5FU doses

This study demonstrated that a difference in 5FU dose intensity 1680 and 2600 mg/m<sup>2</sup>/week, and infusion duration of 28 d and 1 d, both given as continuous infusion, did not have an impact to OS and PFS in patients with no previous therapy for metastatic colon cancer.

### 7.B.6 Leichman1995

#### Author and Title

Leichman, et al. Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group study. J Clin Oncol. 1995 Jun;13(6):1303-11.

#### Purpose

To assess efficacy and safety of seven fluorinated pyrimidine-based regimens for the treatment of disseminated colorectal cancer afforded by biochemical modulation or schedule variations

#### Methods

Patients with histologically confirmed metastatic colorectal cancer that was either recurrent or disseminated were randomized to one of the 7 arms:

1. 5-FU IVP: 5-FU 500 mg/m<sup>2</sup> administered as an intravenous push (IVP) on days 1 to 5 every 5 weeks
2. 5-FU IVP + low dose LV: LV 20 mg/m<sup>2</sup> IVP followed immediately by 5-FU 425 mg/m<sup>2</sup> IVP on days 1 to 5 every 4 weeks for two cycles, then every 5 weeks for the duration of study treatment.
3. 5-FU IVP + high dose LV: LV 500 mg/m<sup>2</sup> administered as a 3-hour infusion followed by 5-FU 600 mg/m<sup>2</sup> IVP weekly for 6 weeks followed by 2 weeks of rest for each 8-week cycle.
4. 5-FU CI: 5-FU administered as a continuous infusion by ambulatory infusion pump and in dwelling venous access at a dose of 300 mg/m<sup>2</sup>/d on days 1 to 28, followed by 1 week of rest for each 5-week cycle.
5. 5-FU CI + low dose LV: paralleled arm 4 as a continuous intravenous infusion of 5-FU by ambulatory infusion pump at a dose of 200 mg/m<sup>2</sup>/d for 28 days with added weekly injections of LV at 20 mg/m<sup>2</sup> on days 1, 8, 15, and 22 of a 5-week cycle.
6. 24 h 5-FU: 24-hour infusion of 5-FU at a dose of 2600 mg/m<sup>2</sup> administered weekly on a 4-week schedule (ie, no scheduled rest breaks).
7. 24 h 5-FU+ PALA: analogous to arm 6, but with PALA administered at a dose of 250 mg/m<sup>2</sup> given over 15 minutes 24 hours before the infusion of 5-FU at 2,600 mg/m<sup>2</sup> administered as a 24-hour infusion.

#### Results

Colorectal cancer patients (n=620) were randomized into one of 7 treatment arms with different 5-FU dose regimens. The survival data are mature, with a median follow up of 37 months. Survival hazards ratios showed a positive trend in favor of the unmodulated infusion regimen. Slightly longer survival trends were observed with 5-FU continuous infusion (arm 4) and 24-hour infusion (arm 6), while the addition of PALA (arm 7) yielded noticeably shorter survival durations. Progression-free survival curves showed little difference among the seven regimens. The median progression-free survival time was 6 months in arms 1 through 6 and 4 months in arm 7. No regimen achieved a higher response rate than single-agent bolus 5-FU. High-grade toxicities occurred more frequently in the 5-FU bolus arms.

	1) 5FU IVP	2) 5FU IVP + low dose LV	3) 5FU IVP + high dose LV	4) 5FU CI	5) 5FU CI + low dose LV	6) 24h 5FU	7) 24h 5FU+ PALA
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	500	531	450	1680	1120	2600	2600
<b>N</b>	89	85	88	85	84	86	86
<b>Median OS (months)</b>	Not reported explicitly						
<b>OS Hazard Ratio (reference /comparison arm)</b>	reference	1.03 (0.75-1.43)	0.96 (0.69-1.34)	1.17 (0.84-1.63)	1.07 (0.77-1.49)	1.18 (0.84-1.64)	0.75 (0.54-1.04)

<b>OS rate 5 y</b>	Not reported explicitly						
<b>Median PFS (months)</b>	6	6	6	6	6	6	4
<b>TTP Hazard Ratio</b>	Not reported						
<b>Response Rate % (95% confidence intervals)</b>	29 (17-41)	27 (16-39)	21 (11-32)	29 (19-43)	26 (15-39)	15 (7-25)	25 (14-36)

N was obtained from the KM plots (N was not equal to the reported n in Table 1).

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Source: Figure 2 of the reference

**Relevance to the comparison of 5FU doses**

This study provides evidence that differences of 5-FU dose intensities ranging from 450 to 2600 mg/m<sup>2</sup>/week did not have an impact to OS, PFS or response rate.

### 7.B.7 Lokich1989

#### Author and Title

Lokich, et al. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. J Clin Oncol. 1989 Apr;7(4):425-32.

#### Purpose

To compare two schedules of delivery for single-agent fluorouracil (5-FU)

#### Methods

Patients with advanced measurable colorectal cancer not previously treated with chemotherapy were randomized into 2 arms:

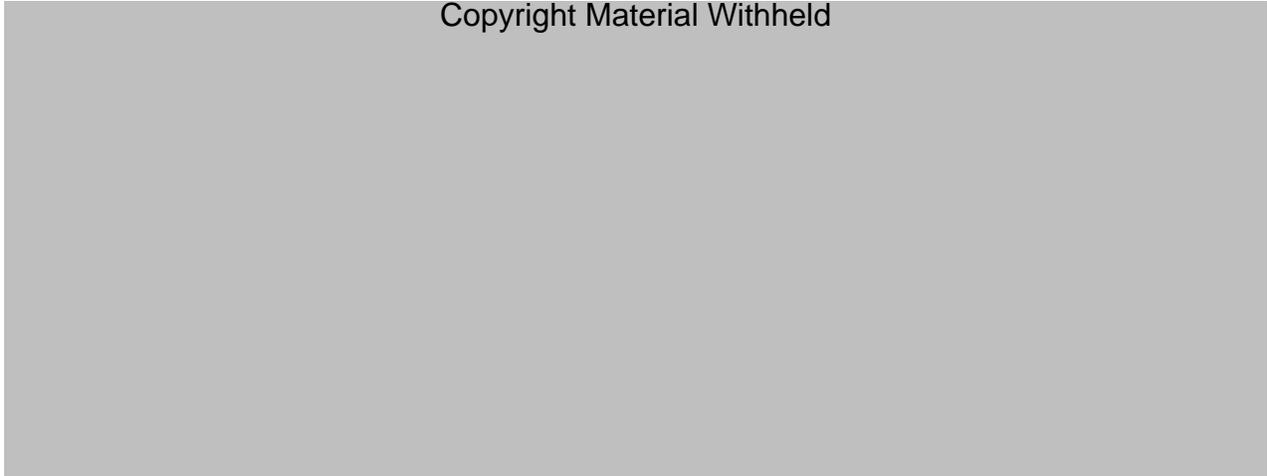
1. Bolus: a daily bolus 5-FU 500 mg/m<sup>2</sup> administered intravenously (IV) for five consecutive days and repeated at 5-week intervals
2. Continuous infusion: 5-FU 300 mg/m<sup>2</sup>/d administered 24 hours a day for a protracted time (10 weeks or more)

#### Results

The number of patients enrolled was 179. Median survival was similar between the infusional 5-FU arm and the bolus 5-FU arm. Overall survival for the two groups was comparable. Patients on the infusional arm had a median survival of 10 months compared with 11 months for the bolus arm, but mean survival on the infusional arm is longer than the bolus arm (13 v 12 months) because of a larger proportion of long-term survivors on the infusion arm. These differences were not significant (P =.379). Using stringent objective criteria requiring independent confirmation of x-ray or scan-documented response, the tumor response rate reached 7% (six of 87) for the bolus arm and 30% (26 of 87) for the infusion arms (P<.001). Toxicity was substantially different for the two arms with major leukopenia observed only on the bolus arm, 22% developing grade 3 (severe) or grade 4 (life-threatening) leukopenia with four sepsis-related deaths. Hand-foot syndrome was observed only in the infusional arm, requiring treatment interruptions and dose reductions in 24% of patients, but with little impact on quality of life.

	1 (bolus 5FU)	2 (CI 5FU)
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	500	2100
<b>N</b>	87	87
<b>Median OS (months)</b>	11.2	10.3
<b>Interquartile range</b>	(5.0-17.4)	(6.1-17.8)
<b>P-value</b>		P=.379
<b>OS Hazard Ratio</b>	Reference	Hazard Ratio not reported P=.38
<b>OS rate 5 y</b>	Not reported	
<b>Median TTP (months)</b>	Not reported	
<b>TTP Hazard Ratio</b>	Not reported	
<b>Response Rate (%)</b>	7%	30%
<b>95% Confidence intervals</b>	(3-14)	(21-41)
<b>P-value</b>		P<.001

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Source: figure 1 of reference

**Relevance to the comparison of 5FU doses**

This study provides evidence that a difference in the 5FU dose intensity of 500 and 2100 mg/m<sup>2</sup>/week did not have any impact to OS, however, higher 5FU dose intensity appears to increase response rate.

### 7.B.8 Poplin2005

#### Authors and Title

Poplin, et al. Phase III Southwest Oncology Group 9415/Intergroup 0153 Randomized Trial of Fluorouracil, Leucovorin, and Levamisole Versus Fluorouracil Continuous Infusion and Levamisole for Adjuvant Treatment of Stage III and High-Risk Stage II Colon Cancer.

#### Purpose

To compare the efficacy of continuous-infusion FU (CIFU) plus levamisole to FU/LV plus levamisole in the adjuvant treatment of high-risk Dukes' B2 and C1 or C2 colon cancer

#### Methods

After surgery, patients with colon cancer were randomly assigned to adjuvant treatment CIFU 250 mg/m<sup>2</sup>/d for 56 days every 9 weeks for three cycles or FU 425 mg/m<sup>2</sup> and LV 20 mg/m<sup>2</sup> daily for 5 days every 28 to 35 days for six cycles. All patients received levamisole 50 mg tid for 3 days every other week.

#### Results

The study closed after an interim analysis demonstrated little likelihood of CIFU showing superiority to FU/LV within the stipulated hazard ratio. A total of 1,135 patients were registered. Median follow-up time was 6.52 years. The 5-year OS is 70% (95% CI, 66% to 74%) for FU/LV and 69% (95% CI, 64% to 73%) for CIFU. The corresponding 5-year disease-free survival (DFS) was 61% (95% CI, 56% to 65%) and 63% (95% CI, 59% to 68%), respectively. For all patients, 5-year OS was 83%, 74%, and 55%; 5-year DFS is 78%, 67%, and 47% for N0, N1, and N2-3, respectively. At least one grade 4 toxicity occurred in 39% of patients receiving FU/LV and 5% of patients receiving CIFU. However, almost twice as many patients receiving CIFU discontinued therapy early compared with those receiving FU/LV. Therefore, CIFU had less severe toxicity but did not improve DFS or OS in comparison with bolus FU/LV.

	FU/LV	CIFU
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	472	1556
<b>N</b>	464	475
<b>Median OS (months)</b>	Not reached	Not reached
<b>OS Hazard Ratio</b>	Reference	1.16 (95%CI: 0.93-1.44 P=.18)
<b>OS rate 5 year</b>	70% (95%CI: 66%-74%)	69% (95%CI: 64%-73%)
<b>DFS rate 5 year</b>	61% (95%CI:56%-65%)	63% (95%CI:59%-68%)
<b>DFS Hazard Ratio</b>	Reference	1.05 (95% CI: 0.86-1.3; P = .65).
<b>Response Rate (%)</b>	Not reported	Not reported

DFS= disease free survival

#### Relevance to the comparison of 5FU doses

This study provides evidence that in the presence of LV and levamisole as adjuvant colon cancer treatment, the difference in 5FU dose intensities of 472 and 1556 mg/m<sup>2</sup>/week with infusion durations of 56 days and 0.25 h did not have any impact on OS or DFS.

### 7.B.9 Shah1985

#### Authors and Title

Shah, et al. 5-FU infusion in advanced colorectal cancer: a comparison of three dose schedules. Cancer Treatment Rep 69:739-742, 1985.

#### Purpose

To compare different dose schedules of 5FU

#### Methods

Patients with advanced colorectal adenocarcinoma were assigned to one of the three arms:

- Group A: 72-hour infusion of 5-FU (30 mg/kg/24 hours) every 3 weeks
- Group B: 72-hour infusion of 5-FU (30 mg/kg/24 hours) every 2 weeks
- Group C: 48-hour infusion of 5-FU (30 mg/kg/24 hours) every week

#### Results

A total of 94 patients with advanced colorectal adenocarcinoma were treated by continuous iv 5-FU infusion on three different dose schedules (Group A, n=33; Group B, n= 31; Group C, n=30). Although this was a sequential nonrandomized study of the dose schedules, the groups were comparable with respect to various prognostic factors. Response rates were as follows: Group A--three patients had minor response (9%) and 30 had no response (91%); Group B--five patients achieved partial response (16%), nine had minor response (29%), and 17 had no response (55%), and Group C--one patient achieved complete response (3%), eight achieved partial response (27%), five had minor response (17%), and 16 had no response (53%). The median survival time for Group A was 9 months, for Group B was 9.5 months, and for Group C was 14 months. Intensifying the dose schedule of 5-FU by increasing the frequency of administration has significantly improved response rates. A prolongation of the median survival time of patients treated with a 48-hour infusion at 1-week intervals was noted, although this was not statistically significant.

	Group A	Group B	Group C
5FU dose intensity (mg/kg/week)	30	45	60
N	33	31	30
Median OS (months)	9 (range= 2-46)	9.5 (range= 4-31; similar KM estimates, P not reported)	14 (range= 1-32+; P=.09)
OS Hazard Ratio	Not reported		
Median TTP (months)	Not reported		
TTP Hazard Ratio	Not reported		
Response Rate (%)	0	16%	30% P=.0004

#### Relevance to the comparison of 5FU doses

This is the first study that provides evidence that the difference in dose intensities of 30 to 60 mg/kg/week (or approximately 1200 to 2400 mg/m<sup>2</sup>/week with a conversion factor of 40 kg/m<sup>2</sup>) does not have an impact to the OS, and that higher 5FU dose intensities may increase response rate.

### 7.B.10 Weinerman1992

#### Authors and Title

Weinerman, et al. Systemic infusion versus bolus chemotherapy with 5-fluorouracil in measurable metastatic colorectal cancer. Am J Clin Oncol. 1992 Dec;15(6):518-23.

#### Purpose

To compare either infusional or bolus 5-fluorouracil (5-FU) for the treatment of metastatic measurable colorectal cancer

#### Methods

Chemotherapy-naive colorectal cancer patients with good performance status was randomized to either infusional or bolus 5-FU. Infusion was administered at an escalated dose schedule starting at 350 mg/m<sup>2</sup> per day for 2 weeks with a 2-week rest period on a monthly basis, while bolus 5-FU was started at 400-450 mg/m<sup>2</sup> for 5 days every 28 days.

#### Results

From January 31, 1986 to January 31, 1989, 184 patients enrolled. No significant difference in survival was observed (p = 0.207). Progression free survival was significantly longer (p = 0.0139) in the infusion group (3.8 versus 2.3 months). The infusion arm produced a response in 11 of 88 patients versus 6 of 82 in the bolus arm (p = 0.384). Neither of these methods of administering fluorouracil results in an exceptional response rate, nor does the infusion have an impact on survival as compared to the bolus route.

	Infusion 5FU	Bolus 5FU
5FU dose intensity (mg/m <sup>2</sup> /week)	1225	500
N	94	90
Median OS (months)	Not Reported	
OS Hazard Ratio	Reference	HR Not Reported; P=.2071
OS rate 5 y	Not Reported	
Median TTP (months)	3.8	2.3
TTP Hazard Ratio	Reference	HR Not Reported P = .0139.
Response Rate (%)	12.5%	7.3% (P=.384)

#### Relevance to the comparison of 5FU doses

This study provides evidence that the difference in 5FU dose intensity of 500 and 1225 mg/m<sup>2</sup>/week given as bolus or continuous infusion did not have an impact on OS in chemotherapy-naive colorectal cancer. Higher 5FU dose intensity was reported to have a higher response rate and longer median TTP.

TIMEKEEPER PAYROLL RECORD

Advisors and Consultants Staff

**Note to Center for Drug Evaluation and Research Special Government Employee.**

Use this record to submit claim for hours worked at your home, place of business, or in any FDA facility located within your commuting area. Please note any dates that you were required to travel outside of your commuting area to perform your assignment. Advisory committee members should not claim salary for hours spent on normal preparation for a committee meeting. Salary paid in response to this time sheet represents compensation in full for all services rendered and supplied by the Special Government Employee during this period.

<u>Date(s)</u>	<u>Hours Worked</u>	<u>Description of Work</u> (Cite IND/NDA if applicable)
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\_\_\_\_\_ (Sign) \_\_\_\_\_  
Special Government Employee Date

Certification:

I certify that this work was done during the period(s) indicated at:

- Government furnished facility
- Employees home/office since there was no Federal office or laboratory space available at which to perform the assigned work.
- Quality and quantity of work meets performance expectations.

\_\_\_\_\_  
Center for Drug Evaluation and Research Executive Secretary/Management Official Authorizing Assignment Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEANNE R VARNEY  
07/09/2015



Dr. David Kelsen  
Sent via email communication

Dear Dr. Kelsen:

We corresponded several weeks ago regarding the possibility of your assistance in the review of a New Drug Application (NDA) 207793, submitted by Merrimack Pharmaceuticals (Merrimack). In this application, Merrimack seeks approval of irinotecan liposome injection for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine. Please note that information concerning this application is confidential.

I received notification from the CDER Division of Advisory Committee and Consultant Management (DACCM) that you are cleared to serve as a Special Government Employee (SGE) for the review of this NDA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for 10:30AM ET on July 14, 2015. The questions we would like to discuss during this teleconference are listed below.

Following our teleconference, please return the completed Timekeeper Payroll Record (enclosed) indicating the amount of time you worked on this review via one of the following methods:

- EMAIL: [Deanne.Varney@fda.hhs.gov](mailto:Deanne.Varney@fda.hhs.gov)
- FedEx or UPS overnight delivery to:  
Deanne Varney  
Division of Oncology Products 2  
Food and Drug Administration  
WO22-2326  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

Enclosed is a summary of the pivotal trial submitted with this application as well as excerpts from the NDA submission.

**FDA Question for Discussion During Teleconference:**

Based upon your review of the summary information provided, do you agree that the observed improvement in overall survival in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms?

If you have questions, please contact me at 301-796-0297.

Sincerely,

Deanne Varney  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosures:

1. NDA 207793 Summary Information
2. Timekeeper Payroll Record



**Proposed Indication:** “Onivyde (irinotecan liposome injection) is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.”

**Applicant:** Merrimack Pharmaceuticals, Inc.

**Information from NDA 207793:**

Irinotecan liposome injection (MM-398) is irinotecan in the form of a sucrosulfate salt, encapsulated in liposomes for intravenous infusion.

Merrimack submitted the NDA as a 505(b)(2) application for which Camptosar (irinotecan) is the reference drug, as Merrimack’s application relies on certain information (e.g., nonclinical, drug interactions, and other clinical pharmacology information) contained in the physician’s package insert for Camptosar.

To support the efficacy of MM-398 for the above-listed proposed indication, Merrimack submitted clinical data from single trial NAPOLI-1, which was an open-label, three-arm, randomized, international, multicenter trial.

NAPOLI-1 was initially designed as a two-arm trial comparing the safety and efficacy of MM-398 at a dose of 120 mg/m<sup>2</sup> every three weeks with 5-fluorouracil 2000 mg/m<sup>2</sup> (with leucovorin) every week for four weeks in a six week cycle (Arms A and B below). After enrollment of 63 patients, Merrimack amended the trial to include a third arm (Arm C) investigating the combination of MM-398, 5-fluorouracil (5-FU), and leucovorin (LV) at the doses shown below. The amended trial was entitled as follows.

**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 (MM-398-07-03-01)”

Under the revised protocol, patients were randomized (1:1:1) to Arms A, B, or C (shown below). Randomization was stratified by albumin level, Karnofsky Performance Score (KPS), and ethnicity.

- **Arm A:** MM-398 at a dose of 120 mg/m<sup>2</sup> every three weeks
- **Arm B:** 5-FU 2000 mg/m<sup>2</sup> over 24 hours and LV 200 mg/m<sup>2</sup> once weekly for 4 weeks of each 6 week cycle

- **Arm C:** MM-398 at a dose of 80 mg/m<sup>2</sup> every two weeks in combination with 5-FU 2400 mg/m<sup>2</sup> over 46 hours and LV 400 mg/m<sup>2</sup> every two weeks

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

The primary endpoint was overall survival (OS) with two co-primary, pair-wise comparisons, one for each MM-398-containing arm compared with the control arm (Arm B; 5-FU/LV), with Type I error controlled using the Bonferroni-Holm approach. The specified population (in the amended statistical plan submitted prior to the final analysis) for the comparison of Arm C to Arm B was limited to patients randomized following the addition of the third arm (Arm C). Secondary endpoints included progression-free survival (PFS) and objective response rate (ORR).

A total of 151 patients were randomized to Arm A, 149 to Arm B, and 117 to Arm C. For the comparison of Arm C vs. Arm B, the trial demonstrated a statistically significant difference in OS [HR=0.67 (95% CI 0.49-0.92); p=0.012]. There was no significant difference in OS for Arm A vs. Arm B [HR 0.99; p=0.9]. Median OS times for the two MM-398-containing arms were 6.1 months for Arm C and 4.9 months for Arm A. Median OS time for the control arm (Arm B) was 4.2 months. The comparison of PFS for Arm C vs. Arm B demonstrated a statistically significant improvement [HR 0.56 (95% CI 0.41-0.75); p=0.0001] with a median PFS of 3.1 months in Arm C and 1.5 months in Arm B.

### **5-FU Dosing Regimens**

The 5-FU/LV dosing regimen assigned to the control arm of NAPOLI-1 was the 5-FU dose and schedule that was employed as the control in the CONKO-003 trial (Pelzer et al., 2011). The MM-398/5-FU/LV dosing regimen assigned to Arm C of NAPOLI-1 was the same regimen (same doses and schedule) tested in the PEPCOL study, a French cooperative group study in patients with metastatic colorectal cancer, from which safety data had become available.

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

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

- Pharmacokinetics (PK) simulation results showing that the 5-FU area under the curve (AUC) in Arm B (control arm) was higher than in Arm C (MM-398/5-FU/LV).

The planned cumulative dose of 5-FU in the 5-FU/LV control arm (Arm B) was higher than in the MM-398/5-FU/LV arm (Arm C): 8000 versus 7200 mg/m<sup>2</sup> over a six-week cycle, equivalent to a dose intensity of 1333 versus 1200 mg/m<sup>2</sup>/week. Merrimack showed that the comparison of observed cumulative doses between Arms B and C was consistent with the comparison of planned cumulative doses between Arms B and C, with six-week average dose intensities of 6718 and 5065 mg/m<sup>2</sup> (or 1119.7 and 844.2 mg/m<sup>2</sup>/week) respectively, and that at any week except for the first week, the planned and observed cumulative 5-FU doses were higher in the control arm than in the MM-398/5-FU/LV arm.

Merrimack further presented PK simulation results showing that the six-week average 5-FU AUC in the MM-398/5-FU/LV arm was 90% of that in the control arm; see Appendix 1 which contains an excerpt from Merrimack's NDA submission describing Merrimack's methods, analyses, and results.

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

In the pancreatic cancer indication, clinical studies reported in English were searched using PubMed. The strategy used a panel of keywords (listed in the NDA) involving 5-FU and pancreatic cancer. The search was further filtered for trials from January 1980 through December 2014, containing more than 10 patients per arm, and in patients with pancreatic cancer with locally advanced or metastatic disease eligible for any line of therapy. References from the search publications were included. One study dated 1974 was included as Merrimack deemed the study relevant. Combinations with agents other than LV were included only if the study included more than one 5-FU dose and regimen. Combinations with radiation therapy were excluded. Merrimack acknowledged that the list may not be exhaustive.

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



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

See Appendix 2 which contains Merrimack's tables and Merrimack's summaries of the published studies identified above.

The review of the published data (most of which is indirect evidence from colorectal cancer trials) does not appear to indicate that the different dosing regimens in the two NAPOLI-1 arms (B vs. C) would result in improved clinical outcomes in the MM-398/5-FU/LV arm solely due to the differences in 5-FU doses between arms (noting that the higher 5-FU cumulative dose per six-week cycle was administered to patients in the control arm).

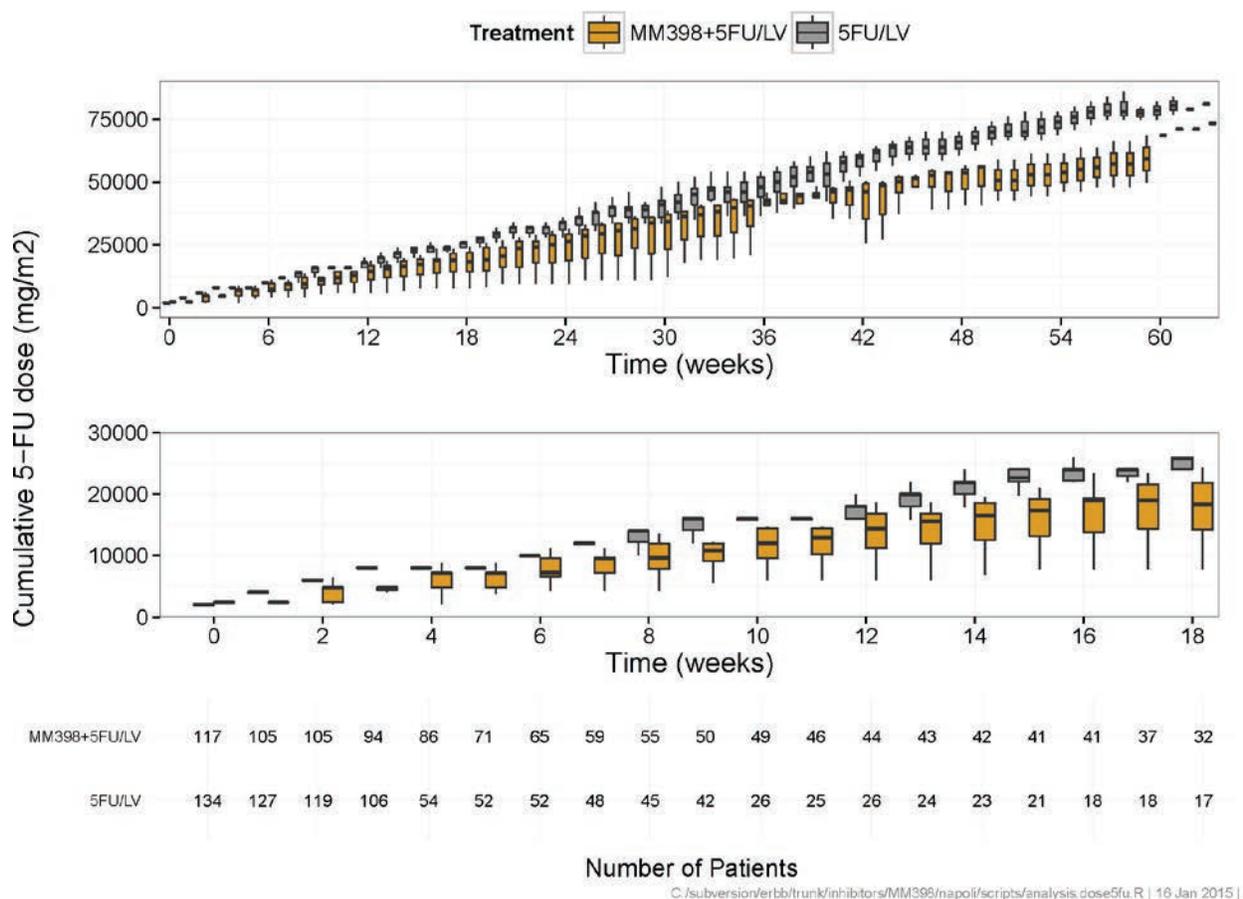
***FDA QUESTION FOR DISCUSSION DURING TELECONFERENCE:***

*Based upon your review of the summary information provided, do you agree that the observed improvement in OS in NAPOLI-1 in the MM-398/5-FU/LV arm compared to the 5-FU/LV arm was not likely to be caused by the difference in 5-FU dosing regimens between the two arms?*



**APPENDIX 1 (excerpt from Merrimack's NDA submission)**

Appears this way on original



**Figure 2-1** Observed 5-FU Doses by Treatment Regimen over Time in the NAPOLI-1 Study

Each box plot includes patients with reported dosing at the respective week. Number of patients in the bottom corresponds to the lower figure in the first 18 weeks.

Source: dose5fu.pdf

## 2.A.2 Clinical Pharmacology of 5-FU

### 2.A.2.1 Literature review: 5-FU therapeutic target AUC of 20-25 h mg/L

Compared to administered dose levels, the pharmacokinetic parameters of 5-FU, specifically the AUC, have been shown to provide a better prediction of efficacy and safety (Saif, Choma, Salamone, & Chu, 2009). A consistent target range of AUC for all infusion based regimens has been established as 20-25 mg h/L, and a therapeutic dose monitoring based on 5-FU AUC has been shown to improve efficacy and safety (Gamelin et al., 2008). **Table 2-2 Literature Review of Target 5-FU AUC** shows that the target AUC of approximately 20 h mg/L is consistent for continuous infusion for a wide range of infusion durations (8h – 96h). Therefore, the time-average (6-week) AUC can be used as a metric to compare the different 5-FU doses of the two arms in NAPOLI-1 study.

