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*APPLICATION NUMBER:*

**208169Orig1s000**

**MEDICAL REVIEW(S)**

Application Type NDA  
Application Number(s) 208169  
Priority or Standard Priority

Submit Date(s) January 8, 2015  
Received Date(s) January 8, 2015  
PDUFA Goal Date September 5, 2015  
Division / Office DGIEP/ODE III

Reviewer Name(s) Carla Epps, MD, MPH  
Review Completion Date September 4, 2015

Established Name Uridine triacetate  
(Proposed) Trade Name Xuriden  
Therapeutic Class Pyrimidine analog  
Applicant Wellstat

Formulation(s) Oral granules, 2 g packets  
Dosing Regimen 60 mg/kg/day up to 120  
mg/kg/day; maximum dose 8  
grams/day  
Indication(s) Uridine replacement therapy  
Intended Population(s) Patients with hereditary orotic  
aciduria

This is an addendum to the clinical review of uridine acetate, dated July 28, 2015. The addendum addresses findings from the drug product manufacturing facilities inspection regarding the dissolution method for uridine triacetate.

On September 4, 2015, the Quality Review team provided an addendum to the Overall Quality Assessment for NDA 208169 that was filed on June 24 2015. The addendum updated the drug product manufacturing facilities assessment. Upon inspection, the applicant's dissolution method was found to be inadequate for long term use. Specifically, the inspection team found that there was variability in dissolution rates between the three exhibit batches submitted for process evaluation (see review addendum for further details). However, the pivotal clinical batch did meet specifications.

The facilities inspection team discussed these findings with the clinical review team due to the concern that a delay in dissolution could lead to a delayed  $T_{max}$  and potentially also a reduced  $C_{max}$ . This reviewer notes that the Biopharmaceutics Review team had identified this issue and had assessed for the impact of variability in dissolution rates on bioavailability. The Biopharmaceutics Review team pointed out that the variability observed in the dissolution rate was only during early part of the dissolution curve (b) (4) and that at (b) (4) dissolution for all batches converged. Since the half-life for the drug is about 2 hours, the variability in rate of dissolution observed in the early stage of the dissolution curve (earlier than (b) (4)) will only have limited impact on actual bioavailability (small shift on  $T_{max}$  and potentially small reduction in  $C_{max}$ ). Therefore, in this reviewer's opinion, the observed variability in dissolution would not have a clinically meaningful impact on the safety or efficacy of the drug. This reviewer agrees with the Quality Review team that the identified deficiencies in the manufacturing process do not warrant withholding approval and that these issues may be addressed as post-marketing commitments.

The following post-marketing commitments were agreed upon by the applicant on September 1, 2015:

- a PMC to update the dissolution method
- a PMC to evaluate the impact of particle size distribution on dissolution, update the manufacturing process, update the final dissolution and particle size distribution specification, and perform a retrospective analysis of the submitted application batches.

The proposed date for submission of the final report for the dissolution study is March 2016.

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/s/  
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CARLA L EPPS  
09/04/2015

*CLINICAL REVIEW*

Application Type	NDA
Application Number(s)	208169
Priority or Standard	Priority
Submit Date(s)	January 8, 2015
Received Date(s)	January 8, 2015
PDUFA Goal Date	September 5, 2015
Division / Office	DGIEP/ODE III
Reviewer Name(s)	Carla Epps, MD, MPH
Review Completion Date	July 28, 2015
Established Name	Uridine triacetate
(Proposed) Trade Name	Xuriden
Therapeutic Class	Pyrimidine analog
Applicant	Wellstat
Formulation(s)	Oral granules, 2 g packets
Dosing Regimen	60 mg/kg/day up to 120 mg/kg/day; maximum dose 8 grams/day
Indication(s)	Uridine replacement therapy
Intended Population(s)	Patients with hereditary orotic aciduria

Template Version: March 6, 2009

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend approval action for uridine triacetate for treatment of hereditary orotic aciduria” (HOA). Currently, there are no approved therapies for the disease.

### 1.2 Risk Benefit Assessment

The benefit-risk analysis of uridine triacetate for the proposed indication is favorable. This is based on a review of retrospective case studies of 18 patients with HOA treated empirically with other unapproved uridine formulations and clinical review findings for four patients enrolled in the single pivotal trial (Study 001). The published case studies and the pivotal trial patients represent all confirmed cases of patients with this disorder. The totality of evidence indicates that patients receiving adequate doses of a replacement source of uridine (the active metabolite of uridine triacetate) experience clinically meaningful improvement in key disease manifestations, including hematologic status and growth.

Published literature for 18 patients with HOA documented improvement or normalization of hematologic, growth and orotic acid levels with uridine replacement therapy. Reductions in orotic acid levels were typically observed within the first week of treatment. The time to treatment response in patients with anemia varied from less than 2 weeks to several months. A similar variability in time to response was observed for white cell abnormalities. Growth delays, most commonly poor weight gain, improved over a span of several months. The majority of patients received the same dose throughout treatment; some patients required a dose increase to achieve their optimal response.

Study 001 was conducted in four patients, including 3 patients who were previously treated with uridine and one treatment-naïve patient, a recently diagnosed (b) (6) of one of the transition patients. The clinical experience of the three patients who were treated with uridine prior to enrolling in Study 001 is consistent with findings in the published literature. Namely, the time to therapeutic response and the uridine dose needed to produce a therapeutic response varied. However, all of the three patients who were previously treated with uridine demonstrated improvement in growth (height velocity) while they were being treated with uridine and achieved normal or near normal urine orotic acid levels. Of note, two of the patients experienced plateaus or declines in growth that improved after their doses were increased or adjusted for weight.

In addition, one patient who had a history of severe neutropenia experienced a clinically significant increase in his neutrophil count after starting uridine. There were no changes in the hematologic status of the other two patients while on uridine. One patient had normal hematologic indices prior to starting uridine replacement therapy; the third patient had macrocytosis (as measured by elevated mean corpuscular volume) that persisted with no improvement while on uridine replacement therapy. The lack of response observed in the patient with macrocytosis may have been due to the patient receiving an inadequate dose of uridine.

During the pivotal trial, the primary efficacy analysis for patients who transitioned from uridine was stability of a pre-specified hematologic endpoint after 6 weeks of treatment with uridine triacetate. The primary efficacy analysis for the treatment-naïve patient was improvement in his pre-specified hematologic endpoint (mean corpuscular volume) after 6 weeks of treatment with uridine triacetate. The endpoints were patient-specific, based on the individual patient's history of hematologic abnormalities. Thus, the intent of the trial was to establish that patients treated with uridine triacetate would receive the same clinical benefit expected from treatment with uridine (i.e., sustained clinical benefit in patients switched from uridine and improvement in clinical status in treatment-naïve patients). Although all three patients who transitioned from uridine maintained stable hematologic parameters after 6 weeks of treatment, based on the prior evidence (or lack thereof) of a hematologic response with uridine, only the neutropenic patient can be considered to have demonstrated sustained clinical benefit. No improvement in hematologic status was observed in the treatment-naïve patient. Therefore, based on the primary efficacy findings for Study 001 alone, there is not sufficient evidence to support efficacy for uridine triacetate.

However, clinical data from the extension phase of the trial lend further support of efficacy. Two patients who were transitioned from uridine demonstrated clear improvement in clinical status after 6 months of treatment with uridine triacetate. The neutropenic patient achieved a neutrophil count that was just below the lower limits of normal- (b) (6) highest recorded neutrophil count. (b) (6) also experienced clinically significant increases in weight (as measured by weight and weight velocity z-scores) and height (as measured by height and height velocity z-scores). The second transition patient also experienced improved weight growth (weight and weight velocity z-scores improved); the third transition patient was an adult and therefore was not included in growth analyses. No clinical improvement was observed in the treatment-naïve patient's growth parameters.

Of note, the three pediatric patients received dose increases during the trial. The (b) (6) doses were doubled after about 4 months of treatment based on PK data that demonstrated low systemic exposure on the starting dose. The neutropenic patient's dose was increased by 50% at the end of Month 6 based on findings of an increased

orotic acid level. Both the published literature and the clinical experience of the patients who were previously treated with uridine highlight the importance of administering an adequate dose of uridine. Patients who were administered low doses of uridine did not improve until their dose was sufficiently increased. Similarly, some patients experienced clinical deterioration if their dose was not adjusted for weight gain or when providers attempted to lower their maintenance dose of uridine.

In this reviewer's opinion, questions remain regarding the optimal dosing of uridine triacetate needed to achieve and maintain the desired hematologic or growth responses in some patients. Therefore, I recommend that the applicant continue to collect efficacy data for total duration of 2 years as an extension study, as well as information on any dose adjustment made during the data collection period (see PMC # 2).

The safety profile of uridine triacetate has been evaluated in HOA patients and other patient populations. No treatment-related adverse events were reported for the pivotal trial. Diarrhea has been reported in patients who received a different formulation of uridine acetate containing an excipient known to cause gastrointestinal irritation.

### *1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies*

Routine surveillance for adverse events is recommended.

### *1.4 Recommendations for Postmarket Requirements and Commitments*

The following post-marketing commitments (PMCs) were being negotiated with the applicant at the time of this review:

1. Develop a discriminating dissolution method appropriate for the proposed product and set dissolution method acceptance criteria based on data from at least 5 commercial batches.
2. Continue to evaluate the long-term efficacy and safety of XURIDEN in patients currently enrolled in Protocol 401-13-001 every 6 months for a total duration of 2 years in an extension study. The extension study should collect data on growth, hematologic indices, and urine biomarkers (orotic acid and orotidine). Growth data should include height, weight, height velocity and weight velocity. Ensure that the growth data are submitted also as z-scores. Provide information on any dose adjustments made during the extension study, including the dose amount, the reason(s) for the adjustment, and the results of any additional clinical or laboratory assessments performed following dose adjustments. (b) (4)

## 2 Introduction and Regulatory Background

### 2.1 Product Information

#### A. Hereditary Orotic Aciduria (HOA)

Hereditary orotic aciduria (HOA) is an extremely rare disorder of pyrimidine nucleotide synthesis (fewer than 25 cases have been identified worldwide- see [Table 9](#) for a summary of published case studies) that is due to a gene mutation that can cause deficiency of the bifunctional enzyme uridine 5'-monophosphate synthase (UMPS) that contains two activities (orotic phosphoribosyltransferase and orotidine monophosphate decarboxylase), resulting in reduced production of uridine, a nucleotide involved in multiple essential physiological functions including biosynthesis of RNA, synthesis of glycogen and glycoprotein, phospholipid synthesis, and DNA synthesis. A deficiency of UMPS also results in accumulation of orotic acid and orotidine in tissues (see [Figure 1](#)).

#### Figure 1: Pyrimidine Metabolism Pathway

(b) (4)



Source: Nyhan WL, Disorders of purine and pyrimidine metabolism, *Mol Genet Metab* 2005; 86: 25-33.

