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APPLICATION NUMBER:

208159Orig1s000

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

Clinical Pharmacology NDA Review

NDA	208159/SDN 3
Brand Name	VISTOGARD [®]
Generic Name	Uridine Triacetate
Submission Date	Rolling submissions 1/16/2015, 6/3/2015 and 7/10/2015
Submission Type; Code	505 (b)(1); NME
Review Classification	Priority, Fast Track, Orphan Drug
PDUFA Due Date	March 10, 2016
Proposed Dosage Form / Strength	Oral granules: 10 grams of orange-flavored oral granules (95% w/w) in (b) (4) packets
Proposed Dosing Regimen	Adult dose: 10 grams (1 packet) orally every 6 hours for 20 doses without regard to meals Pediatric dosage: 6.2 grams/m ² of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses without regard to meals
Proposed Indication	Patients at risk of serious toxicity following an overdose of 5-fluorouracil and patients exhibiting symptoms of serious toxicity within 96 hours of 5-fluorouracil administration
Related IND	39571
Applicant	Wellstat Therapeutics
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1 EXECUTIVE SUMMARY

Wellstat Therapeutics has submitted New Drug Application (NDA) 208159 for Vistogard (uridine triacetate) for the treatment of patients at risk of serious toxicity following an overdose of 5-fluorouracil (5-FU) or patients exhibiting serious toxicity within 96 hours of 5-FU administration.

Uridine triacetate is an acetylated pro-drug of uridine. In cells, uridine competitively inhibits cell damage and cell death caused by 5-fluorouracil. The proposed dose in adults is 10 grams orally every 6 hours for 20 doses without regard to meals. The proposed dose in pediatric patients is 6.2 grams/m² orally every 6 hours for 20 doses without regard to meals for patients with body surface area (BSA) up to 1.44 m². For patients with BSA of 1.44 m² and above, the dose is same as the adult dose of 10 grams orally every 6 hours for 20 doses.

The efficacy and safety of Vistogard was established in two clinical studies (WELL401 and 401.10.001). Based on FDA's analysis, 117 patients were classified as patients with documented overdose and 18 patients were classified as patients who exhibited rapid onset of toxicity. Among the 117 patients with documented overdose, 114 survived thereby accounting for a survival rate of 97%. Among the 18 patients with rapid onset of toxicity, 16 survived. The most common adverse events observed (>2%) were vomiting (10%), nausea (5%) and diarrhea (3%). Serious adverse reactions and Grade \geq 3 adverse reactions were seen in one patient receiving Vistogard (Grade 3 nausea and vomiting). In the trials there were 6 pediatric patients (including 3 under the age of 2 years) who were treated with Vistogard in WELL401. Four patients between the age 1 and 7 received body surface area adjusted dosage of approximately 6.2 grams/m²/dose \times 20 doses. A 15 year old with BSA of 1.55 m² received 10 grams every 6 hours. Another pediatric patient of 16 years of age and BSA of 2.12 m² received 6 grams every 8 hours. All pediatric patients survived the 5-fluorouracil overexposure.

The clinical pharmacology program for uridine triacetate includes two bioequivalence (BE) studies, a food effect study in healthy subjects, supporting pharmacokinetic (PK) data from Trial WELL401 and Trial 401.10.001, as well as multiple dose PK in patients with solid tumors, patients with diabetic neuropathy and children with mitochondrial disorders.

The following are the major findings of the review:

- The proposed dose is reasonable for adults based on the high survival rate and lack of major safety issues observed in the clinical trials.
- The proposed dose is reasonable for pediatric patients based on the efficacy and safety findings in WELL 401. The data is however limited to 6 pediatric patients.
- Food did not impact the pharmacokinetics of uridine and it is recommended to administer uridine triacetate without regard to meals in the labeling.
- There is no clinically meaningful effect of gender, race, age and body surface area on uridine PK in adults and no dose adjustment is needed based on these intrinsic factors.

1.1 RECOMMENDATIONS

NDA208159 is acceptable for approval from a clinical pharmacology perspective. The adequacy of the clinical pharmacology program in the overall drug development plan of uridine triacetate is summarized in the table below.

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Proposed dose of 10 grams orally every 6 hours for 20 doses without regard to meals in adults	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Refer to Sections 2.2.1, 2.2.4.4 and 2.5.2	The proposed dose is reasonable based on the efficacy and safety observed in clinical trials. There is no significant food effect on uridine PK in the fed state.
Proposed dose of 6.2 grams/m ² orally every 6 hours for 20 doses without regard to meals in pediatric patients	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Refer to Sections 2.2.1, 2.2.4.4 and 2.5.2	The proposed dose is reasonable based on the efficacy and safety observed in pediatric patients in clinical trials. Comment: The data was limited (N=6) in pediatric patients.
No dosing adjustment is recommended for any intrinsic or extrinsic factor	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Refer to Sections 2.3 and 2.4	The proposed dose is reasonable because there is no clinically meaningful effect of gender, race, age and creatinine clearance on uridine PK in adults. Additionally CYP450 enzymes are not involved in the metabolism of uridine triacetate or uridine.

1.2 POST-MARKETING REQUIREMENTS (PMRS) AND COMMITMENTS (PMCS)

None.

Signatures:

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1.3 CLINICAL PHARMACOLOGY SUMMARY

Mechanism of Action and Indication:

Uridine triacetate is an acetylated pro-drug of uridine. Following oral administration, uridine triacetate is deacetylated by nonspecific esterases present throughout the body, yielding uridine in the circulation. In cells, uridine competitively inhibits cell damage and cell death caused by 5-fluorouracil.

Dose and Dosing Regimen:

The proposed dose for VISTOGARD in adults and pediatrics patients are as follows:

- Adults: 10 grams (1 packet) orally every 6 hours for 20 doses, without regard to meals.
- Pediatric: 6.2 grams/m² of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses, without regard to meals. For patients with BSA of 1.44 m² and above, the dose is 10 grams orally every 6 hours for 20 doses.

Efficacy and Safety:

The efficacy of VISTOGARD was established in two clinical studies (WELL401 and 401.10.001). Both were open label, expanded access protocols that enrolled patients on the basis of demonstrated overdose or early onset of symptoms following 5-FU administration. Overall survival was the primary endpoint in these studies. A total of 135 patients were included in both studies combined. Based on FDA's analysis, 117 patients were classified as patients with documented overdose and 18 patients were classified as patients who exhibited rapid onset of toxicity. Among the 117 overdose patients, 114 survived thereby accounting for a survival rate of 97%. Based on historical data from 25 patients with 5-FU overdose, it is known that only 4 survived and 21 died; thereby accounting for a low survival rate of only 16%. Among the 18 patients with rapid onset of toxicity, 16 survived.

In terms of safety the most common adverse events observed (>2%) were vomiting (10%), nausea (5%) and diarrhea (3%). Serious adverse reactions and Grade ≥ 3 adverse reactions were seen in one patient receiving Vistogard (Grade 3 nausea and vomiting).

In the trials there were 6 pediatric patients (including 3 under the age of 2 years) who were treated with Vistogard in WELL401. Four patients between the age 1 and 7 received body surface area adjusted dosage of approximately 6.2 grams/m²/dose \times 20 doses. A 15 year old with BSA of 1.55 m² received 10 grams every 6 hours. Another pediatric patient of 16 years of age and BSA of 2.12 m² received 6 grams every 8 hours. All pediatric patients survived the 5-flourouracil overexposure. The only adverse reaction was one non-serious case of vomiting.

Pharmacokinetics:

Uridine triacetate is deacetylated via endogenous esterases to uridine and acetate following oral administration. No uridine triacetate has been detected in the circulation. The bioavailability of uridine after oral administration of uridine triacetate is much higher comparing to administration of equimolar doses of oral uridine. Following a single dose of oral uridine triacetate, the maximum uridine concentrations in plasma achieve within 2-3 hours and the half-life ranges from 2.2 to 2.6 hours. Mean uridine concentrations after 20 doses increased approximately 1.5 times in the clinical studies. Food did not impact the pharmacokinetics of uridine and it is recommended to administer uridine triacetate without regard to meals in the labeling.

Metabolism and Drug Interactions:

Uridine is metabolized via the mammalian pyrimidine pathway as endogenous uridine. CYP450 enzymes are not involved in the metabolism of uridine triacetate or uridine. *In vitro* data suggested that uridine triacetate or uridine did not inhibit or induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A. The potential for uridine triacetate to act as a P-gp inhibitor at the gut level cannot be ruled out.

Specific Populations:

There is no clinically meaningful effect of gender, race, age and body surface area on uridine PK in adults and no dose adjustment is needed based on these intrinsic factors. The proposed pediatric dose of 6.2 gm/m² every 6 hours is supported by the efficacy and safety data from pediatric patients (N=6) in WELL401. Pharmacokinetic data is limited in pediatric patients.

2 QUESTION BASED REVIEW

Uridine triacetate was initially approved as a new molecular entity by FDA as XURIDEN™ oral granules for the indication of uridine replacement for the treatment of hereditary orotic aciduria (HOA). For detailed clinical pharmacology and biopharmaceutical information, please refer to the primary review under NDA 208169 dated June 5, 2015 in DARRTS (reference ID: 3774715). This review includes the clinical pharmacology information pertinent to the indication of 5-fluorouracil (FU) overdose or serious toxicity within 96 hours of 5-FU treatment.

2.1 GENERAL ATTRIBUTES

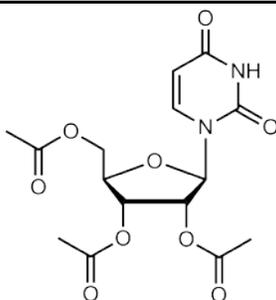
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

VISTOGARD (uridine triacetate) oral granules is a pyrimidine analog. Uridine triacetate has the chemical designation (2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione. The molecular weight is 370.3 and it has an empirical formula of C₁₅H₁₈N₂O₉. The molecular structure of uridine triacetate is shown in Figure 1.

Each (b) (4) 10 gram packet of VISTOGARD orange-flavored oral granules (95% w/w) contains 10 grams of uridine triacetate and the following inactive ingredients: ethylcellulose (0.309 grams), Opadry Clear [proprietary dispersion of hydroxypropylmethylcellulose and Macrogol] (0.077 grams), and natural orange juice flavor (0.131 grams).

The solubility of uridine triacetate in aqueous media is 7.7 mg/ml, and is independent of pH.

Figure 1: Molecular structure of Uridine Triacetate



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

Mechanism of Action : Uridine triacetate is an acetylated pro-drug of uridine. Following oral administration, uridine triacetate is deacetylated by nonspecific esterases present throughout the body, yielding uridine in the circulation. Uridine competitively inhibits cell damage and cell death

caused by fluorouracil.

Fluorouracil is a cytotoxic antimetabolite that interferes with nucleic acid metabolism in normal and cancer cells. Cells anabolize fluorouracil to the cytotoxic intermediates 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). FdUMP inhibits thymidylate synthase, blocking thymidine synthesis. Thymidine is required for DNA replication and repair. Uridine is not found in DNA.

The second source of fluorouracil cytotoxicity is the incorporation of its metabolite, FUTP, into RNA. This incorporation of FUTP into RNA is proportional to systemic fluorouracil exposure. Excess circulating uridine derived from VISTOGARD is converted into uridine triphosphate (UTP), which competes with FUTP for incorporation into RNA.

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.

2.1.3 What are the proposed dosage and route of administration?

The proposed dose for VISTOGARD in adults and pediatrics patients are as follows:

- Adults: 10 grams (1 packet) orally every 6 hours for 20 doses, without regard to meals.
- Pediatric: 6.2 grams/m² of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses, without regard to meals. The VISTOGARD dose to be administered at 6.2 grams/m² is presented in Table 1. The dose should be measured using either a scale accurate to at least 0.1 gram, or a graduated teaspoon accurate to ¼ teaspoon.

Table 1: VISTOGARD Pediatric Dose Based on Body Surface Area (m ²)		
Patient Body Surface Area m ²	Table 1: 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
1.01 to 1.11	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 10 grams/dose.

2.2 GENERAL CLINICAL PHARMACOLOGY

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

The clinical pharmacology program for uridine triacetate includes two bioequivalence (BE) studies, a food effect study in healthy subjects, supporting pharmacokinetic (PK) data from two safety and efficacy studies 401.10.001 and WELL401, and multiple dose PK in children with mitochondrial disorders, cancer patients with solid tumors and diabetic neuropathy patients. The clinical pharmacology studies are briefly described in Table 2.

Table 2: Summary of Clinical Pharmacology Studies of Uridine Triacetate

Study No.	Study Design	Dose and Dosing Regimen
401.10.PKL.01	Phase 1, open-label, randomized, crossover, single dose PK profile of two different lots of tablets (fasted) and fed/fasted (one lot of tablets) [n=6 patients]	6 g (500 mg tablet), oral single dose
PN401.07.001	Phase 1, open-label, randomized, 2-way crossover, single dose PK profile of oral drug substance or coated granules (fasted) [n=20 patients]	6 g (drug substance), oral single dose 6 g (coated granules), oral single dose
PN401.07.002	Phase 1, open-label, randomized, 2-way crossover, single dose food-effect study comparing PK profile of coated granules under fasting and fed conditions [n=20 patients]	6 g (coated granules), oral single dose
WELL401	Open label, single arm, multi-center, efficacy and safety study to treat patients at excess risk of 5-fluorouracil (5-FU) toxicity due to overdosage or rapid onset of serious toxicity [n=69 adults and 6 pediatric (<18 years)]	Adults and pediatric ≥7 years: 10g, Q6h × 20 doses Pediatric < 2 years: 6.2 g/m ² , Q6h × 20 doses

401.10.001	Expanded access of WELL401, open-label, single arm, multi-center study to treat patients at excess risk of 5-FU toxicity due to overdosage or impaired elimination [n=60 patients]	10g, Q6h × 20 doses
P92-1082-PK	PK of uridine in cancer patients treated with 5-FU and uridine triacetate [n=38 patients (16 with evaluable PK data)]	Part 1: 3.3, 6, 6.6, or 9.9 g as a suspension using cherry syrup, Q6h × 10 doses Part 2: 6 g tablet, Q6hr x 10 doses
PN401.09.001-PK	PK of uridine in mitochondrial disease subjects following oral dosing with uridine triacetate [n=4 pediatric]	Oral uridine 333 mg/kg, TID for the first day Oral uridine triacetate 33 mg/kg TID to 100 mg/kg TID, ~ 1.5 years
401.97.201	Phase 2, multi-center, open label, clinical trial to assess the safety and efficacy of uridine triacetate in diabetic neuropathy [n=20 patients]	4 or 8 g/day (2 or 4 g BID) (500 mg tablets), orally, 6 to 12 months

The efficacy of VISTOGARD was established in two clinical studies (WELL401 and 401.10.001). Both were open label, expanded access protocols that enrolled patients on the basis of demonstrated overdosage or early onset of symptoms following 5-FU administration. Based on the protocol the 5-FU overdose was defined as the administration of 5-FU at a dose or infusion greater than the intended dose or MTD for patient's intended regimen.

