CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208159Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208159 SUPPL # HFD #

Trade Name Vistogard®

Generic Name Uridine Triacetate

Applicant Name Wellstat Therapeutics

Approval Date, If Known

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 ☐

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

505(b)(1)

b) 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:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

7 years for Orphan designation, granted May 1, 2009 (Designation request # 08-2738)

d) 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# 208169

NDA#

NDA#

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:

Expanded access clinical studies: WELL401 and 401.10.001

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"):

Expanded access clinical studies: WELL401 and 401.10.001

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 # 039571 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? Not Applicable

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:

==========

Name of person completing form: Jeannette O'Donnell
Title: Regulatory Project Manager
Date: December 7, 2015

Division of Oncology Products 1/Division Director signing form: Geoffrey Kim, MD
Title: Director

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

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

/s/

JEANNETTE L O'DONNELL
12/11/2015

GEOFFREY S KIM
12/11/2015

1.3.3 Debarment Certification

Wellstat Therapeutics Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetics Act in connection with this application.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208159 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Vistogard® Established/Proper Name: Uridine Triacetate Dosage Form: Oral Granules		Applicant: Wellstat Therapeutics Agent for Applicant (if applicable):
RPM: Jeannette O'Donnell		Division: Oncology Products 1

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is March 10, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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 http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] 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.
[2] 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).
[3] 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):
(confirm chemical classification at time of approval)

☒ Fast Track
☒ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ 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	☒ No ☐ 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 12/11/15
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *9/22/15* • Review(s) *9/14/15*	
❖ Labeling reviews: *(indicate date for each review)* RPM labeling Review: 9/8/15 CMC labeling Review: 10/27/15, 10/30/15 DPMH – Pediatrics Review: 11/16/15 DPMH – Maternal Health Review: 11/27/15, 11/28/15 OPDP Review: 11/23/15 DMEPA Review: 11/23/15 ADL Review: TBD: 12/9/15	RPM: ☒ None DMEPA: ☒ None DMPP/PLT (DRISK): ☒ None OPDP: ☒ None SEALD: ☐ None CSS: ☐ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *9/8/15* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC Not Applicable If PeRC review not necessary, explain: Orphan Drug Designation	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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 Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	N/A
❖ 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)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting	☒ N/A or no mtg
• Pre-NDA/BLA meeting	☒ No mtg
• EOP2 meeting	☐ No mtg 7/6/10 and 8/15/13
• Mid-cycle Communication	☐ N/A 10/29/15
• Late-cycle Meeting	☐ N/A 12/4/15
• Other milestone meetings	CMC EOP2: 8/21/13 Type A guidance: 8/27/14
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 12/10/15
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12/7/15
PMR/PMC Development Templates *(indicate total number)*	☐ None 1 PMC
Clinical	
❖ Clinical Reviews	

• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review 11/25/15
• Clinical review(s) *(indicate date for each review)*	11/25/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not	In Clinical Review, Page 13, Signed 11/25/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date for each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 11/20/15
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 11/13/15 and 11/16/15
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 12/8/15
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/1/15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review - None
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 12/8/15
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/1/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☐ None 10/25/15, 10/27/15
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None 10/27/15, 10/29/15
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 11/6/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None Biopharmaceutics: 10/29/15, 11/2/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	10/27/15, 10/30/15
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*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)*	☒ Acceptable, 11/4/15 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

JEANNETTE L O'DONNELL
12/14/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/label - format correction PPI
Date: Tuesday, December 08, 2015 2:34:00 PM
Attachments: NDA 208159_final-labeling-text-vistogard_recieved 12-7.docx
Importance: High

Hi Mike,

Please find attached the label for NDA 208159. There are a couple of spacing issues on the PPI.

Please correct and re-submit by COB tomorrow, December 9, 2015.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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

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/s/

JEANNETTE L O'DONNELL
12/09/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/late cycle meeting/label
Date: Friday, December 04, 2015 12:09:00 PM
Attachments: NDA 208159 uridine triacetate - DRAFT Label.docx
Importance: High

Dear Dr. Bamat,

Please find attached the label as discussed during today's Late Cycle Meeting. We've accepted the changes and added the phrase "regardless of symptoms" to the indication (and incorporated this into the patient information) as discussed during the meeting. Please review the label and submit formally by COB Monday, December 7, 2015.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
12/04/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/labeling discussion
Date:	Thursday, December 03, 2015 4:48:00 PM
Attachments:	The phrases in red text in Section 12.doc
Importance:	High

Hi Mike,

Please see attached document regarding our omission of specific language from Section 12.1 of the label which includes our rationale for this decision. Please be advised we are willing to discuss this issue further at the meeting tomorrow.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

The phrases in red text in Section 12.1 Mechanism of Action are not appropriate or necessary for the safe and effective use of uridine triacetate for the proposed indications.

> Uridine triacetate is an acetylated pro-drug of uridine. Following oral administration, uridine triacetate is deacetylated by nonspecific esterases present throughout the body, yielding uridine in the circulation. Uridine competitively inhibits cell damage and cell death caused by fluorouracil (b) (4).
>
> Fluorouracil is a cytotoxic antimetabolite that interferes with nucleic acid metabolism in normal and cancer cells. Cells anabolize fluorouracil to the cytotoxic intermediates 5-fluoro 2' deoxyuridine 5'-monophosphate (FdUMP) and 5 fluorouridine triphosphate (FUTP). FdUMP inhibits thymidylate synthase, blocking thymidine synthesis. Thymidine is required for DNA replication and repair. Uridine is not found in DNA (b) (4).

Rationale

The phrases (b) (4) and (b) (4) do not provide the prescriber with information that is necessary for the safe and effective use of this drug in the emergency setting for which indications are being sought.

In addition, these phrases are potentially promotional and may imply to the prescriber that uridine triacetate does not interfere with (b) (4) fluorouracil or capecitabine in patients. In your cover letter dated November 30, 2015, you state that (b) (4) Whether or not treatment with uridine triacetate affects the course of treatment with fluorouracil would need to be answered by clinical evidence, as the relative contributions of RNA toxicity and DNA toxicity in various disease settings may differ in patients and may not correlate with data from in vitro or animal studies. (b) (4)

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/s/

JEANNETTE L O'DONNELL
12/04/2015
sent on 12/3/15

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR Clinical- Urgent
Date: Tuesday, December 01, 2015 2:08:00 PM
Importance: High

Dear Mike,

Please provide the following information by close of business Monday 12/1:

1) Patient ID numbers (including those that may have been in the 120-day safety update) for early onset cases whose only initial presenting symptom was "unusually early onset of moderate stomatitis or mucositis within 96 hours of the patient's first administration of fluorouracil or during the first 7 days of patient's first cycle of capecitabine", so that we may review these cases again. Please also define what you mean by "moderate".

2) Patient ID numbers for the 4 pediatric patients dosed by BSA.

Please provide by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
12/03/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/Late Cycle meeting
Date: Tuesday, December 01, 2015 10:03:00 AM
Importance: High

Hi Mike,

Due to several conflicts we had to reschedule the late cycle meeting again. The new time and date will be Friday, December 4, 2015, from 10:00 – 11:00 am. There will be no further changes and I'm sorry for the confusion; however, these have been unexpected circumstances.

Thank you.

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
12/01/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR - Clin pharm/pediatrics/ Time sensitive
Date: Wednesday, November 25, 2015 3:24:00 PM
Importance: High

Dear Mike,

In reference to NDA 208159, please provide the dosing history for the 6 pediatric patients in WELL401 in a tabular form. The dosing history should provide the following key information:

1. Subject ID
2. AGE
3. Body Surface area (BSA)
4. Gender
5. Dose per administration
6. Time/ Date of administration
7. Relative time of subsequent dosing since first uridine triacetate dose
8. Total daily dose
9. Formulation/ Lot number

Please ensure that dosing history provided in the table mentioned above is consistent with the dosing information provided in patient narratives. In case of a discrepancy, please explain the discrepancy. For each patient and dose administration, clearly mention if the BSA adjusted dosing was employed and the sequence number of the dose when it was employed. Additionally provide pharmacokinetic information if available.

Please provide the following information by November 30, 2015.
Please provide by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/30/2015
sent on 11/25/15

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/Late Cycle Meeting - Rescheduled Time and Day
Date:	Monday, November 30, 2015 8:42:00 AM
Importance:	High

Hi Mike,

Due to unforeseen circumstances, we have re-scheduled the late cycle meeting. The new meeting is scheduled to take place: Thursday, December 3, 2015 from 2:00-3:00 pm. The topics and background package have not changed.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/30/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/labeling changes
Date: Tuesday, November 24, 2015 2:05:00 PM
Attachments: NDA 208159_Uridine triacetate label_11-24-15.docx

Hi Mike,

Please find attached labeling for NDA 208159. Please review and return to us by 9:00 am Monday, November 30, 2015.

Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/24/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/carton & container labeling
Date:	Wednesday, November 25, 2015 8:32:00 AM
Importance:	High

Dear Mike,

In reference to NDA 208159, uridine triacetate, carton and container labels, we have the following comments:

To improve readability of the "Directions for use" information, please revise the current language.
For example, revise to:

- **Directions for use**: Each Vistogard dose should be mixed into a soft food (such as applesauce, pudding, or yogurt) immediately prior to administration. For pediatric administration, see prescribing information and discard unused portion of granules.
- **Usual dosage**: See prescribing information

Revise the statement (b) (4) to "single-dose" to remain consistent with changes in the PI.

Your recently submitted stability information is currently under review and the expiration date will be decided upon at a later time. Please submit the changes to the carton and container labels by **12:00 pm Monday, November 30, 2015**. Please submit by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/25/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR/Clinical - deviations cont"d
Date: Friday, November 20, 2015 9:08:00 AM
Importance: High

Dear Mike,

In reference to NDA 208159, please submit the following:

1. Resubmit the protocol deviations information(for each study) in the same format as Table 14.1.5 submitted yesterday, however only include the original 60 patients on Study 401 and the 75 patients on WELL401 in the table (exclude the 120 day safety update patients).

2. Provide us with all patient IDs for the patients who had violations due to not starting UT within 96 hours.

Please respond by **1:00 today, November 20, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/20/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/PMC - particle size distribution
Date:	Friday, November 20, 2015 1:03:00 PM
Importance:	High

Dear Mike,

In reference to NDA 208159, response to PMC communication, submitted to the FDA on November 16, 2015. At this time, setting particle size distribution limits for the drug substance with respect to setting drug product particle size distribution limits is not being requested. However, as Wellstat Therapeutics Corporation continues its manufacturing development and fulfills the requirements of the PMC, FDA expects Wellstat to consider controls for the drug substance particle size distribution (b) (4) . Additional controls may be added as additional manufacturing data is collected and as would be expected for continual improvement in the manufacturing process.

If you have any further questions please do not hesitate to ask.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/20/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208159

MID-CYCLE COMMUNICATION

Wellstat Therapeutics
Attention: Michael K. Bamat, PhD
930 Clopper Rd.
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vistogard™ (uridine triacetate), Oral granules.

We also refer to the teleconference between representatives of your firm and the FDA on November 6, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jeannette O'Donnell, Regulatory Project Manager at (240) 402-4978 or email: Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Acting Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: November 6, 2015; 2:30 – 3:00 pm

Application Number: NDA 208159
Product Name: Vistogard™ (uridine triacetate)
Indication: Under Review
Applicant Name: Wellstat Therapeutics

Meeting Chair: Julia Beaver, MD
Meeting Recorder: Jeannette O'Donnell

FDA ATTENDEES
Geoffrey Kim, MD, Director
Amna Ibrahim, MD, Deputy Director
Julia Beaver, MD, Acting Clinical Team Leader
Gwynn Ison, MD, Clinical Reviewer
Jeannette O'Donnell, Regulatory Project Manager

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese, Eastern Research Group, Inc.

APPLICANT ATTENDEES
Michael Bamat, Ph.D., VP Research & Development
Joan Helton, Manager Regulatory Affairs and Clinical Quality Assurance
Jeffrey Miller, PhD, Director Analytical R&D and Manufacturing
Rita O'Neil, PhD, Senior Director, Regulatory Project Management
Julie Vanas, Director, Clinical Projects
Reid von Borstel, PhD, VP Discovery Research
Nadine Wohlstadter, President

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

The application is not being reviewed using the animal rule. Upon review of the submitted application, it was determined that there was sufficient clinical information for a review of both safety and efficacy.

At this time the final indication is still under review.

We have identified one product quality Post Marketing Commitment (PMC); this will be relayed to you shortly.

3.0 INFORMATION REQUESTS

The only outstanding information request (IR) is the clinical pharmacology IR, sent on November 4, 2015. Response to this IR is expected by close of business, November 10, 2015.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time there are no major safety concerns.

No REMS will be needed.

5.0 ADVISORY COMMITTEE MEETING

No advisory committee meeting is needed.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for December 1, 2015, from 11:00-11:30 am. You may choose to change this face-to-face meeting to a T-con or cancel altogether if you feel it is not needed given the expedited nature of this application and continued regular communications.

We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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/s/

JEANNETTE L O'DONNELL
11/19/2015

JULIA A BEAVER
11/19/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/IR - protocol deviations/ Time Sensitive
Date:	Thursday, November 19, 2015 8:54:00 AM
Attachments:	well401-16-2-2-list-protocol-deviations.pdf 401-10-001-16-2-2-list-protocol-deviations.pdf
Importance:	High

Dear Mike,

In reference to NDA 208159, we note in your clinical study reports for 401 and WELL that no patients discontinued the studies due to protocol violations. However, in the attached documents, there were extensive protocol violations recorded on both studies. While these were presumably minor deviations, we need you to provide a summary table for each of the 2 studies, with a breakdown of the tally of protocol deviations on each study. In this table, you should provide a summary of what the main categories were for protocol deviations (for instance, it appears that many patients had deviations involving laboratory assessments not being performed at the protocol-specified times), including whether they were major vs. minor deviations, and how many patients had deviations in each category. This should be depicted by study arm.

Please respond by **COB today, November 19, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/19/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR/Clinical - Urgent - Time Sensitive
Date: Wednesday, November 18, 2015 9:15:00 AM
Attachments: SKM_C754e15111808030.pdf
Importance: High

Dear Mike,

In reference to NDA 208159, In your initial NDA submission Clinical Study Reports for each study (401 and WELL401), you included **shift tables** for hematology and chemistry laboratory parameters from baseline to Week 4 in the safety population (Tables 12-7 and 12-8 in the respective study reports, please see attached document showing the tables we refer to).

We need you to provide an **updated** shift table(s) (including baseline to Week 4 shifts), to include 120-day safety update hematology and chemistry laboratory values, **in a format that combines the two studies with updated hematology and chemistry laboratory parameters** (as shown in the examples attached). We want one table to combine BOTH studies, ideally (rather than individual tables for studies 401 and WELL). In addition, you may provide one table for hematology and one for chemistry, or you may combine all labs into one table.

The tables you have referenced in the 120-day safety update do not provide the information in the format that we are looking for.

Please submit this to us ASAP, but no later than **COB today, November 18, 2015**. Please submit by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208159

MID-CYCLE COMMUNICATION

Wellstat Therapeutics
Attention: Michael K. Bamat, PhD
930 Clopper Rd.
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vistogard™ (uridine triacetate), Oral granules.

We also refer to the teleconference between representatives of your firm and the FDA on November 6, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jeannette O'Donnell, Regulatory Project Manager at (240) 402-4978 or email: Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Acting Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: November 6, 2015; 2:30 – 3:00 pm

Application Number: NDA 208159
Product Name: Vistogard™ (uridine triacetate)
Indication: Under Review
Applicant Name: Wellstat Therapeutics

Meeting Chair: Julia Beaver, MD
Meeting Recorder: Jeannette O'Donnell

FDA ATTENDEES
Geoffrey Kim, MD, Director
Amna Ibrahim, MD, Deputy Director
Julia Beaver, MD, Acting Clinical Team Leader
Gwynn Ison, MD, Clinical Reviewer
Jeannette O'Donnell, Regulatory Project Manager

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese, Eastern Research Group, Inc.

APPLICANT ATTENDEES
Michael Bamat, Ph.D., VP Research & Development
Joan Helton, Manager Regulatory Affairs and Clinical Quality Assurance
Jeffrey Miller, PhD, Director Analytical R&D and Manufacturing
Rita O'Neil, PhD, Senior Director, Regulatory Project Management
Julie Vanas, Director, Clinical Projects
Reid von Borstel, PhD, VP Discovery Research
Nadine Wohlstadter, President

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

The application is not being reviewed using the animal rule. Upon review of the submitted application, it was determined that there was sufficient clinical information for a review of both safety and efficacy.

At this time the final indication is still under review.

We have identified one product quality Post Marketing Commitment (PMC); this will be relayed to you shortly.

3.0 INFORMATION REQUESTS

The only outstanding information request (IR) is the clinical pharmacology IR, sent on November 4, 2015. Response to this IR is expected by close of business, November 10, 2015.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time there are no major safety concerns.

No REMS will be needed.

5.0 ADVISORY COMMITTEE MEETING

No advisory committee meeting is needed.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for December 1, 2015, from 11:00-11:30 am. You may choose to change this face-to-face meeting to a T-con or cancel altogether if you feel it is not needed given the expedited nature of this application and continued regular communications.

We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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/s/

JEANNETTE L O'DONNELL
11/19/2015

JULIA A BEAVER
11/19/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Bcc:	Beaver, Julia
Subject:	FDA Communication: NDA 208159/uridine triacetate/label/ Time Sensitive - Urgent
Date:	Friday, November 13, 2015 4:59:00 PM
Attachments:	NDA 208159_label to sponsor - 11-13-15.docx
Importance:	High

Dear Mike,

In reference to NDA 208159, please find attached labeling revisions for sections 1-17, we have not yet reviewed the Patient labeling portion. Please note that this does not constitute the final agreed upon version.

Please review the changes and respond by no later than **COB Wednesday, November 18, 2015**.
Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/16/2015
Sent on 11-13-15

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR/laboratory reporting - Time sensitive
Date: Monday, November 16, 2015 2:41:00 PM
Importance: High

Dear Mike,

In reference to NDA 208159, we have 2 requests regarding laboratory reporting/ parameters:

1) In your initial NDA submission Clinical Study Reports for each study (401 and WELL401), you included shift tables for hematology and chemistry laboratory parameters from baseline to Week 4 in the safety population (Tables 12-7 and 12-8 in the respective study reports). Provide an updated shift table combining the two studies with corrected hematology parameters or describe where these are located within the 120 day safety update.

2) Although you state you have corrected the hematology laboratory data that had been entered incorrectly (as identified by OSI for 8 of 69 subjects records) on the 2 studies, we request that you provide a summary of the exact corrections made, including patient ID #s, so that we may confirm these corrections.

Please respond by **COB Tuesday, November 16, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/16/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR/clin pharm - Time Sensitive
Date: Friday, November 13, 2015 6:51:00 AM
Importance: High

Dear Mike,

Reference is made to your response submitted on November 10, 2015, to the Clinical Pharmacology Information Request (IR) dated Nov 04, 2015. We requested that: "for each of the PK parameter (CL/F, Cmax, etc.) of interest, provide scatter plots with regression line (for continuous covariates) or box plots (categorical covariates) of the PK parameter versus covariates. Clearly mention the number of subjects included in each analysis, number of subjects in each category for categorical covariates and range for each continuous covariate. For categorical covariates provide the mean and median of the PK parameter in each category. Consider performing this analysis 1) only in adults and 2) adults and 4 pediatric subjects included"

In your submission we observed that for several plots the axes labels and values are missing. The symbols in the figures (e.g., circle or cross) have not been described. The range of the continuous covariate (e.g., range [min,max] of CRCL) is not mentioned.

Please submit updated plots for CL/F and Vd/F by **COB today**.
Please submit updated plots for other PK parameters by **noon on Monday, November 16, 2015**. Please submit by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/13/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/narrative/IR - time sensitive
Date: Thursday, November 12, 2015 1:27:00 PM
Importance: High

Hi Mike,

Please Submit the narrative for subject OD160? It appears that this narrative was replaced by a duplicate OD158 in the narratives submitted.

Please submit by **noon, Friday November 13, 2015**. Please submit by 1) email to facilitate review 2) formal submission to the NDA.

Thanks,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
11/12/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/CMC/PMC - time sensitive
Date:	Monday, November 09, 2015 11:20:00 AM
Attachments:	208159- Process PMC.doc
Importance:	High

Dear Mike,

Please find attached the PMC we would like to implement in regards to the facilities inspection for NDA 208159.

Please review and either note changes you would like to recommend or provide agreement by **Friday, November 13, 2015**.
Please provide by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA # 208159
Product Name: Vistaguard (uridine triacetate)

PMC Description: The PMC will result in a retrospective analysis of the drug product manufacturing process development to further examine the relationship between particle size distribution and dissolution. Interbatch and intrabatch variability in dissolution is observed, but the cause has not been established. This analysis will provide data that will lead to more consistent quality in the drug product.

PMC Schedule Milestones:
Final Protocol Submission: 02/2016
Final Report Submission: 08/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☒ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   This product meets an unmet medical need for a potentially life-threatening indication. The drug product has no known toxic dose, so super-therapeutic doses are not a concern. For the 5-fluorouracil overdose indication, patients are dosed 10 grams every 6 hours for 20 doses, so variation in dose is likely to be mitigated by the high dose and frequency of dosing. Clinical data demonstrates that the key determinant in efficacy is early administration relative to the onset of symptoms and that lower doses of Vistogard have demonstrated efficacy. Therefore, the observed variation in dose strength is mitigated by the need to make this product available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Interbatch and intrabatch variability in dissolution is observed. The PMC is proposed to examine the relationship between particle size distribution and dissolution. As a result, the manufacturing process will be updated to improve the consistency of the product quality with regards to the impact of formulation material attributes, manufacturing process parameters, manufacturing unit operations.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

As part of the dissolution method revision, perform retrospective analysis and confirm the dissolution studies submitted to support this manufacturing process, including:

a) (b) (4)

b)

c) Study the effect of drug substance particle size distribution and final granule particle size distribution on dissolution to determine the size limits at which dissolution may become retarded. Establish justified drug substance and granule particle size distribution limits based on this understanding.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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/s/

JEANNETTE L O'DONNELL
11/09/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/IR/AE assessment/time sensitive
Date:	Tuesday, November 03, 2015 3:15:00 PM
Importance:	High

Dear Mike,

With regard to your response to the AE assessment, the table you provided in Appendix 1 (attached for reference) is generally acceptable. However the safety assessment for labeling should also include grading according to the Common Terminology Criteria for Adverse Events (CTCAE) for each AE, and an assessment of how many and which Adverse Reactions were serious should also be included.

Therefore, resubmit Appendix 1 with the following additional columns: **CTCAE Grade, and Serious AE ("Yes, "No")**.
Finally, although there did not appear to be many discontinuations due to adverse event, please also note in the table which (if any) of the AEs resulted in treatment discontinuation.

We request this response by **COB Thursday, November 5, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA

Thanks,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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JEANNETTE L O'DONNELL
11/03/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: RE: FDA Communication: NDA 208159/uridine triacetate/MidCycle Communication
Date: Monday, November 02, 2015 2:12:00 PM
Importance: High

Hi Mike,

The call in information for Friday, November 6, 2015, MidCycle communication is below. As stated earlier the time will be from 2:30 pm – 3:00 pm. The agenda will be sent out on Wednesday.

