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APPLICATION NUMBER:

208159Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208159
Priority or Standard	Priority
Submit Date(s)	July 10, 2015
Received Date(s)	July 10, 2015
PDUFA Goal Date	March 10, 2016
Division / Office	DOP1/OHOP
Reviewer Name(s)	Gwynn Ison, MD Julia Beaver, MD (TL)
Review Completion Date	November 24, 2015
Established Name	Uridine triacetate
(Proposed) Trade Name	Vistogard™
Therapeutic Class	Pyrimidine analogue
Applicant	Wellstat Therapeutics
Formulation(s)	Oral granules
Dosing Regimen	Adult: 10 grams (1 packet) orally every 6 hours for 20 doses, without regard to meals. Pediatric: 6.2 g/m2 of BSA (not to exceed 10 grams per dose) orally every 6 hours for 20 doses, without regard to meals.
Indication(s)	Uridine triacetate (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

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based upon the findings described in this clinical review of the new drug application for uridine triacetate (NDA 208159), this reviewer recommends approval of uridine triacetate for the following indication:

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

Limitations of use:

- Uridine triacetate is not recommended for the treatment of adverse reactions associated with fluorouracil or capecitabine that are not severe or life-threatening because it may diminish the efficacy of these drugs.
- The safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established.

1.2 Risk Benefit Assessment

Approximately 300,000 patients in the United States receive treatment with the chemotherapy agent 5-fluorouracil (5-FU) per year. Studies report a minimum incidence of approximately 0.5% mortality (~1300 deaths per year) from 5-FU toxicity. Another 8250 estimated patients experience potentially life-threatening toxicities related to 5-FU annually[1,2]. There are currently no approved therapies to treat patients who have either received an overdose of 5FU (or capecitabine) or who have experienced life-threatening toxicities from 5FU (or capecitabine).

The recommendation for approval of uridine triacetate is based on the results of two single-arm, open-label, multicenter, expanded access clinical studies, WELL401 and 401.10.001. Patients were eligible for treatment with uridine triacetate if they received an overdose of 5-FU or an oral pro-drug capecitabine, or because they experienced unexpected, early-onset, life-threatening toxicity after treatment with 5-FU or capecitabine.

A total of 135 patients were treated on studies 401.01.001 and WELL401. There were 117 patients treated with uridine triacetate following an overdose of 5-FU or capecitabine, and of these 97% survived. These patients received doses and rates of 5-FU infusions which would be expected to result in morbidity and mortality. As a comparison, 84% of 25 5-FU overdose historical control patients died. Eighteen patients received uridine triacetate for early-onset severe or life-treatening toxcity (cardiac, central nervous system, gastrointestinal toxicity, and/or neutropenia), and of these 89% survived.

The overall risk to patients from treatment with uridine triacetate is low and the safety profile is acceptable. Uridine triacetate was generally well tolerated, with only Grade 1 to Grade 2 nausea, vomiting, and diarrhea reported in some patients. There were no deaths on either study which were attributable to uridine triacetate therapy. Likewise, only two patients discontinued uridine triaceate therapy due to an adverse event, and only one patient experienced serious adverse events related to uridine triacetate.

Major issues are summarized as follows:

Both trials were single-arm and non-randomized, and the applicant submitted historical controls for comparison. This study design and use of historical controls was acceptable since it would not be ethical to do a randomized trial in this life-threatening therapeutic setting. In addition, there was supportive nonclinical data, comparable doses and rates of overdose between the study patients and historical controls, and supportive reviews from all disciplines.

The indication of early-onset of severe or life-threatening toxicity from 5-FU or capecitabine without an overdose was supported by small numbers and required in-depth review. Detailed analysis of the individual cases supportive of this indication showed that there was undisputable benefit for a subset of patients who presented very early (within 96 hours) after 5FU dosing, and displayed specific, life-threatening toxicities affecting certain organs systems including cardiovascular, neurologic (central nervous system), gastrointestinal and hematologic systems.

The specific time frame for administration of uridine triacetate after overdose or early-onset required further consideration. Of the 135 patients, 131 were treated within the protocol specified 96 hour window and 98% lived. Four patients were treated outside of the 96 hour window, and 50% died. Additional information from the 120 day safety update was supportive of specifying treatment as soon as possible within 96 hours and that the efficacy after 96 hours was not demonstrated.

Only five patients were treated with capecitabine. However, all of these patients survived, and based upon the mechanism of action, and understanding of capecitabine

as a pro-drug of 5-FU, this reviewer recommends inclusion of capecitabine in the indication.

Only six pediatric patients were treated with uridine triacetate. However, all of these patients survived. The safety profile of uridine triacetate is acceptable with a low risk to pediatric patients. Based upon these cases, as well as supportive adult data, and a strong biologic and clinical rationale, this reviewer supports inclusion of the pediatric indication in the label.

A strong biologic rationale, supportive and consistent nonclinical data, demonstration of clinical efficacy in a unmet medical need situation and a safe toxicity profile provide for a favorable risk-benefit profile. The use of historical control was acceptable as the use of an ineffective or placebo control arm would be unethical in this setting. Therefore, this reviewer recommends approval of uridine triacetate for patients following an overdose of 5-fluorouracil or capecitabine, or who exhibit early-onset severe or life threatening toxicity affecting the cardiac or central nervous system, and/or certain early-onset unexpectedly severe adverse reactions (such as those involving gastrointestinal toxicity and/or neutropenia) within 96 hours following 5-fluorouracil or capecitabine administration. In order to address the concern that the effect of uridine triacetate on 5-FU efficacy is not known, this reviewer also recommends a limitation of use explaining this potential risk and that patients should not be treated with uridine triacetate to treat typical 5-fluorouracil or capecitabine toxicity. Another limitation of use is recommended to describe the lack of data on efficacy if uridine triacetate is initiated more than 96 hours following the end of administration of 5-fluorouracil or capecitabine.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations from the review team for postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no clinical postmarketing requirements or commitments.

There is one CMC post-marketing commitment for this application (rationale discussed in Section 4.2), as follows:
As part of the dissolution method revision, perform retrospective analysis and confirm the dissolution studies submitted to support this manufacturing process, including:

(b) (4)

(b) (4)

(b) (4) Study 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.

2 Introduction and Regulatory Background

2.1 Product Information

Uridine triacetate is a pro-drug of uridine. It is rapidly deacetylated by nonspecific esterases present throughout the body, yielding uridine in the circulation. The major components found in the plasma after ingestion of uridine triacetate are uridine (active) and uracil (inactive). Uridine is a direct biochemical antagonist of 5-FU toxicity.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no other available therapies, approved or unapproved, for the proposed indication.

2.3 Availability of Proposed Active Ingredient in the United States

As noted in the CMC review, uridine triacetate is (b) (4) Uridine is a well-characterized compound and is commercially available. Therefore, the proposed active ingredient is readily available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no other agents with similar activity, as a biochemical antagonist of 5-fluourouracil, approved in the U.S.

The effect of uridine triacetate on the efficacy on 5-fluorouracil and capecitabine is not known, but there is concern for the potential that uridine triacetate may diminish the anti-cancer activity of 5-fluorouracil and capecitabine, based upon its mechanism of action (see Section 4.3 for further discussion on mechanism of action).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

May 1992- IND 039571 opened. Uridine triacetate was to be used (b) (4) for solid tumors treated with 5-FU. All patients were treated under single patient INDs.

May 2009- Uridine triacetate received orphan drug designation (b) (4) in the treatment of 5-FU poisoning.

July 2010- EOP2 meeting occurred. The FDA recommended that the Applicant conduct a prospective, single-arm trial for the proposed indication. Also recommended that animal rule may not apply in this case.

September 2011- Protocol 401.10.001 (Expanded Access Protocol) opened.

April 2014- The Applicant submitted their application (b) (4)

May 2014- FDA recommended (b) (4). FDA also recommended that the Applicant request a meeting with FDA to discuss NDA submission.

July 2014- Fast-track designation was granted for "uridine triacetate (b) (4) to treat patients at risk of excess 5-FU toxicity due to overdose".

September 4, 2015- Uridine triacetate received approval for the indication of orotic aciduria under the trade name Xuriden™.

July 10, 2015- NDA submission for current indication for 5-FU toxicity.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contained the required components of the eCTD. The overall quality and integrity was reasonable.

3.2 Compliance with Good Clinical Practices

The Division of Oncology Products 1 (DOP1) consulted the Office of Scientific Investigation (OSI) to perform an audit of two clinical sites as well as the applicant to identify any data quality issues and to document that the trial was performed according to GCP.

The sites inspected are shown in Table 1 below, with VAI (voluntary action indicated) assessments given to two of the three sites inspected, including the applicant. .

Table 1 OSI Inspection Sites and Preliminary Outcomes

Planned inspections:	Scheduled dates for inspection	Status	Preliminary Outcome	Site Number
Applicant: Wellstat Therapeutics	October 5-7, 2015	Completed	VAI	N/A
CI: Steven Duffy, MD Richmond, VA	Mid-September, 2015	Completed	NAI	Subject ID: OD-134
CI: Yudhish Markan, MD Glen Burnie, MD	August 26 – September 9, 2015	Completed	VAI	Subject ID: OD-092

OSI Inspection result: It was noted by the OSI investigator that the case report forms for all patients were completed by Wellstat personnel rather than by study site staff. It was noted that this is not the usual way in which CRFs are filled out.

Dr. Markan's clinical site was identified as having multiple findings, including failure to obtain IRB approval within the appropriate timeframe, data inconsistencies between source documents and data reported by the Applicant, incomplete drug accountability records, failure to follow the study protocol, and failure to maintain study records.

The OSI investigator performed an audit of 69 out of the 135 study subject records (51%). The assessment of these records involved examining primary and secondary efficacy endpoint information, CI compliance, and applicant monitoring of data. The conclusion was that the data were generally acceptable, with the exception of the hematology data entered into the case report forms, and subsequently submitted to the application. Specifically, it was found that eight (12%)of the 69 audited records had incorrect units of hematology data entered into the case report forms resulting in incorrect assignment of high, low, or normal values. Consequently, the incorrect data was then submitted with the hematology laboratory data in the NDA.

Reviewer comment: FDA requested the applicant submit corrected hematology laboratory data for all subjects, as a result of the OSI findings. The applicant submitted these corrected data in the 120 safety update. After a careful analysis of the issues

found at Dr. Markan's site, none of the violations or issues would have affected the overall findings of the study, only one patient was enrolled there, and the applicant did have all source documents for that patient. Despite irregularities in the applicant filling out the CRFs at a later date, this was due to the overall expanded access study designs and were acceptable in the emergency study setting. Overall, the findings reported by the OSI inspection do not change the overall risk-benefit assessment of this application.

3.3 Financial Disclosures

In accordance with 21 CFR 54.2, the Applicant submitted a list of Study 401.10.001 and Study WELL401 investigators attached to FDA form 3454 certifying that none of the Principal Investigators or Sub-investigators had financial information to disclose as defined in 21 CFR 54.2(a, b, and f) that could affect the outcome of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See the CMC review by Drs. Xavier Ysern, Xiao Hong Chen, Christina Capacci-Daniel, Ge Bai, Rabiya Laiq, Olen Stephens, and Paul Perdue.

According to the CMC review team, the applicant provided sufficient CMC information to assure identity, strength, purity, and quality of the drug product. The office of Compliance found the facilities involved in the application to be acceptable. The commercial manufacturing process was adequately described. Its adequacy to ensure consistent manufacturing of acceptable drug substance batches is fully supported by release and stability data.

The CMC team has recommended approval for uridine triacetate, and has granted a 24 month shelf life for the drug product when stored in the proposed container configuration at 25°C (excursions permitted 15°-30°C).

As noted in Section 1.4 of this review, there is one post-marketing commitment for this NDA from the CMC team. It was noted that in NDA 208169 (Xuriden™; cross-referenced; orotic aciduria indication), the process validation batches demonstration variability in dissolution of products intra-batch and inter-batch. This is presumed to be due to dissolution dependence on particle size of the granules. As a result, a PMC for

the current NDA was established and is similar to one established under cross-referenced application, NDA 208169.

4.2 Clinical Microbiology

See joint CMC team review, specifically, the microbiology section by Dr. Christina Capacci-Daniel. The tests and proposed acceptance criteria for microbial burden were considered to be adequate to assure the microbial quality of the drug product.

4.3 Preclinical Pharmacology/Toxicology

See the Pharmacology/ Toxicology review by Dr. David McGuinn.

The original intention, prior to NDA submission, was that this NDA would be reviewed, and potentially approved, under the Animal Rule. However, after review of both nonclinical and clinical data submitted by the Applicant, it was determined that the nonclinical studies submitted did not meet the requirements of the Animal Rule. It was also determined that there was enough clinical data submitted that use of the Animal Rule would not be necessary.

The nonclinical safety package for uridine triacetate included safety pharmacology, repeat dose toxicology studies (3 month in dogs; 3 and 6 month in rats), genetic toxicology studies, and reproductive toxicology studies in rats). Uridine triacetate did not inhibit hERG channels at physiologically relevant concentrations. There was no observable cardiac toxicity in dogs or rats. In the 3 month dog study, the NOAEL was determined to be 1500 mg/kg/day (administered in 2 equal doses, 6 hours apart). Uridine triacetate was also not genotoxic. In addition, carcinogenicity studies were not required for this indication, which mostly includes cancer patients.

The studies reviewed by the nonclinical team that the clinical dose of uridine triacetate may be higher than necessary to achieve the desired clinical response.

(b) (4)

Finally, from the cross-reference approval for Xuriden (NDA 208169) for orotic aciduria, a post-marketing requirement was agreed upon, such that Wellstat will do a Segment 3 pre- and postnatal development study.

4.4 Clinical Pharmacology

See the Clinical Pharmacology Review by the primary reviewers Anshu Marathe, PhD, Runyan Jin, PhD, and Sarah Dorff, PhD.

One issue of note is that the applicant originally (b) (4)

4.4.1 Mechanism of Action

The proposed language from section 12.1 of the product label is as follows:

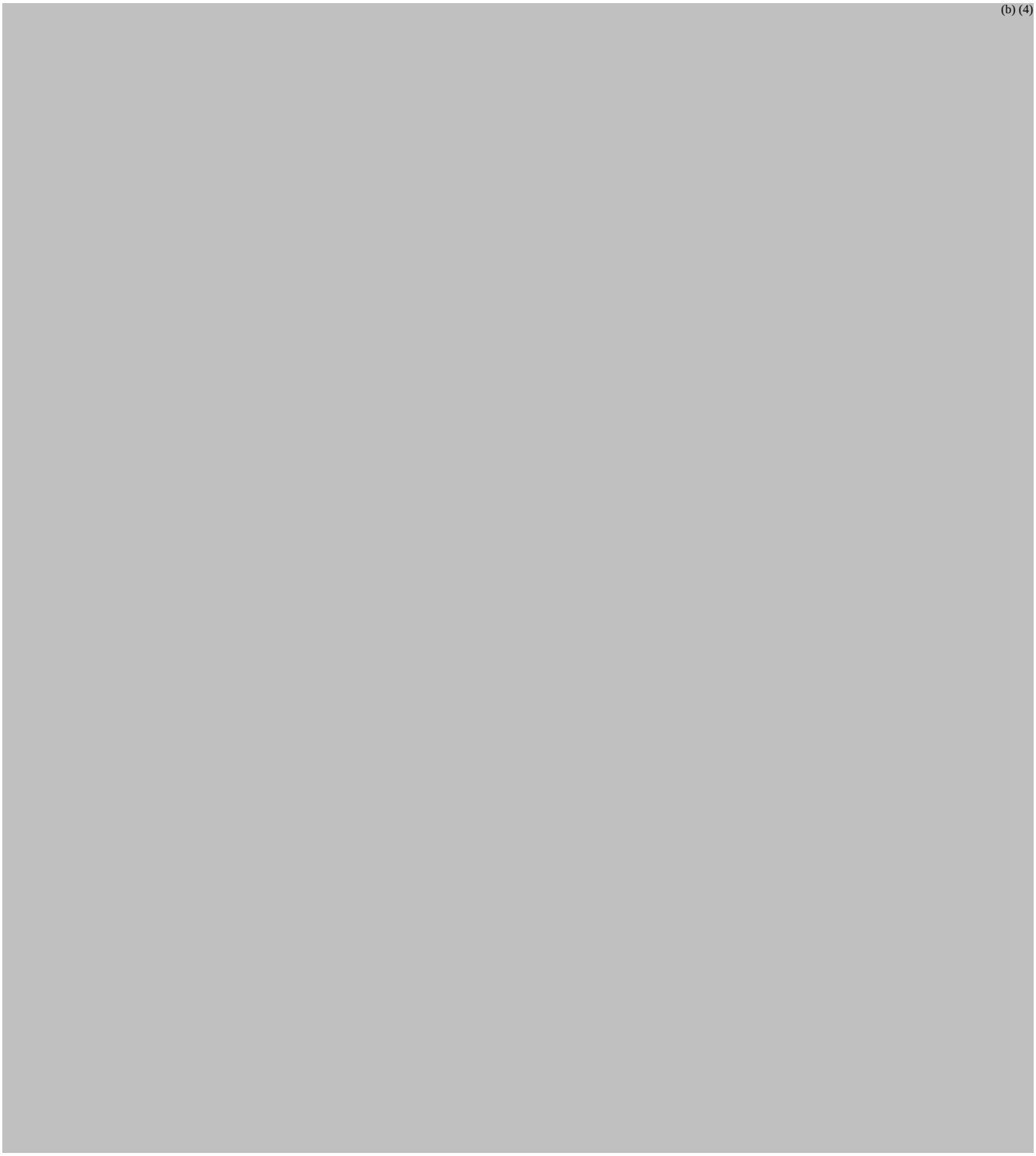
Uridine triacetate is an acetylated prodrug of uridine. Uridine triacetate is deacetylated (b) (4) the body (b) (4) yielding uridine in circulation. (b) (4) uridine competitively inhibits cell damage and cell death caused by 5-fluorouracil.

4.4.2 Pharmacodynamics

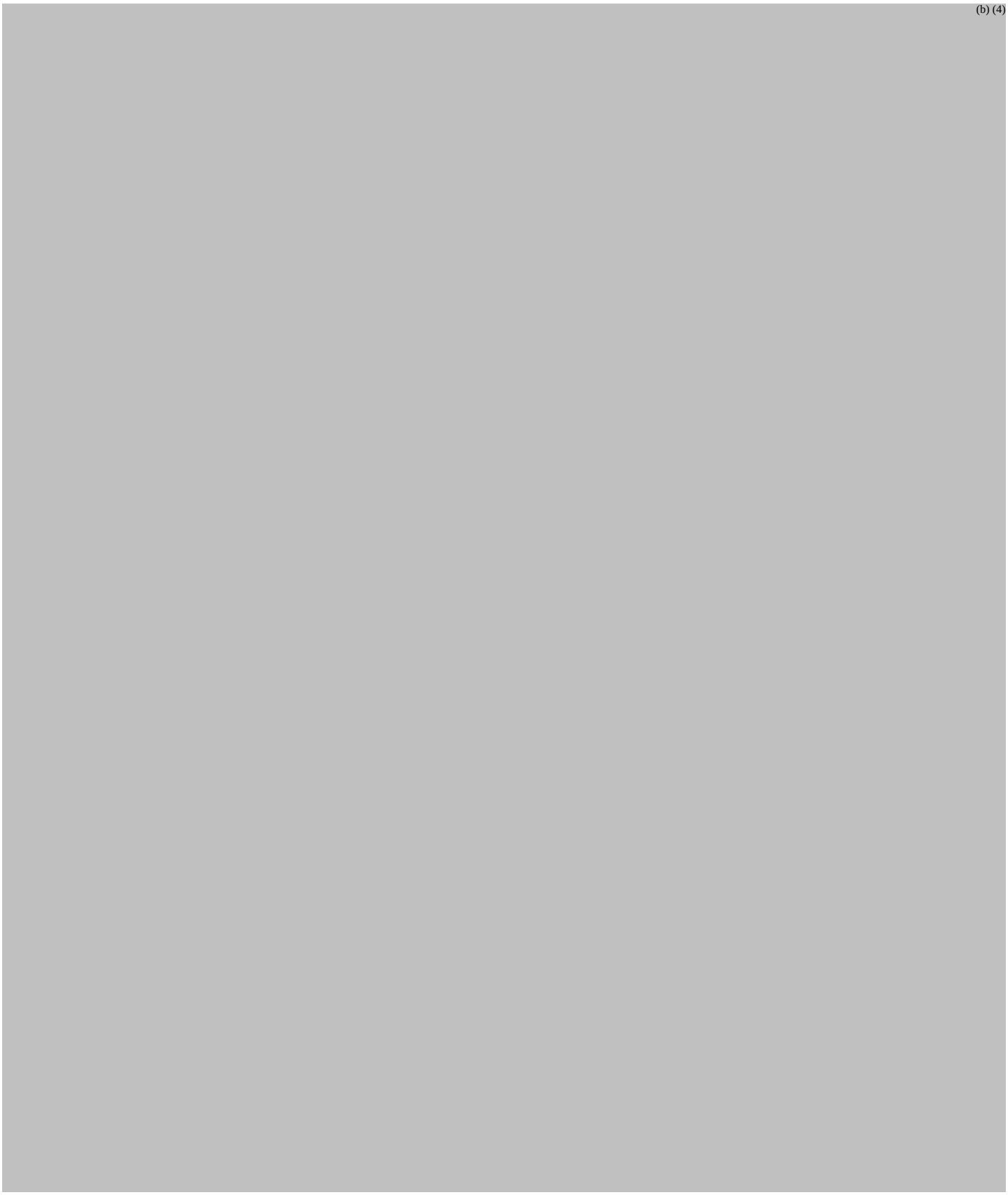
Not applicable.

4.4.3 Pharmacokinetics

(b) (4)



(b) (4)



(b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The primary evidence to support the efficacy and safety of uridine triacetate is derived from data from Trials 401.10.001 and WELL401. Table 3 lists the clinical trials included in the NDA submission.

Table 3 Tabular Listing of Clinical Trials

Study Number	Enrollment dates	Design	Population	Endpoint	Number patients enrolled
WELL401	10/1995-8/2011	Open-label, single arm, multicenter emergency use study; collection of single patient INDs.	Adult and pediatric patients at risk of serious toxicity following 5-fluorouracil or capecitabine overdose or patients with rapid onset serious toxicity (within 1 to 4 days)	Survival through D30	75
401.10.001	9/2011-present	Open-label, expanded access protocol	Adult patients at risk of serious toxicity following 5-fluorouracil over dosage or patients with rapid onset of serious toxicity	Survival through D30	60
Total					135

5.2 Review Strategy

The FDA clinical NDA review consisted of one primary clinical reviewer. The NDA submission contained Studies WELL401 and 401.10.001, as well as case reports of 47 historical controls. The clinical review of efficacy focused on the subjects treated with uridine triacetate in the two studies (n=135) as well as the 25 historical controls for

whom dose and rate of 5-FU overdose were known. The review of safety focused on the 135 patients between the two studies and focused on distinguishing between toxicity of 5-FU overdose or early-onset toxicity and toxicity from uridine triacetate. Both reviews of safety and efficacy included reviews of the clinical study report (CSR), case report forms (CRFs), narratives for all patients, and raw datasets.

The clinical review included the following:

- Review of the current literature on 5-FU toxicity overdose, epidemiology, and treatment.
- Review of Applicant submitted Study WELL401 and 401.10.001 including CSR, protocols, and protocol amendments and datasets
- Review and assessment of Applicant analysis of uridine triacetate efficacy and safety, for evaluation of Applicant's claims
- Review of datasets submitted as .xpt files
- Review of patient narratives of serious adverse events, deaths, and early-onset toxicity cases
- Review of meeting minutes conducted during drug development
- Assessment of the Module 2 summaries including the Summary of Clinical Safety
- Review of reviews conducted by other FDA disciplines including Clinical Pharmacology and Nonclinical
- Review of consultation reports of Office of Scientific Investigations
- Review of consultation report of Office of Surveillance and Epidemiology Provision of Pharmacovigilance Data Dated 6/19/2014
- Requests for additional information from the Applicant and review of Applicant responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

Criteria for Inclusion of Patients in FDA Analysis (FDA Agreement):

In addition, for efficacy, we analyzed the patients with 5-FU or capecitabine overdose and early-onset groups separately in both studies. For each group of patients, we set forth specific criteria, which we used in our analysis of each patient. The criteria were used to decide on a case-by-case basis whether each patient should be counted as a successfully treated case (either for overdose or for rapid onset).