**Table 2-2 Literature Review of Target 5-FU AUC**

reference	Indication Cancer Type	N	Type	Dose	Interval	Infusion duration (h)	Target AUC (h mg/L)
Fety1998	head neck	122	continuous infusion	4g/m <sup>2</sup> /cycle AUC-adjusted	every 2 weeks	96	Dose reduced if AUC <sub>48</sub> >20
Gamelin2008	colorectal	208	continuous infusion	1500mg/m <sup>2</sup> /week AUC-adjusted (mean=1790mg/m <sup>2</sup> /week)	every 1 week	8	AUC <sub>8</sub> 20-24
Ychou2003	colorectal	53	continuous infusion	400mg/m <sup>2</sup> (bolus)+ 600mg/m <sup>2</sup> /day	2 days every 2 weeks	22	AUC <sub>46</sub> 20
DiPaolo2008	colorectal	115	Bolus	370mg/m <sup>2</sup> /day	5 days every 4 weeks	2 m	AUC <sub>bolus</sub> 8.4

### 2.A.2.2 Comparison of 5-FU pharmacokinetics in the NAPOLI-1 Study

MM-398 and 5-FU have different metabolic pathways and therefore are unlikely to have drug-drug interactions. The disposition of irinotecan was not altered when 5-FU was co-administered (Camptosar package insert). The metabolism of 5-FU is via catabolism by dihydropyrimidine dehydrogenase (DPD), while the active ingredient of MM-398 is irinotecan, for which conversion to the active metabolite, SN-38, is mediated by carboxylesterase enzymes. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite (irinotecan USPI).

Simulation of 5-FU pharmacokinetic parameters was performed for the two 5-FU regimens of NAPOLI-1 ([Figure 2-2 Simulated 6-Week Average 5-FU AUC for 5-FU Dose Regimens of NAPOLI-1](#)) using three published 5-FU pharmacokinetic parameters (listed in [Table 2-3 Simulated and Observed 5-FU Pharmacokinetics by Dose Regimens](#)). Two simulation approaches were evaluated: 1) to simulate based on Monte-Carlo random parameters generated based on the previously published parameters, without using 5-FU samples in NAPOLI-1; or 2) to estimate the pharmacokinetic parameters based on the 5-FU samples in NAPOLI-1 using Empirical Bayesian Estimation, with priors from the previously published parameters. The 6-week average AUCs were used as the primary comparison, because of the findings that total exposure AUC appears to be the 5-FU pharmacokinetic driver of efficacy ([Saif et al., 2009](#)); and a 6-week duration provides a common duration for both the 5-FU/LV and MM-398+5-FU/LV arms of NAPOLI-1. Details of the simulation methods and results are provided in [Section 6](#).

The simulation results from approach 1, which was based on previously published parameters without using 5-FU samples in NAPOLI-1, showed that the 5-FU 6-week average AUC in the MM-398+5-FU/LV arm was 90% of the AUC in the 5-FU/LV control arm ([Table 2-3 Simulated and Observed 5-FU Pharmacokinetics by Dose Regimens](#)). Moreover, the percentage of patients with a 6-week average 5-FU AUC greater than the target AUC (of 20 mg h/L) was 2%-7% lower in the MM-398+5-FU/LV arm compared to that in the 5-FU/LV arm.

The simulation results from approach 2, which was on the 5-FU samples in NAPOLI-1 using Empirical Bayesian Estimation, with priors from the previously published parameters, showed a similar result as those obtained without using the measured NAPOLI-1 5-FU samples (rows 1 and 3 of [Table 2-3](#)). It was noted that evaluation of the estimation results showed some bias in the goodness of fit, see [Section 6D](#).

The observed 5-FU concentrations for both 5-FU containing treatment arms in NAPOLI-1 were lower than the predicted steady-state concentrations; this is likely due to the fact that the majority (75%) of pharmacokinetic samples in NAPOLI-1 were collected after the end of infusion and during the time of rapid clearance of 5-FU, which, with a known a half-life of 16 minutes ((b) (4)) would result in lower concentrations that are not representative of steady-state levels. The predicted steady-state concentration ratio of the MM-398+5-FU/LV arm to the 5-FU/LV arm was 0.626, similar to the observed concentration ratio of 0.63 [95%CI 0.28-1.39] (of note, the 5-FU concentrations measured in NAPOLI-1 were a mixture of steady-state and post-infusion).

**Table 2-3 Simulated and Observed 5-FU Pharmacokinetics by Dose Regimens**

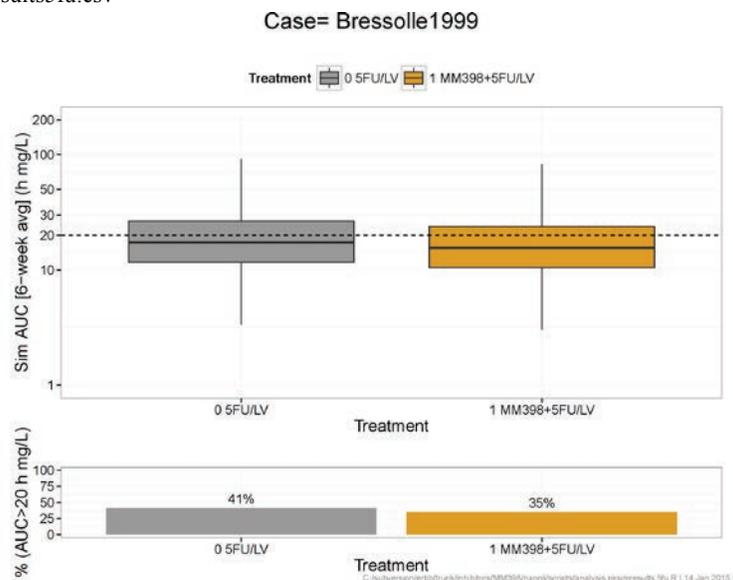
Reference for 5-FU PK Parameters	Steady-state Conc (mg/L)			Predicted 6-week Average AUC					
	GLS Mean		Ratio <sup>2</sup> Mean [95%CI]	AUC (h mg/L)			% AUC>20 h mg/L		
	5-FU/LV	MM-398 +5-FU/LV		5-FU/LV	MM-398 + 5-FU/LV	Ratio <sup>2</sup>	5-FU/LV	MM-398 + 5-FU/LV	Diff <sup>3</sup>
Bressolle1999	1.091	0.683	0.626	17.456	15.710	0.9	41%	35%	-6%
Mueller2013	0.901	0.564	0.626	14.418	12.976	0.9	10%	4%	-6%
Bressolle1999+ NAPOLI-1 5-FU concentration	1.212	0.759	0.626	19.392	17.453	0.9	49%	42%	-7%
Woloch2012	2.771	1.735	0.626	44.329	39.896	0.9	96%	94%	-2%
NAPOLI-1 observed 5-FU concentration <sup>1</sup>	0.22	0.14	0.63 [0.28-1.39]						

<sup>1</sup> The majority (75%) of the 5-FU concentrations were collected after the end of infusion, therefore, the observed concentration is lower than steady-state concentration (5-FU was cleared rapidly after the end of infusion with the estimated half-life of 8-14 minutes).

<sup>2</sup> Ratio is defined as concentration or AUC ratio of MM-398+5-FU/LV relative to 5-FU/LV

<sup>3</sup> Difference is defined as percentage of MM-398+5-FU/LV minus percentage for 5-FU/LV

Source: summary.pksimresults5fu.csv



**Figure 2-2 Simulated 6-Week Average 5-FU AUC for 5-FU Dose Regimens of NAPOLI-1**

Simulation was performed using 5-FU pharmacokinetic parameters in (Bressolle et al., 1999).

Source: pk5fu.pdf

## 6 APPENDIX: DETAILED PHARMACOKINETICS ANALYSES OF 5-FU TO EVALUATE DIFFERENT 5-FU DOSES IN STUDY MM-398-07-03-01 (NAPOLI1)

### A. OBJECTIVES

1. To compare the 5-FU pharmacokinetic difference that arises from the difference in the 5-FU dose regimens of the control and investigational treatment arms in NAPOLI-1 Study

### B. METHODS

#### 6.B.1 Study design

Subjects in NAPOLI-1 Study MM-398-07- randomized to the two 5-FU/LV containing arms, MM-398+5-FU/LV and 5-FU/LV, were to receive the following planned dose regimens:

- MM-398+5-FU/LV arm: MM-398 80 mg/m<sup>2</sup> IV and 5-FU 2400 mg/m<sup>2</sup> IV over 46 hours and LV 400 mg/m<sup>2</sup> IV over 30 minutes, every 2 weeks
- 5-FU/LV arm: 5-FU 2000 mg/m<sup>2</sup> IV over 24 hours and LV 200 mg/m<sup>2</sup> IV over 30 minutes, administered weekly for the first 4 weeks, followed by 2 weeks of rest, in a 6 weekly cycle

#### 6.B.2 Dataset

Pharmacokinetic samples of 5-FU from both arms were collected at the end of 5-FU infusion (Cycle 1 Day 2). A total of 163 samples from 129 subjects were collected, and 75% (122/163) of the samples were collected after the end of infusion.

#### 6.B.3 Models

Pharmacokinetics of 5-FU is described as a one-compartmental model, based on the previously published studies (Bressolle et al., 1999; Mueller et al., 2013; Woloch et al., 2012). The published effects of covariates to 5-FU pharmacokinetics were not implemented because some of the covariates were not collected in the NAPOLI-1 Study. Fixed and random effect parameter estimates from the literature are summarized in Table 6-1.

**Table 6-1 Pharmacokinetic Models of 5-FU from Literature that are Used in the Simulation Study**

reference	N	Clearance (L/week)		Volume (L)	
		<i>Fixed effect</i>	<i>Random effect</i>	<i>Fixed effect</i>	<i>Random effect</i>
Bressolle1999	85	21504	56%	18.4	114%
Woloch2012	127	8568	43%	22.0	50%
Mueller2013	32	26544	22%	54.9	18.5%

Source: (Bressolle et al., 1999; Mueller et al., 2013; Woloch et al., 2012)

Pharmacokinetic analyses were conducted using 2 approaches:

1. To estimate the pharmacokinetic parameters based on the 5-FU samples in NAPOLI-1 using Empirical Bayesian Estimation, with priors from the previously published parameters
2. To simulate based on Monte-Carlo random parameters generated based on the previously published parameters, without using 5-FU samples in NAPOLI-1

In the first approach, measured concentrations below limit of quantification (BQL) were modeled by the mixed continuous and categorical method (M3 method, (Bergstrand & Karlsson, 2009)). The M3 method was implemented using log-transformed values of concentration and the LAPLACIAN estimation method.

#### 6.B.4 Simulation Methods

Simulation was conducted by comparison of the 5-FU pharmacokinetic simulations in both 5-FU regimens (in the control and the investigational arms of NAPOLI-1). The PK parameters were either obtained from Empirical Bayesian Estimate from the NAPOLI-1 study or obtained by sampling, 1000 times, the random clearance and volume estimates from the distribution as specified in Table 6-1. Planned 5-FU doses as specified in Section 6.B.1 were used, which represent the optimistic boundary for the analysis because of the higher percentage of 5-FU dose reductions in the MM-398+5FU/LV arm than in the 5FU/LV alone arm. As the doses were BSA-based, the distribution of BSA follows those observed in the NAPOLI-1 study.

Compared to the weekly dose intensity, pharmacokinetic parameters of 5-FU have been shown to provide a better prediction of efficacy and safety (reviewed in (Saif et al., 2009)). A consistent target range of AUC for all infusion based regimens has been established as 20-24 mg h/L (Gamelin et al., 2008). A therapeutic dose monitoring based on 5-FU AUC has been shown to improve efficacy and safety (Gamelin et al., 2008). Table 6-2 showed that the target AUC is consistent for continuous infusion with varying infusion durations (8h – 96h). Therefore, time-average (6-week) AUC is used as a metric to compare the different 5-FU doses of the two arms in NAPOLI-1 study.

From the simulation results, 6-week average AUC of 5-FU were compared by treatment arms. Moreover, the percentage of patients who have 6-week AUC greater than target AUC of 20 mg h/L was evaluated.

**Table 6-2 Literature review of target 5-FU AUC**

reference	Indication	N	Type	Dose	Interval	Infusion duration (h)	Target AUC (h mg/L)
Fety1998	head neck	122	continuous infusion	4g/m2/cycle AUC-adjusted	every 2 weeks	96	Dose reduced if AUC <sub>48</sub> >20
Gamelin2008	colorectal	208	continuous infusion	1500mg/m2/week AUC-adjusted (mean=1790 mg/m2/wk)	every 1 week	8	AUC <sub>8</sub> 20-24
Ychou2003	colorectal	53	continuous infusion	400mg/m2 (bolus)+ 600mg/m2/day	2 days every 2 weeks	22	AUC <sub>46</sub> 20
DiPaolo2008	colorectal	115	bolus	370mg/m2/day	5 days every 4 weeks	2 min	AUC <sub>bolus</sub> 8.4

#### 6.B.5 Software

All data preparation and presentation was performed using SAS® Version 9.3 or later (SAS Institute) and R Version 3.0.2. PK modeling used NONMEM version 7.3, with default setting to be FOCEI with the Laplacian method. Package Perl Speaks NONMEM (PSN) was used for interface to NONMEM. Package Xpose4 was used for model diagnostics.

### C. SIMULATION RESULTS: COMPARISON OF THE 5-FU PHARMACOKINETICS BY DIFFERENT 5-FU DOSE REGIMENS

To evaluate the contribution of different 5-FU regimens, a simulation study was conducted to compare different 5-FU doses. Details of the simulation are provided in [Section 6.B.4](#). The 6-week average AUC was used as the primary comparison because of the findings that time-average AUC appears to be the 5-FU pharmacokinetic driver of efficacy and safety ([Saif et al., 2009](#)).

The simulation results are summarized in Table 6-3. The 6-week average AUC of the MM-398+5-FU/LV arm is predicted to be 90% of the AUC of 5-FU/LV control regimen. The percentage of patients with 6-week average AUC greater than the target AUC (of 20 h mg/L) is 2%-7% lower in the MM-398+5-FU/LV arm compared to those in the 5-FU/LV control arm. The simulation results from the Bayesian estimates were comparable to the results without using 5-FU concentration samples collected in the NAPOLI-1 Study (it is noted that evaluation of the estimation results showed some bias in the goodness of fit, see [Section D](#)). Because of sparsity of the samples and the bias in the goodness of fit, exposure-efficacy and exposure-safety analyses were not conducted.

**Table 6-3 Summary statistics of simulated and observed 5-FU pharmacokinetics from multiple reference pharmacokinetic models**

reference for 5-FU PK Parameters	Steady-state Conc (mg/L)			Predicted 6-week Average AUC					
	GLS Mean		Ratio <sup>2</sup> Mean [95%CI]	AUC (h mg/L)			% AUC>20 h mg/L		
	5-FU/LV	MM-398 +5-FU/LV		5-FU/LV	MM-398 + 5-FU/LV	Ratio <sup>2</sup>	5-FU/LV	MM-398 + 5-FU/LV	Diff <sup>3</sup>
Bressolle1999	1.091	0.683	0.626	17.456	15.71	0.9	41%	35%	-6%
Mueller2013	0.901	0.564	0.626	14.418	12.976	0.9	10%	4%	-6%
NAPOLI1+Bressolle1999	1.212	0.759	0.626	19.392	17.453	0.9	49%	42%	-7%
Woloch2012	2.771	1.735	0.626	44.329	39.896	0.9	96%	94%	-2%
NAPOLI-1 observed 5-FU concentration <sup>1</sup>	0.22	0.14	0.63 [0.28-1.39]						

<sup>1</sup> The majority (75%) of the 5-FU concentrations were collected after the end of infusion, therefore, the observed concentration is lower than steady-state concentration (5-FU was cleared rapidly after the end of infusion with the estimated half-life of 8-14 minutes).

<sup>2</sup> Ratio is defined as concentration or AUC ratio of MM-398+5-FU/LV relative to 5-FU/LV

<sup>3</sup> Difference is defined as percentage of MM-398+5-FU/LV minus percentage for 5-FU/LV

Source: [summary.pksimresults5fu.csv](#)



**APPENDIX 2 (excerpt from Merrimack's NDA submission)**

Appears this way on original

**Table 2-6 Published Studies in Pancreatic Cancer Containing 5-FU alone or 5-FU/LV Dose Regimens**

PubMed ID:	Author, Year	5-FU administration					Line of treatment	N	Median Overall Survival (mo)
		Adm	Dose (mg/m <sup>2</sup> ) [duration]	Schedule	Cycle	Dose intensity (mg/m <sup>2</sup> /wk)			
24982456	Oettle, 2014	CI	2000 [24h]	d1, d8, d15, d22	q6w	1333	2nd	84	3.3 (95% CI: 2.7-4.0)
NA	Gill, 2014 (1)	CI	2400 [46h]		q2w	1200	2 <sup>nd</sup>	54	9.9 (95%CI: 6.7-16.9)
NA	Von Hoff, 2014 (NAPOLI-1)	CI	2000 [24h]	W1-4+2w rest	q6w	1333	2 <sup>nd</sup>	119	4.24 (95%CI 3.29-5.32)
		CI + MM-398	2400 [46h]		q2w	1200	2 <sup>nd</sup>	117	6.14 (95%CI 4.76-8.87)
8052479	Takada, 1994	BL	310	d1-d5 w1 and w3	q6w	517	≥1st	36	6.0 (95% CI: 5.8-10.1)
1960554	DeCaprio, 1991	BL	600	d1, d8, d15, d22, d29, d36	q8w	450	1st	42	6.2 (range: 0.2-33)
11128566	Figer, 2000	BL	900	d1	q2w	450	≥1st	22	9
		BL	370	d1-d5	q4w	463		25	5
10955877	Choi, 2000	BL	375	d1-d5	q4w	469	≥1st	23	6
2189551	Cullinan, 1990	BL	500	d1-d5	q5w	500	≥1st	64	3.5
4812773	Kovach, 1974	BL	506*	d1-d5	q5w	506	1st	31	7.4
9196156	Burris, 1997	BL	600	d1	q1w	600	1st	63	4.4
2579257	Cullinan, 1985	BL	500	d1-d5	q4w	625	≥1st	50	5.1 mo (22 wk)-
12181240	Ducreux, 2002	BL	500	d1-d5	q4w	625	≥1st	103	3.4 (102 d)
15341982	Van Rijswijk, 2004	CI	2600 [24h]	d1, d8, d15, d22, d29, d36	q8w	1950	1st	33	4.4 mo (19 wk, 95% CI: 12-35)

BL= bolus; CI= continuous infusion;

\* Drug Conversion: based on assumption that weight is 60 kg and body surface area is 1.6m<sup>2</sup>

(1) OS was noted by the authors to have a potential bias because of imbalances in subsequent treatments (23% received subsequent therapies) and disease characteristics within the younger patient subgroup

**Table 2-7 Published Studies in Metastatic Colorectal Cancer Comparing 5-FU Doses**

reference	Study Name	Cohort	Drug Regimens	5-FU Dose Regimen			N	Overall Survival					Response Rate (%)
				Dose (mg/m <sup>2</sup> or mg/m <sup>2</sup> /d) [infusion duration in h]	Adm	Dose Intensity (mg/m <sup>2</sup> /w)		HR	P	Median (m)	Rate 3 y	Rate 5 y	
Kohne 2013	PETACC-2	Metastatic	5FU+LV	370-425mg/m <sup>2</sup> /d for 5d q4w	BL	463-531	804	0.96	0.74	nrd	85%	79%	NR
Kohne 2013	PETACC-2	Metastatic	5FU+LV	(1) 3500mg/m <sup>2</sup> [48h] q1w (2) 2600mg/m <sup>2</sup> [24h] q1w (3) 400mg/m <sup>2</sup> BL +600mg/m <sup>2</sup> [22h] for 2 d q2w	CI	3500 2600 800	797	ref		nrd	85%	79%	nr
Leichman 2005	NA	Metastatic	5FU	300mg/m <sup>2</sup> /d [28d] q5w	CI	1680	347	nr	0.70	13	nr	nr	nr
Leichman 2005	NA	Metastatic	5FU	2600mg/m <sup>2</sup> [24h] q1w	BL	2600	361	ref		13	nr	nr	nr
Andre 2007	GERCOR C96.1	Metastatic	5FU+LV	400mg/m <sup>2</sup> for 5d q4w	BL	500	453	1.02	0.91	nrd	nr	78% <sup>1</sup>	nr
Andre 2007	GERCOR C96.1	Metastatic	5FU+LV	400mg/m <sup>2</sup> BL + 600mg/m <sup>2</sup> [22h] for 2 d q2w	CI	800	452	ref		nrd	nr	76% <sup>1</sup>	nr
Shah 1985	NA	Metastatic	5FU	30mg/kg/d [48h] q1w	CI	2400 <sup>2</sup>	30	ref		14	nr	nr	30%
Shah 1985	NA	Metastatic	5FU	30mg/kg/d [72h] q2w	CI	1800 <sup>2</sup>	31	nr	nr	9.5	nr	nr	16%
Shah 1985	NA	Metastatic	5FU	30mg/kg/d [72h] q3w	CI	1200 <sup>2</sup>	33	nr	.09	9	nr	nr	0%
Weinerman 1992	NCIC	Metastatic	5FU	350mg/m <sup>2</sup> /d [2w] q4w	CI	1225	94	nr	0.21	nr	nr	nr	13%
Weinerman 1992	NCIC	Metastatic	5FU	400-450mg/m <sup>2</sup> /d for 5d q4w	BL	500-562	90	ref		nr	nr	nr	7%
Hansen 1996	ECOG	Metastatic	5FU	300mg/m <sup>2</sup> /d	CI	2100	159	nr	0.22	13	nr	nr	28%
Hansen 1996	ECOG	Metastatic	5FU	500mg/m <sup>2</sup> for 5d, then 600mg/m <sup>2</sup> /d q1w	BL	600	153	ref		10.4	nr	nr	18%
Leichman 1995	SWOG	Metastatic	5FU	500mg/m <sup>2</sup> for 5d q5w	BL	500	60	ref	nr	14	nr	nr	29%
Leichman 1995	SWOG	Metastatic	5FU+LV	425mg/m <sup>2</sup> for 5d q4w twice, then q5w	BL	425-531	61	0.97	nr	14	nr	nr	27%
Leichman 1995	SWOG	Metastatic	5FU+LV	600mg/m <sup>2</sup> q1w 6 times over 8 weeks	BL	450	60	1.04	nr	13	nr	nr	21%
Leichman 1995	SWOG	Metastatic	5FU	300mg/m <sup>2</sup> for 28d q5w	CI	1680	61	0.85	nr	15	nr	nr	29%
Leichman 1995	SWOG	Metastatic	5FU+LV	200mg/m <sup>2</sup> for 28d q5w	CI	1120	58	0.93	nr	14	nr	nr	26%
Leichman 1995	SWOG	Metastatic	5FU	2600mg/m <sup>2</sup> /d q1w	CI	2600	63	0.85	nr	15	nr	nr	25%
Leichman 1995	SWOG	Metastatic	5FU+PALA	2600mg/m <sup>2</sup> /d q1w	CI	2600	63	1.33	nr	11	nr	nr	15%
Lokich 1989	MAOP	Metastatic	5FU	300mg/m <sup>2</sup> /d	CI	2100	87	nr	0.38	10.3	nr	nr	30%
Lokich 1989	MAOP	Metastatic	5FU	500mg/m <sup>2</sup> for 5d q5w	BL	500	87	ref		11.2	nr	nr	7%
Poplin 2005	INT0153	Adjuvant	5FU+LV +levamisole	250mg/m <sup>2</sup> /d for 56d q9w	CI	1556	475	1.16	0.18	nrd	nr	69%	nr
Poplin 2005	INT0153	Adjuvant	5FU+LV +levamisole	425mg/m <sup>2</sup> /d for 5d q4w twice, then q5w	BL	455	464	ref		nrd	nr	70%	nr
Goldberg 2004	N9741	Metastatic	5FU+LV +oxaliplatin	400mg/m <sup>2</sup> BL +600mg/m <sup>2</sup> [22h] for 2 d q2w	CI	800	267	0.66	0.0001	19.5	nr	nr	45%
Goldberg 2004	N9741	Metastatic	5FU+LV +irinotecan	500mg/m <sup>2</sup> weeks 1,2,3,4 q6w	BL	333	264	ref		15.0	nr	nr	31%

ref= reference; nr= not reported; NA= not available. nrd= not reached. HR= hazard ratio. qXw= every X weeks (X is a number). d= day. h=hour. w=week, m=month; y= year. Adm= dose administration type (CI= continuous infusion; BL= bolus). <sup>1</sup>OS rate at 6 years <sup>2</sup>Dose was converted from per weight to per BSA using a conversion factor of 40 kg/m<sup>2</sup>

## **7 APPENDIX: SUMMARY OF PUBLICATIONS INCLUDED IN THE LITERATURE REVIEW**

### **A. PUBLICATIONS IN PANCREATIC CANCER**

#### **7.A.1 Oettle2014**

##### **Authors and Title**

Oettle et al. Second-Line Oxaliplatin, Folinic Acid, and Fluorouracil Versus Folinic Acid and Fluorouracil Alone for Gemcitabine-Refractory Pancreatic Cancer: Outcomes From the CONKO-003 Trial. *J Clin Oncol* 32(23):2423-2429, 2014.

##### **Purpose**

To assess the efficacy of a second-line regimen of oxaliplatin and folinic acid–modulated fluorouracil in patients with advanced pancreatic cancer who have experienced progression while receiving gemcitabine monotherapy.

##### **Patients and Methods**

A total of 168 patients who experienced disease progression during first-line gemcitabine therapy were randomized to folinic acid and fluorouracil (FF) (n=84) or oxaliplatin and FF (OFF) (n=76). FF comprised IV folinic acid 200 mg/m<sup>2</sup> followed by a continuous IV infusion of fluorouracil 2,000 mg/m<sup>2</sup> over 24 hours on days 1, 8, 15, and 22. OFF comprised FF and oxaliplatin 85 mg/m<sup>2</sup> IV administered before FF on days 8 and 22.

##### **Results**

The median overall survival in the OFF group (5.9 months; 95% CI, 4.1 to 7.4) versus the FF group (3.3 months; 95% CI, 2.7 to 4.0) was significantly improved (HR, 0.66; 95% CI, 0.48 to 0.91; log-rank p = .010). Time to progression with OFF (2.9 months; 95% CI, 2.4 to 3.2) versus FF (2.0 months; 95% CI, 1.6 to 2.3) was significantly extended also (HR, 0.68; 95% CI, 0.50 to 0.94; log-rank p = .019).

##### **Relevance to 5-FU dose comparisons**

As the two arms of this study had the same 5-FU regimen (24 hour continuous infusion), no conclusions can be drawn about the 5-FU dose. The dose and schedule for the FF was used for the control arm of NAPOLI-1.

## 7.A.2 Gill2014

### Authors and Title

Gill et al. PANCREOX: A randomized phase 3 study of 5-FU/LV with or without oxaliplatin for 2nd line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. 2014 ASCO Annual Meeting, BC Cancer Agency, Canada. Abstract 4022.

### Purpose

To compare 5-FU/LV with and without oxaliplatin for 2nd line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy

### Patients and Methods

One hundred eight patients with advanced pancreatic cancer previously treated with gemcitabine were randomized to either the 5-FU/LV treatment group (5-FU/LV without oxaliplatin) as in the FF regimen published by Oettle, et al, 2013, IV folinic acid 200 mg/m<sup>2</sup> followed by a continuous IV infusion of fluorouracil 2,000 mg/m<sup>2</sup> over 24 hours on days 1, 8, 15, and 22 (n=54) or the mFOLFOX6 treatment group (5-FU/LV with oxaliplatin), oxaliplatin 85 mg/m<sup>2</sup> IV over two hours on days 1 and 15, leucovorin 400 mg/m<sup>2</sup> IV over two hours concurrent with oxaliplatin, fluorouracil 400 mg/m<sup>2</sup> IV bolus, followed by fluorouracil 2400 mg/m<sup>2</sup> IV over 46 hours (n=54)

### Results

The median progression free-survival was 3.1 months with 5-FU/LV and 2.9 months with mFOLFOX6 (HR=1.00 [95% CI: 0.66-1.53], p value = 0.989). The overall response rate was 8.5% in the 5-FU/LV group and 13.2% in the mFOLFOX6, p = 0.361, no p value, CI, or Odds Ratios reported. The complete response was 0% in both treatment groups. The median duration of overall survival was 9.9 months (95% CI: 6.7 – 16.9) with 5-FU/LV and 6.1 months (95% CI: 3.2 – 8.0) with mFOLFOX6 (HR=1.78 [95% CI: 1.08 – 2.93], p value = 0.024). OS was noted by the authors to have a potential bias because of imbalances in subsequent treatments (23% received subsequent therapies) and disease characteristics within the younger patient subgroup

### Relevance to 5-FU dose comparisons

In contrast to the results presented by Oettle et al. for CONKO-003, overall survival was better in the cohort without oxaliplatin in this study in second-line disease, and is much longer than previously published results with this treatment.

### **7.A.3 Takada1994**

#### **Authors and Title**

Takada et al. Comparison of 5-Fluorouracil, Doxorubicin and Mitomycin C with 5-Fluorouracil Alone in Treatment of Pancreatic-Biliary Carcinomas. *Oncology* 51:396-400, 1994.

#### **Purpose**

To compare the safety and efficacy of a modified FAM regimen (5-FU, doxorubicin, and mitomycin C [MMC]) to 5-FU alone in the treatment of patients with nonresectable carcinomas of the pancreas or biliary tract.

#### **Patients and Methods**

Seventy-one patients with previously treated nonresectable cancers of the pancreas or biliary tract were randomized to two chemotherapy regimens: Arm A (n=35), 5-FU, doxorubicin, and MMC or Arm B (n=36), 5-FU alone. Arm A consisted of MMC 6 mg/m<sup>2</sup> administered intravenously on day 1; 5-FU 310 mg/m<sup>2</sup>/day IV was administered by bolus injections for 5 days in week 1 and week 3; ADR 12 mg/m<sup>2</sup>/day IV was administered in week 2. Each drug administration was repeated every 6 weeks. Arm B consisted of 5-FU alone, administered in the same manner as Arm A.

#### **Results**

PR was achieved in 1 patient (4%) in Arm A. No change and PD were observed in 10 (40%) and 14 (56%) in Arm A, and 12 (46%) and 14 (54%) in Arm B, respectively. Median time to PD was 3.1 months (95% CI: 6.9-3.3 months) in Arm A and 2.5 months (95% CI: 4.9-2.5 months) in Arm B, with no significant differences between the two arms (log rank test, p =0.18). Median overall survival was 6.2 months (CI: 10.8-6.6 months) in Arm A and 6.0 months (CI: 10.1-5.8 months) in Arm B, with no significant differences between the two (log rank, p =0.67). One year survival rate was 14.3% (CI: 4.8-30.3%) in Arm A, and 25% (CI: 12.2-42.2%) in Arm B, no p value or CI reported.