1. Call toll free: (b) (4)
2. Follow the instructions that you hear on the phone.

   Cisco Unified MeetingPlace meeting ID (passcode): (b) (4)
3. Hit # if it asks for a participant ID #

Thanks,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

From: O'Donnell, Jeannette
Sent: Monday, November 02, 2015 12:40 PM
To: 'Bamat, Mike'
Subject: FDA Communication: NDA 208159/uridine triacetate/MidCycle Communication

Hi Mike,

I would like to schedule a1/2 hour T-con as our Mid Cycle communication. The T-con is currently scheduled for next Friday, November 6, 2015.
Time 2:30 pm – 3:00 pm. I will provide call in information tomorrow.

Sincerely,

Jeannette O'Donnell

Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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JEANNETTE L O'DONNELL
11/02/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/midcycle communication agenda
Date:	Wednesday, November 04, 2015 9:54:00 AM
Attachments:	NDA 208159 - MidCycle Agenda.doc
Importance:	High

Dear Mike,

Please find attached a copy of the agenda for Friday's MidCycle communication.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

PDUFA V Program Mid-Cycle Communication Agenda

1. Applicant/FDA Review Team/ERG Independent Assessor Introductions
2. Introductory Comments
3. Significant Review Issues
4. Information Requests
5. Major Safety Concerns
6. Risk Management Update
7. Advisory Committee Meeting Plans – None Scheduled
8. Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

The Late Cycle meeting is currently scheduled from **December 1st, from 11:00-11:30 am**. You may choose to change this face-to-face meeting to a T-con or cancel altogether if you feel it is not needed given the expedited nature of this application and continued regular communications.

This application has been identified for early action under an expedited review. We intend to send you the LCM background package two business days in advance of the scheduled LCM.

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JEANNETTE L O'DONNELL
11/04/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/labeling changes - Time Sensitive
Date:	Wednesday, November 04, 2015 9:57:00 AM
Attachments:	NDA 208159 - Labeling revisions for sponsor - Sections 11-13.docx
Importance:	High

Dear Mike,

Please find attached changes made to the label for NDA 208159 sections 11-13. While at this time, these change may not represent the final label we would like to ask you to submit a clean new label incorporating these changes and address any of the questions and comments listed in the margins.

Due to the expedited nature of this NDA please submit these changes and information by 12:00 pm Friday, November 6 2015. Please submit by 1) email to facilitate review 2) formal submission to the NDA. If you have any further questions please do not hesitate to ask.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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JEANNETTE L O'DONNELL
11/04/2015

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Wednesday, October 28, 2015 12:01 PM
To: mbamat@wellstat.com
Cc: O'Donnell, Jeannette; Kacuba, Alice
Subject: FDA Communication: Clinical Information Request for NDA 208159, uridine - Respond by November 6, 2015

Dear Dr. Bamat,

Please respond by return e-mail and official submission to the following information request.

Submit your response by November 6, 2015.

1. If possible, as discussed this morning, submit corrected lab dataset and corrected tables (such as laboratory shift tables) affected by the error in the 120-day safety update. If not possible to include in the 120-day update, submit separately corrected lab datasets and corrected tables (such as laboratory shift tables).

2. What study records were collected from the sites to aid in filling out the CRFs?

3. In particular what study records were obtained from clinical site Yudhish Markan, MD Glen Burnie, MD? And from this site, what study records were used to determine OD92 verification of overdose and dose administration of uridine as entered into the CRF and reported in the narrative?

Thank you,
Frank Cross, Jr., RPM (for Jeannette O'Donnell, RPM)

Frank Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager Division of Oncology Products 1 Office of Hematology and Oncology Products Office of New Drugs Center for Drug Evaluation and Research US Food and Drug Administration White Oak Bldg 22, 2nd floor, Room 2110
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0876 (office)
(301) 796-9845 (fax)
(301) 796-2330 (Division Main #)
frank.crossjr@fda.hhs.gov<mailto:frank.crossjr@fda.hhs.gov>

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/s/

FRANK H CROSS
10/28/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Tuesday, October 27, 2015 2:42 PM
To: 'Bamat, Mike'
Cc: O'Donnell, Jeannette
Subject: FDA Information Request NDA 208159- Please Respond by COB November 3, 2015

Dear Mike:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uridine Triacetate.

CMC has the following information requests.

1. *Clarify whether future* [redacted] (b) (4) *changes to the manufacturing processes should be reported to the Agency as appropriate. For additional information, see the FDA Guidance for Industry: Changes to an Approved NDA or ANDA, and SUPAC: Manufacturing Equipment Addendum.*

2. *Product temperature* [redacted] (b) (4) *. Please verify that the proposed product temperature range for commercial manufacturing is* [redacted] (b) (4) *and that there are adequate controls in place to maintain that range.*

3. *Provide the sealing* [redacted] (b) (4) *operation.*

4. *The proposed and justified operation range for* [redacted] (b) (4) *Provide evidence, such as particle size distribution and dissolution data, to support that material from batch W017892 is representative of material to be made at the range proposed for commercial operations and provide* [redacted] (b) (4) *ranges for all sub-lots for batches W017893 and W017895.*

We would appreciate a curtesy email response followed by an official submission though the gateway by November 3, 2015.

Kindly confirm receipt of this email.

Thank you,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

From:	Tilley, Amy
To:	Bamat, Mike (mbamat@wellstat.com)
Cc:	O"Donnell, Jeannette
Bcc:	Ison, Gwynn; Beaver, Julia
Subject:	TIME SENSITIVE re NDA 208159 Uridine Triacetate
Date:	Friday, October 16, 2015 3:56:58 PM

Mike,

On behalf of Jeannette O'Donnell, below is the Clinical Information Request which we request your response to **no later than Tuesday, October 20, 2015.** As always, please send your response both via email and as an official submission to the NDA.

We note that patients who were ineligible for study 401.10.001 may have been eligible for treatment on WELL401, and this specifically included pediatric patients, ex-US patients, and patients who received capecitabine. However, the eligibility criteria in the protocol for WELL401 appear identical to those in Study 401.10.001- namely, there is no mention of including pediatric patients, ex-US patients, or patients who received capecitabine. (It actually seems that the 2 protocols only differ by date of enrollment, with patients enrolled prior to Aug 2011 going onto WELL401, and those after going onto 401.10.001).

Please explain this discrepancy and provide the protocol for WELL401, where the inclusion of these patients is described. In addition, you should describe how capecitabine overdose was defined for eligibility.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/16/2015

From:	Tilley, Amy
To:	"Bamat, Mike"
Cc:	O"Donnell, Jeannette
Bcc:	Beaver, Julia; Ison, Gwynn
Subject:	RE: FDA Communication: NDA 208159/uridine triacetate/IR - label
Date:	Wednesday, October 14, 2015 10:42:39 AM
Attachments:	NDA 208159 0028-cover-ltr.pdf

Mike, the review team has reviewed Wellstat's attached response/proposal regarding the timeline for providing a more accurate assessment of adverse events actually causally related to Vistogard for label purposes. The proposed timeline is acceptable.

We look forward to receiving the official submission.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

From: Bamat, Mike [mailto:mbamat@wellstat.com]
Sent: Tuesday, October 13, 2015 4:26 PM
To: O'Donnell, Jeannette; Tilley, Amy
Subject: RE: FDA Communication: NDA 208159/uridine triacetate/IR - label

Dear Amy and Jeannette,

Reference is made to NDA 208159 and to an Information Request (Label) from FDA sent by email (below) on 09 October 2015 requesting Wellstat's proposed timeline for providing a more accurate assessment of adverse events actually causally related to Vistogard for label purposes. FDA asked for a response to this request by close of business on 13 October 2015.

Please find attached Wellstat's response/proposal. The attached document will be submitted formally via FDA's electronic gateway tomorrow as SN0028.

Kind regards,

Mike

Michael Bamat, Ph.D.
Vice President R&D
Wellstat Therapeutics Corporation
930 Clopper Road
Gaithersburg, MD 20878
240 631-2500 ext 3205
mbamat@wellstat.com

From: O'Donnell, Jeannette [mailto:Jeannette.Odonnell@fda.hhs.gov]
Sent: Friday, October 09, 2015 2:17 PM
To: Bamat, Mike
Cc: Tilley, Amy
Subject: FDA Communication: NDA 208159/uridine triacetate/IR - label
Importance: High

Dear Mike,

In reference to NDA 208159, you have previously indicated that you will revisit the adverse reactions portion of the labeling and will provide a more accurate assessment of those adverse events that are actually causally related to uridine triacetate in a future edition of the labeling, rather than simply reporting/including all that were attributed as possibly related. Please provide an estimated time line for when this will occur for FDA concurrence.

Please provide by COB Tuesday October 13, 2015. Please provide by 1) email to facilitate review 2) formal submission to the NDA.

Please reply to all.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

AMY R TILLEY
10/14/2015

From:	Tilley, Amy
To:	Bamat, Mike (mbamat@wellstat.com)
Cc:	O"Donnell, Jeannette
Subject:	FW: FDA Communication: NDA 208159/uridine triacetate/IR/pediatric dosing - time sensitive
Date:	Tuesday, October 13, 2015 1:40:54 PM
Attachments:	draft-labeling-text-4-tracked-changes.docx draft-labeling-text-4.docx

Mike, I am able to open these 2 Word docs.

Thank you.

Amy

From: Bamat, Mike [mailto:mbamat@wellstat.com]
Sent: Tuesday, October 13, 2015 12:56 PM
To: Tilley, Amy
Cc: O'Donnell, Jeannette
Subject: FW: FDA Communication: NDA 208159/uridine triacetate/IR/pediatric dosing - time sensitive

Hello again, Amy.

Please find attached both the clean and tracked changes Word version of proposed label and PPI. If you have any difficulty with these, please let me know. Our IT folks indicate these should be fine and we've done a couple of test sends to external email addresses without a problem on the other end.

My apologies.

Mike

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Tuesday, October 13, 2015 12:35 PM
To: Bamat, Mike
Cc: O'Donnell, Jeannette
Subject: RE: FDA Communication: NDA 208159/uridine triacetate/IR/pediatric dosing - time sensitive

Your newest email I am still unable to open the Word version.

Please check with your IT folks for errors in the file and resend to me with tracked changes.

Amy

From: Bamat, Mike [mailto:mbamat@wellstat.com]
Sent: Tuesday, October 13, 2015 11:48 AM
To: Tilley, Amy
Cc: O'Donnell, Jeannette
Subject: Re: FDA Communication: NDA 208159/uridine triacetate/IR/pediatric dosing - time sensitive

Thank you, Amy. Appreciate your note.

Perhaps you have also seen my follow up email - I made an error in attaching a document to the first response sent this morning. My apologies for any confusion that may have caused.

Mike

On Oct 13, 2015, at 11:43 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:

> Thank you I am in receipt of the emailed response.
>
> *Amy*
>
> **From:** Bamat, Mike [mailto:mbamat@wellstat.com]
> **Sent:** Tuesday, October 13, 2015 11:08 AM
> **To:** O'Donnell, Jeannette; Tilley, Amy
> **Subject:** RE: FDA Communication: NDA 208159/uridine triacetate/IR/pediatric dosing - time sensitive
>
> Dear Jeannette and Amy,
>
> Reference is made to NDA 208159 and to an Information Request from FDA sent on 08 October 2015 (included below) with regard to pediatric dosing of Vistogard, providing graduated teaspoons, and revising the proposed PPI to include relevant instructions. FDA asked for a response to this request by 10:00 a.m. on 14 October 2015.
>
> This email provides Wellstat's responses to this Information Request. Please find the responses attached in the Cover Letter for SN0026 as well as instructions for use of the graduated teaspoon in the now revised PPI (PDF with tracked changes and Word versions provided).
>
> The formal submission of SN0026 through FDA's electronic gateway will be made later today or tomorrow morning. The documents have been sent to your eCTD publisher.
>
> Kind regards,
>
> Mike
>
> Michael Bamat, Ph.D.
> Vice President R&D
> Wellstat Therapeutics Corporation
> 930 Clopper Road
> Gaithersburg, MD 20878
> 240 631-2500 ext 3205
> mbamat@wellstat.com
>
>

From: O'Donnell, Jeannette [mailto:Jeannette.Odonnell@fda.hhs.gov]
Sent: Thursday, October 08, 2015 3:39 PM
To: Bamat, Mike
Subject: FDA Communication: NDA 208159/uridine triacetate/IR/pediatric dosing - time sensitive
Importance: High

Dear Mike,

In reference to NDA 208159 for uridine triacetate, submitted on July 10, 2015, please confirm you are planning to provide a graduated teaspoon for pediatric dosing in each package size, and submit instructions for use to accompany the previously proposed PPI. Also, please provide all relevant details including manufacturing information.

Please provide this information by **10:00 am Wednesday, October 14, 2015**. Please provide by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

AMY R TILLEY
10/13/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/IR/pediatric dosing - time sensitive
Date:	Thursday, October 08, 2015 3:38:00 PM
Importance:	High

Dear Mike,

In reference to NDA 208159 for uridine triacetate, submitted on July 10, 2015, please confirm you are planning to provide a graduated teaspoon for pediatric dosing in each package size, and submit instructions for use to accompany the previously proposed PPI. Also, please provide all relevant details including manufacturing information.

Please provide this information by **10:00 am Wednesday, October 14, 2015**. Please provide by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
10/09/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Cc:	Tilley, Amy
Subject:	FDA Communication: NDA 208159/uridine triacetate/Clin pharm IR - time sensitive
Date:	Friday, October 09, 2015 1:51:00 PM
Importance:	High

Dear Mike,

In reference to NDA 208159 please provide the following information:

1) Please provide detailed explanation on how the nomogram using historical data was generated (Figure 1 in the label). Explain how the boundaries for the expected tolerated, expected serious toxicity and expected lethal were generated. Provide the values represented by dotted vertical and horizontal dashed line that establishes the boundary for the expected lethal region. Provide sample calculation and/or any code that was used to establish the boundaries. Provide us the data in tabular form for the 5-FU maximum tolerated dosage for standard bolus and infusion regimens used in the nomogram and associated references. The historical dataset shows there were multiple subjects with the same actual dose administered at the same dosing rate and same outcome (e.g., 7 subjects with actual dose of 7500 mg administered at 3000 mg/hr with death as outcome). Please clarify if all such subjects or a single subject was used in your calculation of the boundaries.

2) Please identify the nine patients as you mentioned in the proposed labeling who were received Vistogard via nasogastric tube, gastric tube or orogastric tube in study WELL401 and study 401-10-001. Please provide a summary of the Vistogard dose, PK, efficacy and safety profile for such patients.

Please provide this information by COB Wednesday, October 14, 2015. Please reply by 1) email to facilitate review 2) formal submission to the NDA.

Please reply to all as Amy will be covering for me next week.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
10/09/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Cc:	Tilley, Amy
Subject:	FDA Communication: NDA 208159/uridine triacetate/IR - label
Date:	Friday, October 09, 2015 2:17:00 PM
Importance:	High

Dear Mike,

In reference to NDA 208159, you have previously indicated that you will revisit the adverse reactions portion of the labeling and will provide a more accurate assessment of those adverse events that are actually causally related to uridine triacetate in a future edition of the labeling, rather than simply reporting/including all that were attributed as possibly related. Please provide an estimated time line for when this will occur for FDA concurrence.

Please provide by COB Tuesday October 13, 2015. Please provide by 1) email to facilitate review 2) formal submission to the NDA.

Please reply to all.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
10/09/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/clinical - IR/Time sensitive
Date:	Tuesday, October 06, 2015 1:07:00 PM
Importance:	High

Dear Mike,

In reference to your response, October 2, 2015, to our prior IR regarding definition of 5FU overdose, provide information about the ISMP, including why and how they determined the definition of a 5FU overdose (as 10% greater than the planned dose or greater than 1.25 times the intended rate). Also, justify the rationale for using the ISMP's criteria in your submission.

Please reply by **COB October 8, 2015**. Please reply by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
10/06/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/ define 5FU overdose - Time sensitive
Date: Friday, October 02, 2015 8:05:00 AM
Importance: High

Dear Mike,

In reference to NDA 208159 we have the following IR:

In the SUPPFAOD dataset for each trial, clarify if the QLABEL parameter value of planned treatment dose and actual treatment dose includes both the bolus 5FU dose and infusion dose, or just infusion dose?

For instance, patient OD62 received 904 mg for the amount of bolus 5FU dose, then was planned to have 5424 mg infusion over 46 hours, but actually received 5425 mg over 4.5 h. Confirm whether the planned dose of 5424 mg included the 904 mg bolus in the calculation.

This is important, particularly given that your proposed labeling is worded such that an overdose could be due to:

- administration of 5FU at a dose at least >10% greater than the intended dose
- or at a rate greater than 1.25 times the intended rate.

We need to understand how a 5FU dose >10% of the intended dose was calculated in your trials (and should be calculated by clinicians concerned that their patients have received a 5FU overdose), particularly for patients receiving a bolus, followed by an infusion. (We acknowledge that in the example of OD62, the overdose was clearly related to the rate of the infusion, but want to be sure we understand how you have presented the data for all patients in the trial).

Please reply by COB today, October 2, 2015. Please reply by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845

Email: *Jeannette.Odonnell@fda.hhs.gov*

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/s/

JEANNETTE L O'DONNELL
10/02/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/IR - clin. pharm/ Time Sensitive
Date:	Tuesday, September 29, 2015 3:25:00 PM
Importance:	High

Dear Mike,

In reference to NDA 208159, submitted on July 10, 2015 we have the following IR:

To minimize medication errors from using a balance to weigh out the appropriate pediatric dose (particularly since patients might be receiving later doses at home), provide pediatric dosing by a range of BSA, with dose in grams, and equivalent dose based on an adjustable measuring teaspoon. Please provide an explanation on how the doses in grams were converted to doses based on an adjustable measuring teaspoon. Also provide updated Prescribing Information with updated Section 2 Dosage & Administration including a table (showing equivalent volume measures, e.g. teaspoonful).

Please respond by no later than **noon on October 5, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
09/29/2015

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/IR - Time Sensitive
Date:	Tuesday, September 29, 2015 3:29:00 PM
Importance:	High

Dear Mike,

In reference to NDA 208159 submitted on July 10, 2015, please provide a dataset which includes a per patient listing of all historical control cases with all of the following columns, filled in as much as possible (we realize some of this information is already depicted in Tables 13-1 and 13-2 in the Study 401.10.001 CSR):

- 5FU actual dose (mg)
- 5FU planned dose
- 5FU actual infusion time (hours)
- 5FU planned infusion time (hours)
- 5FU actual rate
- 5FU planned rate
- outcome

Please provide this information by **COB on Tuesday, October 6, 2015**. Please provide by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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JEANNETTE L O'DONNELL
09/29/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/clinical IR
Date: Thursday, September 24, 2015 11:21:00 AM
Importance: High

Dear Mike,

In reference to NDA 208159, submitted on July 10, 2015, we have the following clinical information requests (IRs)

1. Please identify which patients (by Subject ID) on both studies 401.10.001 and WELL410 were treated all or partly as outpatients. Please also provide the number of doses for these subjects which were received inpatient and outpatient.

2. Did Patient OD68 on Study 401.10.001 resume chemotherapy, and if so, provide the date.

3. Patient OD61- Please confirm the times and dates of 5FU start and stop, the time of uridine initiation and the interval in hours that elapsed between when this patient's 5FU infusion stopped and when uridine triacetate therapy was initiated. We are coming up with discrepant values, depending on the data source (74 hours vs. 67 hours).

4. Patient OD65- Please confirm the exact date and time that uridine was initiated for this patient. There is discrepancy between the CRF and the narrative on these times and dates. We also note that the narrative for this patient indicates that this patient completed all 20 doses of uridine, however, on the CRF, there are no doses recorded on the entire uridine dosing log page. Please explain.

5. Patient OD66- Please confirm the exact date and time that uridine was initiated for this patient. There is discrepancy between what is conveyed in the narrative and the dataset (19 hours vs. 32 hours 20 min).

Please reply by COB Monday, September 29, 2015. Please reply by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
09/24/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208159

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Wellstat Therapeutics Corporation
930 Clopper Road
Gaithersburg, MD 20878

ATTENTION: Michael K. Bamat, PhD
Vice President, Research and Development

Dear Dr. Bamat:

Please refer to your New Drug Application (NDA) dated July 10, 2015, received July 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uridine Triacetate Oral Granules, 10g per packet.

We also refer to:

- your July 10, 2015, correspondence, received July 10, 2015, requesting review of your proposed proprietary name, Vistogard
- your September 3, 2015, amendment, received September 3, 2015, to your request for name review

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

If any of the proposed product characteristics as stated in your above 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 Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Jeannette O'Donnell, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4978.

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/

KELLIE A TAYLOR on behalf of TODD D BRIDGES
09/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208159

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Wellstat Therapeutics
Attention: Michael K. Bamat, PhD
930 Clopper Rd.
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your New Drug Application (NDA) dated July 10, 2015, received July 10, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vistogard™ (uridine triacetate), oral granules.

We also refer to your amendments dated July 20 and 30, August 5, 20, 25, and 28, and September 3, 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 March 10, 2016. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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

February 4, 2016. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

In addition, the planned date for our internal mid-cycle review meeting is October 29, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

CMC

1. The dissolution method and acceptance criteria for the proposed product Vistogard™ (NDA 208159) should be in agreement with the interim dissolution method and acceptance criteria for Xuriden® (NDA 208169) listed in the dissolution PMC for NDA 208169. Please update the Drug Product Specification to reflect the interim dissolution method and acceptance criteria.

2. Particle size distribution of the oral granules and dissolution as a function of particle size has the potential to impact bioavailability. Given the patient population for the proposed indication, particle size distribution may be a critical quality attribute for this product. Establish a particle size distribution specification for the (b) (4) drug product to ensure rapid, consistent dissolution of the product or provide data to demonstrate variability in the process is not clinically relevant for this patient population. The data should include an analysis of assay versus particle size of the granules as well as an evaluation of the improved dissolution method under development that can discriminate the impact of particle size and other relevant attributes and process parameters on drug release.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

CMC:

1. For product batches used in clinical trials, provide a table of the batch numbers, dissolution data, and particle size distribution for individual samples measured. If possible, include a description of how these samples were taken from the filling operation (b) (4). Provide an analysis to determine if segregation occurred during filling and if there is a correlation to dissolution changes.

Non-Clinical:

1) In report 421-r-401-03-V2, Experiment 5, pages 68 and following for the animals necropsied on day 4, the animal numbers for the experiment are discontinuous. The following animal numbers are missing: 6, 7, 8, 9, 10, 21, 22, 23, 24, 25

   Please explain the reason for this discontinuity.

2) Likewise in the group of animals necropsied on day 10 (Page 72) the following animal numbers are missing: 5, 7, 8, 20

   Please explain the reason for this discontinuity.

3) In both parts of this experiment there are missing values for villus area: Animals 11, 16 and 30 in section 1, animal 15 in section 3 for the Day 4 necropsy, and 22 in section 1, of the day 10 necropsy.

   Please explain the reason for the missing data.

4) In the group of animals necropsied on day 4, the villus area values are on the order of 50. In the animals necropsied on day 10 the villus area values are on the order of 500, a factor of 10 different. Please explain the reason for this difference. Also please provide the units for villus area, perimeter, radius and intestinal area.

5) The certificate of analysis for the uridine triacetate that you used in this study is dated July 5, 1995. You initiated the study in March 2010. Please provide a justification for using drug that was 15 years old at the time you initiated this study. Please provide any information you have on the storage conditions of the drug in the intervening 15 years and on the stability of this drug lot over this period. Please also provide a new certificate of analysis for this drug lot (Batch Number 1911-C-4P).