Overall survival was the primary endpoint in these studies. A total of 135 patients were included in both studies combined.

Based on FDA's analysis, 117 patients were classified as patients with documented overdose and 18 patients were classified as patients who exhibited rapid onset of toxicity. Among the 117 overdose patients, 114 survived thereby accounting for a survival rate of 97% (Table 3). Based on historical data from 25 patients with 5-FU overdose, it is known that only 4 survived and 21 died; thereby accounting for a low survival rate of only 16%. Among the 18 patients with rapid onset of toxicity, 16 survived. In terms of safety the most common adverse events observed (>2%) were vomiting (10%), nausea (5%) and diarrhea (3%). Serious adverse reactions and Grade ≥3 adverse reactions were seen in one patient receiving Vistogard (Grade 3 nausea and vomiting).

In the trials there were 6 pediatric patients (including 3 under the age of 2 years) who were treated with VISTOGARD in WELL401. Patients under the age of 7 received 6.2 grams/m²/dose × 20 doses. All pediatric patients survived the 5-flourouracil overexposure. The only adverse reaction was 1 non-serious case of vomiting

Overall the clinical team has determined that the efficacy of VISTOGARD was demonstrated in both adults and pediatrics and the safety was deemed to be acceptable. No major safety concerns have been identified with the administration of VISTOGARD. For further details see Dr. Gwynn Ison's clinical review.

	Overdose N=117	Rapid Onset N=18	Overall N=135
Death	3 (3%)	2 (11%)	5 (4%)
Survival	114 (97%)	16 (89%)	130 (96%)

*Survival includes patients who survived at 30 days or patients who resumed chemotherapy prior to 30 days.
Source: Section 14 of Label.*

The formulation of uridine triacetate changed during clinical development from initial cherry syrup to tablets and to coated granules at present. The compositions of formulation development in various clinical studies are listed in Table 4.

Table 4: Uridine Triacetate Formulation Used in Various Studies

	Study WELL401 and 401.10.001		Study 401.07.001 and 401.07.002		Study 401.10.PKL.01		Study P92- 1082-PK	
	% w/w	Unit Dose (g)	% w/w	Unit Dose (g)	% w/w	Unit Dose (mg)	% w/w	Unit Dose (mg)
Uridine Triacetate	95	10	91	10	50	500	71.7	750
Hypromellose and Macrogol	0.73	0.077	(b) (6)					
Ethylcellulose	2.94	0.309						
Orange Juice Flavor	1.25	0.131						
(b) (6)								
Total	100	10.517						

In addition, a 2-stage PK analysis was performed to evaluate the potential influence of various intrinsic and extrinsic factors on the disposition of uridine after oral administration of uridine triacetate.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The major efficacy outcome measure was overall survival in the clinical studies.

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

Uridine triacetate is a prodrug of uridine. Uridine is the active moiety in the plasma, which was determined using validated HPLC method. The assay to detect uridine triacetate was not validated as the sponsor claimed that uridine triacetate was not stable in biological fluids. See Section 2.6 for additional information.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response (E-R) relationships for the primary efficacy endpoint?

An exposure-response analysis was not conducted because it was not considered important for assessing the adequacy of sponsor's dose selection as at the proposed dose, 97% of the patients who had documented overdose survived. Among the 135 patients in the trials, there were only 5 deaths. Additionally all 6 pediatric patients in the trials survived. See section 2.2.1. Thus based on robust efficacy results, E-R analysis for efficacy was not deemed important.

2.2.4.2 What are the characteristics of the exposure-response (E-R) for safety?

No major safety concerns have been identified with the administration of VISTOGARD. Since the safety profile of the drug is considered benign, E-R analysis for safety was deemed not necessary.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The effect of uridine triacetate on QT or QTc prolongation has not been studied. The applicant submitted a request for waiver of TQT study under IND 118931. The QT-IRT accepted the applicant's waiver request. The QT-IRT stated that "given the clinical history of uridine, the pharmacology profile of uridine triacetate, and the preclinical cardiac evaluation, we agree with the sponsor that uridine triacetate is unlikely to prolong QT significantly in the targeted population and a TQT seems not needed."

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

The proposed dose of 10 grams orally every 6 hours in adults is reasonable because efficacy at this dose has been demonstrated in studies WELL401 and 401.10.001. Among the 117 overdose patients, 114 survived thereby accounting for a survival rate of 97% (Table 3). Among the 18 patients with rapid onset of toxicity, 16 survived. Additionally no major safety concerns have been identified with administration of uridine triacetate. The most common adverse events observed (>2%) were vomiting (10%), nausea (5%) and diarrhea (3%). Serious adverse reactions and Grade ≥ 3 adverse reactions were seen in one patient receiving Vistogard (Grade 3 nausea and vomiting). For details see section 2.2.1.

The proposed dose in pediatric patients is 6.2 grams/m² of body surface area (not to exceed

10 grams per dose) orally every 6 hours for 20 doses, without regard to meals. The VISTOGARD dose to be administered at 6.2 grams/m² is presented in Table 1. The dose should be measured using either a scale accurate to at least 0.1 gram, or a graduated teaspoon accurate to ¼ teaspoon. The administration of uridine triacetate is likely to be entirely in a hospital setting where the can be measured using a scale. However for those rare events when a patient is discharged early and needs to administer uridine triacetate at home, the label provides dosing instructions based on graduated teaspoon (Table 1). The data in pediatric patients was limited as only 6 pediatric patients (including 3 less than 2 years) were treated with uridine triacetate in WELL401. Four patients between the age 1 and 7 received body surface area adjusted dosage of approximately 6.2 grams/m²/dose × 20 doses. A 15 year old with BSA of 1.55 m² received 10 grams every 6 hours. Another pediatric patient of 16 years of age and BSA of 2.12 m² received 6 grams every 8 hours. All 6 pediatric patients survived and in terms of safety only 1 non-serious case of vomiting was observed. Pharmacokinetic data was available from only 2 patients in WELL401. The uridine concentration two hour post dosing of uridine triacetate were 82 uM and 26 uM. Given that all pediatric patients survived, sponsor's proposed pediatric dose of 6.2 grams/m² to be given every 6 hours seems reasonable. Table 1 suggests that a body surface areas (BSA) based dose should be considered for BSA ranging from 0.34 m² to 1.43 m². Pediatric patients with BSA of 1.44 m² or above should receive the full adult dose. The lower cut-off for BSA of 0.34 m² is reasonable because accidental ingestion of capecitabine tablets is extremely unlikely to occur in infants (BSA < 0.34 m²) that are not yet self-mobile. Based on CDC growth chart, a BSA of 0.34 m² corresponds to approximately a pediatric who is 1 year old based on median body weight and height. The upper cut-off for BSA for BSA based dosing should ideally be 1.6 m² (= [10 g] / [6.2 g/m²]). However an upper cut-off of 1.44 m² is proposed to account for dosing instructions based on graduated teaspoon which is reasonable. The doses in grams were converted to teaspoons based on multiple measurements of VISTOGARD showing that 1 level teaspoon of granules weighs approximately 2.9 grams. Doses are rounded up to achieve the approximate dose. The rounding up ensures that pediatric patients are slightly overdosed. This is considered reasonable given the safety margin associated with uridine triacetate and the low survival that is expected based on historical controls when uridine triacetate is not administered.

2.2.4.5 Is the proposed window of therapy for initiation of treatment with uridine triacetate within 96 hours post 5-FU dose appropriate?

The initiation of treatment with uridine triacetate within 96 hours of post 5-FU dose is appropriate because in the clinical trials among the 5 deaths that occurred, 3 occurred in patients who were treated with uridine triacetate after 96 hours of 5-FU dose. Additionally animal studies suggested that there was increase in survival with earlier intervention in mice.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single-dose and multiple dose pharmacokinetic parameters?

Uridine concentrations [mean \pm standard deviation (SD)] were determined from 1 to 4 hours after the first and last doses of oral 10 gram dose of uridine triacetate in a subgroup of patients in Studies WELL401 and 401.10.001, which are summarized in Table 5. Plasma samples were collected approximately around the time to reach maximum concentration of uridine following single dose and multiple doses. Mean uridine concentrations after 20 doses increased approximately 1.3 times in Study WELL401 and 1.6 times in Study 401.10.001.

Table 5: Uridine Concentration (μM) in Study WELL401 and Study 401.10.001

	Study WELL401	Study 401.10.001	Overall
1-4 hours post-first dose	119 (\pm 59) N=26	99 (\pm 64) N=49	106 (\pm 63) N=75
1-4 hours post-last dose	153 (\pm 68) N=24	160 (\pm 81) N=40	157 (\pm 76) N=64

The PK of uridine following single dose and multiple doses of oral uridine triacetate was also assessed in cancer patients in Study P92-1082-PK. Uridine triacetate was used as a rescue agent for 5-FU to determine the maximum tolerated dose of 5-FU when co-administering uridine triacetate. Uridine triacetate was given to separate cohorts at doses of 3.3, 6.6, or 9.9 grams powder in ^{(b)(6)} syrup suspension Q6h for a total of 10 doses in study Part 1. Concentration samples were collected after the 1st and 9th doses up to 6 hours. Mean (\pm SD) values of uridine exposure after 1st and 9th dose of 9.9 gram uridine triacetate are listed in Table 6. The exposure data support that uridine accumulates in the plasma after multiple dose, although the formulations of uridine triacetate used in cancer patients are different from the one used in the above two clinical studies (Table 4).

Table 6: Mean C_{max} , AUC_{0-6} and C_{ss} of Plasma Uridine after 1st and 9th Dose

9.9 gram	C_{max} (μM)	AUC_{0-6} ($\mu\text{M}\cdot\text{hr}$)	C_{ss} (μM)
1 st dose (n=3)	205 (\pm 4)	791 (\pm 66)	NA
9 th dose (n=2)	293 (\pm 89)	975 (\pm 178)	163 (\pm 30)

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

The concentration of uridine in healthy volunteers was measured following administration of 6 gram single oral dose of uridine triacetate in three studies. The PK profiles of uridine were comparable between two lots of uridine triacetate in Study 401.10.PKL.01, between active ingredient (API) and formulated uridine triacetate granules in Study 401.07.001 and between fasted and fed subjects in Study 401.07.002. PK parameters of uridine in each study are listed in Table 7. The PK parameters of uridine given as sprinkles in study 401.07.001 and in fasted/fed status in study 401.07.002 are similar. The C_{max} of uridine in study 401.10.PKL.01 is relatively higher than that in other two studies, which may be due to different formulations used (Table 4).

Table 7: Mean value of PK Parameters (\pm SD) of Uridine in Healthy Subjects

Study 401.10.PKL.01				
	C_{max} (μ M)	T_{max} (hr)	AUC_{0-10} (μ M·hr)	$t_{1/2}$ (hr)
Lot A (fasted, n=6)	163 (\pm 33)	2.1 (\pm 0.5)	678 (\pm 120)	2.2 (\pm 0.4)
Lot B (fasted, n=6)	157 (\pm 27)	2.4 (\pm 0.9)	692 (\pm 132)	2.2 (\pm 0.4)
Study 401.07.001				
	C_{max} (μ M)	T_{max}^* (hr)	AUC_{0-inf} (μ M·hr)	$t_{1/2}$ (hr)
API (n=20)	131 (\pm 23)	2 (1, 3)	742(\pm 85)	2.1 (\pm 0.5)
Sprinkles (n=20)	106 (\pm 23)	2.5 (1.5, 5)	670 (\pm 105)	2.2 (\pm 0.7)
Study 401.07.002				
	C_{max} (μ M)	T_{max}^* (hr)	AUC_{0-inf} (μ M·hr)	$t_{1/2}$ (hr)
Fasted (n=20)	111 (\pm 27)	2.5 (1, 5)	686 (\pm 124)	2.3 (\pm 0.7)
Fed (n=20)	96 (\pm 23)	2.5 (1.5, 4)	659 (\pm 116)	2.5 (\pm 0.5)
Note: * T_{max} is presented as median (minimum, maximum)				

The mean concentrations of uridine after first dose in patients in two clinical studies (Table 5) are similar to C_{max} after single dose given as sprinkles in healthy subjects in studies 401.07.001 and in fasted/fed status in study 401.07.002. However, caution needs to be used in the interpretation as there is formulation difference in various studies (Table 4).

Six pediatric patients were administered oral uridine triacetate in Study WELL401. Three of these pediatric patients were between 1 to 2 years old and the other three pediatric patients were 7, 15 and 16 years old, respectively. Four patients between age of 1 and 7 received approximately 6.2 grams/m² in granules Q6h for twenty doses. A 15 year old received 10 gram in granules Q6h for twelve doses. A 16 year old received 6 gram in tablets Q8h for eight doses. Only two pediatric patients under age of 2 had uridine concentrations, which were 82 μ M and 27 μ M 2 hours post first dose, respectively, and 102 μ M 2 hours post last dose.

Uridine concentrations are also available in four pediatric patients with a uridine-responsive neurological syndrome associated with excess 5'-nucleotidase activity in Study 401.09.001. Each patient started with uridine orally 333 mg/kg, three times a day (TID) on the first day of treatment, then received oral uridine triacetate 33 mg/kg, TID. The dose of uridine triacetate was periodically increased to 100 mg/kg, TID in 1.5 year period. PK parameters of uridine for 4 pediatric patients are shown in the Table 8. Refer to clinical pharmacology review for NDA 208169 for details.

Table 8: Summary of Uridine Exposure in Pediatric Patients Following Oral Uridine or Uridine Triacetate

Treatment	Dose (mg/kg) *	N	AUC ₀₋₈ (μM·hr)	C _{max} (μM)	Trough (μM)	C _{ss} (μM)	Exposure Ratio**
Uridine	333	4	644.8	119.5	28.9	80.6	—
	33	8	269.0	64.6	12.6	33.6	4.2
	50	4	374.1	95.9	11.5	46.8	3.9
Uridine Triacetate	67	4	517.5	148.8	16.7	64.7	4.0
	83	4	579.5	157.6	22.5	72.4	3.6
	100	4	932.3	205.1	52.7	116.5	4.8
Average:							4.1

Note: **Exposure ratio is based on weights of administered doses of uridine versus uridine triacetate

(Source: Table 2.7.2.3-9 on page 43 in the applicant's summary of clinical pharmacology studies)

2.2.5.3 What are the characteristics of drug absorption?

Uridine triacetate is converted to uridine following oral administration by nonspecific esterases in plasma. No uridine triacetate was detected in the circulation. In children with mitochondrial disorders in study PN401.09.001, uridine exposure in plasma was 6.2 times greater after uridine triacetate treatment compared to orally administered uridine on a molar equivalent basis in four pediatric patients.