For the overdose group of patients, the criteria for "FDA Agreement" included:

1) Documentation of 5-FU overdose.
2) Uridine triacetate initiated within 96 hours.
3) Patient received >80% uridine triacetate doses.
4) Documentation of survival at Day 30.

Since the analysis of the early-onset patients in both studies involved additional assessment of the presence of life-threatening symptoms, a more detailed review of each narrative and case report form was required for analysis of these cases. After reviewing the early-onset cases, each patient was also given an "agree" or "disagree" for the FDA assessment, similar to the overdose cases. However, the analysis also included whether life-threatening symptoms were present.

The criteria for "undisputable" FDA agreement for the early onset patients were as follows:

1) Documented 5FU dosing.
2) Uridine triacetate initiated within 96 hours.
3) Patient received >80% uridine triacetate doses.
4) Documentation of survival at D30.
5) Presence of early-onset life-threatening symptoms.

For patients in the early onset group to be distinguished as having undisputable benefit, all 5 criteria had to be met. Patients who met some, but not all 5 criteria, if deemed to have potentially benefited from uridine triacetate were classified as "reasonably likely" agreement cases.

5.3 Discussion of Individual Studies/Clinical Trials

Unlike randomized, controlled, clinical studies, clinical sites were not established in advance and investigators contacted the applicant in emergency circumstances when a patient was considered to have overdosed or exhibited rapid onset of 5-FU of capecitabine. Prior to the initiation of Study 401.10.001, or if the patient did not qualify for Study 401.10.001 the physician requested an emergency-use single patient IND and would be treated on WELL401, but was treated according to the same Clinical Operations Procedures as were those subjects treated on Study 401.10.001. The two studies, shown in Table 3 above were 401.10.001 and WELL401. The protocol (procedures) used for both studies were identical, except that patients overdosed with capecitabine, pediatric patients, and ex-US patients were included in WELL401 only. A description of the 401.10.001 protocol is as follows.

Protocol ID: 401.10.001: An open-label protocol for the use of uridine triacetate as an antidote to treat patients at excess risk of 5-FU toxicity due to overdosage or impaired elimination (original protocol released October 12, 2010; study initiated in the US 9/1/11. The study is ongoing).

Protocol phase: Expanded access.

Primary objectives:

1) To provide uridine triacetate as an antidote to treat patients at excess risk of 5-FU toxicity due to overdosage (defined as administration of 5-FU at a dose, or infusion rate, greater than maximum tolerated dosage (MTD) for the patient's intended regimen) or impaired elimination.
2) To evaluate survival for 30 days in patients treated with uridine triacetate initiated between 3 and 96 hours after completion of 5FU dosing, who are at excess risk of 5FU toxicity due to overdosage or impaired elimination.

Secondary objectives:

1) To assess the occurrence, severity, and duration of neutropenia, thrombocytopenia, and leukopenia, commonly associated with 5FU dosing, in patients at excess risk of 5FU toxicity due to overdosage or impaired elimination.
2) To assess the occurrence, severity, and duration of mucositis, diarrhea, and skin and neurological toxicities, commonly associated with 5FU dosing, in patients at excess risk of 5FU toxicity due to overdosage or impaired elimination.
3) To assess systemic levels of uridine and uracil in treated patients.
4) To assess the tolerability of uridine triacetate in treated patients.

Protocol design: Open-label protocol for use of uridine triacetate as an antidote to treat patients at excess risk of 5FU toxicity due to overdosage or impaired elimination.

Protocol procedure: Once an investigator was aware of a patient who may be eligible for treatment with uridine triacetate, they contacted Wellstat to request treatment. Wellstat would request enrollment documents from the investigator, including patient demographic information, disease information, prior chemotherapy including 5FU, and details of 5FU overexposure including dose, cause and timing. At that point, Wellstat would determine whether a patient was eligible (criteria described below) and offer enrollment to the patient.

Methodology: Patient's clinical course and outcome, including survival, following 5FU overdose was evaluated for 30 days unless the patient died or resumed chemotherapy within the 30 day period. Safety and tolerability of uridine triacetate was evaluated by assessing:

1) Vital signs (BP, pulse, temp, respiratory rate).
2) Lab values (hematology and chemistry)
3) Adverse events.
4) Systemic levels of uridine and uracil in plasma samples were also evaluated.

Overdose description: Overdose of 5FU defined as administration at a dose or infusion rate greater than the MTD for the patient's intended regimen. Based upon Institute for Safe Medication Practices (ISMP, 2007), a patient could be at excess risk for 5FU toxicity if the dose of 5FU was either

- at least 10% greater than the intended dose; or
- at least 25% greater than the intended rate for the patient.

Reviewer Comment: There were two descriptions of overdose in the protocol, one in the overdose description section and one in the eligibility criteria. The eligibility criteria appear to be what was actually used for enrollment into the study and therefore that is what is reflected in the description of the study in the label. This reviewer analyzed all cases of overdose as detailed in Section 6 in order to better describe what constituted an overdose patient in these studies.

Impaired elimination description: Patients with impaired 5FU elimination receiving standard doses of 5FU may experience severe toxicities due to clearance deficits. Most common cause of impaired 5FU elimination is dihydropyrimidine dehydrogenase deficiency (DPD), the initial rate-limiting enzyme of 5FU catabolism. Diagnosis or suspicion of impaired 5FU elimination could be based upon a number of factors including, but not limited to:

- Measurement of plasma 5FU can identify patients with impaired 5FU elimination (for instance, impaired 5FU elimination should be suspected if detectable 5FU levels (i.e. > 10 µM) are found in plasma more than 3 hours following completion of 5FU dosing.
- Previous medical history from earlier 5FU chemotherapy regimens (at standard doses) that indicated unusual susceptibility to 5FU toxicity within 7-10 days of receiving 5FU, such as G3-4 diarrhea, G3-4 mucositis, or G4 neutropenia.
- Leukocyte DPD enzyme activity <70% of that observed in normal population (10 +/- 3.4 nmol/hr)
- Presence of deleterious mutation in DPD gene known to reflect reduced DPD activity and consequent increased risk of 5FU toxicity.
- Measurement of plasma uracil and dihydrouracil (DHU), the product of uracil degradation by DPD. A ratio of plasma uracil to DHU of greater than 2.0 signifies probable DPD deficiency.
- Early onset or unusual susceptibility to 5FU toxicity such as G3-4 diarrhea, G3-4 mucositis, G3-4 neutropenia, G3-4 neurologic toxicities, or severe or sudden onset cardiotoxicity.
    - Cardiotoxicity and neurotoxicity are rare but potentially serious or life-threatening consequences of 5FU overexposure. Symptomatic cardiotoxicity ranging from chest pain to palpitations to cardiogenic shock and fatal cardiac arrest occur in 1.2%-4.3% of patients treated with 5FU.

Reviewer comment: Regarding the eligibility for patients with "impaired elimination": The criteria used to define potential candidates for uridine triacetate therapy due to

impaired elimination of 5FU were discussed with the Applicant in meetings in and prior to 2014. FDA historically expressed concern about defining the impaired elimination population, and one of the biggest concerns was regarding the eligibility criteria involving measurements of DPD enzyme levels, DPD mutations, and plasma levels for uracil and related breakdown products. After reviewing the clinical data submitted, all of the early onset patients enrolled on studies 401.01.001 and WELL410 were eligible for therapy with uridine triacetate therapy based upon clinical presentation of severe or life-threatening toxicity. There were some patients who had documentation of DPD enzyme deficiency described in their narratives, but this factor did not have a substantial impact on the FDA analysis of these cases, as the results reported for these tests were often difficult to interpret or not reported, despite the fact that the tests were sent.

Primary endpoint: Outcome (survival or death) in uridine triacetate treated patients. Survival was assessed for 30 days following 5FU overdose unless the patient expired or resumed chemotherapy within the 30 day period.

Secondary endpoints:

- Assessment of the occurrence, severity, and duration of:
  - Neutropenia
  - Thrombocytopenia
  - Leukopenia
  - Mucositis
  - Skin toxicities
  - Neurologic toxicities
- Systemic levels of uridine and uracil.

Inclusion criteria:

1. Patients at excess risk of toxicity due to overdosage (defined as administration of 5-FU at a dose, or infusion rate, greater than the MTD for the patient's intended regimen) of 5-FU or its oral prodrug capecitabine, or impaired 5-FU elimination
2. Judged by the Investigator to have the initiative and means to be compliant with the protocol
3. Able to take oral medications
4. Age ≥ 18 years
5. Able to start treatment with uridine triacetate between 3 and 96 hours after the overdose
6. Provides written informed consent (patient or legally authorized representative).

Exclusion criteria:

1. Known allergy to uridine triacetate.
2. Unable to have initiative and means to be compliant with protocol.
3. Unable to be compliant with taking oral medications.
4. More than 96 hours had elapsed since completion of 5-FU dosing.

5. Unable to provide informed consent (or have legally authorized representative to sign).

Protocol restrictions/ prohibited medications:
Use of allopurinol, leucovorin, and chemotherapy was prohibited during the dosing course of uridine triacetate. Careful consideration was to be given to the timing of restart of chemotherapy. Drugs that could interfere with absorption of uridine triacetate were to be discontinued or avoided, including kaolin, bismuth, sucralfate, cholestyramine.

Protocol exceptions:
Exceptions to the eligibility criteria were to be considered based on consultation with and judgment of the Medical Monitor.

Dose selection:
According to protocol, the dosage of uridine triacetate granules was 1 (b) (4) (containing 10g active uridine triacetate) every 6 hours x 20 doses (200 g active total dosage). This dose was shown to be clinically well tolerated and was selected based upon data from PK studies and the published literature. The data showed that at the proposed dose and regimen, steady-state plasma uridine concentration exceeded 70µM, a reported threshold for protecting normal tissues from toxic effects of 5FU (Martin et al., 1989).

Dosing procedures:
Treatment with uridine triacetate was to begin between 3 and 96 hours after the 5FU overdose. Patient was to remain at the site or facility for observation and completion of applicable procedures for the first 6 hours after taking the first dose. Uridine triacetate could be mixed with foods easy to swallow, such as pudding, yogurt, or applesauce. It could be given with or without food. Adherence to the every 6 hour dosing procedure was to be maintained, without regard to meals. Given the importance of receiving the doses of uridine triacetate, antiemetics were allowed to be given 20-30 minutes prior to each dose, as well as post-dose, if necessary. If a dose was vomited, another complete dose was to be initiated within 15 minutes of vomiting. The next dose was to be taken at the regularly scheduled time, regardless of whether additional vomiting episodes occurred. Additional uridine triacetate could be requested from the Applicant, to ensure that patients received all 20 doses.

Schedule of assessments:

	Relative to Days of Uridine Triacetate Dosing			Relative to the Day of 5-FU Overdose*							
	Prior to 1st Dose of Uridine Triacetate	2 Hours (± 10 minutes) After 1st Dose	2 Hours (± 10 minutes) After Last Dose	Week 1* (Days 1-7)			Week 2 (Days 8-14)			Week 3 (Days 15-21)	Week 4 (Days 22-30)
Inclusion/Exclusion Criteria Assessment	X										
Informed Consent	X										
Demographics/ Baseline Characteristics	X										
Medical History (a)	X										
Vital Signs/ Weight (b)	X (c)			X	X	X	X	X	X	X	X
Plasma Sample	X	X	X								
Hematology (b) (d)	X (e)			X	X	X	X	X	X	X	X
Chemistry (d)	X (e)				X			X		X	X
Concomitant Medication	X (f)	→									
Adverse Event Monitoring	→										
Neutropenia, Thrombocytopenia, Leukopenia, Mucositis, Diarrhea, and Skin and Neurological Toxicities Assessment/Grading (b)				X	X	X	X	X	X	X	X
Physical Exam					X			X		X	X

*The day of the 5-FU overdose is considered Day 1; therefore, week 1 begins with the date of the 5-FU overdose. However, Week 1 blood draws should be obtained *after* the start of uridine triacetate treatment. Therefore, if treatment begins on the 3rd day after the overdose, for example, all 3 blood draws would need to be collected between Day 3 (after 1st dose of uridine triacetate) and Day 7.

(a) Including disease-directed therapy
(b) Assessments will be performed 3x/week for the first 2 weeks, then weekly thereafter, for up to 30 days
(c) Pre-overdose vital signs, including height & weight
(d) See Appendix 2 for details
(e) Pre-overdose laboratory tests
(f) Taken within 14 days prior to overdose and throughout the 30 day follow-up period

Clinical laboratory tests included:

APPENDIX 2: CLINICAL LABORATORY TESTS

Hematology	Chemistry
White blood cell count	Alkaline phosphatase (ALP)
Red blood cell count	Aspartate aminotransferase (AST)
Hemoglobin	Alanine aminotransferase (ALT)
Hematocrit	Albumin
Platelet count	Bilirubin (total)
MCV	Blood urea nitrogen (BUN)
MCH	Calcium
MCHC	Chloride
Differential counts (neutrophils, lymphocytes, basophils, monocytes, eosinophils)	Creatinine
	Glucose
	Lactate Dehydrogenase (LDH)
	Magnesium
	Potassium
	Sodium
	Total protein
	Uric acid

Adverse events:
An AE was defined as any unwarranted medical occurrences in a patient that does not necessarily have a causal relationship with the treatment (ICH/WHO). The incidence of

clinical AEs was assessed and documented by the Investigator, according to severity, duration, and relationship to uridine triacetate or overdose event. When assessing relationship, special consideration was to be given to AEs know to be caused by 5FU, 5FU overdose, other chemotherapy, other treatments, and patient's underlying disease.

Reviewer comment: It is notable that the Applicant did not pre-specify in the protocol whether adverse events would be recorded and graded according to the Common Toxicity Criteria (CTC). The FDA had to request this from the Applicant after NDA submission, causing a delay in the safety analysis and making this an atypical safety review.

Serious AEs:
Any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/ birth defect, or is an important treatment-emergent medical condition considered serious by the investigator.

Evaluation of endpoints:
Primary efficacy endpoint was outcome (survival or death) in uridine triacetate-treated patients receiving 5-FU dosages, who, if not treated with uridine triacetate within 96 hours after completion of 5-FU dosing, would be expected to be at excess risk of 5-FU toxicity due to overdosage or impaired elimination. Survival was assessed for 30 days following 5-FU overdose unless the patient died or resumed chemotherapy within 30 days.

Secondary endpoints included assessment of occurrence, severity, and duration of specific adverse events or laboratory abnormalities, including neutropenia, thrombocytopenia, leukopenia, mucositis, diarrhea, skin toxicities, neurologic toxicities. Also included was assessment of systemic levels of uridine and uracil.

Demographics, baseline characteristics, safety and tolerability were summarized using descriptive statistics. Exposure to uridine was evaluated in plasma samples before and after first and last doses of uridine triacetate.

Case report forms: Investigators were to maintain adequate patient records, which acted as source documents of all protocol activities. Documentation was to include original notes, forms completed during patient contact, lab reports, other relevant documentation. Information was transcribed from source documents to the CRFs. Unavailable or missing information was also to be indicated as such. Documents and records were to be retained for at least 2 years after approval of a marketing application.

Protocol 401.10.001 Amendments:

Protocol 401.10.001 was originally released on 10/12/10 (v.1.0). A second version2.0 was released in 12/7/10, but no major changes were described. Amendment 1 to the protocol (referred to as protocol version 3.0) was released in 1/26/12. Changes in version 3 included updates to the background section, where language was added, stating that effectiveness of uridine triacetate as an antidote is well supported by data from accidental overdose cases. Relevant human experience was updated to with this protocol version to include 53 patients treated with uridine triacetate. In addition, the drug product changed from "sprinkles" to granules in this protocol version. Amendment 2 (protocol version 4.0) was released on 8/1/13 and is the most recent version of the protocol. Major changes with this amendment included clarification on the definition of early onset/ unusual susceptibility, where the applicant added literature references describing G3-4 diarrhea, mucositis, neutropenia, neurotoxicity, and severe sudden cardiotoxicity to describe the clinical presentation for early onset toxicity due to 5FU.

Protocol ID: WELL401: SPI Clinical Operations Procedure (original release October 1995)

The WELL401 Clinical Operations Procedures were developed prior to the initiation of Protocol 401.10.001 to provide emergency access to uridine triacetate as an antidote for patients at excess risk of 5FU toxicity due to overdose or rapid onset toxicities. The procedures under WELL401 were utilized for patients treated with uridine triacetate from October 1995 through August 2011. These procedures were similar to those used for study 401.10.001 except that WELL401 allowed for enrollment of pediatric patients, capecitabine treated patients, patients outside of the United States, and patients who were outside of the 96 hour window of treatment with 5-FU or capecitabine.

Protocol WELL401 Amendments:

Protocol WELL401 was entitled "SPI clinical operations procedure" with US and ex- US versions. The dates of release for the US and ex- US versions are same. Version 1.0 was released on 9/2/11, Version 2.0 was released on 1/26/12 (same date as release of version 3.0 of protocol 401.10.001. Version 3.0 was released on 8/1/13, which is the same date as Version 4.0 of protocol 401.01.001.

Upon review of the two protocols, 401.10.001 and WELL401other than the eligibility, they were found to be identical, except for the eligibility criteria (mentioned above). Therefore, both protocols were reviewed herein.

Reviewer comment: It is notable that although patients began to be enrolled onto WELL401 in October 1995, the actual protocol and clinical operations procedures were not written and released until later, at the same time as when study 401.10.001 was opened in September 2011.

6 Review of Efficacy

Efficacy Summary

This NDA contains data from 135 patients treated on Study WELL401 (n=75) and Study 401.10.001 (n=60), both open-label, expanded access trials evaluating the treatment of patients with uridine triacetate who had either received an overdose of 5-fluorouracil or capecitabine, or presented with serious or life-threatening symptoms of 5-fluorouracil toxicities within 96 hours after the end of receiving 5-fluorouracil or capecitabine. Overdose was defined as administration of 5-fluorouracil at a dose, or infusion rate, greater than the intended dose or maximum tolerated dose for the patient's intended regimen of 5-flourouracil. Uridine triacetate was administered at 10g every 6 hours for 20 doses except for three patients between one and two years of age who were administered a body surface area adjusted dosage of 6.2 grams/m^2/dose for 20 doses. The primary efficacy outcome was survival at 30 days or until the resumption of chemotherapy if prior to 30 days.

Out of the 135 treated patients, 117 were treated with uridine triacetate following an overdose of 5-FU (n=112) or capecitabine (n=5), and 18 were treated after exhibiting severe or life-threatening 5-FU toxicites within 96 hours following the end of 5-FU administration. Out of the 117 patients with overdose of 5-FU or capecitabine on the two studies, 97% survived. In the patients receiving uridine triacetate for early-onset severe or life-treatening toxcity (cardiac, central nervous system, gastrointestinal toxicity, and/or neutropenia), 89% survived. Overall, 96% of patients survived to 30 days or resumed chemotherapy prior to 30 days. In examination of 25 historical control cases with known doses and rate of 5-FU overdose, 84% of patients died.

6.1 Indication

The applicant proposed the following indication for the uridine triacetate label:

(b) (4)

The efficacy of VISTOGARD initiated more than 96 hours following the end of (b) (4) fluorouracil has not been established.

The reviewer recommends the following indications for Vistogard:

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

Limitations of use:

- Uridine triacetate is not recommended for the treatment of adverse reactions associated with fluorouracil or capecitabine that are not severe or life-threatening because it may diminish the efficacy of these drugs.
- The safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established.

Reviewer Comment:
Labelling discussions over the indication are ongoing at the time of this review submission (see Sections 1 and 9.2).

6.1.1 Methods

The clinical review is based primarily on the clinical study reports from study 401.10.001 and study WELL401, case report forms, patient narratives, and data sets for efficacy submitted by the Applicant. These studies are described in detail in Section 5.3. Additionally, the Applicant submitted literature references for 47 historical control data, and these were also utilized in the review of this application as was an OSE consult examining morbidity and mortality from capecitabine and 5-FU in patients with impaired elimination.

6.1.2 Demographics

In the entire database, including both studies 401.10.001 and study WELL401, 135 patients were treated. The breakdown according to study and group (overdose or early-onset), as reclassified by FDA, are shown in Table 4. Study 401.10.001 enrolled patients from 77 centers in the US only. Study WELL401 included patients from both the US and outside of the US. Patients enrolled to WELL401 came from 82 centers. Countries outside of the US included Canada, Denmark, France, Germany, Spain, Greece, Paraguay, Singapore, and Australia.

Table 4: Patient Enrollment in both studies by Group (FDA classified)

	Overdose	Early-onset	Total
Study 401.10.001	46	14	60
WELL401	71	4	75
Total	**117**	**18**	**135**

Applicant Classification of Overdose or Early-Onset Severe or Life-threatening Toxicity

In describing the patients on each study the applicant classified patients as meeting enrollment criteria due to either receiving an overdose or early onset of severe or life-threatening toxicity for various reasons. In Study 401.01.001 of the 60 patients, the applicant classified 18 as rapid onset and 42 as having received an overdose of 5-FU. Of the 75 patients on Study WELL401, the applicant classified 69 as receiving an overdose of 5-FU or capecitabine and 6 as presenting with early-onset of severe or life-threatening toxicity from 5-FU for various reasons.

FDA Analysis: Reclassification of patients to overdose group

In analyzing Study 401.10.001, there were 4 patients classified as early onset cases by the applicant, who were re-classified as overdose cases in the FDA analysis and agreed upon reclassification by the applicant. As a result, the denominators for the two groups differ from the applicant's initial assessment. The specific ID numbers for the patients moved from the rapid onset to the overdose group were: OD118, OD126, OD113, and OD128. In all four of these cases, the patients received documented overdoses of 5FU, as defined in the protocol as dose or rate above the planned infusion. In addition, none of the cases met criteria (described in Section 5.2) to be included as early onset cases, and therefore, it was determined to be most appropriate to re-classify them as overdose

cases. In analyzing Study WELL401, there were two patients reclassified from the early onset group to the overdose group. These were patients OD059 and OD046. They will be described below.

Study 401.10.001 reclassified patients
The narratives for the four patients reclassified to the overdose group on Study 401.10.001 are discussed as follows:

- **OD118 (moved to overdose group from early onset):** 56 y/o AAM with head and neck cancer. This patient was labeled as an early onset case, but really is an overdose case. On 8/22/13, he received 8000 mg 5FU over 36 hours, rather than the intended 96 hour infusion. He also received carboplatin 430 mg. This was his first cycle of chemotherapy (of any kind). The overdose occurred due to a pump programming error. The infusion ended at 0100 on 8/22/13. Uridine triacetate was begun on 8/23/13 at 1045, which was approximately 34 hours after overdose event. He completed all 20 doses of uridine triacetate ending on 8/28/13. The patient was also tested for DPD mutation and was found to be heterozygous for DPYD c. 85T>C. He also had 2 TYMS mutations. The patient developed G1 mucositis beginning on 8/23/13 and resolving on 9/4/13. It was decided that the patient would not receive further chemotherapy due to the event and the presumed mutation status. In the week following the overdose, the patient experienced mild (G1) cytopenias. There is no mention of other adverse events.

  Reviewer comment OD118: This patient was re-categorized from the early onset group, to the over dose group. He did receive a documented overdose of 5FU, but his history was not compelling to support the diagnosis of early onset toxicity due to 5FU. We have counted this case only as an overdose case only.