#### **Relevance to 5-FU dose comparisons**

As the two arms of this study had the same 5-FU regimen (bolus injection for d1-5 of week one and three, repeated every six weeks), no conclusions can be drawn about the impact of different 5-FU dose and schedule on patients with previously treated nonresectable pancreatic cancer. Time to progression and overall survival were similar to what has been seen in other studies of pancreatic cancer.

#### **7.A.4 DeCaprio1991**

##### **Authors and Title**

DeCaprio et al. Fluorouracil and High-Dose Leucovorin in Previously Untreated Patients With Advanced Adenocarcinoma of the Pancreas: Results of a Phase II Trial. *J Clin Oncol* 1991; 9:2128-2133.

##### **Purpose**

To evaluate the safety and efficacy of 5-FU and leucovorin in previously untreated patients with histologically proven locally un-resectable or metastatic adenocarcinoma of the pancreas and measurable lesions.

##### **Patients and Methods**

Forty-two previously untreated patients with advanced, measurable adenocarcinoma of the pancreas were treated with weekly IV fluorouracil (5-FU; 600 mg/m<sup>2</sup> IV bolus) and leucovorin 500 mg/m<sup>2</sup> IV for 6 weeks followed by a 2-week rest. The median total dose of 5-FU delivered was 6,400 mg/m<sup>2</sup> (range, 600 to 38,500 mg/m<sup>2</sup>). A median of 11 (range, one to 76) doses was given. A median of two courses was given (range, 0.2 to 13). The main end points were response as measured by shrinkage of the primary and metastatic tumor and survival.

##### **Results**

There were three partial responses (three of 42 [7%]; 95% CI, 1 % to 19%) and no complete responses. Median survival was 6.2 months (range, 0.2 to 33 months), with seven patients surviving longer than 12 months. No HRs were reported.

##### **Relevance to 5-FU dose comparisons**

Patients with untreated advanced pancreatic adenocarcinoma were treated with weekly IV fluorouracil (5 FU; 600 mg/m<sup>2</sup> IV) and leucovorin 500 mg/m<sup>2</sup> IV for 6 weeks followed by a 2-week rest. Survival and response rates are similar to what has been seen with other 5-FU regimens used prior to 1991.

### **7.A.5 Figer2000**

#### **Authors and Title**

Figer et al. A Comparison of Two Dose Regimens in Pancreatic Cancer. *J Chemother.* 2000; 12(5):442-445.

#### **Purpose**

To evaluate the safety and efficacy of 5-FU and leucovorin (LCV), comparing standard and dose intense schedules in patients with histologically proven pancreatic cancer

#### **Patients and Methods**

Forty-seven consecutive patients on two hospital campuses with histologically proven pancreatic cancer were treated with a standard or dose intense 5-FU regimen, based on their treatment center. The dose intense schedule was a regimen of 5-FU 900 mg/m<sup>2</sup> IV preceded by LCV 200 mg/m<sup>2</sup>, both as rapid IV infusion every 2 weeks. The standard regimen schedule was: LCV 20 mg/m<sup>2</sup> followed by 5-FU 370 mg/m<sup>2</sup> IV bolus for 5 consecutive days every 28 days. The median duration of treatment was 4.3 months (5.1 for the dose intense and 3.6 for the standard schedule).

#### **Results**

Partial response was observed in one standard dose regimen patient (4%). No change was observed in 4 (40%) standard dose regimen patients and 8 (53%) intense schedule regimen patients (total 12 patients [48%]). Progression of disease was observed in 5 (50%) standard dose regimen patients and 7 (47%) intense schedule regimen patients (total 12 patients [48%]). Clinical benefit, measured by symptomatic improvement, was observed in 3 (12%) standard dose regimen patients and 6 (27%) intense schedule regimen patients (total 9 patients [19%]). Median survival was 8 months for all the patients (5 months for standard dose regimen and 9 months for intense dose regimen). The 1 year survival rate was 32% (dose groups not reported). No p values, CIs, or HRs were reported. There was no survival benefit for the dose intense regimen.

#### **Relevance to 5-FU dose comparisons**

When comparing a dose intense 5-FU administration regimen to the standard 5-FU administration regimen in pancreatic cancer patients, it was determined that the study regimens give similar outcome results, with some improvement in quality of life for a small percentage of patients. Authors conclude that “the dose-intense schedule is of little benefit in treating pancreatic cancer”

### **7.A.6 Choi2000**

#### **Authors and Title**

Choi et al. Effects of 5-Fluorouracil and Leucovorin in the Treatment of Pancreatic-Biliary Tract Adenocarcinomas. *Am J Clin Oncol* 23(4): 425-428, 2000.

#### **Purpose**

To study the efficacy of 5-Fluorouracil (5-FU), modulated with leucovorin, in patients affected by advanced pancreatic and biliary tract cancer

#### **Patients and Methods**

Fifty-one patients with advanced adenocarcinoma of the pancreas (23 stage IV pancreatic cancer patients) or biliary tract (9 stage IV gallbladder cancer patients and 19 cholangiocarcinoma patients), previously untreated with chemotherapy, received chemotherapy consisting of leucovorin 25 mg/m<sup>2</sup>/day by 2-hour intravenous infusion, followed by 5-FU 375 mg/m<sup>2</sup>/day by bolus intravenous infusion, from day 1 to 5. The treatment was repeated every 4 weeks. Chemotherapy was continued until progression of disease or unacceptable toxicity ensued. Efficacy endpoints included: complete response (CR), partial response (PR), stable disease, and progressive disease.

#### **Results**

Of the 23 pancreatic adenocarcinoma patients, one patient showed CR with a survival duration of 13 months (response duration was 9 months). Three pancreatic adenocarcinoma patients had PRs with survival times of 6, 12, and 15 months. The overall response rate was 17.4% (95% CI, 7.2%-36.2%). The median time of overall survival was 6 months (95% CI not reported, range: 1-15 months). Of the 28 biliary tract cancer patients, CRs were observed in 2 patients (7.1%). Seven patients had PRs. The overall response rate was 32.1% (95% CI, 20.3%-57.5%). HRs were not reported.

#### **Relevance to 5-FU dose comparisons**

5-FU was dosed on a schedule of 375 mg/m<sup>2</sup>/day on day 1 to 5 every four weeks in combination with leucovorin in previously untreated patients with adenocarcinomas of the pancreas or biliary tract, resulted in a median survival of 6 months. Results in this small trial showed a slightly better response rate than the historical results for 5-FU monochemotherapy (15% in Mayo Clinic experience), but these response rates and overall survival are not superior to those using 5-FU monochemotherapy historical controls at that time.

### **7.A.7 Cullinan1990**

#### **Authors and Title**

Cullinan et al. A Phase III Trial on the Therapy of Advanced Pancreatic Carcinoma, Evaluations of the Mallinson Regimen and Combined 5-Fluorouracil, Doxorubicin, and Cisplatin. *Cancer*. 1990 May 15;65(10):2207-12.

#### **Purpose**

To compare the safety and efficacy of the following three chemotherapeutic regimens in the treatment of advanced pancreatic carcinoma: 5-fluorouracil (5-FU) versus Mallinson Regimen versus Combined 5-Fluorouracil, Doxorubicin, and Cisplatin (FAP)

#### **Patients and Methods**

One hundred eighty-four patients with previously untreated, histologically proven advanced pancreatic adenocarcinoma were randomly assigned to therapy with 5-fluorouracil alone (5-FU; n=64), to the Mallinson regimen (combined and sequential 5-FU, cyclophosphamide, methotrexate, vincristine, and mitomycin C; n=61), or to combined 5-FU, doxorubicin, and cisplatin (FAP; n=59). Patients with both measurable and nonmeasurable disease were included. The primary study end point was survival. 5-FU alone: 5-FU was given in undiluted form by rapid intravenous injection at a dosage of 500 mg/m<sup>2</sup>/d for 5 consecutive days. Courses were repeated every 5 weeks. Mallinson regimen: As an induction therapy 5-FU was given by rapid intravenous injection at a dosage of 270 mg/m<sup>2</sup>/d for 5 consecutive days. Cyclophosphamide was administered by rapid intravenous injection at a dose of 160 mg/m<sup>2</sup> on days 1 and 5, methotrexate was given by rapid intravenous injection at 11 mg/m<sup>2</sup> on days 1 and 4, and vincristine was given by rapid intravenous injection at 0.7 mg/m<sup>2</sup> on days 2 and 5. For maintenance therapy the patient was initiated on 5-FU (350 mg/m<sup>2</sup>) and mitomycin C (3.5 mg/m<sup>2</sup>) at 5 weeks, both given by rapid intravenous injection daily for 5 consecutive days and repeated every 6 weeks. FAP: 5-FU was given in undiluted form by rapid intravenous injection at a dosage of 300 mg/m<sup>2</sup>/d for 5 consecutive days. Doxorubicin was given by rapid intravenous injection on day 1 at a dose of 40 mg/m<sup>2</sup>. In jaundiced patients (total serum bilirubin level < 2 mg) the dose was reduced by 30%. The maximum total dose allowed was 500 mg/m<sup>2</sup>. Cisplatin was administered by 2-hour to 3-hour intravenous infusion in 1000 ml of 5% dextrose and 0.5 normal saline together with 25 g of mannitol. It was given at a dose of 60 mg/m<sup>2</sup> on the first day of each course of therapy and infusion was initiated immediately after administration of 5-FU and doxorubicin. Courses of this three-drug combination were repeated every 5 weeks.

#### **Results**

Only 41 patients had measurable disease, objective tumor responses were seen for one patient (7%) treated with 5-FU alone, three patients (21%) for the Mallinson regimen, and two patients (15%) treated with FAP. One hundred sixty-eight of the 184 evaluable patients were dead at the time of the report. The median interval to progression for each of the three regimens was 2.5 months. Survival curves intertwined with similar median survival times for patients treated with FAP and 5-FU (3.5 months) and those who received the Mallinson regimen (4.5 months). Neither combination regimen offers a survival advantage over 5-FU alone (both one-sided, P > 0.48, CI not reported).

#### **Relevance to 5-FU dose comparisons**

The dose and schedule of 5-FU treatment varied by regimen in this trial. Increased toxicity was seen in regimens using a combination of agents, without a benefit in overall survival.

### **7.A.8 Kovach1974**

#### **Authors and Title**

Kovach et al. A Controlled Study of Combined 1,3-BIS-(2-Chloroethyl)-1-nitrosourea and 5 fluorouracil Therapy for Advanced Gastric and Pancreatic Cancer. *Cancer* 33: 563-567, 1974.

#### **Purpose**

Treatment with the combination of 1, 3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) and 5-FU was compared to therapy with each drug used alone in a prospective randomized study of 167 patients with advanced adenocarcinoma of the stomach and pancreas.

#### **Patients and Methods**

A total of 167 patients with histologically proven unresectable adenocarcinoma of the stomach or pancreas were randomized to treatment with 5-FU, or BCNU, or a combination of BCNU and 5 FU according to the primary site of origin of the adenocarcinoma, the grade of anaplasia, and the site of the primary indicator lesion. All drugs were given intravenously by rapid injection according to the following schedules: 5-FU alone, 13.5 mg/kg/day x 5 days (n=59); BCNU alone, 50 mg/m<sup>2</sup>/day x 5 days (n=44); and 5-FU plus BCNU, 10 mg/kg/day x 5 days and 40 mg/m<sup>2</sup>/day x 5 days (n=64), respectively.

#### **Results**

Therapy with the combination of 5-FU and BCNU was associated with the highest rate of objective response, 41.3% in carcinoma of the stomach and 33.3% in carcinoma of the pancreas. Although these percentages are more favorable than those observed with 5-FU alone, the differences are not significant (gastric carcinoma,  $p \approx 0.3$ ; pancreatic carcinoma  $p \approx 0.15$ ). Therapy with the combination, 5-FU and BCNU, and with 5-FU alone was more effective ( $p < 0.05$ ) than BCNU alone in producing objective responses in both pancreatic and gastric adenocarcinoma. The corresponding rates of objective response with 5-FU alone were 28.6% and 16.1%, and with BCNU alone the rates were 17.4% and 0%. In pancreatic carcinoma, there was no discernible difference in survival among patients in each treatment arm. In gastric carcinoma, however, both 5-FU and the combination therapy produced an increase in survival when compared to BCNU alone, and the combination of 5-FU and BCNU produced an increase in long-term survival compared to 5-FU alone (5-FU, 7% surviving; 5-FU + BCNU, 26.5% surviving;  $p < .05$ ). CIs were not reported.

#### **Relevance to 5-FU dose comparisons**

In both pancreatic carcinoma and gastric carcinoma patients, the 30% difference in dose intensity of 5-FU, 13.5 mg/kg/day vs 10 mg/kg/day, did not significantly affect the efficacy measurements.

### **7.A.9 Burris1997**

#### **Authors and Title**

Burris et al. Improvements in Survival and Clinical Benefit With Gemcitabine as First Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial. *J Clin Oncol* 15:2403-2413, 1997.

#### **Purpose**

To compare the efficacy of gemcitabine in patients with newly diagnosed advanced pancreas cancer

#### **Patients and Methods**

One hundred twenty-six patients with previously untreated advanced symptomatic pancreas cancer were randomized to receive either gemcitabine (n= 63), or to single agent 5 FU (n= 63). Gemcitabine was given at 1,000 mg/m<sup>2</sup> weekly x 7 followed by 1 week of rest, then weekly x 3 every 4 weeks thereafter, and 5 FU given at 600 mg/m<sup>2</sup>, once weekly, by IV over 30 minutes, with a cycle defined as one 4-week period. Treatment with gemcitabine or 5-FU continued until disease progression or until there was significant clinical deterioration because of tumor-related symptoms.

#### **Results**

There was a clinical benefit response experienced by 23.8% of gemcitabine-treated patients versus 4.8% of 5-FU-treated patients (p = .0022). The median survival durations were 5.65 months (95% CI not reported) and 4.41 (95% CI not reported) months for gemcitabine-treated and 5-FU-treated patients, respectively (p = 0.0025, no CI reported). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients. The 5-week extension translates into a 28% relative improvement in median survival. In addition, the 6-, 9-, and 12-month survival rates were higher with gemcitabine (46%, 24%, and 18%, respectively) than with 5-FU (31 %, 6%, and 2%, respectively). Despite a modest tumor response rate of only 5.4% in the gemcitabine arm and 0% in the 5-FU arm, there was a statistically significant improvement in survival for patients who received gemcitabine. Other measures of efficacy included response rate, time to progressive disease, and survival. Only three (4.8%) 5-FU patients experienced clinical benefit (sustained [ $\geq$  4 weeks] improvement in at least one parameter without worsening in any others), as assessed by their primary measures (pain and Karnofsky performance status). The median time to achieve a clinical benefit response was 7 weeks for the gemcitabine-treated patients (n=15) and 3 weeks for the 5-FU-treated patients (n = 3). The mean duration of clinical benefit was 18 weeks and 13 weeks for gemcitabine-treated and 5-FU-treated patients. The median time to progressive disease for gemcitabine was 9 weeks compared with 4 weeks for the 5-FU arm (log-rank test, p = .0002, CI not reported). Among fifty seven 5-FU -treated patients with measurable disease, none (0%) achieved a complete or partial response. Eleven patients (19%) had stable disease. The difference in partial response rates was not statistically significant. HRs were not reported.

#### **Relevance to the comparison of 5-FU doses**

The high initial response rates reported for several multi-agent regimens, such as the Mallinson regimen (5-FU, methotrexate, vincristine, and cyclophosphamide induction followed by maintenance 5-FU and mitomycin), the 5-FU, doxorubicin, and mitomycin (FAM) regimen, the cisplatin, cytarabine, and caffeine (CAC) regimen, and the streptozotocin, mitomycin, and 5-FU (SMF) regimen appeared to herald advances in the treatment of patients with advanced pancreas cancer. When the present study was designed, single-agent 5-FU was selected as the control treatment, as it had been the previous standard and the dose would be approximately equitoxic to the dose of gemcitabine. The weekly schedule of 5-FU was selected to allow the trial to be conducted on a single-blind basis. The survival duration with this 5-FU regimen in this setting, previously untreated advanced pancreatic cancer, was consistent with previously reported data.

### **7.A.10 Cullinan1985**

#### **Authors and Title**

Cullinan et al. A Comparison of Three Chemotherapeutic Regimens in the Treatment of Advanced Pancreatic and Gastric Carcinoma: Fluorouracil vs Fluorouracil and Doxorubicin vs Fluorouracil, Doxorubicin, and Mitomycin. JAMA. 1985 Apr 12;253(14):2061-7.

#### **Purpose**

At the time of this study, conflicting literature existed as to the benefit of adding other chemotherapeutic agents to single agent 5-FU. This study was designed to compare the safety and efficacy of the following three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma: fluorouracil versus fluorouracil and doxorubicin (FA) versus fluorouracil, doxorubicin, and mitomycin (FAM).

#### **Patients and Methods**

Two hundred ninety-five patients with previously untreated un-resectable or metastatic gastric or pancreatic adenocarcinoma were stratified according to primary tumor (gastric or pancreatic), stage of disease (regionally un-resectable or distant metastasis), the presence of measurable disease, and performance status (Eastern Cooperative Oncology Group [ECOG] performance score). Patients were randomized to treatment with fluorouracil alone (n=101), FA (n=93), or FAM (n=101). The fluorouracil alone regimen was given by a five-day intensive course at a daily dose of 500 mg/m<sup>2</sup>. Courses were repeated at four weeks, eight weeks, and every five weeks thereafter. The FA combination was administered with fluorouracil given by a four-day course at a daily dose of 400 mg/m<sup>2</sup> and with 40 mg/m<sup>2</sup> of doxorubicin given on the first day of each course. Courses were repeated at four weeks, eight weeks, and every five weeks thereafter. The FAM combination was administered with fluorouracil was given at 600 mg/ m<sup>2</sup> on days 1, 8, 29, and 36; doxorubicin at 30 mg/ m<sup>2</sup> on days 1 and 29; and mitomycin at 10 mg/ m<sup>2</sup> on day 1. All drugs were given by rapid intravenous injection. The primary end point of the study was survival. Other endpoints included disease progression, objective response rates, and palliative effects (improved performance, body weight, or symptoms).

#### **Results**

The median survival time for patients with pancreatic cancer was 22 weeks, and for patients with gastric carcinoma it was 29 weeks. There was no difference in survival between the three different regimens tested. The median interval to progression for all patients with pancreatic carcinoma was nine weeks, and for all with gastric carcinoma, 17 weeks. As with survival times, the distribution of progression times between the three treatment arms within each tumor type completely overlapped.

#### **Relevance to 5-FU dose comparisons:**

Because the FAM combination was becoming an increasingly employed therapy for gastric and pancreatic carcinoma, it was important that the therapeutic claims for this regimen be evaluated by randomized controlled comparison with the previously accepted standard, fluorouracil used alone. The two-drug combination of fluorouracil plus doxorubicin (FA) was evaluated because of a very small but randomized trial indicating a possible therapeutic advantage in gastric cancer for this regimen over fluorouracil as a single drug. The dosing regimens for 5-FU varied between the different arms to conform with concomitant medications and prior studies. In the 5 FU alone arm dosing was 5 days of 500 mg/m<sup>2</sup>, in the FA arm it was given as 4 days of 400 mg/m<sup>2</sup>, and in the FAM arm the dose was 600 mg/m<sup>2</sup> on days 1, 8, 29 and 36 of an 8-week cycle. While there were different combination medications, no differences in efficacy outcomes were apparent, and survivals were consistent with other reported outcomes for patients with previously untreated unresectable or metastatic pancreatic cancer with bolus 5-FU treatment.

### **7.A.11 Ducreux2002**

#### **Authors and Title**

Ducreux 2002. A randomized trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma. *Ann Oncol* (2002) 13 (8): 1185-1191.

#### **Purpose**

To compare the safety and efficacy of 5-FU versus 5-fluorouracil (5-FU) plus cisplatin (FUP) in pancreatic adenocarcinoma patients

#### **Patients and Methods**

Two hundred seven patients with untreated cytologically or histologically proven metastatic or locally advanced adenocarcinoma of the pancreas were randomized to one of two chemotherapy regimens. The two chemotherapy regimens consisted of a control FU arm (5 FU 500 mg/m<sup>2</sup>/day administered by rapid infusion for 5 days) (n=103) and the investigational FUP arm (continuous infusion 5-FU 1000 mg/m<sup>2</sup>/day for 5 days plus cisplatin 100 mg/m<sup>2</sup> on day 1 or day 2) (n=104). In both arms, chemotherapy was repeated at day 29. Among the 202 patients who received chemotherapy, the median total dose of 5-FU received was 5 g/m<sup>2</sup> in the FU arm and 10 g/m<sup>2</sup> in the FUP arm.

#### **Results**

The tumor response rate was 0% with FU and 10% with FUP (95% CI, 4-16%). Median survival was 102 days in the FU arm and 112 days in the FUP arm, and there was no difference in the relative risk of death between treatment arms (log-rank test 0.10). However, the percentage of survivors at 1 year was 17.3% in the FUP arm compared with 8.7% in the FU arm (p = 0.07, no CI reported). The median duration of progression free-survival was 59 days with FU and 73 days with FUP. At 6 months, 4% of patients in the FU arm and 19% in the FUP arm were free from progression. At 1 year, seven patients in the FUP arm were free from progression compared with none in the FU arm (p = 0.0001, log rank test, CI not reported). Survival was compared after adjusting for absence of metastases, ampulloma, the number of target lesions and eligibility, and the FUP regimen was not found to be superior to the FU regimen in terms of survival (p = 0.08, CI not reported). No HR was reported.

#### **Relevance to 5-FU dose comparisons**

Median survival was 102 days in the FU arm and 112 days in the FUP arm, within the range for bolus 5-FU treatment for untreated pancreatic cancer.

### **7.A.12 Van Rijswijk2004**

#### **Authors and Title**

Van Rijswijk et al. Weekly high-dose 5-fluorouracil and folinic acid in metastatic pancreatic carcinoma: a phase II study of the EORTC GastroIntestinal Tract Cancer Cooperative Group. *Eur J Cancer* 40: 2077–2081, 2004.

#### **Purpose**

The aim of the study was to assess the response rate and toxicity of high-dose 24 h infusion of 5 FU in metastatic adenocarcinoma of the pancreas.

#### **Patients and Methods**

Patients with measurable disease, performance status 0–2, and no prior chemotherapy were registered to receive cycles of leucovorin (LV) 500 mg/m<sup>2</sup> (or 1-LV 250 mg/m<sup>2</sup>) over 1 h followed by 5-FU 2600 mg/m<sup>2</sup> as a 24 h infusion, weekly for 6 weeks, followed by a 2-week rest.

#### **Results**

The number of enrolled was 37. Three patients (9%, 95% CI: 2-24) out of 33 patients with reportable activity outcome achieved a partial response, and another 7 (21%, CI not reported) patients had stable disease. The median time to progression was 7 weeks (95% CI: 6.4 11.7), and the median survival 19 weeks (95% CI: 12-35.2).

#### **Relevance to 5-FU dose comparisons**

The improved response rate of protracted infusion that exists in colorectal cancer is not evident in pancreatic cancer. This trial showed a low response rate of 9%, which was below the present level of interest (20%) of this schedule, and no clear prolongation of overall survival based on historical controls.

## B. PUBLICATIONS IN COLORECTAL CANCER

### 7.B.1 Andre2007

#### Authors and Title

Andre, et al. Phase III Study Comparing a Semimonthly With a Monthly Regimen of Fluorouracil and Leucovorin As Adjuvant Treatment for Stage II and III Colon Cancer Patients: Final Results of GERCOR C96.1. *J Clin Oncol* 25:3732-3738, 2007.

#### Purpose

To compare the efficacy and safety of a semimonthly regimen of fluorouracil and leucovorin (the LV5FU2 group) *versus* a monthly regimen of fluorouracil and leucovorin (the mFU/LV group) as adjuvant treatment of stage II and III colon cancer

#### Patients and Methods

Patients with stage II or III colon or high rectum cancer were randomly assigned to two adjuvant chemotherapy regimens (LV5FU2 or mFU/LV) and two treatment durations (24 or 36 weeks) using a 2x2 factorial design. Patients assigned to the LV5FU2 group received racemate (*dl*-)LV 200 mg/m<sup>2</sup> or levogyre (*l*-)LV 100 mg/m<sup>2</sup> (according to drug availability in each institution), as a 2-hour infusion, followed by bolus fluorouracil 400 mg/m<sup>2</sup> and a 22-hour infusion of fluorouracil 600 mg/m<sup>2</sup> for 2 consecutive days every 14 days. Patients in the mFU/LV group received an infusion of *dl*-LV 200 mg/m<sup>2</sup> (or *l*-LV 100 mg/m<sup>2</sup>) for 15 minutes, followed by a 15-minute bolus fluorouracil 400 mg/m<sup>2</sup> for 5 consecutive days every 28 days.

#### Results

A total of 905 patients with stage II (43%) and III (57%) colon cancer were enrolled. The median follow-up was 6 years. No statistically significant difference was observed between LV5FU2 (n=452) and mFU/LV (n=453) in terms of overall survival (OS; HR= 1.02; 95% CI= 0.77-1.34; *P* =.91) or Disease-Free Survival (DFS, hazard ratio [HR], 1.01; 95% CI, 0.81-1.27; *P* =.74). The median time to OS was not reached. The 6-year OS were 78% and 76% for mFU/LV and LV5FU2, respectively).

	LV5FU2	mFU/LV
<b>5FU dose intensity (mg/m2/week)</b>	800	500
<b>N</b>	452	453
<b>Median OS (months)</b>	Not reached	Not reached
<b>OS Hazard Ratio</b>	Reference	1.02 (95%CI: 0.77-1.34 <i>P</i> =.91)
<b>OS rate 6 year</b>	76%	78%
<b>DFS Hazard Ratio</b>	Reference	1.01 (95% CI: 0.81-1.27; <i>P</i> = .74).
<b>Response Rate (%)</b>	Not reported	Not reported

#### Relevance to the comparison of 5FU doses

This study demonstrates that a difference in 5-FU dose intensities of 500 and 800 mg/m<sup>2</sup>/week (mFU/LV and LV5FU2, respectively) and infusion durations of 15 min and 22 h in adjuvant therapy for patients with Stage 2 and 3 colon cancer did not have an impact to the OS and DFS.

## 7.B.2 Goldberg2004

### Authors and Title

Goldberg, et al. A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer.

### Purpose

To compare the activity and toxicity of two-drug combinations out of three drugs (fluorouracil, irinotecan, and oxaliplatin) in patients with metastatic colorectal cancer who had not been treated previously for advanced disease.

### Methods

Patients were concurrently randomly assigned to receive irinotecan and bolus fluorouracil plus leucovorin (IFL, control combination), oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX), or irinotecan and oxaliplatin (IROX). The primary end point was time to progression, with secondary end points of response rate, survival time, and toxicity. The regimens (doses in mg/m<sup>2</sup>) were as follows: IFL was irinotecan 125 and bolus FU 500 plus LV 20 on days 1, 8, 15, and 22 every 6 weeks; FOLFOX was oxaliplatin 85 on day 1 and bolus FU 400 plus LV 200 followed by FU 600 in 22-hour infusions on days 1 and 2 every 2 weeks; and IROX was oxaliplatin 85 and irinotecan 200 every 3 weeks.

### Results

A total of 795 patients were randomly assigned between May 1999 and April 2001. Median follow-up time is 20.4 months. A median time to progression of 8.7 months, response rate of 45%, and median survival time of 19.5 months were observed for FOLFOX. These results were significantly superior to those observed for IFL for all end points (6.9 months, 31%, and 15.0 months, respectively) or for IROX (6.5 months, 35%, and 17.4 months, respectively) for time to progression and response.

	<b>IFL</b>	<b>FOLFOX</b>	<b>IROX</b>
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	333	800	-
<b>N</b>	264	267	264
<b>Median OS (months)</b>	15.0	19.5	17.4
<b>OS Hazard Ratio (compared to IFL)</b>	Reference	0.66 (95%CI 0.54-0.82; P=.0001)	0.81 (95%CI 0.66-1.00; P=.04)
<b>Median TTP (months)</b>	6.9	8.7	6.5
<b>TTP Hazard Ratio (compared to IFL)</b>	Reference	0.74 (95% CI, 0.61 to 0.89; P=0.0014)	1.02 (95% CI 0.85-1.23; P > .50)
<b>Response Rate (%)</b>	31%	45% (P=.002)	35% (P=.03)

### Relevance to the comparison of 5FU doses

This study provides an example of a pivotal trial containing two different 5FU dose intensities (333 and 800 mg/m<sup>2</sup>/week for IFL and FOLFOX, respectively) in patients with untreated metastatic colorectal cancer. While the authors acknowledged that the study does not allow isolation of the relative independent contributions of oxaliplatin versus irinotecan and infused versus bolus FU, the authors recommended the use of FOLFOX a first-line standard of care for patients with advanced colorectal cancer, because the superiority the FOLFOX arm is most likely attribute-able to oxaliplatin (vs. irinotecan) rather than to the difference in the 5-FU dose regimen.

### 7.B.3 Hansen 1996

#### Authors and Title

Hansen, et al. Phase III Study of Bolus Versus Infusion Fluorouracil With or Without Cisplatin in Advanced Colorectal Cancer

#### Purpose

This phase 3 study in adults with metastatic colorectal cancer was planned as a comparison of objective response rates, toxicity, and survival in patients receiving bolus versus protracted-infusion 5-FU with or without cisplatin.

#### Methods

Previously untreated patients with advanced, measurable metastatic colorectal cancer were randomly assigned to receive one of 4 treatment arms:

- A (bolus 5-FU at 500 mg/m<sup>2</sup> for 5 days followed in 2 weeks by weekly bolus 5-FU at 600 mg/m<sup>2</sup>);
- B (bolus 5-FU at 500 mg/m<sup>2</sup> for 5 days followed in 2 weeks by weekly bolus 5-FU at 600 mg/m<sup>2</sup>, plus weekly cisplatin at 20 mg/m<sup>2</sup>);
- C (5-FU at 300 mg/m<sup>2</sup> per day by continuous infusion), or
- D (5-FU at 300 mg/m<sup>2</sup> per day by continuous infusion plus weekly cisplatin at 20 mg/m<sup>2</sup>).