A relative bioavailability (BA) of a single 6 g dose of uridine triacetate active pharmaceutical ingredient (API) to the same dose of orange-flavored sprinkle granules was compared in 20 healthy subjects in the Study 401.07.001. The mean ratios of uridine AUC_(0-t) and AUC_(0-inf) for sprinkle granules versus API were 89% and 90%, respectively. The 90% confidence interval (CI) of the mean ratio was within 80 to 125% for both AUCs. However, the median T_{max} was longer (2.5 vs. 2 hours) and the mean C_{max} was approximately 19% lower (104 vs. 129 μM, 90% CI: 76-85%) following the 6 g sprinkle granules compared to uridine triacetate API indicating slightly slow rate of absorption.

The absolute BA of uridine triacetate in human is unknown.

Following a single dose of oral uridine triacetate, the maximum uridine concentrations in plasma achieve within 2-3 hours and the half-life ranges from 2.2 to 2.6 hours in study 401.10.PKL.01.

Of note, the drug formulation used in the studies PN401.07.001 and 401.10.PKL.01 are different from the one used in the registration studies WELL401 and 401.10.001 (Table 4). The formulation used in the clinical studies WELL401 and 401.10.001 is composed of more active ingredient than the one used in the Study 401.07.001 (95% vs. 91%).

2.2.5.4 What are the characteristics of drug distribution?

The applicant did not conduct formal studies on distribution of uridine triacetate and relied on the literature data. Exogenous uridine derived from uridine triacetate is taken up into various mammalian cells via specific nucleoside transporters and incorporated into nucleotide pools and RNA. Uridine is also capable of crossing the blood brain barrier. Uridine is soluble in aqueous media, up to 800 mg/mL in water. It does not bind nonspecifically to plasma proteins.

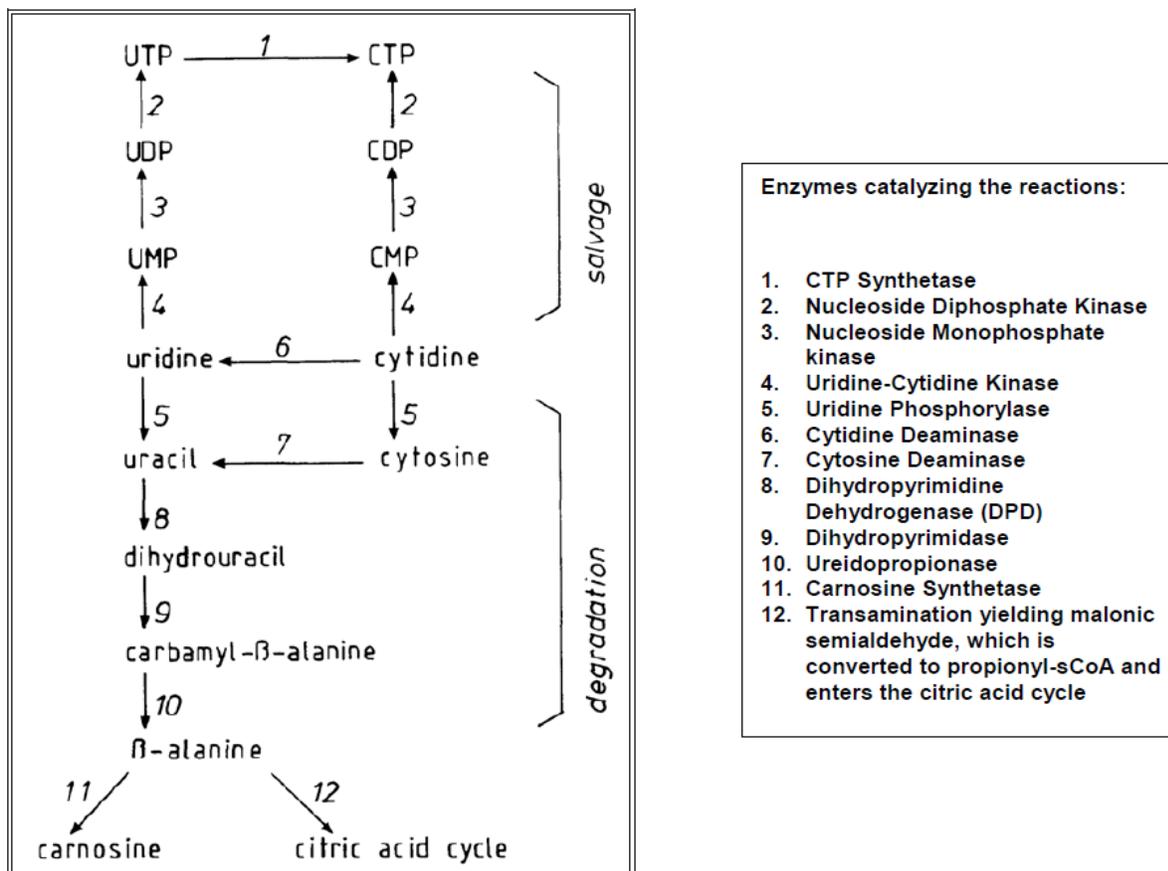
2.2.5.5 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

The applicant did not conduct formal mass balance study of uridine triacetate.

2.2.5.6 What are the characteristics of drug metabolism?

Uridine triacetate is deacetylated via endogenous esterases to uridine and acetate following oral administration. No uridine triacetate has been found in the circulation. Uridine enters into the anabolic and catabolic pathways as the endogenous uridine. In brief, uridine is synthesized to intracellular uridine monophosphate (UMP) by uridine kinase, which is further anabolized to uridine diphosphate (UDP) and uridine triphosphate (UTP). If cellular capacity for uridine anabolism is exceeded, uridine is degraded by dihydropyrimidine dehydrogenase (DPD) to uracil and further to dihydrouracil and beta-alanine, which can enter the tricarboxylic acid (TCA) cycle. The metabolism profile of uridine is shown in Figure 2.

Figure 2: Metabolism Pathways of Uridine



(Source: Figure 2.7.2.1-4 on page 15 in the applicant's summary of clinical pharmacology studies)

2.2.5.7 What are the characteristics of drug elimination and excretion?

Uridine can be metabolized by pyrimidine catabolic pathways present in most tissues as well as excreted via the kidneys. Based on the literature data, the urinary excretion of uridine was approximately 24% of the dose following 2 to 12 g/m² uridine IV infusion and approximately 1% of the dose following oral uridine 8 to 12 g/m².

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

In study P92-1082-PK, C_{max} and C_{ss} increased with dose following oral suspension of uridine triacetate at 3.3, 6.6 and 9.9 g every 6 hours for nine doses (Table 9). However, it cannot be concluded that the increase is in a dose-proportional manor due to the small sample size.

Table 9: PK Parameters (Mean \pm SD) of Plasma Uridine after Ninth Dose of Uridine Triacetate Suspensions

Uridine Triacetate (g)	C _{max} (μ M)	C _{ss} (μ M)
3.3 (n=3)	102 (\pm 27)	74 (\pm 8)
6.6 (n=3)	161 (\pm 12)	112 (\pm 3)
9.9 (n=2)	293 (\pm 89)	163 (\pm 30)

In study 401.09.001, C_{max}, C_{ss}, C_{trough} and AUC_{0-8hr} increased with dose in four pediatric patients as well following oral uridine triacetate at 33 mg/kg TID and titration up to 100 mg/kg TID (Table 10). Again, the sample size is too small to decide the degree of linearity or non-linearity.

Table 10: Mean Uridine Exposure in Pediatric Patients Following Oral Uridine Triacetate

Uridine Triacetate (mg/kg)	C _{max} (μ M)	C _{ss} (μ M)	C _{trough} (μ M)	AUC _{0-8hr} (μ M·hr)
33 (n=8)	65	34	13	269
50 (n=4)	96	47	12	374
67 (n=4)	149	65	17	518
83 (n=4)	158	72	23	580
100 (n=4)	205	117	53	932

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

The mean accumulation ratio was 1.3 in Study WELL401 and 1.6 in Study 401.10.001 comparing uridine concentrations after first dose and last dose (Table 5). The T_{max} was approximately 2 hours after ninth dose of oral suspension uridine triacetate at 3.3 g, 6.6 g or 9.9 g, which is in the same range of 2-3 hours after first dose of each dose level in study P92-1082-PK.

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

The inter-subject variability of uridine concentrations ranged from 44% to 65% for 10 gram dose in Study WELL401 and Study 401.10.001 (Table 5). In addition, the variability of uridine concentrations is higher in patients with 5-FU toxicity compared to healthy volunteers (Table 7), which may be due to different characteristics of the population, and different drug formulation.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

A two stage pharmacokinetic analysis was conducted by the applicant to determine the effect of various intrinsic factors on the PK of uridine triacetate. The studies included in the analysis are shown in Table 11. It should be noted that the formulation of uridine triacetate varied across the

studies as mentioned earlier (Table 4). The results presented below are from adults as data from pediatric patients is limited.

Table 11: Clinical Studies included in the two stage pharmacokinetic analysis

Clinical Study	Uridine Triacetate Dose	No. of Patients
Studies of Uridine Triacetate with 5-FU		
Expanded Access Protocol 401.10.001	10 g q6h × 20 doses	TBD
Study WELL401 (these are the 5-FU overdose patients treated under SPI or ex-US, should be distinguished from patients treated under Protocol 401.10.001) *	10 g q6h × 20 doses	TBD
Phase 1: PN401-MSK-1	3.3, 6, 6.6, or 9.9 g q6h × 10 doses	3 to 7
Studies in Healthy Subjects [no 5-FU]		
Phase 1: 401.10.PKL.01 (two lots of tablets, fed/fasted)	6 g (single dose crossover)	6
Phase 1: PN401.07.001 (API vs. coated granules)	6 g (single dose crossover)	20
Phase 1: PN401.07.002 (fed/fasted, coated granules)	6 g (single dose crossover)	20
Studies in Other Indications [no 5-FU]		
Phase 2: 401.97.201 (diabetic polyneuropathy)	4 or 8 g/day (2 or 4 g BID)	12 to 15
Comp. Use (mitochondrial /neurometabolic disorders)	33 to 100 mg/kg	4 **

* Study WELL401 included one pediatric patient aged 19 months.

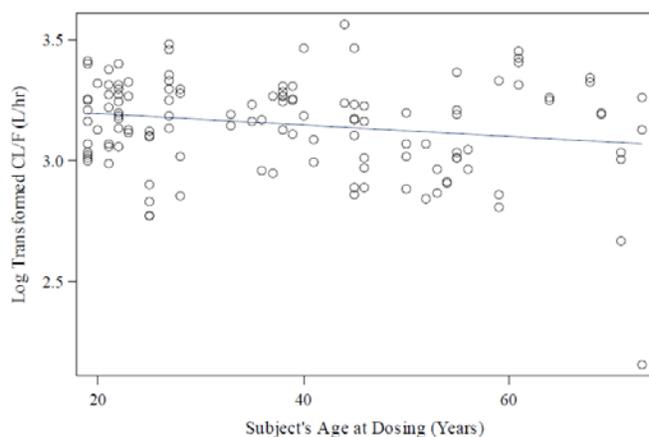
** Patients aged 4 to 12 years.

Source: Table 1 of 401-POP-PK-ANALYSIS-REPORT (Version 2)

2.3.1.1 Age

There is no effect of age on the apparent clearance (CL/F) of uridine as shown in Figure 3.

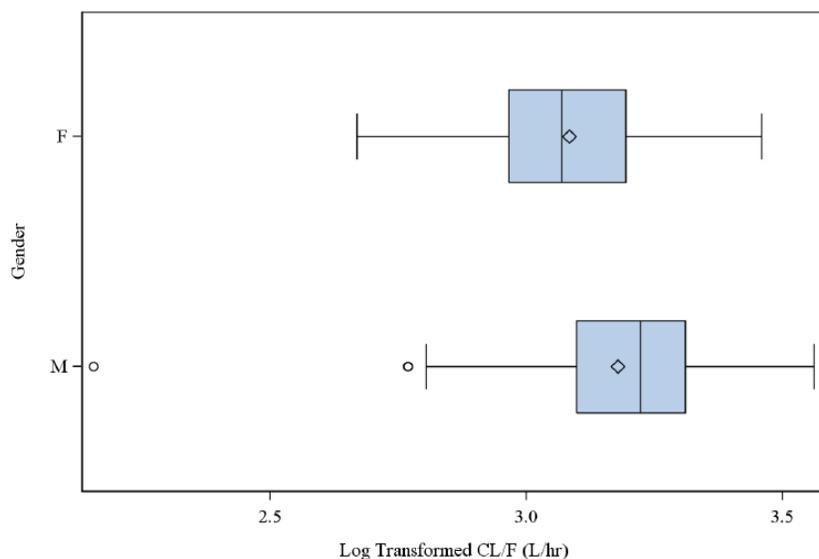
Figure 3: Effect of age on CL/F of uridine



2.3.1.2 Gender

There is no effect of gender on the apparent clearance (CL/F) of uridine as shown in Figure 4. Analysis included data from 35 men and 25 women.