Please provide this information by September 25, 2015.

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* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- 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 several labeling issues. Please see the attached label with comments.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 18, 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), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient 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 for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jeannette O'Donnell, Regulatory Project Manager, at (240) 402-4978 or email: Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure: Labeling with comments

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

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/s/

GEOFFREY S KIM
09/08/2015

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

Memorandum

Date: September 2, 2015
From: Frances Fahnbulleh, PharmD, OSE Project Manager
Subject: NDA 208159 (Uridine triacetate), Proposed Proprietary Name "Vistogard"

Attention: Michael Bamat, PhD.
Vice President R & D
Wellstat Therapeutics Corporation
930 Clopper Road
Gaithersburg, MD 20878

Dear Mike,
Reference is made to FDA's August 31, 2015 request for clarification regarding your submission for proprietary name review for Vistogard under NDA 208159. Further reference is made to your response via email to Jeannette O'Donnell, also dated 8/31/15. The Division of Medication Error Prevention and Analysis has reviewed the information and would like to convey the following responses:

1. Delete reference to [redacted] (b) (4) & its dose? **YES**
2. Add the proposed pediatric dosing regimen? **YES**

We ask that you submit this information as an amendment to your Request for Proprietary Name Submission and submit it officially, preferably by COB September 10, 2015. Please be sure to copy Jeannette O'Donnell (DOP1 Project Manager) on any emails, and do contact me if you have any questions regarding your Proprietary Name Request.

Respectfully,
Frances

Frances Fahnbulleh, RPh, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/WO22 , Rm#4404
Ph: 301-796-0942/Fax: 301-796-9832
Email: Frances.Fahnbulleh@fda.hhs.gov

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/s/

FRANCES G FAHNBULLEH
09/02/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR/pediatric use
Date: Monday, August 31, 2015 12:13:00 PM
Importance: High

Dear Mike,

In reference to NDA 208159 we have the following information requests:

1. We note in your request for proprietary name review submission for Vistogard submitted on July 10, 2015, the product profile information includes a therapeutic enhancement of 5-FU indication at a dose of 6 gram every 8 hours for a total of 8 doses. This therapeutic indication and dosing are not included in the proposed Prescribing Information (PI) draft labeling text submitted on July 10, 2015.

   Additionally, in the proposed PI draft labeling text, there is a pediatric dosing recommendation for Vistogard "6.2 gram/m^2 of body surface area (not to exceed 10 gram per dose) orally every 6 hours for 20 doses, without regard to meals". It is unclear what the pediatric indication is for this dosing. This pediatric dosing is not included in the proprietary name review submission.
   Please clarify the discrepancy regarding the proposed (b) (4) indication/dose and pediatric indication/dose in the proposed PI draft labeling text and proprietary name review submission, respectively.

2. The request for proprietary name review submission and the proposed PI draft labeling text indicated Vistogard will be packaged in 10 gram (b) (4) packets (in two different carton sizes).
   Please describe how a partial content of your proposed 10 gram packet should be measured for a (b) (4) dose (6 gram) and a pediatric dose that is less than 10 gram.

Please respond by **COB, Tuesday September 8, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845

Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
08/31/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR/genomics
Date: Monday, August 31, 2015 12:16:00 PM
Importance: High

Dear Mike,

In reference to NDA 208159 for uridine triacetate we have the following information request:

- In reference to NDA 208159, some patients in studies 401.10.001 or WELL401 were reported to have mutations in DPYD, TYMS, and/or MTHFR genes (please refer to Clinical Study Report 401.10.001 Table 11-5 and Clinical Study Report WELL401 Table 11-5). Please submit all available patient-level mutation data including the specific mutations in DPYD, TYMS, and/or MTHFR identified in patients enrolled in studies 401.10.001 and WELL401 as well as available information on the assays used to detect the mutations.

Please respond by **COB, September 14, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
08/31/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA communication: NDA 208159/uridine triacetate/clinical IR - time sensitive
Date: Friday, August 28, 2015 2:56:00 PM
Importance: High

Dear Mike,

In reference to NDA 208159 we have the following request:

Please provide narratives and case report forms for ALL patients treated on studies 401.10.001 and WELL401. We acknowledge that many of these have already been submitted (deaths and SAEs), however since we have now begun our review, we have found that having access to the remaining patient data will be important to conduct our risk-benefit analysis. In particular, it will be critical for our review to have narratives on all patients who were treated due to rapid onset of severe symptoms from 5FU or capecitabine.

Please respond by **COB Friday, September 11, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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JEANNETTE L O'DONNELL
08/28/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/RMP plan request - withdrawn
Date: Wednesday, August 26, 2015 1:11:00 PM
Importance: High

Dear Mike,

In reference NDA 208159, information request sent on August 17, 2015, please consider this request withdrawn. After further review you do not need to submit a Risk Management Plan for uridine triacetate.

Thank you,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
08/26/2015

From: O"Donnell, Jeannette
To: "Bamat, Mike"
Subject: FDA Communication: NDA 208159/uridine triacetate/IR - Time Sensitive
Date: Monday, August 17, 2015 2:44:00 PM
Importance: High

Dear Mike,

In reference to NDA 208159, submitted on July 10, 2015, the Division of Risk Management notes that a risk management plan was not submitted with this application. Please submit as an amendment to your application a copy of your most recent EU Risk Management plan and a U.S. risk management plan if you have one available.

Please respond with **COB, August 28, 2015**. Please respond by 1) email to facilitate review 2) formal submission to your NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
08/17/2015

O'Donnell, Jeannette

From:	Laiq, Rabiya
Sent:	Monday, August 03, 2015 4:26 PM
To:	Bamat, Mike
Cc:	O'Donnell, Jeannette
Subject:	FDA Information Request NDA 208159- Please Respond by latest early morning of August 5, 2015
Follow Up Flag:	Follow up
Flag Status:	Flagged
Categories:	Urgent

Hello Mike,

We have the following information request in regards to NDA 208159 (b) (4) to your NDA 208169. On 23-January-15 you responded to an information requesting an outline of the differences between the two applications. There have been several amendments to NDA 208169 since January 2015. Please send an update as a formal amendment to NDA 208159 that outlines all differences at this time between NDA 208159 and NDA 208169. Highlight all sections where there are differences and provide a summary of these differences.

We would appreciate a curtesy email response followed by an official submission though the gateway by early morning of August 5, 2015.

Thank you,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

From:	O"Donnell, Jeannette
To:	"Bamat, Mike"
Subject:	FDA Communication: NDA 208159/uridine triacetate/IR - time sensitive
Date:	Tuesday, July 28, 2015 10:22:00 AM
Attachments:	Study 401.10.001 information request table.doc
Importance:	High

Dear Mike,

In reference to NDA 208159 please see attached table. Please fill in the data for all patients enrolled onto Study 401.10.001 (this should be 60 patients in total).

Additionally, Please confirm whether you have retained source documents on each of the patients treated on Study 401.10.001 at your location in Gaithersburg? Do you have source documents on patients treated on Study WELL401 at their Gaithersburg location, as well?

Please complete respond by **12:00 pm, Friday July 31, 2015.** Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

Subject Number	Site Number	Principal Inv/ Site Name/ Address	Current location of PI (if different from time of patient treatment)	Reason for on-study (overdose vs. impaired elimination)	Date of first dose study drug	Date last dose study drug	Date study completion/ discontinuation	Completed all doses? y/n	Reason for discon. /early completion

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/s/

JEANNETTE L O'DONNELL
07/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208159

NDA ACKNOWLEDGMENT

Wellstat Therapeutics
Attention: Michael K. Bamat, PhD
930 Clopper Rd.
Gaithersburg, MD 20878

Dear Dr. Bamat:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Vistogard™ (uridine triacetate), Oral granules

Date of Application: July 10, 2015

Date of Receipt: July 10, 2015

Our Reference Number: NDA 208159

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 September 8, 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 1
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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (240) 402-4978 or email Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

JEANNETTE L O'DONNELL
07/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: December 31, 2015

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

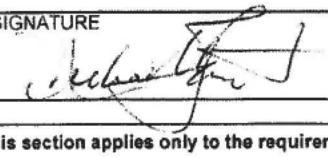
Please mark the applicable check box.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Protocol 401.10.001 (please see attached list)	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Michael K. Bamat, Ph.D.	Vice President, Research and Development
FIRM/ORGANIZATION	
Wellsat Therapeutics Corporation	
SIGNATURE	**DATE** *(mm/dd/yyyy)*
	06/08/2015

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to. a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

FORM FDA 3454 (4/13)

PSC Publishing Services | 301-443-6740 EF

Reference ID: 3863656

1.3.4 Financial Certification and Disclosure

This section contains a list of clinical investigators and sub-investigators participating in Protocol 401.10.001 for whom financial disclosure was obtained by Wellstat.

Wellstat certifies that no financial arrangements with any listed investigator were made where study outcome could affect compensation, that the investigators had no proprietary interest in uridine triacetate, that the investigators do not have a significant equity interest with Wellstat, and that the investigators have not received significant payments of other sorts.

1.3.4.1.1.1 List of Investigators and Sites

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572	Current Address	Phone Number
OD-060	George A. Sotos, MD - Principal Investigator	Suburban Hospital	8600 Old Georgetown Road Bethesda, MD 20814	Suburban Hospital 6420 Rockledge Drive, Suite 4200 Bethesda, MD 20817-7847	301-929-0765
OD-061	Andrew Coveler, MD - Principal Investigator	University of Washington Medical Center	1959 Northeast Pacific Street Seattle, WA 98195	Seattle Cancer Care Alliance 825 Eastlake Avenue. E Seattle, WA 98109-4405	206-288-6491 206-288-7222 206-288-7509
* OD-062	Derek Serna, MD - Principal Investigator	Reid Hospital	1100 Reid Parkway Suite 105 Richmond, IN 47374	Reid Hospital/Reid Oncology Associate 1100 Reid Parkway, Suite 105 Richmond, IN 47374	765-935-8773 765-983-3000
OD-064	Hans Boedecker, MD - Principal Investigator	Bridgton Hospital	10 Hospital Drive Bridgton, ME 04009	Bridgton Hospital 10 Hospital Drive Bridgton, ME 04009	207-647-6120
**OD-065	Mohamad Masri, MD - Principal Investigator	Florida Hospital Fish Memorial	1061 Medical Center Drive Suite 305 Orange City, FL 32763	Florida Hospital Fish Memorial Cancer Institute 1061 Medical Center Drive Suite 305 Orange City, FL 32763	386-917-7630 (b) (6)
OD-067	Malgorzata McMasters, MD - Principal Investigator	Hallmark Health Hematology and Oncology Center	41 Montvale Avenue Stoneham, MA 02180	Beth Israel Deaconess Medical Center 330 Brooklin Ave., KS121 Boston, MA 02215	617-667-9920
OD-068	Jerry Liu, MD - Principal Investigator	North Shore Oncology-Hematology	525 East Congress Parkway Suite 300 Crystal Lake, IL 60014	North Shore Hematology and Oncology Associates 525 East Congress Parkway Suite 300 Crystal Lake, IL 60014	815-759-9260
OD-069	Manal Robin-Hanna, MD - Principal Investigator (b) (6)	Comanche County Memorial Hospital	3401 West Gore Blvd. Lawton, OK 73505	Comanche County Memorial Hospital 3401 West Gore Blvd. Lawton, OK 73505	580-536-2121 580-574-6646
OD-070	Michael Gu, MD - Principal Investigator (b) (6)	St. Louis Oncology Associates, Inc.	510012 Kennerly Road Suite 100 St. Louis, MO 63128	St. Louis Oncology Associates 10012 Kennerly Road, Suite 100 St. Louis, MO 63128	314-849-6066

1.3.4 Financial Certification and Disclosure

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572	Current Address	Phone Number
OD-071	Rex Mowat, MD - Principal Investigator	Hickman Cancer Center at Flower Hospital	5200 Harroun Road Sylvania, OH 43560	Hickman Cancer Center at Flower Hospital 5200 Harroun Road Sylvania, OH 43560	419-824-1011
OD-076	Robert Schwert, DO - Principal Investigator	Robert Schwert P.C.	4960 Skyview Court Traverse City, MI 49684	Robert Schwert P.C. 4960 Skyview Court Traverse City, MI 49684	231-392-8400
OD-079	Ruben Saez, MD - Principal Investigator	Texas Health Physicians Group	6957 West Plano Parkway Suite 2500 Plano, TX 75093	Plano Cancer Institute 6957 West Plano Parkway Suite 2000A Plano, TX 75093	214-483-6933
OD-080	Roy Cromartie, MD - Principal Investigator (b) (6)	WakeMed Hospital	4101 Macon Pond Road Raleigh, NC 27610	Rex Hematology Oncology Associate at Blue Ridge 2605 Blue Ridge Road Suite 190 Raleigh, NC 27607	919-785-4919
OD-081	Kevin Peacock, MD - Principal Investigator	Ginnett Medical Center	1000 Medical Center Blvd. Lawrenceville, GA 30046	Suburban Hematology-Oncology Associates, LLC 631 Professional Drive, Suite 450 Lawrenceville, GA 30045	770-963-8030 404-550-8255
OD-082	Brad McGregor, MD - Principal Investigator	David Grant Medical Center	101 Boden Circle Travis Air Force Base, CA 94535	David Grant Medical Center 101 Boden Circle Travis Air Force Base, CA 94535	707-423-5129
OD-083	Christopher Jones, MD - Principal Investigator (b) (6)	NorthEast Oncology Associates/Batte Cancer Center	100 Medical Park Drive Suite 110 Concord, NC 28025	Levine Cancer Institute - Concord 100 Medical Park Drive, Suite 110 Concord, NC 28025	704-403-1370
OD-084	Avi Markowitz, MD - Principal Investigator (b) (6)	The University of Texas Medical Branch	Internal Medicine – Division of Hematology/Oncology 301 University Blvd. Galveston, TX 77555-0565	UTMB Victory Lakes Cancer Center 2240 Gulf Freeway South League City, TX 77573	409-747-2278
OD-085	Colleen Austin, MD - Principal Investigator	St. Joseph's Hospital	5665 Peachtree Dunwoody Road, NE Atlanta, GA 30342	Atlanta Cancer Care 5670 Peachtree Dunwoody Road Suite 11 Atlanta, GA 30342	404-851-2300
OD-087	Catherine Heltsley, MD - Principal Investigator	The Medical Center at Bowling Green	250 Park Street Bowling Green, KY 42101	The Medical Center at Bowling Green 1325 Andrea Street, Suite 107 Bowling Green, KY 42104	270-796-8881

1.3.4 Financial Certification and Disclosure

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572	Current Address	Phone Number
OD-088	James Posey III, MD - Principal Investigator	University of Alabama at Birmingham	625 19th Street South Birmingham, AL 35294	UAB Medical Center 1802 6th Avenue South, NP2540U Birmingham, AL 35294	205-934-0916
OD-089	Kenneth D. Deaton, Jr., MD - Principal Investigator (b) (6)	Central Georgia Cancer Care, P.C.	1062 Forsyth Street Suite 1B Macon, GA 31201	Central Georgia Cancer Care 1062 Forsyth Street, Suite 1B Macon, GA 31201	478-743-7068
OD-091	Yacoub Faroun, MD - Principal Investigator (b) (6)	St. Luke's University Hospital and Health Network	801 Ostrum Street Bethlehem, PA 18015	St. Luke's Hospital 701 Ostrum Street, Suite 403 Bethlehem, PA 18015	484-526-7000
OD-092	Yudhish Markan, MD - Principal Investigator	Baltimore Washington Medical Center	300 Hospital Drive Glen Burnie, MD 21061	Chesapeake Oncology Hematology Associates Tate Cancer Center 305 Hospital Drive Glen Burnie, MD 21061	410-761-9896
OD-093	Charles R. Dibb, MD - Principal Investigator	Rogue Regional Medical Center	2828 E. Barnett Avenue Medford, OR 97504	Hematology Oncology Associates, P.C. 2828 E. Barnett Road Medford, OR 97504	541-774-5853
OD-094	J. Marc Pipas, MD - Principal Investigator	Dartmouth-Hitchcock Medical Center Norris Cotton Cancer Center	One Medical Center Drive Lebanon, NH 03756	Dartmouth-Hitchcock Memorial Hospital Hematology/Oncology One Medical Center Drive Lebanon, NH 03756	603-650-9474
OD-095	Chao H. Huang, MD - Principal Investigator (b) (6)	Kansas City VA Medical Center	4801 East Linwood Blvd. Kansas City, MO 64128	Kansas City VA Medical Center 4801 East Linwood Blvd. Kansas City, MO 64128	816-861-4700
OD-096	Alfonso Cutungo, MD - Principal Investigator	Benedictine Hospital	105 Marys Avenue Kingston, NY 12401	Benedictine Hospital 105 Mary's Avenue Kingston, NY 12401	845-340-2100
OD-097	Patrick Williams, MD - Principal Investigator (b) (6)	Audubon Hospital Norton Healthcare	1 Audubon Plaza Drive Louisville, KY 40217	Norton Healthcare 3991 Dutchmans Lane Suite 405 Louisville, KY 40207	502-899-3366

1.3.4 Financial Certification and Disclosure

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572	Current Address	Phone Number
OD-098	Nora Bucher, MD - Principal Investigator (b) (6)	St. Joseph's Hospital Center for Cancer Care	2900 N Lake Shore Drive 7th Floor Chicago, IL 60657	Desert Regional Medical Center Comprehensive Cancer Center 1150 N. Indian Cyn Drive Suite E218 Palm Springs, CA 92262	760-416-4918 847-999-8029
OD-100	Scott Cole, MD - Principal Investigator (b) (6)	Tulsa Cancer Institute	12697 East 51st Street South Tulsa, OK 74146	Tulsa Cancer Institute 12697 East 51st Street South Tulsa, OK 74146	918-505-3200
* OD-101	Xiusheng Qin, MD - Principal Investigator	Reid Hospital & Health Care Services	1100 Reid Parkway Richmond, IN 47374	Richmond Cancer Center, LLC 2302 Chester Blvd., Suite A Richmond, IN 47374	765-983-3600
OD-102	Jonathan Bender, MD - Principal Investigator (b) (6)	Peachtree Hematology Oncology Consultants	1267 Highway 54 West Suite 4200 Fayetteville, GA 30214	Peachtree Hematology Oncology Associates 1267 Highway 54 West, Suite 4200 Fayetteville, GA 30214	678-829-1060
OD-106	Muhammad A. Mirza MD - Principal Investigator	Mercy Hospital Washington	901 E. 5th Street Washington, MO 63090	Mercy Hospital Washington 901 E. 5th Street Washington, MO 63090	636-239-8000 636-390-1600 314-376-3532

1.3.4 Financial Certification and Disclosure

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572	Current Address	Phone Number
OD-107	Brandon Johnson, MD - Principal Investigator	East Alabama Medical Center	2000 Pepperell Parkway Opelika, AL USA 36801	East Alabama Medical Center 2000 Pepperell Parkway Opelika, AL 36801	334-528-2687
OD-108	Thomas Buroker, MD - Principal Investigator (b) (6)	Iowa Methodist Medical Center	1200 Pleasant Street Des Moines, IA 50309	Medical Oncology and Hematology Associates of Iowa 1221 Pleasant Street, Suite 100 De Moines, IA 50309	515-282-2921
OD-109	Kelly Godby, MD - Principal Investigator	University of Alabama Hospital	619 19th Street South Birmingham, AL US 35249	UAB School of Medicine Hematology & Oncology 1720 2nd Avenue South, NP 2540 Birmingham, AL 35294	205-975-3409 205-934-4669
OD-110	Haider Khadim, MD - Principal Investigator	Upstate University Hospital	750 E. Adams Street Syracuse, NY USA 13210	CCS Oncology 45 Spindrift Drive Williamsville, NY 14221	716-565-0355
OD-113	Lotfi Mamlouk, MD - Principal Investigator (b) (6)	West Chester Hospital	7700 University Drive West Chester, OH 45069	Medicine Inpatient Group, LLC 6936 Southampton Lane West Chester, OH 45069	513-298-3000 513-618-7430 518-884-7480
OD-115	Daniel Dubovsky, MD - Principal Investigator (b) (6)	Northside Hospital	100 Peachtree Dunwoody Road Atlanta, GA USA 30342	Atlanta Cancer Care 5670 Peachtree Dunwoody Road Suite 1100 Atlanta, GA 30342	404-851-2340
OD-116	Kathleen Beekman, MD - Principal Investigator	St. Joseph's Mercy Hospital	5301 E. Huron River Drive Ann Arbor, MI USA 48106	IHA Hematology/Oncology Consultants 5301 E. Huron River Drive Suite C139 Ypsilianti, MI 48197	734-712-1000
OD-117	Jihad Khattah, MD - Principal Investigator (b) (6)	Saint Francis Hospital Warren Clinic Oncology	6161 South Yale Avenue Tulsa, OK 74136	Saint Francis Hospital Warren Clinic Oncology 11212 East 48th Street Tulsa, OK 74146	918-556-3000
OD-118	Jiahuai Tan, MD - Principal Investigator	North Mississippi Medical Center	990 S. Madison Street Suite 2 Tupelo, MS USA 38801	North Mississippi Medical Center 830 South Gloster Street Tupelo, MS USA 38801	662-844-9166

1.3.4 Financial Certification and Disclosure

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572	Current Address	Phone Number
OD-119	Cheryl Harth, MD - Principal Investigator (b) (6)	Methodist Dallas Medical Center	1441 N. Beckley Avenue Dallas, TX USA 75203	Methodist Dallas Medical Center 1441 N. Beckley Avenue Suite 101 & 102 Dallas, TX USA 75203	214-943-9911
OD-121	Jeffrey Hancock, MD - Principal Investigator	Mountain View Hospital	1957 East 17th Street Idaho Falls, ID USA 83404	Teton Cancer Institute 1957 E. 17th Street Idaho Falls, ID USA 83404	208-523-1100
OD-122	Leopoldo Eisenberg, MD - Principal Investigator	Huron Valley Sinae Hospital	1 William Carls Drive Commerce, MI USA 48382	Huron Valley Sinae Hospital DMC Hematology Oncology 28455 Haggerty Road, Suite 203 Novi, MI USA 48377	248-324-4444 269-587-0770
OD-124	Marc Greenblatt, MD - Principal Investigator (b) (6)	Fletcher Allen Health Care, Inc.	111 Colchester Avenue Burlington, VT USA 05401	University of Vermont Medical Center EP-2 Hematology/Oncology 111 Colchester Avenue Burlington, VT USA 05401	802-847-8400
OD-126	William Newberry, MD - Principal Investigator	Medical University of South Carolina	171 Ashley Avenue Charleston, SC USA 29417	Lowcountry Medical Group Arthur S. Jenkins Medical Bldg. 300 Midtown Drive Beaufort, SC USA 29906	843-770-0404
OD-127	Gregory Brouse, MD - Principal Investigator (b) (6)	Carolinas Medical Center - Union	600 Hospital Drive Monroe, NC USA 28112	Carolinas Medical Center - Union 1550 Faulk Street, Suite 1500 Monroe, NC USA 28112	980-442-0430
OD-128	Wen Wee Ma, MD - Principal Investigator	Roswell Park Cancer Institute	Roswell Park Cancer Institute Elm and Carlton Street Buffalo, NY USA 14263	Roswell Park Cancer Institute Elm and Carlton Streets Buffalo, NY USA 14263	716-845-2300
OD-129	Linda S. Couch, MD - Principal Investigator	Christus Santa Rosa- Westover Hills	11212 State Hwy 151 San Antonio, TX USA 78251	Christus Santa Rosa-Westover Hills 11212 State Hwy 151 Professional Bldg. #2, Suite 120 San Antonio, TX USA 78251	210-595-5300
OD-130	Eunice Kwak, MD, PhD - Principal Investigator (b) (6)	Massachusetts General Hospital	55 Fruit Street Boston, MA USA 02114	Massachusetts General Hospital Cancer Center, 7th Floor, Suite E 55 Fruit Street Boston, MA USA 02114	617-724-4000