#### Results

A total of 497 (477 eligible) patients were assigned to A, B, C, or D. Because of excessive toxicity, treatment B was discontinued after only 12 patients had begun treatment. The median survival time was 10.4, 13.0, and 13.0 months for patients in A (bolus 5-FU), C (continuous-infusion 5-FU alone), and D (cisplatin added to continuous-infusion 5-FU); these differences were not statistically significant. Median time to disease progression was 5.1, 6.2, and 6.5 months for A, C, and D, respectively; these differences achieved statistical significance. Objective tumor response was observed in 28 (18%) of 153 patients receiving treatment A, in 45 (28%) of 159 patients receiving treatment C (C versus A; P = .045), and in 47 (31%) of 153 patients receiving treatment D (D versus A; P = .016).

	<b>A (bolus 5FU)</b>	<b>B (bolus 5FU+DDP)</b>	<b>C (CI 5FU)</b>	<b>D (CI5FU+DDP)</b>
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	600	600	2100	2100
<b>N</b>	153	12	159	154
<b>Median OS (months)</b>	10.4		13.0	13.0
<b>OS Hazard Ratio</b>	Reference		Not Reported P=.223	Not Reported P=.586
<b>OS rate 5 y</b>	Not reported			
<b>Median TTP (months)</b>	5.1		6.2 (C vs A, P=.007)	6.5 (D vs A, P=.017)
<b>TTP Hazard Ratio</b>	Not reported			
<b>Response Rate (%)</b>	18%		28% (C vs A, P=.045)	31% (D vs A, P=.016)

5FU= fluorouracil, DDP= cisplatin, CI= continuous infusion

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**Fig. 2. Overall survival: all patients with follow-up. FU = fluorouracil; DDP = cisplatin.**

**Relevance to the comparison of 5FU doses**

This study provides evidence that a difference in 5FU dose of 600 mg/m<sup>2</sup>/week bolus and 2100 mg/m<sup>2</sup>/week continuous infusion did not have a statistically significant impact to OS, with and without the addition of cisplatin, in patients with chemotherapy-naïve metastatic colorectal cancer. Higher 5FU dose intensity resulted in longer time to disease progression and higher response rate.

### 7.B.4 Kohne2013

#### Authors and Title

Kohne, et al. A randomised phase III intergroup trial comparing high-dose infusional 5-fluorouracil with or without folinic acid with standard bolus 5-fluorouracil/folinic acid in the adjuvant treatment of stage III colon cancer: the Pan-European Trial in Adjuvant Colon Cancer 2 study. Eur J Cancer. 2013 May;49(8):1868-75.

#### Purpose

To investigate whether infusional high-dose 5-fluorouracil (HD-FU) provides a significant improvement in recurrence-free survival (RFS) and overall survival (OS) compared with a standard bolus 5-FU regimen (MayoClinic) in patients with curatively resectable stage III colon cancer

#### Patients and Methods

Patients with UICC stage III, histologically confirmed adenocarcinoma or mucinous adenocarcinoma of the colon who had undergone curative radical resection within the 8 weeks prior to randomization were randomised to receive either the bolus 5-FU/FA regimen (Mayo Clinic) or one of the three HD-FU regimens as follows:

- Bolus 5-FU/FA (the Mayo-Clinic regimen): FU 370-425 mg/m<sup>2</sup>/day on day 1-5 every 4 weeks
- HD-FU: (1) the Spanish TTD regimen: HD-FU alone 3500 mg/m<sup>2</sup> [over 48h] q1w; (2) the German AIO regimen: day 1, FA, 500 mg/m<sup>2</sup> i.v. 2-h infusion, followed by 5-FU, 2600 mg/m<sup>2</sup> [over 24-h], given weekly during a 6-week cycle for 3-cycles; (3) the French de Gramont regimen LV5FU2: day 1–2 of a 2-week cycle, DL-FA, 200 mg/m<sup>2</sup> 2-h infusion, followed by 5-FU, 400 mg/m<sup>2</sup> i.v., bolus, followed by 5-FU, 600 mg/m<sup>2</sup> [over 22-h ], for 12-cycles

#### Results

A total of 1601 patients were randomised to receive a bolus 5-FU/FA or a HD- FU regimen. No differences in OS were observed between the two treatment arms (HR=0.96, 95%CI= 0.78-1.20; p = 0.74), with 3-year OS rate of 84.5% and 85.0% in bolus vs HDFU, respectively. A five-year OS rate of 78.9% was observed in both arms. No differences were observed in RFS (HR =0.997, 95%CI=0.84-1.18; p = 0.98); 3-year and 5-year RFS rates were also similar.

	<b>Bolus 5-FU/FA</b>	<b>HD-FU</b>
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	463-531	3500 2600 800
<b>N</b>	804	797
<b>Median OS (months)</b>	Not reached	Not reached
<b>OS Hazard Ratio</b>	Reference	0.96 (95%CI: 0.78-1.20 P=.74)
<b>OS rate 3 year</b>	84.5%	85.0%
<b>OS rate 5 year</b>	78.9%	78.9%
<b>Median RFS (months)</b>	Not reached	
<b>RFS Hazard Ratio</b>	Reference	0.997 (95%CI=0.84 1.18; P = .98)
<b>Response Rate (%)</b>	Not reported	

#### Relevance to the comparison of 5FU doses

This is the largest (1600 patients) and the most recent study that provides strong evidence that a difference in 5FU dose intensity of 463-531 mg/m<sup>2</sup>/week and 800-3500 mg/m<sup>2</sup>/week and in infusion duration of 15 min and 22-48 h did not have an impact on the OS and RFS in patients with stage 3 colon cancer after adjuvant therapy

### 7.B.5 Leichman 2005

#### Author and Title

Leichman, et al., Assessment of Infusional 5-Fluorouracil Schedule and Dose Intensity: A Southwest Oncology Group and Eastern Cooperative Oncology Group Study. *Clinical Colorectal Cancer*, Vol. 5, No. 2, 119-123, 2005.

#### Purpose

To compare low-dose continuous infusion (LDCI) of 5-fluorouracil (5-FU) versus intermittent high-dose infusion (HDI) of 5-FU in disseminated colorectal cancer (CRC) for evidence of survival advantage based on dose intensity

#### Methods

Eligibility included histologic diagnosis of disseminated CRC, measurable or evaluable disease, no previous therapy for metastatic disease, performance status of 0-2, and adequate renal, hepatic, cardiac, and hematologic function. Patients were randomized to receive (1) LDCI 5-FU 300 mg/m<sup>2</sup> per day continuous infusion for 28 days every 5 weeks or (2) HDI 5-FU 2600 mg/m<sup>2</sup> for 24 hours each week.

#### Results

Between April 1995 and May 1999, 730 patients were accrued (LDCI arm, n = 360; HDI arm, n = 370). Of these, 708 eligible patients were assessable for survival and 690 for toxicity. No significant survival difference was seen between the 2 treatment arms (P = 0.70). Hazard ratio was not reported. Median survival for both groups was 13 months. Kaplan Meyer plot was provided, but no OS rates were reported. Median progression-free survival times were 6 months for the LDCI arm and 5 months for the HDI arm; this difference was not statistically significant (P = 0.93).

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Source: Figure 1 of the reference.

#### Relevance to the comparison of 5FU doses

This study demonstrated that a difference in 5FU dose intensity 1680 and 2600 mg/m<sup>2</sup>/week, and infusion duration of 28 d and 1 d, both given as continuous infusion, did not have an impact to OS and PFS in patients with no previous therapy for metastatic colon cancer.

### 7.B.6 Leichman1995

#### Author and Title

Leichman, et al. Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group study. J Clin Oncol. 1995 Jun;13(6):1303-11.

#### Purpose

To assess efficacy and safety of seven fluorinated pyrimidine-based regimens for the treatment of disseminated colorectal cancer afforded by biochemical modulation or schedule variations

#### Methods

Patients with histologically confirmed metastatic colorectal cancer that was either recurrent or disseminated were randomized to one of the 7 arms:

1. 5-FU IVP: 5-FU 500 mg/m<sup>2</sup> administered as an intravenous push (IVP) on days 1 to 5 every 5 weeks
2. 5-FU IVP + low dose LV: LV 20 mg/m<sup>2</sup> IVP followed immediately by 5-FU 425 mg/m<sup>2</sup> IVP on days 1 to 5 every 4 weeks for two cycles, then every 5 weeks for the duration of study treatment.
3. 5-FU IVP + high dose LV: LV 500 mg/m<sup>2</sup> administered as a 3-hour infusion followed by 5-FU 600 mg/m<sup>2</sup> IVP weekly for 6 weeks followed by 2 weeks of rest for each 8-week cycle.
4. 5-FU CI: 5-FU administered as a continuous infusion by ambulatory infusion pump and in dwelling venous access at a dose of 300 mg/m<sup>2</sup>/d on days 1 to 28, followed by 1 week of rest for each 5-week cycle.
5. 5-FU CI + low dose LV: paralleled arm 4 as a continuous intravenous infusion of 5-FU by ambulatory infusion pump at a dose of 200 mg/m<sup>2</sup>/d for 28 days with added weekly injections of LV at 20 mg/m<sup>2</sup> on days 1, 8, 15, and 22 of a 5-week cycle.
6. 24 h 5-FU: 24-hour infusion of 5-FU at a dose of 2600 mg/m<sup>2</sup> administered weekly on a 4-week schedule (ie, no scheduled rest breaks).
7. 24 h 5-FU+ PALA: analogous to arm 6, but with PALA administered at a dose of 250 mg/m<sup>2</sup> given over 15 minutes 24 hours before the infusion of 5-FU at 2,600 mg/m<sup>2</sup> administered as a 24-hour infusion.

#### Results

Colorectal cancer patients (n=620) were randomized into one of 7 treatment arms with different 5-FU dose regimens. The survival data are mature, with a median follow up of 37 months. Survival hazards ratios showed a positive trend in favor of the unmodulated infusion regimen. Slightly longer survival trends were observed with 5-FU continuous infusion (arm 4) and 24-hour infusion (arm 6), while the addition of PALA (arm 7) yielded noticeably shorter survival durations. Progression-free survival curves showed little difference among the seven regimens. The median progression-free survival time was 6 months in arms 1 through 6 and 4 months in arm 7. No regimen achieved a higher response rate than single-agent bolus 5-FU. High-grade toxicities occurred more frequently in the 5-FU bolus arms.

	1) 5FU IVP	2) 5FU IVP + low dose LV	3) 5FU IVP + high dose LV	4) 5FU CI	5) 5FU CI + low dose LV	6) 24h 5FU	7) 24h 5FU+ PALA
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	500	531	450	1680	1120	2600	2600
<b>N</b>	89	85	88	85	84	86	86
<b>Median OS (months)</b>	Not reported explicitly						
<b>OS Hazard Ratio (reference /comparison arm)</b>	reference	1.03 (0.75-1.43)	0.96 (0.69-1.34)	1.17 (0.84-1.63)	1.07 (0.77-1.49)	1.18 (0.84-1.64)	0.75 (0.54-1.04)

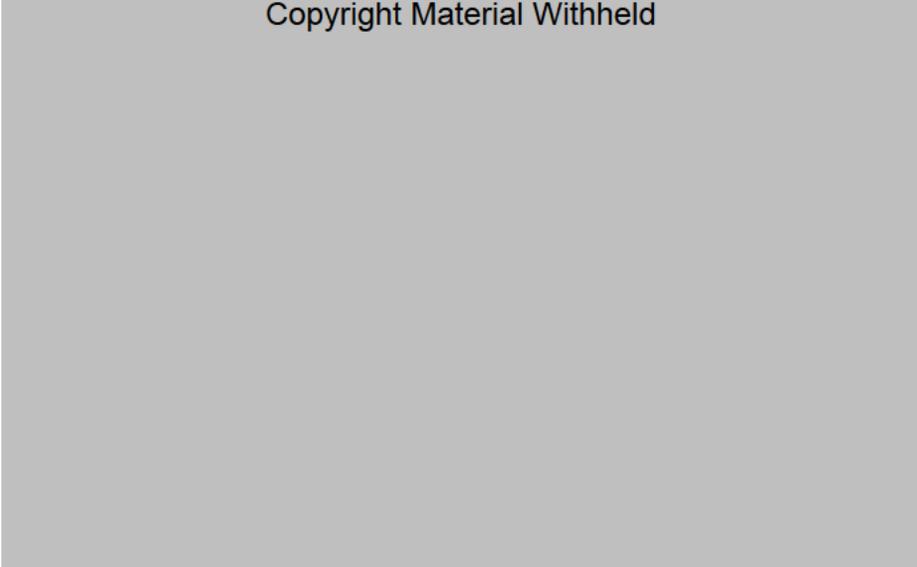
<b>OS rate 5 y</b>	Not reported explicitly						
<b>Median PFS (months)</b>	6	6	6	6	6	6	4
<b>TTP Hazard Ratio</b>	Not reported						
<b>Response Rate % (95% confidence intervals)</b>	29 (17-41)	27 (16-39)	21 (11-32)	29 (19-43)	26 (15-39)	15 (7-25)	25 (14-36)

N was obtained from the KM plots (N was not equal to the reported n in Table 1).

Copyright Material Withheld



Copyright Material Withheld



Source: Figure 2 of the reference

**Relevance to the comparison of 5FU doses**

This study provides evidence that differences of 5-FU dose intensities ranging from 450 to 2600 mg/m<sup>2</sup>/week did not have an impact to OS, PFS or response rate.

### 7.B.7 Lokich1989

#### Author and Title

Lokich, et al. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. J Clin Oncol. 1989 Apr;7(4):425-32.

#### Purpose

To compare two schedules of delivery for single-agent fluorouracil (5-FU)

#### Methods

Patients with advanced measurable colorectal cancer not previously treated with chemotherapy were randomized into 2 arms:

1. Bolus: a daily bolus 5-FU 500 mg/m<sup>2</sup> administered intravenously (IV) for five consecutive days and repeated at 5-week intervals
2. Continuous infusion: 5-FU 300 mg/m<sup>2</sup>/d administered 24 hours a day for a protracted time (10 weeks or more)

#### Results

The number of patients enrolled was 179. Median survival was similar between the infusional 5-FU arm and the bolus 5-FU arm. Overall survival for the two groups was comparable. Patients on the infusional arm had a median survival of 10 months compared with 11 months for the bolus arm, but mean survival on the infusional arm is longer than the bolus arm (13 v 12 months) because of a larger proportion of long-term survivors on the infusion arm. These differences were not significant (P =.379). Using stringent objective criteria requiring independent confirmation of x-ray or scan-documented response, the tumor response rate reached 7% (six of 87) for the bolus arm and 30% (26 of 87) for the infusion arms (P<.001). Toxicity was substantially different for the two arms with major leukopenia observed only on the bolus arm, 22% developing grade 3 (severe) or grade 4 (life-threatening) leukopenia with four sepsis-related deaths. Hand-foot syndrome was observed only in the infusional arm, requiring treatment interruptions and dose reductions in 24% of patients, but with little impact on quality of life.

	1 (bolus 5FU)	2 (CI 5FU)
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	500	2100
<b>N</b>	87	87
<b>Median OS (months)</b>	11.2	10.3
<b>Interquartile range</b>	(5.0-17.4)	(6.1-17.8)
<b>P-value</b>		P=.379
<b>OS Hazard Ratio</b>	Reference	Hazard Ratio not reported P=.38
<b>OS rate 5 y</b>	Not reported	
<b>Median TTP (months)</b>	Not reported	
<b>TTP Hazard Ratio</b>	Not reported	
<b>Response Rate (%)</b>	7%	30%
<b>95% Confidence intervals</b>	(3-14)	(21-41)
<b>P-value</b>		P<.001

Copyright Material Withheld



Source: figure 1 of reference

**Relevance to the comparison of 5FU doses**

This study provides evidence that a difference in the 5FU dose intensity of 500 and 2100 mg/m<sup>2</sup>/week did not have any impact to OS, however, higher 5FU dose intensity appears to increase response rate.

### 7.B.8 Poplin2005

#### Authors and Title

Poplin, et al. Phase III Southwest Oncology Group 9415/Intergroup 0153 Randomized Trial of Fluorouracil, Leucovorin, and Levamisole Versus Fluorouracil Continuous Infusion and Levamisole for Adjuvant Treatment of Stage III and High-Risk Stage II Colon Cancer.

#### Purpose

To compare the efficacy of continuous-infusion FU (CIFU) plus levamisole to FU/LV plus levamisole in the adjuvant treatment of high-risk Dukes' B2 and C1 or C2 colon cancer

#### Methods

After surgery, patients with colon cancer were randomly assigned to adjuvant treatment CIFU 250 mg/m<sup>2</sup>/d for 56 days every 9 weeks for three cycles or FU 425 mg/m<sup>2</sup> and LV 20 mg/m<sup>2</sup> daily for 5 days every 28 to 35 days for six cycles. All patients received levamisole 50 mg tid for 3 days every other week.

#### Results

The study closed after an interim analysis demonstrated little likelihood of CIFU showing superiority to FU/LV within the stipulated hazard ratio. A total of 1,135 patients were registered. Median follow-up time was 6.52 years. The 5-year OS is 70% (95% CI, 66% to 74%) for FU/LV and 69% (95% CI, 64% to 73%) for CIFU. The corresponding 5-year disease-free survival (DFS) was 61% (95% CI, 56% to 65%) and 63% (95% CI, 59% to 68%), respectively. For all patients, 5-year OS was 83%, 74%, and 55%; 5-year DFS is 78%, 67%, and 47% for N0, N1, and N2-3, respectively. At least one grade 4 toxicity occurred in 39% of patients receiving FU/LV and 5% of patients receiving CIFU. However, almost twice as many patients receiving CIFU discontinued therapy early compared with those receiving FU/LV. Therefore, CIFU had less severe toxicity but did not improve DFS or OS in comparison with bolus FU/LV.

	FU/LV	CIFU
<b>5FU dose intensity (mg/m<sup>2</sup>/week)</b>	472	1556
<b>N</b>	464	475
<b>Median OS (months)</b>	Not reached	Not reached
<b>OS Hazard Ratio</b>	Reference	1.16 (95%CI: 0.93-1.44 P=.18)
<b>OS rate 5 year</b>	70% (95%CI: 66%-74%)	69% (95%CI: 64%-73%)
<b>DFS rate 5 year</b>	61% (95%CI:56%-65%)	63% (95%CI:59%-68%)
<b>DFS Hazard Ratio</b>	Reference	1.05 (95% CI: 0.86-1.3; P = .65).
<b>Response Rate (%)</b>	Not reported	Not reported

DFS= disease free survival

#### Relevance to the comparison of 5FU doses

This study provides evidence that in the presence of LV and levamisole as adjuvant colon cancer treatment, the difference in 5FU dose intensities of 472 and 1556 mg/m<sup>2</sup>/week with infusion durations of 56 days and 0.25 h did not have any impact on OS or DFS.

### 7.B.9 Shah1985

#### Authors and Title

Shah, et al. 5-FU infusion in advanced colorectal cancer: a comparison of three dose schedules. Cancer Treatment Rep 69:739-742, 1985.

#### Purpose

To compare different dose schedules of 5FU

#### Methods

Patients with advanced colorectal adenocarcinoma were assigned to one of the three arms:

- Group A: 72-hour infusion of 5-FU (30 mg/kg/24 hours) every 3 weeks
- Group B: 72-hour infusion of 5-FU (30 mg/kg/24 hours) every 2 weeks
- Group C: 48-hour infusion of 5-FU (30 mg/kg/24 hours) every week

#### Results

A total of 94 patients with advanced colorectal adenocarcinoma were treated by continuous iv 5-FU infusion on three different dose schedules (Group A, n=33; Group B, n= 31; Group C, n=30). Although this was a sequential nonrandomized study of the dose schedules, the groups were comparable with respect to various prognostic factors. Response rates were as follows: Group A--three patients had minor response (9%) and 30 had no response (91%); Group B--five patients achieved partial response (16%), nine had minor response (29%), and 17 had no response (55%), and Group C--one patient achieved complete response (3%), eight achieved partial response (27%), five had minor response (17%), and 16 had no response (53%). The median survival time for Group A was 9 months, for Group B was 9.5 months, and for Group C was 14 months. Intensifying the dose schedule of 5-FU by increasing the frequency of administration has significantly improved response rates. A prolongation of the median survival time of patients treated with a 48-hour infusion at 1-week intervals was noted, although this was not statistically significant.

	Group A	Group B	Group C
5FU dose intensity (mg/kg/week)	30	45	60
N	33	31	30
Median OS (months)	9 (range= 2-46)	9.5 (range= 4-31; similar KM estimates, P not reported)	14 (range= 1-32+; P=.09)
OS Hazard Ratio	Not reported		
Median TTP (months)	Not reported		
TTP Hazard Ratio	Not reported		
Response Rate (%)	0	16%	30% P=.0004

#### Relevance to the comparison of 5FU doses

This is the first study that provides evidence that the difference in dose intensities of 30 to 60 mg/kg/week (or approximately 1200 to 2400 mg/m<sup>2</sup>/week with a conversion factor of 40 kg/m<sup>2</sup>) does not have an impact to the OS, and that higher 5FU dose intensities may increase response rate.

### 7.B.10 Weinerman1992

#### Authors and Title

Weinerman, et al. Systemic infusion versus bolus chemotherapy with 5-fluorouracil in measurable metastatic colorectal cancer. Am J Clin Oncol. 1992 Dec;15(6):518-23.

#### Purpose

To compare either infusional or bolus 5-fluorouracil (5-FU) for the treatment of metastatic measurable colorectal cancer

#### Methods

Chemotherapy-naive colorectal cancer patients with good performance status was randomized to either infusional or bolus 5-FU. Infusion was administered at an escalated dose schedule starting at 350 mg/m<sup>2</sup> per day for 2 weeks with a 2-week rest period on a monthly basis, while bolus 5-FU was started at 400-450 mg/m<sup>2</sup> for 5 days every 28 days.

#### Results

From January 31, 1986 to January 31, 1989, 184 patients enrolled. No significant difference in survival was observed (p = 0.207). Progression free survival was significantly longer (p = 0.0139) in the infusion group (3.8 versus 2.3 months). The infusion arm produced a response in 11 of 88 patients versus 6 of 82 in the bolus arm (p = 0.384). Neither of these methods of administering fluorouracil results in an exceptional response rate, nor does the infusion have an impact on survival as compared to the bolus route.

	Infusion 5FU	Bolus 5FU
5FU dose intensity (mg/m <sup>2</sup> /week)	1225	500
N	94	90
Median OS (months)	Not Reported	
OS Hazard Ratio	Reference	HR Not Reported; P=.2071
OS rate 5 y	Not Reported	
Median TTP (months)	3.8	2.3
TTP Hazard Ratio	Reference	HR Not Reported P = .0139.
Response Rate (%)	12.5%	7.3% (P=.384)

#### Relevance to the comparison of 5FU doses

This study provides evidence that the difference in 5FU dose intensity of 500 and 1225 mg/m<sup>2</sup>/week given as bolus or continuous infusion did not have an impact on OS in chemotherapy-naive colorectal cancer. Higher 5FU dose intensity was reported to have a higher response rate and longer median TTP.

TIMEKEEPER PAYROLL RECORD

Advisors and Consultants Staff

**Note to Center for Drug Evaluation and Research Special Government Employee.**

Use this record to submit claim for hours worked at your home, place of business, or in any FDA facility located within your commuting area. Please note any dates that you were required to travel outside of your commuting area to perform your assignment. Advisory committee members should not claim salary for hours spent on normal preparation for a committee meeting. Salary paid in response to this time sheet represents compensation in full for all services rendered and supplied by the Special Government Employee during this period.

<u>Date(s)</u>	<u>Hours Worked</u>	<u>Description of Work</u> (Cite IND/NDA if applicable)
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\_\_\_\_\_ (Sign) \_\_\_\_\_  
Special Government Employee Date

Certification:

I certify that this work was done during the period(s) indicated at:

- Government furnished facility
- Employees home/office since there was no Federal office or laboratory space available at which to perform the assigned work.
- Quality and quantity of work meets performance expectations.

\_\_\_\_\_  
Center for Drug Evaluation and Research Executive Secretary/Management Official Authorizing Assignment Date

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/s/  
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DEANNE R VARNEY  
07/09/2015

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Thursday, July 09, 2015 3:18 PM  
**To:** MSlater@merrimackpharma.com  
**Subject:** NDA 207793 / Irinotecan Liposome Injection / Merrimack --- Statistical Information Request

Hello Michael,

The statistical team has the below information requests related to NDA 207793. Please provide a response via email by July 20, 2015, followed by a formal submission to your NDA.

For Study NAPOLI-1:

1. There was an imbalance for the number of patients who withdrew consent among the 3 study arms. For all patients who withdrew consent, if their dates of death can be collected from a public registry, use such death dates as the event dates and conduct analyses for the primary endpoint OS.
2. In the document of Summary of Clinical Efficacy, it stated that since there was an imbalance in the 5-FU/LV arm for the number of patients who did not receive study drug, a Bayesian analysis was used to impute OS times for the patients who did not receive treatment. Conduct a Bayesian analysis which only imputes OS times for 7 patients who did not receive 5-FU/LV and withdrew consent from study follow-up within 1 month from randomization (i.e., first 7 patients in Table 1).

Please confirm receipt and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

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DEANNE R VARNEY  
07/09/2015



NDA 207793

**INFORMATION REQUEST**

Merrimack Pharmaceuticals, Inc.  
Attention: Jim Williams  
Director Regulatory Affairs  
One Kendall Square, Suite B7201  
Cambridge, MA 02139-1670

Dear Mr. Williams:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onivyde (Irinotecan Liposome Injection).

We also refer to your April 23, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. DMF# (b) (4) has been reviewed and found inadequate. The DMF holder has been notified.

2. (b) (4)  
(b) (4), additional validation tests will be requested.

3. (b) (4)

4. It is acknowledged that the endotoxins test and the sterility test are performed per USP. Please note that the Agency's recommendation is for a liposomal disruption technique to be validated and implemented for routine sterility and endotoxins testing. The liposomal disruption is necessary to detect the presence of endotoxins and antimicrobial properties that may be encapsulated by the liposomal membrane. Please revise protocols for the endotoxins test and the sterility test and provide validation results accordingly. Please also confirm that the exhibit batches meet the acceptance criteria with the revised methods.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by July 31, 2015.

Sincerely,

*{See appended electronic signature page}*

Olen Stephens, Ph.D.  
Branch Chief, Branch II  
Office of New Drug Products  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Olen  
Stephens -S

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# TEAM MEETING MINUTES

## June 24, 2015

New 505(b)(2) NDA 207793  
Irinotecan Liposome Injection  
Merrimack Pharmaceuticals, Inc.

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**Submission Date:** April 24, 2015 (final portion of rolling submission)  
**Received Date:** April 24, 2015  
**PDUFA:** October 24, 2015

**Proposed Indication:** Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine

### Core Review Team:

Patricia Keegan, Director DOP2  
Deanne Varney, RPM  
Shan Pradhan, Medical Officer  
Steven Lemery, Medical Officer Team Leader  
Hui Zhang, Statistics  
Kun He, Statistics Team Leader  
Sarah Schrieber, Clinical Pharmacology  
Gene Williams, Clinical Pharmacology Team Leader  
Anshu Marathe, Pharmacometrics Reviewer  
Margot Brower, Non-Clinical  
Whitney Helms, Non-Clinical Team Leader  
Mike Adams, CMC  
Liang Zhou, CMC Team Leader  
Olen Stephens, CMC (Branch Chief)  
Rabiya Laiq, CMC RPM  
Anuradha Ramamoorthy, Genomics Reviewer  
Rosane Charlab Orbach, Genomics Team Leader  
Banu Zolnik, Biopharmaceutics Reviewer  
Okpo Eradiri, Biopharmaceutics Team Leader

### Consults:

Carole Broadnax, OPDP / Jessica Cleck Dereneck, OPDP TL  
Margaret Rand, DPV / Tracy Salaam, DPV TL  
Naomi Redd, DRISK / Doris Auth, DRISK TL  
Otto Townsend, DMEPA / Alice Tu, DMEPA TL  
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL  
Lauren Iacono-Connors, OSI / Susan Thompson, OSI TL  
Miriam Dinatale, PMHS / Tamara Johnson, TL /Denise Pica-Branco

**Agenda Items:**

**1. Review Status:**

- Priority Review requested (6 month review – not in the Program)
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of irinotecan liposome has been conducted under IND 102799

**2. Milestone Dates for 6-Month Priority Review Clock:**

<b>Milestone</b>	<b>6 month review</b>
<b>Acknowledgment Letter</b>	<i>Issued April 30, 2015</i>
<b>Priority Review Determination OR Filing Issues Identified/Not Identified Letter</b>	June 23, 2015 <i>Issued June 23, 2015</i>
<b>Filing Issues Identified (74 Day Letter) — if not sent in Day 60 letter</b>	<i>July 7, 2015</i>
<b>Mid-Cycle Meeting</b>	July 20, 2015
<b>Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)</b>	October 3, 2015
<b>Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant</b>	October 10, 2015
<b>Advisory Committee Target Date</b>	Month 4-5 (August –September)
<b>Review Target Due Dates:</b> <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i>	September 30, 2015 October 3, 2015 October 10, 2015 October 24, 2015
<b>Wrap-Up Meeting w/ Safety discussion</b>	September 26, 2015
<b>Compile and circulate Action Letter and Action Package</b>	October 10, 2015
<b>FINAL Action Letter Due</b>	<b>October 24, 2015</b>

3. **Midcycle Preparation:** Midcycle will be held July 20<sup>th</sup>. The team will have the opportunity to practice/review slides during the July 15<sup>th</sup> team meeting.