- ***OD126* (moved to overdose group from early onset)***:* 58 y/o female with anorectal squamous cell carcinoma receiving 5FU and cisplatin. According to the narrative, on C1 she "rapidly developed significant 5FU toxicities, including neutropenic fever and mucositis", although details of clinical course are not provided. Her physician performed DPD testing after C1, which revealed mutation(s), but the exact abnormalities are not mentioned. Her physician did decide to continue with 5FU therapy, and she initiated C2 with dose reduction starting on 11/15/13. The plan was for her to receive 25% reduction of 5FU for 24h, followed by 75% reduction for the next 24h, followed by 50% dose reduction for the last 24h (total 72-h infusion). Due to a pump infusion malfunction, the total dose of 2935 mg, which started on (b) (6) at 10:30 and ended on (b) (6) at 0800, was given over 22h instead of over the intended 72 hours. Due to the patient's history, she was

hospitalized and uridine triacetate was initiated on (b) (6), approximately 18 hours after the 5FU infusion ended. She received 17 of 20 doses (85%), ending of (b) (6). Her only complaint was of slight mouth soreness. On (b) (6), 10 days later, she was noted to be doing well with minimal mucositis. She had only experienced mild cytopenias. She was subsequently lost to follow up.

Reviewer comment OD126: Based upon the treating physician's plan to reduce her dose of 5FU, as described, this was counted as an overdose case, since she received an overdose above the intended infusion rate. It is notable, however, that it is unclear how the treating physician derived the dose adjustments, as described. Nevertheless, there are not enough details or documentation in the narrative about the patient's prior treatment with 5FU to support classifying this case as an early onset case. Therefore, this was counted as an overdose case.

- ***OD113*** **(moved to overdose group from early onset)***:* 49 y/o WF metastatic colorectal cancer. Was due for C3 FOLFOX consisting of 2318 mg 5FU to be given over 46 h, along with oxaliplatin 137 mg. The 5FU was accidentally given over 6h instead of 46h, and the error was recognized on (b) (6), which was approximately 12 hours after the overdose occurred. The patient had apparently previously been diagnosed with DPD deficiency on 6/22/11, and her 5FU dose had been decreased by 60%, as a result (details of the previous dosing and side effects were not provided). The specific mutations documented included 1 heterozygous mutation on the DPYD gene, associated with reduced DPD activity. The patient also had a history of Crohn's disease, with chronic diarrhea. She presented to the ER and was tachycardic and had a WBC ranging 17-19K. She was admitted to the hospital on (b) (6) and began uridine triacetate at 21:15 on (b) (6), approximately 24h after the overdose was recognized, and this is estimated to be approximately 36 hours after the actual overdose. She received all 20 doses of uridine ending on (b) (6), and she was discharged from the hospital. She was reported to have anemia and mucositis, which were improving at the time of discharge. She was subsequently lost to f/u, although the narrative states that she lived "well beyond the 30-day study period was documented." It was subsequently found that she died on (b) (6) due to colon cancer, therefore she did survive beyond D30.

Reviewer comment OD113: This was not deemed to be a compelling case for early onset of severe toxicity due to 5FU. Details about the actually toxicities and the timing of onset are missing. Likewise, she had received prior cycles with 5FU, and although she was being dosed with a decrease dose of 5FU due to prior history, this cannot be confirmed for the purposes of this event. However, she did receive a documented overdose of 5FU, based upon her intended regimen, and she received all prescribed doses of 5FU. The documentation of survival beyond day 30 is

implied, due to the known date of death (which is well beyond the 30 day window). Therefore, this case will be re-classified as an overdose case.

- ***OD128*** **(moved to overdose group from early onset)**: 49 y/o WF with metastatic appendiceal adenocarcinoma originally diagnosed 9/25/12. Following initial surgery, she received FOLFOX chemotherapy beginning in 11/12. According to the narrative, she had "excessive toxicity" related to 5FU, such that 5FU was eliminated after Cycle 3. She was apparently found to be heterozygous for a missense mutation in DPD, and had possible mutation in TYMS gene. On 12/26/13 she received an overdose of 5FU- which was either C4 or C8 of second ling FOLFIRI (conflicting information). Was planned to receive 4030 mg over 46h, but due to unknown reason, the infusion went in over 15 min. This was recognized on 12/26/13 at 1800. Uridine triacetate was initiated on 12/27/13 at 1235, which was approximately 18 hours after overdose. She received all 20 doses of uridine. Last dose of uridine was 1/1/14 and she completed D30 on 1/26/14. She resumed FOLFIRI on 2/2/14 with reduced dose irinotecan and no bolus of 5FU. She was retested for DPD and found to be heterozygous for a missense mutation in DPD. She also had 3 copies of a repeat in the TMYS gene. Toxicities that were reported included G2-3 mucositis and cytopenias, hand-foot syndrome.

  Reviewer comment OD128: This was not deemed to be a compelling story to support classification as an early onset case. The patient had received 3 prior cycles with 5FU, and although she was reported to have had excessive toxicity with those cycles, the documentation about the exact toxicities and timing is missing. However, she did receive a documented overdose of 5FU, above the intended dose (by infusion rate). Therefore, this case was reclassified as a valid over dose case, given that she received all doses of uridine triacetate, and resumed chemotherapy with 5FU (prior to day 30).

<u>Study WELL401 reclassified patients</u>

- **OD046 (moved to overdose group from early onset)-** 46 y/o WM with Stage IIIB colorectal cancer. He had a history of life-threatening 5FU toxicity after a dose of 1710 mg given over 96 hour infusion. He had documented history of DPD and TYMS mutations. Following recovery from the toxicities, over a 6 month period, his cancer had progressed and his physician opted to treat him again with 5FU, but at an "extremely" low dose. He was to receive 100 mg 5FU bolus on 10/15/10, but inadvertently received 1000 mg over 1 minute (thus, an overdose). Given the patient's history, the physician was concerned that the patient would experience life-threatening toxicity again, and he therefore requested uridine triacetate. The first

dose of uridine triacetate was given on 10/15/10 at 2350, which was 8.4 hours after the overdose of 5FU. The patient had no symptoms of 5FU toxicity. He received all 20 doses of uridine triacetate, ending on 10/20/10. He tolerated the dosing well. He did not display any symptoms of 5FU overdose. His hematologic parameters had declined slightly, including a platelet count of 75K. By 11/12/10, the physician considered the patient to be fully recovered from the 5FU overdose. Chemotherapy with 5FU was restarted on 11/12/10 at the low dose of 100 mg bolus (in addition to oxaliplatin). The patient apparently tolerated this repeat dose of 5FU well with only mild pancytopenia.

Reviewer comment OD046: Given that there was no documentation of the patient's prior events related to 5FU, which lead the physician to believe that the patient would have rapid onset of toxicity from 5FU, this patient was not counted as a rapid onset case for the purposes of the present review. However, since this patient was only intended to receive 100 mg 5FU, and he actually received 1000 mg, he was counted as an overdose case, and moved to the overdose group in Study WELL401. He technically did not complete the 30 day follow-up period, since he restarted chemotherapy with 5FU prior to that window, however, he otherwise fulfilled criteria for a valid case of 5FU overdose, and was successfully treated with uridine triacetate. In addition, he obviously did survive to D30, giving the reclassification of this patient to the overdose group more credence.

- **OD059 (moved to overdose group from early onset)**- 59 y/o WM colorectal cancer diagnosed 6/23/11. He was scheduled to receive the modified FOLFOX-6 regimen. On 7/18/11, he received 200 mg oxaliplatin with 400 mg leucovorin, followed by 5FU 800 mg IV bolus and then scheduled to receive 4800 mg over 46-h infusion. However, due to the infusion pump being mis-programmed, the 4800 mg infused over 5 hours instead of the prescribed 46h. Uridine triacetate was requested and was started on 7/19/11 at 10:20, which was approximately 18h after completion of the 5FU infusion (23 hours after start of 5FU. The patient took all 20 doses of uridine, ending on 7/24/11. Genetic testing for DPD revealed him to carry a heterozygous mutation for the DPYD c.85T>C mutation, as well as heterozygous for the MTHFR gene c.677C>T. The patient did "remarkably well", and was therefore started on C2 of 5FU with oxaliplatin on 8/1/11 (therefore, did not complete the full 30 day f/u). The dose for 5FU in cycle 2 was unchanged from C1.

  Reviewer comment OD059: The history provided by the Applicant on this patient did not include enough details on his history to consider him a valid early onset case, however, he did receive a documented 5FU overdose by rate, and received the prescribed 20 doses of uridine triacetate. He survived, although did initiate the next course of therapy prior to D30.

Patient Characteristics

The demographics for patients on Study 401.10.001 are shown in Table 5.
This was not a randomized trial, so there was not an expectation that there would be similar demographics in the overdose and early-onset groups. However, there was an equal distribution of males and females across these groups. Likewise, most patients were white and had a diagnosis of colorectal cancer, which is in keeping with the common patient population that would typically receive 5-FU based chemotherapy. Other tumor types included other gastrointestinal tract cancers, head and neck cancers, and a few others, including breast cancer.

Table 5 Demographics of Patients Enrolled in Study 401.10.001

	Overdose N=46 (%)	Early Onset N=14 (%)	Total N=60 (%)
Age (years)			
Mean (SD)	60 (11)	61 (9)	60 (11)
Median	60	58	59
Min, Max	29, 83	49, 81	29,83
Gender, n (%)			
Male	23 (50)	6 (43)	29 (48)
Female	23 (50)	8 (57)	31 (52)
Race, n (%)			
White	34 (74)	11 (79)	45 (75)
Black or African American	6 (13)	2 (14)	8 (13)
Asian	1 (2)	1 (7)	2 (3)
Hispanic	4 (9)	0	4 (7)
Other/Unknown	1 (2)	0	1 (2)
Cancer diagnosis, n (%)			
Colorectal	32 (70)	8 (57)	40 (67)
Pancreatic	1 (2)	0	1 (2)
Head and Neck	7 (15)	3 (22)	10 (17)
Gastric	1 (2)	0	1 (2)
Other	5 (11)	3 (22)	8 (13)
Height (cm)			
Min, Max	152, 188	154, 180	152, 188
Weight (kg)			
Min, Max	45, 128	45, 112	45, 128

Source: Data derived from dm.xpt.

The demographics for patients treated on WELL401 are shown in Table 6. The breakdown is similar to the patients on Study 401.10.001, although even fewer patients are in the early onset group on study WELL401.

Table 6 Demographics of Patients Enrolled in Study WELL401

	Overdose N=71 (%)	Early Onset N=4 (%)	Total Number of Patients N=75 (%)
Age (years)			
Mean (SD)	56 (18)	49 (25)	56 (18)
Median	59	54	59
Min, Max	1, 78	16, 70	1,78
Gender, n (%)			
Male	45 (63)	2 (50)	47 (63)
Female	26 (37)	2 (50)	28 (37)
Race, n (%)			
White	49 (69)	3 (75)	52 (70)
Black or African	4 (6)	0	4 (5)
American	3 (4)	0	3 (4)
Asian	15 (21)	1 (25)	16 (21)
Cancer diagnosis, n (%)			
Colorectal	34 (48)	2 (50)	36 (48)
Pancreatic	5 (7)	0	5 (7)
Head and Neck	11 (15)	1 (25)	12 (16)
Gastric	6 (8)	1 (25)	7 (9)
Breast	2 (3)	0	2 (3)
Other cancer NOS	8 (11)	0	8 (11)
No cancer diagnosis	5 (7)	0	5 (7)
Height (cm)			
Min, Max	81, 191	165, 185	81, 191
Weight (kg)			
Min, Max	11, 122	58, 98	11, 122

Source: Data derived from dm.xpt.

Reviewer Comment:
The subjects with no cancer diagnoses included accidental capecitabine ingestions and one non-cancer patient who got 5FU instead of the intended cyclophosphamide for her non-cancer diagnosis.

Applicant Overdose Cases

Of the 117 patients classified by FDA as receiving an overdose of 5-FU or capecitabine, five had accidental ingestion of capecitabine (subject IDs: OD052, OD063, OD103, OD111, and OD123). The remaining 112 experienced 5-FU overdoses. Of those 112, four were overdosed by dose only (subjects OD108, OD018, OD046 and OD112), three were overdosed by rate and dose (subjects OD028, OD042, and OD032), and the remainder 105 patients were overdosed by infusion rate only. The infusion rate overdoses (n=108) ranged from 1.3 to 720 times the planned infusion rates.

Retrospective Historic Control Cases

As part of the NDA, the applicant submitted 47 historic control cases of 5-FU overdose from multiple sources including the Institute for Safe Medication Practices (ISMP), US FDA Manufacturers and User Facility Device Experience database (FDA MAUDE), US FDA Adverse Events Databases (FDAble), FDA MedSun (FDA Medica Product Safety Network), legal documents, and physician/ hospital reports. These cases were to serve as a comparison with the uridine triacetate treated patients. Of these 47 cases, 25 had fully documented doses and rates of 5-FU overdose. Of these 25 cases, one case was due to an overdose by both dose and rate (300% greater than planned) and the rest of the cases were overdosed only by rate with a range of 1.9 to 64.0 times the planned infusion rate).

Reviewer Comment:
The majority of overdoses on studies 401.10.001 and WELL401 were from 5-FU rate increases above planned rate, and are comparable to the historic control data submitted by the Applicant.

6.1.3 Subject Disposition

A total of 135 patients were enrolled on the two studies. The disposition for patients at the end of studies 401.10.001 or WELL401 are shown in Table 7. Most patients (61%) completed the dosing of uridine triacetate and the protocol specified 30-day follow-up. Approximately 33% of patients resumed chemotherapy prior to study day 30, most of whom were in the overdose group. As will be discussed later in the review, most patients (96%) in both groups survived. Likewise, only 2% of patients treated with uridine triacetate discontinued therapy due to an adverse event.

Table 7 Patient Disposition on Studies 401.10.001 and WELL401 combined

	Overdose N=117 (%)	Early onset N=18 (%)	Total N=135 (%)
Completed study through Day 30	71 (61)	12 (67)	83 (61)
Resumed chemotherapy prior to Day 30	41(35)	3 (17)	44 (33)
Discontinued due to AE prior to Day 30	2 (2)	1 (6)	3 (2)
Death prior to Day 30	3 (2)	2 (10)	5 (4)

Protocol deviations

There were only 4 patients (all in the early onset group) between the two studies with a major protocol deviation of *initiating uridine triacetate therapy outside of the protocol-specified 96 hour window*.

On Study 401.10.001, these were patients OD97 and OD134, and on Study WELL401, they were patients OD138 and OD120. Two of these 4 patients (OD134 and OD120) died, and the delay in initiation of therapy with uridine triacetate therapy was considered to be a possible contributing factor in these deaths. The other two patients survived, despite initiation of therapy outside of the 96 hour window. However of these two patients, OD138 was a case that FDA disagreed with, as a valid case of early onset toxicity with successful treatment with uridine triacetate. Although this patient did survive, she had irreversible morbidity related to the 5FU toxicities, and this may have been attributable to the late initiation of therapy with uridine triacetate.

Reviewer comment: It is again notable that the outcomes of the patients described, with deviation from the 96 hour window, lend support to the recommendation that therapy with uridine triacetate should be initiated within 96 hours of the onset of life-threatening toxicity.

There were additionally multiple minor protocol deviations, which included the following categories: protocol specified procedure not done or done outside of the pre-specified window of time, missed or incomplete uridine triacetate dosing, withdrawal before end of study, concomitant administration of prohibited medications, failure to perform required evaluations, and “other” deviations. After review, these minor deviations were found to occur in small numbers of patients, with the exception of procedures not being done or not being done within the predefined time interval, which occurred in 96% of patients on both studies. Nevertheless, none of the minor protocol deviations appeared to impact the study integrity or results.

6.1.4 Analysis of Primary Endpoint(s)

The primary study endpoint for both studies was survival at day 30 or initiation of chemotherapy if this occurred first. Although there was no control group on either study, the applicant provided data from retrospective historical controls to help define the overdose patient population in particular, with regard to the expected outcome (death) after 5FU overdose when patients receive only supportive care and no uridine triacetate therapy. The studies are presented initially together with all groups and then presented separately by study and by group (overdose and early onset).

Efficacy Studies 401.10.001 and WELL401

Of the 135 patients treated in both studies, 117 were classified as receiving uridine triacetate for 5-FU or capecitabine overdose and 18 were classified as receiving uridine triacetate for early-onset of 5-FU severe or life-threatening toxicity. The overall survival for these studies is summarized in Table 8. Of the combined studies, 97.4% of patients receiving a 5-FU overdose survived and 88.9% of patients exhibiting early-onset severe or life-threatening toxicity from 5-FU survived and 96% of the combined population survived.

Table 8: Survival Analysis for Studies 401.10.001 and WELL401 (Applicant Analysis)

	Overdose N=117	**Early onset N=18**	**Total N=135**
Study 401.10.001	46	14	60
• **Death within 30 Days**	1	1	2
• **Survived/resumed chemotherapy**	45	13	58
WELL401	71	4	75
• **Death within 30 Days**	2	1	3
• **Survived/resumed chemotherapy**	69	3	72
Combined Studies, n (%)			
• **Death within 30 Days**	**3 (2.6%)**	**2 (11.1%)**	**5 (3.7%)**
• **Survived/resumed chemotherapy**	**114 (97.4%)**	**16 (88.9%)**	**130 (96.3%)**

Source: Clinical study reports for 401.10.001 and WELL401, patient narratives and case report forms.

Reviewer Comment:
As described in detail below for each study, FDA conducted their own analysis (described in Section 5.2) of each of the 135 cases to determine if uridine triacetate could be attributed to the survival of the patient. For 401.10.001, there was one case of overdose and two cases of early onset for which FDA did not agree and for WELL401 there were three cases of overdose and two cases of early onset for which FDA did not agree. However this does not change the overall finding and conclusion that the vast majority of subjects receiving 5-FU overdose or exhibiting early onset of severe or life-threatening toxicity survived. Taking the FDA analysis into account removing the cases which FDA did not agree with, overall survival results are shown in Table 9.

Table 9: Survival for Studies 401.10.001 and WELL401 (FDA analysis)

	Overdose N=113	**Early onset N=14**	**Total N=127**
Study 401.10.001	**45**	**12**	**57**
• Death within 30 Days	**1**	**1**	**2**
• Survived/resumed chemotherapy/FDA agreed	**44**	**11**	**55**
WELL401	**68**	**2**	**70**
• Death within 30 Days	**2**	**1**	**3**
• Survived/resumed chemotherapy	**66**	**1**	**67**
Combined Studies, n (%)			
• Death within 30 Days	**3 (2.7%)**	**2 (14.3%)**	**5 (3.9%)**
• Survived/resumed chemotherapy	**110 (97.3%)**	**12 (85.7%)**	**122 (96.1%)**

Source: Clinical study reports for 401.10.001 and WELL401, patient narratives and case report forms.

Retrospective Historic Control 5-FU Overdose Cases

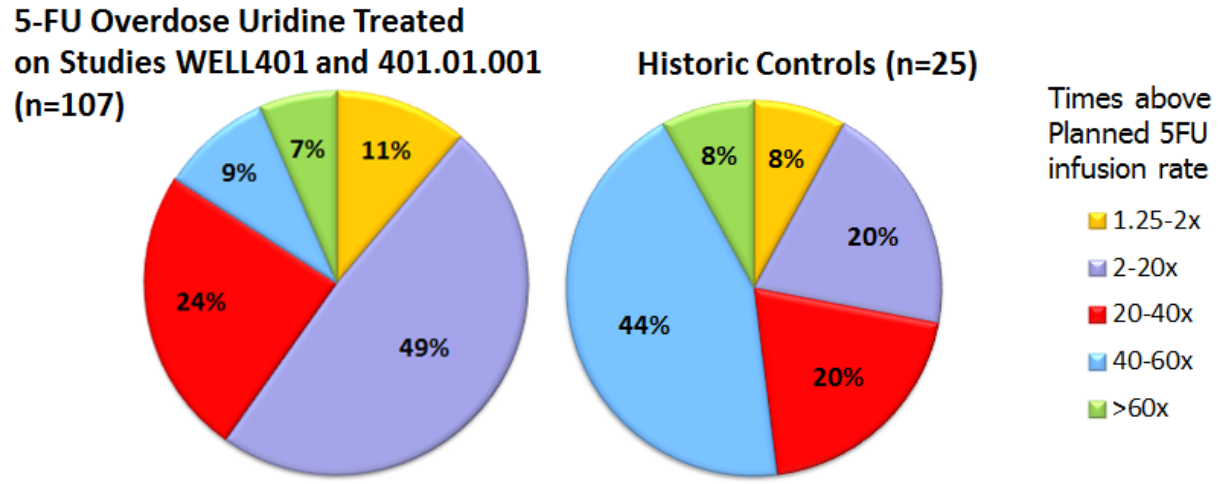
As noted above, the applicant provided a retrospective analysis of 'representative' historical controls (reported in the literature) to help define 5FU overdose and the usual outcome (death). Of the historical control cases provided, there were 25 cases for which 5-FU overdose was verified with documentation of both dose and rate, and 84% of those patients died. For the historical control cases, and for the patients on trials WELL401 and 401.10.001 rates and doses were analyzed. The majority of cases in the studies (79%) were overdosed by rate above planned infusion rate of 5-FU and the historical control cases were all overdosed of by rate above planned infusion rate for 5-FU. Table 10 shows comparison of overdoses by rate above the intended rate for the historical control cases, compared to the uridine triacetate treated cases. Figure 1 shows a similar comparison graphically.

Table 10: Historic Control and Uridine Treated Cases Comparison of 5-FU Overdose Rates

Rate Ratio (amount times the intended infusion rate)[a]	**Studies WELL401 and 401.10.001** Total patients who overdosed by rate (n=107)[b]	**Historical Controls** Total patients who overdosed by rate (n=25)
(1-1.25]	0	0
(1.25-1.5]	3	0
(1.5-1.75]	2	0
(1.75-2]	7	2
(2, 10]	33	3
(10, 20]	19	2
(20, 30]	18	5
(30, 40]	8	0
(40, 50]	8	10
(50, 60]	2	1
(60, 70]	0	2
(70, 80]	1	0
(80, 90]	0	0
(90, 100]	1	0
(100, 720]	5	0

a: Max Rate Ratio for the two studies was 720. Max Rate Ratio for the historical controls was 64. Numbers reflect the patients for which dose and rate of 5-FU overdose was recorded and for whom an overdose by rate above what was planned was recorded.
b: This does not include Subject OD094 who was dosed daily with three bolus doses for three dose at 1750mg each day, but was planned to get these doses as continuous infusions.

Figure 1 5-FU Rate Overdose Comparison between historic controls and WELL401/401.01.001



Between the historic controls and the subjects on the uridine treated studies, deaths occurred across the whole range of rates, see Table 11.