Figure 4: Effect of gender on CL/F of uridine

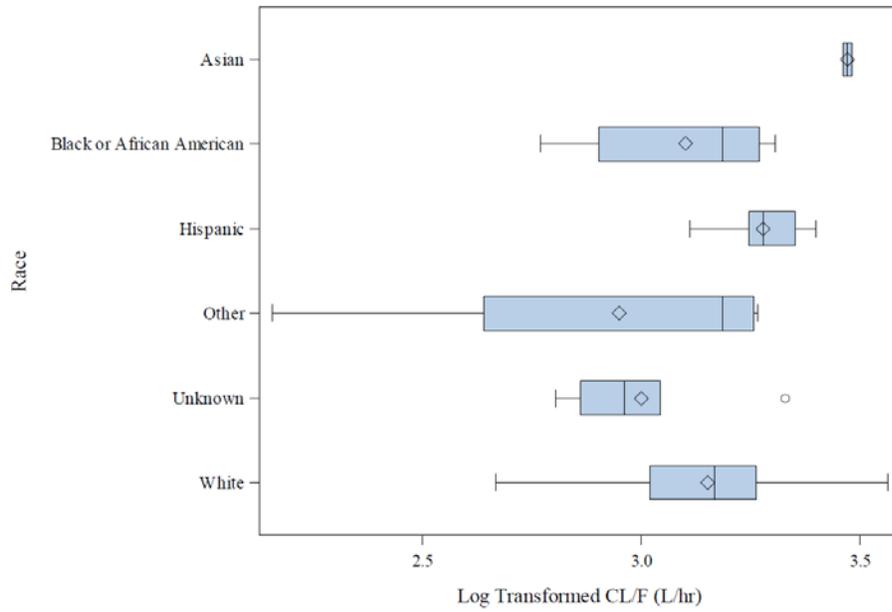


Source: 401-POP-PK-ANALYSIS-REPORT (Version 2)

2.3.1.3 Race

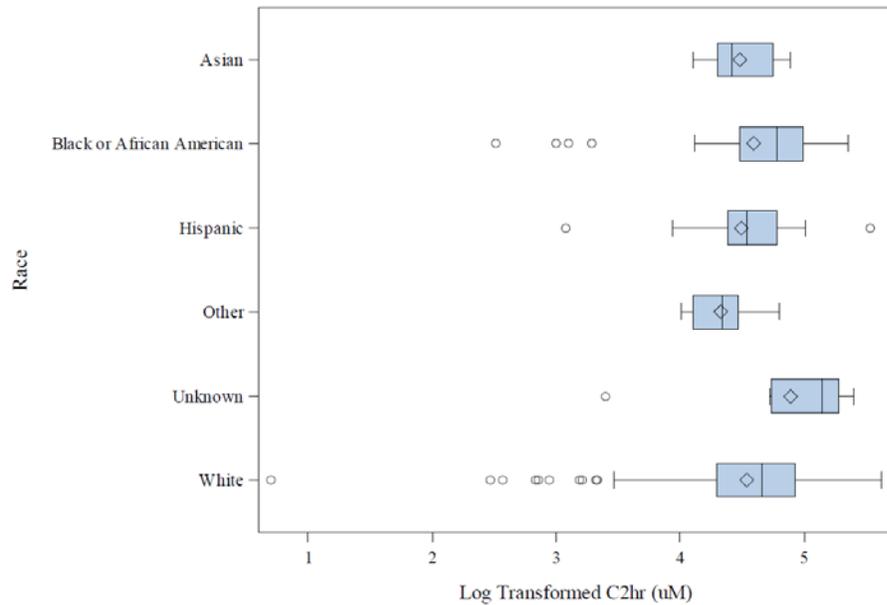
There is insufficient data based on current analysis to assess the effect of race on clearance of uridine. The majority of the subjects in the data were whites (N=48). There were 4 African Americans, 3 Hispanics and 1 Asian subject. Based on the limited data, the CL/F appears similar among Whites, African Americans and Hispanics (Figure 5). Note that the concentration of uridine 2 hour post dosing was similar among Whites (N=125), African Americans (N=15), Hispanic (N=7) and Asians (N=5).

Figure 5: Effect of race on CL/F of uridine



Source: 401-POP-PK-ANALYSIS-REPORT (Version 2)

Figure 6: Effect of race on concentration of uridine two hour post dosing of uridine triacetate

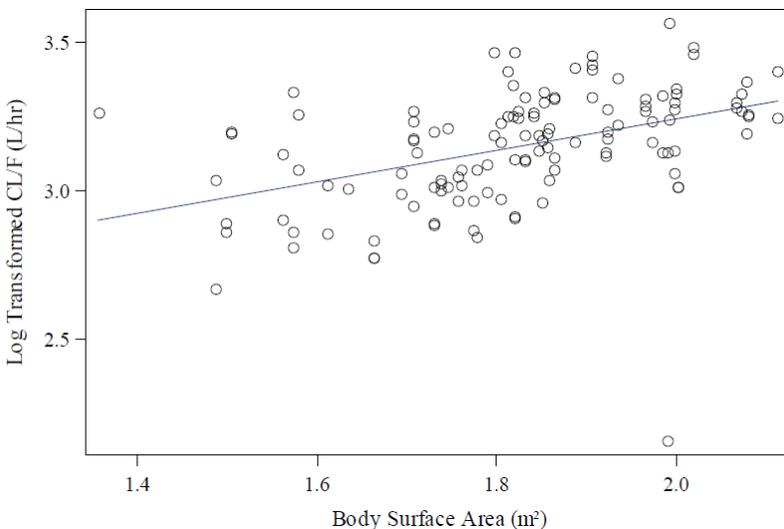


Source: 401-POP-PK-ANALYSIS-REPORT (Version 2)

2.3.1.4 Body Size

There is a trend for increase in CL/F with increasing body surface area (BSA) in adults (Figure 7). This was not considered clinically meaningful given the high survival rate observed in clinical studies and large safety margin associated with uridine triacetate. Thus dose adjustment based on BSA is not needed in adults.

Figure 7: Effect of body surface area (BSA) on CL/F of uridine triacetate



Source: 401-POP-PK-ANALYSIS-REPORT (Version 2)

2.3.1.5 Disease

See section 2.2.5.2.

2.3.1.6 Genetics

Genetic variation in genes encoding enzymes involved in 5-FU metabolism or mechanism of action may influence exposure and/or toxicity to 5-FU. Dihydropyrimidine dehydrogenase (DPD), encoded by the DPYD gene, is the first and rate-limiting enzyme responsible for the catabolic breakdown of >80% of administered 5-FU to inactive metabolites. Approximately 0.2% and 3-5% of the general population are reported to have genetic variation in DPYD leading to complete or partial DPD deficiency, respectively, providing a pharmacogenetic basis for 5-FU toxicity [PMIDs: 15709212; 23988873]. Patients with DPD deficiency, especially those with absent or nearly absent DPD activity, are considered to be at increased risk for early-onset of toxicity and severe, life-threatening, or fatal adverse reactions. In addition, variation in other genes including thymidylate synthetase (TYMS) and methylenetetrahydrofolate reductase (MTHFR) have been reported to be associated with 5-FU toxicity [PMID: 20601926].

Per the applicant, 24 patients (6 patients in WELL401 and 18 patients in 401-10-001) were

categorized as having rapid onset of serious toxicity. Of note, 6 patients in this group also had evidence of a 5-FU overdose [see Clinical Review by Dr. Gwynn Ison]. Of the 24 patients, 19 had available genotyping results from tests performed at the investigator’s discretion and reported to the applicant. Genetic variants were identified in 15 out of 19 patients (Table 12). Different tests were used by the investigators to detect potential pharmacogenetic variants in DPYD, TYMS, and/or MTHFR and most patients had more than one variant identified. Four patients had genotypes often associated with complete (N = 2) or partial (N = 2) DPD deficiency. Additional variants were also identified in DPYD, TYMS, and MTHFR, however their pharmacogenetic role and functional impact are unclear.

Table 12. Genetic Variants Identified^a in the Rapid Onset of Serious Toxicity Group

Study	N	Test Results	Test Name ^b
401-10-001	1	DPYD*2A heterozygous, DPYD*9A homozygous, TYMS rs 34489327 heterozygous, TYMS 2R/3RC	5-FU Toxicity Response
	1 ^c	DPYD*9A heterozygous, MTHFR rs 1801131 homozygous	5-FU Sensitivity
	1 ^c	DPYD*9A heterozygous, TYMS 3RC/3RC	5-FU Panel
	1 ^c	DPYD*9A heterozygous, TYMS rs 34489327 heterozygous, TYMS 2R/2RC	5-FU Toxicity and Chemotherapeutic Response, 7 Mutations
	1	DPYD*9A homozygous, TYMS 2R/3RC	5-FU Toxicity and Chemotherapeutic Response, 7 Mutations
	1	TYMS 2R/3R	TheraGuide 5-FU
	1	TYMS rs 34489327 heterozygous, MTHFR rs 1801131 heterozygous	5-FU Sensitivity
	1	TYMS rs 34489327 heterozygous, TYMS 2R/2R	5-FU Toxicity and Chemotherapeutic Response Panel
	1	TYMS rs 34489327 homozygous, TYMS 2R/3RG	5-FU Toxicity and Chemotherapeutic Response, 7 Mutations
	1	TYMS rs 34489327 homozygous, TYMS 3RG/3RG	DPYD
WELL401	1 ^c	DPYD rs 67376798 deleterious, DPYD*2A deleterious, TYMS 2R/3R	TheraGuide 5-FU
	1	DPYD rs 67376798 heterozygous, TYMS rs 34489327 homozygous, TYMS 3RG/3RG	5-FU Toxicity Response
	1	DPYD*2A homozygous, TYMS 2R/3RG	5-FU Toxicity and Chemotherapeutic

			Response, 7 Mutations
	1 ^c	DPYD*9A heterozygous, MTHFR rs1801133 heterozygous	5-FU Sensitivity

Source: Response to Information Request dated September 9, 2015.

^a Of the 24 patients in the rapid onset of toxicity group, 4 patients (in study 401-10-001) had no variant identified and 5 patients (3 patients in study 401-10-001 and 2 patients in study WELL401) were either not tested or did not have genetic test results provided to the applicant. These 9 patients are not represented in Table X.

b Test name as reported by the applicant.

c Patients identified as having received a 5-FU overdose.

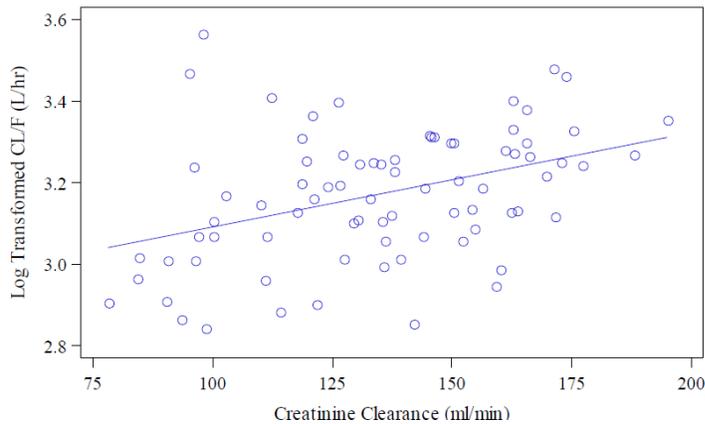


Reviewer Comment: The available genetic results cannot account for the rapid onset of serious toxicity in most patients evaluated. The inconsistency introduced by the use of different tests across patients, which could employ different methods and assess different alleles, and the unclear functional impact of some of the variants identified make the results difficult to interpret. In addition, the classification of rapid onset by the applicant included 6 patients who received a documented overdose, one of which was identified as having DPD deficiency, resulting in reclassification of those patients to the overdose group by the FDA. The other 3 patients with complete or partial DPD deficiency based on DPYD genotyping were not considered to meet the FDA's criteria for efficacy such as receiving uridine triacetate within 96 hours of last 5-FU dose [see Clinical Review by Dr. Gwynn Ison].

2.3.1.7 Organ dysfunction

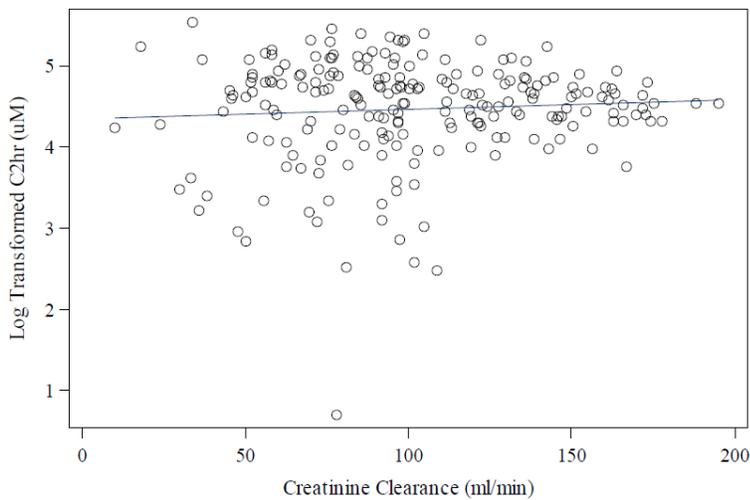
There is insufficient data from current analysis to assess the effect of creatinine clearance (CRCL) on clearance of uridine. As shown in Figure 8 most of the subjects have normal renal function with few subjects with mild renal impairment. Note that no effect of CRCL (10 to 195 ml/min) on uridine concentration 2 hour post dosing is observed (Figure 9).

Figure 8: Effect of creatinine clearance (CRCL) on CL/F of uridine



Source: 401-POP-PK-ANALYSIS-REPORT (Version 2)

Figure 9: Effect of creatinine clearance (CRCL) on uridine concentration two hour post dosing of uridine triacetate



Source: 401-POP-PK-ANALYSIS-REPORT (Version 2)

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

Based on the high survival rate observed in clinical studies, large safety margin associated with uridine triacetate and lack of effect of gender, race, and creatinine clearance on uridine PK (see section 2.3.1), dose adjustment is not needed based on gender, race or renal status.

Pediatric Patients

The proposed dose for pediatric patients is 6.2 grams/m² to be given every 6 hours. The dose is reasonable based on limited data from 6 pediatric patients (including 3 less than 2 years) who were treated with uridine triacetate in WELL401. All 6 pediatric patients survived and in terms of safety only 1 non-serious case of vomiting was observed. Pharmacokinetic data was available from only 2 patients in WELL401. The uridine concentration two hour post dosing of uridine triacetate were 82 uM and 26 uM.

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

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

2.4 EXTRINSIC FACTORS

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

The applicant did not conduct *in vivo* drug-drug interaction studies to evaluate the effects of drugs or herbal products on the PK of uridine triacetate.

2.4.2 Drug-drug interactions

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

Yes, uridine triacetate appears to be an inhibitor of P-gp transporter. See Question 2.4.2.4 for details.

2.4.2.2 Is the drug a substrate of CYP enzymes?

CYP450 enzymes are not involved in the metabolism of uridine triacetate or uridine. After oral administration, uridine triacetate is deacetylated to uridine during absorption from the gastrointestinal tract. Then uridine is metabolized via the mammalian pyrimidine pathway as endogenous uridine.