1.3.4 Financial Certification and Disclosure

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572	Current Address	Phone Number
OD-131	Christian Shull, MD - Principal Investigator	Mountain View Hospital	1957 E. 17th Street Idaho Falls, ID USA 83404	Mountain View Hospital Teton Cancer Institute 1957 E. 17th Street Idaho Falls, ID USA 83404	208-356-9559
OD-132	Charles Riggs, MD - Principal Investigator (b) (6)	Gainesville NF/SG VHS Facility	1601 SW Archer Road (573) Gainesville, FL USA 32608	UFHealth, Division of Hematology & Oncology 1600 SW Archer Road PO Box 100278 Gainesville, FL USA 32610	352-273-7832
OD-134	Steven M. Duffy, MD - Principal Investigator	Bon Secour St. Mary's Hospital	5801 Bremo Road Richmond, VA USA 23226	Bon Secour Medical Oncology at St. Mary's Hospital 5875 Bremo Road Medical Office Bldg. South Suite G11 Richmond, VA USA 23226	804-287-7804
OD-136	Regan Rostorfer, MD - Principal Investigator (b) (6)	Orlando Health, Inc.	1400 South Orange Avenue Orlando, FL USA 32806	UF Health Cancer Center at Orlando Health, Inc. 1400 South Orange Avenue Orlando, FL USA 32806	407-648-3800
OD-137	Lala Cornelius, MD - Principal Investigator (b) (6)	Exempla Saint Joseph Hospital SCL Health System	1835 Franklin Street Denver, CO USA 80218	Kaiser Permanente Hematology/Oncology Clinic 2045 Franklin Street Denver, CO USA 80205	303-861-3302
OD-139	Jacob Matthew, MD - Principal Investigator	Harrison Medical Center	2520 Cherry Avenue Bremerton, WA USA 98310	Harrison HealthPartners Bremerton Hematology & Oncology 2720 Clare Avenue, Suite A Bremerton, WA USA 98310	360-479-6154
OD-140	Madappa N. Kundranda MD - Principal Investigator	Western Regional Medical Center, Inc.	14200 W. Celebrate Life Way Goodyear, AZ USA 85338	Banner MD Anderson Cancer Center 2946 E. Banner Gateway Drive Gilbert, AZ USA 85234	480-256-6444
OD-141	Craig Adam Kovitz, MD - Principal Investigator	Millennium Physicians Association, PLLC	9319 Pinecroft Drive Suite 100 The Woodlands, TX 77380 USA	Millennium Physicians Association, PLLC 9319 Pinecroft Drive, Suite 100 The Woodlands, TX 77380 USA	281-298-8444

1.3.4 Financial Certification and Disclosure

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572	Current Address	Phone Number
*** Site OD-062 and Site OD-101 are the same site/hospital** **** Site OD-065: Per phone contact 16Jun2015, Mohamad Masri, MD, Principal Investigator, has moved out of the country. The Florida Hospital Fish Memorial, Cancer Institute administrative office is storing all the records for this patient and will make them available as needed.**					

1.3.4 List of Investigators (Study WELL401)

This section contains a list of clinical investigators including address and phone number who treated patients under Compassionate Use programs in the US and worldwide and for whom clinical efficacy and safety data were obtained and are reported in NDA 208159 in Study WELL401.

Most of the US patients were treated under Investigator-Sponsored Single Patient INDs (SPIs), although some were treated under Wellstat's IND 039571. For each of the US (SPI) patients, Wellstat provided a letter of authorization for the investigator-sponsor to cross-reference IND 039571.

Patients treated outside of the US ("ex-US") received uridine triacetate under each individual country's special access programs.

A final study report containing safety and efficacy data from these patients is included in this application (Study WELL401).

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
OD-001	Richard Gray, MD - Principal Investigator	Northwest Georgia Oncology Centers	1700 Hospital S. Drive Suite 102 Austell, GA 30001 USA	Northwest Georgia Oncology Centers 1700 Hospital S. Drive, Suite 300 Austell, GA 30106 USA	039571^
OD-002	Donald Berdeaux, MD - Principal Investigator	Columbus Hospital	500 Fifteenth Avenue South, Suite 102 Great Falls, MT 59405 USA	Columbus Hospital 500 15th Avenue South Great Falls, MT, 59403 USA	049248
OD-003	Charles Bowers, MD - Principal Investigator	Dixie Professional Plaza	620 South 400 East #109 St. George, UT 84770 USA	Dixie Professional Plaza 380 Serpentine Drive #200 Spartanburg, SC 29303 USA	049249
OD-004	Stephen M. Hahn, MD - Principal Investigator	Redwood Regional Oncology Center	121 Sotoyome Street Santa Rosa, CA 95405 USA	Redwood Regional Oncology Center 121 Sotoyome Street #101 Santa Rosa, CA 94954 USA	049717
OD-005	Anna C. Ferrar, MD - Principal Investigator (b) (6)	Mt. Sinai Medical Center	One Gustave L. Levy Place Box 1129 New York USA, NY 10029-6574	Mt. Sinai Medical Center One Gustave L. Levy Place New York, NY 10029-6574 USA	053304
OD-006	Margaret Block, MD - Principal Investigator	Oncology Hematology West	8303 Dodge Street Omaha, NE 68114 USA	Oncology Hematology West 7710 Mercy Road Omaha, NE 68124 USA	**
OD-007	Alvin Otsuka, MD - Principal Investigator	Rocky Mountain Cancer Centers	8015 W. Alameda Suite 260 Lakewood, CO 80226 USA	Rocky Mountain Cancer Centers 11750 W. 2nd Place, Medical Plaza 1 Suite 150 Lakewood, CO 80228 USA	059958
OD-008	Philip Bonomi, MD - Principal Investigator	Rush Presbyterian/St Luke's Medical Center	1725 West Harrison St. Suite 862 F Chicago IL 60612 USA	Rush Cancer Institute/St. Luke's Medical Center 1725 W Harrison Street #1010 Chicago, IL 60612 USA	**
OD-009	Kathleen Neville, MD - Principal Investigator	Texas Children's Hospital	6621 Fannin Street Houston, TX 77030 USA	Texas Children's Hospital 6621 Fannin Street Houston, TX 77030 USA	065265

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
OD-010	M. Daud Nawabi, MD - Principal Investigator	East Cooper Hematology & Oncology, PA	900 Bowman Road Suite 203 Mt. Pleasant, SC 29464 USA	East Cooper Hematology & Oncology, PA 900 Bowman Road, Ste 303 Mt. Pleasant, SC 29464 USA	039571^
OD-011	Ira S. Jaffrey, MD - Principal Investigator	Western Slope Oncology Associates, P.C.	622 19th Street Suite 301 Glenwood Springs, CO 81601 USA	Western Slope Oncology Associates, P.C. 622 19th Street, Ste 301 Glenwood Springs, CO 81601 USA	066772
OD-012	Howard Bruckner, MD - Principal Investigator	Lutheran Medical Center	150 55th Street Brooklyn, NY 11220 USA	Lutheran Medical Center 150 55th Street Brooklyn, NY 11220 USA	039571^
OD-013	Robert Laugan, MD - Principal Investigator	Valley Hospital and Medical Center		Valley Hospital and Medical Center 12606 East Mission Avenue Spokane, WA 99216 USA	074544
OD-014	Bassema Antabli, MD - Principal Investigator	Kaiser Permanente		Kaiser Permanente 12255 Fairlakes Parkway Fairfax, VA 22033 USA	078385
OD-015	Chao Hui Huang, MD - Principal Investigator	Kansas City VA Medical Center	4801 Linwood Blvd. Mail Stop 151 Kansas City, MO 64128 USA	Kansas City VA Medical Center 4801 Linwood Blvd. Kansas City, MO 64128 USA	102416
OD-016	Daniel Cameron, MD - Principal Investigator	Infirmary West Oncology and Infusion Services	3 Mobile Circle, Suite 301 Mobile, AL 36607 USA	Infirmary West Oncology and Infusion Services 3 Mobile Infirmary Circle, Suite 301 Mobile, AL 36607 USA	103764
OD-017	David Lovett, MD - Principal Investigator	Cape Cod Hospital	27 Park Street Hyannis, MA 02601 USA	Cape Cod Hospital 27 Park Street Hyannis, MA 02601 USA	103840
OD-018	Hugo Gomez, MD - Principal Investigator	Sanitorio San Roque		Sanitorio San Roque Eligio Ayala 1383 y Pai Perez Asuncion, CP 1540, Paraguay	Ex-US
OD-019	Dana Boyers, PharmD - Principal Investigator	Texas Oncology-Mesquite	4700 North Galloway Avenue Mesquite, TX 75150 USA	Texas Oncology-Mesquite 4700 North Galloway Avenue Mesquite, TX 75150 USA	039571^

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
OD-020	Imran Ahmed, MD - Principal Investigator	Las Vegas Cancer Center	2904 West Horizon Ridge Pkwy, Suite 200 Henderson, NV 89052 USA	Las Vegas Cancer Center 2904 West Horizon Ridge Pkwy, Suite 200 Henderson, NV 89052 USA	105772
OD-021	Stephen Leong, MD - Principal Investigator	University of Colorado Cancer Center	12801 E. 17th Ave. Aurora, CO 80045 USA	University of Colorado Hospital 12605 E 16th Avenue Aurora, CO 80045 USA	106330
OD-022	Naveen Lobo, MD - Principal Investigator	Clearview Cancer Institute	310 8th Ave. NE Decatur, AL 35601 USA	Clearview Cancer Institute 310 8th Avenue NE Decatur, AL 35601 USA	106300
OD-023	John Anagnost, MD - Principal Investigator	Hanover Medical Specialists, P.A	1520 Physicians Drive Wilmington, NC 28401 USA	Hanover Medical Specialists P.A. Hematology-Oncology 1520 Physicians Drive Wilmington, NC 28401 USA	106517
OD-024	John P. Whitecar, MD - Principal Investigator	Columbus Hemotology & Oncology, P.A.	Whitecar Cancer Care Ctr. 425 Hospital Dr., Ste. 4 P.O. Box 8489 Columbus, MS 39705-0011 USA	Baptist Memorial Hospital Golden Triangle 2520 Fifth Street North Columbus, MS 39705 USA	106565
OD-025	Pankaj Gupta, MD - Principal Investigator	Minneapolis VA Medical Center	One Veterans Drive Hem/Onc (111E) Minneapolis, MN 55417 USA	VA Medical Center One Veterans Drive Minneapolis, MN 55417 USA	106702
OD-026	Sheow Lei Lim, MD - Principal Investigator	KK Women's & Children's Hospital		KK Women's & Children's Hospital 100 Bukit Timah Road 229899 Singapore	Ex-US
OD-027	Charles Young, MD - Principal Investigator	Riverside Community Hospital	4445 Magnolia Avenue Riverside, CA 92501 USA	Riverside Community 4445 Magnolia Avenue Riverside, CA 92501 USA	107478
OD-028	C. Eric Hartz, MD - Principal Investigator	Eastern Maine Medical Center/Cancer Care of Maine	417 State Street Bangor, ME 04401 USA	Eastern Maine Medical Center/Cancer Care of Maine 417 State Street Bangor, ME 04401 USA	107290

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
OD-029	Lawrence Gynther, MD - Principal Investigator	Emory Healthcare	734 Camellia Drive LaGrange, GA 30240 USA	Emory Clark-Holder Clinic 1610 E 10th Street West Point, GA 31833 USA	107832
OD-030	Venu G. Bathini, MD - Principal Investigator	UMass Memorial Medical Center	55 Lake Avenue North Worcester, MA 01655 USA	UMass Memorial Medical Center 55 Lake Avenue North Worcester, MA 01655 USA	107670
OD-031	Viralkumar Bhanderi, MD - Principal Investigator	Hematology & Oncology Associates of Northwest Florida	1632 Riggins Road Tallahassee, FL 32308 USA	Hematology-Oncology Associates of Northwest Florida 1632 Riggins Road Tallahassee, FL 32308 USA	107882
OD-032	Jack E. Saux, III, MD - Principal Investigator	North Shore Cancer Care, Covington	39 Starbrush Circle Covington, LA 70433 USA	Mary Bird Perkins Cancer Center at St. Tammany Parish Hospital 1203 S. Tyler Street Covington, LA 70433 USA	108004
OD-033	Dimitrios Dionysopoulos, MD - Principal Investigator	Papageorgiou General Hospital		General Hospital of Thessaloniki PAPAGEORGIOU, Ringroad Municipality Paul Mela Area N. Efkarpia Thessaloniki 56 403 Greece	Ex-US
OD-034	Wen Wee Ma, MD - Principal Investigator	Roswell Park Cancer Institute	Elm and Carlton Streets Buffalo, NY 14263 USA	Roswell Park Cancer Institute Elm and Carlton Streets Buffalo, NY 14263 USA	108400
OD-035	Brea Lipe, MD - Principal Investigator	Dartmouth-Hitchcock Medical Center	One Medical Center Drive Lebanon, NH 03750 USA	Dartmouth-Hitchcock Medical Center One Medical Center Drive Lebanon, NH 03766 USA	108249
OD-036	Amanda Glasgow, MD - Principal Investigator	The Wollongong Hospital		The Wollongong Hospital Crown Street, Wollongong NSW 2500 Australia	Ex-US
OD-037	Rishi Sawhney, MD - Principal Investigator	Bayhealth Medical Center	640 South State Street Dover, DE 19901 USA	Bayhealth Kent General640 South State StreetDover, DE 19901 USA	108746

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
OD-038	Jayanthi Ramadurai, MD - Principal Investigator	Little Company of Mary Hospital	2800 West 95th Street Evergreen Park, IL 60805 USA	Little Company of Mary Hospital and Health Care Centers 2800 West 95th Street Evergreen Park, IL 60805 USA	109652
OD-039	Daryl Roitman, MD - Principal Investigator	North York General Hospital		North York General Hospital 4001 Leslie Street Toronto, Ontario M2K 1E1 Canada	Ex-US
OD-040	Nina J. Karlin, MD - Principal Investigator	Mayo Clinical Hospital	13400 E. Shea Blvd. Scottsdale, AZ 85259 USA	Mayo Clinical Hospital 5777 East Mayo Blvd. Phoenix, AZ 85054 USA	109715
OD-041	Shakir Sarwar, MD - Principal Investigator	Grant Medical Center	111 South Grant Avenue Columbus, OH 43215 USA	Grant Medical Center 111 South Grant Avenue Columbus, OH 43215 USA	110047
OD-042	Peter Eisenberg, MD - Principal Investigator	California Cancer Care Inc.	1350 South Eliseo Drive Ste. 200 Greenbrae, CA 94904 USA	California Cancer Care Inc. Crystal Springs Village 218 De Anza Blvd San Mateo, CA 94402 USA	110084
OD-043	Ibrahim Sbeitan, MD - Principal Investigator	Conemaugh Cancer Care Center	1020 Franklin Street Johnstown, PA 15905 USA	Conemaugh Cancer Care Center 1020 Franklin Street Johnstown, PA 15905 USA	110192
OD-044	Janak Choksi, MD - Principal Investigator	Alamance Regional Medical Center	1236 Huffman Mill Road, Suite 120 Burlington, NC 27215 USA	Alamance Regional Medical Center 1240 Huffman Mill Rd Burlington, NC 27215 USA	110265
OD-045	Thomas Braun, MD - Principal Investigator	Denver VA Medical Center	1055 Clermont Street Denver, CO 80220 USA	Denver VA Medical Center 1055 Clermont Street Denver, CO 80220 USA	999000
OD-046	Stephen Eberwine, MD - Principal Investigator	American Health Network Hematology Oncology	1111 N. Ronald Reagan Pkwy, Suite B 1600 Avon, IN 46123 USA	Clarion West Cancer Center 1111 Ronald Reagan Pkwy Avon, IN 46123 USA	110277
OD-047	Puneet Cheema, MD - Principal Investigator	Healtheast St. John's Hospital	1575 Beam Avenue Maplewood, MN 55109 USA	Healtheast Cancer Center 1575 Beam Avenue Maplewood, MN 55109 USA	999000

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
OD-048	Bernard-Marty Chantal, MD - Principal Investigator	Institut Claudius Regaud		Institut Claudius Regaud IUCT Oncopole, 1 avenue Irène Joliot-Curie Toulouse 31053 France	Ex-US
OD-049	Nikhil Uppal, MD - Principal Investigator	Arena Oncology Associates	1999 Marcus Avenue New Hyde Park, NY 11042 USA	Arena Oncology Associates 1999 Marcus Avenue Suite 120 New Hyde Park, NY 11042 USA	110615
OD-050	Yashar Hirshaut, MD - Principal Investigator	Lenox Hill Hospital	860 5th Ave. New York, NY 10065 USA	Lenox Hill Hospital 100 E 77th Street New York, NY 10065 USA	110643
OD-051	John Hamm, MD - Principal Investigator	Louisville Oncology	315 E. Broadway, Fourth Floor Louisville, KY 40202 USA	Norton Cancer Institute Oncology Practices Norton Healthcare Pavilion, Fourth Floor 315 E. Broadway Louisville, KY 40202 USA	110747
OD-052	William Dribben, MD - Principal Investigator	St. Louis Children's Hospital	One Children's Place St. Louis, MO 63110 USA	St. Louis Children's Hospital One Children's Place St. Louis, MO 63110 USA	111067
OD-053	Bernard Poiesz, MD - Principal Investigator	SUNY Upstate Medical University	750 East Adams Street Syracuse, NY 13210 USA	State University of New York Upstate Medical Center 750 East Adams Street Syracuse, NY 13210 USA	111788
OD-054	Philippe Pouderoux, MD - Principal Investigator	Centre Hospitalier et University de Nimes, Hospital Carneau		Centre Hospitalier et University de Nimes, Hospital Carneau CHU de Nîmes - Place du Pr R. Debré 30029 Nîmes cedex 9, France	Ex-US
OD-055	Matthias Ritgen, MD - Principal Investigator	Universitatskliniku m Schleswig-Holstein		Universitatsklinikum Schleswig-HolsteinArnold-Heller-Straße 324105 Kiel Germany	Ex-US
OD-056	Matilda H. So, MD - Principal Investigator	Holy Cross Hospital	1500 Forest Glen Road Silver Spring, MD 20910-1484 USA	Kaiser Permanente Largo Oncology 1221 Mercantile Lane Largo, MD 20774 USA	112063

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
OD-057	Lucio Gordon, MD - Principal Investigator	Florida Cancer Specialists & Research Institute	1147 Northwest 64th Terrace Gainesville, FL 32605 USA	Florida Cancer Specialist of Gainesville 1147 Northwest 64th Terrace Gainesville, FL 32605 USA	112136
OD-058	Herbert Rappaport, MD - Principal Investigator	Cedars-Sinai Medical Center	8733 Beverly Blvd Los Angeles, CA 90048 USA	Herbert Rappaport MD, Corp. 8733 Beverly Blvd, Suite 312 Los Angeles, CA 90048 USA	112558
OD-059	David D. Powell, DO - Principal Investigator	St. Rita's Medical Center	730 W. Market Street Lima, Ohio 45801 USA	Cancer Care West Central Ohio 2740 West Market Street Lima, OH 45805 USA	112851
OD-063	Amy Holder, MD - Principal Investigator (b) (6)	Methodist Children's Hospital	7700 Floyd Curl Drive San Antonio, TX 78229 USA	Methodist Children's Hospital 7700 Floyd Curl Drive San Antonio, TX 78229 USA	113779
OD-072	Barbara John, MD - Principal Investigator (b) (6)	Theresienkrankenhouase und St. Hedwig-Klinik Gmb H		Theresienkrankenhouase und St. Hedwig-Klinik Gmb H Bassermanstrasse 1 Mannheim, 68165 Germany	Ex-US
OD-073	Jose Maria Mazo Gil, MD - Principal Investigator	Hospital General de Llerena		Hospital General de Llerena Avda. Badajoz, 1, Llerena Badajoz, 06900 Spain	Ex-US
OD-074	Laurent Mosser, MD - Principal Investigator	Hospital Jacques Puel/Centre Hospitalier de Rodez		Hospital Jacques Puel/Centre Hospitalier de Rodez Avenue de l'Hôpital Rodez, 12000 France	Ex-US
+OD-075	Miquel Nogue, MD	Hospital General de Granollers		Hospital General de Granollers Av. Francesc Ribas s/n Granollers Barcelona, 08400 Spain	Ex-US
+OD-077	Vicente Guillem, MD	Hospitales Nisa 9 de Octubre		Hospitales Nisa 9 de Octubre Carrer de la valle de la Ballestera, 59 València, 46015 Spain	Ex-US

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
*OD-078	Corneliu Mocanu, MD - Principal Investigator	CHI Ere-Seine site Evreux		CHI Ere-Seine site Evreux rue Leon Schwartzenberg Evruex cedex, 27015 France	Ex-US
OD-086	Mathilde Jehanne, MD - Principal Investigator	Chu Felix Guyon		Chu Felix Guyon Centre Hospitalier Universitaire Fe Hopital Bellepierre Saint-Denis, 97400 France	Ex-US
OD-090	Charlotte Kristiansen, MD - Principal Investigator	Odense Universitetshospital		Odense Universitetshospital Sdr. Boulevard 29 Odense C, DK-5000 Denmark	Ex-US
OD-099	Philippe Sultanik, MD - Principal Investigator	Service d'hepatologie-unite d'oncologie		Hopital Cochin Department d'Hepatologie Medicale 27 rue du Faubourg Saint-Jacques Paris, 75014 France	Ex-US
OD-103	Krishna Soujanya Gunturu, MD - Principal Investigator (b) (6)	Tufts Medical Center	800 Washington Street Boston, MA 02111 USA	Tufts Medical Center 800 Washington Street Boston, MA 02111 USA	118140
OD-111	Brian Passalacqua, MD - Principal Investigator	St. Mary's Regional Medical Center	235 West 6th Street Reno, NV 89503 USA	St. Mary's Regional Medical Center 235 West 6th Street Reno, NV 89503 USA	118890
OD-112	Nadine Jay, MD - Principal Investigator	CHU BREST		CHU BREST 5 av Foch Brest cedex, 29609 France	Ex-US
*OD-114	Corneliu Mocanu, MD - Principal Investigator	Centre Hospitalier Intercommunal Eure-seine-site d'Evreux		Centre Hospitalier Intercommunal Eureseine site d'Evreux rue Léon Schwartzenberg Evreux cedex, 27015 France	Ex-US
OD-120	Julio Peguero, MD - Principal Investigator	Kindred Town & Country Hospital	925 Gessner, Suite 600 Houston, TX 77024 USA	Kindred Town & Country Hospital 925 Gessner, Suite 600 Houston, TX 77024 USA	119869
OD-123	Michael Antoniolli, MD - Principal Investigator	Children's Hospital of Michigan	3901 Beaubien Street Detroit, MI 48201 USA	Children's Hospital of Michigan 3901 Beaubien Street Detroit, MI 48201 USA	120219

List of Investigators (Study WELL401)

WT Case Number	Principal Investigator/Sub-Investigator	Hospital or Site Name	Address from 1572/1571	Current Address	IND #
OD-125	Ritwik Pandey, MBBS, MD, DM, FRACP - Principal Investigator	Cairns Hospital/Liz Plummer Cancer Center		165 The Esplanade Cairns, Queensland 04870 Australia	Ex-US
OD-138	Louise Ligresti, MD - Principal Investigator	Valley Hospital	223 N. Van Dien Ave. Ridgewood, NJ 07450 USA	One Valley Health Plaza Paramus, NJ 07652 USA	122446

* Site OD-078 and Site OD 114 are the same site/hospital

** Investigators contacted FDA but no IND's were issued for OD-006 and OD-008

^ OD-001, 010, 012, and 019 treated under Wellstat IND

+ OD-075 and OD-077 Investigators are included in this list for completeness, as Wellstat supplied uridine triacetate under compassionate/emergency use, but was unable to confirm patients' informed consent so the data were not included in the report for these patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 039571

MEETING MINUTES

Wellstat Therapeutics Corporation
Attention: Michael Bamat, PhD
Vice President, Research and Development
930 Clopper Road
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Uridine Triacetate (PN401).