Discussion points are outlined below:

- Discipline Specific Reviews of Application
  - Applicable studies/information submitted
  - Status of your review of the data
  - Discussion of findings so far
    - a. Are there issues requiring resolution? Discuss in presentations or state no issues have been identified.
    - b. Are there any major labeling issues? Discuss in presentation or state there are no issues identified.
    - c. Are there PMC and Risk Management Plan Issues? Discuss during presentation or state that there are no plans/need for PMC/PMRs/REMS.
  - Identification of need for additional input from review team or through additional consults
  - Information requests to be sent to sponsor
  - Presentations
    - a. Regulatory/Introduction (Deanne Varney)=less than 5 minutes
    - b. Clinical/Statistical (Shan Pradhan/Hui Zhang)=30 minutes
    - c. Clinical Pharmacology (Sarah Schreiber)=10 minutes
    - d. Non-Clinical (Margot Brower)=10 minutes
    - e. CMC (Mike Adams)& Biopharmaceutics (Banu Zolnik) = 10 minutes
- Pending Inspections
  - OSI Inspections: Status Update -
  - OMPQ Inspection: Status Update

**Discussion:** The team will send final TL-cleared slides to the CDTL and RPM by Monday, July 13, 2015.

4. **SGE's:** Two SGEs have been cleared. The team will aim to have the teleconferences complete prior to the midcycle on July 20<sup>th</sup>.

- Target date for sending briefing document to SGEs: Monday, July 6<sup>th</sup>
- Target date for SGE teleconferences: *no later than* Thursday, July 16<sup>th</sup>

**Discussion:** The team will target sending the briefing document to the SGEs by Thursday, July 9<sup>th</sup> instead of Monday, July 6<sup>th</sup>.

5. **ODAC:** The team would like to receive SGE feedback early to help determine if an ODAC is necessary.

**Discussion:** The clinical team noted that it is unlikely that an ODAC will be required.

**Target AC date: August/September**

6. **Review Issues:**

- a. **Clinical:** None.
- b. **Statistics:** None.
- c. **Clinical Pharmacology:** QT-IRT determined that there is not an adequate assessment of irinotecan on QT prolongation. A PMR might be required. QT-IRT has requested and received the CITS protocol for review in order to determine if the ongoing CITS trial will fulfill the QT assessment requirement. The team discussed that an information request could potentially be sent to ask applicant to prepare QT results from the study; however, we would need to determine if it would be considered a major amendment.
- d. **Pharmacometrics:** None.
- e. **Genomics:** None.
- f. **Nonclinical:** None.
- g. **CMC:** None.
- h. **Biopharmaceutics:** None.
- i. **Regulatory:** None.

7. **Inspections:**

a. **Clinical Site Inspections:**

**Discussion:** The status of inspections is that all assignments for five clinical sites were issued in early May, and are currently pending FDA field investigator assignments and site inspection schedules.

Sites 881 and 882 in Taiwan.

Site 366 in Hungary.  
Site 617 in Australia.  
Site 120 in US.

- b. Manufacturing Site Inspections:** Drug product manufacturing facilities to be inspected. Any updates on scheduled inspections?

**Discussion:** An update was not available at this time.

**8. Internal Team Meetings:**

- **Mid-Cycle Meeting:** July 20, 2015
- **Labeling Meetings:** “Big ticket” issues communicated to the applicant in the filing letter on June 23<sup>rd</sup> with updated labeling requested by July 13<sup>th</sup>. The updated labeling will be placed on SharePoint as soon as possible so the team can begin reviewing in advance of the first labeling meeting on July 23<sup>rd</sup>.
- Order of labeling meetings is outlined below:
  - a. July 23, 2015: Clinical and Statistics – Sections 1 and 14
  - b. July 28, 2015: CMC, DMEPA, Clinical – Sections 3, 11, 16
  - c. July 29, 2015: Clinical – Sections 4, 5, 6, 17
  - d. August 18, 2015: Clinical, Maternal Health, Nonclinical – Sections 5.1, 8.1, 8.3, 8.4, 12.1, 13
  - e. August 20, 2015: Clin Pharm, Clinical and DMEPA – Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3
  - f. September 15, 2015: Highlights, Remaining issues
  - g. October 8, 2015: Review of applicant and consult edits
- **Monthly Team Meetings:**
  - a. June – June 24, 2015
  - b. July – July 15, 2015
  - c. August – August 19, 2015
  - d. September – September 16, 2015
  - e. October – October 14, 2015

- **Wrap- Up Meeting:** September 23, 2015

**9. Additional Items or Issues:**

**Discussion:** None.

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/s/  
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DEANNE R VARNEY  
06/24/2015



NDA 207793

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Merrimack Pharmaceuticals, Inc.  
Attention: Michael Slater  
Vice President, Regulatory Affairs  
One Kendall Square, Suite B7201  
Cambridge, MA 02139

Dear Mr. Slater:

Please refer to your New Drug Application (NDA) dated April 24, 2015, received April 24, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Onivyde [*proposed*] (irinotecan liposome injection), 50 mg/10 mL single use vial.

We also refer to your amendments dated April 29, May 4, May 14, May 29, and June 4, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is October 24, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 3, 2015.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. For the Form 3455 that was included in the NDA, either identify within the NDA the location of the statement of steps taken to minimize bias or submit such a statement to the NDA.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

2. As this product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in Highlights: “Onivyde (irinotecan liposome injection) is a topoisomerase 1 inhibitor indicated for ...”
3. In the following statement in the Adverse Reactions section in Highlights: “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch),” please insert a complete phone number for the manufacturer.

We have also identified several labeling content issues. These issues are described in track changes and using the track changes “comment” function within the text of your PI, and are included as an attachment to this letter. Please review all content issues and revise your PI accordingly.

We request that you resubmit labeling (in both clean and tracked-changes Microsoft Word format) that addresses these issues by July 13, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Deanne Varney, Senior Regulatory Project Manager, at (301) 796-0297.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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

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/s/  
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PATRICIA KEEGAN  
06/23/2015



NDA 207793

**INFORMATION REQUEST**

Merrimack Pharmaceuticals, Inc.  
Attention: Jim Williams  
Director Regulatory Affairs  
One Kendall Square, Suite B7201  
Cambridge, MA 02139-1670

Dear Mr. Williams:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onivyde (Irinotecan Liposome Injection).

We also refer to your April 24, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In NDA sections 3.2.P.5 and 3.2.P.8, revise the tables to specify the manufacturing site and process or formulation for the bulk drug product and drug product batches.
2. In NDA section 3.2.P.5, provide a detailed description of each analytical method; and provide method validation data [REDACTED] (b) (4)
3. Confirm that [REDACTED] (b) (4) is the only drug substance manufacturer for this NDA. (Can this be removed this has been confirmed?)
4. Provide analysis data for the following batches of drug substance: HS4420121104 and HS4420121001. These drug substance batches were used to produce drug product that was used in Phase 3 clinical study, primary stability study, and PPQ.
5. [REDACTED] (b) (4) Provide table summary information on actual [REDACTED] (b) (4) observed between each unit operation during the manufacture of phase 3 batches, primary stability batches and PPQ batches.

Provide chemical stability data to support (b) (4)

[Redacted]

6. [Redacted] (b) (4)

7. [Redacted] (b) (4)

Describe also unit operation conditions during labeling and packaging.

8. Explain how the batch formula for each component is proportionally related to the amount for each component described in the composition of the drug product (e.g. (b) (4)).
9. Provide comparative summary Tables showing critical operating parameters and equipment used for the manufacture of phase 3 batches, primary stability batches and PPQ batches. Provide also operating ranges if there are differences from the operating ranges provided in Table 3 under 2.3.P Description of Manufacturing Process and Process Controls.
10. Provide a master batch record for the commercial manufacturing process.
11. Clarify whether the manufacturing process used for the manufacture of the primary stability batches or PPQ batches will be used for commercial batch production.
12. Regarding the container closure integrity validation test (b) (4) please state the sensitivity of the test and provide results to validate the sensitivity. Please also provide additional information (b) (4)

[Redacted] (b) (4)

13. Please indicate the type of container closure system ([Redacted] (b) (4))  
[Redacted] Please comment on how this container is  
(b) (4) and whether any container closure integrity testing was performed.

14. [Redacted] (b) (4) Please discuss in detail the in  
process controls utilized to maintain microbiological control of the solution. (b) (4)  
[Redacted]

15. Regarding the manufacturing process of [Redacted] (b) (4) please state the proposed  
maximum commercial batch size.

16. [Redacted] (b) (4)

17. Please state the bioburden level of [Redacted] (b) (4).

18. Regarding the validation of [Redacted] (b) (4):

- a) [Redacted] (b) (4)
- b) [Redacted]
- c) [Redacted]

19. Please state the [Redacted] (b) (4)  
[Redacted] Please provide validation results showing the bioburden of [Redacted] (b) (4)  
[Redacted]

20. [Redacted] (b) (4)

21. Regarding the Bacterial Endotoxins Test provided in 32R:

a)

b)

c)

(b) (4)

22. Microbiological studies in support of the post-dilution storage time (as stated in the proposed product labeling, p4/46) have not been provided. Please provide a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions, (i.e. (b) (4) hours at approximately 25°C and 24 hours at approximately 2-8°C after dilution with the specified diluents). Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.

23. Please include a description of the test methods and results of studies that are designed using a minimum countable inoculum ( $\leq 100$  CFU/mL) to simulate potential microbial contamination that may occur during product constitution. It is generally accepted that growth is evident when the population increases more than  $0.5 \log_{10}$ , however other evidence of growth may be significant. Please perform the test using the storage conditions (temperature and duration) and diluents specified in product labeling. Please provide justification for the selected test conditions and/or diluents as necessary. Please consider periodic intermediate sample times, as well as extended sample time points demonstrating that the reconstituted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora, species associated with nosocomial infection, or psychrophilic organisms. Please provide a positive control that demonstrates the viability of the organisms over the duration of the test period. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature or 24 hours at 2-8°C.

**Other comments:** In addition to responding to information request #23 presented above, please note and acknowledge the following comments in your response:

The container closure integrity validation test using microbial ingress method is not reviewed.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by June 5, 2015.

Sincerely,

*{See appended electronic signature page}*

Olen Stephens, Ph.D.  
Branch Chief, Branch II  
Office of New Drug Products  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Olen Stephens -S

Digitally signed by Olen Stephens -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Olen Stephens -S,  
0.9.2342.19200300.100.1.1=2000558826  
Date: 2015.05.20 16:31:03 -04'00'

## Varney, Deanne

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**From:** Varney, Deanne  
**Sent:** Thursday, May 14, 2015 9:27 AM  
**To:** MSlater@merrimackpharma.com  
**Subject:** NDA 207793 / Merrimack / Irinotecan Liposome Injection --- Clinical Pharmacology Information Requests

Hello Michael,

We have the following clinical pharmacology information requests related to your new NDA 207793:

1. Submit the PK analysis datasets and PK parameter datasets in .xpt format for the following studies: PEP0201, PEP0202, PEP0203, PIST-CRC, and PEP0206. Please submit these to your NDA by **Wednesday, May 27, 2015**.
2. Provide the UGT genotyping method(s) and submit the pharmacogenetic datasets (UGT1A1 and UGT1A9 genotyping analysis) in .xpt format for the following studies: PEP0202, PEP0203, PIST-CRC and PEP0206. Please submit these to your NDA by **Wednesday, May 27, 2015**.
3. Please complete the attached ClinPharm and Cardiac Safety Table and return it to me via email by **Thursday, May, 21, 2015**.



Microsoft Word document icon

Please confirm receipt and let me know should you have any questions.

Thank you,  
Deanne

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0297

**Table 1. Highlights of Clinical Pharmacology and Cardiac Safety**

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/  
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DEANNE R VARNEY  
05/14/2015

# PLANNING/FILING MEETING MINUTES

## May 12, 2015

New 505(b)(2) NDA 207793  
Irinotecan Liposome Injection  
Merrimack Pharmaceuticals, Inc.

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**Submission Date:** April 24, 2015 (final portion of rolling submission)  
**Received Date:** April 24, 2015  
**PDUFA:** October 24, 2015

**Proposed Indication:** Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine

### Core Review Team:

Patricia Keegan, Director DOP2  
Deanne Varney, RPM  
Shan Pradhan, Medical Officer  
Steven Lemery, Medical Officer Team Leader  
Hui Zhang, Statistics  
Kun He, Statistics Team Leader  
Sarah Schrieber, Clinical Pharmacology  
Gene Williams, Clinical Pharmacology Team Leader  
Jian Wang, Pharmacometrics Reviewer  
Margot Brower, Non-Clinical  
Whitney Helms, Non-Clinical Team Leader  
Mike Adams, CMC  
Liang Zhou, CMC Team Leader  
Olen Stephens, CMC (Branch Chief)  
Rabiya Laiq, CMC RPM  
Anuradha Ramamoorthy, Genomics Reviewer  
Rosane Charlab Orbach, Genomics Team Leader  
Banu Zolnik, Biopharmaceutics Reviewer  
Okpo Eradiri, Biopharmaceutics Team Leader

### Consults:

Carole Broadnax, OPDP / Jessica Cleck Dereneck, OPDP TL  
Margaret Rand, DPV / Tracy Salaam, DPV TL  
Naomi Redd, DRISK / Doris Auth, DRISK TL  
Otto Townsend, DMEPA / Alice Tu, DMEPA TL  
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL  
Lauren Iacono-Connors, OSI / Susan Thompson, OSI TL  
Miriam Dinatale, PMHS / Tamara Johnson, TL /Denise Pica-Branco

**Agenda Items:**

**1. Review Status:**

- Priority Review requested (6 month review – not in the Program)
  - Confirm Priority Review
  - **Discussion:** Priority review will be granted.
  
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of irinotecan liposome has been conducted under IND 102799

**2. Milestone Dates for 6-Month Priority Review Clock:**

<b>Milestone</b>	<b>6 month review</b>
<b>Acknowledgment Letter</b>	<i>Issued April 30, 2015</i>
<b>Priority Review Determination OR Filing Issues Identified/Not Identified Letter</b>	June 23, 2015
<b>Filing Issues Identified (74 Day Letter) --- if not sent in Day 60 letter</b>	July 7, 2015
<b>Mid-Cycle Meeting</b>	July 24, 2015
<b>Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)</b>	October 3, 2015
<b>Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant</b>	October 10, 2015
<b>Advisory Committee Target Date</b>	Month 4-5 (August –September)
<b>Review Target Due Dates:</b> <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i>	September 30, 2015 October 3, 2015 October 10, 2015 October 24, 2015
<b>Wrap-Up Meeting w/ Safety discussion</b>	September 26, 2015
<b>Compile and circulate Action Letter and Action Package</b>	October 10, 2015
<b>FINAL Action Letter Due</b>	<b>October 24, 2015</b>

### 3. **Filing Issues:**

- Filing reviews will need to be uploaded and signed off on in DARRTs *prior to* day 60 (and should target completion by May 24, 2015)
- Please be prepared to discuss any significant filing issues for inclusion in the day 74 letter.
  - a. **Clinical:** No filing issues but will have information requests for inclusion in the filing or 74-day letter
  - b. **Statistics:** No filing issues and no information requests.
  - c. **Clinical Pharmacology:** Application is missing datasets for six studies. Team will double-check population PK data to ensure the datasets aren't included there. If datasets cannot be found the team will contact the applicant to request them.
  - d. **Genomics:** Team will contact the applicant in conjunction with clinical pharmacology regarding the missing datasets.
  - e. **Nonclinical:** No filing issues and no information requests.
  - f. **CMC:** No filing issues but will have information requests for inclusion in the filing or 74-day letter (or earlier).
  - g. **Biopharmaceutics:** No filing issues and no information requests.
  - h. **Regulatory:** The application was missing a patent certification statement and a debarment statement, but both have been requested and received. No other issues at this time. Labeling comments will be included in the 74-day letter.

### 4. **Inspections:**

- a. **Clinical Site Inspections:** All inspection assignments have been issued and will be scheduled as soon as possible.
- b. **Manufacturing Site Inspections:** Drug substance facilities are okay but drug product manufacturing facilities will need to be inspected. OPQ will work with the facilities group and will inform the team when inspections are scheduled.

**5. Internal Team Meetings:**

- **Mid-Cycle Meeting:** July 20, 2015
- **Labeling Meetings:** Will target commencing meetings in mid-late July. It was noted that the label will require significant updates. The team will send “big ticket” issues to the applicant to address early in the review cycle, in the filing or 74-day letter. Comments will be provided to RPM by June 12, 2015.
- Order of labeling meetings is outlined below:
  - a. July 23, 2015: Clinical and Statistics – Sections 1 and 14
  - b. July 28, 2015: CMC, DMEPA, Clinical – Sections 3, 11, 16
  - c. July 29, 2015: Clinical – Sections 4, 5, 6, 17
  - d. August 18, 2015: Clinical, Maternal Health, Nonclinical – Sections 5.1, 8.1, 8.3, 8.4, 12.1, 13
  - e. August 20, 2015: Clin Pharm, Clinical and DMEPA – Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3
  - f. September 15, 2015: Highlights, Remaining issues
  - g. October 8, 2015: Review of applicant and consult edits
- **Monthly Team Meetings:**
  - a. June - TBD
  - b. July - TBD
  - c. August - TBD
  - d. September - TBD
  - e. October - TBD
- **Wrap- Up Meeting:** TBD, By September 26, 2015.

**6. Applicant Orientation Presentation:** Scheduled for June 15, 2015. There is also a technical walkthrough of the application for the clinical and statistics teams scheduled for May 21, 2015.

**7. ODAC:**

**Discussion:** The team would like to receive SGE feedback early to help determine if an ODAC is necessary.

**Target AC date: August/September**

*If not needed, for an original NME or BLA application, include the reason in the RPM filing review memo. For example:*

- *this drug/biologic is not the first in its class*
- *the clinical study design was acceptable*
- *the application did not raise significant safety or efficacy issues*
- *the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*

*If we plan on going to Advisory Committee, we will need a planning meeting and \_\_\_\_\_ practice sessions.*

**8. SGE's:**

**Discussion:** Clinical team has started contacting potential SGE's in order to consult with them as soon as possible.

**9. Additional Items or Issues:**

**Discussion:** Clinical pharmacology requested that the QT-IRT consult response be due by the date of the mid-cycle meeting.

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/s/  
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DEANNE R VARNEY  
05/13/2015



NDA 207793

**NDA ACKNOWLEDGMENT**

Merrimack Pharmaceuticals, Inc.  
Attention: Michael Slater  
Vice President, Regulatory Affairs  
One Kendall Square, Suite B7201  
Cambridge, MA 02139

Dear Mr. Slater:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

**Name of Drug Product:** Irinotecan Liposome Injection, 50 mg/10 mL single use vial

**Date of Application:** April 24, 2015

**Date of Receipt:** April 24, 2015

**Our Reference Number:** NDA 207793

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 23, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 2  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-0297.

Sincerely,

*{See appended electronic signature page}*

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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DEANNE R VARNEY  
04/30/2015



NDA 207793

**MEETING REQUEST GRANTED**

Merrimack Pharmaceuticals, Inc.  
Attention: Michael Slater  
Vice President, Regulatory Affairs  
1 Kendall Square, Suite B7201  
Cambridge, MA 02139

Dear Mr. Slater:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for irinotecan liposome injection.

We also refer to your April 28, 2015, email correspondence requesting an application orientation meeting.

The meeting is scheduled as follows:

**Date:** Monday, June 15, 2015  
**Time:** 10:30AM – 12:00PM  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Room 2205  
Silver Spring, Maryland 20903

**FDA participants:**

Richard Pazdur, Director, OHOP  
Patricia Keegan, Director, DOP2  
Deanne Varney, RPM  
Shan Pradhan, Medical Officer  
Steven Lemery, Medical Officer Team Leader  
Hui Zhang, Statistics Reviewer  
Kun He, Statistics Team Leader  
Sarah Schreiber, Clinical Pharmacology Reviewer  
Gene Williams, Clinical Pharmacology Team Leader  
Margot Brower, Non-Clinical Reviewer  
Whitney Helms, Non-Clinical Team Leader  
Mike Adams, Product Quality Reviewer  
Liang Zhou, Product Quality Team Leader  
Olen Stephens, Product Quality Branch Chief  
Rabiya Laiq, Product Quality RPM  
Banu Zolnik, Biopharmaceutics Reviewer

Please e-mail me your attendee list at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Deanne Varney, 301-796-0297

If you have any questions, call me at (301) 796-0297.

Sincerely,

*{See appended electronic signature page}*

Deanne Varney  
Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Foreign Visitor Data Request Form

## FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Merrimack
MEETING START DATE AND TIME	June 15, 2015, 10:30AM
MEETING ENDING DATE AND TIME	June 15, 2015, 12:00PM
PURPOSE OF MEETING	Application Orientation
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22 Room 2205
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Deanne Varney, RPM, 22/2326, 6-0297
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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DEANNE R VARNEY  
04/30/2015



NDA 207793

INFORMATION REQUEST

Merrimack Pharmaceuticals, Inc.  
Attention: James Williams, Sr. Director Regulatory Affairs  
One Kendall Square  
Suite B7201  
Cambridge, MA 02139-1670

Dear Mr. Williams,

Please refer to your original New Drug Application received April 24, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onivyde (Irinotecan Liposome) Injection.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, September 29, 2015.

**The FDA has reviewed your response to the Information Request; the provided revision of the proposed in-vitro release acceptance criteria is not acceptable. It is not FDA's practice to recommend or accept in-vitro drug release acceptance ranges based on  $\pm$ SD for all dosage forms, including liposomal suspensions for injection. Based on the totality of the data submitted, including those for two new batches, FDA recommends the following in-vitro release acceptance criteria for batch release and stability testing (based on Level 2 testing; the means should be within the ranges at 2 and 4 h):**

2 h:	(b) (4) %
4 h:	(b) (4) %
16 h:	$\geq$ (b) (4) %

**Update the Specifications table with the above recommended in-vitro release acceptance criteria.**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen  
Stephens -S

Digitally signed by Olen Stephens -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Olen Stephens -  
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Date: 2015.09.25 09:01:32 -04'00'

Olen Stephens, Ph.D.  
Branch Chief, Branch II  
Office of New Drug Products  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



NDA 207793

**ACKNOWLEDGE NDA PRESUBMISSION**

Merrimack Pharmaceuticals, Inc.  
Attention: Michael Slater  
Senior Director of Regulatory Affairs and Quality Assurance  
One Kendall Square Suite B7201  
Cambridge, MA 02139

Dear Mr. Slater:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Onivyde (Irinotecan liposome Injection), 5 mg

Date of Submission: December 26, 2014

Date of Receipt: December 29, 2014

Our Reference Number: NDA 207793

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA listed above at the top of the first page of any communications concerning this application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 2  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to

set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-1273.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Chief, Project Management Staff (acting)  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MELANIE B PIERCE  
01/14/2015



IND 102799

**MEETING MINUTES**

Merrimack Pharmaceuticals, Inc.  
Attention: Michael Slater  
Senior Director of Regulatory Affairs and Quality Assurance  
One Kendall Square Suite B201  
Cambridge, MA 02139

Dear Mr. Slater:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Onivyde (MM398).

We also refer to the meeting between representatives of your firm and the FDA on December 2, 2014. The purpose of the meeting was to obtain FDA's guidance and agreement on content, structure, and formatting questions relating to the NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at, (301) 796-1273.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Senior Regulatory Health Project Manger  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** December 2, 2014; 3:00 PM-4:00 PM  
**Meeting Location:** CDER White Oak Bldg. 22; Room 1309

**Application Number:** 102799  
**Product Name:** Onivyde (MM398)  
**Indication:** Pancreatic cancer  
**Sponsor/Applicant Name:** Merrimack Pharmaceuticals, Inc.

**Meeting Chair:** Steven Lemery  
**Meeting Recorder:** Melanie Pierce

**FDA ATTENDEES**

**Office of Hematology and Oncology Products**

**Division of Oncology Products 2**

Patricia Keegan, MD	Director
Steven Lemery, MD, MHS	Clinical Team Leader
Shan Pradhan, MD	Clinical Reviewer
Melanie Pierce, BSc	Project Manager

**Office of Hematology and Oncology Products**

**Division of Hematology Oncology Products**

Whitney Helm, PhD	Pharmacology/Toxicology Supervisor
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**Office of New Drugs Quality Assessment:**

William M. Adams, PhD	Quality/Product Reviewer
Banu S. Zolnik, PhD	Biopharmaceutics Reviewer
Olen Stephens, PhD	Chemistry Reviewer

**Office of Clinical Pharmacology**

Hong Zhao, PhD	Clinical Pharmacology DCPV Team Leader
Runyan Jin, PhD	Clinical Pharmacology DCPV Reviewer
Liang Zhao, PhD	Pharmacometrics Team Leader

**Office of Biostatistics**

Kun He, PhD

Vivian Yuan, PhD

Statistics Team Leader

Statistics Reviewer

**Office of Surveillance and Epidemiology**

Sue Kang, PharmD

Frances Fhanbulleh, RPh, PharmD

Mona Patel, PharmD

Team Leader, Project Management Staff

OSE Project Manager

OSE, DRISK Reviewer

**MERRIMACK ATTENDEES**

Bambang Adiwijaya,

Tony Awad,

Eliel Bayever,

Bruce Belanger,

Navreet Dhindsa,

Sara Green,

Jaeyeon Kim,

Peter Laivins,

Andrew O'Brien,

Marion Scocca,

Michael Slater,

James Williams,

Michelle Motta Darden

Daryl Drummond

Grace Yeh,

Kameswara Rao Kuchimanchi,

Investigator, Clinical Pharmacology and  
Pharmacometrics

Senior Director, Process Sciences and  
Manufacturing

Vice President, Medical

Vice President, Biostatistics

Director Clinical Operations

Senior Associate, Regulatory Affairs

Principal Scientist, Clinical Pharmacology and  
Pharmacometrics

Senior Vice President, Development

Director, Quality Control

Director, Regulatory Affairs

Vice President, Regulatory Affairs and Quality  
Systems

Director, Regulatory Affairs

Senior Director, Pharmacovigilance and Risk  
Management

Vice President, Discovery

CEO, PharmaEngine

Director, Global Regulatory Affairs, Baxter  
Healthcare Corp.

Consultant to Merrimack Pharmaceuticals

(b) (4)

**BACKGROUND:**

On October 3, 2014, Merrimack Pharmaceuticals, Inc. (Merrimack) submitted a request for a preNDA meeting. The meeting briefing package was submitted October 31, 2014. The proposed indication that Merrimack is seeking is:

“for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in patients previously treated with gemcitabine”.

*Regulatory History*

Merrimack stated that MM-398 was invented at Hermes Biosciences, Inc. (CA) as a liposomal form of irinotecan and was licensed to PharmaEngine, Inc. of Taiwan, for clinical development. PharmaEngine commenced clinical trials in January 2005, in Taiwan. In October 2008, PharmaEngine filed IND 102799 for the product, then named PEP02, and commenced trials under that IND including the following study in pancreatic cancer, Protocol PEP0208: “A Phase II Study of PEP02 as a Second Line Therapy for Patients with Metastatic Pancreatic Cancer.”

In June 2011, sponsorship of IND 102799 was transferred to Merrimack Pharmaceuticals, Inc.

An End-of-Phase 2 (EOP2) meeting was held on August 19, 2011, with Merrimack to discuss the results of PEP0208 (e.g., 6-month and 12-month survival rates) and a proposed trial (to be entitled NAPOLI-1) that would enroll patients with previously treated metastatic pancreatic cancer. The trial discussed during the meeting was a two-arm, randomized, open-label trial comparing the safety and efficacy of MM-398 versus 5-fluorouracil plus leucovorin in patients with metastatic pancreatic cancer. During the meeting, FDA agreed with overall survival as the primary endpoint. FDA further recommended that Merrimack conduct two adequate and well-controlled trials to demonstrate the effectiveness of MM-398. During this meeting, Merrimack stated that an NDA would most likely be submitted under the provisions of 505(b)(2).

In July 2013, orphan drug designation was granted to MM-398 for the treatment of pancreatic cancer (11-3443).

On July 25, 2014, FDA requested clarification regarding Merrimack’s intended regulatory pathway. In an email dated July 28, 2014, Merrimack stated intent to rely on FDA’s prior findings of safety and effectiveness for nonclinical, drug interactions, special populations, overdose, and clinical pharmacology information for which Merrimack does not have right of reference and concluded that the proposed NDA should be a 505(b)(2) submission. Merrimack stated that their intent to submit an NDA under the provisions of 505(b)(2) (b) (4)

[REDACTED]

(b) (4)

On August 1, 2014, a Type C, general advice meeting held between DOP2 and Merrimack on August 1, 2014, to discuss the top-line results of NAPOLI-1 and Merrimack's plans for an NDA submission based on the results were discussed. As part of a response to a question posed by Merrimack regarding flexibility accorded to timing of submission of CMC information to an NDA, FDA stated that Merrimack could consider submission of a fast track designation request in order to request a rolling NDA submission.

In the August 1, 2014, meeting, FDA conveyed concerns that the ability to conclude that the reported OS effect observed in Arm C of NAPOLI-1 can be attributed to MM-398 may be confounded by the use of different 5-FU/LV regimens in Arm C and Arm B. FDA stated that Merrimack will need to address this issue in the planned NDA.

On November 17, 2014, FDA granted a Request for Fast Track Designation for “the investigation of MM398 in combination with 5-fluorouracil and leucovorin for the treatment of metastatic adenocarcinoma of the pancreas, in patients previously treated with gemcitabine, to demonstrate an improvement in overall survival”.

On October 3, 2014, Merrimack Pharmaceuticals, Inc. (Merrimack) submitted a request for a preNDA meeting. The meeting briefing package was submitted October 31, 2014.

*CMC, non-clinical toxicology, and clinical pharmacology*

In the briefing package, Merrimack stated that MM-398 (irinotecan liposome injection) is irinotecan sucrosulfate salt encapsulated in liposomes, for intravenous infusion. The proposed proprietary name is Onivyde. The drug product would be supplied as a sterile, white opaque liposomal dispersion in vials in a single strength (50 mg irinotecan hydrochloride trihydrate) at a concentration of 5 mg irinotecan hydrochloride trihydrate/mL. The proposed dose is 80 mg/m<sup>2</sup> administered intravenously over 90 minutes every two weeks.