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

In vitro inhibition

The potential for systemic enzyme inhibition by uridine and uridine triacetate appears to be low. The inhibition potential of uridine and uridine triacetate on most relevant CYP enzymes for drug metabolism in humans (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) was measured in human liver microsomes in Study 13WELLP1R1_Study 1 (Table 13). The IC₅₀ values for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6,

CYP2E1, and CYP3A (with testosterone as the probe substrate) were greater than the highest tested concentration of uridine and uridine triacetate (10 mM). The IC₅₀ values of uridine and uridine triacetate for CYP2C19 were 5.1 and 6.6 mM, respectively. The IC₅₀ values of uridine and uridine triacetate for CYP3A (with midazolam as the probe substrate) were 2.0 and 8.3 mM, respectively.

Considering the mean concentrations of uridine at approximately C_{max} at steady state (1-4 hours post last dose) in studies WELL401 and 401.10.001 (153 and 160 μM, respectively) are far below 10 mM, the inhibition on CYP450 enzymes are clinical irrelevant. The gut concentration of uridine triacetate is expected to be high (~21 mM) given the solubility of uridine triacetate in aqueous media is 7.7 mg/ml which is corresponding to an oral dose of 1925 mg uridine triacetate in 250 mL of gastrointestinal lumen liquid after oral administration of 10g dose; however, the potential inhibition of uridine triacetate on CYP3A in the intestine is low as esterase activity is generally much higher in gut and liver than in blood or plasma and the R_{alternate} is estimated less than 11.

Table 13: CYP Inhibition and Induction Studies with Uridine and Uridine Triacetate

Title	Test System	Conc/ Results	Endpoint(s)
CYP Inhibition (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A)	Human liver microsomes	<u>Uridine & Uridine Triacetate:</u> CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A (w/ testosterone substrate): IC ₅₀ > 10,000 μM <u>Uridine:</u> CYP2C19: IC ₅₀ = 5100 μM CYP3A (w/ midazolam substrate): IC ₅₀ = 2000 μM <u>Uridine Triacetate:</u> CYP2C19: IC ₅₀ = 6600 μM CYP3A (w/ midazolam substrate): IC ₅₀ = 8300 μM	Percent inhibition of each CYP isoform under reversible conditions
CYP Induction (CYP1A2, CYP2B6, CYP3A4)	Fresh human hepatocytes from 3 donors	<u>Uridine:</u> IC ₅₀ > 5000 μM <u>Uridine Triacetate:</u> IC ₅₀ > 500 μM *	Effects of test compounds on functional activity and mRNA induction

* The highest concentration of uridine triacetate able to be tested due to cytotoxicity.

(Source: Table 2.6.4.5-1 on Page 31 of Pharmacokinetics Written Summary in the NDA)

In vitro induction

The induction potential of uridine and uridine triacetate appears to be low. Uridine (at 50, 500, and 5000 μM) and uridine triacetate (5, 50, and 500 μM) did not induce CYP1A2, CYP2B6, or CYP3A4 mRNA in the Study 13WELLP1R1_Study 1 using fresh human hepatocytes (Table 13).

2.4.2.4 Is the drug a substrate and/or an inhibitor/inducer of transporters?

Substrate of P-gp transporter

Uridine triacetate appears to be a weak P-gp substrate. The potential transport of uridine triacetate by P-gp was investigated using Caco-2 cell in Study 13WELLP1R1_Study 2. The results showed that the efflux ratios were 3.08 at concentration of 5 μM uridine triacetate and 2.05 at 50 μM . The efflux ratios of uridine triacetate were reduced to 0.993 and 0.549, respectively, in the presence of valsopodar (a known P-gp inhibitor).

The P-g substrate assessment of uridine was not conducted because the applicant stated that the receiver concentration of uridine were either not detected or were less than 10% in two independent experiments to assess non-specific binding due to unknown reasons.

Inhibition of P-gp transporter

Uridine is unlikely to be a P-gp inhibitor at the proposed clinical dose. The percentage inhibition on the bi-directional transport of digoxin was 9.1% at the tested uridine concentration of 15 mM in Study 13WELLP1R1_Study 2 which is much higher than the mean concentrations of uridine at approximately C_{max} at steady state (1-4 hours post last dose) in the Studies WELL401 and 401.10.001 (153 and 160 μM).

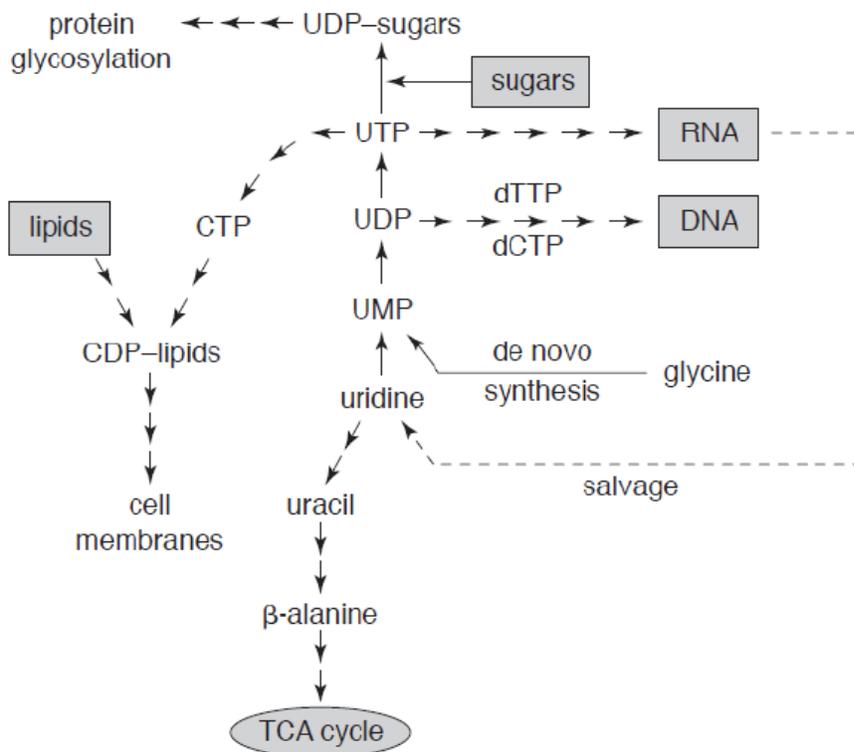
The potential inhibitory effect of uridine triacetate on P-gp substrate at the proposed clinical dose drugs cannot be ruled out. The IC_{50} value of uridine triacetate using digoxin as an indicator of P-gp activity was found to be 344 μM in the same study. Given the solubility limit of uridine triacetate in aqueous media is 7.7 mg/ml which results into $[\text{I}]_{\text{gut}}$ of 21 mM. Thus $[\text{I}]_{\text{gut}}/\text{IC}_{50}$ is above the threshold of 10 and an in vivo drug interaction study with a P-gp substrate such as digoxin is recommended according to the DDI guidance. However, the applicant's proposal to waive the clinical assessment of P-gp inhibition potential is acceptable considering the short duration of dosing (5 days) and the lack of any observed drug-drug interactions to date with uridine triacetate in the intended population.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Uridine derived from uridine triacetate enters into the pyrimidine metabolism pathways as the endogenous uridine (Figure 10). Briefly, uridine monophosphate (UMP) is formed by uridine kinase after uridine is uptaken intracellularly via nucleoside transporters. UMP is further anabolized to uridine diphosphate (UDP) and uridine triphosphate (UTP). UMP can be synthesized de novo from glycine. UTP can become conjugated to various sugars, forming UDP-glucose and UDP-galactose which are critical cofactors for biosynthetic glycosylation reactions. UTP and UDP can be used in

the synthesis of RNA and DNA. UTP can also be converted to cytidine 5'-triphosphate (CTP) which conjugates with various lipids (cytidine 5' diphosphate (CDP)-lipids) to form cellular membrane constituents. Uridine is catabolized to uracil and beta-alanine, which can enter the tricarboxylic acid (TCA) cycle.

Figure 10: Metabolism of Uridine and Some of Its Derivatives



(Source: Figure 2.7.2.1-3 on Page 14 of Summary of Clinical Pharmacology in the NDA)

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

No co-administration of other drugs is specified in the label as uridine triacetate is used as monotherapy in the proposed indication.

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

No formal DDI study was conducted by the applicant.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The applicant states that the formulation used in the clinical studies 4001.10.001 and WELL401 is the same as the to-be-marketed formulation.

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

The food effect on PK of uridine was investigated in 20 healthy subjects in Study PN401.07.002 entitled “A Phase 1, Single-Center, Open-Label, Randomized, Single Dose, 2-way Crossover Study to Evaluate the Effect of Food on Uridine Pharmacokinetics and Relative Bioavailability After a Single 6 g Dose of PN401 Sprinkle”. All subjects fasted for at least 10 hours prior to drug administration. For subjects in the fed group, standardized high fat/high calorie meal was administered after 10-hour fasting and approximately 30 minutes prior to dosing. In both fasted and fed group, 6 gram uridine triacetate was sprinkled on approximately ½ cup of Mott's® original applesauce (no sugar added) and immediately administered to the subject followed by 500 mL of bottled water in the morning. Dosing for each study period was separated by a minimum 7-day washout interval. Mean uridine C_{max} was approximately 15% lower in the fed group compared to that in the fasted group (Figure 11 and Table 14). Median T_{max} occurred at 2.5 hours in both fed and fasted groups. The mean t_{1/2} was similar between the fed and fasted groups. The mean ratio of fed vs. fasted was 88% for uridine C_{max} and 96% for both AUC_(0-t), and AUC_(0-inf), and the 90% CIs for C_{max}, AUC_(0-t), and AUC_(0-inf) were all within 80% – 125% (Table 15), which indicates that the rate and extent of uridine exposure was similar in both fed and fasted state.

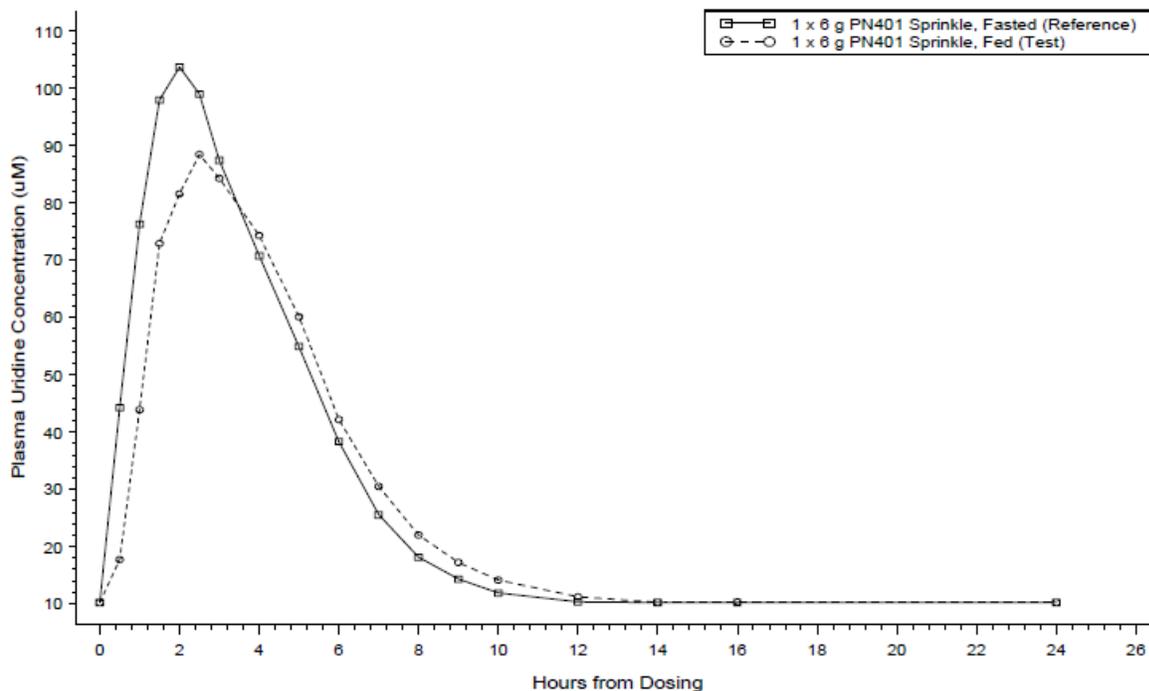
Table 14: Arithmetic Mean (SD) Plasma Uridine Pharmacokinetic Parameters in the Fasted and Fed Conditions

Pharmacokinetic Parameters	PN401 Sprinkle, Fasted (Reference)	PN401 Sprinkle, Fed (Test)
	Mean ± SD	Mean ± SD
C _{max} (µM)	110.73 ± 27.14	96.46 ± 22.60
T _{max} (hr)	2.50 (1.00, 5.00)	2.50 (1.50, 4.02)
K _{el} (1/hr)	0.321 ± 0.0570	0.287 ± 0.0556
T _{1/2} (hr)	2.27 ± 0.667	2.50 ± 0.486
AUC _(0-t) (µM*hr)	652.3 ± 124.7	622.1 ± 115.5
AUC _(0-inf) (µM*hr)	685.8 ± 124.0	659.1 ± 115.7

T_{max} is presented as Median (Minimum, Maximum)
 All subjects have a baseline uridine set to the LLOQ (10.24 µM), thus AUC(0-t) = AUC(0-24).
 Source: Tables 14.2.1.3 Through 14.2.1.4

(Source: Table 11.4.1.2:1 on Page 33 of Study Report PN40107.002 in the NDA)

Figure 11: Mean Uridine Plasma Concentration-Time Profile after Single Oral Dose of 6 g Uridine Triacetate under the Fed and Fasted Conditions



(Source: Figure 11.4.1.1:1 on Page 32 of Study Report PN40107.002 in the NDA)

Table 15: Statistical Comparisons of Plasma Uridine Pharmacokinetic Parameters

Parameter	Geometric LS Means		Confidence Intervals (90% Confidence)	Mean Ratio
	PN401 Sprinkle, Fed (Test)	PN401 API, Fasted (Reference)		
C_{max}	94.331	107.736	81.81 - 93.71	87.56
$AUC_{(0-t)}$	612.994	641.302	90.99 - 100.41	95.59
$AUC_{(0-inf)}$	650.360	675.399	91.87 - 100.93	96.29

All subjects have a baseline uridine set to the LLOQ (10.24 μ M), thus $AUC(0-t) = AUC(0-24)$.
Parameters were ln-transformed prior to analysis.
Geometric least squares means (LS Means) are calculated by exponentiating the LSMEANS from the ANOVA.
Mean Ratio = $100 \times (\text{test}/\text{reference})$
Source: [Table 14.2.1.9](#)