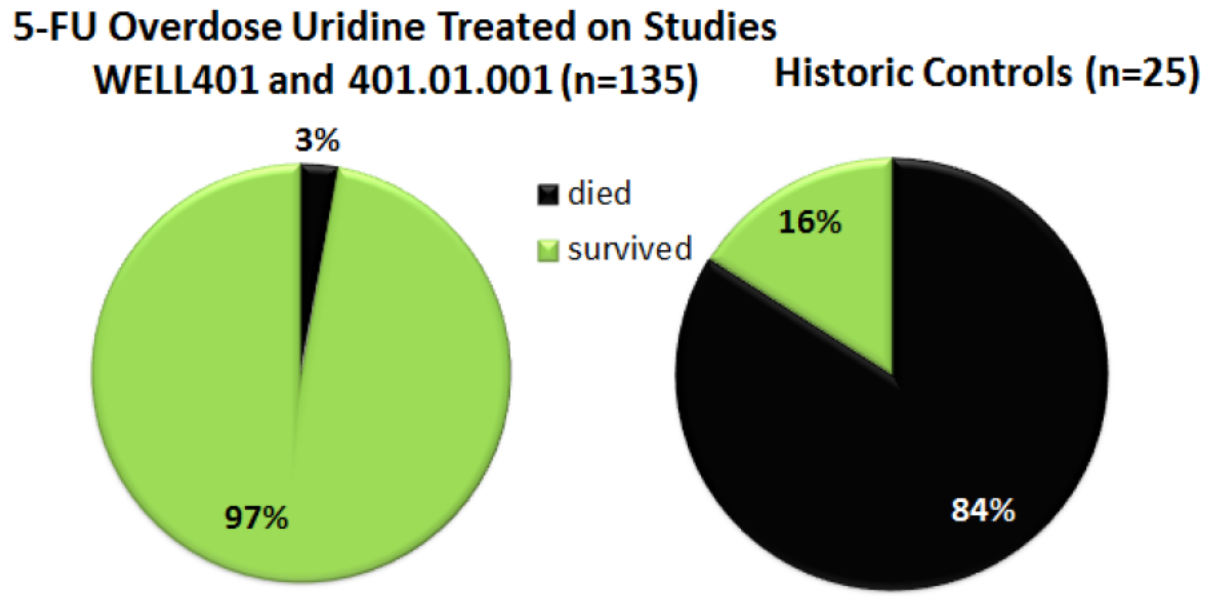
Table 11 Comparison of patients who died due to 5-FU overdose by rate on Studies WELL401 and 401.10.001 vs. historic controls

Rate Ratio (amount times the intended infusion rate)[a]	Studies WELL401 and 401.10.001 Patients who died	Historical Controls
(1-1.25]	0	0
(1.25-1.5]	1	0
(1.5-1.75]	0	0
(1.75-2]	0	0
(2, 10]	0	3
(10, 20]	0	1
(20, 30]	2	5
(30, 40]	0	0
(40, 50]	0	9
(50, 60]	0	1
(60, 70]	0	2
(70, 80]	0	0
(80, 90]	0	0
(90, 100]	0	0
(100, 720]	0	0

a: Numbers reflect the patients for which dose and rate of 5-FU overdose was recorded and for whom an overdose by rate above what was planned was recorded.

Of the 25 historic controls who received an overdose of 5-FU by rate, 21 died (84%). In comparison, 97% of the uridine treated patients lived after receiving similar overdoses, as shown in Figure 2.

Figure 2 Comparison of outcome of 5-FU overdose in historic controls and uridine treated on Studies WELL401 and 401.01.001



Reviewer Comments:

1. *The patients overdosed by 5-FU in the uridine trials were comparable to those in the historical control in terms of type of overdose with overdose by rate being the most common, rates above the planned infusion.*
2. *The comparison of the rate overdoses between the uridine treated and historic controls demonstrates deaths across a range of rate overdoses (one death was seen at 1.25-1.5 x the intended rate) as well as generally comparable rates.*
3. *The main point for considering the historic controls in our analysis, is that they did appear to be comparable to the overdose patients treated with uridine triacetate in the studies 401.10.001 and WELL401, and they do give a striking frame of reference, where by 84% of the historic control cases of 5FU overdose died, compared with 96% who survived after treatment with uridine triacetate.*
4. (b) (4)

5. *It is not clear that the exact overdose which would result in death is possible to quantify because patients may have a variable expression of toxicity. Therefore this reviewer favors leaving the indication as overdose and explaining the range of overdoses seen in the studies in Section 14 of the label as well as the inclusion criteria for the study.*

Study 401.10.001 Efficacy

Overall survival for Study 401.10.001 by patient group (overdose or rapid onset toxicity) is shown in Table 12. The FDA assessment of overall survival, as determined by specific criteria described in Section 5.2, is also shown in the table. After considering the cases where patients died within 30 days (which was the primary study endpoint), and the cases that were determined to be invalid cases after FDA review, there were a total of 55 patients on Study 401.10.001 who were successfully treated with uridine triacetate, and who survived through Day 30 or resumed chemotherapy prior to Day 30.

As was described in Section 5.2 of this review, the FDA used specific criteria to determine FDA agreement, as valid cases of overdose or early onset toxicity, with successful treatment with uridine triacetate. They are summarized here again:

For the overdose group of patients, the criteria for "FDA Agreement" included:

1) Documentation of 5-FU overdose.
2) Uridine triacetate initiated within 96 hours.
3) Patient received >80% uridine triacetate doses.
4) Documentation of survival at Day 30.

The criteria for "undisputable" FDA agreement for the early onset patients were as follows:

1) Documented 5FU dosing.
2) Uridine triacetate initiated within 96 hours.
3) Patient received >80% uridine triacetate doses.
4) Documentation of survival at D30.
5) Presence of early-onset life-threatening symptoms.

Reviewer comment: We used 80% as the cut off for uridine triacetate doses received in our assessment for efficacy because we wanted to have a high bar for concluding that uridine triacetate was effective. However, we acknowledge that it is not clear what the

appropriate amount of uridine triacetate required to achieve efficacy really is, and in fact, patients may have derived benefit from far fewer doses. .

Table 12 Survival: Study 401.10.001 (FDA Analysis)

	Overdose N=46	Early Onset N=14	Overall N=60
FDA agreement as successfully treated case with survival at Day 30	44	11*	55
FDA Disagree	1	2	3
Death within 30 day	1	1	2

*11/14 rapid onset cases gained FDA agreement. All cases were either deemed to be undisputable cases (meeting all 5 criteria) or reasonably likely (meeting less than the 5 criteria).

"Disagree" cases Study 401.10.001: As shown in Table 12, on study 401.10.001, there were three patients with whom we *disagreed as cases* successfully treated with uridine triacetate based on the strict criteria we set forth (see Section 5.2). One case was in the overdose group (patient OD076) and two were in the early onset group (patients OD061 and OD081). The narratives are discussed below:

- **OD076 (overdose group, "disagree" case)**: was a 56 y/o white male with colorectal cancer who was receiving FOLFOX plus Avastin chemotherapy. On 4/10/12, he began C6 of FOLFOX. During this cycle, he received an overdose of 5FU, such that the infusion was supposed to go in over 46 hours, but it reportedly went in over approximately 24 hours instead (due to pump programming error). The physician requested uridine triacetate, and the first dose was given on (b) (6) at approximately 1550; this was approximately 25.5 hours after the overdose occurred. The patient had difficulty tolerating the uridine triacetate, due to the taste. He could not take the entire first dose. He was scheduled to take the remaining 19 doses as an outpatient, however on (b) (6), he informed his physician that he had failed to take the evening dose on (b) (6), due to the taste. For this reason, the patient informed the physician that he would not attempt any further doses. His physician instructed him of the risks, but the patient refused any further doses of uridine triacetate. On (b) (6), he was seen in follow-up. He was well appearing and only reported oral numbness, thought to be related to oxaliplatin. It was decided that he would resume chemotherapy, switching to FOLFIRI instead of FOLFOX due to the oral numbness. This began on (b) (6), which was approximately 21 days from the 5FU overdose.

Reviewer comment on OD076: Using the criteria set forth for the FDA analysis, this case was not deemed to be a case of 5FU overdose with successful treatment with uridine triacetate. The main reason for exclusion in the FDA analysis is that the patient only took two of the 20 doses of uridine triacetate. Additionally he restarted chemotherapy with 5FU approximately 21 days after the overdose and did not present for the 30 day survival follow-up. For these reasons, he was not included as a successful case in the FDA analysis, but we acknowledge that it is really unknown whether uridine triacetate benefitted (or did not benefit) this patient.

- **OD061 (early onset group, "disagree" case)** was a 55 y/o white female with anal cancer originally diagnosed in 2010. Her initial therapy in 2010 consisted of 5FU continuous infusion with mitomycin and XRT. She reportedly experienced "significant morbidity" with that regimen, including severe thrombocytopenia, neutropenia, and rectal bleeding requiring hospitalization and delay of radiation therapy. More specific details were not provided in the narrative. She was subsequently diagnosed with metastases to the lungs and liver in 7/11 and was initially sent to hospice. However, she sought a second opinion and began chemotherapy with infusional 5FU and carboplatin + paclitaxel on (b) (6). The planned dose of 5FU was to be 2380 mg over 7-day infusion (168 h). The infusion of 5FU started on (b) (6) and she did not complete entire dose, but had 5FU stopped early due to toxicity. At that point, she had received 1600 mg at 120 hours (5 days -on (b) (6)). Toxicities experienced by the patient included nausea and fatigue (no grade given) beginning on (b) (6) (24 hours into the infusion). At 48 hours, on 9/2/11, she developed G3 mucositis. By (b) (6) (Day 5 of infusion), she reported blood tingled mucous in her vomitus. She was admitted to the hospital due to the G3 mucositis, nausea, poor oral intake, decreasing blood counts (exact counts not given). The 5FU was discontinued on (b) (6) and blood was sent for DPD testing at that time. By 9/5/11, she developed febrile neutropenia and required Dilaudid for pain management. Oral intake began to improve with dilaudid. She also was started on broad spectrum antibiotics and filgrastim, after which she was afebrile. There is poor documentation as to whether this patient experienced diarrhea up to this point, however, by 9/6/11 she had diarrhea controlled by loperamide, and was afebrile. As per the narrative, "patient's neutropenia continued… but nausea, mucositis, and diarrhea were improving with symptomatic management". It was at this point that Wellstat was contacted regarding uridine triacetate for suspected DPD deficiency. The patient began uridine 9/7/11 at 1100 (narrative and dataset states that this was 74 hours after 5FU stopping), however, this is inaccurate and it was actually 67 hours. She only

received 4 complete uridine doses (and only attempted 6 doses), due to vomiting 1 dose and did not attempt 1 dose). She had great difficulty tolerating the uridine. She was clinically afebrile by the evening of 9/7/11. She managed to take half of the uridine triacetate dose on 9/8 at 0400. She continued to be neutropenic, with ANC 700 on 9/8, but nausea and oral intake were improving. The oncologist determined to stop therapy with uridine triacetate at this point, as the patient was not tolerating taking the pills, and still did not have a definitive diagnosis of DPD deficiency. By 9/9/11, patient again had a fever, but was no longer neutropenic (on filgrastim). Uridine triacetate had been discontinued- in particular, the patient did not complete study through week 4. Oral intake improved and patient was well appearing by 9/10/11; antibiotics were discontinued. She was discharged from the hospital on (b) (6). On 9/20/11, the results of the DPD test were negative for the IVS14+1G>A mutation, however this test did not rule out the presence of other mutations in the DPD gene. The investigator actually determined that the toxicities may have even been due to carboplatin sensitivity. She resumed chemotherapy on 9/23/11, which consisted of capecitabine 1000 mg BID, but no details were provided as to how this patient tolerated the capecitabine.

Reviewer comment on OD061: This was determined to be an unlikely (disagree) case of early onset toxicity with successful treatment with uridine triacetate in the FDA analysis. The main reasons for this assessment included the lack of life threatening toxicities, and the fact that the patient only received 4 of the 20 doses of uridine triacetate, before refusing further doses. We again acknowledge that the exact number of doses needed for efficacy is unknown, however, based upon the Applicant's recommendation for 20 doses, and upon our interest in maintaining a high bar to declare efficacy for the use of uridine triacetate therapy, we determined that the fact that this patient only received 4 doses of the uridine triacetate, it was difficult to conclude that the therapy yielded undisputable benefit for this patient. In addition, she went on to receive further chemotherapy with capecitabine, and although this was not a hard criterion for "disagreement " with an early onset case, it was typical in other true early onset cases, that the treating physician opted to not treat with further 5FU-based therapy, based upon the risk to the patient.

- **OD081 (early onset group, disagree case**): 73 y/o male with metastatic esophageal cancer. He had never received 5FU before the event described. He was receiving 5FU at a dose of 7000 mg by 120-h infusion, plus cisplatin and docetaxel. Infusion began on 7/19/12 and ended on 7/24/12 at 1200. Toxicities began approximately 24 hours from the end of the 5 day infusion of 5FU (7/25/12) and included cytopenias and mucositis. There was no CTC grading for the toxicities, but they were described as "severe". The patient began uridine on

7/26/13 at 0130, approximately 38 hours after the 5FU infusion ended. He only took 8 doses of the planned 20 doses uridine (~40%). He completed the follow-up through study D30. He did not receive any further therapy with 5FU. Although he is listed as being "suspected" as having DPD deficiency, this was not documented.

Reviewer comment on OD081: This was also a "disagree" case in the FDA assessment. The case is unlikely to be a true early onset case, with rescue from uridine triacetate, for the following reasons. The onset of toxicities was later than what was considered to be "early onset" (at approximately 144 hours, or 6 days from initiation of 5FU), and the severity of the toxicities was poorly documented and of questionable clinical significance. Likewise, the patient completed fewer than half of the prescribed doses of uridine, making it impossible to ascribe whether he had any benefit from the therapy, or to what extent (despite our acknowledgment that the true number of doses needed for efficacy is not known). Finally, there was no documentation of DPD or other enzyme deficiency for this patient. Therefore, this was not considered to be a true case of early onset toxicity from 5FU, nor was it considered to be case of successful treatment with uridine triacetate.

Deaths Study 401.10.001

Also shown in Table 12, one patient died on each group in study 401.10.001. On the overdose group, the death was patient OD127. On the early onset group, the death was patient OD134. Both narratives for the patient deaths on 401.10.001 are discussed below:

- ***OD127 (overdose group, death)*** was 66 y/o white female with metastatic colorectal cancer to the lungs, who was receiving her first cycle of FOLFOX chemotherapy. She received a documented overdose of 5FU, such that the pump was programmed to deliver the dose of 4152 mg 5FU over46 hours, but instead, the infusion went in over 2 hours. Uridine triacetate was initiated ~24 after the overdose, however the patient became ill very quickly, on the same day that uridine triacetate was initiated. She developed respiratory failure, was intubated, and subsequently developed renal failure and cardiogenic shock. She had only received 3 doses of uridine triacetate when her family requested comfort care measures only, and she died 24hours later. Although the events, including respiratory failure and cardiogenic shock, may have been related to 5FU, it was unclear from the information provided.

  Reviewer Comment on OD127: This case could represent a rare uridine

triacetate failure, as treatment was initiated within the appropriate time frame, yet the patient expired.

- ***OD134 (early onset group, death*)** was a 59 y/o Asian male with Stage IIIB colorectal cancer. Began his first cycle of FOLFOX chemotherapy on (b) (6) with 160 mg oxaliplatin, 5FU 760 mg bolus followed by 4560 mg 5FU infusion to be given over 46 h with leucovorin. The infusion ended as planned on (b) (6). Approximately 24 hours after the end of the infusion, on (b) (6), the patient presented with facial swelling, redness of the face and chest, and loss of appetite and taste, which started on (b) (6) (48 hours after infusion began). The symptoms were not immediately recognized as being related to 5FU. The patient then presented on (b) (6) to the ER with diarrhea and swelling around the eyes. By (b) (6), the patient again presented to the oncologist with G3 mucositis, facial swelling, inability to take PO. This was 96 hours from the end of 5FU infusion. At this point, the physician suspected a 5FU elimination defect and request uridine triacetate. The therapy with uridine triacetate was initiated on (b) (6), which was 100h after the end of infusion and 148h from the beginning of the 5FU. It was noted that *protocol exception was authorized* for this patient to be treated. On (b) (6), the patient became septic with neutropenia. By dose #12 of uridine triacetate, he was unable to swallow the doses, and he was on TPN due to lack of ability to take PO at all. By (b) (6), he was lethargic and confused, and the physician suspected the onset of encephalopathy. By (b) (6), he was severely septic and hypotensive. By (b) (6), he was intubated in the ICU. Genetic testing for DPD was sent. He was found to be heterozygous for the c.1905+1 G>A (a.k.a. IVS14+1 G>A DPYD*2A) mutation. On (b) (6), he had sustained SVT requiring “3 shocks”, and received amiodarone. On (b) (6), he developed pulmonary edema, was critically ill on pressors. Continuous veno-venous hemofiltration (CVVH) was initiated. On (b) (6), he developed severe bradycardia, requiring epinephrine. He remained pancytopenic. By (b) (6), EEG was performed, revealing generalized slowing. He was unresponsive off all sedation. On (b) (6), he suffered cardiac arrest, but was unable to be resuscitated and died.

  Reviewer comment on patient OD134: This is an unfortunate case, as the patient died as a result of early onset 5FU toxicity. The toxicities did begin within 96 hours of beginning 5FU, however he did not present to his physician right away (main toxicity was mucositis at first), and then the clinical picture was not immediately recognized as being due to 5FU toxicity. As a result, therapy was initiated approximately 148 hours after initiation of the 5FU infusion and 100 hours from the end of the infusion (requiring protocol exception from the

Applicant). This case does not necessarily demonstrate a uridine triacetate failure, but instead may support the recommendation that uridine triacetate therapy should begin within 96 hours from the onset of severe symptoms.

Study WELL401 Efficacy

Overall survival for study WELL401 by patient group (overdose or early onset toxicity) is shown in Table 13. The FDA assessment of overall survival as determined by specific criteria described in Section 5.2 is also shown in the table. After considering the cases where patients died within 30 days (which was the primary study endpoint), and the cases that were determined to be invalid cases after FDA review, there were a total of 67 patients on Study WELL401 who were successfully treated with uridine triacetate, and who survived through Day 30 or resumed chemotherapy prior to Day 30.

Table 13 Survival: Study WELL401 (FDA Analysis)

	Overdose N=71	**Early Onset N=4**	**Overall N=75**
FDA agreement as successfully treated case with survival at Day 30	66	1	67
FDA Disagree	3	2	5
Death within 30 days	2	1	3

Disagree cases Study WELL401

As shown in Table 13, on WELL401, there were five patients with whom we disagreed to be valid cases successfully treated with uridine triacetate, three in the overdose group and two in the rapid onset group. The narratives and reviewer comments for these 5 disagree cases are discussed below.

- **OD057 (overdose group, disagree)**- 57 y/o WM with head and neck cancer. Received an overdose of 5FU, as part of TAX324 protocol (5FU, cisplatin, docetaxel). His first cycle began on 4/6/11, and the course was complicated by hospitalization for a neck abscess. C2 began on 4/25/11. The dose of 5FU 7000 mg was to be given over 96h. The infusion started at 1330 on 4/25/11, and patient was sent home to complete infusion. He returned for dose of cisplatin on 4/26/11 (24 h into 5FU infusion). On 4/27/11 at 1730, he contacted the clinic to report that the 5FU infusion pump was empty. This was 52h into the planned 96 h infusion. The physician subsequently contacted Wellstat on 4/28/11, but the patient did not return to clinic until 4/29/11. Uridine was started at 4/29/11 at 10:00, which was

approximately 40.5h after the 5FU infusion was thought to have prematurely ended. The patient was instructed for outpatient administration of uridine. He subsequently reported significant nausea and vomiting with each attempt at uridine dosing, and admitted to intolerance for several doses. The last dose that was even attempted was #9 on 5/1/11. The patient then refused taking any further doses, and the physician concurred, given the patient's poor tolerance and low suspicion that there would be untoward effects from the 5FU overdose. The patient was seen in follow-up on (b) (6) and was admitted due to volume depletion and nausea and vomiting. The physician actually suspected cisplatin to be the causative agent. He was admitted and hospitalized for several days. During the stay, he experienced several runs of wide-complex tachycardia, and was noted to have a worsening neck abscess. Cardiac work up was unremarkable, although he was hypokalemic, which was corrected during the hospital stay. By (b) (6), the patient's hospital stay was felt to be "uneventful" and he was discharged to home. He was scheduled for clinic follow-up on 5/12/11, with a possible plan to restart chemoradiation. He was actually not seen until 5/19/11, and restart of chemoradiation was delayed due to pending dental clearance. He finally restarted chemotherapy on 6/2/11, only receiving carboplatin. No further follow-up was provided.

Reviewer comment on OD057: This was a disagree case, on FDA assessment, as a successfully treated overdose case. First, the documentation of the actual overdose were not clear enough to reliably determine whether the patient did indeed receive a 5FU overdose. Second, the patient only attempted nine of the 20 uridine triacetate (45%) doses, and he vomited several of those. Therefore, he did not receive at least 80% of the doses. The patient admittedly did survive through day 30, there simply was not enough evidence to support the inclusion of this patient in the successfully treated group of overdose patients.

- **OD103 (overdose group, capecitabine, disagree)**- 74 y/o Asian female with Stage IV gastric cancer. She intentionally overdosed with capecitabine in a suicide attempt. She was being treated for her cancer with a palliative regimen of Epirubicin, oxaliplatin and capecitabine (500 mg), starting on 3/20/13. She underwent a paracentesis at the hospital on (b) (6) and was discharged home. Later that day, (b) (6), at approximately 2200, she ingested approximately 14 x 500 mg tablets (7000 mg) of capecitabine in a suicide attempt. However, there were estimates that she could have taken as many as 30 too mg tablets (dose 15,000 mg). Within 30-60 minutes of the ingestion, she reported 4-5 loose stools. She also reported vomiting, approximately 2 hours after the ingestion. Her family took her to

a small local hospital, and she was transferred to a larger hospital. At that point, the patient reported abdominal pain, and had nausea, vomiting, and diarrhea. Initially, it was recommended that she be started on immediate hemodialysis, but this did not occur. The patient was admitted to the ICU, although vital signs were stable. She initiated therapy with uridine triacetate on (b) (6) at 2230, approximately 24.5 hours after the capecitabine ingestion. She had emesis with at least 1 dose of uridine triacetate. She also complained of painful swallowing and had to have some doses mixed with pudding. By (b) (6), the patient was tolerating the uridine triacetate doses and was receiving an aggressive anti-emetic regimen. She was having multiple symptoms related to her advanced underlying cancer, including worsening ascites, and the medical team and family were attempting to make decisions regarding the best course of treatment for the progressing underlying cancer. After her 11th dose of uridine triacetate, on (b) (6), she decided not to continue further therapy with uridine triacetate. She withdrew consent from the investigational protocol. On (b) (6), she was discharged to hospice care and she died due to progressive cancer on (b) (6). She received 11 of 20 doses and did survive the 30 days.

Reviewer comment on OD103: This was not counted as a successfully treated overdose case due to the fact that the patient only received 55% of the uridine triacetate doses. However, she met the other criteria, including initiating therapy within 96 hours, surviving to day 30, and having a documented "overdose", ingestion.

- **OD123 (overdose group, pediatrics, capecitabine, disagree)**- 2 y/o AAM- capecitabine ingestion. On (b) (6), he was found gagging by his mother, who noted that the patient had the grandfather's bottle of capecitabine pills and had pill residue in his mouth. The mother took him to the ER. The dose of capecitabine was 500 mg tablets, and total dose was unknown; the time of the dose was approximated to be 0330. Child was admitted and uridine triacetate began on (b) (6) at 1650, approximately 37 hours after the ingestion. The patient received 13 of 20 recommended doses at the proposed pediatric dose of 6.2 g/m^2. He reportedly remained asymptomatic, with respect to side effects from capecitabine. After the 13th dose, the boy refused to take further doses. It was suggested that an NG tube be place to complete the dosing, but the mother refused. He was discharged from the hospital on (b) (6), which was 5 days post-accidental ingestion of capecitabine. Patient was in stable condition at that time. It was recommended that weekly CBCs be checked for 1 month, however it was not clear if this occurred. The mother was counseled on signs of capecitabine toxicity. No further f/u is provided after (b) (6).

Reviewer comment on OD123: This was counted as one of the FDA disagree cases, mainly due to the fact that the patient received only 13 of the 20 doses of uridine triacetate. Admittedly, the cases of capecitabine overdose, particularly in a pediatric patient, are much harder to document. Therefore, it is still possible that this patient benefitted from the doses of uridine triacetate he received. In addition, the patient was essentially lost to follow-up, and there was no documentation of survival at day 30. Therefore, using the criteria set forth prior to our review, this was counted as a "disagree" case in the primary efficacy analysis.

- **OD058 (early onset group, disagree)**- 70 y/o WM colorectal cancer was receiving 2500 mg 5FU over 120h infusion. On cycle 4 he received 2261 mg over 120h, which began on 6/10/11. By 6/11/11, he developed abdominal cramps and mucositis. By 6/13/11, his physician stopped the 5FU infusion early, as the patients platelet count had dropped. On 6/14/11, his physician suspected DPD deficiency and requested uridine triacetate. The first dose of uridine was given on 6/14/11 at 1630- this was 95.5 h after 5FU had stopped.