#### B. Natural History of HOA

Disease onset occurs during the neonatal or infant period. Biochemical manifestations of the disease are elevated urine levels of orotic acid and orotidine. HOA is a clinically heterogeneous disorder; individuals who have some UMPS activity (e.g., individuals who are heterozygous for defective UMPS) may be asymptomatic or only mildly affected. Clinical features of the more severe forms of HOA include megaloblastic anemia that is not responsive to treatment with vitamin B12 or folic acid, neutropenia,

renal tract obstruction (due to aggregation of orotic acid crystals), immune dysfunction, congenital anomalies, and physical and intellectual developmental delays. Some patients may present with delayed growth and development prior to developing hematologic abnormalities. There has been at least one confirmed case of HOA without megaloblastic anemia.<sup>1</sup>

Three of the 22 known patients with HOA have died from overwhelming infections. All three patients had severe underlying disease; one patient also had documented immune dysfunction.<sup>2</sup>

### **C.Current Therapy**

Currently, there is no approved therapy for HOA. However, nucleotide replacement therapy has been the mainstay of treatment for HOA patients for decades following publication of the first case report of HOA by Huguley et al., in which the authors describe disease remission in a patient treated empirically with a mixture of nucleotides.<sup>3</sup> Subsequent case reports have documented rapid hematologic response with administration of uridine (within days to weeks). Conversely, patients experience relapse of disease when administration of uridine is suspended. Some patients treated chronically with uridine have reached adulthood. There are also case reports of patients treated lifelong with uridine that have fathered or given birth to normal children.<sup>4</sup> Uridine dosing has ranged from 50 mg/kg/day to 300 mg/kg/day for patients with HOA. Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.

#### *2.3 Availability of Proposed Active Ingredient in the United States*

Uridine triacetate is not currently marketed in any country. Uridine (the active moiety of uridine triacetate) is commercially available in the US as a dietary supplement.

#### *2.4 Important Safety Issues with Consideration to Related Drugs*

In clinical trials in healthy volunteers and cancer patients, diarrhea was observed following administration of high doses of oral uridine (single dose of 10 gram/day); fever and chills were observed following administration of high doses of intravenous uridine (1

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<sup>1</sup> Bailey CJ, Orotic aciduria and uridine monophosphate synthase, *J Inherit Metab Dis* 2009; 32 (Suppl 1): S227-S233.

<sup>2</sup> Webster DR., Becroft DM et al., Hereditary Orotic Aciduria and Other Disorders of Pyrimidine Metabolism, *Scriver's Online Metabolic & Molecular Bases of Inherited Disease* 2001, Chapter 113: 1-86.

<sup>3</sup> Huguley CM, Bain JA et al., Refractory megaloblastic anemia associated with excretion of orotic acid, *Blood* 1959; 14: 615-634.

<sup>4</sup> Webster DR., Becroft DM et al., Hereditary Orotic Aciduria and Other Disorders of Pyrimidine Metabolism, *Scriver's Online Metabolic & Molecular Bases of Inherited Disease* 2001, Chapter 113: 1-86.

to 2.5 g/m<sup>2</sup>/hr).<sup>5,6</sup> In clinical trials in patients with HIV lipodystrophy treated chronically with oral uridine doses of 108 grams/day, diarrhea was reported as an adverse reaction.<sup>7</sup> Based on my independent review of case studies for patients with HOA treated with uridine, there do not appear to have been any adverse events reported that were assessed as drug-related (see [Section 7.4.1](#)). As noted earlier, uridine dosing for patients with HOA ranged up to 300 mg/kg/day.

*Reviewer Comments:*

*As discussed later, the events of diarrhea reported in other patient populations appear to be due to excipients in the oral formulations used rather than higher exposures to uridine itself. Some formulations used excipients known to cause gastrointestinal irritation.*

## *2.5 Summary of Presubmission Regulatory Activity Related to Submission*

### **Regulatory history**

**December 2012:** The Agency was informed of an impending drug shortage for patients with HOA being treated with uridine under expanded access protocols due to the sole supplier discontinuing its clinical development programs for uridine. At the time, five patients with HOA were being treated with uridine through expanded access all five patients received uridine through emergency or individual patient INDs.

**January 2013:** The Agency identified the applicant Wellstat, manufacturer of uridine acetate (a prodrug of uridine) as a potential alternative source of uridine for patients with HOA in expanded access protocols.

**March 22, 2013:** The Agency met with the applicant to discuss development of uridine triacetate as uridine replacement therapy in patients with HOA.

**August 7, 2013:** The Agency held a pre-IND meeting with the applicant to discuss a regulatory pathway for receiving an indication for treatment of patients with HOA. During the meeting, the Agency reached agreement with the sponsor that a single adequate and well-controlled trial could serve as the basis for approval and that study endpoints for the trial could be individualized by patient.

**August 9, 2014:** The Agency granted Pediatric Rare Disease Voucher Program designation for uridine triacetate for HOA.

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<sup>5</sup> van Groeningen CJ, Peters TGJ, et al. Clinical and Pharmacologic Study of Orally Administered Uridine, *J Natl Cancer Inst* 1991; 83(6): 437-441.

<sup>6</sup> Leyva A, van Groeningen CJ et al., Phase I and pharmacokinetic studies of high-dose uridine intended for rescue from 5-fluorouracil toxicity, *Cancer Res* 1984; 44 (12 Pt 1): 5928-2933.

<sup>7</sup> McComsey GA, Walker UA et al., Uridine supplementation in the treatment of HIV lipodystrophy: results of ACTG 5229, *AIDS* 2010; 24(16): 2507-15.

**August 9, 2014:** The Agency granted Orphan Product designation for uridine triacetate for HOA.

**November 22, 2013:** The applicant submitted protocol 401.13.001, "Open-Label Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria."

**April 25, 2014:** The Agency granted Breakthrough Product designation for uridine triacetate for HOA based on clinical data presented from published case studies and clinical summaries for the expanded access INDs.

**December 16, 2014:** The Agency held a pre-NDA meeting with the applicant. During the meeting, the Agency agreed that the battery of nonclinical studies that the applicant proposed to submit was adequate to support filing of the NDA. The Agency requested that the applicant submit additional clinical data to support the application, including historical data and data from the extension treatment phase for patients enrolled in the registration trial, and a summary of published case studies on HOA patients treated with uridine.

The applicant was also granted a separate pre-NDA meeting scheduled December 11, 2014 to discuss CMC issues. The applicant withdrew the CMC pre-NDA meeting request after receiving Meeting Preliminary Comments sent by the Agency on December 5, 2014, noting that the written comments were sufficient.

**January 8, 2015:** The applicant submitted NDA 208-169.

#### *2.6 Other Relevant Background Information*

None.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

This was an electronic submission. The overall quality of the data submitted by the applicant was adequate for comprehensive review of the data. The Division of Scientific Investigations (DSI) inspected the two sites involved in the registration trial and determined that the data were reliable to support the application.

There were no amendments to the original protocol for 401.13.001 (Version 3.0 dated February 19, 2014) during the course of the trial. (b) (4)

#### *Reviewer Comments:*

*The applicant provided listings of available hematologic data for the four patients enrolled in 401.13.001. This reviewer agrees that the amount of data was insufficient to perform formal statistical analyses. However, the data were useful in assessing the clinical significance of the trial results and are included in my review of the efficacy data.*

#### 3.2 Compliance with Good Clinical Practices

The applicant stated that trials for the clinical development program were conducted in accordance with Good Clinical Practices (GCP) and the Declaration of Helsinki.

#### 3.3 Financial Disclosures

The applicant certified that there were no financial arrangements to disclose (see [Section 9.4](#)).

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

CMC data for this product were reviewed by the Quality Review Team (see Quality Review dated June 22, 2015). The review team deemed the application not ready for approval at this time. Outstanding deficiencies included the following:

- Inadequate dissolution method and acceptance criteria; the current method and acceptance criteria are acceptable only on an interim basis
- Additional information needed to determine the appropriateness of the proposed dosage form for infants and young children (uridine triacetate mixed in milk, (b) (4), or infant formula)
- Recommendations from the Office of Compliance for facilities were still pending Facilities inspections were still in process
- Unresolved label/labeling issues

The Quality Review Team recommended that development of a dissolution method and dissolution method acceptance criteria be addressed as a post-marketing commitment.

#### *Reviewer Comments:*

*At the time of this review, Division communications with the applicant regarding these deficiencies were ongoing. A Late-Cycle Meeting (LCM) was held on July 8, 2015 to discuss unresolved review issues, including the aforementioned issue of dosage form for younger children. Performance and appropriateness of uridine triacetate granules for dosing of young pediatric patients were reviewed by Arzu Selen, Ph.D., the product performance reviewer. Dr. Selen raised the concern that mixing the drug product with small amounts of liquid*

*(b) (4) concurs with Dr. Selen's recommendation.*

### 4.2 Clinical Microbiology

Clinical microbiology considerations do not apply to this application because uridine triacetate is not an antimicrobial agent.

#### 4.3 Preclinical Pharmacology/Toxicology

The nonclinical program for this product was reviewed by Sruthi King, Ph.D. The preclinical program included: a single-dose oral limit test in rats, a 5-day oral safety study in dogs, a 6-week oral dose toxicity study in rats, 12-week oral dose toxicity studies in rats and dogs, a 6-month chronic toxicity study in rats, Segment 1 and Segment II reproductive toxicity studies in rats, and genotoxicity testing. In the 12-week toxicity studies, the No Observed Adverse Effects Level (NOAEL) was 1000 mg/kg/day for rats (human equivalent dose of about 160 mg/kg/day) and 1500 mg/kg/day for dogs (human equivalent dose of 833 mg/kg/day). In the 6-month toxicity study in rats, the NOAEL was 2000 mg/kg/day (human equivalent dose of about 320 mg/kg/day), the highest dose tested. In the reproductive toxicity studies in rats, the NOAEL dose for paternal, maternal and developmental toxicity was 2000 mg/kg/day (human equivalent dose of about 320 mg/kg/day), the highest dose tested. No target organ toxicities were identified in any of the toxicity studies. Genotoxicity testing was negative.

Dr. King deemed the nonclinical program to be adequate to support marketing approval. Please refer to Dr. King's review (dated June 18, 2015) for further details.

#### *Reviewer Comments:*

*During the PIND meeting for uridine triacetate, the applicant had agreed to conduct a Segment III pre- and postnatal development study as a post-marketing requirement. However, based on the favorable safety profile of uridine triacetate demonstrated in the non-clinical studies conducted to date, the non-clinical review team determined that a Segment III study was no longer required to support this application.*

#### 4.4 Clinical Pharmacology

The clinical pharmacology data for this product were reviewed by Sandhya Apparaju, Ph.D. Please refer to Dr. Apparaju's review (dated June 5, 2015) for further details. Dr. Apparaju recommended an approval action for this product.

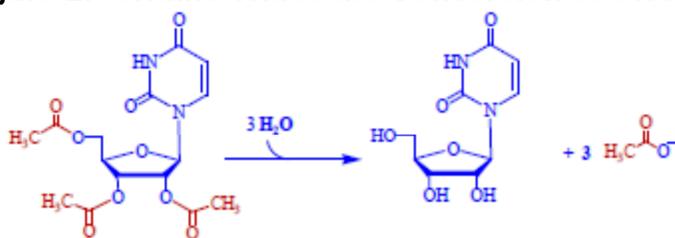
##### 4.4.1 Mechanism of Action

The rationale for uridine replacement therapy is that exogenous administration of uridine will mitigate the deficiency of endogenous uridine in patients with HOA and thus facilitate pyrimidine nucleotide synthesis. Replenishment of circulating uridine also helps to correct orotic acid overproduction by inhibiting carbamoyl phosphate synthetase 2, the enzyme involved in the first step in pyrimidine nucleotide synthesis.