We also refer to the meeting between representatives of your firm and the FDA on August 27, 2014. The purpose of the meeting was to seek guidance on the Animal Rule regulatory pathway and to discuss details of the existing preclinical efficacy studies and additional studies, if needed.

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 Tracy Cutler, Regulatory Health Project Manager at (301) 796-9608.

Sincerely,

{See appended electronic signature page}

Tracy Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Patricia Cortazar, MD
Clinical Team Leader
Division of Oncology Products 1
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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	Guidance
Meeting Date and Time:	August 27, 2014; 2:00 pm – 3:00 pm
Meeting Location:	White Oak; Building 22, Room 1315
Application Number:	IND 039571
Product Name:	Uridine Triacetate (PN401)
Indication:	(b) (4) [redacted]
Sponsor/Applicant Name:	Wellstat Therapeutics Corporation
Meeting Chair:	Patricia Cortazar, MD
Meeting Recorder:	Tracy Cutler, MPH, CCRP, CIP

FDA ATTENDEES

Amna Ibrahim MD, Acting Director, DOP1
Geoffrey Kim, MD, Acting Deputy Director, DOP1
Patricia Cortazar, MD, Clinical Team Leader, DOP1
Gwynn Ison, MD, Medical Officer, DOP1
Jonathan Jarow, MD, Medical Officer, DOP1
Sanjeeve Balasubramaniam, MD, Medical Officer, DOP1
Todd Palmby, PhD, Pharm/Toxicology Supervisor, DHOT
W. David McGuinn, Jr., MS, PhD, DABT, Pharm/Toxicology Reviewer, DHOT
Qi Liu, PhD, Clinical Pharmacology Team Leader, DCP5
Pengfei Song, PhD, Clinical Pharmacology Reviewer, DCP5
Jeanne Fourie-Zirkelbach, PhD, Clinical Pharmacology Reviewer, DCP5
Michael Pacanowski, PhD, Associate Director, Genomics/OCP
Rosane Charlab Orbach, PhD, Hematology /Oncology Team Leader, Genomics/OCP
Tracy Cutler, MPH, CCRP, CIP, Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES

Michael Bamat, PhD, Vice President, Research & Development, Wellstat
Jeffrey Carey, BA, Senior Director, Regulatory Affairs, Wellstat
Joan Helton, Quality Assurance, Wellstat
Rita O'Neil, PhD, Senior Director, Regulatory Project Management, Wellstat
Robert Tremmel, PharmD, Clinical Safety Manager, Wellstat
Reid von Borstel, PhD, Vice President, Discovery Research, Wellstat
Nadine Wohlstadter, President, Wellstat
(b) (4) [redacted]

Reference ID: 3863656

1.0 BACKGROUND

A telephone conference was held between FDA and Wellstat on May 28, 2014, during which a proposal for an NDA submission was discussed. FDA informed the Sponsor that an application based upon the Animal Rule, along with available clinical data from EAP 401.10.001 and various SPIs, may be sufficient to support an NDA submission. Since that teleconference, fast-track designation was granted on July 23, 2014, for uridine triacetate (b) (4) to treat patients at risk of excess 5-FU toxicity due to overdosage.

The main purpose of the current meeting is for the Sponsor to provide a summary of the available preclinical data on uridine triacetate, and to discuss whether it could be sufficient to support an NDA submission.

In previous submissions to the IND and in previous meeting packages, the Sponsor indicated the completed nonclinical toxicology studies conducted with uridine triacetate. In the current meeting package, the sponsor highlighted the completed nonclinical pharmacology and efficacy studies conducted with uridine triacetate. A number of studies have been conducted in mice administered uridine triacetate following administration of a toxic dose of 5-FU. Study endpoints in the 5-FU overdose model included hematology, survival, and pharmacokinetics of both 5-FU and uridine. Data supporting a dose-response relationship for uridine on hematology parameters were provided. Effects on survival with different time intervals of uridine triacetate administration following a toxic dose of 5-FU were provided, indicating a greater survival outcome correlated with a shorter time interval. The data provided did not include dose response survival data for uridine triacetate, or time interval analysis for hematology parameters. Data provided for pathological changes to the intestinal mucosa was from animals that received 5-FU and 5-ethynyl uracil followed by uridine triacetate, and did not include detailed pathological evaluation of the tissues.

To date, more than 140 patients (n=143 according to Question 4) have been treated with uridine triacetate for 5-FU overexposure due to overdose, DPD deficiency, and/or early onset of severe toxicity due to 5-FU. It is notable, that an update on survival of the 143 treated patients reveals that 137/143 (96%) have survived after treatment with uridine triacetate for overexposure to 5-FU. No further details are given in the current meeting package.

2.0 DISCUSSION

FDA Preamble: We cannot fully respond to specific questions about whether data resulting from nonclinical studies supports approval of an NDA for a given indication prior to reviewing all available data submitted in an NDA. These nonclinical data will be reviewed in the context of the all available clinical and CMC information at the time of an NDA submission. Responses in these preliminary meeting minutes are intended to convey that the nonclinical data described in your meeting package from completed studies may be adequate to support submission of an NDA in combination with available clinical data and provide suggestions of additional information that may aid in our review.

2.1 5-FU Overdose Model

Question 1: Does FDA agree that the effective time window for administration of uridine triacetate, and a dose-response relationship in the 5-FU overdose model have been adequately demonstrated?

FDA Response: Based on nonclinical data provided in your briefing package, it appears that the shorter the time interval between administration of 5-FU and uridine triacetate, the better the outcome on survival in mice. You will need to provide a justification for the proposed time window for administration of uridine triacetate, including integration of all available nonclinical and clinical data, in your NDA submission.

In experiment 2 of the 5-FU overdose model in study R.401.14.01, hematological parameters were assessed 8 and 12 days after administration of 4 dose levels of uridine triacetate in animals that received a non-lethal dose of 150 mg/kg IP 5-FU. This appears to provide a dose-response relationship with regard to hematology. In your NDA, provide any additional dose-response data on survival, body weight, clinical signs or other clinically relevant parameter in the 5-FU overdose mouse model. For example, the publication you provided in your briefing package by Muhammad Wasif Saif and Reid von Borstel states that "About 12 separate variations on the colon 26 experiments (slightly different dosing regimens, different comparison arms) were done, all corroborating the reported results. Such variations included individual dose as well as the cumulative dose of PN401 administered following 5-FU, timing between 5-FU and the first dose of PN401 ranging from 2 to 24 h, and the number of doses of PN401 required following 5-FU".

> **Sponsor Response:** Wellstat will provide a full justification for the proposed time window for administration of uridine triacetate, integrating all available nonclinical and clinical data, in the NDA submission.
>
> In the NDA submission, Wellstat will also provide all additional dose-response data on survival, body weight, clinical signs and other clinically relevant parameters in the 5-FU overdose mouse model.
>
> In addition, dose-response data for uridine triacetate from Phase 1 studies in humans in which the dose of uridine triacetate was escalated along with the dose of 5-FU will be provided in the NDA.
>
> ***Meeting Discussion:*** **No discussion took place during the meeting.**

Question 2: Does FDA agree that the functional effects of uridine triacetate given at various intervals after 5-FU as assessed by improvements in survival, hematologic parameters, bone marrow cellularity and body weight changes have been adequately demonstrated?

FDA Response: This will be a review issue. We acknowledge the data from the Saif and von Borstel publication and experiment 3 in study R.401.14.03 on survival following administration of uridine triacetate given at various intervals after 5-FU. If available,

include these data on hematologic parameters, bone marrow cellularity and body weight in the 5-FU overdose mouse model in your NDA submission.

Sponsor Response: Wellstat will ensure that all relevant nonclinical and clinical data supporting the functional effects of uridine triacetate given at various intervals after 5-FU will be included in the NDA.

Meeting Discussion: **No discussion took place during the meeting.**

Question 3: Does FDA agree that the pharmacokinetics of uridine in mice have been adequately characterized?

FDA Response: **Possibly. The PK data for uridine in mice appears appropriate to support an NDA submission. Nevertheless, the adequacy of the pharmacokinetic data in mice will depend on our acceptance of your rationale for selection of an effective dose in humans. Provide this rationale in your NDA submission and include all available nonclinical and clinical data on which it is based.**

Sponsor Response: Wellstat will provide a complete rationale for selection of the effective dosage of uridine triacetate in humans, supported by all available preclinical and clinical data. The rationale and data will be comprised of the following:

- The mechanisms of 5-FU toxicity and (b) (4) uridine triacetate
- The importance of achieving steady-state plasma uridine concentrations greater than 70 micromolar, a threshold for protecting normal tissues from the toxic effects of 5-FU
- Uridine PK data in animals and humans
- Safety and effectiveness of uridine triacetate in animals
- Safety and effectiveness of uridine triacetate at the chosen dose in humans

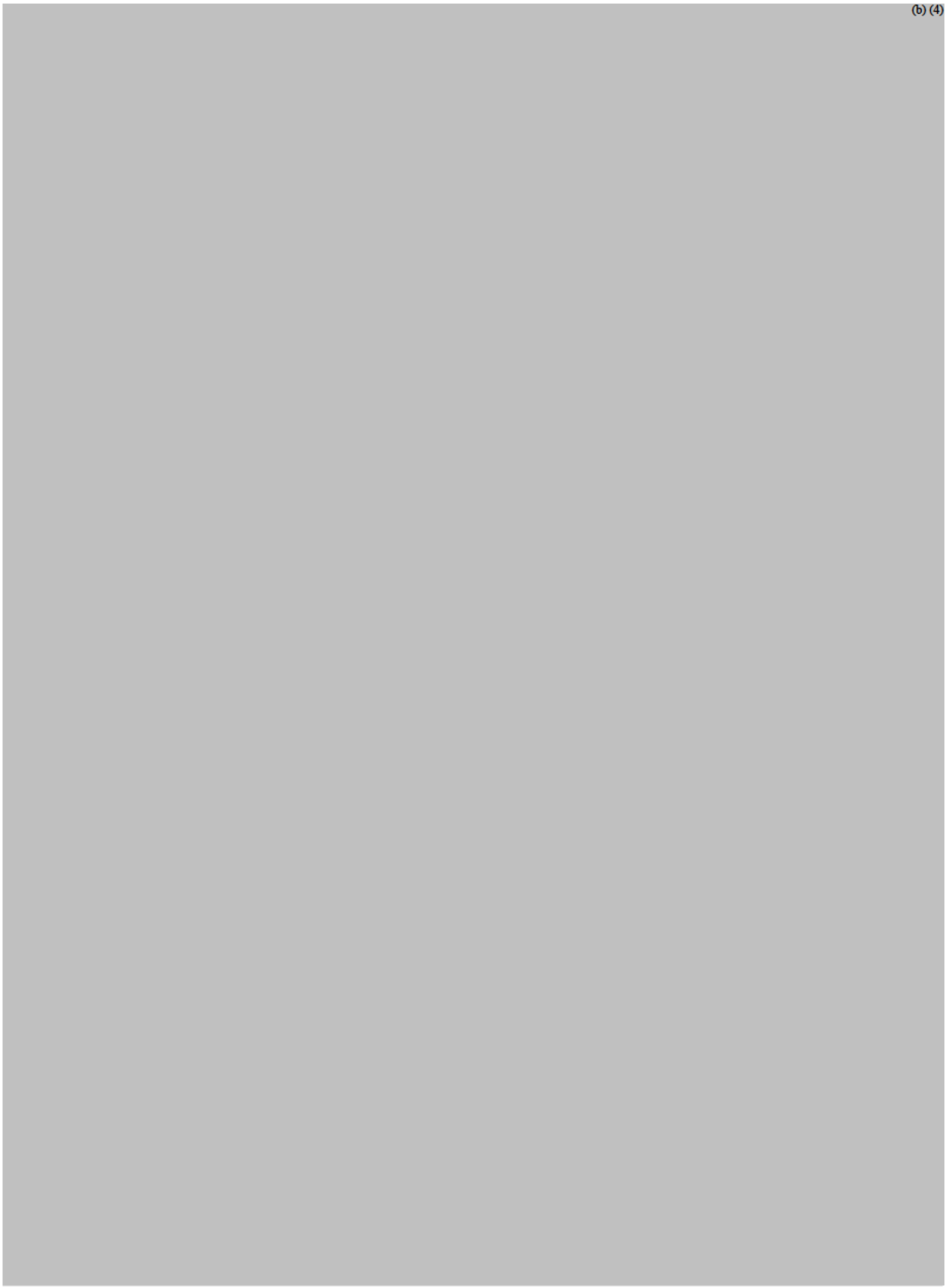
Meeting Discussion: **FDA clarified that the Sponsor should justify the clinical dose and provide a link between the animal data and clinical data. In addition, the Sponsor should provide a comparison of the animal systemic PK exposure at the dose shown to be effective in the animal models versus the human PK exposure at the clinical dose and regimen (with the intended clinical formulation). This information should be included as part of the NDA submission.**

2.2 (b) (4)

Question 4: (b) (4)

FDA Response: **No. Our review of nonclinical data will focus on studies relevant to the clinical indication being considered. Therefore, at this time we expect nonclinical studies in the 5-FU overdose mouse model to be the most relevant.**

(b) (4)



(b) (4)

Meeting Discussion: **FDA reiterated that the nonclinical data that will be considered as supportive for an NDA will depend on the population being considered.** (b) (4)

Question 5: (b) (4)

FDA Response: **No. Please see our response to Question 4.**

Sponsor Response: Please also refer to our response to Question 4.

Meeting Discussion: **No discussion took place during the meeting.**

Question 6: (b) (4)

FDA Response: **Please see our response to Question 4.**

Sponsor Response: Please also refer to our response to Question 4.

Meeting Discussion: **No discussion took place during the meeting.**

Question 7: Wellstat provided information on the absence of differences between genders with respect to 5-FU toxicities and uridine pharmacokinetics in humans or mice. 5-FU dosing guidelines are identical for males and females, and differences in lean body mass account for reports of possible increased incidence of 5-FU toxicities in females. Menopause does not affect 5-FU dosing guidelines, reflecting a lack of effect of sex hormones on 5-FU PK or toxicity. Uridine exposure after oral uridine triacetate does not appear to differ between males and females apart from possible minor body weight effects. To date, a total of 78 male and 65 female patients at risk of excess 5-FU toxicity have been treated with uridine triacetate as an antidote using a common treatment regimen (10g q6h × 20 doses) with no apparent gender differences identified. Therefore, Wellstat proposes that there are no additional gender issues that need to be addressed.

Does FDA agree?

FDA Response: Based on the summary clinical PK data submitted at the 6g dose, there does not appear to be a difference in the uridine triacetate AUC values between males and females. In your NDA submission, provide literature references or data to support the following statement from your briefing package, "There are no known gender differences in 5-FU sensitivity in mice or other animals". The final determination will be a review issue based on the total data submitted.

Sponsor Response: Wellstat will provide literature references and data to support the absence of gender differences in 5-FU sensitivity in mice and other animals in the NDA.

Meeting Discussion: **No discussion took place during the meeting.**

Question 8: Wellstat has treated 143 patients at risk of excess 5-FU toxicity (b) (4) and early onset of severe 5-FU toxicities (b) (4) to 5-FU toxicities. The survival and toxicities data are compelling (137/143 patients survived; 96%) and clearly illustrate the efficacy of uridine triacetate when compared to outcomes in comparably poisoned patients who did not receive uridine triacetate.

In the "hybrid" type of submission that FDA described at the 28 May 2014 teleconference, would the existing animal efficacy data together with the clinical data, supported by multiple case studies of matched patients from the published literature who did not receive uridine triacetate, be adequate to support the NDA filing?

FDA Response: Your proposed approach appears to be appropriate to support submission of an NDA. The acceptability of the nonclinical and clinical data to support approval of an NDA will be determined following our review of your complete submission.

At the time of NDA submission, you will need to provide in depth data (narratives, patient charts, autopsy findings, if available) on all patient deaths, including the 3 additional deaths that have occurred since the last meeting.

Sponsor Response: Wellstat will provide as much in depth data as possible on all patient deaths at the time of NDA submission. Please note that none of the patient deaths were attributed to uridine triacetate.

Briefly, for the six patients who died (3 under SPI, 3 under EAP 401.10.001):

- One death was attributed to tumor lysis syndrome within several days of a 5-FU overdose and occurred within hours after treatment with rasburicase;
- One was due to disease progression and pre-existing MRSA infection under hospice care (the patient was noted as recovering from all 5-FU-related overdose toxicities prior to decision to enter hospice);
- One was due to respiratory failure and sepsis in a patient treated far outside the presumed window of effective intervention (≤96 hours) with uridine triacetate.

The patient received a standard dose of 5-FU, but was found later to be DPD deficient and to have a TYMS mutation;

- One patient with a long history of chronic pulmonary disorders and lung metastases had a standing "do not resuscitate" (DNR) order and was allowed to expire due to respiratory failure;
- One patient, also treated outside the presumed window of effective treatment (≤96 hours) with uridine triacetate and also later shown to be DPD-deficient and to have a TYMS mutation, died of sepsis and organ failure following a standard dose of 5-FU.

Meeting Discussion: **No discussion took place during the meeting.**

Question 9: Does FDA concur that under the proposed "hybrid NDA" regulatory pathway consisting of animal efficacy studies supported by clinical data from patients at risk of excess 5-FU toxicity treated with uridine triacetate and matched case study comparisons as described in Question 4 would be adequate to support full regular approval of uridine triacetate (b) (4) to treat patients at risk of excess 5-FU toxicity due to overdosage, (b) (4) early onset of severe toxicities (b) (4) to 5-FU toxicities?

FDA Response: We will point out again that it is unlikely that you will be granted (b) (4)

The main focus of our review will be on the patients who received a documented overdosage of 5-FU. Please separate the subset of patients with 5-FU overdose from the rest of the population.

Sponsor Response: Wellstat will separate out the subset of patients with 5-FU overdose from the patients presenting with early onset of severe 5-FU toxicities.

However, Wellstat disagrees that the (b) (4) early onset populations are not well characterized. There is extensive published literature on these populations, (b) (4)
Wellstat has treated a number of these patients under the Expanded Access Protocol 401.10.001 (with FDA concurrence) and under Single Patient INDs (with FDA review and approval) as shown in Table 1 below and can readily specify which patients should be considered candidates for treatment and when they should be treated. The preclinical data fully support the clinical observations.

Table 1: Patients with Early Onset of Severe Toxicities or Known DPD Deficiency Treated with Uridine Triacetate

Case	Type	5-FU Dose Number	Presenting Toxicity	Genetic Testing	Hours post Completion of 5-FU (hrs from start of 5-FU)	Outcome
OD-009	Early Onset*	1	Neurotoxicity	DPD Neg. (only major mutation tested)	64 (112)	Recovery
OD-058	Early Onset*	4	Mucositis	Not Done	95.5 (215.5)	Recovery
OD-060	Early Onset*	1	Neurotoxicity	DPD Neg. (only major mutation tested)	33 (79)	Recovery
OD-061	Early Onset*	1	Mucositis	DPD Neg. (only major mutation tested)	84 (180)	Recovery
OD-064	Early Onset*	1	GI, hematotox	DPD Neg. (only major mutation tested);TS Pos.	89 (185)	Recovery
OD-081	Early Onset*	1	GI, hematotox	Unknown	48.5 (168.5)	Recovery
OD-084	Early Onset*	1	GI, hematotox	DPD Neg.; TS Pos.; MTHFR Pos.	40.5 (136.5)	Recovery
OD-088	Early Onset*	1	GI, hematotox	DPD Neg.; TS Pos.	60 (180)	Recovery
OD-093	Early Onset*	1	Neurotoxicity	DPD Neg.;TS Pos.	60 (105)	Recovery
OD-097	Early Onset*	1	Cardiotoxicity	DPD Neg.	106 (142)	Recovery
OD-106	Early Onset*	1	Cardiotoxicity	DPD Neg.;TS Pos.	29.75 (96.75)	Recovery
OD-116	Early Onset*	1	GI	Pending	33.5 (153.5)	Recovery
OD-120	Early Onset*	1	Hematotox	DPD Pos.; TS Pos.	264 (360)	Death
OD-124	Early Onset*	1	Neurotoxicity	DPD Neg.;TS Pos.	67 (82.25)	Recovery
OD-134	Early Onset*	1	GI	DPD Pos.; TS Pos.	101 (148)	Death
OD-138	Early Onset*	1	GI, hematotox	DPD Pos.	528 (574)	§
OD-139	Early Onset*	1	Neurotoxicity	Pending	87 (183)	Recovery
OD-046	Known DPD	1	N/A	Double Mutant (Major Mutation) DPD Pos.	8.5 (8.5)	Recovery
OD-126	Known DPD	2	N/A	DPD Pos.	17.45 (39.45)	Recovery
OD-059	Overdose**	1	N/A	DPD Pos.;MTHFR Pos.	17.5 (22.5)	Recovery
OD-118	Overdose**	1	N/A	DPD Pos.;TS Pos.	33.45 (69.45)	Recovery
OD-128	Overdose**	1	N/A	DPD Pos.	18.75 (19)	Recovery

* Early Onset - Cases reported due to early onset (b) (4) to 5-FU toxicity - Grade 3-4 diarrhea, mucositis, neutropenia, thrombocytopenia, neurological, cardiac

** Overdose - On Dose 1, genetic testing showed DPD and other mutations

Key: DPD - Dihydropyrimidine Dehydrogenase; TS - Thymidylate Synthase; MTHFR - Methylene Tetrahydrofolate Reductase; Pos. - Positive; Neg. - Negative; CI- Continuous Infusion; IVP - IV Push (Bolus); N/A - Not Applicable

§ Recovered from hematotox and GI toxicities; patient remains comatose

In clinical studies of 5-FU-based regimens and in standard clinical practice, onset of serious to severe dose-limiting toxicities within several days of the first dose of 5-FU are uncommon and, when they occur, can progress to life-threatening or lethal toxicity. There is no effective antidote apart from uridine triacetate that has shown benefit in such patients and little can be done currently for these patients beyond palliative care. Many

such cases are subsequently found to be due to 5-FU clearance defects, (b) (4) as other mutations that lead to increased sensitivity to 5-FU.