  Reviewer comment on OD058: *This was an unlikely case of early onset toxicity from 5FU. The patient had received 3 prior cycles with 5FU prior to experiencing "early onset" symptoms. In addition, the toxicities he experienced were not life threatening, though possibly more severe than with prior cycles. The patient did not receive further therapy with 5FU. This is more likely a case of poor tolerability of 5FU, not that this patient experienced life-threatening toxicities related to 5FU.*

- **OD138 (early onset group, disagree)-** 42 y/o white female with Stage III colorectal cancer diagnosed 2/14. She initiated C1 of adjuvant FOLFOX chemotherapy on (b) (6). The dose of 5FU was 740 mg bolus, followed by a 46 h infusion of 4400 mg 5FU, which ended on (b) (6). On (b) (6) (11 days after initiation of 5FU), she presented to the ER with nausea, vomiting, and chills. She was neutropenic and thrombocytopenic. It was not until (b) (6) that the physician requested uridine triacetate, which was 480 hours after 5FU infusion completed (well outside of the 96 hour window). The company denied the physician's request, however, a second request was made (with "pressure" from the FDA), and the request was approved. On (b) (6) (another 12 days later), her platelet count was 23K and DPD testing results revealed that she had a homozygous mutation. At that point, the patient was obtunded, with G4 encephalopathy, G4 mucositis, G3 nausea and vomiting, G3 diarrhea, G3-4 pancytopenia. The first dose of uridine triacetate was administered on (b) (6) at 2143, which was 24 days after the 5FU dose. She received all 20 doses, ending on (b) (6). The patient remained obtunded by Day 30 of follow-up, however the pancytopenia and mucositis had almost resolved. Unfortunately, her

neurologic status did not improve, and she remained in a coma in the ICU. By (b) (6) (4 months later), she still suffered from neuroencephalopathy secondary to 5FU, but she was still alive.

Reviewer comment: This was not counted as a valid case of early onset toxicity from 5FU, with successful treatment with uridine triacetate. The main reason is due to the timing of the symptom onset, which was quite delayed (11 days), according to the history provided. As a result of the late presentation, the uridine triacetate was clearly initiated well outside of the 96 hour window. Her outcome is unfortunate- although she did survive, it seems that she had irreversible morbidity related to 5FU. It is unclear if she would have benefitted, had she received the uridine triacetate therapy earlier in her course. This cannot be predicted, given the delayed onset of her symptoms, to begin with.

Deaths Study WELL401

As shown in Table 13, three patients died within 30 days of therapy with uridine triacetate on study WELL401, two overdose cases and one early onset case. A description of the patient narratives for these 3 deaths is as follows:

- **OD039 (overdose group, death)-** 64 y/o white male with metastatic colorectal cancer diagnosed July 2010. His disease involved the GI tract and the liver. He had a near obstructing colonic lesion, for which he underwent stenting on (b) (6). His performance status was reported to be 70%. He was to be initiated on palliative chemotherapy with FOLFIRI. When he presented for his first dose on (b) (6), he was febrile and started on antibiotics. Chemotherapy was delayed until (b) (6). Due to a nursing error, the patient was inadvertently given 5FU 3900 mg IV over 2h, instead of leucovorin, which was to be given over 2h. (The dose of 5FU was intended to be given over 46h infusion). The patient was admitted to the hospital. Wellstat was contacted, and the first dose of uridine triacetate was given on (b) (6) at 1300, approximately 19h after the erroneous dose of 5FU. It only appears that he took or was able to take 4 doses of uridine. Also, his laboratory tests were abnormal prior to initiation of 5FU, including renal insufficiency and WBC 17.8. He was also hypotensive around the time and following the overdose. The patient's physician was concerned about tumor lysis syndrome and administered rasburicase on (b) (6) and other supportive measures including hydration and alkalinization of the urine. Through the day on (b) (6), the patient had decreased level of consciousness. Into (b) (6), he became hypotensive and died on (b) (6) at 0240. The cause of death was said to be due to the patient's underlying malignancy and to tumor lysis syndrome. An autopsy was performed, but the family declined making results available to Wellstat.

Reviewer comment on OD039: The most likely cause of death in this patient does seem to be related to his underlying cancer and possibly to some extent from tumor lysis. It is unlikely, given the rapid decline after the overdose of 5FU, that the death was directly related or due to the overdose /excess toxicity due to 5FU or counted as a uridine triacetate failure. Also does not appear to be related to uridine triacetate, in particular.

- **OD042 (overdose group, death)**- 63 y/o white female with metastatic colorectal cancer, diagnosed on 9/2/10. Extensive disease including liver metastases, adenopathy, and ascites. Started on FOLFOX + Bevacizumab 9/18/10. She received 6000 mg 5FU over 48h infusion, ending on 9/20/10. The intended dose of 5FU was to be 4000 mg over 48h infusion. The reason for the error is listed as "physician error, dose miscalculated". It appears that the error was not noticed until 9/23/10, 5 days after initiation of the infusion. Uridine was requested right away and was begun on 9/24/10 at 0130- it is listed as 123.5 hours from beginning of 5FU infusion and 75.5 hours from end of infusion. She received all 20 doses of uridine, ending on 9/28/10. The patient had felt unwell as early as 9/24/10. She had ascites and mouth pain. By 9/26/10, mucositis had worsened and TPN was started. By (b) (6), she developed diarrhea and bloody stools. She was transfused. She had worsening lower extremity edema and rectal bleeding. U/S was done and DVT was ruled out. She was intermittently fearful and reported visual hallucinations. On 9/29, she was more somnolent. On 9/30, she was intermittently hypotensive, with low grade fever and bilateral toe ischemia. She was reported to be in "liver failure" and was more confused. On 10/1, WBC started improving. On 10/2, mucositis and diarrhea were better. By 10/3 she was uncomfortable and more short of breath. LFTs were rising (AST 83 and ALT 155), of 'unclear origin'. Thoracentesis was performed. On (b) (6), she was found to be bacteremic, WBC was 42.5. Psychiatry saw her d/t mental status changes. On (b) (6), she and family made her DNR. She was septic, on Vancomycin, secondary to line infection. Over the next several days, she was intermittently short of breath, volume overloaded, with worsening liver function. She died on (b) (6) at 1635. The cause of death, according to the physician, was listed as bacteremia and underlying cancer.

Reviewer comment on OD042: Although the patient had very advanced cancer at baseline and was in poor health, the contribution of the 5FU overdose to her ultimate death is unclear, and may certainly have contributed. The uridine triacetate was initiated late in the process, and depending upon whether the calculation is from the start of the 5FU or the end of the 5FU, one could argue that the timeframe was as long as 123 hours from the overdose, and therefore too late. I suspect that the 5FU

overdose may have contributed, and even been the main reason, for this patient's ultimate death.

- **OD120 (early onset group, death)**- 66 y/o white female with Stage IV gastric cancer with liver metastases and ascites. She began therapy first cycle of therapy with 5FU continuous infusion 6800 mg over 96h on (b) (6), as well as oxaliplatin 215 mg. This completed without incident on (b) (6). It is notable that liver enzymes and renal function were abnormal at baseline. On (b) (6) (10 days since beginning of 5FU infusion), she was admitted to the ICU with shortness of breath. It is unclear when the symptoms actually started. She had severe mucositis, pancytopenia, electrolyte abnormalities. She was diagnosed with a pulmonary embolus. The physician suspected DPD deficiency and requested uridine triacetate on (b) (6), however the first dose was not started until (b) (6), which was approximately **378 hours** after the beginning of 5FU and **282 hours** from end of infusion. She had continued to decline, requiring transfusions and was severely neutropenic in the ICU. Uridine was administered via NG tube, however she only completed 8 doses. On (b) (6), the patient became septic, requiring pressors. She had developed worsening encephalopathy, as well. On (b) (6), she was totally comatose and patient's family requested that she be made DNR. She died on (b) (6). The testing sent for DPD testing did reveal a mutation in DPD and TYMS genes known to be associated with increased 5FU toxicity.

  Reviewer comment on OD120: This case seems to have a reasonable likelihood of being a true early onset case, however, the patient started uridine triacetate therapy well beyond the 96 hour window (although difficult to pinpoint exact timeframe from when toxicities started), and died as a result of her 5FU toxicities. In addition, it is unclear when the actual onset of toxicities related to 5FU began. Based upon the narrative, the first mention of any toxicity is 10 days after initiation of first dose of 5FU and 6 days from 5FU completion. This case cannot be counted as a success, since the patient died within 30 days of uridine triacetate.

Detailed FDA analysis of efficacy in Early Onset Group for both studies

Although the survival numbers would indicate that the majority of patients treated with uridine triacetate for early onset toxicity of 5-FU survived, it was not initially clear if these patients benefited from treatment and thus the analysis of efficacy in the early onset patient group was more complex than for the overdose patient group., Clinical judgment played an important role in making a determination about the diagnosis of "early onset" of severe or life-threatening symptoms from 5-FU, and in making a determination of whether uridine triacetate treatment resulted in these patients' survival. Unlike in the overdose group, where patients, for the most part, did not have signs or symptoms

related to the 5FU overdose at the time of treatment initiation with uridine triacetate, the early onset patients displayed severe and/or life threatening symptoms by the time of therapy with uridine triacetate was initiated. In the majority of these cases, this was the first time the patient had ever received 5FU therapy, and initiation of uridine triacetate therapy required the treating physician to recognize the clinical presentation as being atypical or more extreme than would be expected, based upon experience in treating other patients with 5FU. Thus, a high index of suspicion was often required on the part of the treating physicians to make a correct diagnosis and seek out therapy (in a timely manner) that could potentially benefit these patients.

The analysis of the early onset cases, including assessment of agreement from FDA for Study 401.10.001 is shown in Table 14, and the analysis of rapid onset cases for Study WELL401 is shown in Table 15. Narratives for all "agree" cases in both tables are also described in this section. Death and disagree narratives have been discussed previously in this review.

Table 14 Assessment of Patients with Severe, Early Onset of Toxicity Treated on Study 401.10.001

Pt	ID number (study)	FDA assessment of benefit from Uridine	Strength of FDA agreement	Death within 30 days
1	OD060 (401)	Agree	Undisputable.	No
2	OD064 (401)	Agree	Reasonably likely	No
3	OD084 (401)	Agree	Undisputable	No
4	OD088 (401)	Agree	Reasonably likely	No
5	OD093 (401)	Agree	Undisputable	No
6	OD097 (401)	Agree	Reasonably likely	No
7	OD106 (401)	Agree	Undisputable	No
8	OD116 (401)	Agree	Undisputable	No
9	OD124 (401)	Agree	Reasonably likely	No
10	OD132 (401)	Agree	Undisputable	No
11	OD139 (401)	Agree	Undisputable	No
12	OD134 (401)	Death	Death	Yes
13	OD61 (401)	Disagree	-	No
14	OD81 (401)	Disagree	-	No

The narratives for the patients in Table 14 are discussed next, with the exception of the narratives for patients OD134, OD061, and OD081, which have been discussed previously.

- **OD060 (early onset group, agree, undisputable)**- 81 y/o white female with colorectal cancer. Toxicity occurred after very first dose of 5FU for colorectal cancer diagnosis. 5FU started 8/30/11 at 1430. Infused till 9/1/11 at 0800— 18h from start. (b) (6) 0800 patient was taken to ER by family b/c unresponsive (5FU ongoing at the time). She had previously had lethargy. Necessitated intubation due to pulmonary edema (documented G3-4 lethargy, encephalopathy, pulmonary edema, respiratory failure, intubation, and cardiomyopathy). Uridine began on (b) (6) at 2100 (approx. 37h after presenting to ER and having 5FU stopped). She completed 20 doses on (b) (6) at 1500. She recovered from most toxicity- extubated, discharged from hospital. Still had G1 expressive aphasia and G1 cardiomyopathy by (b) (6) and (b) (6), respectively. She did not receive any further chemotherapy with 5FU. Specimen for DPD was sent, but only for most common mutation *2A, and this was negative.

  Reviewer comment OD060: This case demonstrated undisputable benefit of uridine triacetate and FDA agreed that this is a case of early onset with recovery after uridine triacetate. She had all 5 criteria, including 5FU dosing (including that it was her very first dose of 5FU ever). The symptoms she exhibited were life-threatening, including encephalopathy, respiratory failure requiring intubation, and cardiomyopathy. She received all doses of uridine within the appropriate time. She survived through D30, with almost complete recovery from the life threatening toxicities of 5FU. She did not receive further therapy with 5FU, due to the way she responded to the first dose.

- **OD064 (early onset group, agree, reasonably likely)**- 55 y/o WM SCC of tongue. C1 docetaxel, cisplatin, and continuous infusion 5-FU over 96 h from (b) (6) Dose of 5FU was 7800 mg starting at 1800 on (b) (6). NO ISSUES during infusion. On (b) (6) (48 h after completing infusion), he was seen in ER with diarrhea, weakness, vomiting, difficulty swallowing, mucositis. Had neutropenia, fever, pancytopenia as well. He was admitted to the hospital on (b) (6). CT scan showed diffuse colitis. (b) (6), cytopenias worsened, Neulasta was initiated. Physician suspected undiagnosed DPD deficiency due to the "sudden onset of serious toxicities". Contacted Wellstat, began uridine (b) (6)— 66 hours after infusion completed; 162 hours after infusion started. He received all 20 doses uridine triacetate and completed them on (b) (6). His condition

gradually improved during his hospital stay- by (b) (6), he was clinically improving, and he was discharged from the hospital on (b) (6) to a rehabilitation facility, and home on (b) (6). He was tested for DPYD deficiency (common loci), and test was negative. He was diagnosed with thymidylate synthetase mutation (2R/3R). Patient was not treated with further 5FU, due to toxicities. He resumed concurrent chemo-radiation on 12/2/11 with cisplatin and XRT.

Reviewer comment OD064: This patient was assessed as a "reasonably likely" case of early onset toxicity from 5FU. A missing component to the picture was documentation of the severity of some of the toxicities experienced by the patient. It was not clear that the events he experienced were necessarily life-threatening, and therefore he was classified as a reasonably likely to have benefited from uridine triacetate case (rather than undisputable).

- **OD084 (early onset group, agree, undisputable)**: 57 y/o WF with head and neck cancer (squamous cell carcinoma of anterior tongue) that had become metastatic. She had a PEG tube in place. She received the first of 4 planned courses of 5FU, cisplatin, docetaxel on (b) (6). She first received cisplatin 132 mg IV at 2230 on (b) (6), followed by 132 mg docetaxel at 0035 on (b) (6). The dose of 5-FU was to be 6600 mg via continuous infusion over 120 hours (5 days), and the infusion began on (b) (6) at 0415. She reportedly had "normal" CBC at baseline. She experienced rapid decline in blood counts (pancytopenia), diarrhea, and severe mucositis, which began during the 120 hour infusion. In particular, nausea and inability to eat began (b) (6) (24 hours into the 5FU infusion). Her blood counts began to decline on 8/20 (D3), with platelets 46K (no specific baseline value reported). By (b) (6) (D3-4), she had G3 neutropenia, G4 leukopenia, G3 thrombocytopenia, and G1 diarrhea. She also had "severe" mucositis. Because of the rapidity of development of these severe toxicities, her physician suspected DPD deficiency and discontinued the 5FU infusion early, on (b) (6) (Day 4 of the infusion); she had received a total dose of 5280 mg 5FU. The physician initiated neupogen, sent testing for DPD deficiency, and requested uridine triacetate. Uridine triacetate was initiated on (b) (6), which was approximately 16 hours after the 5FU infusion was discontinued and 112 hours after 5FU had begun, and was administered via PEG tube. She had also been initiated on Zosyn for positive blood cultures, and several other antibiotics were added over the next several days. Imodium was used for diarrhea. Diarrhea began to improve by (b) (6). On (b) (6), mucositis was improved and she completed Dose #20 of uridine triacetate. Blood counts began to improve on (b) (6), including WBC 3.5, and the pancytopenia was considered to be resolved as of (b) (6). She unfortunately started having blood from the PEG site on

(b) (6), and was transferred to ICU for emergent EGD. It was reported that a T-clip at the PEG site was causing pressure necrosis over a gastric vessel. This was repaired, and the bleeding was stopped. On (b) (6), she continued antibiotics for sepsis, as well as electrolyte repletion. She was transferred out of the ICU, and by (b) (6), was improving and antibiotics were discontinued. She was discharged home on (b) (6). She failed to follow-up with her oncologist, as scheduled on (b) (6). Several attempts were made to contact the patient. The oncologist discovered the patient's obituary later that month, stating she had died on (b) (6) (slightly outside of the 30 day window), due to her cancer. Results of DPD, TS, MTHFR studies showed no mutations in the genes that were tested for.

Reviewer comment OD084: This was deemed to be an undisputable case of early onset of toxicity from 5FU due to the severe, life-threatening symptoms related to 5FU and benefit of uridine triacetate. However, it is notable that she was also quite ill from her underlying cancer. She ultimately died slightly after the 30-day f/u period due to progressive cancer, but given the rapidity and severity of onset of symptoms after 5FU, and the fact that she could not complete the entire prescribed dose of 5FU due to the toxicity, this seems to be an undisputable case of early onset toxicity, with successful treatment with uridine triacetate.

- **OD088 (early onset group, agree, reasonably likely)**: 59 y/o AA female Stage III anal cancer. She began her first treatment with combined chemo radiation therapy, including mitomycin C, 9650 mg 5FU over 120-h continuous infusion, and XRT on (b) (6). On (b) (6), she was reported to be doing well. The 5FU infusion completed on (b) (6) without incident. On (b) (6), she was seen and complained of mucositis, such that she was completely unable to eat and her entire face felt swollen. Exam revealed "severe" oral ulcers, facial edema, and swelling of the lips. She was sent to the ER, where labs revealed significant reductions in WBC, hemoglobin, and platelets, as well as elevated BUN, Cr, and glucose levels. She was admitted to the ICU with acute renal failure and was initiated on TPN due to her inability to take anything by mouth. Renal ultrasound did not reveal obstruction. The physician suspected possible DPD deficiency, due to the rapid onset of her symptoms, and testing was sent. Wellstat was contacted and she was initiated on uridine triacetate therapy on (b) (6) at midnight, approximately 96 hours after 5FU infusion ended and 216 hours after it began. She took all 20 doses of uridine triacetate, and completed the course on (b) (6). By (b) (6), the mucositis had resolved and the neutrophils and platelets were recovering. Glucose and creatinine were also improving. She was discharged from the hospital on (b) (6). She was seen in follow-up on (b) (6) and she had almost fully recovered, including lab parameters. Finally, on 12/13/12, the

physician and patient opted to resume radiation therapy, but she did not receive any further therapy with 5FU. Genetic testing failed to reveal DPD deficiency, however she was found to be homozygous for a 6 base pair deletion of the thymidylate synthase gene (del/del genotype), on both alleles, in addition, there was a single nucleotide polymorphism (G>C) absent on both 3R alleles (3RG/3RG).

Reviewer comment (OD088): This case was determined to be a "reasonably likely" case of early onset toxicity, with successful treatment with uridine triacetate. The exact time of onset of symptoms is not totally clear from the narrative; however it seemed to be slightly late- potentially as late as 8 days from start of 5FU infusion. The main symptom was mucositis (she subsequently developed renal failure likely related to poor oral intake), however it was clearly very severe, requiring parenteral nutrition. She did not go on to receive any further therapy with 5FU. Given that the window for onset of symptoms was slightly late, and that the main symptom was mucositis (which by itself is not typically life threatening), this was given the designation of a 'reasonably likely' rather than an 'undisputable case' of uridine triacetate benefit.

- **OD093 (early onset group, agree, undisputable):** 73 y/o WM colon cancer patient (Stage 3- T3N2b M0). Received first dose 5FU ever, (along with oxaliplatin and leucovorin) starting on (b) (6). Specifically, he received 825 mg bolus of 5FU followed by continuous infusion of 4925 mg 5FU over 46-hour infusion. On (b) (6), during the 5FU infusion, he developed nausea, vomiting, confusion, and agitation. He was reportedly restless, with episodes of shaking and rigors. On (b) (6), toward the end of the 5FU infusion, patient had worsening symptoms, became combative and was then obtunded. He was brought to the ER by ambulance, where the 5FU infusion was stopped (at approximately 1200). He was unable to follow commands. Head CT showed no definitive intracranial abnormality. EEG showed a marked diffuse non-epileptiform disturbance in brain function. He remained agitated and received platelet transfusion for "rapid onset thrombocytopenia". Initial diagnosis included acute delirium, severe thrombocytopenia, severe lactic acidosis, and acute vs. chronic renal insufficiency. He was admitted to the ICU with encephalopathy, rigors, renal failure, and elevated liver enzymes. He became unresponsive to pain, and had episodes of tachypnea, hypertension, and tachycardia. His gaze became fixed upward and he was thought to be in status epilepticus. He was intubated for airway protection. Feeding tube was placed and electrolyte replacement was begun. The physician contacted Wellstat on (b) (6), due to suspicion that the patient may have a "5FU clearance defect". Testing was sent for DPD mutation.

Brain MRI on (b) (6) showed no mass, hemorrhage, infarct. On (b) (6), he remained obtunded, unresponsive, intermittently agitated. He was tachycardic, but hemodynamically stable. Uridine triacetate was begun on (b) (6) at 23:59, 72 hours after 5FU was discontinued and 108 hours after 5FU had begun. He completed all 20 doses on (b) (6). During the course of the 5 day therapy, he began to clinically improve. On (b) (6) (Day 2-3 of uridine triacetate), he awoke and was able to follow commands. He also passed a breathing trial and was extubated on (b) (6). Renal function began to improve. On (b) (6), he was transferred out of the ICU. On (b) (6), he had improved sufficiently to be discharged from the hospital. The encephalopathy was thought to be due to impaired elimination of 5FU, given that it began to recover within 24 hours after initiating uridine triacetate. (Genetic testing results came back on 1/24/13, indicating no DPD mutation among those tested for. The testing did reveal homozygous base pair deletion variant rs16430 in the 3-prime untranslated region of the thymidylate transferase gene (TYMS), as well as the TYMS 5-prime TSR genotype, *2R/3RC abnormality). Based upon the patient's experience with the first dose of 5FU and on the genetic testing results, he re-started chemotherapy on 1/30/13 (within 30 days of study participation). His chemotherapy regimen was modified, such that he received modified FOLFOX, which included omission of the 5FU bolus, and reduction of the infusional 5FU dose by 25%. He reportedly tolerated this modified regimen well.

Reviewer comment (OD093): Agree that this case is an undisputable case of early onset of toxicity from 5FU, given the occurrence of life-threatening symptoms, mainly neurologic, within 24 hours of starting his first dose of 5FU and of benefit of uridine triacetate The symptoms required ICU admission and intubation. Likewise, the symptoms rapidly reversed upon initiation of uridine triacetate (within 2-3 days of starting, neurologic status markedly normalized). The patient was reported to have fully recovered within 30 days of onset of symptoms. He was able to re-start chemotherapy, though with dose reduction of 5FU (which was reportedly much better tolerated). Although DPD mutation testing revealed no mutation, he did have mutation in TYMS gene, which likely contributed to the susceptibility to 5FU.