Uridine triacetate is a pro-drug of uridine that forms uridine and free acetate upon metabolism (see [Figure 2](#)). One of the challenges of uridine replacement therapy noted

in published literature is the low bioavailability of orally administered uridine. In a published study of the pharmacokinetic profile of uridine in healthy volunteers and cancer patients, the bioavailability of orally administered uridine was observed to be less than 10%).<sup>8</sup> As discussed in [Section 4.4.3](#), the applicant submitted data that demonstrated higher bioavailability with orally administered uridine triacetate compared to orally administered uridine.

**Figure 2: Uridine Triacetate Conversion to Uridine**



Source: Protocol 401.13.001, Version 3.0 (dated February 19, 2014), Figure 1.

#### 4.4.2 Pharmacodynamics

In the registration trials for uridine triacetate, pharmacodynamic endpoints included hematologic endpoints and disease biomarker endpoints (urine orotic acid and urine orotidine).

#### 4.4.3 Pharmacokinetics

[Table 1](#) and [Figure 3](#) summarize individual patient PK information for Study 001. PK assessments were performed at baseline to assess the PK characteristics of uridine and at Days 1 and 28 following uridine triacetate dosing of 60 mg/kg/day. For patients previously treated with uridine, uridine dosing ranged from 150 mg/kg/day to 211 mg/kg/day. Inpatient values for the half-life of uridine triacetate were similar to those observed with uridine ( $t_{1/2}$  values ranged from 1.1 to 4.7 hours).

At Day 28, uridine exposure was observed to be about two-fold higher in the patients at Site 1 (Patients (b) (6)) compared to the patients at Site 2 (Patients (b) (6) and (b) (6)). During the extension phase of the trial, Patients (b) (6) and (b) (6) received uridine triacetate dose increases of 120 mg/kg/day with subsequent increase in plasma uridine exposure. PK parameters were reassessed in these two patients 44 days after the dose increase (Day 160).

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<sup>8</sup> van Groeningen CJ, Peters GJ et al. Clinical and pharmacologic study of orally administered uridine, *J Natl Cancer Inst* 1991; 83: 437-441.

**Table 1: Study 001 – Summary of Individual Patient PK Parameters**

Patient	Visit	Dose (mg/kg)	AUC <sub>0-8</sub>	C <sub>0h</sub>	C <sub>max</sub> (uM)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)
(b) (6)	Baseline	211*	158	15	49	2.0	1.1
	Day 1	56	282	2	90	2.0	1.1
	Day 28	56	330	2	119	1.0	1.2
	Baseline	194*	131	2	44	1.0	1.3
	Day 1	60	529	21	137	2.0	2.1
	Day 28	59	466	2	126	1.0	2.0
	Baseline	150*	426	13	75	4.0	2.5
	Day 1	59	262	2	69	2.1	2.2
	Day 28	59	161	2	33	2.5	4.7
	Day 160	120	533	2	95	4.0	3.3
	Baseline	--	--	2	--	--	--
	Day 1	65	172	2	69	1.2	1.2
Day 28	65	158	2	77	1.5	1.2	
Day 160	120	398	10	67	2.0	13.0	

\*Baseline dose=previous uridine dose

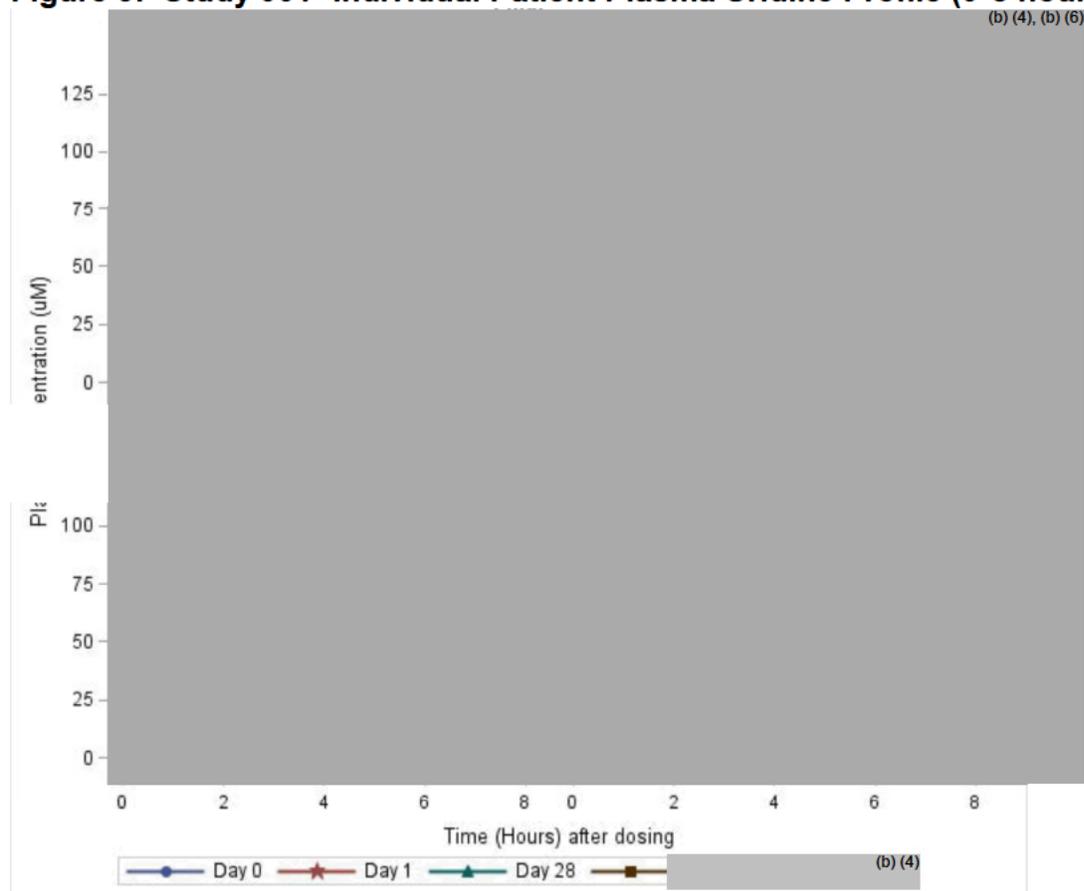
Source: Protocol 401.13.001, Version 3.0 (dated February 19, 2014), Table 11-30/

*Reviewer Comments:*

*The reason for the observed differences in the PK profile between the two sites is unclear. The site inspections did not reveal any inconsistencies in dosing between the two sites. Given that the (b) (6) the observed variability may be due to genetic differences.*

*PK data were not available for uridine triacetate. Dr. Apparaju recommended that the applicant consider developing an assay to measure plasma uridine triacetate levels for future clinical trials for other indications.*

**Figure 3: Study 001- Individual Patient Plasma Uridine Profile (0-8 hours)**



Note: For Patient (b)(4), the Day 0 pre-dose sample was drawn 15 minutes post-dose with uridine

Source: Protocol 401.13.001, Version 3.0 (dated February 19, 2014), Figure 14.32.

#### 4.4.4 Metabolism

In vitro metabolic studies performed by the applicant indicated that uridine triacetate is a P-glycoprotein (P-gp) inhibitor and may be a P-gp substrate. Uridine triacetate was not observed to induce CYP1A2, CYP2B6 or CYP3A4.

The applicant also performed in vitro hERG and action potential studies to assess for the clinical risk of QTc prolongation and Torsades de Pointes. The QT Interdisciplinary Review Team (QT-IRT) concurred with the applicant that these studies demonstrated an adequate safety margin for uridine and uridine triacetate. Based on a review of the nonclinical study results and clinical safety data for uridine triacetate in other study populations, the QT-IRT determined that requirements for a QTC study for uridine triacetate could be waived (see QT-IRT Memo dated December 17, 2014 for further details).

## 5 Sources of Clinical Data

The applicant submitted the following data in support of the application: data from a single registration efficacy and safety trial in four patients with HOA (Protocol 401.13.001), data from four clinical pharmacokinetics trials, safety data from two open-label trials conducted in patients with diabetic neuropathy, and 12 investigator-sponsored INDs for treatment of patients with mitochondrial and neurometabolic disorders. An extension phase of the registration trial and four compassionate use protocols are ongoing; all other clinical trials have been completed.

### 5.1 *Tables of Studies/Clinical Trials*

[Table 2](#) summarizes clinical trials reviewed for the application.

Clinical Review  
 Carla Epps, MD, MPH  
 NDA 208169  
 Xuriden (uridine triacetate)

**Table 2: Uridine Triacetate Clinical Trials**

Trial	Phase	N Enrolled (completed)	Design	Dosing	Study population	Duration	Status
<b>Safety &amp; Efficacy</b>							
401.13.001*	3	4 (4)	R, DB, PC Efficacy Safety	60 mg/kg/day oral	Patients with HOA ages ≤19 years	6 weeks (main trial); unspecified (extension)	ongoing (extension)
<b>Pharmacokinetic &amp; Bioavailability Studies</b>							
401.10.PKL.01	1	6 (6)	OL, R, 2-way crossover	6 gram single dose, oral tablets- used two different lots (fasted-both lots; fed- one lot)	Adult male volunteers	Single dose	completed
PN401.07.001	1	20 (20)	OL, R, 2-way crossover	6 gram single dose, oral granules(fasted)	Adult volunteers	Single dose	completed
PN401.07.002	1	20 (20)	OL, R, 2-way crossover Food effect study	6 gram single dose, oral granules	Adult volunteers	Single dose	completed
PN401.09.001- PK	2	4	OL PK	33 mg/kg TID to 100 mg/kg TID	Patients with mitochondrial disease - pts also enrolled in IND 047399; age range was 4 to 10 yrs	~1.5 yrs	Completed-
<b>Safety</b>							
401.97.201	2	38 (29) Group 1:20 Group 2:18	OL, 2-arm , multi-center	Group 1: 2 g BID Group 2: 4 g BID	Patients with Type I or II diabetes with diabetic neuropathy	6-12 months	completed
401.97.202	2	15 (10)	OL, 2-arm , single-center	2 gram BID	Patients with Type I or II diabetes with diabetic neuropathy	6 months	completed

\*Trial or compassionate use program is ongoing

Clinical Review  
 Carla Epps, MD, MPH  
 NDA 208169  
 Xuriden (uridine triacetate)

**Table 2: Uridine Triacetate Clinical Trials (Cont'd)**

Trial	Phase	N Enrolled	Design	Dosing	Study population	Duration	Status
<b>Compassionate Use Programs</b>							
Investigator INDs: 047399 (b) (4) 058063* 058069* (b) (4) 068467* (b) (4) 069715* 069716 (b) (4)		30 (22 pediatric, 8 adults)	OL	33 mg/kg TID to 19.8 grams/day	Children ages >1 yr and adults with mitochondrial and neurometabolic disorders	Variable-treatment in ongoing programs is up to >19 years	4 ongoing programs

\*Trial or compassionate use program is ongoing

## 5.2 Review Strategy

This section discusses trial design and efficacy results for Protocol 401.13.001 (Study 001). Safety data are discussed in [Section 7](#) of this review.