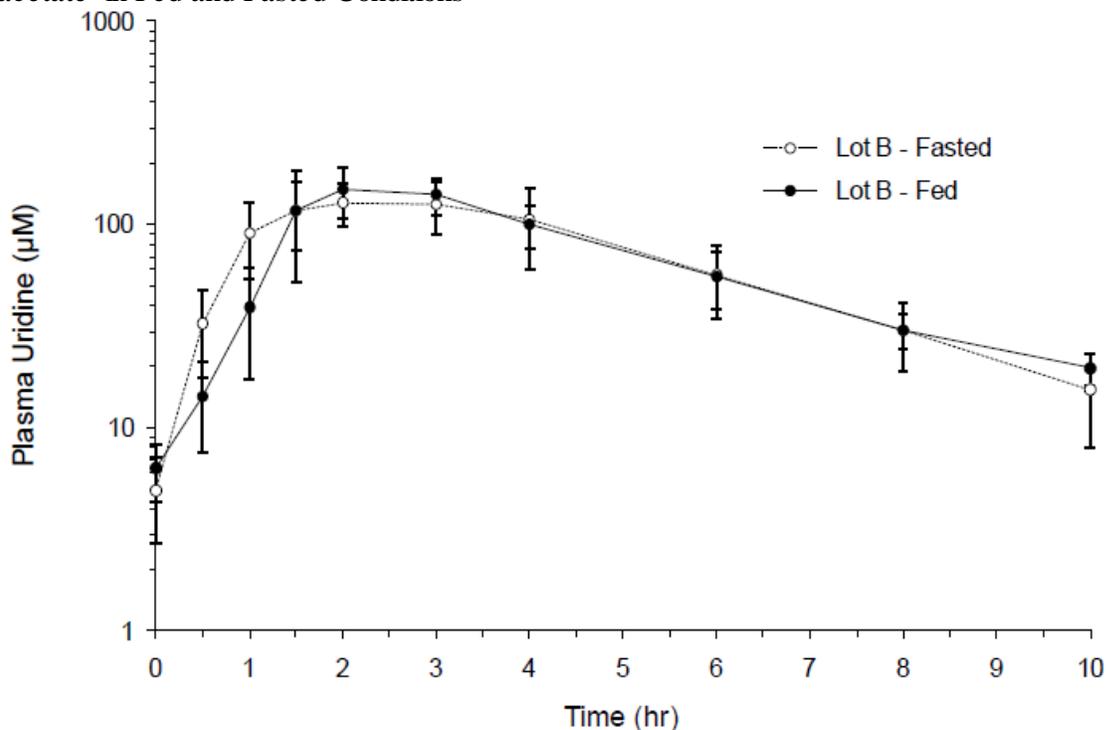
(Source: Figure 11.4.2.2:1 on Page 34 of Study Report PN40107.002 in the NDA)

The food effect on uridine PK was also investigated as one of the objectives in Study 401.10.PKL.01 using tablet formulation. It was a randomized, single oral dose, three-period, two-sequence crossover study in 6 healthy subjects. Twelve 500 mg tablets Lot B (a total of 6 gram) was administered with at least 240 mL of water in both fed and fasted groups. A standard FDA breakfast was administered approximately 30 minutes prior to dosing in fed group. The PK data of uridine and concentration time profile for both fed and fasted group are shown in Table 16 and Figure 12. The results demonstrated that uridine plasma exposure was similar under fed and fasted conditions.

Table 16: PK Parameters (Mean \pm SD) of Uridine Following A Single Oral 6 g Dose of Uridine Triacetate in Fed or Fasted Conditions

Treatment	C _{max} (μ M)	T _{max} (hr)	AUC _{0-10hr} (μ M \cdot hr)	t _{1/2} (hr)
Lot B (fasted)	158 (\pm 27)	2.4 (\pm 0.9)	692 (\pm 132)	2.2 (\pm 0.4)
Lot B (fed)	164 (\pm 29)	2.3 (\pm 0.6)	683 (\pm 148)	2.6 (\pm 0.2)

Figure 12: Concentration Time Curves for Uridine Following A Single Oral 6 g Dose of Uridine Triacetate in Fed and Fasted Conditions



(Source: Figure 2.7.2.3-2 on page 33 in the applicant's summary of clinical pharmacology studies)

Of note, the drug formulation used to investigate the food effect in both Study PN401.07.002 and Study 401.10.PKL.01 are different from the one used in the clinical Studies 401.10.001 and WELL401 (Table 4). The formulation used in the two clinical studies contains more active ingredient (95%) than that in Study PN401.07.002 (91%) and Study 401.10.PKL.01 (50%). In addition, uridine triacetate was to be mixed with soft food (such as applesauce, yogurt, or pudding) immediately prior to the schedule dose and was administered without regard to meals in the two clinical studies. Considering the totality of the data and the wide safety margin of uridine triacetate, the current review team agrees that uridine triacetate can be administered without regard to meals.

2.5.3 What is the effect of a nasogastric, gastric or orogastric tube on the PK of uridine? What dosing recommendation should be made, if any, regarding administration of uridine triacetate via a nasogastric, gastric or orogastric tube?

There were nine patients in Study 401.10.001 and four patients in Study WELL401 receiving the same proposed uridine triacetate dose via a nasogastric, gastric or orogastric tube as these patients had difficulty to swallow due to severe mucositis or coma. A clinical pharmacology information request was sent to the applicant on October 9, 2015 to ask for the patient identification for this subgroup and a summary of uridine triacetate PK, efficacy and safety profile. Plasma uridine concentrations were not collected in four patients in Study WELL401. The uridine concentrations for nine patients in Study 401.10.001 and efficacy and safety results for all thirteen patients are summarized in Table 17. The uridine concentrations post last dose ($178 \pm 71 \mu\text{M}$) in nine patients are close to those in 68 patients ($157 \pm 75 \mu\text{M}$) from both studies who received uridine triacetate in soft food (e.g. applesauce, yogurt and pudding) and who had uridine concentration collected.

Table 17: Uridine Concentrations, Efficacy and Safety in Patients Treated via Nasogastric, Gastric or Orogastric Tube

	Study 401.10.001 (n=9)	Study WELL401 (n=4)
Uridine Concentration post first dose (μM)	66 (± 32)	NA
Uridine Concentration post last dose (μM)	178 (± 71)	NA
Efficacy	All survived	3 survived
Safety	1 case of mild diarrhea 1 case of mild nausea	1 case of vomit

Although the sample size is small for patients who received uridine triacetate via nasogastric, gastric and orogastric tube, the proposed uridine triacetate dose appears to be reasonable for this subgroup given the totality of the data showing the similar uridine concentration post last dose, high survival rate and low incidence of adverse events. Therefore, it is recommended in the labeling to administer uridine triacetate via a nasogastric tube or gastrostomy tube when necessary for both adult and pediatric patients.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The method of high performance liquid chromatography (HPLC) with ultraviolet (UV) absorbance detection was developed and validated for the identification and quantification of uridine and uracil in human plasma. Protein precipitation and liquid/liquid extraction with ethyl acetate was used to extract the analytes from 250 μL of plasma with 5-chlorouracil as the internal standard (IS).

2.6.2 Which metabolites have been selected for analysis and why?

Uridine and uracil are selected for analysis because uridine triacetate is deacetylated after oral administration and uracil is the initial inactive degradation product of uridine.

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

Total plasma uridine concentrations were measured as uridine does not bind to plasma proteins and is extremely soluble in aqueous media.

2.6.4 What bioanalytical methods are used to assess concentrations?

Uridine and Uracil

The concentrations of uridine and uracil were quantified by HPLC with UV absorbance detection at a wavelength of 260 nm. Analytes were prepared using protein precipitation and liquid/liquid extraction with ethyl acetate from 250 µL of plasma. The extract was evaporated, reconstituted and analyzed with an HPLC assay using a (b) (4) column. The peak area ratios of the analytes/IS and the theoretical concentrations of the calibration samples were fit to a linear function with $1/x^2$ weighting, excluding the origin. Concentrations were back-calculated from the results of the regression analysis using the Quantify program in the Chromeleon software.

Of note, the initial calibration method to quantify uridine and uracil in human plasma using HPLC with UV detection was developed and validated by (b) (4) as shown in validation report 930003V. (b) (4) ceased operations in 2003 and the initial method was transferred to (b) (4) and was further developed and validated as shown in report (b) (4) 480002. Therefore, method (b) (4) 480002 was used for the following studies: PN40107.001, PN401.07.002, Study WELL401 and Study 401.10.001. The validation data in the method (b) (4) 480002 are used to answer the following questions.

Uridine Triacetate

The development of an LC/MS assay for the quantification of uridine triacetate in human plasma or whole blood could not be validated as the applicant claims that uridine triacetate is instable in both matrices. Data from stability studies suggested rapid loss of uridine triacetate in the incubations (less than 6.5% remained by 15 minutes, and virtually nothing remained by 30 minutes) at physiologic temperatures (37°C). At 0°C, the rate of drug loss was slower but most of it was broken down by the 60 minute incubation period.

The current review team is in alignment with the review team for NDA 208169 that considering the wide safety margin of uridine triacetate and the clinical urgent need, this is not a major deterrent for reviewing current application

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

The range of the standard curve for uridine calibration was from 2.5 to 200 µg/mL at 7 concentrations (2.5, 5, 10, 25, 50, 100 and 250 µg/mL).

The range of the standard curve for uracil calibration was from 0.25 to 20 µg/mL at 7 concentrations (0.25, 0.5, 1, 2.5, 5, 10, and 20 µg/mL).

Later on, the calibration curve was improved in 2014 for uracil over the concentration range of 0.75 to 20 µg/mL while the range for uridine was the same.

The mean (\pm SD) baseline concentrations of uridine and uracil and concentrations after first and last doses are listed in Table 18 for Study WELL401 and Study 401.10.001. In general, most of concentrations of uridine and uracil fall in the range of standard curve for each compound. Samples with concentrations beyond the range of calibration curve were diluted with appropriate dilution factor. Therefore, the standard curve appears suitable to calibrate the plasma concentration of uridine and uracil in cancer patients.

Table 18: Mean (\pm SD) Concentrations of Uridine and Uracil in Study WELL401 and Study 401.10.001

	Uridine			Uracil	
	Study WELL401	Study 401.10.001		Study WELL401	Study 401.10.001
Baseline	5 (\pm 17)	8 (\pm 33)	Baseline	1.0 (\pm 0)	2 (\pm 5)
1-4 hours post 1 st dose	119 (\pm 59)	99 (\pm 64)	2 hours post 1 st dose	9 (\pm 8)	17 (\pm 33)
1-4 hours post last dose	153 (\pm 68)	160 (\pm 81)	2 hours post last dose	35 (\pm 49)	95 (\pm 197)

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ for uridine was 2.5 µg/mL and 0.75µg/mL for uracil in human plasma.

The ULOQ for uridine was 200 µg/mL and 20 µg/mL for uracil in human plasma.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

The applicant states that the relative standard deviation (% RSD) of the calculated QC concentrations was used as a measure of assay precision. The difference between the theoretical and calculated mean QC concentrations (% relative error, % RE) was used as a measure of assay accuracy. The measured % RSD and % RE for QC concentrations are listed in Table 19. The precision and accuracy appear to be acceptable as both % RSD and % RE are within \pm 15% and the assay selectivity was confirmed.

Table 19: Measured %RSD and % RE of QC Samples for Uridine and Uracil

Quality Control Samples		
	<u>Relative Standard Deviation</u> (%)	<u>Relative Error</u> (%)
Uracil	1.2 to 2.4	-2.8 to 2.7
Uridine	3.0 to 4.0	-2.7 to 2.0

(Source: Table on Page 21 of Study Report (b) (4) 480002)

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Stability of uracil and uridine was evaluated in stock solutions, in plasma samples during long-term frozen storage (approximately -70°C and -20°C), after short-term (approximately 4 hours) room temperature storage, during the freeze-thaw process and in processed samples after refrigerated storage. The results are shown in the Table 20. Overall, stability of the analyte in stored and processed samples was not less than 85% of the target concentration.

Table 20: Stability Results at Various Conditions

Stock Solution Stability after 7 and 14 Days of Refrigerated Storage		
	Stock Solution Stability (% of Time-Zero)	
<u>Storage Conditions</u>	<u>Uracil</u>	<u>Uridine</u>
Refrigeration for 7 Days	99.9%	99.4%
Refrigeration for 14 Days	101%	100%
Stock Solution Stability after 7.5 Hours of Room Temperature Storage		
	Uridine: 95.8%	Uracil: 98.7%
Processed Plasma Sample Stability after 2 and 15 Days of Refrigerated Storage		
	Processed Plasma (% Of Target)	
<u>Storage Conditions</u>	<u>Uracil</u>	<u>Uridine</u>
Refrigeration for 2 Days	94.4% to 101%	103% to 106%
Refrigeration for 15 Days	98.5% to 96.5%	91.1% to 89.8%
Processed Plasma Sample Stability after 4 hours of Room Temperature Storage		

<u>Storage Conditions</u>	Processed Plasma Stability (% Of Target)	
	<u>Uracil</u>	<u>Uridine</u>
-70°C, 4 hours at room temperature	94.9% to 98.2%	96.6% to 106%
-20°C, 4 hours at room temperature	97.7% to 98.3%	93.6% to 102%
Freeze –Thaw Stability		
<u>Storage Conditions</u>	Freeze-Thaw Stability (% Of Target)	
	<u>Uracil</u>	<u>Uridine</u>
Frozen at -70°C	94.2% to 104%	98.1% to 108%
Frozen at -20°C	98.0% to 116%	94.7% to 105%
Long Term Frozen Stability at 10, 29 and 101 Days		
<u>Storage Conditions</u>	Long-Term Stability (% Of Target)	
	<u>Uracil</u>	<u>Uridine</u>
Frozen at -70°C	96.1% to 104%	87.0% to 108%
Frozen at -20°C	95.2% to 115%	69.9% to 105%

(Source: Tables from Page 22 to 26 of Study Report (b) (4) 480002 in the NDA)

2.6.4.5 What is the QC sample plan?

The QC samples were at 3, 15, and 150 µg/ml for uridine and at 0.3, 1.5, and 15 µg/ml for uracil. QC samples were prepared in triplicates.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. Blue font represents FDA recommended labeling modification, and ~~strikethroughs~~ represents content that is taken out from the Applicant proposed labeling.

12.3 Pharmacokinetics

Absorption

VISTOGARD delivers 4- to 6-fold more uridine into the systemic circulation compared to equimolar doses of uridine itself. Maximum concentrations of uridine in plasma following oral VISTOGARD are generally achieved within 2 to 3 hours, and the half-life ranges from approximately 2 to 2.5 hours.