Clinical pharmacology data to be provided in the NDA will include detailed pharmacokinetics of MM-398 administered as a single agent from Studies PEP0201, PEP0206, and PIST-CRC (n=59 patients), MM-398 administered in combination with 5-fluorouracil and leucovorin (5FU/LV) in Study PEP0203 (n=16) supplemented by PK data from NAPOLI-1 (n=260; MM-398 alone or with 5FU/LV) and the CITS studies (n=13; MM-398 alone). In addition, the NDA will contain the results of a population PK to assess the effects of demographics and organ dysfunction on PK and conduct exploratory analyses of exposure-response and exposure-toxicity relationships. An evaluation of the stability of MM-398, through assessment of the PK of total irinotecan and encapsulated irinotecan, will be provided using SN-38 as a surrogate for unencapsulated irinotecan.

*Trials supporting proposed indication*

Merrimack proposes to support the efficacy of MM-398 in the proposed NDA based on the results of a single trial, NAPOLI trial, which is an open-label, three-arm, randomized, multicenter trial. The following is a summary of the top-line results provided in the briefing package for the August 1, 2014, Type C meeting.

NAPOLI-1 was initially designed as a two-arm trial comparing the safety and efficacy of MM-389 at a dose of 120 mg/m<sup>2</sup> every three weeks with 5-fluorouracil 2000 mg/m<sup>2</sup> (with leucovorin) every week for four weeks in a six week cycle (Arms A and B below). After enrollment of 63 patients, Merrimack amended the trial to include a third arm (Arm C) investigating the combination of MM-398, 5-fluorouracil (5-FU), and leucovorin at the doses shown below. The amended trial was entitled: “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 (MM-398-07-03-01).”

Under the revised protocol, patients were randomized (1:1:1) to Arms a, B, or C (below). Randomization was stratified by albumin level, Karnofsky Performance Score (KPS), and ethnicity.

- **Arm A:** MM-398 120 mg/m<sup>2</sup> every three weeks
- **Arm B:** 5-fluorouracil (5-FU) 2000 mg/m<sup>2</sup> over 24 hours and leucovorin (LV) *d,l*-racemic form 200 mg/m<sup>2</sup> once weekly for 4 weeks of each 42-day (6 week) cycle
- **Arm C:** MM-398 80 mg/m<sup>2</sup> every two weeks in combination with 5-fluorouracil 2400 mg/m<sup>2</sup> over 46 hours and leucovorin *d,l*-racemic form 400 mg/m<sup>2</sup> every two weeks

With inclusion of the third arm, the statistical plan (SAP) was revised and the total sample size was increased from 270 to 405. The primary endpoint of NAPOLI-1 is overall survival (OS) with two co-primary, pair-wise comparisons for each MM-398-containing arm compared with the control arm; Type I error is controlled using the Bonferonni-Holm approach. As revised, the trial was powered to detect a hazard ratio for OS of 0.67 (Arm A vs. Arm B) and of 0.5 (Arm C vs. Arm B), based on the assumptions of a median OS of 4.5 months in Arm A, 3 months in Arm B (control), and 6 months in Arm C. Secondary endpoints included progression-free survival (PFS) and objective response rate (ORR). The specified population (in an amended SAP submitted prior to the final analysis) for the comparison of Arm C to Arm A was limited to patients randomized following the initiation of the amendment that introduced the third arm. For the safety analysis, the safety population includes all patients receiving any study-specified treatment, regardless of when they were enrolled.

### Results

A total of 151 patients were randomized to Arm A, 149 to Arm B, and 117 to Arm C. Merrimack stated that the trial demonstrated a statistically significant difference in OS for the comparison of Arm C vs. Arm B [HR=0.67 (95% CI 0.49-0.92); p=0.012] but no significant difference in OS for Arm A vs. Arm B [HR 0.99; p=0.9]. The median OS times for the two MM-398-containing arms were 6.1 months (Arm C) and 4.9 months (Arm A) and 4.2 months in the control arm (Arm B).

Merrimack stated that the comparison of PFS for Arm C vs. Arm B demonstrated a statistically significant improvement [HR = 0.55; ( 95% CI:0.41-0.75), p=0.0001] with a median PFS of 3.1 months in Arm C and median PFS of 1.5 months in Arm B.

The most common adverse reaction of MM-398 was myelosuppression, with a per-patient incidence of  $\geq$  Grade 3 neutropenia (based on reported laboratory values) of 20% in Arm C and 16% in Arm A compared with 2% in Arm B. The per-patient incidence of febrile neutropenia was 2% in Arm A and 4% in Arm C, while no cases of febrile neutropenia were reported in Arm B. Growth factors were administered to 17% of patients in Arm C and 12% in Arm A compared with 1% in Arm B. The most common non-hematologic Grade 3 or greater treatment-related adverse events in Arm C were fatigue (14%), diarrhea (13%), and vomiting (11%).

*Clinical data supporting NDA*

The October 31, 2014 briefing package included Merrimack's proposed approach for the contents of Module 2, Section 2.7.3 of the planned NDA, to include the text for the ISE as well as literature intended to support a conclusion that 5-FU dose intensities and regimens did not have an effect on OS, data intended to demonstrate that the planned cumulative doses of 5-FU in the 5-FU/LV control arm of NAPOLI-1 were higher than in the MM-398/5-FU/LV arm over a 6-week cycle, and simulation results intended to show that 5-FU area under the curve (AUC) in Arm B was higher than in the MM-398/5-FU/LV arm.

In addition, the briefing package identifies 9 additional studies (Table 1, page 11 of 42) to be included in the Integrated Summary of Safety (ISS) intended to provide information on the adverse reaction profile of MM-398. Datasets containing safety and exposure data in STDM and ADaM formats will be provided for 7 of these 9 studies (as well as for the NAPOLI-1 trial). Safety data will be presented in a side-by-side format, rather than pooled, with an emphasis on safety results obtained with MM-398 in combination with 5FU/LV, based on safety data in 123 patients enrolled in either Arm C of NAPOLI-1 (n=117) or in Study PEP0203, a sequential dose-escalation trial of MM-398 in combination with 5FU/LV in various solid tumors (n=16). The dosing schedules studied in PEP0203 differ from NAPOLI-1 in that this trial evaluated MM-398 in doses of 60, 80, 100, or 120 mg/m<sup>2</sup> in a every 21-day dosing schedule in combination with 5-FU 2000 mg/ m<sup>2</sup> and leucovorin 200 mg/ m<sup>2</sup> as a 24-hour IV infusion on Days 1 and 8 of a 21-day cycle. Study PEP0203, a randomized trial evaluating the safety and activity of 5FU/LV in combination with PEP02 or with irinotecan, with or without bevacizumab, (n=28) employed the same dose and schedule of MM-398 as NAPOLI-1, however patient level data are not available and only a safety summary will be provided.

In addition, side-by-side analyses of safety data from patients receiving MM-398 as a single agent will be provided for 279 patients enrolled in the following trials: Arm A of NAPOLI-1 (n=147), PEP0206 (n=44), PEP0208 (n=40), PEP0201 (n=11), PIST-CRC (n=18), or CITS (n=13), or PEP0202 (n=6).

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**SPONSOR QUESTIONS AND FDA RESPONSE:****REGULATORY:**

1. Does the Agency agree that the NDA and all associated copies may be submitted electronically in eCTD format, once, via the ESG Gateway (or if there are ESG gateway transmission issues associated with a fully validated submission, once in eCTD format via electronic media)?

**FDA Response:** The preferred method of submissions is via the FDA Electronic Submissions Gateway (ESG). FDA recommends that Merrimack direct questions regarding the preparation of submissions in electronic format to the following contact: [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov). Questions regarding submission of datasets to CDER should be directed to [edata@fda.hhs.gov](mailto:edata@fda.hhs.gov).

**Discussion during meeting:** Merrimack has no additional comments.

2. Does the agency concur with the sponsor plan to use the following language to describe MM-398?

*Onivyde™ (Irinotecan Liposome Injection) is irinotecan, encapsulated in liposomes, for intravenous infusion. Onivyde is supplied as a sterile, white to light yellow opaque liquid liposomal dispersion in a 10 mL single use glass vial. Each 10 mL vial contains the equivalent of 50 mg irinotecan hydrochloride trihydrate, at a concentration of 5 mg/mL.*

**FDA Response:** The proposed drug product established name (irinotecan liposome injection) appears acceptable. All other labeling statements will be addressed in the course of the NDA review. Provide the amount of the active ingredient, irinotecan that is equivalent to 50 mg irinotecan hydrochloride trihydrate.

**Merrimack response sent via email on December 2, 2014:** We have a question for clarification regarding the exact language to be used.

**Discussion during the meeting:** Merrimack requested clarification regarding the inclusion of the irinotecan freebase amount (43.3 mg) per 50 mg irinotecan hydrochloride. FDA confirmed that the freebase concentration should be cited on the carton/container labeling and in sections 3 and 11 in the package insert in accordance with FDA's salt policy. FDA requested Merrimack refer to the Guidance for Industry: Naming of Drug Products Containing Drug Substance Salt, 2013 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf>.

#### CLINICAL:

3. Does the Agency consider Merrimack's approach to a proposed justification for the lack of impact on efficacy of different dosing regimens of 5-FU + leucovorin to be appropriate?

**FDA Response:** FDA does not object to Merrimack's proposed approach to address potential impacts of the different 5-FU dosing regimens across the study arms of NAPOLI-1. The proposed approach includes submitting literature intended to support a conclusion that 5-FU dose intensities and regimens did not have an effect on OS, data intended to demonstrate that the planned cumulative doses of 5-FU in the 5-FU/LV control arm of NAPOLI-1 were higher than in the MM-398/5-FU/LV arm over a 6-week cycle, and PK simulation results intended to show that the 5-FU area under the curve (AUC) in the 5-FU/LV control arm was higher than in the MM-398/5-FU/LV arm.

In the NDA, provide justification for the studies selected for inclusion in the proposed approach to address potential impacts of the different 5-FU dosing regimens across the study arms of NAPOLI-1. Additionally, provide a summary of each of the studies selected and how each is relevant to Merrimack's position. Ultimately, FDA will review the adequacy of Merrimack's justification during the review of the NDA.

In the background provided by Merrimack for this question, Merrimack proposed submitting this justification in Module 2 of the NDA. Please note that Module 2 should summarize clinical information; the clinical summary sections are subject to space limitations in the eCTD of about 400 pages. In general, the appropriate location for analyses of data from more than one study is in Module 5.3.5.3, the Integrated Summary of Efficacy.

**Merrimack response sent via email on December 2, 2014:** Merrimack requests clarification of FDA's comment.

**Discussion during meeting:** Merrimack will include justification for the studies selected in the proposed approach to address potential impacts of the different dosing regimens including search strategy. FDA agreed to review Merrimack's justification when the information is submitted. FDA requested and Merrimack agreed to provide a brief summary of study design, results, and strengths limitation study in text and tabular format as well as copies of the publications. FDA stated that this would be acceptable and could be include prior to or in an early module of the rolling NDA submission.

4. Does the Agency agree with the sponsor's proposal for how the MM-398 Clinical Studies will be included into the NDA?

**FDA Response:** The proposal to provide a clinical study report for a single efficacy trial (NAPOLI-1) and to provide clinical study reports with limited patient level data from seven studies as outlined in table 1 of the briefing package, in addition to complete safety information from the NAPOLI -1 trial, is acceptable for filing of the application.

However, Merrimack should also include all information available to Merrimack that would reasonably affect the Contraindications, Warnings and Precautions, or Adverse Reactions sections of the product label from any investigator-sponsored studies of MM-398 not described on pages 11-13 of the briefing package or that are listed but not for inclusion.

**Discussion during meeting:** There was no additional discussion during the meeting.

5. Does the Agency agree with the proposal presented for content and format of the Integrated Summary of Safety? Also, in view of the small number of studies included in the dossier, does the Agency agree with Merrimack's plans to include the textual parts of safety analyses in Module 2, Section 2.7.4 Summary of Clinical Safety, and to include pertinent cross-references in Module 5, Section 5.3.5.3 Reports of analyses of data from more than one study?

**FDA Response:** The proposed content of the ISS, as summarized in FDA's response to question 4, provides a sample size which is sufficient to detect adverse events occurring at a per-patient incidence of 2% or higher for patients receiving MM-398 or a per-patient incidence of 4% or higher for patients receiving MM-398 plus 5-FU and leucovorin.

Whether this database is adequate to characterize the toxicity profile of MM-398 for the proposed use, i.e., in combination with 5FU and leucovorin, is dependent on the incidence of serious or irreversible morbidity observed across clinical trial experience with MM-398.

FDA agrees with Merrimack's proposal for the format, in accordance with the FDA Guidance for Industry referenced in the background information provided by Merrimack for this question. However, with regard to the location of these data, Section 2.7.4 is subject to space limitations and FDA may refuse to file an application if these limitations are exceeded. While it may be appropriate for text and summary tables to be located in Module 2, large appendices of tables, figures, and datasets typically should be provided in Section 5.3.5.3 of the NDA.

**Discussion during meeting:** Merrimack has no additional comments.

6. Does FDA agree with Merrimack's proposal to include the following information in the 120 Day Safety Update, maintaining the presentation of any new safety data in the same version of MedDRA as in the filing?

**FDA Response:** No. Please only provide narratives and CRFs for any previously unreported serious and unexpected adverse events occurring in NAPOLI-1 for the following: patients who died within 30 days of the last dose of study-specified therapy, patients who withdrew from the study or discontinued study-specified therapy due to an adverse event, or patients who experienced a serious and unexpected adverse event. In addition, provide narrative descriptions for all new serious and unexpected adverse events occurring in other studies. FDA prefers that the safety update occur at 90 days rather than at 120 days, if possible.

In addition, if Merrimack plans to submit an update to the overall survival analysis, the update should be pre-specified based on a set number of events or on a set cutoff date.

**Merrimack Response sent via email on December 2, 2014:** Merrimack agreed to provide safety update at day 90 and will pre-specify the overall survival update timing criteria.

**Discussion during meeting:** FDA prefers that the updated survival analysis be event-driven rather than calendar-driven. FDA further stated that whether additional information is included in labeling depends on whether it would be informative for prescribers.

7. Does the FDA agree with the proposed inclusion of Case Report Forms (CRF) and detailed information (including patient narratives) for the NAPOLI-1 study that will be provided for the NDA?

**FDA Response:** No. Refer to FDA comments 15i and 15j contained in the minutes of the August 1, 2014 Type C meeting between Merrimack and FDA. Provide detailed information including a narrative for all patients who died (including for deaths assessed

as due to disease progression) while receiving MM-398 or within 30 days of receiving the last dose of MM-398, and for those patients who terminated treatment for reasons other than disease progression. Provide complete CRFs for all patients who: died within 30 days of the last dose of study-specified therapy, experienced a treatment-emergent serious adverse event, or discontinued study-specified therapy due to an adverse event.

**Discussion during meeting:** There was no additional discussion during the meeting.

#### CLINICAL PHARMACOLOGY:

8. Does the Agency agree with the current updated population pharmacokinetic analysis plan to address analyses requested by the FDA at the August 1, 2014 Type C Meeting?

**FDA Response:** In general, the updated population PK analysis plan seems reasonable. Depending on results of the planned graphical displays of each efficacy/safety endpoint versus exposure stratified by the covariates of interest, further exposure-response analysis may be required to assess effect of exposure and other confounding risk factor(s) on clinical outcomes. Of note, a justification should be provided for the exposure metric, such as trough, maximum, or average concentration at steady state of irinotecan and/or SN-38, whichever is used for your final exposure-response analysis. The effect of dose modifications on the exposure metric should also be taken into account in the analysis.

**Discussion during meeting:** There was no additional discussion during the meeting

9. Does the Agency agree with use of the current pharmacokinetic data analysis to support labeling in hepatic impairment and that a dedicated hepatic impairment study is not required?

**FDA Response:**

- The use of the results of population PK analysis to support labeling for patients with hepatic impairment appears to be acceptable. The final determination will be made during review of the complete PK analysis and data in the future NDA.
- FDA recommends re-evaluating  $C_{\text{average,CPT-11}}$  and  $C_{\text{average,SN-38}}$  in patients with baseline bilirubin level stratified by <1 mg/dL, 1-2 mg/dL and > 2 mg/dl using all the data from studies PEP0201, PEP0203, PEP0206, and NAPOLI-1.

**Discussion during meeting:** There was no additional discussion during the meeting.

10. Does the Agency agree with the proposal to use the pharmacokinetic data from Phase 1 Study PEP0201 (which measured both total and encapsulated irinotecan) to support the determination of the *in vivo* stability of the liposome, and to use the differences between total and encapsulated irinotecan and SN-38 concentration to determine the un-encapsulated irinotecan?

**FDA Response:** FDA does not object the proposal under the condition that justification will be provided in the NDA submission for not being able to develop the bioanalytical method which can distinguish between encapsulated and unencapsulated irinotecan.

**Discussion during meeting:** There was no additional discussion during the meeting.

CLINICAL/STATISTICS:

11. Does the Agency agree to our proposed approach for the submission of MedDRA coding of Adverse Event Data?

**FDA Response:** FDA does not object to Merrimack's proposal to use MedDRA v14.1 to code adverse events.

**Discussion during meeting:** There was no additional discussion during the meeting.

CHEMISTRY, MANUFACTURING AND CONTROLS:

12. Does the Does FDA agree with Merrimack's proposal to include updated stability data with the (b) (4)?

**FDA Response:** The proposal is not acceptable. Under PDUFA V, all components of the NDA should be provided in the NDA, with only minor components submitted no later than 30 days after filing.

**Discussion during meeting:** There was no additional discussion during the meeting.

13. FDA Does the Agency agree to our proposed approach for the submission of Stability Data Sets, as Merrimack does not currently have electronic databases for capturing and trending of stability data?

**FDA Response:** The proposal for submitting stability data in tabular form is acceptable.

**Discussion during meeting:** There was no additional discussion during the meeting.

14. Does the Agency agree the redeveloped discriminating *in vitro* release method is suitable as a critical quality attribute test for drug product release, NDA approval, and in support of future process changes?

**FDA Response:** The newly developed *in vitro* release method seems reasonable. However, the information related to the methodology in the meeting package is limited. Therefore, at this time FDA cannot conclude that newly developed method is fully suitable for QC testing and other future process changes. Additionally, it should be noted that a final determination on the *in vitro* release method and acceptance criteria will be made during the NDA review.

**Discussion during meeting:** There was no additional discussion during the meeting.

ADDITIONAL STATISTICAL COMMENTS:

15. Please include the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

**Merrimack Response sent via email on December 2, 2014:** Merrimack requests clarification regarding the submission of the SAS programs to CDER should be directed to [edata@fda.hhs.gov](mailto:edata@fda.hhs.gov).

**Discussion during meeting:** Merrimack request clarification regarding how to submit the SAS programs. FDA stated that the SAS programs should be submitted together with the datasets in separate folders. FDA requested that tables in the CSRs should have footnotes identifying the programs used to generate the results.

16. Please provide SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert.

**Merrimack Response sent via email on December 2, 2014:** Please see Merrimack's comment in question 15.

**Discussion during meeting:** See discussion under question 15.

17. Provide a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined PFS (or investigator-assessed PFS) event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity Analysis of the SAP should be included as well.

- Please provide raw and derived datasets with adequate documents(s) in PDF file (define.pdf). In the define document, please provide adequate comment for variable label, data format decode of categorical and numerical variable(s), and algorithm(s) to derive new variable from raw data to derived data.
- Please provide executable SAS program(s) with adequate document(s) to duplicate the analysis datasets derivation from raw datasets.
- Please provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.
- Please provide SAS programs with adequate document(s) for the derived datasets and the analyses associated with the results presented in the proposed package insert.

**Merrimack Response sent via email on December 2, 2014:** Merrimack requests clarification of FDA's comments.

**Discussion during meeting:** Merrimack confirmed that the data in the application will be in SDTM and ADaM formats and Merrimack will provide the define file in pdf format with hyperlinks.

**Merrimack request for clarification sent via email on December 2, 2014:**

Merrimack confirms that they submitted a request for rolling submission as IND 102799 SN0133 on 25 November, 2014. Merrimack has submitted a plan, including submission of the Nonclinical portion of the NDA in late-December 2014. Can the Agency comment on its response or expected response to the Request for Rolling Submission?

**Discussion during the meeting:** FDA will respond to the request for rolling submission following the meeting. FDA requested Merrimack include:

- Letters of Authorization to Device Master Files (DMFs) for all critical excipients. Merrimack confirmed that they will include the requested information.
- The DS information in the NDA will be summary information and specifications with other data residing in the referenced DMFs.
- A revised TOC to include study titles in Module 4.
- Copies of all correspondences and meeting minutes for this development program in Module 1.
- The clinical study report for NAPOLI-1 containing the charter and minutes for the DMC as an appendix or a stand-alone document linked to the CSR.
- Form 356h with a complete list of all manufacturing and testing facilities including all contact information.

FDA encouraged Merrimack to submit the datasets requested by OSI in the August 1, 2014 meeting minutes, and the justification described in question 3 prior to the complete submission of Module 5. These data may be submitted to the IND and also included in the NDA when the appropriate Module is submitted.

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

Multidisciplinary:

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and discussed during the August 1, 2014 Type C meeting and it was determined, based on the limited information provided, that a REMS does not appear to be necessary in order to file the NDA. This determination has not changed.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting was held on September 18, 2014. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements of Prescribing Information website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

### **505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies

described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>

3. <i>Example: NDA YYYYYY</i> <i>"TRADENAME"</i>	<i>Previous finding of safety for</i> <i>Carcinogenicity, labeling section XXX</i>
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

#### **Office of Scientific Investigations (OSI) Requests**

Please reference the minutes from the Type C meeting held on August 1, 2014 for a listing of OSI requests.

#### **ISSUES REQUIRING FURTHER DISCUSSION**

- Please see action items below

#### **ACTION ITEMS**

- FDA will respond to Merrimack's rolling review request submitted on November 25, 2014

#### **ATTACHMENTS AND HANDOUTS**

- Attendees list

## MEETING ATTENDANCE LIST

Meeting between Merrimack Pharmaceuticals and  
the Center for Drug Evaluation and Research.

DATE: December 2, 2014 TIME: 3:00 PM ROOM: WO 22; Rm 1309

NAME - Please print	AFFILIATION
Olen Stephens	ONDOA
Banu S. Zolnick	ONDOA / Biopharm
Hong Zhao	OPC/DEPV
Runjian Jin	OCP/DCPV
Liang Zhao	OCP/OPM
Wendy Helms	OSE-DOPZ
Frances Fambrella	OSE-RPM
Mona Patel	OSE-DRISK
PATRICIA KEEGAN	FDA/CDER/OND/OHOP/DOPZ
Steven Lemery	" " "
Shan Pradhan	" "
Weishi Yuan	FDA/CDER/OTS/OB/DBV
Melanie Puerce	FDA/CDER/OHOP/DOPZ
MARION SCODCA	Merrimack Pharma
BRUCE BELANGER	Merrimack Pharmaceuticals
Eliel Bagever	Merrimack Pharma
Michael Slater	Merrimack Pharmaceuticals
Peter Lavins	" "
Nareet Shindea	Merrimack Pharmaceuticals
Bambang Adnyaya	Merrimack Pharmaceuticals
Daryl Drummond	Merrimack Pharmaceuticals
Tony Awad	Merrimack Pharmaceuticals
Michelle Motta DARDENO	Merrimack Pharmaceuticals
Andrew Bacon	Merrimack Pharma
JaeYeon Kim	Merrimack Pharmaceuticals
James Williams	Merrimack Pharmaceuticals
Sara Green	Merrimack Pharmaceuticals
Grace Yeh	Pharma Engin, Inc
(b) (4)	Consultant to Merrimack
Kamesh K	Baxter Healthcare

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MELANIE B PIERCE  
12/19/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 102799

MEETING MINUTES

Merrimack Pharmaceuticals, Inc.  
Attention: Michael Slater  
Senior Director of Regulatory Affairs and Quality Assurance  
One Kendall Square Suite B201  
Cambridge, MA 02139

Dear Mr. Slater:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Onivyde (MM398).

We also refer to your July 3, 2014, correspondence, received July 3, 2014, requesting a meeting to discuss CMC components for our NDA application submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teicher Agosto, Regulatory Project Manager at (240) 402-3777.

Sincerely,

*{See appended electronic signature page}*

Ali H. Al Hakim, PhD  
Branch Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** September 18, 2014, 12:00 – 1:00 pm EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315  
Silver Spring, Maryland 20903

**Application Number:** 102799  
**Product Name:** Onivyde (MM398)  
**Indication:** Treatment of pancreatic cancer

**Sponsor/Applicant Name:** Merrimack Pharmaceuticals Inc.

**Meeting Chair:** Ali Al Hakim, Branch Chief  
**Meeting Recorder:** Teicher Agosto, Regulatory Project Manager

**FDA ATTENDEES**

Ali Al Hakim, Ph.D., Branch Chief, ONDQA  
Liang Zhou PhD, CMC Lead, ONDQA  
William Adams, PhD, CMC Reviewer, ONDQA  
Banu Zolnik, PhD, Biopharmaceutics Reviewer, ONDQA  
Okpo Eradiri, PhD, Biopharmaceutics Acting Team Leader, ONDQA  
Robert Wittorf, Pharm D, Compliance Officer, OMPQ  
Vipul Dholakia, Ph.D., Compliance Officer, OMPQ  
Teicher Agosto, PharmD, Regulatory Project Manager, ONDQA

**SPONSOR ATTENDEES**

Tony Awad, Senior Director, Process Sciences and Manufacturing  
Robert Corcoran, Vice President, Quality Systems  
Daryl Drummond, Vice President, Discovery  
Sara Green, Senior Associate, Regulatory Affairs  
Kevin Kesper, Group Leader, Nanoliposomal Process Development  
Peter Laivins, Senior Vice President, Development  
Andrew O'Brien, Director, Quality Control  
Michael Slater, Vice President, Regulatory Affairs and Quality Systems  
Erin Soley, Manager, Formulations  
Jim Williams, Director, Regulatory Affairs  
Grace Yeh, CEO, PharmaEngine, Inc

## 1.0 BACKGROUND

Merrimack Pharmaceuticals Inc. submitted a Type B, Pre-NDA CMC meeting request on July 3, 2014. A meeting requested granted letter was issued on July 29, 2014. Merrimack Pharmaceuticals Inc. sent meeting briefing packages on August 19, 2014. Meeting preliminary comments were sent to Merrimack Pharmaceuticals Inc. on September 12, 2014. On September 16, 2014, after reviewing the agency preliminary responses, the sponsor stated that they would like to seek further clarification and discuss questions 2, 3, 5 and 8. The sponsor sent additional information to be discussed during the meeting on September 16, 2014.

## 2.0 DISCUSSION

### Question #1:

*Does the FDA agree that the expectation of expedited regulatory designation such as a Fast Track or Priority Review Designation can be taken into consideration when advising the sponsor on the timing of submission of CMC elements of the NDA?*

### FDA response to Question #1

FDA expects that each section of the NDA will be complete and include all the required information. If Fast Track Designation is requested and granted, Merrimack may request a rolling NDA submission before the NDA is submitted. Refer to the FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>)

### Meeting Discussion:

**No Further Discussion required**

### Question #2:

*Does the Agency agree with the timing presented in the briefing package for submission of CMC documentation to the NDA and for availability of CMC documentation at the Pre-Approval Inspection (PAI)?*

### FDA response to Question #2

No, we do not agree with the proposal as outlined in tables 2 and 3. Modules 2 & 3 of the NDA should contain complete CMC information at the time of NDA submission. In the event of rolling submission, the entire CMC package could be submitted before or after the other modules of the NDA.

**Response from Sponsor:**

*We propose to address this question in the context of discussion of Question #3*

**Meeting Discussion:**

The Agency stated that the contractor will perform an (b) (4) media fill simulation using a worst case scenario and submit this in the NDA.

**Question #3:**

*Does the Agency agree that inclusion of the following documents in the initial NDA submission is appropriate and sufficient to satisfy the requirements of the relevant sections of the NDA?*

- 1. The Pharmaceutical Development Section, which will include a detailed discussion of the relationship between the manufacturing, testing, formulation, and packaging of the DP used in the Phase 3 studies, the Primary Stability batches, and the Commercial scale final drug product intended for marketing*
- 2. Three Batch Records from the 3 Primary Stability batches of BDP manufactured at Merrimack Pharmaceuticals (executed)*
- 3. Three Batch Records from the 3 Primary Stability batches of drug product manufactured at (b) (4) (executed)*
- 4. Commercial Master Batch Record for the BDP manufactured at Merrimack Pharmaceuticals*
- 5. Pre-validation commercial process Batch Record (executed) for the BDP manufactured at Merrimack Pharmaceuticals*
- 6. MM-398 Validation Master Plan (VMP)*
- 7. Facility VMP (Merrimack)*
- 8. Analytical Method Validation summaries*
- 9. Summary reports of the facility and equipment validation programs at both the Merrimack and (b) (4) manufacturing sites*
- 10. Process Performance Qualification protocol (s) for BDP*
- 11. (b) (4) Validation summaries*
- 12. (b) (4) Media Fill summary, specific to the commercial fill line that will be used to fill MM-398 DP*

### ***13. Shipping Validation summaries***

#### **FDA response to Question #3**

FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)]. However, FDA does not prescribe how that is to be accomplished and does not review or approve process/facility validation plans and PPQ protocols used for process validation studies other than commercial scale process simulations for aseptically manufactured products. The process validation will depend on multiple factors such as actual facility, utilities, qualified equipment, process parameter, control strategies and the trained personnel, some of which are specific to the complexity of the product and manufacturing process. The actual protocols, acceptance criteria, its execution, and study outcomes will be evaluated during an inspection.

It is ultimately your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product. For additional information, please refer to "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.

In addition, we have the following comments:

\* For item 1, the pharmaceutical development section should provide the packaging qualification study reports including the extractables and leachables studies for the proposed primary packaging components.

\* Items 2 and 3 indicate that a single drug substance supplier will be proposed, however question 8 indicates that two suppliers will be proposed. See response to question 8 below.

\* For item 8, completed method validation reports with supporting information for all analytical methods should be provided in the NDA. Summaries are not sufficient.

\* For item 13, see the response to question 7 below regarding the (b) (4)

In vitro release method should include, but not limited to, the following information:

- A detailed description of the in vitro release method being proposed for the evaluation of your product and development parameters (selection of the equipment/apparatus, in vitro release media, agitation, pH, sink condition, liposomal integrity, biorelevance, etc.) used to select the proposed in vitro release method as the optimal method for your product. In addition, describe any discriminating ability of the in vitro release method with respect to (b) (4)

The testing conditions used for each test should be clearly specified. The release profile should be complete and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend the use of at least twelve samples per testing variable.