(b) (4)

Therefore, physicians and other healthcare workers can readily identify patients with early (rapid) onset (within approximately 96 hours of 5-FU dose termination) of serious-severe toxicity (e.g., GI, hematologic, neurologic, and/or cardiac). This is particularly important when it occurs following dose 1 of course 1 (i.e., in 5-FU naïve patients). Timely treatment of these patients with uridine triacetate appears to be efficacious within the same time window as with 5-FU overdose cases. Wellstat contends that the data are adequate to support this aspect of the desired indication with clinical and preclinical data, considering the following similarities to the 5-FU overdose indication:

- The mechanisms of 5-FU toxicity in people (and mice) at risk of excess 5-FU toxicity are the same (b) (4).
- Toxicity is primarily a function of the AUC of plasma 5-FU (b) (4)) and its intracellular correlate of 5-FU incorporation into RNA.
- The antidotal mechanism of uridine triacetate is the same; namely dilution of toxic 5-FU metabolites with uridine nucleotides and uridine catabolites.
- The dose and regimen for uridine triacetate is the same as for frank overdose, as are the duration of dosing, the route of administration, and the safety profile.
- The time window for efficacy is the same, up to 96 hours after 5-FU administration (though earlier treatment is more effective in preventing mortality), corroborated in studies in mice (b) (4)
- The preclinical data from the well-characterized model (b) (4) fully support and corroborate clinical observations in patients with early onset of serious-severe 5-FU toxicities.
- Since 2011, Wellstat has been operating under the assumption that, as FDA stated, "to include this indication in the approved label, it will be necessary to submit several cases supporting it". Significantly more than several cases now support this indication (RE: Table 1), along with preclinical data.

Therefore, we respectfully request that FDA consider the clinical and preclinical data for the following indication: "**Uridine triacetate is indicated** (b) (4) ."

Meeting Discussion: **FDA asked the Sponsor to address the efficacy of 5-FU when uridine triacetate was given, including any information on re-treatment with 5-FU. FDA advised that the Sponsor provide all information available to support the proposed indication. The final wording of the indication will be a review issue.**

Additional Comments

- **You should clarify whether the human PK data you provide in Figure 3 (Kelsen et. al., 1997) characterizes your investigational agent at the proposed dosing regimen. If possible, please provide human PK data with the intended clinical formulation in the NDA.**

  Sponsor Response: The PK data shown from Kelsen et al. (1997) are from a nearly identical dosing regimen – 9.9g given every 6 hours for 10 doses. It is expected that steady state is would be achieved after 10 doses of uridine triacetate, and other studies show no remarkable accumulation of uridine in plasma following repeated dosing with uridine triacetate.

  Additionally, Wellstat has clinical PK data with uridine triacetate with the intended clinical formulation and will provide these data.

  Meeting Discussion: **No discussion took place during the meeting.**

- **Your NDA should address all the issues discussed in the September 9, 2013 EOP2 meeting. Please consider requesting a CMC pre-NDA meeting if you feel there are unresolved issues.**

  Sponsor Response: Wellstat will address all issues discussed at the 2013 EOP2 meetings and is considering requesting a CMC pre-NDA meeting, though we are not aware of unresolved issues at this point.

  Meeting Discussion: **No discussion took place during the meeting.**

3.0 OTHER IMPORTANT MEETING LANGUAGE

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 (5-FU Overdose) 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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting.

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/s/

TRACY L CUTLER
09/04/2014

PATRICIA CORTAZAR
09/04/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 28, 2014

Application Number: IND 039571
Product Name: (b) (4) (uridine triacetate)
Sponsor/Applicant Name: Wellstat Therapeutics

Subject: (b) (4)

FDA Participants

Richard Pazdur, MD, Director, Office of Hematology and Oncology Products (OHOP)
Amna Ibrahim, MD, Acting Division Director, Division of Oncology Products 1 (DOP1)
Tamy Kim, PharmD, ADRA, OHOP
Patricia Cortazar, MD, Clinical Team Leader, DOP1
Gwynn Ison, MD, DOP1
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Reviewer, DCP5
Todd Palmby, PhD, Pharmacology/Toxicology Supervisor, DHOT
W. David McGuinn, Jr., MS, PhD, DABT, Pharmacology/Toxicology Reviewer, DHOT
Jonathan Jarow, MD, Medical Officer, DOP1
John Leighton, PhD, Acting Division Director, DHOT
Nam Atiqur Rahman, PhD, Clinical Pharmacology Supervisor, DCP5
Sarah Dorff, PhD, Clinical Pharmacology Reviewer, OCP
Alice Kacuba, RN, MSN, RAC, CPMS, DOP1
Tracy Cutler, MPH, Regulatory Health Project Manager, DOP1

Sponsor/Applicant Participants

Michael Bamat, PhD, Vice President, Research & Development, Wellstat
Jeff Carey, B.A., Senior Director, Regulatory Affairs, Wellstat
Joan Helton, BA, CCRP, Quality Assurance
Rita O'Neil, Ph.D., Senior Director, Regulatory Project Management, Wellstat
Robert Tremmel, PharmD, Clinical Safety Manager, Wellstat
Reid von Borstel, PhD, Vice President, Discovery Research, Wellstat
Nadine Wohlstadter, President, Wellstat

1.0 BACKGROUND:

FDA requested the teleconference to discuss the Wellstat Therapeutics (b) (4) for uridine triacetate under IND 039571 for the treatment of patients at risk of excess 5-FU toxicity.

2.0 DISCUSSION:

- FDA noted that uridine triacetate is a potentially important product for the treatment of 5-FU overdose/toxicity, and asked about the Wellstat's plan to support the future New Drug Application (NDA) submission.
- FDA stated that uridine triacetate may be eligible for development under the Animal Rule as a regulatory pathway approach to support approval of uridine triacetate in patients with 5-FU overdose, as it is not ethical or feasible to conduct randomized controlled trials to study the effectiveness in this setting. The group discussed the non-clinical efficacy studies in mice that have already been conducted using uridine triacetate. FDA informed Wellstat Therapeutics of the need to conduct an additional non-clinical study in a mouse model to evaluate survival and additional endpoints relevant to the clinical 5-FU overdose setting to support an NDA. This study needs to be conducted under a special protocol assessment (SPA), so that the details of the study could be agreed upon prior to study conduct. In particular, this study should include the following:
    - Multiple dose levels of uridine triacetate with treatment given within 2-3 hours of 5-FU overdose, to mimic the clinical setting
    - Focus on survival and additional endpoints to evaluate the effect of uridine triacetate to mitigate toxicities of 5-FU on the bone marrow and gastrointestinal (GI) tract
    - Suggested endpoints including hematology, clinical observations (specifically diarrhea as possible) and histopathology of multiple tissues (of particular interest are GI tract and bone marrow)
    - Focus on timing of evaluations relative to 5-FU and uridine triacetate administration
    - Pharmacokinetics of uridine triacetate
- FDA encouraged Wellstat Therapeutics to apply for fast track designation, which would allow for a rolling submission of the NDA. (b) (4)
- (b) (4). As a result, FDA advised the Sponsor that the focus of their NDA submission should be on the 5-FU overdose indication, with clinical and non-clinical data to support this indication.

3.0 ACTION ITEMS:

- Sponsor to respond to the DOP1 RPM by **Wednesday, June 4th** as to whether they would like to proceed with a Fast Track request (b) (4)
- Sponsor to submit a meeting request as soon as possible to discuss the details of completed non-clinical efficacy studies and the additional non-clinical efficacy study in mice that will likely need to be conducted.

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/s/

TRACY L CUTLER
06/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 39571

MEETING MINUTES

Wellstat Therapeutics Corporation
Attention: Michael Bamat, PhD
Vice President, Research and Development
930 Clopper Road
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for uridine triacetate (PN401).

We also refer to the meeting between representatives of your firm and the FDA on August 21, 2013. The purpose of the meeting was to discuss Wellstat's plan for commercial manufacturing and process validation for the uridine triacetate drug substance and the drug product (Uridine Traicetate Oral Granules) and to determine if plans are adequate to support a 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) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	CMC, EOP2
Meeting Date and Time:	August 21, 2013, 11:00 -12:00PM (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 39571
Product Name:	uridine triacetate (PN401)
Indication:	Treatment of 5-FU overdosage (b) (4)
Sponsor/Applicant Name:	Wellstat Therapeutics Corp.
Meeting Chair:	Ali Al Hakim, Branch Chief, ONDQA
Meeting Recorder:	Jewell Martin, Project Manager, ONDQA

FDA ATTENDEES
Ali H Al Hakim, PhD, Branch Chief, ONDQA
Haripada Sarker, PhD, CMC Lead, ONDQA
Joyce Crich, PhD, CMC Reviewer, ONDQA
John Duan, PhD, Biopharmaceutics Reviewer, ONDQA
David McGuinn, PhD, Pharmacologist, DHOT
Skarupa, Lisa, Regulatory Project Manager, DOP 1
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager, ONDQA

SPONSOR ATTENDEES
Michael Bamat, PhD, Vice President, Research & Development, Wellstat
(b) (4) Chemistry and Manufacturing Consultant to Wellstat
Joan Helton, Quality Assurance, Wellstat
Jeffrey Miller, Ph.D., Director, Analytical Research & Development, Wellstat
Rita O'Neil, Ph.D., Senior Director, Regulatory Project Management, Wellstat
Reid von Borstel, PhD, Vice President, Discovery Research, Wellstat
Nadine Wohlstadter, President, Wellstat

1.0 BACKGROUND

In a letter dated June 10, 2013, Wellstat Therapeutics Corporation requested a Type B, End-of-Phase 2 (EOP 2), Chemistry, Manufacturing, and Controls (CMC) meeting. The purpose of this meeting is to discuss Wellstat's plan for commercial manufacturing and process validation for the uridine triacetate drug substance and the drug product (Uridine Traicetate Oral Granules) and to determine if plans are adequate to support a NDA. The Office of New Drug Quality Assessment (ONDQA) issued a Meeting Granted letter to Wellstat Therapeutics Corporation on June 18, 2013. [redacted] (b) (4) submitted their meeting background package on July 22, 2013. The Agency issued preliminary responses on August 15, 2013. On August 20, 2013, Wellstat provided additional comments and requested that the meeting be focused on Questions 3, 6, and 7 and the portion of FDA's Additional Comment #2 relating to compatibility with intended foods in which drug product will be mixed, with limited discussion as necessary regarding the remaining questions.

2.0 DISCUSSION

Question 1:
Does the Division agree with the designation of [redacted] (b) (4) as the regulatory starting material and to Wellstat's receipt specifications?

FDA Response to Question 1:
In addition to your proposed specification [redacted] (b) (4) as a regulatory starting material, consider providing the following additional information:

[redacted] (b) (4)

Alternately, you may consider providing the CMC information [redacted] (b) (4) in DMF with Letter of Authorization (LOA) as appropriate. Final evaluation of [redacted] (b) (4) CMC information will be made during NDA review.

Meeting Discussion:
No further discussion required.

Question 2:
Does the Division agree that the specifications for uridine triacetate drug substance are justified and acceptable?

FDA Response to Question 2:
Your justifications for the proposed specifications for impurities in uridine triacetate drug substance appear appropriate.

The proposed specifications for [redacted] (b) (4) or any individual metal appear appropriate. However, given the total proposed dose of 40 g/day of oral uridine triacetate, the proposed specifications for [redacted] (b) (4) in the uridine triacetate drug substance would result in patient

exposures that exceed emerging standards for Permitted Daily Exposures (PDE). In your NDA submission, lower the specifications for [redacted] (b) (4) based on a total daily dose of uridine triacetate of 40 g/day to result in PDE's within emerging standards, or provide an adequate justification for the propose specifications. Your justification should include safety assessments for the specific risks involved for each element in the context of the total duration of exposure (5 days) and the specific indication for use being proposed.

The final acceptability of your specifications and supporting justifications will be determined only after we review your NDA submission.

For additional information, refer to the following guidance documents:

ICH Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substance and New Drug Products: Chemical Substances.

ICH Guidance on Q3A Impurities in New Drug substances

Meeting Discussion:
No further discussion required.

Question 3:
Does the Division agree with the stability plan for the drug substance validation batches?

FDA Response to Question 3:
No. At NDA submission, a minimum of twelve (12) months of stability data under long term storage conditions and a minimum of six (6) months of stability data under accelerated conditions for at least three primary batches should be included in the NDA. Refer to *ICH Q1A(R2) Stability Testing of New Drug Substances and Products* for information on sufficient stability data package for a registration application.

Meeting Discussion:

See August 20, 2013 comments from Wellstat in Section 5: Handouts and Attachments.

The Agency reiterated response and strongly recommends submitting 12 months of stability data with the NDA. The Sponsor inquired about submitting rolling submission with 9 months of stability data. The sponsor was intending on submitting the NDA at the end of March. Twelve (12) months of stability would not be available until June 2014. The Agency stated that the acceptance of a rolling submission would be determined by the clinical division.

Question 4:
Does the Division agree that the drug product process validation plan is acceptable?

FDA Response to Question 4:
The FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. The sponsor has provided a high-level overview of a proposed process validation plan. This plan should be (b) (4)

The FDA does not approve process validation approaches, protocols, or a number of specific batches used in process validation studies. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection of your manufacturing facility(ies). The product design and the suitability of manufacturing processes will be evaluated during an on-site inspection. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

For more information, please refer to the Guidance for Industry, Process Validation: General Principles and Practices (January 2011).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Meeting Discussion:
No further discussion required.

Question 5:
Does the Division agree that the specifications for drug product are justified and acceptable?

FDA Response to Question 5:
Your justifications for the proposed specifications for related substances in uridine triacetate drug product appear appropriate. The final acceptability of your specifications and supporting justifications will be determined only after we review your NDA submission.

In Addition, include a test for Particle Size Distribution, tests for degradation products (each specified identified degradation product, each specified unidentified degradation product, any unspecified degradation product, and total degradation products). Refer also to response to Question 7.

For additional information, refer to the following guidance documents:
ICH Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substance and New Drug Products: Chemical Substances.

ICH Guidance on Q3B Impurities in New Drug Products

Meeting Discussion:
No further discussion required.

Question 6:
Does the Division agree with the drug product registration stability plan and that the available stability data for the validation drug product batches at the time of filing as described above, supported by historical drug product batch stability data, are acceptable?

FDA Response to Question 6:
No. Refer to Agency's response to Question 3.

Meeting Discussion:
No further discussion required at the meeting, see meeting discussion from question 3.

Question 7:
Does the Division agree that with the classification of uridine triacetate as a BCS Class (b) (4), the use of a two point dissolution acceptance criteria with (b) (4)% at (b) (4)minutes and (b) (4)% at (b) (4) minutes is justified, and that the dissolution method is acceptable?

FDA Response to Question 7:
There is insufficient data in the meeting package to reach a conclusion on the acceptability of your proposed dissolution method and acceptance criteria.

We have the following comments regarding the biopharmaceutics information (not limited to) that should be provided in your NDA supporting your dissolution specifications:

1. Dissolution Test: Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

a. **Solubility profile data for the drug substance covering the physiologically pH range;**
b. **Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;**
c. **Provide the complete dissolution profile data (individual, mean, SD, profiles) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and**
d. **Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);**
e. **Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables); In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.**
f. **Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).**

2. **Dissolution Acceptance Criteria: For the selection of the dissolution acceptance criteria of your product, the following points should be considered:**

   a) **The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).**
   b) **Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).**
   c) **For low solubility drug substances, a two-point criterion is recommended. These time points should cover the early-middle and late stages of the release profile. The last time point should be the time point where at least 80% of drug has release. If the maximum amount release is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.**
   d) **Data supporting the low solubility across the physiological pH should be submitted.**

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

Meeting Discussion:

See August 20, 2013 comments from Wellstat in Section 5: Handouts and Attachments.

FDA stated that 2 point specification would be acceptable however; the time points selected should be based on the data. Without looking at the data FDA cannot confirm that 15 min and 60 min would be adequate. FDA indicated that when the NDA is submitted the sponsor provide the individual data for the clinical and the 3 registration stability batches.

FDA stated that (b) (4) may affect the formulation performance. The sponsor stated that they have data to support bioequivalence with or without (b) (4). FDA emphasized that the clinical formulation and the to-be-marketed formulation should be properly linked. The linkage can be established by a bioequivalence study or by dissolution profile comparison depending on the difference between the two formulations.

FDA Additional Comments:

1. **Note that your statement "In accordance with FDA's Biopharmaceutics Classification System (BCS) Guidance, uridine triacetate drug product is classified as a Class (b) (4) immediate release solid oral dosage form for which bioequivalence may be assessed based on in vitro dissolution tests" is not accurate. Bioequivalence may be assessed based on in vitro dissolution test for those drug products for which there is an acceptable IVIVC or the drug substance is classified as BCS class 1 and the drug product is considered rapidly dissolving.**

2. **Provide complete information on container closure system for the proposed drug product; specify whether if there is an overfill for the proposed drug product and the related acceptance limit; conduct compatibility and stability studies of the proposed drug product with the intended foods to be mixed with prior to administration.**

Meeting Discussion:

See August 20, 2013 comments from Wellstat in Section 5: Handouts and Attachments.

The Agency stated that this would be a review issue and that a determination will be after the NDA was submitted.

3.0 POST MEETING COMMENTS

1. **Please collect complete dissolution profile data at 15, 20, 30, 45, and 60 minutes (n=12) for the bio-batches (batches used in the PK and clinical studies) and the registration stability batches. The selection of your proposed dissolution acceptance criteria should be based on these data.**

2. **Please conduct the compatibility and stability studies of the proposed drug product with the intended foods or/and beverages that the drug product will be mixed, taking into consideration the effect of pH on stability and the dissolution prior to its administration.**

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

5.0 ATTACHMENTS AND HANDOUTS

Handout provided by Wellstat on August 20, 2013, see attached.

6.0 CONCURRENCE

[See appended electronic signature page]

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{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

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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.

/s/

JEWELL D MARTIN
09/09/2013

ALI H AL HAKIM
09/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 039571

MEETING MINUTES

Wellstat Therapeutics Corporation
Attention: Michael K. Bamat, Ph.D.
Vice President, Research & Development
930 Clopper Road
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for uridine triacetate (PN401).

We also refer to the meeting between representatives of your firm and the FDA on August 15, 2013. The purpose of the meeting was to discuss topics as you prepare for the NDA submission and to discuss the proper studies and analyses for uridine triacetate in the treatment of 5-FU overdosage (b) (4).

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, Regulatory Project Manager at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Phase 2 (medical, statistical, clinical pharmacology)
Meeting Date and Time:	August 15, 2013 from 10 am to 11am
Meeting Location:	White Oak Campus Bldg 22 Conference Room 1315
Application Number:	IND 039571
Product Name:	uridine triacetate (PN401)
Indication:	treatment of 5-FU overdosage (b) (4)
Sponsor/Applicant Name:	Wellstat Therapeutics Corp.
Meeting Chair:	Patricia Cortazar, M.D., Lead Medical Officer, DOP1
Meeting Recorder:	Lisa Skarupa, Project Manager, DOP1

FDA ATTENDEES

Robert Justice, M.D., Division Director, DOP1
Amna Ibrahim, M.D., Deputy Division Director, DOP1
Tamy Kim, PharmD, Associate Director of Regulatory Affairs, OHOP
Anthony Murgo, M.D., M.S. FACP. Associate Director for Regulatory Science, OHOP
Patricia Cortazar, M.D., Lead Medical Officer, DOP1
Gwynn Ison, M.D., Medical Officer, DOP1
Todd Palmby, Ph.D., Toxicology Supervisor, DHOT
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, OTS/OCP/DCPV
Sarah Schrieber, Ph.D., Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Sarah Dorff Ph.D., Senior Staff Fellow, Division of Pharmacometrics, OTS/OCP
Jingyu Yu, Ph.D., Visiting Associate, Division of Pharmacometrics, OTS/OCP/DPM
Rosane Charlab Orbach, Ph.D., Interdisciplinary Scientist, OTS/OCP/DCPV
Shenghui Tang, Ph.D., Lead Mathematical Statistician, DB5
Lijun Zhang, Ph.D., Mathematical Statistician, DB5
Lisa Skarupa, Project Manager, DOP1

SPONSOR ATTENDEES

Michael Bamat, PhD, Vice President, Research & Development, Wellstat
(b) (4) Consulting Pharmacokineticist to Wellstat
Joan Helton, BA, CCRP, Quality Assurance
Rita O'Neil, Ph.D., Senior Director, Regulatory Project Management, Wellstat
(b) (4), Consulting Statistician to Wellstat
Robert Tremmel, PharmD, Clinical Safety Manager, Wellstat
Reid von Borstel, PhD, Vice President, Discovery Research, Wellstat
Nadine Wohlstadter, President, Wellstat

1.0 BACKGROUND

The current meeting package is for a Type B EOP2 meeting. Wellstat is developing uridine triacetate, an orally active prodrug of the pyrimidine nucleoside uridine, (b) (4) to treat patients at risk of excess 5-FU toxicity due to overdosage (b) (4). Wellstat intends to file a 505(b)(1) NDA to the FDA and will request Priority Review. FDA granted orphan drug designation for uridine triacetate in May 2009, " (b) (4) in the treatment of 5-FU poisoning".

The proposed indication is as follows:
" (b) (4) **(uridine triacetate) Oral Granules is indicated** (b) (4)

An EOP2 meeting occurred on 7/6/10. Subsequent correspondences have also occurred between the Sponsor and FDA. An expanded access program was opened in August 2011 (EAP 401.10.001), such that uridine triacetate is provided for compassionate use, in patients at risk for excess 5FU toxicity due to overdose (b) (4)

According to the meeting package, a total of 97 patients have been treated with uridine triacetate, with the following breakdown:

- 29 adult patients on EAP 401.10.001
- 49 adults on SPIs
- 15 adults ex-US
- 3 pediatric on SPIs
- 1 pediatric ex-US

There is also mention in the meeting package that "supportive efficacy data from Phase 1, Phase 2, and Phase 3 studies in which high-dose 5FU enabled by uridine triacetate was administered weekly will also be included in Module 2.7.3". It is unclear how this information will contribute to the NDA (b) (4)

Wellstat previously agreed to conduct 2 new genotoxicity studies, a new reproductive toxicity study, and a battery of *in vitro* drug metabolism studies. FDA also previously requested that the Sponsor evaluate QT/QTc interval prolongation in patients taking uridine triacetate, and the meeting package states that the Sponsor intends to submit this in 3rd quarter 2013.

Wellstat provided Pre-Meeting comments to the FDA responses and have additional questions for the Agency. During the meeting with the Sponsor, FDA stated that there was not enough time to review the additional material and the additional questions could not be answered (see attachment).

2.0 DISCUSSION

Regulatory

Question 1: *Does the Division agree with the proposed wording of the orphan-designated indication: "Uridine triacetate is indicated* [redacted (b) (4)] *?*

FDA Response to Question 1:
In general, the indication will reflect the population studied and will be a review issue. Based upon our current assessment, the proposal for an indication in patients who have [redacted (b) (4)] **as identified by the Sponsor, is problematic. See additional responses in Question 6.**

Wellstat Pre-Meeting comments received via email on August 14, 2013: The Sponsor provided comments (see attached document) and required no further meeting discussion.

In CTD Module 1.3.4 "Financial Disclosure", Wellstat proposes to provide Form FDA 3454 along with a list of investigators (Name, Address, Telephone, Fax) who participated in the Expanded Access Protocol (EAP) 401.10.001 and a list of investigators who treated patients at risk of excess 5-FU toxicity due to overdosage [redacted (b) (4)] with uridine triacetate under Single Patient INDs (SPIs).