- **OD097 (early onset group, agree, reasonably likely):** 49 y/o WF anal cancer began first cycle of mitomycin C followed by 96 h continuous infusion 5FU- total dose to be given of 5FU- 7500 mg- infusion started (b) (6) at 12:30. By 48h, on (b) (6), she was experiencing nausea and vomiting that had become intractable and unresponsive to promethazine and ondansetron. She had also developed confusion, diarrhea, sweats, and leg cramps. She was instructed to go to the ER

on (b) (6), where she was noted to have mucositis around the mouth, as well as anal ulcers. She was vomiting and short of breath, saturating in the 70s on high flow O_2. 5FU was still ongoing, and was d/c in the ER. Laboratory tests revealed acute renal failure, metabolic acidosis, anemia, elevated troponin levels, and cardiac echo revealed an EF of 20%. She was admitted to the ICU, and necessitated intubation and ventilator support. By (b) (6), she was transferred to a tertiary care facility for more intensive treatment. She was in cardiogenic shock, with EF 5%, acute renal failure, and hypotensive. She required pressors including norepinephrine, milrinone, and phenylephrine. She was placed on an intra-aortic balloon pump for left ventricular assistance. She also was started on emergent hemodialysis on (b) (6), at which time serum creatinine was 6.2. On (b) (6), her physician requested uridine triacetate from Wellstat, due to suspicion of impaired 5FU elimination and possibly Takotsubo syndrome of acute cardiomyopathy due to 5FU. Uridine was begun via NG tube at 0100 on (b) (6), which was 107 after the 5FU infusion was d/c and 143 hours after infusion began. All 20 doses were given by (b) (6). Her course after initiating uridine triacetate was as follows:

- (b) (6)- platelets nadired at 34K.
- LVEF was 10-15%, balloon pump assistive device was able to be removed.
- (b) (6)- patient arousable, but still on ventilator. Repeat echo showed "normal EF", though value not reported.
- (b) (6)- patient responsive, urine output improving. Completed dose #20 of uridine. Transferred out of the ICU.
- (b) (6)- developed ARDS, needed re-intubation. Tracheostomy was performed on (b) (6). Other clinical parameters, including liver function and renal function were improving. Repeat echo revealed EF 59%. EKG revealed sinus rhythm.
- (b) (6)- Physician believed this to be a case of Takotsubo-like syndrome of acute cardiomyopathy following 5FU.
- (b) (6)- Patient reported feeling well. Tracheostomy was removed on (b) (6) and vitals were normal. She was put on a regular diet. She recovered completely from the 5FU toxicities and survived thru D30.

Reviewer comment (OD097): *This was classified as a reasonably likely early onset case to have benefited from uridine triacetate. The symptoms were clearly*

life-threatening, possibly the most dramatic of all patients treated on this study. The only outlying piece of information is that the uridine triacetate therapy was initiated later than the 96 hour window from the initiation of 5FU. However, the therapy clearly benefitted the patient, and an argument can be made that the uridine triacetate was initiated within 96 hours of symptom onset, given that the actual start of the patient's symptoms is not well documented. This gives credence to the proposal for labeling to specify therapy initiation within 96 hours of symptom onset, rather than infusion of 5FU, particularly for patients receiving longer infusions of 5FU.

- **OD106 (early onset group, agree, undisputable)**: 65 y/o WF with squamous anal carcinoma Stage IIIA and h/o Type 2 diabetes and chronic kidney disease. Began first cycle of chemotherapy with mitomycin C and 5FU continuous infusion to be given over 96h. The total dose of 5FU to be given was to be 5967 mg over 96-h infusion. The infusion of 5FU started on (b) (6) at 1515. On (b) (6), 48 h into the infusion, patient presented to ER with severe nausea, vomiting, and generalized weakness, which she reported had been going on for 2 days. Nausea and vomiting was unrelieved by prescribed medications (not stated what the medications were). She reported having had an episode of chest pain on (b) (6), as well. Labs on (b) (6) revealed hyperglycemia (glucose 214), BUN 44 (ULN 20), and Cr 1.5. The infusion of 5FU was held and IV hydration was started in the ER. She was admitted to the hospital, at which point she had received 3788 mg of the 5FU dose. At the time of admission, she was diagnosed with acute renal failure, hyperglycemia, nausea and vomiting. However, she developed weakness and aphasia, and there was concern for CVA, so she was transferred to the ICU. MRI brain revealed bilateral changes suggested of encephalopathy ("possibly related to 5FU neurotoxicity"). She was given the diagnosis of acute cerebellar syndrome. Tests for DPYD and TYMS mutations were sent at that time. Labs on (b) (6) indicated liver injury. Echocardiogram was performed and EF was 48%. On (b) (6), patient experienced 3 episodes of cardiac arrest (ventricular fibrillation). Each time, CPR was initiated and she was successfully defibrillated. However, she was intubated and placed on amiodarone, norepinephrine, bicarbonate, insulin infusion, and hypothermia protocol. Because the physician suspected the clinical picture to be consistent with toxicity related to 5FU, possibly due to undiagnosed DPD deficiency, uridine triacetate was requested on (b) (6). The first dose of uridine triacetate was given via NG tube on (b) (6), which was ~29 hour after the 5FU infusion had been stopped (97 hours from start of 5FU). Patient was "rewarmed" starting on (b) (6), and during the process, suffered a 4th episode of ventricular defibrillation, which was successfully defibrillated. Cardiac ejection fraction at that point was 40%. On (b) (6), during uridine therapy,

patient had developed multi-organ failure, likely secondary to the episodes of cardiac arrest. She remained on pressors for hemodynamic support, as well as sodium bicarbonate infusion for lactic acidosis. She also had G3 pancytopenia. On (b) (6), she was transferred to a tertiary care facility for increased intensive care. A dialysis catheter was placed for emergent hemodialysis. Her prognosis was considered to be grave. Dosing with uridine triacetate continued, but she remained unresponsive and intubated on (b) (6). She completed the 20th dose of uridine triacetate on (b) (6), and it was noted that she attempted to open her eyes in response to verbal command, and withdrew in response to pain. Pressor agents and amiodarone were weaned on (b) (6), and she was extubated 2 days later on (b) (6). Her mental status was documented to be alert and oriented, at that time, although still weak. On (b) (6), her neurologic status and liver function were improving. She was discharged to home on (b) (6). She was seen in follow-up on 6/3/13 and was reported to have fully recovered from the multi-organ failure. (Laboratory results said to be "unremarkable"). Radiation therapy was started on 6/4/13, but the patient and physician did not opt for any further chemotherapy (which as to be given concurrently with XRT). Results of genetic testing showed no DPYD mutations, however, patient was heterozygous for a deletion in the TYMS gene, which may have been the reason for the patient's unusual susceptibility to 5FU.

Reviewer comment OD106: This is deemed to be an undisputable case of early onset, life-threatening toxicity related to 5FU that benefited from uridine triacetate. Patient had multi-organ failure, and suffered several episodes of cardiac arrest. Her clinical picture began to improve just at the end of the 5 days of uridine dosing, and had almost completely normalized so that she was discharged to home approximately 16 days after the 5FU infusion had begun.

- **OD116 (early onset group, agree, undisputable):** 55 y/o WF with anal squamous cell carcinoma Stage IIIb diagnosed 3/12. She underwent chemoradiation for several months, although it is unclear what chemotherapy was used with the XRT. She then developed a groin mass in 6/13, and was found to have recurrent disease. It was decided to treat with cisplatin + infusional 5FU. On (b) (6), she received cisplatin 200 mg IV, followed by initiation of 5FU at a dose of 10,100 mg to be given over 120 hour infusion (5 days). No issues were "reported" during the infusion, but when she arrived on (b) (6) (D5) to have infusion disconnected, she reported having developed severe mucositis, diarrhea, nausea, vomiting, weakness and fatigue during the infusion. She was admitted to the hospital, and was found to be in acute renal failure with thrombocytopenia and a wound infection. EKG revealed sinus bradycardia and T-wave inversions, with

no prior EKG for comparison. The physician suspected impaired 5FU elimination, due to the rapid onset of symptoms, and requested uridine triacetate. At that point, patient had mucositis and was receiving IV fluids, due to renal insufficiency. Uridine triacetate was initiated on (b) (6), approximately 33.5h after 5FU completed (153.5 hours after 5FU started). She received all 20 doses of uridine triacetate, ending on (b) (6). Her clinical course was complicated initially after uridine triacetate started. On (b) (6), renal function continued to worsened to G4, oral intake worsened and an NG tube was placed due to inability to take food or fluid due to the mucositis and nausea. Diarrhea continued as well. On (b) (6), the patient was initiated on hemodialysis, and platelet count continued to decline. On (b) (6), patient was found unresponsive, in cardiac arrest vs. having a seizure (not clear from narrative). Code blue was called and the patient was transferred to the ICU. The patient's glucose was very low and patient was given dextrose. She soon was more responsive and speaking clearly. The last dose of uridine triacetate was given on (b) (6). Echocardiogram showed EF 60%. Patient reported she was feeling well and requested to go home. She was transferred out of the ICU on (b) (6). Laboratory parameters, including renal function and CBC were improving. NG tube was removed on (b) (6) and patient tolerated soft diet. Diarrhea was improving with loperamide. On (b) (6), the patient suffered 2 episodes of status epilepticus and required re-intubation. CT scan of the head was negative for intracranial abnormality. She was started on antibiotics and anticonvulsants. On (b) (6), the mucositis was said to have resolved. She had no further seizure activity and was extubated. The seizure was believed to be related to encephalopathy related to 5FU (unclear that this is temporally feasible). On (b) (6), the WBC seemed to have declined, although platelet count was improving, so neupogen was initiated on (b) (6) and continued till (b) (6), once counts were rising. On (b) (6), the patient was well enough to be discharged to inpatient rehab. Brain MRI was repeated on (b) (6) and compared with (b) (6). Abnormalities on the MRI from (b) (6) that had been thought to be consistent with posterior reversible encephalopathy seem to have resolved by (b) (6). Patient's blood counts, including CBC and renal function had improved by (b) (6), although patient was still needing hemodialysis. She was discharged home from rehab on (b) (6), and transferred to outpatient hemodialysis. The patient survived beyond Day 30 and most of the 5FU toxicities ultimately resolved. No genetic testing results were available to Wellstat. It was noted that the patient did resume therapy with XRT for her anal cancer approximately 28 days after completing uridine triacetate, but she did not receive further therapy with 5FU.

Reviewer comment OD116: This is an undisputable case of early onset, life-threatening toxicity from 5FU elimination with and benefit of uridine triacetate. Some details are missing, particularly the exact timing of onset of symptoms, but the severity of the neurologic, GI, renal, and hematologic abnormalities is compelling. The rapid resolution of symptoms after initiation of uridine triacetate and the fact that she was discharged to rehab (and then home) within 30 days of being intubated in the ICU with severe encephalopathy makes for a compelling story favoring the benefit that uridine triacetate had for this patient.

- **OD124 (early onset group, agree, reasonably likely):** 70 y/o male with colon cancer. Began chemotherapy with 5FU as initial bolus dose of 860mg on 11/4/13 at 1245, followed by intended 46 hour infusion of 5160mg. Within 24 hours of the bolus, on 11/5/13 at 0500, patient became- all neurologic sx- agitated, confused, and delirious (G3 severity). The patient's caregiver noted that the patient had self-discontinued the 5FU infusion at that time (11/5/13 at 0500- 16 hours into the infusion), due to the agitation. Uridine was initiated at 1830 on 11/7/13, which was 48 hours after 5FU had been stopped. Patient completed all 20 doses of uridine, and survived. He did not complete the 30 day follow-up, however, because he resumed chemotherapy on 11/19/13, approximately 15 days after the initial 5FU dose began. The chemotherapy he resumed was only oxaliplatin; he received no further 5FU. DPD testing was sent, and results did reveal one genetic mutation in the DPYD gene and one in the TYMS gene.

  Reviewer comment OD124: This case was deemed to be a reasonably likely case of early onset toxicity from 5FU with benefit of uridine triacetate. The main factor calling it into question was that the patient only had neurologic symptoms, and no other symptoms such as cytopenias or GI. Also, documentation of the reversal of symptoms was lacking, although he was treated mostly as an outpatient with the uridine, which would make documentation more difficult. He received no further therapy with 5FU, thereafter, which supports the notion that the treating physician was convinced that the events were caused by 5FU.

- **OD132 (early onset group, agree, undisputable):** 57 y/o AAM head and neck cancer (Stage IV) squamous, laryngeal cancer diagnosed 12/13/13. Chemotherapy to be given was cisplatin, docetaxel, and 5FU 1745 mg continuous infusion D1-4. He began first full cycle of chemotherapy on (b) (6). That evening, and on (b) (6) he complained of transient, intermittent lightheadedness. On (b) (6) (D3 of therapy), he was found sitting on the floor of his hospital room and was confused. He had been given several doses of lorazepam for nausea. CBC was noted to be "below normal" and peg-filgrastim was initiated on (b) (6). His

mental status deteriorated by (b) (6), and he was reported to be delirious, combative, and have neck stiffness. The patient self-discontinued the 5FU prematurely on (b) (6) (D4), as a result of his confusion; a total dose of 1308 mg (intended 1745 mg) had been infused. He was found to be in acute renal failure on laboratory values on that day. By (b) (6) (~96h after initiation of 5FU), he became unresponsive, and had lost gag reflex. He was intubated at that time. His condition further deteriorated by (b) (6), such that renal function was worsening, he had hyperuricemia and hyperphosphatemia. The physician suspected possible DPD deficiency and sent specimen for genotyping on (b) (6). EEG was performed on (b) (6) and indicated "very abnormal EEG with diffuse slowing and evidence of diffuse encephalopathic changes. No epileptiform changes". Patient remained comatose on (b) (6), and had pancytopenia and severe mucositis. The physician requested uridine triacetate, and the first dose was given via NG tube on (b) (6) at 22:59, which was approximately 80 hours after the 5FU had been discontinued, but 6 days (~154 h) since the start of 5FU, and roughly 96hours from the onset of confusion symptoms on 2/7/14. The patient received all 20 doses of uridine triacetate, ending on (b) (6) at 1730. He was said to have improving mental status on (b) (6), and was stable for transfer out of the ICU. The course of recovery is not well documented, but neurologic symptoms were said to be markedly improved or resolved by (b) (6) (2 days after completion of uridine dosing). Mucositis and cytopenias were resolving on (b) (6). He was undergoing hemodialysis on (b) (6), but urine function began improving on (b) (6). Patient was discharged home on (b) (6) and completed the 30-day f/u on (b) (6). Results of DPD genotyping were not reported. Also, at the time of follow-up, alternatives to 5FU chemotherapy were being considered.

Reviewer comment OD132: This is counted as an undisputable case of early onset of 5FU toxicity with benefit of uridine triacetate. Although the patient had received 5FU once before, it is notable that he did not receive the full cycle, due to leaving AMA from the hospital. Therefore, this really was the first attempt at a full dose of 5FU for this patient. The neurotoxicity appears to have started rather quickly, although not recognized as potentially due to 5FU right away. His status quickly deteriorated, requiring intubation and ICU admission, prior to the end of the 96h 5FU infusion. He also developed renal failure, cytopenias, and mucositis. The uridine triacetate was initiated just at the end of the 96h window from the onset of symptoms, but the patient obviously recovered fairly quickly, with neurologic function being almost back to baseline 2 days after completing uridine. This meets criteria as a case with undisputable benefit from uridine triacetate.

- **OD139 (early onset group, agree, undisputable):** 51 y/o WF with squamous anal cancer T3. Received first dose of 5FU. Her regimen included mitomycin C, followed by 7360 mg 5FU via 96h continuous infusion, beginning on (b) (6), ending (b) (6). On (b) (6), approx. 48 hours into the infusion, she was noted to have become confused and had nausea and vomiting. By (b) (6), the confusion had worsened such that the patient was incoherent and unable to speak. She was seen in the ER for mental status changes. Also on (b) (6), she was experiencing G4 nausea, G4 vomiting, G4 confusion and decreased consciousness, G2 cytopenias, G4 encephalopathy, G2 lethargy. On (b) (6), she developed respiratory failure requiring intubation. On (b) (6), the physician suspected impaired elimination of 5FU and sent test for DPD deficiency. He also requested uridine triacetate, and the first dose was administered on (b) (6)- this was 79 hours from the end of the 5FU infusion, but 175 hours from the start of 5FU. It was also approximately 6 days from the onset of symptoms. The patient missed 1 dose of uridine triacetate on (b) (6), and completed 19 of 20 doses on (b) (6). However, on (b) (6), just one day after initiation of uridine triacetate, the patient was extubated. The neurologic toxicities improved and resolved by (b) (6), when patient was discharged from the hospital. By 4/25/14, she had recovered sufficiently from the toxicities to resume radiation therapy. It was determined that no further 5FU would be given, and the patient actually refused chemotherapy of any kind. NO confirmation of DPD testing or results was provided.

  Reviewer comment OD139: This was deemed to be an undisputable case of successful therapy with uridine triacetate after early onset symptoms, mainly neurologic, gastrointestinal, and hematologic. This patient did have a delay in the timing of initiation of uridine triacetate (partly due to the prolonged infusion time of 5FU in this regimen, as well as the fact that the patient seemed to remain at home for the first few days of symptoms, since they were initially limited to nausea and vomiting). Nevertheless, the patient's course quickly improved once uridine triacetate therapy was started and she recovered. She did not receive any further therapy with 5FU after the events.

Table 15 Assessment of Patients with Severe, Early Onset of Toxicity Treated on Study WELL401

Pt	ID number (study)	FDA assessment of benefit from Uridine	Strength of FDA agreement	Death within 30 d?
1	OD009 (WELL) *pediatric patient*	Agree	Reasonably likely	No
2	OD058 (WELL)	Disagree	-	No
3	OD138 (WELL)	Disagree	-	No
4	OD120 (WELL)	Death	Death	Yes

Of the early onset patients on Study WELL401shown in Table 15, the only narrative that has not been discussed elsewhere in the review is for patient OD009, which will be discussed below.

- **OD009 (early onset group, agree, reasonably likely, pediatric case)** - 16 year old Hispanic male with Stage III nasopharyngeal carcinoma. Began first cycle of chemotherapy with methotrexate, cisplatin, 5FU, leucovorin, and mannitol. Dose of 5FU was to be 3-day continuous infusion of 5550 mg. This began on (b) (6) - he had not previously received chemotherapy or 5FU. Within 24 hours on (b) (6) he developed mental status changes, became psychotic and agitated- the infusion of 5FU was ongoing. He was transferred to the ICU. He had received 3700 mg of the 5FU dose over approx. 48h. The infusion was discontinued before completion due to the mental status changes. He was initially thought to improve when infusion stopped, however he then became incoherent and eventually unresponsive, except to pain, on (b) (6). CT scan and LP were not remarkable. EEG did not show evidence of seizure. Treating physician suspected encephalitis related to 5FU. Hematologic labs had started to decline, as well. Physician requested uridine triacetate, and the first dose was administered on (b) (6) at 2000, which was 64 hours after 5FU infusion stopped and 112 hours after it had started. Testing for DPD was sent on (b) (6). He also had c/o abdominal pain and diarrhea, and had mucositis. At this point in the development of uridine triacetate, the formulation was tablet, given as 6g dose (12 x 500 mg tablets) every 8 hours for a total of 8 doses. This was due to the fact that he was considered an 'early onset' case, rather than overdose, and because he was under 18 y of age. The patient received 6 full doses and 2 partial doses of the uridine triacetate. On (b) (6), the doses were completed, and physician was impressed with patient's improvement. By (b) (6), he was afebrile, taking PO, and was discharged. He as seen in f/u on (b) (6) - all neurologic symptoms had

resolved, but he still c/o some nausea. On [redacted], the patient was admitted for a modified C2 of chemotherapy, which did NOT include 5FU- only cisplatin, MTX, and leucovorin. He tolerated this cycle well, except for some nausea. He was discharged home as planned on [redacted]. He received C3 of chemotherapy without 5FU on [redacted]. Initial DPD testing showed activity that appeared to be within the normal range – 0.22 nmol/min/mgprotein (normal: 0.064-0.314). Follow-up testing was sent, but not reported.

Reviewer comment OD009: This was deemed to be a reasonably likely case of early onset toxicity related to 5FU which benefited from uridine triacetate. The neurologic symptoms were really the only symptoms, but they did occur during the course of the 5FU infusion (within 24 h of starting the infusion). The uridine was started later than typical, at approximately 112 h after start of 5FU, but the patient recovered fairly rapidly and did not receive further 5FU chemotherapy, but did resume other chemotherapy fairly quickly, at 17 days after the event (so did not complete 30 day f/u). Reasons that this is only a reasonably likely case are related to the somewhat delayed start of uridine triacetate. In addition, although it seems his predominant symptoms were neurologic, there is minimal documentation of other symptoms such as mucositis, diarrhea, renal impairment, cytopenias- grading and documentation of these would be helpful. Also, DPD testing was sent, and at least for mutations which were checked, there was no evidence of DPD (although this is not mandatory, but would have been supportive).

Historical Cases of Early-Onset 5-FU and Capecitabine toxicity

Unlike the overdose indication, the applicant did not provide examples of historical control cases to support the early onset indication. However, in June 2014, the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology (OSE) conducted an analysis of fatal adverse event reports on patients treated with 5FU, capecitabine, or floxuridine, in whom DPD deficiency was documented. [redacted] The analysis summarized relevant fatal adverse event reports between 1/1/65 and 6/18/14, including 58 reports for 5FU, 145 reports for capecitabine, and 0 reports for floxuridine. In many of the cases described in the analysis, there was documentation of genetic test results indicating DPD deficiency, which could have contributed to the patients' responses to therapy with 5FU or similar agents. This analysis lends support to the conclusion that there are patients with an impaired ability to adequately metabolize standard doses of 5FU and/or capecitabine. The outcome in many of these historic cases could be expected to be death, when the patients were treated only with supportive care.

Reviewer Comment: To summarize, based upon the analysis of the early onset cases submitted by the applicant, it was determined that there were twelve total cases (11 on

study 401 and 1 on WELL401) that displayed a clinical history consistent with early onset of severe, life-threatening toxicity following 5FU dosing that benefited from uridine triacetate. Many of these cases undisputedly benefited. The key toxicities demonstrated by all patients included severe or life-threatening neurologic and cardiac toxicities, as well as certain unexpectedly severe GI and hematologic toxicities. All twelve patients received therapy with uridine triacetate within 96 hours of the onset of symptoms, they completed the prescribed uridine triacetate dosing, and they survived to Day 30 post-therapy. Of the twelve, eight of the cases were deemed to have had undisputable benefit from uridine triacetate therapy, and four of them were deemed to have had a high likelihood that uridine triacetate afforded them benefit. All of these patients showed improvement and/or resolution of 5FU toxicities over varying timeframes following uridine triacetate, but many of them recovered within days or weeks. When viewing these cases of patients treated with uridine triacetate after early onset of toxicity, we are recommending very specific guidance in the labeling, to assist clinicians in determining when and to whom uridine triacetate therapy should be administered.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints were descriptive endpoints and included:

- To assess the occurrence, severity, and duration of hematological, GI (mucositis and diarrhea), skin, neurologic, and cardiovascular toxicities in patients at risk of excess 5FU toxicity due to overdosage or impaired elimination.
- To assess systemic levels of uridine and uracil in treated patients.
- To assess safety and tolerability of uridine triacetate in treated patients.

Reviewer comment: With regard to the first and third "secondary endpoints", they are addressed to in the safety analysis of this review (Sections 7.3 and 7.4), since they are safety endpoints. However, it is also difficult to make any conclusions from these descriptive endpoints. Overall, the assessment of these endpoints, from a safety standpoint, is consistent with a favorable risk-benefit profile for uridine triacetate. The assessment of systemic uridine and uracil levels is discussed next.

Systemic levels of uridine and uracil

Plasma uridine and uracil concentrations were determined from patient samples taken between 1-4 hours after the first and last doses of uridine triacetate in some patients. The decision was made to gather these samples after the study was underway, and only at sites in the US.

Table 16 below was provided by the Applicant in the 120-day safety update, regarding plasma uridine concentrations in select patients from Study 401.10.001 and Study WELL401.