Efficacy parameters evaluated in the trial include the following hematologic parameters: neutrophil count, white blood cell count, and mean corpuscular volume (MCV). Efficacy endpoints were individualized for each patient, based on the presence of clinically significant abnormalities in these parameters prior to initiation of uridine replacement therapy. Secondary efficacy endpoints included pharmacokinetic parameters and biomarkers for HOA (urine orotic acid and orotidine). Growth and development assessments will be performed during the extension phase of the trial.

## 5.3 Discussion of Individual Studies/Clinical Trials

### Protocol 401.13.001 (Study 001)

#### 5.3.1 General Design and Objectives

This was a 6-week open-label efficacy and safety trial followed by an extension trial (length unspecified). The target enrollment for the trial was 4 to 10 patients with HOA.

The primary objectives for the 6-week main trial were:

- to replace oral administration of uridine with oral administration of uridine triacetate in pediatric patients with HOA who have received (or would reasonably be expected to receive) clinical benefit from treatment with exogenous uridine
- to document the continued clinical benefit of exogenous uridine when patients are switched from oral administration of uridine to oral administration of uridine triacetate.

The primary objectives for the extension trial are:

- to provide continued access to uridine triacetate treatment for patients who have completed the main trial

### Secondary Objectives

The secondary objectives for both phases of the trial are:

- to assess the safety and tolerability of uridine triacetate in treated patients
- to assess levels of orotic acid and orotidine in urine in treated patients
- to assess levels of uridine in plasma

The trial is being conducted at two sites in the United States (b) (4) and (b) (4). The main trial period was from May 2014 to August 2014; an extension treatment phase is ongoing. The final clinical study report submitted with this application provides data on 4 patients, including three patients transitioning from treatment with uridine and one patient who had not received prior treatment with uridine.

#### 5.3.2 *Inclusion Criteria*

- Age  $\leq$  19 years
- Diagnosis of hereditary orotic aciduria
- Able to take oral medications
- Negative pregnancy test at screening ((females of childbearing potential)
- Use of acceptable birth control method (females of childbearing potential or males with partners of childbearing potential)

#### 5.3.3 *Exclusion Criteria*

- Known allergy to uridine triacetate or any of its excipients
- Known ornithine transcarbamoylase deficiency
- Unable to take oral medications
- Pregnant or lactating females

#### 5.3.4 *Individual Patient Withdrawal Criteria*

- Anaphylactic reaction to uridine triacetate
- Ongoing unexplained Grade 3 or greater diarrhea or vomiting lasting for more than one week and considered to be related to uridine triacetate<sup>9</sup>
- Pregnancy
- Risk deemed by the investigator to outweigh the benefit of continued treatment

#### 5.3.5 *Study Stopping Criteria*

- Any Grade 3 or greater serious adverse event in two or more patients considered to be related to uridine triacetate. Adverse events were classified using NCI CTCAE (v4.03).<sup>10</sup>
- Risk deemed by the investigator to exceed the benefit of continued treatment

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<sup>9</sup> This criterion was included due to reports of diarrhea in clinical trials in diabetic patients treated with a different formulation of uridine triacetate. However, as discussed later, the reported events in diabetic patients likely were due to underlying disease and/or an excipient in the formulation used in these trials.

<sup>10</sup> NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events

### 5.3.6 Endpoints

#### **Primary endpoint:**

For patients switching from oral uridine to oral uridine triacetate, the primary efficacy endpoint was stability of pre-determined hematologic parameters (neutrophil count, white blood cell count, or mean corpuscular volume) individualized by patient. Stability was defined as:

- Maintenance of a normal baseline value at Days 28 and 42
- Improvement in an abnormal baseline value or worsening no more than 15% to 30% at Days 28 and 42

For patients not previously treated with uridine, stability was defined as improvement in an abnormal baseline value or worsening no more than 15% to 30% at Days 28 and 42.

#### **Secondary endpoints:**

- Urine orotic acid and orotidine levels
- Plasma uridine levels

#### **Other endpoints:**

During the extension phase of the trial, growth and development assessments will be performed every 6 months.

### 5.3.7 Treatment

#### **Dosing and Method of Administration**

Patients were instructed to take uridine triacetate granules with or without food. The protocol did not limit what foods could be used for mixing the granules, stating only that the drug “may be mixed with foods or liquids that are easily swallowed.”

The minimum starting dose of uridine triacetate was 60 mg/kg/day for all patients. For patients who were switching from uridine to uridine triacetate, the dose could be escalated up to a maximum dose of 300 mg/kg/day. The minimum starting dose was based on published data that reported that total daily production of uridine by de novo synthesis in human subjects ranged from 4 millimoles to 5.6 millimoles of uridine per day.<sup>11,12</sup> The sponsor provided PK data in pediatric patients with mitochondrial diseases that indicated that the weight-based exposure ratio was 4-fold greater for uridine acetate compared to uridine. Based on this 4:1 ratio, the applicant calculated that a dose of  $\frac{(b)}{(4)}$  mg/kg/day of uridine triacetate (rounded up to 60 mg/kg/day) represented the minimum dose needed to compensate for blockage of uridine nucleotide synthesis and achieve physiologic levels of uridine.

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<sup>11</sup> Bono VH, Weissman SM, Frei F, The effect of 6-azauridine administration on de novo pyrimidine production in chronic myelogenous leukemia, *J Clin Invest* 1964; 43: 1486-1494.

<sup>12</sup> Weissman SM, Eisen AZ et al, The metabolism of ring-labeled orotic acid in man, *J Clin Invest* 1962; 41: 1546-1552.

Dose adjustments were recommended for weight changes of 10 percent or greater. Dose adjustments required for reasons other than body weight changes were allowed in 25% increments. Dose increases were allowed for the following:

- Increasing levels of urine orotic acid compared to baseline and/or level above normal or expected ranges for the patient
- Area under the curve (AUC for plasma uridine following uridine triacetate <85% of AUC following triacetate
- Evidence of worsening of the patient's primary efficacy endpoint ( $\geq 15\%$  change)
- The investigator deemed the patient's signs and symptoms of HOA were worsening.

Dose decreases were allowed if a patient experienced an unexplained Grade 3 or greater event of diarrhea or vomiting persisting for at least one week and considered to be related to treatment with uridine triacetate.

Patients received their first dose of uridine triacetate at the clinic site and were monitored for up to 6 hours afterwards.

### **Trial Schedule of Assessments**

The trial consists of three periods: baseline, main treatment, and treatment extension (see [Table 3](#)). Baseline assessments (Day 0) were performed while patients were still receiving uridine and included a medical history, physical examination, vital signs, height and weight, clinical laboratory assessments (CBC, chemistry, plasma uridine levels, urine orotic acid and orotidine levels), pregnancy testing (female patients of child-bearing potential), concomitant medications, and adverse events.

On Day 1 of the main treatment period, patients received uridine acetate and underwent additional assessments (vital signs, physical exam, plasma uridine, urine orotic acid and orotidine, concomitant medications, and adverse events). Day 28 and Day 42 assessments included vital signs, physical examination, growth and development, plasma uridine, urine orotic acid and orotidine, serum chemistry and hematology, concomitant medications, and adverse events.

The protocol noted that all physical examinations would include assessment of signs and symptoms commonly associated with HOA, including the following:

- Elevated urine orotic acid and orotidine
- Orotic acid crystalluria
- Renal tract obstruction
- Megaloblastic anemia unresponsive to vitamin B12 or folic acid
- Other hematologic abnormalities including lymphopenia, neutropenia, and/or thrombocytopenia
- Increased incidence or risk of infection
- Growth delays

- Mental-intellectual delays
- Diarrhea

Sampling times for plasma uridine at baseline and during the main treatment period were the following: within 30 minutes of the first morning dose of uridine or uridine acetate and then at 0.5, 1, 2, 4, 6 and 8 hours post-dosing.

During the treatment extension period, assessments are being performed every 6 months. Assessments will include physical examination, growth and development, vital signs, height and weight, serum chemistry and hematology, plasma uridine levels, urine orotic acid and orotidine levels, concomitant medications and adverse events.

Laboratory evaluations for uridine, orotic acid, and orotidine levels were performed at central laboratories; all other laboratory evaluations were performed locally at the study sites.

**Table 3: Study 001- Schedule of Assessments**

Procedures	Main Study				Treatment Extension
	Day 0* (Baseline)	Day 1	Day 28	Day 42	Every 6 months
Inclusion/Exclusion Criteria	X				
Informed Consent	X				
Demographic/ Baseline characteristics	X				
Medical History	X				
Vital Signs/ Weight & Height	X	X	X	X	X
Physical Exam	X	X	X	X	X
Pregnancy test	X				X
Uridine levels (plasma)	X	X	X		
Hematology	X		X	X	X
Chemistry	X		X	X	X
Orotic acid & orotidine levels (urine)	X	X	X	X	X
Concomitant Medications	→				
Adverse Event Monitoring	→				

\*Assessments were performed while patients were still on their usual dose of uridine (or prior to any treatment for Patient (b) (4))

Source: Study 401.13.001 Clinical Study Report dated December 17, 2014, Table 9.1

### 5.3.8 Concomitant Medications & Prohibited Medications

Concomitant medications were recorded at baseline and throughout the trial. No medications were prohibited during the trial.

### 5.3.9 Safety Considerations/Monitoring

Safety assessments for the trial included vital signs, laboratory tests (serum chemistry and hematology), pregnancy testing, concomitant medications, and adverse events. The protocol stated that adverse events and serious adverse events will be monitored during the trial period until they resolve or stabilize.

### 5.3.10 Statistical Analysis Plan

The applicant provided descriptive statistics for efficacy and safety analyses.

#### **Determination of Sample Size**

The trial sample size was not based on formal statistical considerations.

#### **Efficacy Analyses**

As noted earlier, the primary efficacy endpoint was stability (for patients switching from uridine to triacetate uridine) or improvement of a pre-determined hematological parameter (for the single patient who had not previously received uridine).

#### **Analysis of Efficacy Endpoints**

Abnormalities of hematologic parameters are hallmark features of HOA. As noted earlier in the overview of the natural history of HOA, improvement in hematologic parameters with uridine replacement therapy has been documented since the earliest case studies of patients with HOA. Additionally, growth and development are considered important clinical measures in pediatric patients with HOA.

The trial design for Study 001 meets the regulatory requirements for adequate and well-controlled trials as delineated in 21 CFR 314.126. The study objectives are clearly defined. The use of individualized hematologic endpoints is appropriate for evaluation of HOA due to the clinical heterogeneity of the disease. The design provides a reasonable assessment of treatment benefit in patients being switched from uridine to uridine triacetate because interruption or withdrawal of adequate uridine replacement therapy in patients with baseline abnormalities in hematologic parameters is known to result in worsening status within several weeks.<sup>13</sup> Thus, the six-week study duration should be sufficient to evaluate for clinical stability in patients who were previously treated with uridine.