Question 2: *Does the Division agree with this proposal?*

FDA Response to Question 2:
This seems acceptable, but more information may be requested during review of the NDA. You will be required to submit the Financial Disclosures (Form 3454) for all investigators in the Expanded Access Protocol and the SPIs.
Link:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf

Wellstat Pre-Meeting comments received via email on August 14, 2013: The Sponsor acknowledged FDA's response and required no further meeting discussion.

Clinical Efficacy

Question 3: *Does the Division concur that an Integrated Summary of Efficacy (ISE) in CTD Module 5 is not needed, and that the clinical summary in CTD Module 2.7.3 incorporating data from EAP, SPI and ex-US patients treated with uridine triacetate* [redacted (b) (4)] *along with supportive efficacy data from the Phase 1, 2, and 3 studies of high-dose 5-FU enabled by uridine triacetate can be used to present the summary of efficacy?*

FDA Response to Question 3:
No. You should submit all clinical data that will support this NDA in Module 5. You should also submit an ISE in Module 2. Please clarify what Phase 1-3 studies you are referring to.

Meeting Discussion to Question 3:
The Agency clarified that the Expanded Access Study report should be submitted under Module 5 and the pooled data from the SPIs, ex-US cases, and patients from the EAP be submitted under Module 2.

Question 4: *Does the Division agree with the use of historical control groups to support the efficacy of uridine triacetate* (b) (4) *to treat patients at risk of excess 5-FU toxicity due to overdosage* (b) (4)*?*

FDA Response to Question 4:
Your proposal is very problematic. Due to the lack of information on 5FU dosing, baseline characteristics, and the small number of patients in the historical control group, the control group may not be comparable to the experimental group. This will be a review issue.

Meeting Discussion to Question 4:
The Agency stated that the acceptability of the historical control groups will be a review issue. The Agency suggested that the submitted data should have complete information from the historical control groups. The Sponsor should also submit information on the methodology used for collecting data from the historical control groups.

Question 5: *With the understanding that uridine triacetate will be used to treat pediatric patients under rare circumstances, does the Division agree that Wellstat should include guidance for pediatric dosing in the package insert?*

FDA Response to Question 5: Possibly, depending on the adequacy of the data.

Wellstat Pre-Meeting comments received via email on August 14, 2013: The Sponsor acknowledged FDA's response and required no further meeting discussion. Please also refer to the attached document to the Sponsor's responses to FDA's Additional Comment.

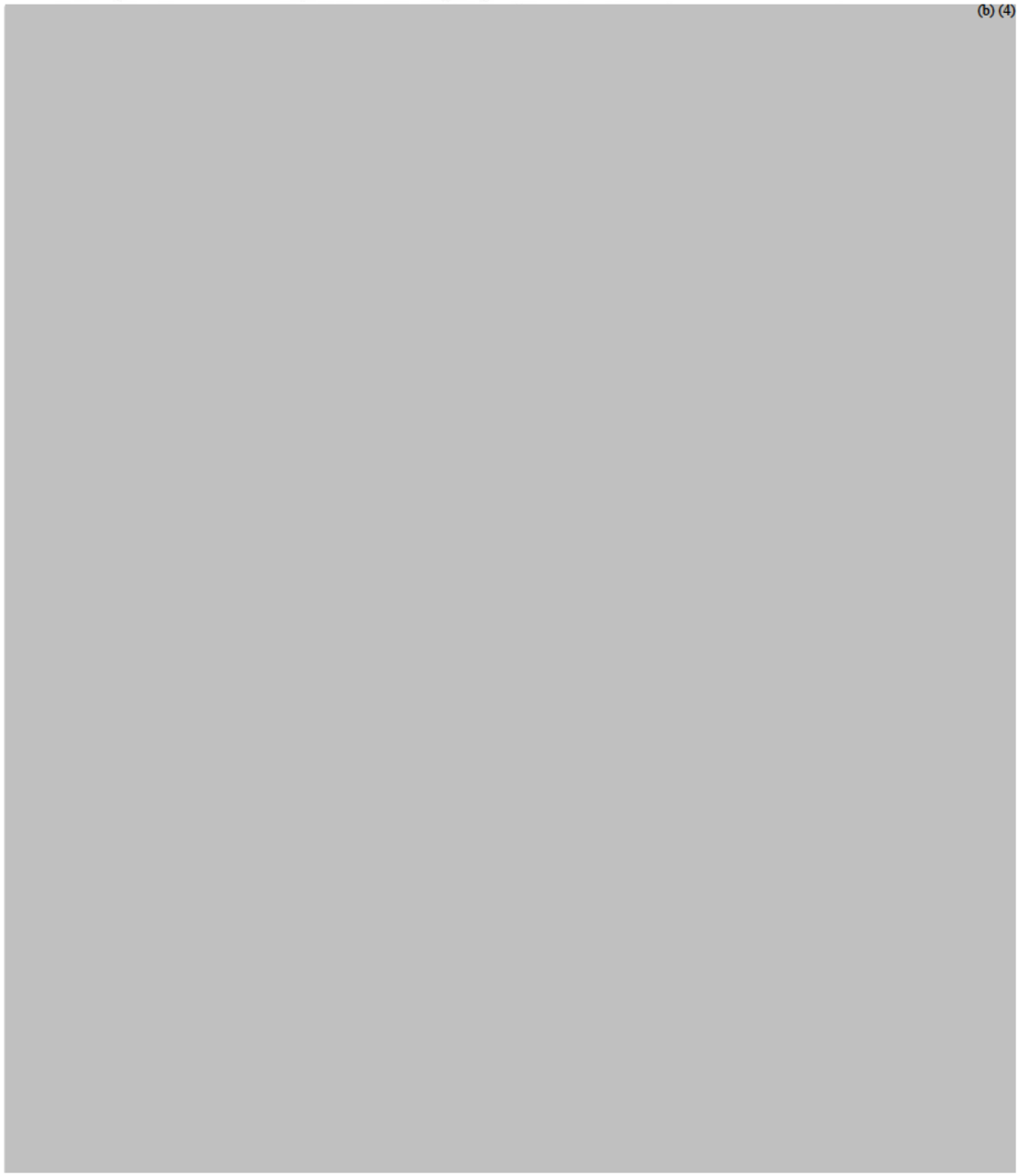
Question 6: *Does the Division agree with the criteria for identifying* (b) (4) *patients at risk of excess 5-FU toxicity* (b) (4)*?*

FDA Response to Question 6:
No, we do not agree with your definition of (b) (4) **patients.**
We also have the following additional comments about the proposed criteria:

- **We note that, with the exception of the first method listed, "*early onset* (b) (4) *to 5FU toxicity such as G3-4 diarrhea, G3-4 mucositis, G3-4 neutropenia, G3-4 neurological toxicity, or severe, sudden onset cardiotoxicity*", none of the other methods for identifying patients with** (b) (4) **are widely available or routinely used by clinicians. The likelihood of finding a predictive allele upon testing patients**

who could be at risk for (b) (4) and most patients who suffer G3-4 5FU-related toxicity (b) (4). It is also known that patients who lack one of the high-risk variants may still suffer G3-4 5FU-related toxicity. Therefore, most patients are likely to be Group 1 patients

(b) (4)



Meeting Discussion to Question 6: The Agency did not have sufficient time to review the new information emailed the day before the meeting, regarding an updated (b) (4)

patient definition. The Sponsor can provide the data on this population at time of NDA submission and its acceptability will be a review issue.

Clinical Safety

For the summary of clinical safety, the primary safety population is proposed to be patients enrolled in EAP 401.10.001, SPI and ex-US patients (N=97 as of Jan 2013). Supporting safety information will be provided from five (5) Wellstat-sponsored clinical trials of high- dose 5-FU enabled by uridine triacetate (N=288), and from monotherapy studies of uridine triacetate in healthy subjects (N=46) and in non-cancer indications (N=83). In total, safety information will be provided from a grand total of 514 patients (as of Jan 2013; Table 18).

The summary of clinical safety is planned to consist of individual and, where possible, side- by-side tabulations of safety data from EAP, SPI and ex-US patients and from five (5) studies of high-dose 5-FU enabled by uridine triacetate. These Phase 1, 2 and 3 clinical studies involved weekly administration of high-dose 5-FU (escalated to new MTDs based upon 5-FU-induced toxicities) with the purpose of maximizing the anticancer efficacy of 5-FU with acceptable toxicity. In contrast, the patients enrolled in EAP 401.10.001, SPI and ex- US patients were treated with uridine triacetate (b) (4) in an emergency setting with the goal of preventing or minimizing toxicities after a single potentially life-threatening 5-FU overexposure.

Given the substantial differences between the EAP and the Phase 1, 2, and 3 studies of high- dose 5-FU enabled by uridine triacetate as well as the studies in healthy subjects and in non- cancer indications, no Integrated Summary of Safety (ISS) or pooling of safety data among studies is planned for the NDA submission. These differences include the following:

- The treatment evaluated in the Phase 1, 2, and 3 studies was the combination of high- dose 5-FU and uridine triacetate (not uridine triacetate alone) whereas the treatment evaluated in EAP, SPI / ex-US patients is uridine triacetate itself. For example, adverse events in the Phase 1, 2 and 3 studies were assessed and attributed to the combination while in the EAP/SPI and ex-US patients adverse events are assessed and attributed to 5-FU or uridine triacetate separately.
- Most EAP, SPI and ex-US patients received chemotherapy regimens such as FOLFOX or FOLFIRI that include other cytotoxic drugs in addition to 5-FU, whereas the study treatments in the Phase 1, Phase 2 and Phase 3 studies were either "high-dose 5-FU enabled by uridine triacetate" or "high-dose 5-FU enabled by uridine triacetate + leucovorin".
- EAP/SPI/Ex-US patients were treated with a single course of uridine triacetate following a single overexposure to 5-FU compared to weekly administration of very high doses of 5-FU enabled by uridine triacetate in the Phase 1, 2 and 3 patients.

Summaries of supporting monotherapy safety studies will also be included in the summary of clinical safety in CTD Module 2.7.4. These include Phase 1 pharmacokinetic studies in healthy subjects and Phase 2 studies in patients with diabetic neuropathy. Supportive safety information with uridine triacetate (without 5-FU) is also available from long-term compassionate use programs in patients with mitochondrial and metabolic disorders. In these programs, 22 children and 8 adults received uridine triacetate at dosages ranging from 33 mg/kg/day to 19.8 grams/day for more than 17 years without evidence of clinical toxicity.

The SAS datasets to be provided in the NDA will all be legacy (non-CDISC) with the exception of EAP 401.10.001 for which CDISC SAS datasets will be provided.

The length of the clinical summary of safety is anticipated to be less than 400 pages and thus is planned to be placed in CTD Module 2.7.4 and cross-referenced in Module 5.3.5.3.

A tabular summary of Wellstat's proposal for evaluating the clinical safety of uridine triacetate in the NDA is presented in Table 18. This list is inclusive of all clinical studies that will be included in the future NDA.

Table 18: Proposal for Evaluating the Clinical Safety of Uridine Triacetate

Clinical Study	Uridine Triacetate Dosing Regimen	No. of Patients *
PRIMARY SAFETY POPULATION (N = 97)**		
Antidote – Risk of Excess 5-FU Toxicity Expanded Access Protocol 401.10.001	10 g q6h · 20 doses	97**
SUPPORTING SAFETY POPULATIONS (N = 417)		
Studies in Cancer Patients [with 5-FU]		
Phase 1: PX401.MSK.1	3.3, 6, 6.6, or 9.9 g q6h · 10 doses	38
Phase 1: 401.08.IDD	6 g q8h · 8 doses 6 g q2h · 3 doses · 6 g q6h · 12 doses	10 13
Phase 1: 401.09 ***	6 g q8h · 8 doses	48
Phase 2: SWOG S9915 ****	6 g q8h · 8 doses	57
Phase 3: 401.00.001	6 g q8h · 8 doses	122
Studies in Healthy Subjects [no 5-FU]		
Phase 1: 401.10.PKL.01	6 g (single dose crossover)	6
Phase 1: PX401.07.001	6 g (single dose crossover)	20
Phase 1: PX401.07.002	6 g (single dose crossover)	20
Studies in Other Indications [no 5-FU]		
Phase 2: 401.97.201 (diabetic neuropathy)	4 or 8 g/day (2 or 4 g BID)	38
Phase 2: 401.97.202 (diabetic neuropathy)	4 g/day (2 g BID)	15
Compassionate Use (mitochondrial neurometabolic diseases)	33 mg/kg/day to 19.8 g/day	30
	GRAND TOTAL:**	**514 ****

* The number indicated is inclusive of all patients who received at least one dose of uridine triacetate
** As of January 2013, includes SPI and ex-US patients (expected to increase by the time of NDA filing)
*** Twenty-eight (28) of the 48 patients in this study also received leucovorin (IV, 500 mg/m^2)
**** A 58th patient was enrolled, but did not receive uridine triacetate. The treated patients in this study also received leucovorin (IV, 500 mg/m^2)

Question 7: *Does the Division agree with Wellstat's proposal for summarizing the clinical safety data in Module 2.7.4 (< 400 pages in length; cross-referenced in Module 5.3.5.3) as individual study summaries as well as (where possible) side-by-side tabulations of safety data from EAP, SPI and ex-US patients and from the five (5) studies of high-dose 5-FU enabled by uridine triacetate, with the primary safety population consisting of EAP, SPI and ex-US patients (N=97 as of January 2013)?*

FDA Response to Question 7:
You should provide a comprehensive report of the safety data. Data from the EAP should comprise the primary safety data, with all other data (SPIs and ex-US patients) being secondary.

Wellstat Pre-Meeting comments received via email on August 14, 2013:
Sponsor provided comments and required no further meeting discussion. Wellstat will provide a comprehensive report of the safety data and as FDA recommends, data from EAP cases will comprise primary safety data, and data from SPI and ex-US patients will be secondary. Please refer to the Sponsor's attached document for a revised list of efficacy, safety and clinical pharmacology studies to be included in the NDA.

Question 8: *Does the Division agree that no Integrated Summary of Safety (ISS) or pooling of safety data are warranted, given the substantial differences between the EAP/SPI/ex-US patients and the studies in healthy subjects, studies in non-cancer indications and studies of high dose 5-FU enabled by uridine triacetate?*

FDA Response to Question 8:
Yes.

Wellstat Pre-Meeting comments received via email on August 14, 2013:
The Sponsor acknowledges FDA's response and required no further meeting discussion.

Question 9: *Does the Division agree with Wellstat's plan for providing study reports/literature articles/synopses, case report forms and datasets in the NDA (RE: Table 12, Table 13 and Table 14?*

FDA Response to Question 9:
Yes, however, the main focus in our review will be on the safety and efficacy seen in patients treated on the Expanded Access Protocol (EAP) 401.10.001.
It is not clear how the data from the other studies and literature reports will contribute to the application overall, given that the dosing and/or formulation in these other studies was different from the regimen proposed for approval. In addition, the amount of information available on patients from the other studies and the literature will be variable, with considerable missing data.

Meeting Discussion to Question 9: The Sponsor asked if the studies in the Tables B and C (see attachment) will be enough to support the NDA submission. The Agency responded that although the new data has not been reviewed by the Agency, it appears acceptable. Final acceptability of the studies will be a review issue.

Clinical Pharmacology

Question 10: Does the Division agree with the proposals regarding the planned population pharmacokinetic analyses as described in Section 6.5?

FDA Response to Question 10:

The population PK analysis plan may be acceptable. However, a two-stage approach requires individual's dense PK sampling, we recommend you use nonlinear mixed-effects modeling approach as a back-up plan when rich PK data is not available.

Your proposal to submit an excel spreadsheet for the population analysis also appears acceptable. We would like to also refer you to the following pharmacometric data and models submission guidelines at: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm.

Wellstat Pre-Meeting comments received via email on August 14, 2013: The Sponsor provided comments, please see attached document. The Sponsor required no further meeting discussion.

Additional FDA Comments:

1. It is not clear why a BSA-adjusted dosing for pediatrics (6.2 g/m, q6h × 20 doses) was proposed to match adult's exposure without evidence to support that there is clear relationship between the PK parameters and BSA.

2. Examining the role of (b) (4) mutations and their correlation with (b) (4) activity, the influence of additional genes related to 5-FU toxicity, the contribution of different patient populations (e.g. ethnicity, gender, concomitant therapy) and the role of non-genetic and epigenetic factors on the toxicity response to 5-FU may be considered for a more comprehensive attempt to identify (b) (4) subjects.

3. We note that you have a GLP embryo-fetal toxicity study in rats ongoing with uridine triacetate. We remind you that as per ICH S9 recommendations, embryo-fetal toxicity studies should be conducted in two species to support a marketing application, unless a study is positive for embryo-fetal lethality or teratogenicity, in which case a confirmatory study in a second species is not warranted.

Meeting discussion: **FDA agreed that an embryo-fetal toxicity study in a single species is acceptable to support an NDA submission for the proposed indication to treat patients at risk of 5-FU toxicity.**

Additional FDA Comments:
FDA stated that another path to request drug access for multiple patients is using an intermediate size patient population access IND. This approach allows cost recovery option. For additional information, follow the ling of the EAP Guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf.
And the draft Guidance for cost recovery:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351264.pdf.

3.0
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 following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

DATA STANDARDS FOR STUDIES
CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a 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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

See attached document emailed on Wednesday August 14, 2013 providing Wellstat's responses to FDA preliminary comments.

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FOOD AND DRUG ADMINISTRATION
OFFICE OF ONCOLOGY DRUG PRODUCTS

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705-1266

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TO: Wellstat Therapeutics Corporation
Michael K. Bamat, Ph.D.
Vice President, Research & Development
930 Clopper Road
Gaithersburg, MD 20878
Emailed to: mbamat@welstat.com
FROM: Lisa Skarupa, RN, MSN, Regulatory Project Manager
Date: June 4, 2012
Total number of pages: 4
Re: IND 039571, Sponsor requested comments on their submission dated November 30, 2011 SN 0226: "Information Amendment: Sponsor's response to FDA's request for additional Nonclinical and Clinical Studies with uridine triacetate to support a future NDA"

Dear Dr. Bamat:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for uridine triacetate (2', 3', 5' –tri-0-acetyluridine; PN401).

We also refer to your amendment dated November 30, 2011, containing additional nonclinical and clinical information which were requested by FDA during the End-of-Phase2 meeting held on July 6, 2010.

We have the following comments and recommendations. If there are more comments and recommendations from the clinical team, I will forward it to you in a separate communication.

Non-Clinical comments:
Your proposal to conduct two in vitro genotoxicity studies and a single GLP reproductive toxicity study in the rat appears at this time to be sufficient to support the submission of an NDA package. Nevertheless, we can only determine the adequacy of the resulting data from these studies to support approval of your product after we receive and review the final study reports in the original NDA submission.

Clinical Pharmacology comments:

1. Your *in vitro* drug-drug interaction studies with uridine triacetate to evaluate the potential for the drug to inhibit or induce CYP450 enzymes or to affect P-gp substrate and inhibitor transport appear appropriate. The final determination will be made at the NDA review. Please refer to the latest Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf for more information.

2. We will conduct a complete review of your ADME literature justification of uridine triacetate at time of your NDA submission. We encourage you to conduct population pharmacokinetic analysis to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of uridine triacetate in humans. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf.

3. We will comment on your QT evaluation study proposal once it is submitted.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. If your IND is in eCTD format, submit 7-day reports electronically in eCTD format. If your IND is not in eCTD format, you may submit 7-day reports by telephone or fax;

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, please do not hesitate to contact me, Regulatory Project Manager, at 301-796-2219.

Sincerely,
Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
Division of Oncology Products 1
Center for Drug Evaluation and Research

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/s/

LISA M SKARUPA
06/04/2012

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/s/

LISA M SKARUPA
08/20/2013

PATRICIA CORTAZAR
08/22/2013

QUESTIONS

1. There is a strong pharmacologic rationale, considerable preclinical data, and considerable human experience for the use of uridine triacetate (b) (4) The clinical outcomes data are compelling and seem to clearly demonstrate the benefit of uridine triacetate at the proposed dose and schedule in patients that have been overdosed with 5-FU. Most (27 of 35) received overdoses that would be predicted to result in death. The safety and efficacy of uridine in reducing or preventing 5-FU toxicity is directly and fully supported by the clinical data from Wellstat's phase 1, 2 and 3 clinical studies in which uridine triacetate permitted intentional 5-FU dose escalation. Uridine triacetate has a benign safety profile preclinically and clinically. The pharmacology underlying both the safety and efficacy of uridine triacetate (b) (4) to 5-FU overexposure is well understood and clearly documented in the literature and by our studies.

   Wellstat would like to work with the Agency to understand how the existing clinical and preclinical data, along with any additional clinical data that might be collected under Protocol 401.10.001 (refer to SN0189 of IND 39,571), could best be assembled and presented to FDA to maximize the potential to meet the requirements for documentation of efficacy.

   Wellstat proposes that the available clinical efficacy and safety data, supported by animal data showing that 5-FU overdose has high and predictable mortality and the effect of uridine triacetate is self-evident, are sufficient to support an NDA filing for the proposed indication under the clinical regulations definition of an adequate and well-controlled study, 21 CFR 314.126(b)(2)(v).

Q. Does FDA agree that the available clinical and preclinical efficacy and safety data may be adequate to support an NDA filing for the proposed indication?

FDA response: We are concerned about the quality and adequacy of the data collected from Single Patient INDs. We recommend that you conduct a prospective trial to support the proposed indication.

The non-clinical studies you have done to date are inadequate to support the filing of an NDA. You will need to complete an *in vitro* mammalian genotoxicity assay (see ICH guidance S2). You will also need to complete two reproductive toxicology studies as specified by ICH S9.

Wellstat 7-2-10 response: Wellstat seeks clarification about FDA's concern on the quality and adequacy of the data collected from Single Patient INDs. As illustrated in the two sample case reports provided in the EOP2 meeting information package, Wellstat will carefully and thoroughly document the available data for each patient. We also intend to verify data with source data. In general, the data collected from the Single Patient INDs will likely be at least equivalent to the types and amount of data that will be collected under Wellstat's Protocol No.

401.10.001.

Overdose patients cannot be recruited and only present under emergency situations. Thus it is difficult to determine how many patients will have been treated under Wellstat's Protocol No. 401.10.001 by the time of NDA filing.

Wellstat would also like to discuss FDA's requirement for additional nonclinical studies to support the proposed indication, specifically, an in vitro mammalian genotoxicity assay, two reproductive toxicity assays [embryofetal toxicity studies in two species], and a safety pharmacology battery. All patients that will be treated with uridine triacetate (b) (4) will have already been exposed to an overdose of 5-fluorouracil (5-FU) which is a known genotoxin and teratogen. Uridine triacetate is immediately converted in animals and humans in vivo to uridine, which is an endogenous substance that is present in every cell in the body. There are no structural alerts for uridine which would suggest the potential for genotoxicity or teratogenicity, and in fact the two genotoxicity studies conducted to date have produced negative results. With respect to the safety pharmacology studies, the endpoints of these studies – respiratory, CNS, and cardiovascular – have already been assessed in 12-week GLP repeated dose toxicity studies in rats and dogs. There is no evidence that uridine triacetate has the potential to exert adverse effects to these organ systems. Uridine triacetate will be given as a single 5-day course of therapy to patients with life-threatening 5-FU toxicities.

Meeting discussion: In addition to data provided from SPIs, more structured information from the expanded access protocol should be submitted. The sponsor will submit a pre-NDA meeting request in about a year to discuss the results.