Studies 1 and 2 included an assessment of plasma uridine in a subgroup of patients who were overdosed with 5-fluorouracil or experiencing rapid onset of serious 5-fluorouracil toxicities. Samples were obtained prior to VISTOGARD treatment and at 1 to 4 hours (b) (4) following the first and final doses of VISTOGARD given at 10 g (adults) or 6.2 grams/m² (pediatric) every 6 hours for up to 20 doses. Plasma uridine (b) (4) concentrations are summarized in Table 4.

TABLE 4 Plasma Uridine (b) (4) Concentrations (µM) in Studies 1 and 2

Study	Predose	Post First Dose	Post Final Dose
Study 1	N = 49 (b) (4) 8 (33)	N = 49 (b) (4) 99 (64)	N = 40 (b) (4) 160 (81)
Study 2	N = 27 (b) (4) 5 (17)	N = 26 (b) (4) 119 (59)	N = 24 (b) (4) 153 (68)

Values shown are mean (standard deviation)

(b) (4)

Food Effect on Uridine PK: A study in healthy adult subjects receiving a slightly different formulation of uridine triacetate granules (6 gram dose) under fed and fasted conditions showed no difference in the overall rate and extent of uridine exposure.

Distribution

Circulating uridine is taken up into (b) (4) mammalian cells via specific nucleoside transporters, and also crosses the blood brain barrier.

Excretion

Uridine can be excreted via the kidneys, but is also metabolized by normal pyrimidine catabolic pathways present in most tissues.

Drug Interaction Studies

In vitro enzyme inhibition data did not reveal meaningful inhibitory effects of uridine triacetate or uridine on CYP3A4, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. *In vitro* enzyme induction data did not reveal an inducing effect of uridine triacetate or uridine on CYP1A2, CYP2B6, or CYP3A4.

In vitro data showed that uridine triacetate was a weak substrate for P-glycoprotein. Uridine triacetate inhibited the transport of a known P-glycoprotein substrate, digoxin, with an IC₅₀ of 344 µM. Due to the potential for high local (gut) concentrations of the drug after dosing, the interaction of VISTOGARD with orally administered P-gp substrate drugs cannot be ruled out.

In vivo data in humans are not available.

Specific Populations

(b) (4)

Sex

(b) (4) Pharmacokinetics analyses showed that sex did not have a significant effect on uridine pharmacokinetics.

Age (b) (4)

(b) (4) Pharmacokinetics analysis showed that within the age range evaluated ((b) (4) 0 to 83 years), age did not have a significant effect on uridine pharmacokinetics.

(b) (4)

Body Size

Pharmacokinetic analyses showed no clinically meaningful effect of body surface area on uridine PK in adults. (b) (4)



4 APPENDIX

4.1 PHARMACOMETRICS REVIEW

**OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW**

Application Number	208159/SDN 3
Submission Date	Rolling submissions 1/16/2015, 6/3/2015 and 7/10/2015
Compound	Uridine Triacetate
Dosing regimen (route of administration)	Adult dose: 10 grams (1 packet) orally every 6 hours for 20 doses without regard to meals Pediatric dosage: 6.2 grams/m ² of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses without regard to meals
Indication	Patients at risk of serious toxicity following an overdose of 5-fluorouracil and patients exhibiting symptoms of serious toxicity within 96 hours of 5-fluorouracil administration
Clinical Division	Division of Oncology Products 1 (DOP1)
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.

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

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1 BACKGROUND

Wellstat Therapeutics has submitted New Drug Application (NDA) 208159 for Vistogard (uridine triacetate) for the treatment of patients at risk of serious toxicity following an overdose of 5-fluorouracil (5-FU) or patients exhibiting serious toxicity within 96 hours of 5-FU administration. Uridine triacetate is an acetylated pro-drug of uridine. In cells, uridine competitively inhibits cell damage and cell death caused by 5-fluorouracil. The proposed dose in adults is 10 grams orally every 6 hours for 20 doses without regard to meals. The proposed dose in pediatric patients is 6.2 grams/m² orally every 6 hours for 20 doses without regard to meals. The sponsor's proposed dose for adults and pediatric patients were considered reasonable. For details see section 2.2.4.4 of the Clinical Pharmacology Review. Additionally the proposed window for initiation of therapy i.e. within 96 hours of post 5-FU dose was considered reasonable. See section 2.2.4.5 of the Clinical Pharmacology Review.

The sponsor conducted a two stage pharmacokinetic analysis to determine the effect of various intrinsic factors on the PK of uridine triacetate. The analysis suggested that there is no clinically meaningful effect of gender, race, age and body surface area on uridine PK in adults and no dose adjustment is needed based on these intrinsic factors. See sections 2.3.1 and 2.3.2 of the clinical pharmacology review.

The purpose of this Appendix is to provide a summary of sponsor's two stage pharmacokinetic analyses. For details see sponsor's population PK analysis report for uridine triacetate (Document # 401-POP-PK-ANALYSIS-REPORT Version 2).

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 POPULATION PK ANALYSIS

The objectives of sponsor's population PK analysis were:

- To compile population estimates of key uridine PK parameters, after administration of uridine triacetate, across all human clinical studies, for the entire population (adults + pediatrics) as well as for the adults-only population
- To compare the PK of uridine triacetate in healthy volunteers and patients
- To quantify the effects of key demographic, physiologic, or environmental covariates (age, gender, body size, race, renal function, extrinsic factors, etc.) on the PK of uridine triacetate, for the entire population (adults + pediatrics) as well as for the adults-only population, using linear mixed effect modeling as well as univariate analysis

2.1.1 Data

A listing of the studies with plasma uridine data and the number of patients with evaluable PK data is presented in Table 1. In total, five (5) of these subjects were pediatric patients, one (1) in Study WELL401 and four (4) in Compassionate Use (mitochondrial/ neurometabolic disorders). The pharmacokinetic sampling scheme is presented in Table 2.

Table 1: Clinical Studies in PK Analysis

Clinical Study	Uridine Triacetate Dose	No. of Patients
Studies of Uridine Triacetate with 5-FU		
Expanded Access Protocol 401.10.001	10 g q6h × 20 doses	TBD
Study WELL401 (these are the 5-FU overdose patients treated under SPI or ex-US, should be distinguished from patients treated under Protocol 401.10.001) *	10 g q6h × 20 doses	TBD
Phase 1: PN401-MSK-1	3.3, 6, 6.6, or 9.9 g q6h × 10 doses	3 to 7
Studies in Healthy Subjects [no 5-FU]		
Phase 1: 401.10.PKL.01 (two lots of tablets, fed/fasted)	6 g (single dose crossover)	6
Phase 1: PN401.07.001 (API vs. coated granules)	6 g (single dose crossover)	20
Phase 1: PN401.07.002 (fed/fasted, coated granules)	6 g (single dose crossover)	20
Studies in Other Indications [no 5-FU]		
Phase 2: 401.97.201 (diabetic polyneuropathy)	4 or 8 g/day (2 or 4 g BID)	12 to 15
Comp. Use (mitochondrial /neurometabolic disorders)	33 to 100 mg/kg	4 **

* Study WELL401 included one pediatric patient aged 19 months.

** Patients aged 4 to 12 years.

Source: Table 1 of sponsor's POP PK Analysis report.

Table 2: Pharmacokinetic sampling scheme

Clinical Study	Uridine Triacetate Dose(s)	Days of Sampling	Timepoints (hours (h))
Uridine Triacetate with 5-FU			
401.10.001	10 g q6h × 20 doses (adult)	Day 1	Pre-dosing and 1 to 4 h post-dosing
	6.2 g/m ² q6h × 20 doses (pediatric)	Day 5 (or final dose)	Between 1 and 4 h post-dosing
WELL401	10 g q6h × 20 doses (adult)	Day 1	Pre-dosing & Between 1 and 4 h post-dosing
	6.2 g/m ² q6h × 20 doses (pediatric)	Day 5 (or final dose)	Between 1 and 4 h post-dosing
PN401-MSK-1	3.3, 6, 6.6, or 9.9 g q6h × 10 doses	Dose 1 Dose 9	0, 0.5, 1, 2, 3, 4, 6 h
Healthy Subjects			
401.10.PKL.01	6 g (single dose, minimum 1 week between treatments)	Day 1	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 h
PN401.07.001	6 g (single dose crossover, minimum 1 week between treatments)	Day 1	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24 h
PN401.07.002	6 g (single dose crossover, minimum 1 week between treatments)	Day 1	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24 h
Other Indications			
401.97.201	4 or 8 g/day (2 or 4 g BID)	Day 1 Month 3 Month 6	0, 2 h
Compassionate Use (mitochondrial/neurometabolic disorders) *			
	33 to 100 mg/kg, given three times daily (100 to 300 mg/kg/day)	Multiple days (varying by patient) including Day 0 (predose) Day 1 Day 55 to 60 Day 111 to 123 Day 194 to 210 Day 286 to 297 Day 344 to 358 Day 399 to 409 Day 526 to 527	0, 0.5, 1, 2, 4, 6, 8

* Patients aged 4 to 12 years.

Source: Table 2 of sponsor's POP PK Analysis report

2.1.2 Methods

A 2-stage population analysis was performed. First stage data comprised the available non-compartmental PK parameter values derived within each subject or patient from whom full sample profiles were available. The analysis was also used to provide the key dispositional parameter estimates – apparent oral clearance (CL/F) and apparent oral volume of distribution (Vd/F).

The individual parameter estimates obtained during the first stage served as the input data for the second stage. Descriptive summary statistics on the population of parameter estimates were derived, including mean, variance, and covariance. The dependencies between parameters and covariates were evaluated using classical statistical approaches. This same assessment was performed using the observed 2-hour post-dose plasma concentration as a parameter estimate. In addition, PK parameters were compared between healthy subjects and patients to determine if disease state had a notable effect on uridine disposition.

Log-transformed PK parameters, maximum concentration (C_{max}), 2-hour concentration after dosing (C_{2hr}), apparent oral clearance (CL/F), and apparent oral volume of distribution (Vd/F) were considered as dependent variables in the linear mixed effect model. The linear mixed effect model contained factors for study identifier, dose, dose lot number, and demographic covariates (age, gender, body size, race, renal function, extrinsic factors, etc.) as fixed effects. An unstructured covariance matrix was used to allow for unequal variances among covariates and to model the correlation between different covariates within the same subject via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). If the model failed to converge, a simpler covariance structure, such as compound symmetry, was used. A p-value <0.05 was considered to indicate that the covariate contributed significantly to the model.

In addition, univariate analyses were also performed to evaluate the effect of each covariate individually on each of the selected dependent variables. The analysis was similar to that performed in the mixed effect model, except that each cofactor was evaluated one at a time in the univariate analysis. The same variance matrix structure that was used for the mixed effect model was used for the univariate analysis. A p-value <0.05 was considered to indicate that the factor contributed significantly to the model.

2.1.3 Results

Across 7 studies, CL/F values were available in only 5 studies, with 348 observations read in from the database; only 79 observations were used in the analysis. As studies PN401-MSK-1 and 401.10.PKL.01 did not have CrCL results, these two studies were excluded from the analysis. Therefore only two studies, PN401.07.001 and PN401.07.002, were included in CL/F modeling.

- The analysis identified body size (BMI and BSA), drug lot number, and race as covariates.
- Several cofactors related to body size were identified as potentially being highly correlated with each other. Therefore, per FDA request, several body size factors were removed from the multivariate analysis to avoid the effects of collinearity in the mixed effect model

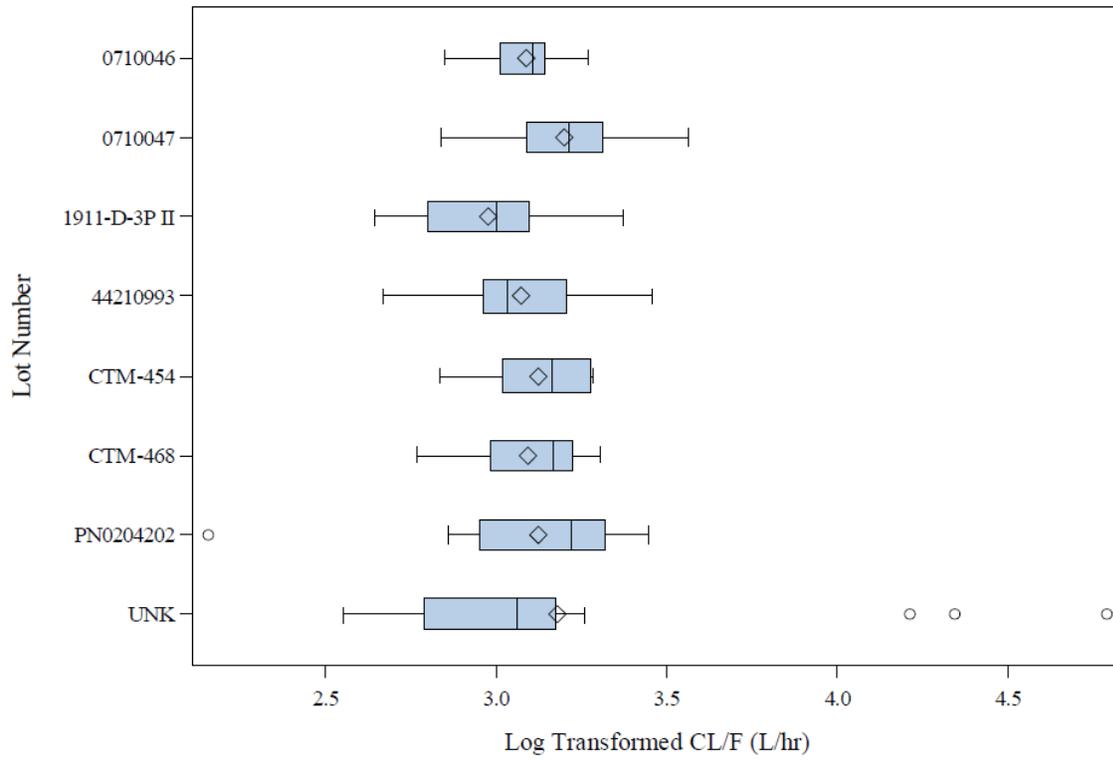
regression analysis. Only two body size factors, BMI and BSA, were retained in the final mixed effect model analysis. Moreover, the retention of both BMI [weight (kg)/height (m²)] and BSA [(height (cm) * weight (kg))/3600]0.5] was supported by the lack of a strict linear relationship between the two.