The use of hematologic endpoints is also adequate to assess treatment benefit in treatment-naïve patients because spontaneous normalization of the pre-specified hematological endpoint(s) is not expected to occur based on the known natural history

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<sup>13</sup> Webster DR, Becroft DM et al., Hereditary Orotic Aciduria and Other Disorders of Pyrimidine Metabolism, *Scriver's Online Metabolic & Molecular Bases of Inherited Disease* 2001, Chapter 113: 1-86.

of the disease.<sup>14</sup> As discussed later, the duration of the main treatment portion of the trial may not have been sufficient to evaluate for *improvement* in hematologic parameters. Although the majority of case studies report improvement in hematologic parameters within the first few weeks of treatment, some patients required dose increases and/or treatment for several months before clinically significant changes in hematologic parameters were observed. Therefore, I reviewed efficacy data, including historical data and data from the extension phase of Study 001 to assess the impact of dose increases (all of the patients remained on the starting dose of 60 mg/kg/day for the 6-week main treatment portion of the trial) and/or a longer treatment period on hematologic status. In addition, I reviewed historical and trial extension phase growth data to assess the impact of uridine replacement therapy on growth in patients with a history of growth failure.

*Reviewer Comments:*

*This reviewer considers the use of patient-specific predetermined hematologic endpoints to be acceptable to evaluate for clinical stability or clinical improvement in patients treated with uridine triacetate who have clinically significant hematologic abnormalities. However, the applicant's definition of clinical stability (any deterioration in value was not more than 15% to 30% worse than the baseline value) for patients with baseline abnormal values is inadequate for identifying clinically significant deterioration in hematologic status. For example, a 15% decline in neutrophil count in a patient with a baseline neutrophil count of 600/mm<sup>3</sup> would not represent a clinically significant decline. However, a 30% decline in neutrophil count in that same patient represents a shift in clinical status from moderate to severe neutropenia. In addition, inpatient day-to-day variability is high for some hematologic indices (neutrophils) and low for other indices (MCV). Published analyses of hematology laboratory values in healthy adults reported about a 20% day-to-day individual variability in neutrophil count, which was attributed to the rapid turnover of neutrophils and sporadic margination of white cells compared to a 2% variability in MCV.<sup>15,16</sup> Therefore, the appropriate margin of change to establish clinical stability should be based on the expected range of inpatient variability for a particular hematologic parameter. As discussed later, based on the aforementioned laboratory references for adults (I did not find similar laboratory reference information for pediatric patients), the trial results for Study 001 indicated that patient hematologic parameters remained clinically stable during the main treatment phase of the trial.*

### 5.3.11 Patient Disposition

#### Patient Disposition

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<sup>14</sup> As discussed later, there is one case report of a patient diagnosed in adulthood with HOA who had episodes of severe anemia that spontaneously improved but he had persisting mild anemia.

<sup>15</sup> Lacher DA, Barletta J, Hughes JP, Biological Variation of Hematology Tests Based on the 1999-2002 National Health and Nutrition Examination Survey, *Natl Health Stat Report* 2012; (54): 1-10.

<sup>16</sup> Winkel P, Statland BE et al., Within-day physiologic variation of leukocyte types in healthy subjects as assayed by two automated leukocyte differential analyzers, *Am J Clin Pathol* 1981; 75(5): 693-700.

All four patients completed the main treatment phase of the trial and are continuing treatment in the extension phase.

### 5.3.12 Protocol Violations and Deviations

There were no reported protocol violations for the trial. Two patients had a “Planned Protocol Deviation” during the extension phase of the trial to allow for additional PK sampling following dose increases (see [Section 4.4.3](#)). Five protocol deviations were reported for 3 patients, including PK sampling performed outside the specified time window (4 patients), and procedure performed outside specified time window (one patient). [Table 4](#) summarizes protocol deviations

**Table 4: Study 001- Protocol Deviations**

Patient ID	Study Visit	Protocol Deviation Description
(b) (4)	Baseline	Baseline pre-dose plasma sample drawn 15 minutes after uridine dose
	Day 28	PK samples 3 -7 drawn 30 minutes after specified time point
	Day 0	Patient given initial study drug dose in increments over one hour (b) (4) had difficulty taking medication); PK sampling time based on when patient completed dosing
	Day 28	PK samples 3 -7 drawn 30 minutes after specified time point

*Reviewer Comment:*

*The protocol deviations did not impact the interpretability of the trial data.*

### 5.3.13 Patient Compliance

#### Compliance

Treatment compliance was assessed by a dosing log completed by the patient or guardian. The dosing log was reviewed by the physician at each visit. Patient compliance was reported as 100% for all patients through Day 42 of the trial.

#### Dose Adjustments

After approximately 4 months of treatment, uridine triacetate dosing was increased from 60 mg/kg/day to 120 mg/kg/day for Patients (b) (6) and (b) (6), due to persistent elevated MCV values. The applicant noted that uridine exposure increased in both patients following the dose increase.

After 6 months of treatment, uridine triacetate dosing was increased from 60 mg/kg/day to about 95 mg/kg/day for Patient (b) (6), due to an elevated orotic acid level. (b) (6) orotic acid value returned to the baseline value following the dose increase.

*Reviewer Comment:*

*See Section 4.4.3 for further discussion of inter-patient differences in PK parameters.*

### 5.3.14 Review of Study 001 Results

#### A. Demographics

[Table 5](#) summarizes patient demographics and clinical disease status prior to administration of uridine triacetate.<sup>17</sup> Patient ages were (b) (6) and (b) (6) years at study entry. Age at time of diagnosis ranged from 1.5 years to 10.4 years. One patient (Patient (b) (6)) had a low neutrophil count (470/mm<sup>3</sup>) and an elevated urine orotic acid level at baseline. One patient (Patient (b) (6)) had normal hematologic values at baseline. Two patients who are (b) (6) had macrocytosis at baseline (Patients (b) (6) and (b) (6) however, their baseline hemoglobin and hematocrit values were normal. At baseline, two patients had growth delays (Patients (b) (6) and (b) (6). Of note, all of the patients had a diagnosis of growth delay in their medical record and/or historical growth measures consistent with a growth delay (i.e., height and/or weight  $\leq 5^{\text{th}}$  percentile for sex and age or clinically significant decrease in height or weight velocity) in infancy; two of the patients also had a history of developmental delays. Two patients had a history of other clinical features associated with HOA; Patient (b) (6) had congenital anomalies and Patient (b) (6) had a history of chronic diarrhea.

Two patients (Patients (b) (6) and (b) (6)) had confirmed gene mutations for HOA. The (b) (6) (Patients (b) (6) had no genetic mutations by DNA sequencing analysis. The applicant noted that the genetic testing performed would not detect other types of genetic mutations (e.g., promoter mutations) and that the patients had clinical manifestations consistent with HOA.<sup>18</sup>

#### *Reviewer Comments:*

*The patients in Study 001 illustrate the heterogeneity of HOA. All of the patients presented with elevated orotic acid levels and growth delays; otherwise, clinical manifestations varied from patient to patient. Regarding the negative genetic testing results for the (b) (6) this reviewer agrees that the (b) (6) clinical presentations are sufficient to establish the diagnosis of HOA to the exclusion of other disorders. Although there are other disorders that can cause orotic aciduria, none of them are associated with macrocytosis.*

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<sup>17</sup> Abnormal values are listed in **bold red italic** font.

<sup>18</sup> Applicant's Response to FDA Information Request submitted May 29, 2015.

**Table 5: Study 001- Baseline Patient Demographics and Disease Severity**

	Patient		
<b>Parameter</b>	(b) (4), (b) (6)		
<b>Prior Uridine Dose</b>			
<b>Duration of Uridine Treatment (yrs)</b>			
<b>Age (years)</b>			
<b>Age at diagnosis (years)</b>			
<b>Sex</b>			
<b>Race</b>			
<b>WBC Count</b>			
<b>Neutrophil Count (<math>10^3/m^3</math>)</b>			
<b>Neutrophil Percent</b>			
<b>MCV (fL)</b>			
<b>Hemoglobin (g/dL)</b>			
<b>Orotic acid</b>			
<b>Height – cm (Height percentile for age)</b>			
<b>Weight- kg (Weight percentile for age)</b>			
<b>History of Growth Delay/Abnormal Growth</b>			
<b>History of Developmental Delay(s)</b>			
<b>Other HOA Clinical Features</b>			
<b>Patient- specific Endpoint</b>			

MCV= mean corpuscular volume  
 Baseline values were obtained on Day 0 (1 day prior to starting uridine triacetate)

### A. Concomitant Medications

Concomitant medications are listed in [Table 6](#).

**Table 6: Study 001- Concomitant Medications**

Patient ID	Concomitant Medications
(b) (6)	None
	Multivitamins, iron, magnesium, cetirizine Topical medications: hydrocortisone, tretinoin, dapsone, adapalene, ketoconazole
	Multivitamins, polyethylene glycol
	Multivitamins

### B. Review of Efficacy

#### Efficacy Summary

Based on my review of the totality of evidence, there appears to be sufficient evidence of the efficacy of uridine triacetate for the treatment of hereditary orotic aciduria.

Published case studies in 18 patients document clinically significant improvements in hematologic status and/or growth in HOA patients when treated with adequate doses of uridine. Conversely, some of the case studies also documented a decline in clinical status with discontinuation of treatment or if dosing was decreased. Reductions in orotic acid levels were typically observed within the first week of treatment. The time to treatment response in patients with anemia varied from less than 2 weeks to several months. A similar variability in time to response was observed for white cell abnormalities. Growth delays, most commonly poor weight gain, improved over a span of several months. The majority of patients received the same dose throughout treatment; some patients required a dose increase to achieve their optimal response.

The clinical experience of the three patients who were treated with uridine prior to enrolling in Study 001 is consistent with findings in the published literature. Namely, the time to therapeutic response and the dose needed to produce a therapeutic response varied. However, all of the three patients who were previously treated with uridine demonstrated improvement in growth while they were being treated with uridine. Specifically, height velocity increased in all three patients after starting uridine. In addition, one patient (Patient (b) (6)) experienced a clinically significant increase in (b) (6) neutrophil count after starting uridine. The treatment effect of uridine on the hematologic parameters of the other two patients is less clear. Patient (b) (6) did not have sufficient historical data available to assess for changes in (b) (6) hematologic status. Patient (b) (6) had an elevated mean corpuscular volume without anemia that remained unchanged after treatment with uridine. (b) (6) was treated with lower doses of uridine than the other two patients. Therefore, in (b) (6) case, the apparent lack of hematologic response with uridine treatment may have been due to underdosing.

Based on the primary efficacy findings for Study 001 alone, there is not sufficient evidence to support efficacy for uridine triacetate. However, at Month 6, two of the patients who transitioned from uridine experienced improvement in their hematologic and/or growth status and the third patient remained stable; no improvement was observed in the treatment-naïve patient's clinical status. All of the patients maintained stable urine orotic acid levels up through Month 6 of treatment.