- Provide the complete in-vitro release profile data (individual, mean, SD, profiles) for your product. The data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim at 5 min, 10 min, 15 min, etc.).

- Data to support the discriminating ability of the selected in vitro release method.  
In

general, the testing conducted to demonstrate the discriminating ability of the selected drug release method should compare the in-vitro release profiles of the target product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables.

- Submit all individual unit in-vitro release data in SAS transport format in the NDA.

**Response from Sponsor:**

- *Merrimack requests that the Agency expands its remarks regarding Table 3: we understand from the FDA response that a complete module 3 submission generally does not include validation data, other than aseptic validation data, which are required. We are proposing to include in the initial NDA media fill data from the commercial fill site, derived from routine periodic (b)(4) fill validation on the commercial fill line that will be used to fill commercial MM-398. MM-398 process specific media fills would not be in the NDA, but available for inspection at*

(b)(4)

- *For item 8, completed method validation reports with supporting information for all analytical methods will be provided in the NDA. We propose to place a summary in Module 3 of the NDA and detailed reports in the Regional section and wish to discuss whether this is acceptable.*
- *With regard to the In vitro release assay discussion:*
  - *We would welcome further explanation as to the number of samples to be tested: (b)(4)*
  - *We were uncertain whether this assay is intended as a validation exercise or as a routine batch release method.*
  - *We do not understand the discussion, "the percentage is based on the product's label claim at 5 min, 10 min, 15 min, etc.," and would ask for further explanation.*

**Meeting Discussion:**

Sponsor indicated that the summary and detailed analytical method validation studies will be included in the NDA. The Agency found this acceptable

The FDA stated that the in vitro drug release test should be part of the batch release and stability testing. In response to FDA's questions regarding incomplete drug release profiles, the Sponsor stated that they will perform further investigations. The Sponsor stated that the in vitro release method discriminates batches that are manufactured with meaningful variations. Since the meeting package did not contain any in vitro release data, there was no further discussion.

**Question #4:**

*In the course of manufacturing development of MM-398 drug product, there have been minor process modifications between the "Phase 3 Clinical Process," the "Primary Stability Process" and the proposed "Commercial Process" which are all detailed in Table 4 Comparison of Process Parameters Used throughout the Entire Process Development of MM-398 (Page 28).*

*Does the Agency agree that (subject to full review in the NDA) the changes described do not appear to represent a significant process change and that the current registration manufacturing pathway is potentially approvable?*

**FDA response to Question #4**

At this time, we are unable to comment on your proposed process modifications and manufacturing strategy as they will be reviewed and evaluated at the time of NDA submission and during an inspection, respectively. It is necessary for firms to justify and confirm earlier process design and development work for their proposed scale up to commercial scale. Firms need to have justification for any proposed changes in the manufacturing process, process parameters, component characteristics, and need to demonstrate how these relate to the final product attributes at commercial scale. Major changes in the formulation (between the clinical and the to-be-marketed products) will require an in-vivo bioequivalence study.

The NDA should include a historical summary of changes (b) (4) and their suppliers; manufacturing process and controls; release specifications; and analytical methods.

**Meeting Discussion:**

**No Further Discussion required**

**Question #5:**

*According to FDA's Draft Guidance for Industry: Liposome Drug Products Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (August 2002), there are a number of "properties specific to liposomal drug products that may be useful to assess." Merrimack has assessed the majority of these properties either for release or as characterization tests; however, other methods have been analytically challenging and may not help to further characterize the MM-398 product. The Characterization*

***Approach described in Section 10.5 Characterization and Specification Tests of MM-398 (Page 36) is considered to be a robust release and characterization analytical package appropriate for MM-398. Does the Agency agree that the planned package is appropriate and sufficient (subject to review) for the NDA?***

**FDA response to Question #5**

Regarding proposed specifications in tables 5 and 6:

- (a) The NDA should include a historical summary of changes to the tests, analytical methods and acceptance criteria.
- (b) The NDA should indicate which tests are included to address a specific excipient or drug substance supplier.
- (c) The specifications should indicate which data represents test results from an inprocess control for bulk drug product or for finished drug product.
- (d) Each test should include specific acceptance criteria; "report result" is not acceptable.
- (e) The specification should include tests for free (unencapsulated) drug substance; specified and unspecified impurities from the drug substance and excipients; identity and content for each excipient; and empty liposomes.
- (f) To support the proposed criteria for (b)(4), the NDA should include a profile of (b)(4) which may be introduced from processing materials and excipients into bulk drug product and/or drug product.
- (g) The specifications should address (b)(4) of the liposome.
- (h) The analytical methods should be described in detail and method validation reports should be provided with supporting chromatogram and spectra.

Regarding the information in table 7, the pharmaceutical development discussion (NDA section 3.2.P.2) should address the effect of each manufacturing step and batch size on the characteristics of the liposome.

Please see FDA Response to question #3 for in vitro release method development manufacturing.

**Response from Sponsor:**

***(e) The specification should include tests for free (unencapsulated) drug substance; specified and unspecified impurities from the drug substance and excipients; identity and content for each excipient; and empty liposomes.***

***The following shows the product excipients and our ability to assay them in drug product:***

<b><i>Critical Excipients</i></b>	<b><i>Testing in Drug Product</i></b>
-----------------------------------	---------------------------------------

<i>Cholesterol High Purity, USP, EP</i>	<i>ID and Quantitation</i>
<i>DSPC</i>	<i>ID and Quantitation</i>
<i>PEG- DSPE</i>	<i>ID only ( (b) (4)</i>
<i>HEPES</i>	<i>Buffering agent - (b) (4) measured</i>
<i>Sodium Chloride, USP, EP</i>	<i>Isotonicity agent - (b) (4) measured</i>

**Meeting Discussion:**

FDA stated that the specification should characterize the identity and assay for each component of in the liposomes. The NDA should include an explanation as to how the proposed specification provides that information.

Merrimac stated that it has been shown that empty liposome do not pose a safety issue. This information will be provided in the NDA. FDA stated that the information would be evaluated during NDA review.

**Question #6:**

*Given the clinical development batch data and primary stability batch data described in Section 10.6 Shelf Life Evaluation (page 42), does the Agency agree that, subject to data review, a (b) (4) month shelf life would be acceptable at NDA filing, with the option of extending to (b) (4) months as further data become available on the Primary Stability batches?*

**FDA response to Question #6**

The cited stability data may not be sufficient to support a (b) (4) month initial expiry period for two reasons. First, only 12 months of primary stability data will be provided. Second, primary stability data will not be provided on drug product made using drug substance from both proposed drug substance suppliers (see response 8). Shelf life will be determined based on the evaluation of the stability data submitted in the NDA.

Based on the information provided in table 4, stability study data on drug product made by the “(b) (4)” cannot be considered as supportive in that the manufacturing process is significantly different from the proposed commercial process. Whether drug product made by the “Phase 3 Clinical Process” can be considered as supportive will be determined during the NDA review based on a comparison of the detailed manufacturing process. Refer to our response to question 4.

**Meeting Discussion:**

***No Further Discussion required***

**Question #7:**

***MM-398 Drug Product is produced***

(b) (4)

(b) (4)

(b) (4) ***Does the Agency agree with this approach of establishing MM- 398 Drug Product shelf life?***

**FDA response to Question #7**

The proposal

(b) (4)

is acceptable. The NDA should specify the

(b) (4)

These parameters should be supported by batch release and stability data which addresses the effect of these factors on the stability of bulk drug product and drug product. Also, the NDA should describe how you will determine that the parameters for storage time and storage condition are met.

**Meeting Discussion:**

**No Further Discussion required**

**Question #8:**

***For API supply, Merrimack intends to reference in the NDA irinotecan hydrochloride trihydrate Drug Master Files (DMFs) from the supplier of API (USP Grade) for the Phase 3 clinical trial ( (b) (4) and a back-up supplier who provided API used in Phase 1 and 2 clinical trials in Taiwan (b) (4) ).***

***Does the Agency agree that it is appropriate to include two API suppliers in the NDA?***

**FDA response to Question #8**

The use of two drug substance suppliers can be accepted in an NDA provided that both suppliers produce the same drug substance and that materials from both suppliers meet the proposed specifications without significant differences. In addition, complete CMC comparability information should be provided for drug substances obtained from both suppliers, This information should address differences in the manufacturing processes;

include supporting batch release data for bulk drug product and drug product; and include primary stability data for bulk drug product and drug product manufactured with drug substance from each proposed drug substance supplier using the proposed commercial manufacturing process and controls.

The type II DMF for each drug substance supplier will be reviewed for complete and acceptable CMC information. Also, all drug substance manufacturing facilities should be ready for GMP inspection at the time of application submission.

**Response from Sponsor:**

*The sponsor proposes to include the two suppliers of Drug Substance (DS) in the NDA. Both manufacturers supply Irinotecan Hydrochloride USP and the required comparability information will be provided in the NDA. We propose to include in the initial NDA* (b) (4)

*We would like to discuss this proposal.*

**Meeting Discussion:**

FDA stated that the initial shelflife will be based on the data from the primary stability studies on commercial drug product. The proposal to qualify a second drug substance supplier (b) (4) would be considered if the NDA is able to establish that the materials are chemically equivalent. This would include information on the molecular structure, physical and chemical characterization, manufacturing process and impurity profiles for the drug substance, and relevant attributes of the drug product. FDA advised the sponsor that it is typically easier to include a single drug substance supplier in the NDA and add the second supplier in a supplemental application. This would permit the development of more complete supporting information.

Regarding the proposal for an NDA stability update, under PDUFA V it is acceptable to submit additional stability data within 30 days of NDA filing.

**Additional Comments:**

*USAN name: Irinotecan Liposome Injection  
NDA submission end of the year 2014*

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There are no specific issues requiring further discussion at this time.

**4.0 ACTION ITEMS**

There are no specific due dates or time lines for submission of information or other action items.

## **5.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALI H AL HAKIM  
10/17/2014



IND 102799

**MEETING MINUTES**

Merrimack Pharmaceuticals, Inc.  
Attention: Michael Slater  
Senior Director of Regulatory Affairs and Quality Assurance  
One Kendall Square Suite B201  
Cambridge, MA 02139

Dear Mr. Slater:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Onivyde (MM398)."

We also refer to the meeting between representatives of your firm and the FDA on August 1, 2014. The purpose of the meeting was to obtain the Agency's general guidance on the regulatory, preclinical, clinical pharmacology, and statistical contents of the planned NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1273.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type C  
**Meeting Category:** Other

**Meeting Date and Time:** August 1, 2014; 10:00 AM-11:00 AM  
**Meeting Location:** CDER White Oak Bldg. 22; Room 1309

**Application Number:** 102799  
**Product Name:** Onivyde (MM398)  
**Indication:** Pancreatic cancer  
**Sponsor/Applicant Name:** Merrimack Pharmaceuticals, Inc.

**Meeting Chair:** Steven Lemery  
**Meeting Recorder:** Melanie Pierce

**FDA ATTENDEES:**

**Office of Hematology and Oncology Products**

**Division of Oncology Products 2**

Patricia Keegan, MD	Director
Steven Lemery, MD, MHS	Clinical Team Leader
Shan Pradhan, MD	Clinical Reviewer
Melanie Pierce, BSc	Project Manager

**Office of Hematology and Oncology Products**

**Division of Hematology Oncology Products**

Margaret Brower, PhD	Pharmacology/Toxicology Reviewer
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**Office of Clinical Pharmacology**

Stacy Shord, Pharm.D.	Clinical Pharmacology DCPV Team Leader (Acting)
Runyan Jin, PhD	Clinical Pharmacology DCPV Reviewer
Liang Zhao, PhD	Pharmacometrics Team Leader (Acting)
Christian Grimstein, PhD	Genomic and Targeted Therapy Reviewer

**Office of Biostatistics**

Kun He, PhD	Statistics Team Leader
Vivian Yuan, PhD	Statistics Reviewer

**Office of New Drugs Quality Assessments:**

Ali Al Hakim, PhD

Quality Team Leader

**Office of Scientific Investigations:**

Lauren Iacono-Connors, PhD

**SPONSOR ATTENDEES:**

Bambang Adiwijaya,

Investigator, Clinical Pharmacology and  
Pharmacometrics

Eliel Bayever,

Vice President, Medical

Bruce Belanger,

Senior Director, Biostatistics

Navreet Dhindsa,

Associate Director Clinical Operations

Sara Green,

Regulatory Affairs Associate

Kaniz Khalifa,

Principal Clinical Data Manager

Peter Laivins,

Senior Vice President, Development

Ken Olivier,

Senior Director of Toxicology

Michael Slater,

Vice President, Regulatory Affairs and Quality  
Systems

**BACKGROUND:**

MM-398 (irinotecan liposome injection) is irinotecan in the form of a sucrosulfate salt, encapsulated in liposomes, for intravenous infusion. In their briefing package, Merrimack Pharmaceuticals, Inc (Merrimack) described the pharmacokinetic (PK) profile for MM-398 as showing a 70-fold higher area under the curve (AUC) for irinotecan as compared to irinotecan. The proposed indication is the treatment of pancreatic cancer in patients previously treated with gemcitabine, as a combination therapy with 5-FU and leucovorin (LV). In July, 2013, orphan drug designation was granted to MM-398 for the treatment of pancreatic cancer (11-3443).

Merrimack reports that MM-398 was invented at Hermes Biosciences, Inc. (CA) as a liposomal form of irinotecan and was licensed to PharmaEngine, Inc. of Taiwan, for clinical development. PharmaEngine commenced Phase 1 trials in January 2005, in Taiwan. In October 2008, PharmaEngine filed IND 102799 for the product, then named PEP02, and commenced trials under that IND including the following study in pancreatic cancer, PEP0208: "A Phase II Study of PEP02 as a Second Line Therapy for Patients with Metastatic Pancreatic Cancer."

In June 2011, sponsorship of IND 102799 was transferred to Merrimack Pharmaceuticals, Inc. and an End-of-Phase 2 meeting was held on August 19, 2011 with Merrimack to discuss the results (6-month and 12-month survival rates observed in PEP0208) and a proposed trial that would enroll patients with previously treated metastatic pancreatic cancer. The trial discussed during the meeting was a two-arm, randomized, open-label trial comparing the safety and efficacy of MM-398 versus 5-fluorouracil plus leucovorin in patients with metastatic pancreatic cancer. During the meeting, FDA agreed with overall survival as the primary endpoint. FDA further recommended that Merrimack conduct two adequate and well-controlled trials to demonstrate the effectiveness of MM-398 because a conclusion based on two persuasive studies will always be more secure. For a single randomized trial to support an NDA, the trial must be well designed, well conducted, well executed, internally consistent and provide statistically and

clinically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.

Following the EOP2 meeting and initiation of the trial with enrollment of 63 patients, and without additional discussion with the Agency, Merrimack amended the protocol to include a third arm, consisting of MM-398 in combination with 5-fluorouracil and leucovorin. The amended protocol (NAPOLI) was entitled: "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."

In the amended protocol, patients were randomized (1:1:1) to one of the following treatment arms:

- **Arm A:** MM-398 at a dose of 120 mg/m<sup>2</sup> every three weeks
- **Arm B:** 5-fluorouracil (5-FU) 2000mg/m<sup>2</sup> over 24 hours and leucovorin *d,l*-racemic form 200 mg/m<sup>2</sup> every week for 4 weeks in each 6 week cycle
- **Arm C:** MM-398 at a dose of 80 mg/m<sup>2</sup> every two weeks in combination with 5-fluorouracil 2400mg/m<sup>2</sup> over 46 hours and leucovorin *d,l*-racemic form 400 mg/m<sup>2</sup> every two weeks

The statistical plan (SAP) was also revised and the total sample size was increased from 270 to 405. The revised SAP described median OS assumptions of 4.5 months in Arm A, 3 months in Arm B (control), and 6 months in Arm C (corresponding to HRs of 0.67 and 0.5 in favor of Arm A and Arm C relative to Arm B, respectively).

The NAPOLI trial was a global study that randomized 417 patients with metastatic pancreatic cancer who received prior gemcitabine-based therapy. Patients were stratified by albumin levels, KPS and ethnicity. A total of 151 patients were randomized to Arm A, 149 to Arm B, and 117 to Arm C (fewer patients were enrolled to this arm as it was added later).

The primary endpoint of the study was overall survival (OS), with each active MM-398-containing arm being compared with the control arm (alpha was controlled using the Bonferonni-Holm approach). Secondary endpoints included progression-free survival (PFS) and ORR. The specified population (in an amended statistical analysis plan submitted prior to the final analysis) for the comparison of Arm C to Arm A consisted of patients randomized following the initiation of the amendment that introduced the third arm. Merrimack stated that a comparison will also be conducted using all patients randomized to the control group. For the safety analysis, the control group consisted of all patients, regardless of when they were enrolled. Safety for the combination arm will also be compared with the concomitantly enrolled patients.

Merrimack stated that patients randomized to the combination arm experienced a median overall survival of 6.1 months, a 1.9 month improvement over the 4.2 month survival in the control arm of 5-FU and leucovorin alone (HR=0.67, 95% CI [0.49-0.92], p=0.01). Merrimack also stated that this arm demonstrated a statistically significant advantage in PFS compared to the control

arm, with a median of 3.1 months compared to 1.5 months (HR = 0.55, 95% CI [0.41-0.75], p=0.0001).

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o difference in OS was observed between the MM-398 arm and the 5FU plus leucovorin arm (HR = 0.99, p = 0.9). The median OS was 4.9 months for MM-398 arm and 4.2 months for the 5FU plus leucovorin arm.

Grade 3 or greater neutropenia (based on reported laboratory values) was recorded in 20% of patients in the combination arm, 16% in the MM-398 monotherapy arm, and 2% in the 5FU/LV arm. The incidence of febrile neutropenia was 2% in the combination arm, 4% in the monotherapy arm and none in the 5FU/LV arm. Growth factors were administered to 17% of patients in the combination arm, 12% in the monotherapy arm, and 1% in the 5FU/LV arm. The most common non-hematologic Grade 3 or greater treatment-related adverse events were (in the combination arm) fatigue (14%), diarrhea (13%), and vomiting (11%).

In response to FDA's request for clarification on the regulatory pathway, Merrimack provided the following information by electronic mail (e-mail) communication. At the EOP2 meeting, Merrimack indicated that an NDA would most likely be submitted under the provisions of 505(b)(2). (b) (4)

Following FDA's request for clarification on July 25, 2014, Merrimack concluded that the proposed NDA should be a 505(b)(2) submission. Merrimack intends to rely on FDA's prior findings of safety and effectiveness for the following information for which Merrimack does not have right of reference. As noted in the e-mail, this list below is not intended to be "all-inclusive" of the information:

 (b) (4)

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**SPONSOR QUESTIONS AND FDA RESPONSE:**

**PREAMBLE:** The meeting package provided insufficient information regarding the format and contents of an application to allow the Agency to provide substantive input into the proposed NDA for submission under the provisions of (b) (4) 505(b)(2). For example, the package did not contain an outline of the proposed (complete) NDA, information regarding which, if any, studies conducted with MM-398 would not be included in the proposed New Drug Application (NDA), an outline of the information to be included in the proposed integrated summaries of safety and efficacy, an outline of the proposed information to be included in the 120-day safety update submission to the NDA, the format of datasets, or any proposals for submission of case report forms and narrative summaries of serious adverse events. The package included limited summary data from the pivotal study (for example, the package did not describe how patients were tested for UGT1A1 or how patients homozygous for the \*28 allele fared compared to other patients).

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If Merrimack intends to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, Merrimack must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Merrimack should establish a "bridge" (e.g., via comparative bioavailability data) between MM-398 and each listed drug upon which Merrimack proposes to rely to demonstrate that such reliance is scientifically justified.

REGULATORY:

1. The draft product labeling shows the indication as: "[REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]. Does the Agency agree that it is appropriate, throughout the labeling, to omit specific discussion of [REDACTED] (b) (4)  
[REDACTED] ?

**FDA Response:** This request is premature because insufficient information was provided to answer this question. [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED].

**Discussion during meeting:** FDA stated that it may be necessary to include some information in the label regarding the lack of evidence for effectiveness of MM-398 as a single agent in order to adequately inform prescribers. Merrimack acknowledged FDA's comments.

2. Does the Agency agree that, as an Orphan-designated product for the pancreatic cancer indication (OOPD Designation #11-3443), the application is exempt from Pediatric Research Equity Act and Merrimack need not submit a waiver request for the pancreatic cancer indication in the NDA?

**FDA Response:** Yes.

**Discussion during meeting:** No further discussion occurred during the meeting.

3. Based on the serious and life-threatening unmet need in the proposed orphan indication, does the Agency agree that the NDA would likely be accorded Priority Review, upon application by the company at the time of NDA submission?

**FDA Response:** FDA will determine priority versus standard review status once the marketing application is received. Please submit a request in the NDA and refer to the FDA guidance document regarding expedited programs located at

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

**Continuation of Merrimack's Question 3:** Also if approved upon application by the Sponsor, would designation as a Breakthrough Therapy prior to NDA submission significantly change the flexibility accorded to timing of submission of the chemistry, manufacturing and controls commercial process information required for NDA approval?

**FDA Response:** FDA disagrees that the modest effect on overall survival observed in the NAPOLI clinical trial that administered a different 5-fluorouracil regimen in the control arm is considered "substantial improvement" over existing therapies. Therefore, FDA does not recommend that Merrimack submit a request for Breakthrough Therapy Designation based on this clinical information. Although DOP2 does not believe that the data would meet the requirements for Breakthrough Therapy designation, if Merrimack chooses to submit a request for Breakthrough Therapy designation, such a request would be reviewed by the Medical Policy Council prior to a decision being.

Merrimack could consider submission of a Fast Track designation request (refer to guidance above) in order to request a rolling submission; however, the PDUFA review clock would start once the application is complete.

**Discussion during meeting:** FDA stated that Breakthrough Therapy Designation (BTD) is reserved for transformative therapies that would change the standard of care across medical oncology for specific cancers. The preliminary clinical experience with MM-398, as an addition to standard chemotherapy, lacks sufficient activity to support a request for BTD, in the Division's opinion. FDA stated that a request for fast track designation may be appropriate if Merrimack intends to request a rolling application for the NDA. Merrimack expressed understanding of FDA's position and had no additional comments

4. Based on the clinical results presented in the Briefing Package, would the Agency object to the initiation of an Expanded Access program, in accordance with CFR Part 312 Subpart I— Expanded Access to Investigational Drugs for Treatment Use? If so, what information would be needed by the Agency in support of that program?

**FDA Response:** In general, consideration for expanded access should be dictated by the potential demand for such access. If demand is limited, then Merrimack should consider either single patient INDs or an intermediate-size patient population protocol. FDA expects that an access protocol submission to include information described in paragraphs 312.305(b)(2)(ii), (iii), (iv), and (viii) and 21 CFR 312.305(b)(3), and will rely on the data and information in the existing IND to satisfy the remaining requirements of 21 CFR 312.305(b). Refer to FDA's guidance document for further information regarding expanded access programs located at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf>.

**Discussion during meeting:** FDA clarified that the submission of an expanded access, treatment protocol may require a facilities inspection as determined by the Office of Compliance based on various factors.

5. We propose, subject to discussion of requirements at the Pre-NDA meeting, that the preclinical and clinical sections of the submission will be complete and that there will be no minor components to be submitted within 30 days after the original NDA submission. Discussion of timing of CMC components will be deferred to the CMC Pre-NDA meeting. Does the Agency agree with this proposal?

**FDA Response:** Yes.

**Discussion during meeting:** FDA clarified that the CMC pre-NDA meeting should be held before the interdisciplinary pre-NDA meeting in order to capture all of the agreements for the proposed NDA to be reviewed under the PDUFA V program.

6. It is the sponsor's position that a risk evaluation and mitigation strategy is not necessary to ensure that the benefits of the drug outweigh the risks of the drug. Does the Agency agree?

**FDA Response:** Yes. Based on the limited information provided, it does not appear that a risk evaluation and mitigation strategy will be necessary in order to file the NDA. Whether a risk evaluation and mitigation strategy (REMS) will be required will be determined during the review of the NDA.

**Discussion during meeting:** No further discussion occurred during the meeting.

#### NONCLINICAL

7. Does the Agency agree that the listed nonclinical studies in the Briefing Package are sufficient to support an NDA application for MM-398 in an oncology indication?

**FDA Response:** The nonclinical studies listed for MM-398 in the Briefing Package submission appear to be sufficient to support the NDA application for patients with metastatic pancreatic cancer. A final determination of the acceptability of these data to support a marketing application will be made upon review at the time of the NDA submission.

**Discussion during meeting:** No further discussion occurred during the meeting.

#### CLINICAL:

8. Does the Agency agree that the listed clinical studies in the Briefing Package are sufficient to support an NDA application for MM-398 in the proposed indication?

**FDA Response:** Insufficient information was provided in the briefing package. For example, Merrimack did not provide a statement regarding whether any completed or ongoing studies were excluded from the list.

**Discussion during meeting:** Merrimack referred to Tables 4 and 5 of the briefing package, which lists the studies intended for inclusion in the NDA and all studies conducted with MM398, respectively. FDA clarified that there was insufficient information to determine why Merrimack chose not to include data from specific studies in Table 5 in the NDA. In addition, FDA requested clarification of which studies would be presented in a side-by-side format and which studies would be integrated based on safety or efficacy based on similarity of patient population or dosing regimen. Merrimack agreed to provide this information in the premeeting briefing package for the interdisciplinary pre-NDA meeting.

#### CLINICAL PHARMACOLOGY:

9. Does the Agency agree that the proposed set of clinical pharmacology studies and the integrated population pharmacokinetic analysis plan described in the Briefing Package are sufficient to support registration?

**FDA Response:** No. In addition to the proposed set of clinical pharmacology studies listed in Table 6 of the meeting package, the PK analysis results of Study PEP0201, PEP0206 and PEP0203, and the integrated population PK and exposure-response (E-R) analysis plan, apply the following advice in preparing the clinical pharmacology program, as well as prior clinical pharmacology comments:

- a. Determine *in vivo* stability of the liposome. Determine the protein (including lipoprotein) binding of MM-398 over the expected therapeutic concentration range. Characterize the pharmacokinetics (encapsulated and unencapsulated) and bioavailability of irinotecan after administration of MM-398. Refer to the FDA Guidance for Industry (draft) for “*Liposome Drug Products*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf>.
- b. Develop a validated bioanalytical method capable of measuring both encapsulated and unencapsulated MM-398. If a method that distinguishes between encapsulated and unencapsulated MM-398 cannot be developed, provide justifications with supporting data as to why it is not feasible. Refer to the FDA Guidance for Industry entitled “*Bioanalytical Method Validation*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf>.
- c. Assess the effect of body size (such as body weight and body surface area) on pharmacokinetics and pharmacodynamics of MM-398 to determine the optimal dosing approach (body size-based or fixed dosing) that minimizes inter-patient variability for the registration trial(s).
- d. Conduct a study to compare the pharmacokinetics of MM-398 and SN-38 in subjects with hepatic impairment compared to subjects without normal hepatic

function to determine an appropriate starting dose for patients with hepatic impairment. Refer to the FDA draft Guidance for Industry entitled “*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>.

In general, the population PK analysis plan appears reasonable. FDA has the following additional comments.

- e. Consider using other visual predictive checks for model validation (e.g., SVPC, PCVPC, and NPDE) in addition to VPC given high PK variability as found in your studies and potential covariate effect.
- f. Reserve  $AUC_{comp}$  as a parameter in your dataset for potentially additional exposure-response analysis.

**Discussion during meeting:** FDA stated that the responses in the preliminary comments differ from the responses presented during the meeting. Merrimack stated that they will review the revised responses provided during the meeting and will follow-up with FDA subsequent to the meeting if there are additional questions regarding FDA Response to Question 9.

In response to Merrimack’s request for clarification, FDA stated that  $AUC_{comp}$  refers to the composite AUC of the parent compound and its active metabolites.

Merrimack asked if a hepatic impairment study must be conducted and results included in the proposed NDA for MM-398. FDA stated that if these data are not provided in the NDA, Merrimack will need to provide adequate justification as to why a dedicated hepatic impairment study is not required to allow FDA to conduct a substantive review and make a risk-benefit assessment of the NDA. FDA will review and provide responses to the acceptability of that justification at the pre-NDA meeting. Merrimack stated that a population pharmacokinetic analysis with covariates for organ impairment will be included in the original NDA submission.

Merrimack asked if the in-vivo stability of the liposome can be determined in a nonclinical study, FDA stated that they will provide clarification on this issue in a post-meeting communication.

**FDA Post-Meeting Comments:** The in vivo stability of the liposome should be conducted in a single-dose study in humans. The bioanalytical method must be able to distinguish between encapsulated and unencapsulated drug substance to determine in vivo stability. The concentration-time profile should be evaluated at multiple time points over an adequate period of time. The concentration of encapsulated and unencapsulated drug substance should be determined at each sampling time point. Refer to the FDA Guidance for Industry (draft) for “*Liposome Drug Products*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf>

for additional in vivo stability considerations.

10. Does the Agency agree with the proposal to use information from studies of the free form of irinotecan hydrochloride, as included in the current approved irinotecan (Camptosar®) labeling, in the MM-398 label and, if so, does there need to be an explicit reference to the origin of, e.g. warnings and precautions that are based on that label?

**FDA Response:** In an electronic mail message dated July 28, 2014, Merrimack Pharmaceuticals stated plans to submit an NDA under the provisions of 505(b)(2) and intends to reference the following information found in the Camptosar labeling: drug interactions, renal impairment, distribution, and metabolism. FDA agrees that it appears reasonable to use this information in the MM-398 labeling.

**Discussion during meeting:** No further discussion occurred during the meeting.

11. Subject to NDA review, does the FDA agree with the inclusion in the proposed label of data from the (b) (4) (as described below) to describe irinotecan and the active metabolite, SN-38, distribution in plasma and tumor tissue?