Q. If the available clinical and preclinical efficacy and safety data are not sufficient, we would like work with FDA to understand how Wellstat could document and present them to FDA in a manner that they might be reviewed and possibly meet FDA requirements for documentation of efficacy (especially considering that mortality resulting from 5-FU overdose is the key endpoint). Do you have recommendations how we can meet the Agency's requirements?

FDA response: See comments below about protocol for treatment of 5-FU overdose.

Meeting discussion: Per ICH S9, separate safety pharmacology studies are not required for marketing for drugs intended for cancer with life threatening disease as long as a thorough clinical examination is done in the pivotal general toxicology studies. FDA reiterates that the in-vitro mammalian genotoxicity study and reproductive toxicology studies are needed and the sponsor will submit information justifying their position.

2. 5-FU toxicity is primarily a function of the plasma AUC of 5-FU, and AUC values that result in toxicity (b) (4) patients or animals, as are the toxic AUCs in patients or animals with normal 5-FU clearance ((b) (4)). However, much lower doses of 5-FU are sufficient to achieve toxic exposure levels in (b) (4) subjects, and standard therapeutic doses of 5-FU can be lethal. Oral uridine triacetate reduces mortality in mice (b) (4) after administration of a normal therapeutic dose of

5-FU. Uridine triacetate is therefore likely to reduce 5-FU toxicity in (b) (4) patents if administered within an appropriate time window after 5-FU. Because of the ethical and practical obstacles to conducting clinical studies in patients (b) (4) Wellstat could conduct a new (GLP) preclinical efficacy study in mice (b) (4). This study could extend the considerable body of evidence already in hand that uridine triacetate reduces 5-FU toxicity in humans and mice receiving high doses of 5-FU to the situation of overexposure at standard doses caused by clearance deficits.

While Wellstat has considerable clinical efficacy data supporting the proposed indication, if the agency deems it appropriate and if the NDA can be filed more quickly with the currently available clinical data, Wellstat would be willing to have elements of the future NDA reviewed under Title 21 of the Code of Federal Regulations (CFR) Part 314, Subpart I "Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible" (the "Animal Rule"; Sections 314.600 and 314.610). An outline for a proposed efficacy study in mice is provided in Appendix D. Of note, the endpoint of the proposed animal efficacy study, survival, is the same as the desired benefit in humans. In addition, the mechanisms by which 5-FU produces toxicity, and by which uridine triacetate reduces 5-FU toxicity, are sufficiently well characterized in mice for predicting the response in humans. Other common laboratory species are not suitable; rats primarily degrade rather than utilize uridine, and dogs are uniquely susceptible to rapid-onset lethal 5-FU neurotoxicity after overdoses.

Q. If FDA does not concur that clinical and preclinical data obtained to date are sufficient to support an NDA filing for treating patients at excess risk of 5-FU toxicity (b) (4) then does FDA agree that in conjunction with the clinical data, that elements of the future NDA can be reviewed under CFR Part 314 "Applications for FDA Approval to Market a New Drug", Subpart I "Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible", Section 314.610 "Approval based on evidence of effectiveness from studies in animals"?

FDA response: No. The Animal Rule is limited to medical countermeasures (MCM; drugs & biologics) against chemical, biological, and radiologic/nuclear threats (of terrorist or military source). The Animal Rule does not apply to other drugs. You should consider alternative approaches. Nevertheless, non-clinical studies of rescue of 5FU overdose may be supportive of your application.

Also, it is not clear why patients who are at excess risk of 5-FU toxicity (b) (4) are receiving 5-FU (b) (4).

3. As of 10 April 2010, 35 patients overdosed with 5-FU have been treated under emergency use provisions with uridine triacetate (most of these under Investigator Sponsored Single Patient INDs) using the regimen proposed in Protocol 401.10.001.[1] Wellstat has the available data from these patients, and is preparing individual case reports to include in Module 5 of the NDA. Wellstat intends to transcribe this information to case report forms (CRFs) and to

[1] Note that by the time of our application, the number of emergency use cases may increase.

verify the source data prior to issuing the final reports. Two examples of draft case reports are attached in Appendix C.

Wellstat proposes to present the data from these patients, along with the data from any additional patients that might be enrolled in Protocol 401.10.001, in Module 2.7 of the NDA as a case series with a historical control group. The historical control group will consist of data from the published literature and other databases (e.g., FDA MAUDE) from patients who received a 5-FU dose and infusion rate predicting a high likelihood of death from 5-FU toxicity, but who received only supportive care (no uridine triacetate) to treat their overdose. Efforts will be made to match the historical control and uridine-triacetate treated groups as closely as possible with respect to demographics and the dose of 5-FU to clearly illustrate the marked increase in survival in uridine triacetate-treated patients.

Q. Is Wellstat's proposal for documenting data from the Investigator Sponsored Single Patient INDs to support the efficacy claim for uridine triacetate-treated 5-FU overdosed patients as described above acceptable? Does FDA have other suggestions for how the data should be reported?

FDA response: See response to Question 1 and additional comments regarding expanded access protocol below.

4. The safety of uridine triacetate has been demonstrated to date in 452 subjects including 288 cancer patients (in combination with high-dose 5-FU), 46 healthy volunteers, 53 adults with diabetic neuropathy, 30 patients with mitochondrial and neurometabolic diseases, and (to date), 35 cases of 5-FU overdoses. No significant safety issues with uridine triacetate have been identified.

   There are currently no clinically effective (b) (4) 5-FU overdose; uridine triacetate will fulfill a serious unmet medical need. The mechanism of action for uridine triacetate does not involve inducing a condition that imposes an additional risk for the patients. Thus, Wellstat proposes that the available safety data in humans treated with uridine triacetate are adequate to support an NDA for the proposed indication.

   Q. Does FDA concur that the available clinical safety data with uridine triacetate are adequate to support an NDA for the proposed indication?

FDA response: See response to Question 1.

5. Pharmacokinetic information is available in humans treated with uridine triacetate, including the final clinical formulation, from Wellstat-sponsored clinical trials. The proposed dosage was carefully selected for safety and maximum efficacy.

   Wellstat proposes that the available clinical pharmacokinetic data are adequate to support the proposed indication and an initial NDA filing.

Q. Does the Division concur that the available pharmacokinetic data are adequate to support the proposed NDA?

FDA response: No. You will need to address the following issues and submit the data with the NDA submission:

1. **Conduct in vitro studies to determine whether uridine triacetate is a substrate, inducer and/or inhibitor of major cytochrome P-450 enzymes. Also assess whether uridine triacetate is a substrate and/or inhibitor of P-glycoprotein. These studies will help determine the potential for in vivo drug-drug interactions and the need for in vivo metabolic drug-drug interaction studies. For more information, please refer to the FDA draft guidance on Drug Interaction Studies at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf).**

Wellstat response 7-2-10: The metabolism of uridine has been well-characterized in humans receiving high-dose intravenous uridine, and there is no evidence that pathways other than those of normal pyrimidine metabolism (none of which are related to cytochrome P450) are involved. Uridine, like other natural nucleosides, is transported in and out of cells via nucleoside transporters unrelated to P-glycoprotein.

Meeting discussion: The sponsor can submit literature to address the DDI potential. However, adequacy of the information will be a review issue.

2. **The absorption, distribution, metabolism and excretion (ADME study) of uridine triacetate need to be addressed in humans. Depending on the outcome of the ADME study, the effect of hepatic and renal impairment on the PK of SCV-07 may need to be addressed. Alternatively, conduct both renal and hepatic impairment trials to address the dose adjustments in patients with such organ dysfunctions. Refer to the guidance's for industry entitled "Pharmacokinetics in Patients with Impaired Renal Function" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf and "Pharmacokinetics in Patients with Impaired Hepatic Function" at http://www.fda.gov/cder/guidance/3625fnl.pdf for more information.**

Wellstat response on 7-2-10: With respect to the need for an ADME study of uridine triacetate in humans, Wellstat proposes to conduct and present a thorough literature review of the absorption, distribution, metabolism, and excretion of uridine in the NDA. As mentioned earlier, uridine triacetate is immediately and completely converted to uridine following oral administration in animals and humans. No acetylated uridine is found in the circulation, as it is rapidly deacetylated by plasma and tissue esterases. The pharmacokinetics of uridine are well-understood in animals and humans (including high-dose intravenous uridine in patients), and an additional ADME study of uridine triacetate in humans would not add substantially to the existing body of knowledge. Uridine clearance is via normal pathways of pyrimidine catabolism and excretion, even after administration of multiple-gram quantities.

Meeting discussion: The sponsor can submit literature to support the ADME of the drug. However, adequacy of the information will be a review issue. The need for renal and hepatic impairment studies will depend on the ADME data.

3. Your clinical development program should include clinical evaluation of the potential for QT/QTc interval prolongation. In oncology, alternative proposals to the "TQT" study may be appropriate. We recommend that you address this issue early in development. Please refer to the guidance for industry entitled "E14 Clinical Evaluation of QT/QTc Interval Prolongation" at http://www.fda.gov/cder/guidance/6922fnl.pdf for more information.

Wellstat response on 7-2-10: With respect for the potential for QT/QTc prolongation, Wellstat has considerable electrocardiographic data in healthy subjects and from the phase 1, 2, and 3 clinical studies in patients receiving high-dose 5-FU and uridine triacetate. Wellstat will present these data in the NDA. In addition, Wellstat has data for 12-lead ECGs in dogs from the 12-week GLP repeated dose toxicity study with uridine triacetate. There have been no adverse electrocardiographic effects to date associated with uridine triacetate treatment in animals or humans.

Meeting discussion: FDA reiterates the need for the QT studies. The sponsor can submit a detailed summary of the available data for IRT review, and proposal for an alternate QT study.

6. Uridine triacetate has been evaluated in a battery of GLP nonclinical safety studies sponsored by Wellstat which include an acute oral limit test in rats, a 5-day oral safety study in dogs, a 6-week oral dose toxicity study in rats, and 12-week oral dose toxicity studies in rats and dogs. The 12-week studies showed that dosages of up to 1680 mg/kg/day (rats) and 1500 mg/kg/day (dogs) did not produce any signs of toxicity. The nonclinical studies incorporated supporting toxicokinetics. Uridine triacetate has also been evaluated for its genotoxic potential in two GLP studies including an in vitro Ames mutagenicity assay and an in vivo mouse micronucleus test. All of these studies were conducted using the maximum feasible dose or concentrations of uridine triacetate.

   Based on the existing nonclinical study data, there are no nonclinical issues posed by the use of uridine triacetate to treat 5-FU overdose patients considering the proposed dosing regimen and the emergency use of the drug in the target patient population. Furthermore, in nearly all cases, uridine triacetate will be administered as a single 20-dose course of therapy (5 days) to each patient. Thus, Wellstat proposes that the existing battery of nonclinical safety studies is sufficient to support an NDA for the proposed indication.

   Q: Does the Division concur that the existing battery of nonclinical safety studies with uridine triacetate is adequate to support a future NDA for uridine triacetate for the proposed indication?

FDA response: No. See our answer to question 1. Also, you need to complete the evaluation of the safety pharmacology of uridine triacetate. This evaluation should include studies of the potential for neurotoxicity and respiratory toxicity.

7. Wellstat filed for fast track status for uridine triacetate (b) (4) in the treatment of 5-FU overdose on 25 June 2009. We understand the difficulty in scheduling meetings with the FDA, and the purpose of this request was to have increased discussion with your division on the regulatory pathway to approval for this promising new investigational agent. This status is still pending as of the time of this meeting request letter.

   Q. Does FDA require any further information or data with respect to our fast track status application?

FDA response: No. The letter for your fast track request was finalized on August 30, 2009. See attached letter.

Additional Clinical Comments:

- **It is not indicated how an oral 5-FU overdose occurs. None of your examples in Tables 3 and 4 (pages 36-41) are the result of oral 5-FU.**

Wellstat response 7-2-10: The most likely way an oral 5-FU overdose could occur is if a patient ingests too many pills or if there is accidental ingestion of Xeloda (capecitabine), an oral pro-drug of 5-FU. A less common means of an oral overdose would be ingestion of a 5-FU topical cream, for example by a child.

Meeting discussion: not discussed due to time ran out.

- **It is not indicated how and when a problem with 5-FU elimination would be known.** (b) (4)

(b) (4)

Meeting discussion: Not discussed due to time ran out.

- **A number of the patients, who experienced 5-FU over dosage, also received leucovorin. The pathway for 5-FU and leucovorin to inhibit thymidylate synthase and the associated toxicities from this combination do not appear to be susceptible to uridine triacetate's target of FUTP. Please explain the basis for activity of uridine triacetate in these potential cases.**

Wellstat response on 7-2-10: One of the Phase 1 studies of uridine triacetate plus high-dose 5-FU was conducted in patients also receiving leucovorin, specifically to determine whether

leucovorin could be included in high-dose 5-FU regimens enabled by uridine triacetate (RE: Protocol Nos. 401.09.COH, PN401.09 and CSR.401.09). Leucovorin did not prevent 5-FU dose escalation enabled by uridine triacetate, and a regimen of high-dose 5-FU (1200 mg/m^2/week x 6) plus leucovorin and uridine triacetate was subsequently used in a Phase 2 study in gastric cancer (Doroshow et al., 2006). Therefore, RNA-directed, uridine-reversible toxicity dominates over thymidylate synthase-related toxicity in the setting of high-dose 5-FU, even if leucovorin is also present.

Meeting discussion: not discussed due to time ran out.

- **Please explain how the treatment of 5-FU overdosage is effective in cases where the doses of 5-FU inadvertently administered is higher than the MTD for 5-FU plus uridine triacetate in your Phase 1 studies?**

Wellstat response on 7-2-10: For inadvertent overdosage, uridine triacetate is given in 20 doses of 10 grams each, every 6 hours for a total of 200 grams per course.

For intentional 5-FU dose escalation for treatment of cancer, the uridine triacetate regimen defined in the Phase 1 studies and carried forward into Phase 2 and Phase 3 studies (with weekly high-dose bolus 5-FU) was 8 doses of 6 grams each, given every 8 hours for a total of 48 grams per course, which is approximately one quarter of the total amount of uridine triacetate given after an inadvertent overdose.

Please note also that in the Phase 1 studies, doses up to 1950 mg/m^2 of 5-FU infused in 30 minutes were administered to patients, yielding an AUC 17-fold above that of a standard weekly bolus dose of 5FU; this exposure is comparable to that of some reported lethal overdoses.

Meeting discussion: not discussed due to time ran out.

<u>Comments regarding the expanded access protocol:</u>

- **It is not clear how an oral 5-FU overdose can occur. Also, it is not clear how and when a problem with 5-FU elimination would be known.**

- **The 5-FU over dosages should be specifically defined in the protocol. Information should include the 5-FU doses, infusion rates, whether or not leucovorin was administered, and other drugs administered. The potential 5-FU regimens should be listed and the deviations from these regimens that define the over dosages should be indicated.**

- **The collection of toxicity data should also include diarrhea, mouth sores, skin toxicity, neurotoxicity, skin toxicity, and hematologic toxicities.**

- **Collect information on all concomitant medications. Prohibit the use of allopurinol or leucovorin after 5-FU over dosage.**

- **Patients under the age of 18 should be excluded.**

- **In general, the protocol should outline:**

  (b) (4)

- **In Appendix 2, use the latest NCI CTC toxicity grading scales. Also, include diarrhea, neurotoxicity, and skin toxicity.**

- **In Appendix 3, add for assessment and grading, diarrhea, neurotoxicity, and skin toxicity.**

- (b) (4)

- **The proposed uridine triacetate dose in adults and pediatrics in protocol 401.10.001 is inconsistent with the proposed clinical dose provided in the EOP2 meeting package and should be rectified.**

Wellstat response on 7-2-10: Wellstat wishes to thank FDA for their comments to the draft expanded access protocol. We will address each of FDA's comments in a separate submission to our IND that will also contain a revised version of this protocol for FDA's final review.

Meeting discussion: Not discussed due to time ran out.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 39, 571

DENY FAST TRACK

Wellstat Therapeutics Corporation
Attention: James D. O'Neil, Ph.D., DABT
Vice President, Drug Development
930 Clopper Road
Gaithersburg, MD 20878

Dear Dr. O'Neil:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [redacted] (b) (4)).

We also refer to your June 25, 2009, request for Fast Track designation for [redacted] (b) (4) the treatment of 5-fluorouracil (5-FU) overdose.

We have reviewed your request. [redacted] (b) (4) is not granted Fast Track Designation because insufficient information was submitted to assess whether the product development program is designed to determine whether the product will [redacted] (b) (4). The degree of specificity should be appropriate to the stage of the development.

[redacted] (b) (4)

For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review". This document is available on the internet at http://www.fda.gov/cder/guidance/index.htm or may be requested from the Office of Training and Communications, Division of Drug Information at (301) 827-4570.

If you have any questions, contact James M. Saunders, Regulatory Project Manager, at (301) 796-0621.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 39571	GI 1	WELLSTAT THERAPEUTICS CORP	(b) (4)

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

/s/

JAMES M SAUNDERS
08/30/2009

ROBERT L JUSTICE
08/30/2009

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208159

LATE-CYCLE MEETING MINUTES

Wellstat Therapeutics
Attention: Michael K. Bamat, PhD
930 Clopper Rd.
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your New Drug Application (NDA) dated July 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vistogard® (uridine triacetate), Oral granules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 4, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannette O'Donnell, Regulatory Project Manager at (240) 402-4978.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Acting Clinical Team Lead
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 4, 2015; 10:00-11:00 am
Meeting Location: White Oak Building 22, Conference Room: 1311

Application Number: NDA 208159
Product Name: Vistogard® (uridine triacetate)
Applicant Name: Wellstat Therapeutics

Meeting Chair: Julia Beaver, MD
Meeting Recorder: Jeannette O'Donnell

FDA ATTENDEES

Richard Pazdur, MD, Director, OHOP
Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Acting Clinical Team Leader, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1
Todd Palmby, PhD, Pharmacology/Toxicology Supervisor, DHOT
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Joyce Cheng, PhD, Biometrics Reviewer, DBV
William Pierce, PharmD, Associate Director for Labeling, DOP1
Qi Liu, PhD, Clinical Pharmacology Team Leader, DCP V
Runyan Jin, PhD, Clinical Pharmacology Reviewer, DCP V
Anshu Marathe, PhD, Pharmacometrics Reviewer, DCP V
Rosane Charlab Orbach, PhD, Genomics Team Leader, DCP V
Sarah Dorff, PhD, Genomics Reviewer, DCP V
Xiao-Hong Chen, PhD, Acting Quality Assessment Lead, ONDP
Sharon Mills, BSN, RN, CCRP, Senior Patient Labeling Reviewer, DMPP
Jeannette O'Donnell, Regulatory Project Manager

FDA ATTENDEES – By Phone

William McGuinn, PhD, Pharmacology Reviewer, DHOT
Susan Jenny, MS, Safety Regulatory Health Project Manager, DOP1
Ethan Hausman, MD, Medical Officer Pediatric Labeling, DPMH
Rowe Medina, Patient Labeling Reviewer, OMPI
Tamara Johnson, MD, MS, Maternal Health Team Leader, ODE IV
Carol Kasten, MD, Maternal Health Team Medical Officer, ODE IV
Shaily Arora, PharmD, Acting Safety Evaluator Team Leader
Carolyn McCloskey, MD, MPH, Epidemiologist, DEPI

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese, Eastern Research Group, Inc.

APPLICANT ATTENDEES
Michael Bamat, Ph.D., VP Research & Development
Joan Helton, Manager Regulatory Affairs and Clinical Quality Assurance
Jeffrey Miller, PhD, Director Analytical R&D and Manufacturing
Rita O'Neil, PhD, Senior Director, Regulatory Project Management
Julie Vanas, Director, Clinical Projects
Reid von Borstel, PhD, VP Discovery Research
Nadine Wohlstadter, President

1.0 BACKGROUND

Wellstat submitted Vistogard® (uridine triacetate), Oral granules on July 10, 2015.

Applicant Proposed indication(s): Vistogard® is (b) (4) Patients receiving an overdose of 5-fluorouracil may not exhibit symptoms for several days or more, but are at risk of developing severe to life threatening toxicities. Therefore, if a patient has received an overdose of 5-fluorouracil, Vistogard® treatment should initiate promptly. Likewise, toxicities developing within several days of administration of intended 5-flourouracil doses, especially during the patient's first cycle, are likely to become more severe or life-threatening. Therefore, initiate Vistogard® treatment as soon as possible because cell death from 5-fluorouracil begins immediately. The efficacy of Vistogard® initiated more than 96 hours following the end of administration of 5-fluorouracil has not been established.

PDUFA goal date: March 10, 2016

On November 24, 2015, FDA issued a Background Package in preparation for this meeting.

2.0 DISCUSSION

Introductory Comments: The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in

this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

1. Discussion of Substantive Review Issues: There are no substantive review issues at this time.

   Discussion:
   None

2. Discussion of Minor Review Issues

   Discussion:
   None

3. Additional Applicant Data

   Discussion:
   According to the PDUFA V agreement stability update data submitted after 30 days from the initial submission, may or may not be reviewed based on agency available resources. According to the regulation, CRF 314.70(d)(2)(vi), you may extend your shelf life post approval based on the stability data obtained according to the approved stability protocol in the NDA and submit your shelf life extension in the annual report.

   The Agency clarified that an extension of the shelf life cannot be extrapolated beyond real time stability data post approval in the annual report. However, you can do so by submitting a Prior Approval Supplement (PAS) to the NDA post approval.

   http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf.

4. Information Requests: There are no outstanding Information Requests.

   Discussion:
   None

5. REMS or Other Risk Management Actions: No issues related to risk management have been identified to date.

   Discussion:
   None

6. Postmarketing Requirements/Postmarketing Commitments: There is one CMC PMC which has already been agreed upon.

Discussion:
None

7. Major Labeling Issues:

Discussion:
The label and indication were discussed and final agreed upon label is attached.

8. Review Plans

Discussion:
The Agency plans to act on NDA 208159 prior to January 2016.

Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

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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.

/s/

JULIA A BEAVER
12/07/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208159

LATE CYCLE MEETING
BACKGROUND PACKAGE

Wellstat Therapeutics
Attention: Michael K. Bamat, PhD
930 Clopper Rd.
Gaithersburg, MD 20878

Dear Dr. Bamat:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vistogard™ (uridine triacetate), Oral granules.

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 1, 2015. Attached is our background package, including our agenda, for this meeting. You may choose to change this face-to-face meeting to a T-con or cancel altogether if you feel it is not needed given the expedited nature of this application and continued regular communications.

If you have any questions, call Jeannette O'Donnell, Regulatory Project Manager, at (240) 402-4978 or email: Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	December 1, 2015; 11:00-11:30 am
Meeting Location:	White Oak Building 22, Conference Room: 1311
Application Number:	NDA 208159
Product Name:	Vistogard™ (uridine triacetate)
Indication (under discussion):	VISTOGARD is indicated for the emergency treatment of adult and pediatric patients: ▪ following a fluorouracil or capecitabine overdose, or ▪ who exhibit early-onset severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration.
Sponsor/Applicant Name:	Wellstat Therapeutics

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues
There are no substantive review issues at this time.

3. Postmarketing Requirements/Postmarketing Commitments
There is one CMC PMC which has already been agreed upon.

ADVISORY COMMITTEE MEETING
An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS
No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting.

2. Major labeling issues – 30 minutes

   Discuss and agree upon any residual labeling issues.

3. Review Plans – 5 minutes

   FDA is working towards an expedited review.

4. Wrap-up and Action Items – 5 minutes

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/s/

GEOFFREY S KIM
11/24/2015