All three patients who transitioned from uridine maintained stable hematologic parameters after 6 weeks of treatment. Patient (b) (6) maintained (b) (6) neutrophil count, indicating a sustained response to uridine replacement therapy after switching from uridine to uridine triacetate. There were insufficient data to confirm whether Patient 01- (b) (6) had a low white blood cell count prior to initiation of uridine replacement therapy as reported, therefore this patient was not included in my analysis of the primary endpoint. (b) (6) Patient (b) (6) had an elevated mean corpuscular volume at baseline that remained unchanged. Patient (b) (6), the treatment-naïve patient and (b) (6) of Patient (b) (6) did not experience an improvement in (b) (6) mean corpuscular volume. The hematologic findings for the (b) (6) may be due to inadequate dosing; PK data demonstrated that their drug exposure was lower compared to the first two patients.

Of note, the three prepubertal patients received dose increases during the extension phase of the trial. Patient (b) (6) received a dose increase at Month 6 due to an elevation of (b) (6) orotic acid level from its baseline value; the orotic acid level returned to the baseline value following the dose increase. Patient (b) (6) experienced increases in height and weight z-scores, and height velocity and weight velocity z-scores at Month 6 compared to baseline. At Month 6, (b) (6) also achieved a neutrophil count that was just below the lower limit of normal for age (b) (6) highest recorded neutrophil count) and a normal neutrophil percent value.

Patients (b) (6) received dose increases at Month 4 due to persisting elevated MCV values. Their MCV values remained unchanged from baseline at Month 6. Patient (b) (6) experienced an increase in weight and weight velocity z-scores at Month 6. Patient (b) (6) experienced a decrease in weight z-score but (b) (6) weight velocity z-score was stable. Patient (b) (6) was maintained on the same dose of uridine triacetate up through Month 6. (b) (6) WBC count remained normal and (b) (6) height and weight measurements were stable.

Thus, although treatment with uridine triacetate appears to be efficacious in this population, questions remain regarding the optimal dosing of uridine triacetate needed to achieve and maintain the desired hematologic or growth responses in some patients. Therefore, I recommend that the applicant continue to collect efficacy data for total duration of 2 years as an extension study as a postmarketing commitment. Data

collection should include information on any dose adjustment made during the data collection period.

### **1. Primary efficacy analysis**

The primary efficacy endpoints for Study 001 were stability (for the three patients who had transitioned from uridine) or improvement (for the newly diagnosed patient) of patient-specific hematologic parameters. The applicant provided historical data documenting the presence of hematologic abnormalities in three patients prior to initiation of uridine replacement therapy. There were insufficient data to confirm whether Patient (b) (6) had a low white blood cell count prior to initiation of uridine replacement therapy as reported, therefore this patient was not included in my analysis of the primary endpoint.

After 6 weeks (Day 42) of treatment with uridine triacetate, two patients (Patient (b) (6) and Patient (b) (6)) who transitioned from uridine remained clinically stable. Patient (b) (6) whose neutrophil count had increased while being treated with uridine, experienced a 15% decrease in neutrophil count, meeting the protocol-specified definition of clinical stability. Patient (b) (6) also remained clinically stable unchanged after transitioning from uridine, with a change in (b) (6) mean corpuscular volume (MCV) of -1%. However, it is unclear whether this finding represents a treatment effect because the patient's MCV values during treatment with uridine and uridine triacetate have remained essentially unchanged from MCV values obtained prior to the patient starting uridine replacement therapy.

No improvement in hematologic status was demonstrated in the treatment-naïve patient (Patient (b) (6) whose MCV value did not change from baseline to Week 6.

Thus, based on the primary efficacy data alone, there are insufficient data to support efficacy. However, ad hoc analyses of hematologic and growth data demonstrate that the three patients who transitioned from uridine to uridine triacetate remained clinically stable or clinically improved after 6 months of treatment with uridine triacetate. No improvement was observed in the treatment-naïve patient's clinical status.

### **2. Ad Hoc Analyses**

#### **a. Hematologic Parameters**

The applicant provided historical data documenting the presence of hematologic abnormalities in three patients prior to initiation of uridine replacement therapy. There were insufficient data to confirm whether Patient (b) (6) had a low white blood cell count prior to initiation of uridine replacement therapy as reported.

*Reviewer Comments:*

*As discussed earlier, the applicant's definition of clinical stability (any deterioration in value not more than 15% to 30% worse than the baseline value) for patients with baseline abnormal values was too broad to identify clinically significant changes in hematologic status in the enrolled patients. I analyzed historical data to assess the severity of patients' hematologic disease prior to receiving any form of uridine replacement therapy and also used laboratory references for inpatient variability as discussed earlier.*

- **Patient** (b) (6)

Patient (b) (6) had historical neutrophil count values of 360/mm<sup>3</sup> to 470/mm<sup>3</sup> (normal range for age is 1600/mm<sup>3</sup> to 7100/mm<sup>3</sup>) and neutrophil percent values of 4% (normal range for age is 38% to 78%).<sup>19</sup> After starting treatment with uridine at age 20 months, (b) (6) neutrophil count increased to 580/mm<sup>3</sup> to 590/mm<sup>3</sup> and neutrophil percent increased to 13%. Uridine dosing was approximately 200 mg/kg/day. (b) (6) baseline neutrophil count was 950; neutrophil percent was 21%. The patient was transitioned to uridine triacetate with dosing of 60 mg/kg/day. After 6 weeks of treatment with uridine triacetate, (b) (6) neutrophil count decreased to 810 (15% decrease), within the pre-specified margin of 15% to 30% worsening from baseline; (b) (6) neutrophil percent value increased to 23%. At Month 6, (b) (6) uridine triacetate dose was increased to about 95 mg/kg/day due to persistent elevation of (b) (6) orotic acid level. At Month 6, (b) (6) neutrophil count had increased to 1400, just below the lower limits of normal (normal range is 1500/mm<sup>3</sup> to 8000/mm<sup>3</sup>; (b) (6) neutrophil percent value was 31%, within the normal range for age (normal range is 26% to 48%).

- **Patient** (b) (6)

Patient (b) (6) had a normal WBC count (WBC count was 7.7) just prior to starting treatment with uridine at age 10 years 11 months.<sup>20</sup> No other historical hematologic data points were available for this patient. (b) (6) WBC count remained normal while on uridine. Uridine dosing was 200 mg/kg/day. The patient was transitioned to uridine triacetate with dosing of 60 mg/kg/day. (b) (6) WBC count was essentially unchanged from baseline (WBC count was 7.8) to Week 6 (WBC count was 7.4) and Month 6 (WBC count was 6.7)

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<sup>19</sup> Reference ranges for hematologic values are age specific and also vary slightly by lab site. Thus, the reference range for the patient's historical lab values refers to the child's age at the time values were obtained. I listed the age-specific laboratory reference ranges provided in the clinical study report.

<sup>20</sup> Patient (b) (6) presented with a number of non-hematologic clinical findings of HOA, including growth and developmental delays, and chronic diarrhea (a disease complication described in two case reports in the literature). These clinical findings appear to be the principal reasons for the patient being started on uridine. The medical history entry in the patient's case report form reports the growth delay as resolved within one year and the chronic diarrhea as resolved within 2 to 3 years following initiation of treatment with uridine.

- **Patient** (b) (6)

Patient (b) (6) had a historical MCV value of 106.6 fL at age 13 months (upper limit of normal for age is 90 fL). (b) (6) started treatment with uridine at age 3 years 2 months. (b) (6) initial uridine dose was 50 mg/kg/day; dose was subsequently increased to 100 mg/kg/day at age 3 years and then to 150 mg/kg/day at age 3 years 8 months. (b) (6) MCV remained abnormal while on uridine. The patient was transitioned to uridine triacetate with an initial dose of 60 mg/kg/day. Based on PK data that demonstrated lower exposures compared to the first two patients and continued elevation of (b) (6) MCV, the patient's dose was subsequently increased to 120 mg/kg/day after approximately 4 months of treatment. The patient's MCV values were essentially unchanged from baseline (MCV 109.9 fL) to Week 6 (MCV was 108 fL) and Month 6 (MCV was 109.7 fL).

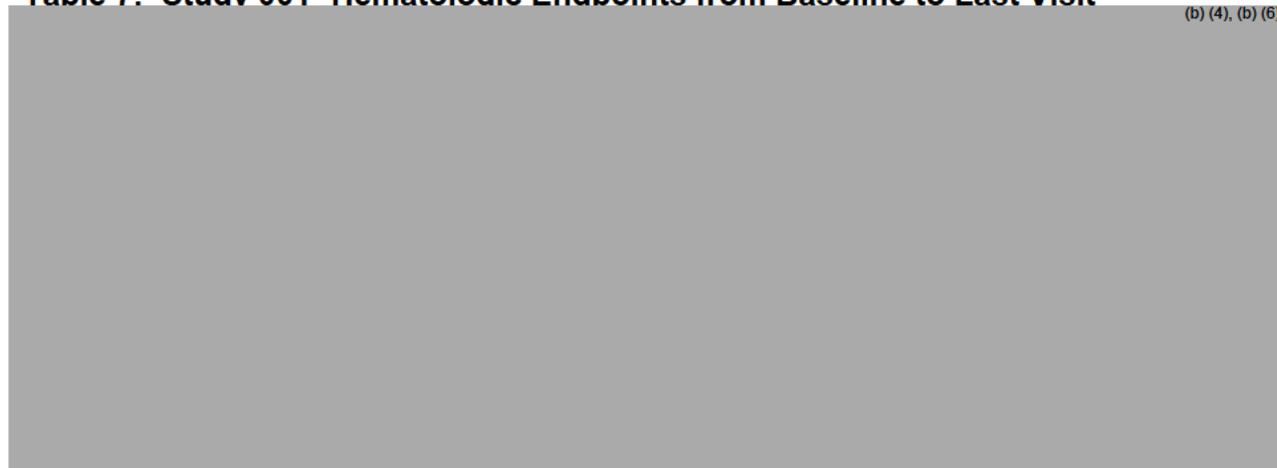
- **Patient** (b) (6)

Patient (b) (6) had historical MCV values of 109.8 fL and 111.7 fL at age 7 months and 12 months (upper limit of normal for children ages 6 months to 3 years is 90fL), respectively. The patient was started on uridine triacetate with an initial dose of 60 mg/kg/day. Based on PK data that demonstrated lower exposures compared to the first two patients and continued elevation of (b) (6) MCV, the patient's dose was subsequently increased to 120 mg/kg/day after approximately 4 months of treatment. The patient's MCV values were essentially unchanged from baseline (MCV 114.6 fL) to Week 6 (MCV was 113.4 fL) and Month 6 (MCV was 113.9 fL).

[Table 7](#) summarizes findings for hematologic parameters for each patient.

**Table 7: Study 001- Hematologic Endpoints from Baseline to Last Visit**

(b) (4), (b) (6)



\*Reference ranges are age specific. Note that MCV reference ranges for Patients (b) (6) differ slightly.