- There was a strong correlation between drug lot number and subject health status (Healthy, Cancer, Diabetic Neuropathy, or Pyrimidine Nucleotide Depletion); therefore, subject health status was removed from the cofactor list.
- Creatinine clearance (CrCL) was not measured in pediatric patients in the Compassionate Use (mitochondrial/neurometabolic disorders) trial. Therefore, these patients were dropped from the mixed effect model analysis of the full population (adults + pediatrics), and the results of the analyses in the adult-only and adult + pediatric populations were identical.

Reviewer's comments:

- *The reviewer agrees that there is a trend for increase in apparent clearance with increase in BSA. However this was not considered clinically meaningful given the high survival rate observed in clinical studies and large safety margin associated with uridine triacetate. Thus dose adjustment based on BSA is not needed in adults. For details see section 2.3.1.4 of the Clinical Pharmacology Review.*
- *Although race is identified as a covariate in sponsor's current analysis, there is insufficient data to assess the effect of race on clearance of uridine. The majority of the subjects in the data were whites (N=48). There were 4 African Americans, 3 Hispanics and 1 Asian subject. Based on the limited data, the CL/F appears similar among Whites, African Americans and Hispanic. For details see section 2.3.1.3 of the Clinical Pharmacology Review.*
- *Although drug lot number was identified as statistically significant covariate in the model, it is unlikely to have a clinically meaningful impact on uridine CL/F (Figure 1).*
- *The sponsor conducted similar analysis for other PK parameters namely C_{max} , C_{2hr} (concentration 2 hour post dosing) and Vd/F . The review focused on apparent clearance as C_{max} and C_{2hr} provide information of the absorption phase and not the elimination phase of the drug.*

Figure 1: Effect of drug lot number on CL/F of uridine



Source: 401-POP-PK-ANALYSIS-REPORT (Version 2)

5 NDA FILLING FORM

See filing form in DARRTs dated 08/19/2015

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

/s/

ANSHU MARATHE
12/02/2015

RUNYAN JIN
12/02/2015

SARAH E DORFF
12/02/2015

ROSANE CHARLAB ORBACH
12/02/2015

YANING WANG
12/02/2015

QI LIU
12/02/2015

NAM ATIQRUR RAHMAN
12/02/2015

I concur with the recommendation.

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	208159	SDN	1
Applicant	Wellstat Therapeutics Corporation	Submission Date	07/09/2015
Generic Name	Uridine Triacetate	Brand Name	Vistogard
Drug Class	Uridine triacetate is an orally bioavailable prodrug of uridine. Uridine (without acetate attachment) has been tested as a 5-FU antidote		
Approved Indication	None		
Newly Proposed Indication in sNDA	To treat patients at risk of serious toxicity following an overdose of 5-fluorouracil and patients exhibiting symptoms of serious toxicity within 96 hours of 5-fluorouracil administration.		
Dosage Regimen	Adult dose: 10 grams (1 packet) orally every 6 hours for 20 doses, without regard to meals. Pediatric dose: 6.2 grams/m ² of body surface area (not to exceed 10 grams per dose) orally every 6 hours for 20 doses, without regard to meals.		
Dosage Form	Oral granules: 10 grams of orange-flavored oral granules (95% w/w) in (b) (4) packets	Route of Administration	Oral Nasogastric tube (NG tube) or gastrostomy tube (G-Tube) when necessary (eg, severe mucositis or coma)
OCP Division	Division V, Division of Pharmacometrics	OND Division	OHOP/ DOP1
OCP Review Team Division	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
	Runyan Jin	Qi Liu	
Pharmacometrics	Anshu Marathe	Yaning Wang	
Genomics	Sarah Dorff	Rosane Charlab Orbach	
Review Classification	<input type="checkbox"/> Standard <input type="checkbox"/> Priority <input checked="" type="checkbox"/> Expedited		
Filing Date	8/11/2015	74-Day Letter Date	9/8/2015
Review Due Date	12/1/2015	PDUFA Goal Date	3/10/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

Yes

No

If no list reason(s)

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

Yes

No

If yes list comment(s): IR regarding Population PK analysis

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

Yes

No

If yes explain

Clinical Pharmacology Package

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

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
<input type="checkbox"/> Metabolism Characterization		Uridine metabolism is well documented in the literature. In the clinical pharmacology summary, the sponsor has summarized the information and provided literature references.
<input checked="" type="checkbox"/> Transporter Characterization		Potential as a substrate or inhibitor of P-gp
<input type="checkbox"/> Distribution		Information from literature
<input checked="" type="checkbox"/> Drug-Drug Interaction		CYP inhibition and induction studies
In Vivo Studies		
Biopharmaceutics		
<input type="checkbox"/> Absolute Bioavailability		
<input checked="" type="checkbox"/> Relative Bioavailability	2	A Phase 1, Single Center, Open-Label, Randomized, Single Dose, 2-Way Crossover Study to Compare Relative Bioavailability of a Single 6 g Dose of PN401 Active Pharmaceutical Ingredient (API) to That of a Single 6 g Dose of a Formulated PN401 Sprinkle When Administered Under Fasted Conditions (Study No. 401.07.001) CSR submitted. Phase 1 open-label, randomized, crossover, single 6 g dose PK profile after two different lots of tablets (fasting) Fed/fasted (one lot of tablets)
<input type="checkbox"/> Bioequivalence		
<input checked="" type="checkbox"/> Food Effect	1	A Phase 1, Single-Center, Open-Label, Randomized, Single-Dose, 2-way Crossover Study to Evaluate the Effect of Food on Uridine Pharmacokinetics and Relative Bioavailability After a Single 6 g Dose of PN401 Sprinkle (Study N0. PN401.07.002) CSR submitted.
<input type="checkbox"/> Other		
Human Pharmacokinetics		
Healthy Subjects	<input type="checkbox"/> Single Dose	
	<input type="checkbox"/> Multiple Dose	
Patients	<input type="checkbox"/> Single Dose	
	<input checked="" type="checkbox"/> Multiple Dose	5

		<p>Pharmacokinetics of plasma uridine following oral dosing of uridine triacetate in patients with a neurometabolic disorder</p> <p>Pharmacokinetics of plasma uridine following oral dosing of uridine triacetate in patients with a neurometabolic disorder (Study No. 401.09.001) CSR submitted</p> <p>Phase I trial of oral triacetyluridine (TAU) [PN401; uridine triacetate] as a rescue agent for 5-Fluorouracil (5-FU) in the treatment of cancer patients (Study No. P92-1082-PK) CSR submitted</p> <p>Phase 2 open, non-controlled, 2-arm, multi-center; Patients with Type I or II diabetes with diabetic neuropathy</p>
<input type="checkbox"/> Mass Balance Study		
<input type="checkbox"/> Other (e.g. dose proportionality)		
Intrinsic Factors		
<input type="checkbox"/> Race		Evaluated as a covariate in pop PK analysis
<input type="checkbox"/> Sex		Evaluated as a covariate in pop PK analysis
<input type="checkbox"/> Geriatrics		Age was evaluated as a covariate in pop PK analysis
<input type="checkbox"/> Pediatrics		<ul style="list-style-type: none"> • A phase 1 study was conducted in neurometabolic disorder (Study No. 401.09.001) • The clinical efficacy/safety study (WELL401) included 6 pediatric subjects • The applicant is asking for the indication in both adults and pediatrics. • Uridine triacetate has been granted orphan drug and thus is exempt from the requirements of the Pediatric Research Equity Act (PREA)
<input type="checkbox"/> Hepatic Impairment		
<input type="checkbox"/> Renal Impairment		
<input type="checkbox"/> Genetics		<p>Study 401.09.001 included 6 patients with deleterious mutations in the DPYD gene, 1 patient with TYMS and MTHFR gene mutations, and 1 patient homozygous for a TYMS gene mutation</p> <p>Study WELL401 included 4 patients with deleterious mutations in the DPYD gene</p>
Extrinsic Factors		
<input type="checkbox"/> Effects on Primary Drug		
<input type="checkbox"/> Effects of Primary Drug		
Pharmacodynamics		
<input type="checkbox"/> Healthy Subjects		
<input type="checkbox"/> Patients		
Pharmacokinetics/Pharmacodynamics		
<input type="checkbox"/> Healthy Subjects		
<input type="checkbox"/> Patients		

<input type="checkbox"/> QT		Sponsor requests for a waiver to conduct thorough QTc studies.
Pharmacometrics		
<input checked="" type="checkbox"/> Population Pharmacokinetics		Two stage analysis was conducted. Covariates were examined.
<input type="checkbox"/> Exposure-Efficacy		Not submitted
<input type="checkbox"/> Exposure-Safety		Not submitted
Total Number of Studies	In Vitro	In Vivo
Total Number of Studies to be Reviewed		

Criteria for Refusal to File (RTF)

RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Registration lots of uridine triacetate drug product manufactured under cGMP were used in the clinical trials in patients with 5-fluorouracil overdose. These lots were manufactured (b) (4) for the commercial product.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Uridine metabolism is well documented in the literature. In the clinical pharmacology summary, the sponsor has summarized the information and provided literature references. In vitro studies were conducted for the following: <ul style="list-style-type: none"> • CYP inhibition and induction studies • Potential as a substrate or inhibitor of P-gp
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	

items 1 to 6 above (in .xpt format if data are submitted electronically)?		
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist

Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		

<p>8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
<p>9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

Filing Memo

Regulatory background:

The development of uridine triacetate as an antidote to 5-FU toxicity has proceeded under IND 039571. The potential use of uridine triacetate as an antidote to 5-FU overdose was first discussed with the Division on May 26, 1996. FDA agreed that a placebo-controlled study cannot ethically be conducted in 5-FU overdosed patients and (by inference) in patients exhibiting rapid onset of serious 5-FU toxicities. Orphan drug designation was granted

EOP2 Meeting (July 6, 2010)

From a clinical pharmacology perspective, the following were recommended at the meeting.

- Conduct in vitro studies to determine whether uridine triacetate is a substrate, inducer and/or inhibition of major cytochrome P-450 enzymes. Also assess whether uridine triacetate is a substrate and/or inhibitor of P-glycoprotein. FDA also indicated that Wellstat can submit literature to address the DDI (drug-drug interaction) potential, and that the adequacy of the information would be a review issue.
- The absorption, distribution, metabolism and excretion (ADME study) of uridine triacetate need to be addressed in humans. Depending on the outcome of the ADME study, the effect of hepatic and renal impairment on the PK of [uridine triacetate] may need to be addressed. Alternatively, conduct both renal and hepatic impairment trials to address the dose adjustments in patients with such organ dysfunctions.
- The clinical development program should include clinical evaluation of the potential for QT/QTc interval prolongation. In oncology, alternative proposals to the “TQT” study may be appropriate. FDA indicated that Wellstat could submit a detailed summary of the available data for IRT review, and a proposal for an alternate QT study or waiver.

Another End of Phase 2 meeting was held on 13 August 2013. Wellstat’s plan for population pharmacokinetic (PK) analyses was discussed

At a teleconference on May 28 2014, FDA indicated that this would be a (b) (4) regulatory pathway, incorporating the Animal Rule and the clinical results obtained by Wellstat.

SUMMARY OF EFFICACY:**Efficacy in Mice**

The efficacy of uridine triacetate has been established in placebo-controlled studies in mouse Models. In mice receiving a lethal acute dose of 5-FU (e.g. 300 mg/kg 5-FU i.p., an LD₁₀₀ dose), initiation of oral dosing with uridine triacetate between 24 and 96 hours after 5-FU significantly improved survival. A similar time window for treatment (up to about 96 hours after 5-FU administration) and dependence of percent survival on time of uridine triacetate treatment initiation was found when 5-FU overexposure in mice was due to inhibition of DPD with 5-ethynyluracil, impairing elimination in mice receiving an otherwise well-tolerated therapeutic dose of 100 mg/kg 5-FU

Efficacy in Humans

Patients included in Study 401.10.001 and WELL401 were enrolled on the basis of demonstrated overdosage or early onset of symptoms following 5-FU administration. Of 135 patients enrolled in the 2 studies, 130 survived through the 30-day treatment and observation period (96%; 95% CI: 0.92, 0.99).

SAFETY

- No major safety concerns
- Common AEs include diarrhea (21%), vomiting (17%) and nausea (15%)

CLINICAL PHARMACOLOGY SUMMARY:

The applicant sponsored three trials of uridine triacetate in healthy subjects, all of which are single-dose clinical pharmacology studies designed to evaluate bioequivalence (Study PN401.07.001, 20 subjects and Study 401.10.PKL.01, 6 subjects) or food effects (Study PN401.07.002, 20 subjects). In addition to these three clinical pharmacology studies, supporting pharmacokinetic data are available from part of the subjects in two clinical safety and efficacy Studies 401.10.001 and WELL401. Exposure data for plasma uridine after multiple doses are available from a study in cancer patients with solid tumors treated with 5-fluorouracil and uridine triacetate (Study P92-1082-PK, 16 subjects] and a study in diabetic neuropathy patients (Study 401.97.201, 20 subjects).

Pharmacokinetic data in children to support the dose selection are available in a study for 4 patients with mitochondrial and neurometabolic disorders (Study PN401.09.001-PK) and 6 pediatric patients in Study WELL401.

The metabolism of uridine is well documented in the literature, which are referred in the summary of clinical pharmacology. Two in vitro studies were conducted to evaluate the drug interaction potential of uridine triacetate and uridine: one is to estimate CYP inhibition and induction potential (13WELLP1R1_Study I) and another is to estimate P-gp substrate and inhibition potential (13WELLP1P1_Study II).

Population PK Analysis:

A two stage analysis was conducted utilizing data from Phase 1 studies, Phase 2 studies, study 401.10.001 and study WELL401. The objective of the analysis were:

- To compile population estimates of key uridine and uracil PK parameters, after administration of uridine triacetate, across all human clinical studies
- To compare the PK of uridine triacetate in healthy volunteers and patients
- To quantify the effects of key demographic, physiologic, or environmental covariates (age, gender, body size, race, renal function, extrinsic factors, etc.) on the PK of uridine triacetate

Pharmacogenomics Summary

Based on the applicant, a total of 12 patients with early onset of 5-FU toxicity had genotype information across the two clinical safety and efficacy Studies 401.10.001 and WELL401. This included 10 patients with deleterious mutations in the DPYD gene, 1 patient with MTHFR and TYMS gene mutations, and 1 patient homozygous for a 6 bp deletion in the 3'-untranslated region of the TYMS gene.

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

/s/

ANSHU MARATHE
08/18/2015

RUNYAN JIN
08/18/2015

SARAH E DORFF
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ROSANE CHARLAB ORBACH
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BRIAN P BOOTH
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