Table 16 Assessment of uridine plasma concentrations (Applicant Table)

Table 1–3 Uridine Concentrations in Plasma (Study 401.10.001 and Study WELL401), Combined ITT populations

Time Point		Overdose	Rapid Onset	Overall
post-first dose	n	71	19	90
	Mean	121.81	80.23	113.03
	SD	70.83	58.67	70.24
	Median	120	68.8	112.5
	Min, max	11.8, 395	2, 187	2, 395
post-last dose	n	66	13	79
	Mean	160.36	157.92	159.96
	SD	77.11	85.71	78.02
	Median	160	173	166
	Min, max	2, 463	31.7, 286	2, 463

Data source: Applicant ISE-a1 Table 14.2.6.2

Reviewer comment: The only thing that the Applicant concludes about these levels is that, the mean and median levels of uridine in the plasma were below the limit of quantitation in most patients before treatment with uridine triacetate, and that after the last of the ~5 day course of uridine triacetate, the mean and median levels had increased to levels thought (by the Applicant) to be necessary to achieve an optimal antidotal effect (70- 100 µM). No further conclusions can be made from this data, nor is it clear that the range of 70-100 is actually "optimal", as there is no objective data or studies to support this.

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

Pediatrics

There were six patients under the age of 18 treated with uridine triacetate. The cases are summarized in Table 17.

Table 17 Pediatrics cases treated with Uridine triacetate in Study WELL401

ID	age	Agent overdosed/ ingested	Planned dose or medication(mg)	Actual Dose (mg)	Time btwn OD and initiation of uridine triacetate	total uridine doses received	Outcome thru week 4
OD052	22 m	capecitabine	n/a	~1125 mg	<24 h	17/20	Survived
OD063	19 m	capecitabine	n/a	Up to 6000 mg (12 tabs, 500 mg)	14 h	20	Survived
OD123	2 y	capecitabine	n/a	≥ 500 mg	37 h	13/20 (refused further doses)	Unknown. No f/u after D5 post -ingestion.
OD112	7 y	5FU (wrong medication)	700 mg cyclophosphamide	574 mg bolus	33 h	20	Survived. Restarted cyclophosphamide prior to D30.
OD086	15 y	5FU (pump error)	1600 mg over 24h	1600 mg over 1h	37 h	20	Survived Restarted chemo prior to D30.
OD009	16 y	5FU- early onset toxicity	5500 mg over 3d infusion	Infusion stopped early at 48h d/t rapid onset toxicity	~64h	6 of 8 -old formulation	Survived Restarted chemo w/o 5FU prior to D30.

The three youngest pediatric patients were all cases of accidental ingestion of capecitabine, and for each, the actual dose ingested could only be estimated, based upon tablet dose in the bottle, and the caregiver's estimate of how many tablets they thought were in the bottle before the child was discovered with the bottle, minus how many tablets remained after the discovery. For all three capecitabine ingestion cases, there was varying success with administering the uridine triacetate doses. For instance, OD 123, in particular, completely refused to take any doses after the thirteenth dose. It was suggested that an NG tube be placed, but the parents refused. This patient was discharged after hospital day 5, and was recommended to follow-up with pediatrician weekly for CBC, but there is no documentation if this occurred.

The two 5FU overdose patients were more typical of the adult 5FU overdose patients. In one case (OD112) the patient inadvertently received 5FU rather than the intended medication, cyclophosphamide, due to an administration error. This patient did complete all doses of uridine triacetate therapy, but did not complete the 30 day f/u, as

he restarted cyclophosphamide prior to day 30. The second case (OD086) received a 5FU overdose due to a pump error, where the 5FU went in over an hour instead of the intended 24hours. He received all 20 doses, and restarted chemotherapy with 5FU prior to day30.

Finally, there was one pediatric patient, OD009, who was a 16 year old patient who experienced onset neurologic toxicity from 5FU. His main symptoms were neurologic. He was treated with an older formulation of uridine triacetate, where pediatric patients were receiving a total of eight doses (instead of the current 20), and this was in tablet form. This patient had some difficulty tolerating all the doses of uridine triacetate. He only received approximately six complete doses and two partial doses. However, he completely recovered from the neurologic symptoms he exhibited. He did not complete the full 30 days of follow up because this physician restarted chemotherapy without 5FU (only cisplatin and methotrexate) at 17 days post -event.

Reviewer comment on pediatric indication: Although there are only six pediatric cases in the database, there is biologic rationale to support including the pediatric indication in the label, and there are no other available therapies for the indication in pediatric patients and the risk of not treating is death. Five of the six patients were known to survive to Day 30 or were able to restart chemotherapy prior to day 30. The sixth patient was lost to follow up after study Day 5, so survival simply could not be confirmed. In addition, one of the pediatric patients presented as a classic case of early onset of 5FU toxicity, and was counted as such. Uridine triacetate was recently approved for treatment of orotic aciduria, which is a disease occurring in pediatric patients and although a different dosage was deemed safe for chronic administration. Finally, based upon animal studies, an unusually safe profile of this agent and the adequate amount of data obtained from the adult patients in the current submission, it is reasonable to consider the pediatric indication. As a result, we conclude that uridine triacetate appears to be safe in pediatric patients, and the indication will be included in patient labeling.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Analysis of dosing recommendations for pediatric patients

As noted, there are differences between the prescribed dosing regimen for adult and pediatric patients. In particular, the recommended pediatric dose for uridine triacetate is less than the adult dose and is: 6.2 g/m^2 BSA (not to exceed adult dose of 10 g dose= 1 packet) given every 6 hours for 20 doses.

The applicant will not market a specific pediatric formulation or a smaller sized dosing packet to accommodate pediatric patients. The instructions for pediatric dosing

provided in the patient label are as follows: The uridine triacetate dose to be administered is 6.2 g/m2 every 6 hours. Measure the dose using either a scale accurate to at least 0.1 g, or a graduated teaspoon accurate to ¼ teaspoon

In the patient labeling for uridine triacetate, the Applicant also provided a table to describe the methodology for measuring the pediatric dose, using the 10 g packets intended for adults. Table 18 is as follows:

Table 18 Uridine triacetate pediatric dose based on body surface area (m^2)

Patient Body Surface Area m^2	Table: VISTOGARD 6.2 grams/m^2/dose§	
	Dose in Grams	Dose in Teaspoons
0.34 to 0.44	2.1 to 2.7	1
0.45 to 0.55	2.8 to 3.4	1 ¼
0.56 to 0.66	3.5 to 4.1	1 ½
0.67 to 0.77	4.2 to 4.8	1 ¾
0.78 to 0.88	4.9 to 5.4	2
0.89 to 0.99	5.5 to 6.1	2 ¼
1.00 to 1.10	6.2 to 6.8	2 ½
1.11 to 1.21	6.9 to 7.5	2 ¾
1.22 to 1.32	7.6 to 8.1	3
1.33 to 1.43	8.2 to 8.8	3 ¼
1.44 and above *	10.0	1 full packet *

§ Dose by body surface area category in this table was rounded to achieve the approximate dose. Each dose is administered every 6 hours for 20 doses.
*May use 1 entire 10 g packet without weighing or measuring. Do not exceed 10g/dose.

Reviewer comment: The Division of Pediatrics and Maternal Health (DPMH) was consulted regarding the pediatric dosing for uridine triacetate (see Review by Ethan Hausman, M.D.). In particular, the DPMH group recommended omission of the word "teaspoon" from the labeling for uridine triacetate, and suggested using only a calibrated device. The rationale was that a teaspoon has no uniform scientific definition. However, after discussion with the Applicant and within the review division it was determined that given the wide safety margin of uridine triacetate, and in light of the rarity of use of this agent by individual pharmacies, it was determined that the proposal to use a "scale or graduated teaspoon" in labeling is appropriate and acceptable. In addition, given that all patients will at least initiate therapy in an inpatient hospital setting, and most will likely receive all or most of the uridine triacetate doses as inpatients, the pharmacies administering uridine triacetate to patients will have the

appropriate teaspoon for dosing, and will be able to provide to the patient. Therefore, the fact that the applicant will not be co-packaging a scale or graduated teaspoon with the drug is acceptable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable. Patients were not dosed for longer than 20 doses (given every 6 hours).

6.1.10 Additional Efficacy Issues/Analyses

Capecitabine
There were five patients treated with uridine triacetate on study WELL401 for capecitabine ingestion. Three of the cases were pediatric patients, discussed in Section 6.1.7 above. There were two additional adult patients who intentionally ingested capecitabine in suicide attempts. All five patients are shown in Table 19, for completeness of the overall assessment for capecitabine. The narratives for these two patients are discussed below the table.

Table 19 Capecitabine Ingestion Cases on WELL401

ID	Age	Accidental vs. intentional	Capecita-bine dose ingested (mg)	Time between OD and initiation of UT	Total UT doses received	Outcome thru week 4
OD111	68 y	Intentional (suicide attempt)	Estimates vary from 3K -10K mg (6 to 20 tabs, 500 mg)	36 h	20	Survived
OD103	74 y	Intentional (suicide attempt)	Estimates vary from 7K- 15K (14-30 tabs, 500 mg)	24- 46 h depending on source)	~11/20 doses (refused further doses)	Survived
OD052	22m	accidental	~1125 mg	<24 h	17/20	Survived
OD063	19 m	accidental	Up to 6000 mg (12 tabs, 500 mg)	14 h	20	Survived
OD123	2y	accidental	≥ 500 mg	37 h	13/20 (refused further doses)	Unknown. No f/u after D5 post - ingestion.

- **OD111** (capecitabine ingestion, adult) -68 y/o WF- intentional capecitabine ingestion. Patient herself was not being treated for cancer, but rather her husband was. She attempted suicide by intentionally ingesting approximately 15-20 capecitabine tablets, 500 mg tablets. The estimated capecitabine dose ingested was 7500- 10000 mg- later, the estimate was lowered to 3000 mg (6 x 500 mg tabs), after counting the pills in husband's pill bottle and calculating, based upon his prescribed capecitabine dose. The patient had apparently been

consuming alcohol, became upset and ingested the capecitabine tablets at approximately 2100 on (b) (6). She was taken to the ER via ambulance. The patient reported suicidal thoughts and feeling depressed. A DPD test was sent on (b) (6). The physician requested uridine triacetate, which was begun on (b) (6) at 0946 (approx. 36 hours from capecitabine ingestion). Treatment with uridine triacetate completed on (b) (6). She had developed oral thrush and vaginal candidiasis, which were treated. After completing all 20 doses, she was transferred to a psychiatric facility, where she was treated until (b) (6). She had not signs of toxicity related to the capecitabine overdose. She did not complete the 30-day f/u, but based upon the date of d/c from the psychiatric facility, it is assumed that she survived at least through Day 30.

Reviewer comment OD111: This was one case of a patient treated with uridine triacetate after intentional capecitabine ingestion. She did received all 20 doses of uridine triacetate, after which she was appropriately transferred for psychiatric care. This case lends support to the proposal to include capecitabine overdose/ ingestion in the label for uridine triacetate, based upon the biologic rationale, and given that no other treatments exist for this indication.

- **OD103**- (capecitabine ingestion, adult)- 74 y/o Asian female with gastric cancer, intentionally overdosed with capecitabine in a suicide attempt. She had Stage IV disease and was being treated with a palliative regimen of Epirubicin, oxaliplatin and capecitabine (500 mg), starting on 3/20/13. She underwent a paracentesis at the hospital on (b) (6) and was discharged home. Later that day, (b) (6), at approximately 2200, she ingested approximately 14 x 500 mg tablets (7000 mg) of capecitabine in a suicide attempt. However, there were estimates that she could have taken as many as 30 too mg tablets (dose 15,000 mg). Within 30-60 minutes of the ingestion, she reported 4-5 loose stools. She also reported vomiting, approximately 2 hours after the ingestion. Her family took her to a small local hospital, and she was transferred to a larger hospital. At that point, the patient reported abdominal pain, and had nausea, vomiting, and diarrhea. Initially, it was recommended that she be started on immediate hemodialysis, but this did not occur. The patient was admitted to the ICU, although vital signs were stable. She initiated therapy with uridine triacetate on (b) (6) at 2230, approximately 24.5 hours after the capecitabine ingestion. She had emesis with at least 1 dose of uridine triacetate. She also complained of painful swallowing and had to have some doses mixed with pudding. By (b) (6), the patient was tolerating the uridine triacetate doses and was receiving an aggressive anti-emetic regimen. She was having multiple symptoms related to her advanced underlying cancer, including worsening ascites, and the medical team and family

were attempting to make decisions regarding the best course of treatment for the progressing underlying cancer. After her 11th dose of uridine triacetate, on (b) (6), she decided not to continue further therapy with uridine triacetate. She withdrew consent from the investigational protocol. On (b) (6), she was discharged to hospice care and she died due to progressive cancer on (b) (6). She received 11 of 20 doses and did survive the 30 days.

Reviewer comment OD103: The case demonstrated documented ingestion, that therapy was initiated within 96 hours of ingestion, and that the patient survived to day 30. Regardless of the missing doses, there are still elements of this case that support the proposal to include the capecitabine indication in patient labeling for uridine triacetate.

Conclusion on Capecitabine indication: It was determined that based upon the clinical data submitted, the biologic rationale, and the unmet medical need due to risk of accidental or intentional overdosages with capecitabine, there is adequate rationale to include the indication for capecitabine overdose and/or related rapid onset toxicity in patient labeling for uridine triacetate. Of note, uridine triacetate has a good safety profile. (b) (6) The petitioner argued that a recommendation for prescreening all patients for DPD deficiency prior to therapy with fluoropyrimidines should be added to patient labeling/ package inserts for all fluoropyrimidine products. The analysis performed by the FDA involved a thorough search of fatal adverse event reports submitted to the FDA between January 1965 and June 2014. The search did retrieve 145 reports of fatalities in patients receiving capecitabine, which were thought to be associated with DPD deficiency. These cases are at risk for early onset of toxicity and severe, life-threatening, or fatal adverse reactions (see capecitabine label). Additionally the same search revealed 58 reports of fatalities in patients receiving 5FU, which were thought to be associated with DPD deficiency. Based upon this data, an indication for treatment of patients receiving an overdose of capecitabine with uridine triacetate will be included in the label. Likewise, the indication for treatment (with uridine triacetate) of early/rapid onset toxicity within 96 hours of dosing with capecitabine is also recommended.

Timing of the 96 hours dosing window

The applicant provided references to animal data in the study report (Clinical Overview, Section 2.5.1.2.4.1) describing that based upon the anabolism of 5FU to fluorouridine nucleotides, which are incorporated into RNA and result in the toxicities from 5FU, the timeframe during which uridine triacetate needed to be administered within was 96 hours. During the first 96 hours after 5FU administration, when uridine triacetate is present, it is converted to uridine, and acts to dilute and compete with fluoronucletides

(derived from 5FU) from being incorporated into RNA. In mouse models, it was shown that after a lethal dose of 5FU, uridine (derived from uridine triacetate) enabled survival. Based upon this animal data, the applicant required that uridine triacetate be initiated within 96 hours of an overdose event. It was also described in the trial eligibility that "rapid onset" toxicity included events starting within 7-10 days of 5FU dosing. Clinical data supports the use of a 96 hour window following the 5FU dose.

In the clinical trials, 2 of the patients (one on each trial) in the early onset group died, both have been discussed previously.

- Patient OD134 on study 401.10.001 displayed toxicity from 5FU within 24 hours of the initiation of 5FU. The toxicities initially only included facial swelling, diarrhea, and mucositis, which were not initially recognized as being signs of rapid onset, life-threatening toxicity from 5FU. However, the patient's clinical course unfortunately progressed, such that he subsequently developed encephalopathy, cardiotoxicity, and cytopenias. Uridine triacetate was initiated approximately 134 hours from the start of 5FU (100 hours from the end of the 5FU infusion). The patient unfortunately died as a result of the toxicities.
- Patient OD120 on WELL401also developed life-threatening toxicities related to 5FU, although it is unclear exactly how quickly the onset of symptoms was. This patient had a significant delay between 5FU dosing and initiation of uridine triacetate, such that 282 hours had elapsed since completion of 5FU (354 hours from start of 5FU) prior to uridine triacetate dosing. The patient did not survive, and the delay in administration of uridine triacetate may have contributed to this.

(b) (4)

Reviewer Comment: Based upon this concern, language has been included in the patient labeling for uridine triacetate, including a limitation of use stating that the effect of uridine triacetate on the efficacy of 5FU and capecitabine is not known, and therefore patients should not be treated with uridine triacetate to treat typical 5-fluorouracil or capecitabine toxicity. (b) (4)

7 Review of Safety

Safety Summary

The safety review for this application included reviewing patient data from the 2 studies, 401.01.001 and WELL401. Adverse events in both studies 401.10.001 and WELL401 are broken down by category and summarized in Table 20. Overall, uridine triacetate was very well tolerated, particularly in light of the fact that most of the patients were very ill from the 5FU, from their underlying cancer, or both. The most common adverse events that are possibly related to uridine triacetate, and which will be described later in this review, include diarrhea, nausea, and vomiting. To some extent, these adverse events are related to the powder formulation of uridine triacetate, which was difficult for some patients to swallow.

Table 20 Safety Overview: Attributable to Uridine Triacetate

	Study 401.10.001 N=60	Study WELL401 N=75	Total N=135
Deaths Within 30 days	2	3	5
Discontinuations due to AE	0	2	2*
SAEs	0	1	1**
G 1-4 AEs	6	16	22
G3-4 AEs	0	1	1

*Includes patients from WELL401: OD033 and OD057 (only patient with G3 AE).
**Includes patient from WELL401: OD057 who had 2 SAEs of nausea and vomiting.

7.1 Methods

The safety review for this application was unique, in that the analysis of the safety of uridine triacetate was confounded by adverse events due to chemotherapy (including 5-FU and capecitabine), as well as by symptoms due to the underlying cancers.

With regard to the safety review in particular, we note that it was confounded by toxicities that patients experienced from 5-FU and concomitant chemotherapy, as well as by their underlying cancers. We requested the Applicant to submit an Appendix subsequent to the primary NDA submission. The purpose of this was to attempt to better separate adverse events that were possibly related to uridine triacetate therapy, compared to those related to chemotherapy and/or underlying cancer. The appendix was used for the primary safety analysis and contained a listing of all adverse events experienced by patients on studies 401.10.001 and WELL401 that were possibly related to uridine. It included CTCAE grading for severity of all events, listing of whether events were serious, as well as attribution to both 5FU and uridine triacetate (which were not included in the original submission of the safety data). The appendix also included additional comments about each patient and event, to assist in better determining attribution of adverse events in our review. Data regarding deaths and discontinuations came directly from the patient narratives and the case report forms, contained in the original NDA submission. Finally, the datasets were used for confirmation of certain adverse events.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

According to the applicant, at the time of NDA submission over 560 people, including healthy volunteers, children with mitochondrial and neurometabolic disorders, children and adults overexposed to 5-FU and capecitabine, children and adults with hereditary

orotic aciduria, and adults with diabetic peripheral neuropathies had received uridine triacetate at daily dosages up to 40 g/day. However, as noted in Section 5.1, the primary evidence to support both the efficacy and safety is derived from the 135 patients treated on Trials 401.10.001 and WELL401. Table 3 above listed the clinical trials included in the NDA submission.

7.1.2 Categorization of Adverse Events

The Applicant graded the severity of AEs observed on both studies using NCI CTCAE version 4.0.

Reviewer comment: As was noted in the protocol review section the Applicant originally did not pre-specify in the protocol whether adverse events would be recorded and graded according to the Common Toxicity Criteria (CTC). The FDA had to request this from the Applicant after NDA submission, and these criteria were used in the FDA safety review of this application.

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

As noted, at the time of NDA submission 560 people have received uridine triacetate at doses up to 40g /day. For the purpose of this review, the database used to perform the safety analysis and determine the incidence of specific adverse events included the 135 patients treated on studies 401.10.001 and WELL401.

7.2 Adequacy of Safety Assessments

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

All patients enrolled were dosed with at least one dose of uridine triacetate. The demographics of patient enrolled on studies 401.10.001 and WELL401 were described in Table 5 and Table 6. As shown in the tables, the median age of the 135 patients treated on the studies was 59 years and 56% of the patients were female. The prescribed dosing duration for adults and children was for uridine triacetate to be administered every 8 hours for a total of 20 doses, which would be completed in approximately 5 days. Most patients received the prescribed 20 doses, but there were patients who discontinued therapy prior to the 20 doses, and there were a few patients who actually received more than the 20 doses, due to reattempts at vomited doses. As

a result the median number of doses in the 135 patients was 20, and the median duration of exposure to uridine triacetate was 4.75 days.

7.2.2 Explorations for Dose Response

Analysis of information submitted by the Applicant, regarding an exposure-efficacy relationship was performed by Anshu Marathe, PhD in the Office of Clinical Pharmacology (see also Clinical Pharmacology review). In summary an exposure-response analysis was not conducted because it was not considered to be important for assessing the adequacy of the Applicant's dose selection, given that 94% of 5FU overdose patients receiving uridine triacetate at the proposed dose survived. Likewise, all six pediatric patients, receiving the proposed pediatric dose, survived. Based upon these efficacy results, a formal exposure-response analysis for efficacy was not deemed to be appropriate or necessary.

7.2.3 Special Animal and/or In Vitro Testing

See the summary of the Pharmacology/ Toxicology review in Section 4.3.

7.2.4 Routine Clinical Testing

Please reference the laboratory and vital signs analyses in Sections 7.4.2 and 7.4.3.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the Clinical Pharmacology review in Section 4.4.

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

Uridine triacetate is a pyrimidine analog. It was approved earlier in 2015 for another indication (orotic aciduria) under the name Xuriden®, and no significant safety issues were reported in that label.

7.3 Major Safety Results

7.3.1 Deaths

The primary study endpoint for both Study 401.10.001 and WELL401 was survival at Day 30. Therefore, an assessment of patient deaths was described in the analysis of the primary efficacy endpoint in Section 6.1.4 of this review. Table 21 shows the number of deaths on each study. The specific patient IDs are listed below the table.

The narratives for each of these 5 patients were discussed in Section 6.1.4, as part of the analysis of the primary efficacy endpoint.

Table 21 Deaths through Day 30

Study	Deaths in Overdose Group N=117	Deaths in Early Onset Group N=18	Total Deaths N=135
401.10.001	1	1	2
WELL401	2	1	3

The two patient deaths on study 401.10.001 were:

- OD127 (overdose)
- OD134 (early onset)

The three patient deaths on WELL401 were:

- OD039 (overdose)
- OD042 (overdose)
- OD120 (early onset).

Reviewer comment: None of the deaths were attributable to uridine triacetate, and as noted previously in Section 6.1.4 of this review, 2 of the deaths (OD134 and OD120) may have been prevented if uridine triacetate had been administered sooner (within the recommended 96 hours).

7.3.2 Nonfatal Serious Adverse Events

The serious adverse events occurring in patients on both studies are shown in Table 22. This analysis was derived from the applicant's adverse event dataset.

Table 22 Serious Adverse Events ≥ 2% on Studies 401.10.001 and WELL401

Preferred terms	Serious adverse events N=135 (%)
Pancytopenia	8 (6)
Neutropenia	6 (4)
Febrile neutropenia	4 (3)
Acute renal failure	3 (2)

Source: ae.xpt.

Reviewer comment: As has been noted, therapy with uridine triacetate was well tolerated, but the safety review was confounded by 5FU toxicity, underlying cancer, and concomitant combination chemotherapy. After reviewing the narratives for patients

experiencing SAEs, and upon review of the Applicant's updated assessment of AE causality, it is clear that the almost none of the SAEs reported in the dataset could be attributed to uridine triacetate. SAEs possibility related to uridine triacetate are discussed below.

There was one patient on Study WELL401 (OD057) with serious adverse events of nausea and vomiting, which were at least possibly related to uridine triacetate.