*Reviewer Comments:*

*The three patients who transitioned from uridine nominally met their pre-specified individualized efficacy endpoints of clinical stability while being treated with uridine triacetate. However, there was only clear evidence of hematologic improvement in response to prior treatment with uridine for one patient: Patient (b) (6). In the case of the other two patients transitioned from uridine, there was either no clear evidence of a hematologic abnormality prior to treatment with uridine (Patient (b) (6)) or no evidence of hematologic improvement following treatment with uridine (Patient (b) (6)).*

*The clinical experience of Patient (b) (6) provides the most compelling evidence for efficacy for a hematologic parameter. Note that this patient had severe neutropenia (neutrophil count <500) prior to starting on uridine replacement therapy. (b) (6) neutropenia improved with treatment, evidenced by a neutrophil count of 950 at baseline. Most significantly, (b) (6) neutrophil count increased to 1400 (47% increase; normal range 1500-8000) and (b) (6) neutrophil percent value was normal after 6 months of treatment with uridine triacetate at 60 mg/kg/day. The applicant noted that the Month 6 neutrophil count was the highest ever observed for this patient.*

*The other three patients had normal or mildly abnormal hematologic values. There were no data available to confirm whether Patient (b) (6) ever had hematologic manifestations of HOA. Thus, it is not possible to interpret hematologic findings for this patient.*

*It is also difficult to interpret findings for Patients (b) (6) and (b) (6) since the MCV values for these patients appear to have been stable prior to initiation of uridine replacement therapy. In addition, the MCV values for Patient (b) (6) had not improved after almost four years of treatment with uridine at 150 mg/kg/day. This reviewer notes that dosing and duration of treatment needed to observe a treatment response on hematologic parameters is variable. Some patients in published case studies experienced clinically significant improvement of hematologic parameters within two or three weeks of treatment with uridine. However, other patients did not improve until their uridine dose was increased and/or until they had been treated for several months. Case studies also illustrate that the dosing needed to achieve a hematologic response may differ from the dose needed for growth. Thus, Patient (b) (6) may not have had a hematologic response while (b) (6) was treated with uridine due to underdosing (note that (b) (6) was being treated a uridine dose of 150 mg/kg/day whereas Patients (b) (6) received doses of 200 mg/kg/day). Similarly, the lower exposures observed in the (b) (6) compared to the patients at the other clinical site during the main treatment phase of the trial suggest that the initial uridine triacetate dosing for the (b) (6) may not have been adequate. In addition, the 8-week period from Month 4 when their uridine triacetate doses were increased to Month 6 may not have been long enough to observe for a treatment effect on MCV parameters.*

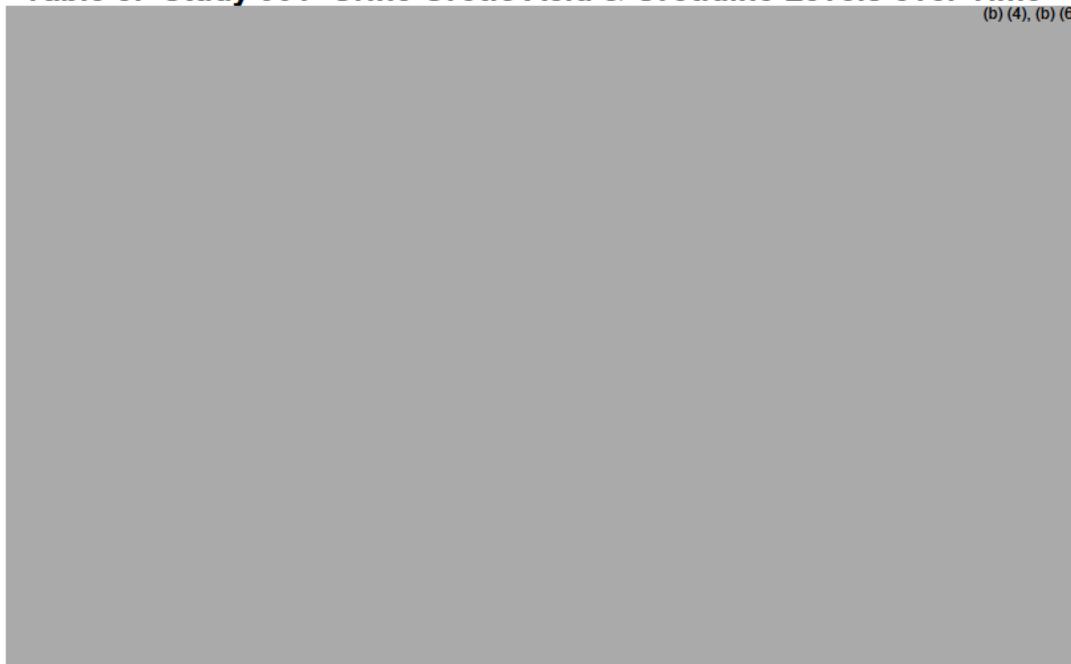
**b. HOA Biomarkers (Orotic acid and orotidine)**

Urine orotic acid and orotidine levels were within normal limits at baseline for all patients except Patient (b) (6) who had a urine orotic acid level just above the reference range at baseline. Patient 0 (b) (6) continued to have a slightly elevated urine orotic acid level at Week 6. Based on further elevation of (b) (6) orotic acid level at Month 6, (b) (6) uridine triacetate dose was increased to 95 mg/kg/day. The applicant notes that Patient (b) (6) urine sample for biomarkers was not sent to the protocol-specified laboratory for biomarker assessments ( (b) (4) ) for the Month 6 assessment and that only the orotic acid assessment was performed. No additional dose adjustments were made. At Month 11 of treatment, additional unscheduled assessments of orotic acid and orotidine levels revealed biomarker levels that were similar to the patient's baseline and Week 6 values. The other patients maintained normal urine orotic acid and orotidine levels at Week 6 and up to Month 6 of the extension phase.

[Table 8](#) summarizes orotic acid and orotidine findings for each patient.

**Table 8: Study 001- Urine Orotic Acid & Orotidine Levels over Time**

(b) (4), (b) (6)



NA= not available; ND= not done

\*Lab testing done at a different laboratory for Patient (b) (6) Month 6 orotic acid level.

*Reviewer Comments:*

*There is a clear pharmacodynamic response in patients treated with uridine replacement therapy. Three of the four patients achieved normal urine orotic acid levels when they were treated with uridine and maintained normal levels when they were transitioned to uridine triacetate. Patient (b) (6) who had the highest urine orotic acid*

*level prior to starting uridine replacement therapy, achieved near normal levels on uridine and these levels remained stable after transitioning to uridine triacetate.<sup>21</sup> Note that during treatment with uridine, Patient (b) (6) experienced an increase in (b) (6) urine orotic acid level while (b) (6) was on a drug holiday; the level returned to baseline when (b) (6) restarted treatment. Patient (b) (6) had orotic acid levels that fluctuated between normal and abnormal prior to starting uridine replacement therapy. (b) (6) levels have remained within the normal range since starting uridine triacetate. [Figure 4](#) presents the individual patients' urine orotic acid levels over time, starting from prior to initiation of uridine replacement therapy up through 6 months of treatment with uridine triacetate.*

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<sup>21</sup> Given that the patient's orotic acid and orotidine results from (b) (4) were stable, the laboratory results from the outside laboratory may reflect differences in sample processing and/or reference ranges.

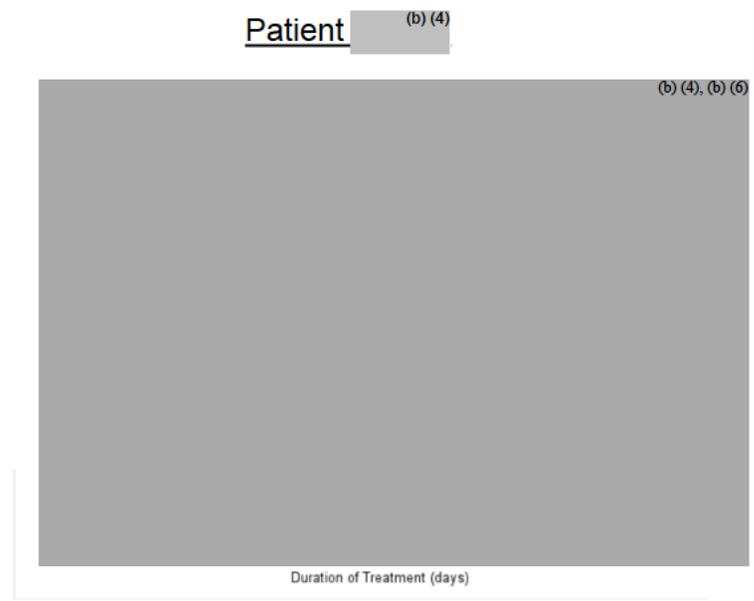
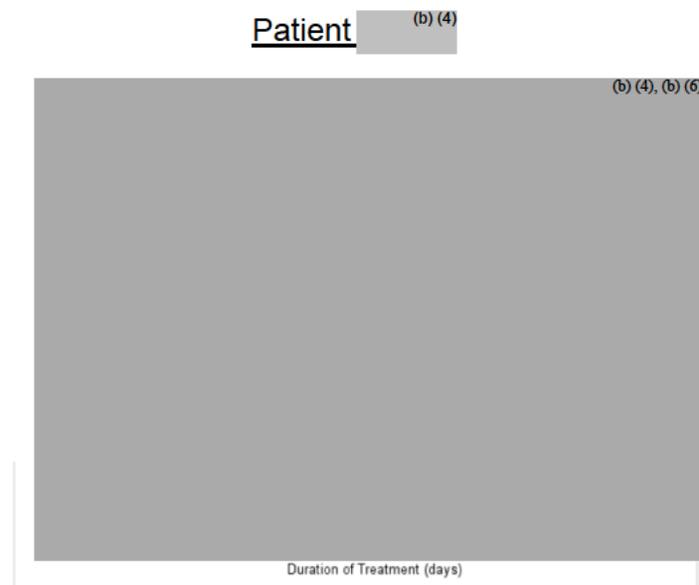
**Figure 4: Study 001- Individual Patient Urine Orotic Acid Levels over Time**



— = Uridine started    — = Uridine triacetate started  
- - - = upper limit of normal values for urine orotic acid

Source: NDA 208169 Statistical Review dated June 16, 2015

**Figure 4: Study 001- Individual Patient Urine Orotic Acid Levels over Time (cont'd)**



— = Uridine started    — = Uridine triacetate started  
- - - = upper limit of normal values for urine orotic acid

Source: NDA 208169 Statistical Review dated June 16, 2015

### c. Growth Parameters

[Table 9](#) summarizes growth data for Study 001, including any available medical history or historical clinical growth measurements (height and weight). As noted earlier, all patients had a history of poor height and/or weight gain prior to starting uridine replacement therapy. Three patients experienced improvements in height and weight following initiation of uridine replacement therapy; one patient (Patient (b) (6)) achieved normal height and weight measurements prior to starting uridine replacement therapy. Height velocity increased in all patients following initiation of uridine replacement therapy, consistent with catch-up increases in growth.