**FDA Response:** The results in (b) (4) study to describe irinotecan and the active metabolite, SN-38, distribution in plasma and tumor tissue are considered exploratory and the biopsy sampling time is not sufficient to characterize the distribution of MM-398 to the tumor. FDA does not agree to include data and results from the (b) (4) study in the proposed MM-398 labeling.

**Discussion during meeting:** No further discussion occurred during the meeting.

#### CLINICAL/STATISTICS:

12. Does the FDA agree with the proposed dataset format for population pharmacokinetic and exposure-response analysis?

**FDA Response:** In the original NDA, submit the data, the NONMEM control streams, and the relevant scripts (e.g. SAS, Splus, or R) used to generate the final population PK, exposure-response models, and simulation plots. Data files should be submitted as SAS transport files with \*.xpt format (e.g. Data1.xpt) and other files should be submitted as ASCII text files with \*.txt extension (e.g.:myfile\_ctl.txt, myfile\_out.txt).

For the population analysis reports, include:

- a. Standard model diagnostic plots
- b. Individual plots including observed concentrations, the individual prediction line and the population prediction line
- c. Model parameter names and units in tables.
- d. Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for more information.

In addition, regarding UGT1A1 polymorphism, include the actual individual UGT1A1 genotypes in the submitted datasets. The analysis report should include the tested alleles and the genotyping method(s) used to determine the UGT1A1 status.

**Discussion during meeting:** Merrimack confirmed that the data in the NDA will be provided in SDTM and ADaM formats; version 3.2. FDA stated that submission in CDISC format is acceptable and preferred.

#### ADDITIONAL CLINICAL COMMENTS:

13. At this time, the major issue regarding the approvability of an NDA that relies on the NAPOLI trial as the single trial supporting efficacy is that the study design is flawed in that it used different 5-fluorouracil regimens in the combination (experimental) and control arms as well as the addition of MM-398 to the combination arm. Introduction of two variables between the experimental and control arms complicates the Agency's ability to conclude that the OS effect can be attributed to MM-398. In the application, Merrimack will need to address this issue. Furthermore, this issue may require discussion with the Oncologic Drugs Advisory Committee (ODAC) prior to taking action on the application.

**Discussion during meeting:** FDA requested that Merrimack provide a scientific argument as to why the differences between the control and MM-398 combination arms are attributable to the addition MM-398 rather than the differences in chemotherapy regimens. FDA will seek advice from the Oncologic Drugs Advisory Committee (ODAC) or individual advice from Special Government Employees during the NDA review on the validity of the argument regarding MM-398 treatment effects.

14. FDA recommends that Merrimack use data standards (i.e., using CDISC) for the submission of datasets in the NDA. Refer to CDER's web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

If Merrimack will not be submitting datasets in CDISC format, Merrimack will need to ensure submission of datasets in a format that can be executed by FDA (i.e., .XPT). Additionally, ensure that the formatting of column titles and data (e.g., age should be numerical units in years in all datasets) is consistent throughout the datasets in order to ensure that datasets can be joined and analyzed. At least one column in the lab datasets

should present data in consistent units to allow analysis, (provide any formulas for conversion). Ensure there is a Guide for reviewers that clearly describes the following:

- a. description of files and documentation
- b. description of analysis datasets
- c. SAS codes for sub-setting and combining datasets
- d. coding dictionary(s) used
- e. methods of handling missing data
- f. list of variables (with definitions as appropriate) contained in every dataset
- g. listing of raw data definitions
- h. analysis data definitions
- i. annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)
- j. documentation of programs

**Discussion during meeting:** No further discussion occurred during the meeting.

15. Ensure that the NDA contains the following (this is a partial list to assist in the submission of an NDA):
  - a. Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
  - b. Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings
  - c. Investigator instructions that may have been produced in addition to the protocol and investigator brochure
  - d. All randomization lists and, if used, IVRS datasets (in SAS transport format)
  - e. Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance.
  - f. Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:
    - Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)).
    - Cancer Drug and Biological Products-Clinical Data in Marketing Applications

([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)).

- g. A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application
- h. A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

**Discussion during the meeting:** No further discussion occurred for items a-h.

- i. Detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:
  - subject age and gender
  - signs and symptoms related to the adverse event being discussed
  - an assessment of the relationship of exposure duration to the development of the adverse event
  - pertinent medical history
  - concomitant medications with start dates relative to the adverse event
  - pertinent physical exam findings
  - pertinent test results (for example: lab data, ECG data, biopsy data)
  - discussion of the diagnosis as supported by available clinical data
  - a list of the differential diagnoses, for events without a definitive diagnosis
  - treatment provided
  - re-challenge and de-challenge results (if performed)
  - outcomes and follow-up information
  - an informed discussion of the case, allowing a better understanding of what the subject experienced.

**Discussion during meeting:** FDA clarified that narratives should be provided for patients who died while receiving MM-398 or within 30 days of receiving the last dose of MM-398 and for those patients who terminated treatment for reasons other than disease progression.

- j. Complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

**Discussion during meeting:** FDA requested that Merrimack describe why they were unable to obtain CRFs for legacy studies to show that due diligence was made.

- k. Analyses of safety and effectiveness for subgroups specifically described in regulations (e.g., based on age  $\geq 65$  years; age  $\geq 75$  years; gender; and ethnicity).

**Discussion during the meeting:** No further discussion occurred for item k.

16. Please revisit each section of the proposed label in order to ensure appropriate implementation of the PLR rule using Guidance documents described at the following link:  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

**Discussion during meeting:** FDA clarified that any statements made in proposed product labeling regarding the mechanism of action must be supported by data. Additional discussion can occur either prior to or during the pre-NDA meeting regarding the types of data needed to support specific claims.

**FDA Post-Meeting Comments:** The following are additional links to labeling guidances for human prescription and biological products:

- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075066.pdf>
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf>
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf>
- <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075096.pdf>

**ADDITIONAL DISCUSSION DURING THE MEETING:**

- FDA clarified that the OSI standard comments only refer to the major efficacy trial (NAPOLI).

## **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

## **PRESCRIBING INFORMATION**

In the proposed application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## **505(b)(2) REGULATORY PATHWAY**

FDA recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and

each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

<p><b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature</b></p>
--

<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

#### **ISSUES REQUIRING FURTHER DISCUSSION**

- See action items below

#### **ACTION ITEMS**

- There are no action items

#### **ATTACHMENTS AND HANDOUTS**

- Meeting Attendance list
- OSI NDA requirements
- Additional DOP2 CDISC Guidance
- DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications

## MEETING ATTENDANCE LIST

Meeting between Merrimack Pharmaceuticals and  
the Center for Drug Evaluation and Research.

DATE: August 1, 2014 TIME: 10:00 AM ROOM: WO 22; Rm 1309

NAME - Please print	AFFILIATION
CHRISTIAN GRIMSTEIN	CDER/OTS/OCP/GENOMICS
Sham Pradhan	CDER/OHOP/DOP2
Karen Jones	FDA/CDER/OHOP/DOP2
Rumyan Jin	FDA/CDER/OTS/OCP
Stacy Shord	FDA/CDER/OTS/OCP/DCP ✓
Tina Ennis	FDA/CDER/DOP2
PATRICIA KEEGAN	FDA/CDER/OHOP/DOP2
Steven Lemery	FDA/CDER/OHOP/DOP2
Liang Zhao	FDA/CDER/OCP/DPM
Weishi Yuan	FDA/CDER/OTS/OB/DBV
Kun He	FDA/CDER/OTS/OB/DBV
Ali Al-Hakim	FDA/CDER/ONDA
Lauren Tarcove-Corcos	
Margaret Brower	
MARCO SCICCA	Merrimack Pharma
BRUCE BELANGER	MERRIMACK PHARMACEUTICALS
Eliel Sanyer	Merrimack Pharma
Michael Stake	Merrimack Pharma
Peter Lavins	Merrimack Pharma
Narspet Alindrea	Merrimack Pharmaceuticals
Ken Oliver	Merrimack
Bambang Adinijaya	Merrimack pharmaceuticals
Kawiz KHALIFA	MERRIMACK PHARMA
Sara Green	Merrimack Pharma

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

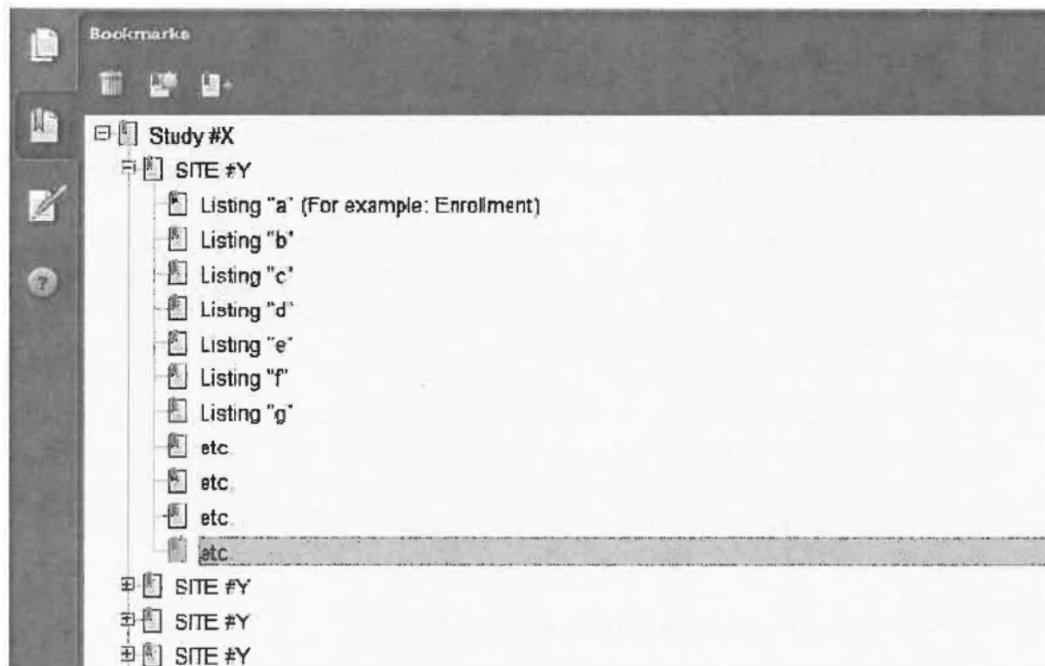
**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
    - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
  4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
  5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

## Attachment 1

### Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```

E.. [m5]
  E.. datasets
    E.. bimo
      E.. site-level
  
```

- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

## Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (<http://www.cdisc.org/sdtm>) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

**Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions**

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE, ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRES, NTGRES & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

**Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review**

DOMAIN	VARIABLE	DATA TYPE
<b>ADaM</b>		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
<b>SDTM</b>		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

## CDISC Oncology Domains

### Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials<sup>(1)</sup>. RECIST (Response Evaluation Criteria in Solid Tumors)<sup>(2)</sup> has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification<sup>(3)</sup> in the assessment lymphomas, or, MacDonald Response<sup>(4)</sup> in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

**TU (Tumor Identification):** The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

**TR (Tumor Results):** The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

**RS (Response):** The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

#### New variables:

**--LINKID** – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

**--ACPTFL** – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

**--EVALID** – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a

particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

- (1) E.A. Eisenhauer,\*, P. Therasse, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER* 45 (2009) 228-247
- (2) RECIST Criteria - <http://www.eortc.be/recist/>
- (3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology*. Vol 25 Number 5 Feb 10 2007
- (4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology*, Vol 8, 1277-1280

## 1. Oncology Domains:

### 1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3..x.x ..... One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be TARGET or NON-TARGET.  When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y  When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality / location / sub-location) then the additional information should be added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST  This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

### 1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The -LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.
2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

- a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".
- b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).
- c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.
4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.
7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

**TUMOR RESULTS - TR**

tr.xpt, Tumor Results - Findings, Version 3..x.x ..... One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement, Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format, copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR</p>	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	<p>The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated.</p> <p>See Assumption 4</p>	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	<p>In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" &amp; "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.</p>	Perm	
VISITNUM	Visit Number	Num		Timing	<ol style="list-style-type: none"> <li>1. Clinical encounter number.</li> <li>2. Numeric version of VISIT, used for sorting.</li> </ol>	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	<ol style="list-style-type: none"> <li>1. Protocol-defined description of clinical encounter.</li> <li>2. May be used in addition to VISITNUM and/or VISITDY.</li> </ol>	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

### 1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

- The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The -LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.
- TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

**Note:** The sponsor should not derive results for any test indicated in the list above (e.g. "Percent Change From Nadir") if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

- The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
- The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

**RESPONSE – RS**

rs.xpt, Response - Findings, Version 3..x.x ..... One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.</p>	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

### 1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.
2. RSTESTCD / RSTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRES	Target Response	
NTRGRES	Non-target Response	
OVLRES	Overall Response	
BESTRES	Best Response	
LESNRES	Lesion Response	
SYMTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. *TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.*
5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

## DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at: [www.fda.gov/RegulatoryInformation/Guidances/default.htm](http://www.fda.gov/RegulatoryInformation/Guidances/default.htm)) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

If you will be submitting your application in CDISC format, a separate **Study Data Standards Common Issues Document** can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration. In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions. These domains and variable specifications have been developed by CDISC and will be included in the implementation guidance in the near future. DOP2 is using these domains

GENERAL
Special Protocol Assessment (SPA) Requests
1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.
SPA Requests for a Single Trial Intended to Support Marketing Approval:
2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document: <ul style="list-style-type: none"><li>• Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products').</li><li>• A description of your drug development plan, including each indication that is being or has been studied and a timetable for submission of the planned studies. You should also include</li></ul>

information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.

**Additional Content for SPA Request Submission:**

3) Please submit/address the items below in your SPA request.

- The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
- If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
- If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
- If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
- If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
  - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
  - Applicability of comparator treatment or of disease characteristics to U.S. population
- Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot ethically be performed.

**Accelerated or Regular Approval:**

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)), which under § 314.510 and 601.41 would usually be underway at the time of accelerated approval in your SPA request and NDA/BLA submission.

- If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

**NDA/BLA content and format**

**CLINICAL**

- 1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
- 2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
- 3) Investigator instructions that may have been produced in addition to the protocol and investigator

brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format)
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: <ul style="list-style-type: none"> <li>a) description of files and documentation</li> <li>b) description of selected analysis datasets</li> <li>c) key variables of interest, including efficacy and safety variables</li> <li>d) SAS codes for sub-setting and combining datasets</li> <li>e) coding dictionary used</li> <li>f) methods of handling missing data</li> <li>g) list of variable contained in every dataset</li> <li>h) listing of raw data definitions</li> <li>i) analysis data definitions</li> <li>j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)</li> <li>k) documentation of programs</li> </ul>
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance ( <a href="http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf">www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf</a> ).
8) <u>Pediatric Studies:</u> All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
9) <u>Quantitative Safety Analysis Plan (QSAP):</u> The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components: <ul style="list-style-type: none"> <li>a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (<a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf">www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf</a>).</li> <li>b) Safety endpoints for Adverse Events of Special Interest (AERI)</li> <li>c) Definition of Treatment Emergent Adverse Event (TEAE)</li> <li>d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology</li> </ul>

<p>Review Charter))</p> <p>e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)</p> <p>f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.</p>
<p>10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:</p> <p>a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (<a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf">www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf</a>)</p> <p>b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (<a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf">www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf</a>)</p>
<p>11) Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report</p>
<p>12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application</p>
<p>13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.</p>
<p>14) <u>References:</u> There should be active links from lists of references to the referenced article.</p>
<p><b>Studies, Data And Analyses</b></p>
<p>15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).</p>
<p>16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:</p> <p>a) Site number</p> <p>b) Principle investigator</p> <p>c) Location: City State, Country</p> <p>d) Number of subjects screened</p> <p>e) Number of subjects randomized</p> <p>f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)</p> <p>g) Number of protocol violations (Major, minor, including definition)</p>
<p>17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (<a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf">www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf</a>).</p>
<p>18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or</p>

subject decision. Narrative summaries should contain the following components:

- a) subject age and gender
- b) signs and symptoms related to the adverse event being discussed
- c) an assessment of the relationship of exposure duration to the development of the adverse event
- d) pertinent medical history
- e) concomitant medications with start dates relative to the adverse event
- f) pertinent physical exam findings
- g) pertinent test results (for example: lab data, ECG data, biopsy data)
- h) discussion of the diagnosis as supported by available clinical data
- i) a list of the differential diagnoses, for events without a definitive diagnosis
- j) treatment provided
- k) re-challenge and de-challenge results (if performed)
- l) outcomes and follow-up information
- m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3

([www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf)). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

- a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
- b) Exposure-Response Relationships – important exposure-response assessments.
- c) Less common adverse events (between 0.1% and 1%).
- d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
- e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
- f) Marked outliers and dropouts for laboratory abnormalities.

- g) Analysis of vital signs focused on measures of central tendencies.
- h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
- j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
- k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
- l) Standard analyses and explorations of ECG data.
- m) Overdose experience.
- n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
- o) Explorations for:
  - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
  - ii) Dosedependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
  - iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
  - iv) Drug-demographic interactions
  - v) Drug-disease interactions
- p) Drug-drug interactions
  - i) Dosing considerations for important drug-drug interactions.
  - ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

#### **Financial Disclosure Information**

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators ([www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm)).

<b>Physician's Labeling Rule</b>
<b>Highlights</b>
1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm">www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm</a> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

## Table of Contents

- 15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
- 16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
- 17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
- 18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
- 19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:
- 8.1 Pregnancy
  - 8.3 Nursing Mothers (*not 8.2*)
  - 8.4 Pediatric Use (*not 8.3*)
  - 8.5 Geriatric Use (*not 8.4*)

- 20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- 22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
- 23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- 24) Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf)).
- 25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf>]
- 26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
- 27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21

CFR 201.57 (c)(18)]

28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.

30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.

32) Refer to [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm) for fictitious examples of labeling in the new format.

33) Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

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MELANIE B PIERCE  
08/29/2014



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** August 19, 2011  
**Meeting Location:** WO Rm 1415

**Application Number:** IND 102799  
**Product Name:** MM-398 (formerly PEP02)  
**Indication:** Pancreatic Cancer  
**Sponsor/Applicant Name:** Merrimack Pharmaceuticals, Inc.  
**Meeting Request Date:** June 14, 2011  
**Meeting BGP date:** July 19, 2011

**Meeting Chair:** John Johnson, M.D., Clinical Team Leader  
**Meeting Recorder:** Amy Tilley, Regulatory Project Manager

**FDA ATTENDEES**

Robert Justice, M.D., M.S., Director, DDOP  
John R. Johnson, M.D., Clinical Team Leader, DDOP (by teleconference)  
Amy McKee, M.D., Clinical Reviewer, DDOP  
Steven Lemery, M.D., Clinical Team Leader, DBOP  
Michael Axelson, M.D., Clinical Reviewer, DBOP  
Whitney Helms, Ph.D., Pharmacologist/Acting Supervisory Pharmacologist  
Debasis Ghosh, Ph.D., CMC Reviewer, ONDQA, DNDQA I  
John Duan, Ph.D., Biopharmaceutics Reviewer, OPS/ONDQA  
Rosane Charlab Orbach, Ph.D., Acting Team Leader Pharmacogenomics, OTS/OCB  
Christian Grimstein, Ph.D., Pharmacogenomics Reviewer, OTS/OCB/DCPIII  
Shenghui Tang, Ph.D., Team Leader, DB 5  
Somesh Chattopadhyay, Ph.D., Mathematical Statistician, DB 5  
Amy Tilley, Regulatory Project Manager

Meeting Minutes  
Type B  
EOP2  
August 19, 2011

OODP/DDOP

## **SPONSOR ATTENDEES**

Navreet Dhindsa, Manager of Clinical Operations  
Daryl Drummond, Ph.D., Senior Director, Liposomal Discovery  
Jonathan Fitzgerald, Ph.D., MM-398 Project Leader  
Fazal R. Khan, Ph.D., Senior Vice President of Manufacturing  
Mark Moody, Ph.D., Vice President, Analytical Services (by teleconference)  
Victor Moyo, MD, Vice President, Clinical Investigations  
James Murray, Senior Director, Clinical Affairs  
Clet Niyikiza, Ph.D., Executive Vice President, Development  
Brian Shen: Associate Director, Clinical Research, PharmaEngine, Inc. (by teleconference)  
Michael Slater, Senior Director, Regulatory Affairs and Quality Assurance  
Sofia Stefanis, Regulatory Affairs Operations Manager  
Erica Wang, Senior Manager, Clinical Research, PharmaEngine, Inc. (by teleconference)  
C. Grace Yeh, Ph.D., President and Chief Executive Officer, PharmaEngine, Inc.

## 1.0 BACKGROUND

MM-398 is a liposomal formulation of irinotecan. According to pharmacokinetic data submitted by the sponsor, the  $C_{max}$  of MM-398 is approximately 50-fold higher than free total irinotecan, and the  $T_{1/2}$  of MM-398 is 2-3 fold longer than irinotecan. The IND was activated in November 2008, and a change in sponsorship from PharmaEngine to Merrimack occurred in March 2011. The sponsor has provided preliminary results from the ongoing Phase 2 trial of MM-398 as second-line therapy in 40 patients with metastatic pancreatic cancer. All patients had received gemcitabine based therapy prior to treatment with MM-398. A partial response has been noted in three patients (7.5%), with stable disease in an additional 16 patients (40%). The primary efficacy endpoint in this trial, the 3-month survival rate, is 75%.

## 2.0 DISCUSSION

### Chemistry Manufacturing and Controls:

MM-398 has been provided to Phase 1 and Phase 2 investigators from PharmaEngine, Inc. in Taiwan, under Sponsor and Sponsor investigator INDs [IND 102799 and (b) (4)]. The Sponsor intends to perform the Phase 3 studies in advanced pancreatic cancer using material manufactured by Merrimack Pharmaceuticals, Inc. ("Merrimack") in Cambridge, MA, the intended initial commercial source.

The Sponsor's approach to compare the product from the two sources will be based upon analytical studies according to section II.G. of the FDA Draft Guidance on Liposome Drug Products 2002. There will also be pharmacokinetic (PK) components to the Phase 3 clinical trials to enable retrospective comparison with previous pharmacokinetic data from clinical trials performed with material from PharmaEngine. Full PK profiles will be obtained on 30 patients and peak and trough levels in all patients in the Phase 3 trial. Details are provided in the clinical study synopsis below. These data will be compared with PK data from 37 patients in the PEP0206 study performed with material from PharmaEngine. The sponsor proposes to introduce material manufactured at Merrimack on the basis of the analytical studies.

### QUESTIONS:

1. Provided that the proposed analytical comparability studies show no significant changes in product derived from the two manufacturing sites, does the Agency agree that no additional non-clinical or clinical pharmacokinetic and bioavailability studies are required in order to effect the change in supply for the proposed Phase 3 clinical trials?

### FDA Response:

**From the Biopharmaceutics perspective, an additional bioavailability study is not necessary, provided the planned Phase 3 clinical trial properly evaluates the bioavailability of MM-398.**

**Meeting Discussion:**

None

**Clinical Pharmacology:**

We plan to investigate the determinants of pharmacokinetic interpatient variability with the existing clinical database and explore the exposure-response relationship between MM-398 and toxicity and efficacy endpoints. Subsequently, we intend to compare exposure-toxicity and efficacy relationships between MM-398 and free irinotecan to better define any improvement in the therapeutic window. These analyses will be performed in accordance with the agency guidances for industry in population pharmacokinetics and exposure response analyses.

2. Does the agency agree with this plan?

**FDA Response:**

Yes.

**Meeting Discussion:**

None

**Clinical:**

The Sponsor intends to perform a Phase 3 clinical trial in pancreatic cancer to confirm the results observed to date in the Phase 2 study, in patients who have previously received gemcitabine-containing regimens and have not been previously exposed to irinotecan.

Patients with advanced pancreatic cancer of exocrine origin have few therapeutic options and, for patients with advanced cancers, the OS rate of all stages is less than 1% at 5 years, with most patients dying within 1 year (NCI, 2010).

The MM-398 Phase 2 6-month and 12-month survival data demonstrate that MM-398 is active in patients with advanced pancreatic cancer who are refractory to or have progressed on gemcitabine-containing regimens. We believe these data show that MM-398 addresses an unmet medical need in a life-threatening indication.

The Agency's procedures in Subpart E of 21 CFR part 312, which expedite the development, evaluation, and marketing of promising therapies to treat individuals with life-threatening and severely debilitating illnesses, specifically provide for approval on the basis of Phase 2 data when the benefits outweigh the risks of a drug for such a disease. As part of this risk-benefit analysis, the Agency will "take into consideration the severity of the disease and the absence of satisfactory alternative therapy" (21 CFR 312.84).

The Sponsor has also applied for orphan drug designation for MM-398 in the treatment of advanced pancreatic cancer (b) (4)

3. Following the initiation of a statistically robust Phase 3 clinical trial, could MM-398 qualify for approval under 21 CFR 312.84 Subpart E - Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses, on the basis of Overall Survival results in the completed Phase 2 study?

**FDA Response:**

**No. Overall survival is not interpretable in a single arm trial. We recommend that you conduct your randomized controlled trial before submitting an NDA.**

**Meeting Discussion:**

**The sponsor asked whether the response rate and disease control rate from the phase 2 trial would support an NDA submission. The FDA responded that the size of the trial and the low PR rate would not support a submission for accelerated approval.**

4. Does the Agency agree that the Phase 2 data obtained to date in pancreatic cancer are sufficient to justify proceeding to Phase 3?

**FDA Response:**

**Whether to proceed to a Phase 3 trial is your decision.**

**Meeting Discussion:**

**None**

5. Does the Agency agree that the proposed randomized Phase 3 clinical trial with Overall Survival as the primary efficacy endpoint, plus supportive data from the Phase 2 study, could potentially provide sufficient safety and effectiveness data in treatment of patients with metastatic pancreatic cancer who have progressed on gemcitabine containing therapy to support a fileable NDA?

**FDA Response:**

**Yes, however this will be a review issue. In general, we suggest that you conduct two adequate and well-controlled trials to demonstrate the effectiveness of your agent because a conclusion based on two persuasive studies will always be more secure. For a single randomized trial to support an NDA, the trial must be well designed, well conducted, well executed, internally consistent and provide statistically and clinically persuasive efficacy findings so that a second trial would be**

**ethically or practically impossible to perform. Please refer to Guidance for Industry: *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* which describes both the characteristics of a single trial and the results that may suffice for approval**

**[www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf)**

**Meeting Discussion:**

**The FDA expressed concerns about the minimization plan and the interim analysis plan, both of the timing and significance level, given the small size of the study. FDA recommends an un-stratified, two sided log rank test with an alpha of 0.05 as the primary analysis with a re-randomization test as a sensitivity analysis. Whether the results of one study with an alpha of 0.05 would be acceptable for approval would be a review issue. FDA cautioned the sponsor about using minimization in a small study such as this. If there are small numbers of factors, stratification can be done at randomization instead of using a minimization procedure.**

6. Does the Agency agree that the control arm of 5-FU and folinic acid (leucovorin), as described in the study outline of the proposed Phase 3 study in pancreatic cancer, is appropriate?

**FDA Response:**

**We do not object to the choice of the control arm based upon safety issues. However, the choice of the control arm is your decision and should be discussed with your investigators.**

**Meeting Discussion:**

**None**

**UGT1A Molecular Genotyping**

Previous attempts to correlate patient safety outcomes with genotype in 87 patients treated to date have not shown any useful correlation. The Sponsor intends to continue to collect data on UGT1A genotype in Phase 3 studies but, based on a proposed dose of (b) (4), does not anticipate a dosing strategy using pharmacogenetic characterization of patients. The protocol defines a dose reduction strategy in case of toxicity.

7. Does the Agency have any concerns regarding the proposed dosing strategy?

**FDA Response:**

**Yes. Safety and efficacy data of MM-398 based on UGT1A genotype were not included in the submission. Therefore we are not able to evaluate the impact of MM-398 dose and schedule on patients homozygous for the UGT1A1\*28 allele. These patients are more likely to develop irinotecan-induced severe neutropenia compared to patients homozygous for the wild-type allele. In study PEP0206, the SN-38 AUC<sub>0-∞</sub> following MM-398 at 120 mg/m<sup>2</sup> (sponsor's table 21) is greater than that observed following a high irinotecan dose (300 mg/m<sup>2</sup>). Thus, we recommend you consider a reduced initial MM-398 dose for patients homozygous for UGT1A1\*28 and carefully monitor for toxicities. Consider submitting your available pharmacogenetic data for review.**

**Meeting Discussion:**

**None**

**Regulatory:**

8. Does the Agency agree that, upon application by the sponsor, this program could qualify for Fast Track development under FDC Act, Section 506?

**FDA Response:**

**Yes. However, you would need to submit a formal Fast Track Designation request.**

**Meeting Discussion:**

**None**

Free irinotecan (Camptosar<sup>®</sup>) is approved for the treatment of first and second-line colorectal cancer.

9. Does the Agency agree that a Section 505(b)(2) NDA, relying in part on FDA's prior findings of safety and effectiveness for Camptosar, is appropriate and acceptable for MM-398?

**FDA Response:**

**We are unable to answer this question based upon the information you have submitted. Please clarify what you intend to rely upon to which you do not have right of reference.**

**The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21**

CFR 314.54, and the October 1999 Draft Guidance for Industry “Applications Covered by Section 505(b)(2)” available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency’s interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/01p-0323-pdn0001-voll.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

**Meeting Discussion:**

FDA encouraged the sponsor to determine what potential data would be relied upon to support their NDA submission so that the FDA could determine whether a 505(b)(2) application would be required.

**Additional Comments:**

Genetic polymorphisms in the irinotecan disposition pathway have been associated to an increase risk of severe toxicity from irinotecan chemotherapy. FDA recommends collecting baseline germline DNA from all patients in MM-398 clinical trials to allow for pharmacogenomic safety analyses.

**Meeting Discussion:**

None

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

**4.0 ACTION ITEMS**

None

**5.0 ATTACHMENTS AND HANDOUTS**

**Sponsor slide**

Minutes Preparer:

*{See appended electronic signature page}*

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Amy Tilley  
Regulatory Project Manager

Meeting Chair:

*{See appended electronic signature page}*

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John Johnson, M.D.  
Clinical Team Leader

(b) (4)



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08/19/2011

JOHN R JOHNSON  
08/19/2011