The narrative for OD057 is discussed as follows:

- **OD057**- overdose case, WELL401- SAEs- Nausea and vomiting- 57 y/o WM with head and neck cancer receiving 5-FU with docetaxel and cisplatin. On C2 of therapy, he received an accidental overdose of 5-FU, such that he was supposed to receive a continuous infusion of 5-FU 7000 mg over 96h, starting on 4/25/11 Due to a pump programming error, he received the infusion of 5FU over 52 hours instead of 96h. When he presented, he had been experiencing nausea and vomiting at home. The physician requested uridine triacetate, and the first dose was administered on 4/29/11, approximately 40.5 hours after the overdose occurred. The patient wanted to receive treatment as an outpatient, and was instructed on the dosing schedule. He was also administered Neulasta on 4/29/11. The patient reported having significant nausea and vomiting with each attempt at uridine triacetate dosing. According to his diary, he missed several doses and had vomiting with several other doses. On (b) (6), the patient took dose #9, and refused taking any further doses, due to the nausea and vomiting he was having with each dose. On (b) (6), he returned for exam. He was noted to be significantly volume depleted, and was admitted to the hospital due to the significant nausea and vomiting. AT that point, the patient had not actually discontinued attempts at dosing with uridine triacetate, but the physician and the patient determined that no further attempts would be made, due to the intractable nausea and vomiting he was experiencing, and because the physician thought that the risk of toxicity from the 5FU overdose, at that point, seemed low. During the hospital stay, on (b) (6), the patient experienced a run of wide-complex tachycardia, which was self-limited. However, he reported intermittent palpitations, as well, and was found to be hypokalemic. His EF by echo on (b) (6) was 50%. On (b) (6), he underwent a nuclear perfusion scan, which revealed LV hypokinesis and an EF of 41%. He was also started on antibiotics for a persistent neck abscess. His clinical course improved and he was discharged home on (b) (6). He followed up with his physician on 5/12/11. At that point, restarting chemotherapy (without 5FU) was discussed, but the patient

necessitated dental clearance prior to restart and was having insurance problems. Finally on 6/2/11 (more than 1 month after 5FU overdose), patient started therapy with carboplatin.

Reviewer comment- It is notable that this patient's narrative is also discussed in the efficacy review in Section 6.1.4, because he only completed approximately 8 of the 20 doses of uridine triacetate due the intractable nausea and vomiting temporally related to uridine triacetate administration. He as obviously hospitalized due to volume depletion from the vomiting, making these events serious AEs. It is possible that the events of G3 nausea and vomiting could have been related to uridine triacetate, but definitive attribution of the events are confounded by the underlying chemotherapy which included 5FU, docetaxel, and cisplatin, all of which can cause nausea and vomiting, as well.

7.3.3 Dropouts and/or Discontinuations

On study 401.10.001, there were no discontinuations due to adverse event.

On WELL401, 3 patients who discontinued therapy due to adverse events (both overdose), as follows:

- **OD033**- Overdose case, WELL401- Discontinuation due to adverse event of diarrhea, nausea, vomiting. 76 y/o WM with colorectal cancer who received a 5FU overdose during C1 of FOLFOX chemotherapy due to pump malfunction. He was to receive 4628 mg 5FU over 46 hours, but instead, received the dose in 20 hours. Uridine triacetate was initiated approximately 76.5 hours after the overdose, but the patient wanted to receive therapy as an outpatient, due to living far from the hospital. After the 13th dose of uridine triacetate, he reported loose stools. He otherwise had no nausea, vomiting, or mucositis. He continued dosing. Prior to dose #16, he again reported loose stools, and around dose #17 of uridine triacetate, he reported 4 episodes of diarrhea, for which he received loperamide. He also reported nausea and sweating. After the 18th dose of uridine triacetate, he discontinued further dosing with uridine triacetate (the date was (b) (6)). The diarrhea was considered to be possibly related to the uridine triacetate, however in the 30 day follow-up period, the continued to have mild diarrhea and was admitted to the hospital on (b) (6) (one day later) with dehydration and mild renal impairment related to the diarrhea and vomiting. He received IV hydration and he improved over the next 2 days- diarrhea, nausea,

and vomiting had resolved by 2 days post discontinuation of uridine triacetate ([(b) (6)]). He was discharged from the hospital on [(b) (6)]. He resumed chemotherapy with FOLFOX on [(b) (6)], 21 days after the overdose event.

Reviewer comment: OD033: This patient experienced events of diarrhea and nausea and vomiting, which were at least possibly related to therapy with uridine triacetate, and resulted in discontinuation of therapy with uridine triacetate after the 18th dose, for reasons related to the diarrhea and nausea/ vomiting. Therefore, this case should be counted as a discontinuation due to adverse event (possibly related to AEs caused by uridine triacetate).

- **OD057**- Overdose case; discontinued therapy due to nausea and vomiting deemed to be possibly related, by the Applicant. Narrative for this patient is described above in sections 6.1.4 and 7.3.2.

- **OD120**- Early onset case; experienced an adverse event of acute respiratory distress syndrome (ARDS) prior to study day 30, which resulted in discontinuation from the study. This patient subsequently died as a result of the ARDS, as well.

Reviewer comment: The ARDS event experienced by patient OD120 was clearly not due to therapy with uridine triacetate and thus not included in the label, however he did discontinue therapy as a result of an adverse event occurring within 30 days of therapy, and was therefore included in this section.

7.3.4 Significant Adverse Events

Grade 3-4 Adverse Events

Grade 3 and Grade 4 AEs occurring up to 30-days after last dose of uridine occurred in 58 (43%) patients treated with uridine triacetate. The most frequent (> 2%) Grade 3-4 AEs are shown in Table 23.

Table 23 Grade 3-4 Adverse Events in Studies Well401 and 401.10.001 Combined

Adverse event by Preferred Term	Grade 3-4 N=135 (%)
Neutropenia	39 (29)
Thrombocytopenia	21 (16)
Anemia	11 (8)
Mucositis	10 (7)
Leukopenia	8 (6)
Febrile neutropenia	5 (4)
Diarrhea	4 (3)
Pancytopenia	4 (3)
Hypokalemia	3 (2)
Hyponatremia	3 (2)
Hypophosphatemia	3 (2)
Sepsis	3 (2)

Source: ae.xpt.

Reviewer comment on G3-4 adverse events: After detailed review of the safety database, including patient narratives, it was determined that the majority of adverse events (including severe events) experienced by patients treated with uridine triacetate were not attributable to the uridine triacetate, but rather to the 5FU, other concomitant chemotherapy, and/or the underlying cancer. According to our assessment, there was only one patient (OD057) who actually experienced a Grade 3 adverse events of nausea and vomiting that were likely to be related to uridine triacetate. The narrative for this patient was described in Section 7.3.2 of this review.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

When assessing common adverse events in the datasets submitted by the applicant, grade 1-4 adverse events (>5%) occurring up to 30 days after the last dose of uridine triacetate are shown in Table 24.

Table 24 Common Grade 1-4 Adverse Events in ≥5% patients, Studies WELL401 and 401.10.001 Combined

Adverse Event by Preferred Term,	Grade 1-4 N=135 (%)
Diarrhea	53 (39)
Mucositis*	51 (38)
Neutropenia**	47 (35)
Leukopenia	42 (31)
Nausea	35 (26)
Anemia	31 (23)
Vomiting	31 (23)
Thrombocytopenia	21 (16)
Fatigue	18 (13)
Hypokalemia	16 (12)
Pancytopenia	15 (11)
Alopecia	14 (10)
Headache	14 (10)
Decreased appetite	13 (10)
Hypomagnesemia	12 (9)
Back pain	11 (8)
Febrile neutropenia	11 (8)
Hyperglycemia	11 (8)
Hyponatremia	11 (8)
Constipation	10 (7)
Hypophosphatemia	10 (7)
Peripheral edema	10 (7)
Pyrexia	10 (7)
Tachycardia	10 (7)
Asthenia	9 (7)
Hypocalemia	9 (7)
Abdominal Pain	8 (6)
Anxiety	8 (6)
Cough	8 (6)
Dizziness	8 (6)
Dyspnea	7 (5)
Leukocytosis	7 (5)

Source: ae.xpt.
*Also includes Preferred term (PT) “stomatitis”
**Also includes PT “neutrophils decreased”
***Also includes PT “white blood cell count decreased”.

Reviewer comment: As was the case with the G3-4 adverse events discussed in 7.3.4, most of the G1-4 events were definitely unrelated to uridine triacetate, and instead were related to concomitant 5FU, other chemotherapy, and/or to the underlying cancer.

The common adverse events at least possibly related to therapy with uridine triacetate are depicted in Table 25. These adverse events included gastrointestinal events including nausea (4 %), vomiting (8 %), and diarrhea (3 %). All were grade 1-2 in severity, and these are shown in Table 25. The numbers of adverse event listings in the original NDA submission were much higher than those listed in the table below, and included events shown in Table 24. However after analysis of the AEs, FDA requested the Applicant resubmit the AE data, including updated grading according to CTCAE, and to include a more extensive analysis of attribution for each event. Based upon this resubmission, the FDA analysis of common adverse events was performed, and the assessment is shown in Table 25.

Table 25 Common Adverse Reactions in >2% of Patients (Attributable to Uridine triacetate) in Studies WELL401 and 401.10.001 Combined

Adverse Reaction	G1 N (%)	G2 N (%)	G3 N (%)	Total n=135 N (%)
Vomiting	11 (8)	1 (1)	1 (1)	13 (10)
Nausea	6 (4)	0	1 (1)	7 (5)
Diarrhea	2 (1)	2 (1)	0	4 (3)

7.4.2 Laboratory Findings

In the original NDA submission, shift tables for laboratory values (hematology and chemistry) were provided by the Applicant for each study (401.10.001 and WELL401) separately. These accounted for shifts in laboratory parameters from baseline to week 4, which was the timeframe of interest for both studies.

In the 120-day safety update, laboratory data from a total of 160 patients (135 from the original submission, plus 25 additional patients) was reported. The shift data, provided by the Applicant, for hematology parameters from baseline to Week 4 is shown in Table 26. The shift table for chemistry parameters from baseline to Week 4 (also provided by the Applicant) is shown in Table 27.

Table 26 Integrated Hematology Laboratory Shift Data on Study 401.01.001 and WELL401 from Baseline to Week 4 (Applicant Table from 120 Day Safety Update)

	Overdose N=131 N (%)	Early Onset N=29 N (%)	Overall N=160 N (%)
Shifts from within or below normal to above normal			
White blood cell count	11 (16.7)	3 (23.1)	14 (17.7)
Red blood cell count	0	0	0
Hemoglobin	0	0	0
Hematocrit	0	0	0
Platelet count	3 (4.5)	1 (7.7)	4 (5.1)
MCV	9 (14.1)	0	9 (11.8)
MCH	11 (17.7)	1 (8.3)	12 (16.2)
MCHC	1 (1.6)	0	1 (1.3)
Neutrophils	12 (20.7)	2 (18.2)	14 (20.3)
Lymphocytes	10 (17.2)	3 (30.0)	13 (19.1)
Monocytes	11 (20.8)	3 (33.3)	14 (22.6)
Basophils	0	0	0
Eosinophils	5 (11.6)	0	5 (10.0)
Shifts from within or above normal to below normal			
White blood cell count	5 (7.6)	1 (7.7)	6 (7.6)
Red blood cell count	9 (13.6)	7 (53.8)	16 (20.3)
Hemoglobin	10 (15.2)	6 (46.2)	16 (20.3)
Hematocrit	9 (13.6)	7 (53.8)	16 (20.3)
Platelet count	6 (9.1)	0	6 (7.6)
MCV	2 (3.1%)	0	2 (2.6)
MCH	0	0	0
MCHC	4 (6.3)	0	4 (5.3)
Neutrophils	3 (5.2)	1 (9.1)	4 (5.8)
Lymphocytes	9 (15.5)	0	9 (13.2)
Monocytes	0	0	0
Basophils	2 (4.9)	2 (33.3)	4 (8.5)
Eosinophils	9 (20.9)	1 (14.3)	10 (20.0)

Percentages are based on non-missing results at Baseline and Week 4. Number of subjects with data at Week 4 (n) can be found in the data source for this table. Data Source: Table 14.3.3.2.1 through Table 14.3.3.2.13
Abbreviations: MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume

Table 27 Integrated Chemistry Laboratory Shift Data on Study 401.01.001 and WELL401 From Baseline to Week 4 (Applicant Table from 120 Day Safety Update)

	Overdose N=131 N (%)	Early Onset N=29 N (%)	Overall N=160 N (%)
Shifts from within or below normal to above normal			
Alkaline phosphatase	7 (14.6)	4 (50.0)	11 (19.6)
Aspartate aminotransferase	6 (12.8)	0	6 (10.9)
Alanine aminotransferase	4 (9.1)	1 (12.5)	5 (9.6)
Albumin	0	0	0
Bilirubin	2 (4.2)	0	2 (3.6)
Blood urea nitrogen	12 (20.3)	4 (33.3)	16 (22.5)
Calcium	0	1 (10.0)	1 (1.6)
Chloride	8 (13.8)	1 (9.1)	9 (13.0)
Creatinine	3 (4.9)	0	3 (4.2)
Glucose	10 (18.5)	0	10 (15.4)
Lactate dehydrogenase	0	0	0
Magnesium	1 (6.3)	0	1 (4.8)
Potassium	1 (1.7)	2 (16.7)	3 (4.2)
Sodium	3 (5.1)	0	3 (4.3)
Total protein	0	0	0
Uric acid	0	0	0
Shifts from within or above normal to below normal			
Alkaline phosphatase	0	0	0
Aspartate aminotransferase	0	0	0
Alanine aminotransferase	0	0	0
Albumin	9 (19.1)	3 (33.3)	12 (21.4)
Bilirubin	3 (6.3)	0	3 (5.4)
Blood urea nitrogen	5 (8.5)	1 (8.3)	6 (8.5)
Calcium	11 (20.4)	2 (20.0)	13 (20.3)
Chloride	4 (6.9)	0	4 (5.8)
Creatinine	4 (6.6)	2 (18.2)	6 (8.3)
Glucose	2 (3.7)	0	2 (3.1)
Lactate dehydrogenase	1 (11.1)	0	1 (10.0)
Magnesium	1 (6.3)	1 (20.0)	2 (9.5)
Potassium	1 (1.7)	3 (25.0)	4 (5.6)
Sodium	8 (13.6)	0	8 (11.4)
Total protein	5 (11.1)	1 (12.5)	6 (11.3)
Uric acid	1 (16.7)	1 (100.0)	2 (28.6)

Percentages are based on non-missing results at Baseline and Week 4. Number of subjects with data at Week 4 (n) can be found in the data source for this table.
Data Source: Table 14.3.2.2.1 through Table 14.3.2.2.16

In general, review of the laboratory data results are heavily confounded by the underlying 5-FU therapy, concurrent chemotherapy, and underlying cancer. However,

based upon the overall assessment of the safety of uridine triacetate, including adverse events thought to be related to uridine triacetate, and the overall reasonable safety profile of this agent, no aberrant laboratory findings due to uridine triacetate would be expected.

7.4.3 Vital Signs

Similar to the assessment of laboratory findings, review of data on vital sign changes occurring during therapy with uridine triacetate are heavily confounded by underlying 5-FU therapy, concurrent chemotherapy, and underlying cancer. There were no vital sign changes to report that could have reasonably been attributed to uridine triacetate therapy.

7.4.4 Electrocardiograms (ECGs)

This application was granted a QTc waiver. There was no ECG data submitted with the NDA.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See also section 7.4.1. All patients were to receive the same dose of uridine triacetate of 10 grams every 6 hours for 20 doses. Uridine triacetate was overall well tolerated, except for mostly mild nausea, vomiting, and diarrhea. Given that all patients received the same dosing and schedule of uridine triacetate, no assessment could be made on the incidence of adverse events, as related to dose.

7.5.2 Time Dependency for Adverse Events

See also section 7.4.1. The main common toxicities were nausea and vomiting, and these events were temporally related to administration of the uridine triacetate, as it is administered in a powder formulation, which was difficult for some patients to tolerate. As a result, many patients did experience nausea and vomiting, associated immediately

with the actual dosing of uridine triacetate. If a given dose was vomited by a patient, the protocol stated that another complete dose was to be initiated within 15 minutes of vomiting, and this appeared to happen frequently. Some patients benefitted from mixing uridine triacetate with certain foods, to make it more palatable, and some patients benefitted from pre-treatment with anti-emetic agents.

7.5.3 Drug-Demographic Interactions

Based upon the Clinical Pharmacology review of the data, there was found to be no clinically meaningful effect of gender, race, age, or creatinine clearance on uridine PK in adult patients. As a result, no dosing adjustment is recommended for any of these intrinsic or extrinsic factors. However, as noted in various parts of this review, including in Sections 6.1.7 and 6.1.8, there are separate dosing instructions for pediatric patients, based upon BSA.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

CYP450 enzymes are not involved in the metabolism of uridine triacetate or uridine. No drug-drug interactions were specifically identified in review of this application. However, as noted throughout this review, the effect of uridine triacetate on the efficacy of 5-FU and capecitabine is not known.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

For the current indication, uridine triacetate will be administered almost exclusively to patients with cancer and for a life-threatening indication. No carcinogenicity studies were required. Uridine triacetate was approved earlier in 9/4/2015 as Xuriden for the indication of hereditary orotic aciduria. As part of the clinical review of that application (Clinical Reviewer: Carla Epps, MD in DGIEP/ODE III) it was noted that:

"the applicant has not done carcinogenicity with uridine triacetate; nevertheless, no findings suggested that the compound was tumorigenic in the 6-month repeat-dose toxicity study in rats. Uridine triacetate did not affect fertility and reproductive ability in rats of either sex and did not produce maternal toxicity during gestation or teratogenic effects in developing fetuses at up to 2000 mg/kg/day, which was the highest dose in the study."

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well controlled trials with uridine triacetate in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

See analysis of pediatric patients treated with uridine triacetate in section 6.1.7. Given the emergent, life-threatening nature of the condition for which uridine triacetate is indicated, and the relatively short-term duration of therapy (approximately 5 days), it is not possible to assess for an effect on growth. However, given that the outcome for pediatric patients after 5-FU or capecitabine overdose would likely be death if uridine triacetate were not given, the benefit to pediatric patients outweighs the risks.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

This drug does not have drug abuse potential.

7.7 Additional Submissions / Safety Issues

The 120-day update, submitted on 11/10/15, included data on 25 additional patients treated with uridine triacetate; 17 on study 401.10.001 and 8 on study WELL401. This included information on six additional deaths, four of rapid onset patients (OD147, OD148, OD142 and OD146) and two who received an overdose (ODOD152 and OD158).

- **OD142** (early onset) developed serious 5FU toxicities within 24 hours of receiving 5FU. Uridine triacetate was requested, however, the patient died before receiving any doses of uridine triacetate (but after signing informed consent), within 72 hours of 5FU completion.
- **OD146** (early onset) developed serious 5FU toxicities however did not receive uridine triacetate until 121 hours later.
- **OD147** (early onset) developed early onset of severe toxicities after receiving capecitabine with mucositis and encephalopathy and received uridine 97.5 hours after the last administered capecitabine.
- **OD148** (early onset) developed severe mucositis and altered mental status after receiving the first cycle of capecitabine and received uridine 132 hours afterward.
- **OD152** (overdose) was overdosed by dose with 15,000 mg of 5-FU over 24 hours and despite starting uridine in the appropriate time frame (approximately 48 hours) he died 8 days after completing uridine triacetate (14 days from the overdose event). He had persistent grade 4 neutropenia at the time of uridine triacetate completion, but was reported to be otherwise “recovering well” after the overdose. However, 7 days after completing uridine, he developed acute

abdominal distention, which was thought to possibly be due to ischemic enteritis or small bowel obstruction. He quickly decompensated, became septic, developed lactic acidosis, and died 24 hours later (8 days from uridine triacetate completion). .

- **OD158** (overdose) was overdosed by 5-FU (receiving 4355 mg over 11.5 hours rather than the intended 46 hour infusion). Uridine triacetate was initiated appropriately, beginning approximately 24 hours after the overdose. He completed all 20 doses of uridine triacetate, and displayed no toxic effects from 5FU at the time of therapy completion. However, 2 days after completing uridine triacetate, he developed multiorgan failure, ARDS, septic shock, and lactic acidosis. He died 24 hours after the onset of multiorgan failure (3 days after completing therapy with uridine triacetate), and despite starting uridine within the recommended 96 hours of the overdose.

Reviewer Comment:
Despite additional submission of deaths, there were no significant additional safety findings that could have been related to uridine. Three of the deaths described above received uridine triacetate after the 96 hour window or did not receive uridine at all and thus are supportive of 96 hour window. The other two deaths (OD152 and OD158) due to ischemic enteritis/ sepsis and ARDS, respectively, were difficult to assess for attribution, and these cases do not change the overall conclusions of this reviewer with respect to the risk:benefit analysis.

Additional cases of efficacy were also submitted including two cases of early-onset toxicity of which one patient developed toxicity of 5-FU and the other from capecitabine. Both of these subjects (OD167 and OD156) survived. The capecitabine case, OD167 developed Grade 4 pancytopenia and diarrhea with Grade 4 mucositis in the middle of their first cycle of capecitabine and initiated uridine triacetate 80 hours after the last dose of capecitabine and survived to day 30. In addition, 18 cases of overdose were also submitted, three with capecitabine (with overdoses of >20,000mg of capecitabine) and 15 of 5-FU. All these additional patients survived (one case was lost to follow-up prior to day 30).

Reviewer comment: The additional case of capecitabine early onset toxicity is supportive of the inclusion of capecitabine in the indication and taken with the two deaths from early onset capecitabine toxicity demonstrate the importance of early initiation of uridine triacetate. The other cases do not change the risk:benefit analysis and add support to the proposed indication statement.

8 Postmarket Experience

No postmarketing experience was submitted with the NDA.

9 Appendices

9.1 Literature Review/References

1. NIH (2008). Public teleconference regarding licensing and collaborative research opportunities for: methods and compositions relating to detecting dihydropyrimidine dehydrogenase (DPD). Federal Register. 73 (129), 38233.
2. van Kuilenburg AB, et al. (2004). Dihydropyrimidine dehydrogenase and the efficacy and toxicity of 5-fluorouracil. Eur J Cancer. 40: 939.

(b) (4)

5. Sorrentino MF, et al. (2012). 5-fluorouracil induced cardiotoxicity: review of the literature. Cardiology Journal. 19 (5): 453

9.2 Labeling Recommendations

The final product labeling is still under negotiation at the time of this review. However, the most significant high-level labelling consideration was revolving the indication.

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(b) (6)

After review of the application and extensive labeling negotiations with the Applicant, the indication was amended at the time of the submission of this review to be:

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

Limitations of use:

- Uridine triacetate is not recommended for the treatment of adverse reactions associated with fluorouracil or capecitabine that are not severe or life-threatening because it may diminish the efficacy of these drugs.
- The safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established.

9.3 Advisory Committee Meeting

None.

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

/s/

GWYNN ISON
11/25/2015

JULIA A BEAVER
11/25/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208159 **Applicant: Wellstat** **Stamp Date: July 10, 2015**

Drug Name: Uridine triacetate (proposed: Vistogard™) **NDA/BLA Type: NDA**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the relied upon listed drug(s)?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: R.401.14.003 (mouse 5FU standard dose rapid toxicity onset model) Study Numbers: R.401.14.001 (mouse overdose) R.401.14.002 (mouse oral PK) Study Number: P92-1082- Phase 1- Rescue agent in	X			Study R.401.14.003 in the mouse. They also cite published clinical data.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	patients with cancer (uridine triacetate dose escalation, 5-FU dose escalation)				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: 401.10.001 Expanded Access Protocol Indication: Patients at excess risk of toxicity due to 5-FU overdosage or impaired elimination Pivotal Study #2: WELL 401 Indication: Patients at excess risk of 5FU toxicity due to overdosage or rapid onset of serious toxicity	X			Neither trial was randomized or controlled due to the rarity of the condition and ethical issues surrounding an antidote.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Neither trial was randomized or controlled due to the rarity of the condition and ethical issues surrounding an antidote.
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The primary endpoint was survival in an open-label study.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		X		A waiver request is under review.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Medra
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan drug; pediatric patients were studied.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			For study 401.10.001
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____Yes___

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

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

Clinical Labeling requests will be included in the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

GWYNN ISON
08/11/2015

JULIA A BEAVER
08/11/2015