At entry to Study 001, weight and height measurements were at or below the lower limit of normal for age (z-score -1.6; 5<sup>th</sup> percentile) for Patients (b) (6) and (b) (6). Baseline height and weight measurements were within the normal range for Patients (b) (6) and (b) (6). At Month 6, growth results varied. Height and weight measurements increased from baseline to Month 6 in all four patients. However, height z-scores for age were essentially unchanged for the three pre-pubertal patients (I excluded Patient (b) (6) the (b) (6) year old patient, from analyses of trial growth data). Patient (b) (6) height velocity increased from the 10<sup>th</sup> percentile to the 30<sup>th</sup> percentile, consistent with catchup growth in height. Height velocity decreased to less than the 25<sup>th</sup> percentile in Patients (b) (6) and (b) (6). Patients (b) (6) and (b) (6) experienced increases in weight z-scores and weight velocity for age. Patient (b) (6) experienced a decrease in (b) (6) weight z-score and (b) (6) weight velocity for age.

#### *Reviewer Comments:*

*Population-based references have been developed for US children, with height and weight measurements between the 5<sup>th</sup> and 97<sup>th</sup> percentile for age representing the normal growth range for age. In addition to evaluation of height and weight measures at a specific point in time, measurement of growth (growth velocity) is another important assessment of whether a child is growing normally. Reference standards have also been constructed for height and weight velocity for pre-pubertal and pubertal children. Some variation in growth velocity is normal; however, a large decrease or increase in growth velocity may indicate growth failure or catch-up growth, respectively. A child whose growth velocity remains constant at the 10<sup>th</sup> percentile for age will progressively decline in height or weight for age.<sup>22</sup>*

*All of the patients in the trial had a history of significant growth delay. I assessed the patients' height, height velocity, weight and weight velocity over time, starting with data obtained before the patients were started on uridine replacement therapy up through the Month 6 growth data for Study 001.*

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<sup>22</sup>Rogol AD, Clark PA, Roemmich JN, Growth and pubertal development in children and adolescent: effect of diet and physical activity, *Am J Clin Nutr* 2000; 72(suppl): 521S-528S.

I used an anthropometric calculator developed by (b) (4) to calculate age-based height and weight z-scores and height and weight percentiles for all 4 patients. The calculator formulas are based on World Health Organization international growth standards for age and sex for children from birth up to 5 years (the recommended growth standards for US as well as international population for the birth-5 years age range) and National Center for Health Statistics standards for older children.<sup>23, 24</sup>

Age-based reference ranges for US children have been developed for both height and weight velocity. Kelly et al. recently published age-based references for height velocity based on approximately 1500 children aged 5 to 19 years enrolled in the Bone Mineral Density in Childhood Study (BMDCS).<sup>25</sup> The (b) (4) calculator included a formula based on the BMDCS reference data to calculate height velocity for children ages 5 years and older. I used the (b) (4) calculator to calculate historical height velocity for Patient (b) (6) from age (b) (6) years up through puberty.

I used growth velocity reference value tables developed by Baumgartner et al. to estimate height velocity and weight velocity for Patients (b) (6). The tables provide age- and gender-based reference ranges for height and weight gain for US children in 6 month increments for the 3<sup>rd</sup>, 5<sup>th</sup>, 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup>, 95<sup>th</sup>, and 97<sup>th</sup> percentiles. The reference values are based on data collected for the Fels Longitudinal Study, an epidemiological study of height and weight growth in 818 healthy white US children from a limited geographic area. The data collection period for the study was 1929 to 1978. The authors of the reference table noted that the Fels Longitudinal Study data agreed with 1977 National Center for Health Statistics (NCHS) growth data used to construct the Centers for Disease Control and Prevention (CDC) growth charts for children.<sup>26</sup> In 2000, the Center for Disease Control and Prevention (CDC) published revised growth charts for children that included additional data from national and state health databases conducted in the 1980's and 1990's.

One potential concern in using the Baumgartner reference tables is that growth patterns have changed over time. However, the CDC noted that the 2000 revised growth charts for children between the ages of 2 and 14 years were similar to the earlier versions.<sup>27</sup> Thus, there do not appear to have been any significant secular shifts in growth patterns

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<sup>23</sup> The hospital has developed three calculators for different populations: Canadian children, US children, and children with Turner, Noonan, Russell-Silver, Prader-Willi, Down syndrome (disorders associated with short stature) :

<http://www.bcchildrens.ca/Services/SpecializedPediatrics/EndocrinologyDiabetesUnit/ForProfessionals/AanthropometricCalculators.htm>

<sup>24</sup> <http://www.who.int/childgrowth/standards/en/>

<sup>25</sup> Kelly A, Winer KK, et al., Age-based reference ranges for annual height velocity in US children, *J Clin Endocrinol Metab* 2014; 99(6): 2104-2112.

<sup>26</sup> Baumgartner RN, Roche AF, Himes JH, Incremental growth tables: supplementary to previously published charts, *Am J Clin Nutr* 1986; 43: 711-722.

<sup>27</sup> [http://www.cdc.gov/nchs/data/series/sr\\_11/sr11\\_246.pdf](http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf)

for children in this age range since the time that the Baumgartner reference tables were constructed.

For all growth velocity estimations, I rounded the patients' ages up to the nearest half or whole year (e.g., age 6.3 years was rounded up to 6.5 years) for comparison to the reference table. There were insufficient data points to be able to use the growth tables to estimate historical height velocity for Patients (b) (6). All calculated weight velocity values were rounded to the nearest decimal fraction (e.g., 0.56 kg was rounded to 0.6 kg) for comparison to the reference table. [Table 9](#) lists the nearest corresponding z-score and percentile (or z-score and percentile interval) for the calculated weight velocity value. If the calculated weight velocity was within 0.1 kg of a listed value, I assigned the corresponding z-score and z-score percentile to the patient's weight velocity. For example, the calculated weight velocity for Patient (b) (6) at Month 6 matched the reference value corresponding to a weight velocity z-score of 0.7 (75<sup>th</sup> percentile) for boys for the 6-month interval between age (b) (6) years (patient's age at baseline) and (b) (6) years (patient's age at (b) (6) Month 6 study visit). All other calculated weight velocity values fell between listed reference values and therefore I provided the corresponding z-score and z-score intervals. For example, Patient (b) (6) gained 1.6 kg from age (b) (6) years (patient's age at baseline) and (b) (6) years (patient's age at (b) (6) Month 6 study visit), which fell between the 50<sup>th</sup> and 75 percentile values for weight gain (1.3 kg and 1.8 kg, respectively) for boys for the 6-month interval between age (b) (6) years and (b) (6) years.

(b) (6)



Growth information for each patient is summarized below:

- **Patient** (b) (6)

Patient (b) (6) began treatment with uridine 1.86 grams/day (200 mg/kg/day) at age 17 months. (b) (6) uridine dose was increased for weight at age 4.3 years and age 5.3 years.

Patient (b) (6) has a medical history of failure to thrive since age 4 months. Historical height and weight values were available from birth for Patient (b) (6). Patient's height (z-score -0.6; 25<sup>th</sup> percentile) and weight (z-score -1.4; 7<sup>th</sup> percentile) z-score values were within normal range for age at birth. However, both height and weight z-scores declined to lower than -3 (<1<sup>st</sup> percentile) by age 4 months. The patient's height z-score increased from -3.1 at age 18 months to -2.6 at age 28 months, then ranged from -3.5 to -3.6 from ages 3.2 years to age (b) (6) years (patient's age at study entry).

The patient's weight z-score was -3 at age 4 months and -2.9 at age 18 months. (b) (6) weight z-score declined to -3.4 at age 28 months, then ranged from -3.3 to -3.8 from ages 2.3 years to age (b) (6) years (patient's age at study entry). From age 2.5 years to 5 years, (b) (6) weight velocity ranged between the 10<sup>th</sup> and 25<sup>th</sup> percentile.

During Study 001, the patient's height z-score increased from -3.5 at baseline to -3.4 at month 6 of treatment (age (b) (6) years). The patient's height velocity z-score increased

from baseline (z-score was -1.4; ~10<sup>th</sup> percentile) to Month 6 (z-score was -0.4; ~30<sup>th</sup> percentile).

The patient's weight z-score increased from -3.8 at baseline to -3.6 at Day 42 and -3.3 at month 6 of treatment (age (b) (6) years). Weight velocity increased from baseline (z-score ~ 10<sup>th</sup> percentile) to Month 6 (z-score was between the 50<sup>th</sup> and 75<sup>th</sup> percentile).

[Figure 5](#) is a chronological summary of Patient (b) (6) height and weight z-scores, with their relationship to initiation and subsequent changes in the patient's uridine replacement therapy regimen.

(b) (6), (b) (4)



*Reviewer Comments:*

*I reviewed trends in Patient (b) (6) height and weight z-scores following initiation of uridine replacement therapy. The patient's height z-scores improved after (b) (6) started treatment with uridine at age 18 months then declined at about 3 years of age. Note that the patient's uridine dose was not adjusted for weight until the patient was (b) (6) years. (b) (6) weight z-scores declined from age 18 months (z-score was -2.9) to age 3 years (z-score was -3.7) then, following the dose adjustment for weight, improved from age 4.3*

years (z-score was -3.7) to age 5.3 (z-score was -3.3). These trends indicate that the patient's growth improved with uridine replacement therapy once the patient was administered an adequate dose of uridine.

Similarly, during Study 001, the patient's weight percentile and weight velocity z-scores (and z-score percentiles) improved from baseline to Month 6, consistent with catch-up growth during this period.

- **Patient** (b) (6)

Patient (b) (6) began treatment with uridine 200 mg/kg/day at age 11 years. (b) (6) uridine dose was increased for weight at age 13.3 years and age (b) (6) years.

The medical history for Patient (b) (6) documents growth delays from about age 1 year to 12 years); historical height and weight values were available from age 6.5 years. From age 7 years to 12 years, the patient's height z-scores were within normal range for age at all time points, but declined from 1 (85<sup>th</sup> percentile) to -0.3 (35<sup>th</sup> percentile). (b) (6) weight z-scores ranged from 2.2 (98<sup>th</sup> percentile) to 1.2 (88<sup>th</sup> percentile), corresponding to weight values in the overweight to obese range.

At age 10.5 years (about 6 months prior to starting uridine), (b) (6) height velocity z-score was -1.5 (7<sup>th</sup> percentile). At age 11.3 years (about 4 months after starting uridine), (b) (6) height velocity z-score was -2.5 (<1<sup>st</sup> percentile). At ages 12 and 13 years, (b) (6) height velocity z-score increased up to approximately -0.5 (30<sup>th</sup> percentile); at age 14 years, (b) (6) height velocity z-score was 0.2 (60<sup>th</sup> percentile). (b) (6) post-pubertal height z-scores and weight z-scores were -0.9 (16<sup>th</sup> percentile) and 1.1 (86<sup>th</sup> percentile).

During Study 001, (b) (6) baseline height z-score was -0.9 (16<sup>th</sup> percentile) and (b) (6) weight z-score was 1.1 (86<sup>th</sup> percentile). At month 6, (b) (6) height z-score was -0.5 (30<sup>th</sup> percentile) and (b) (6) weight z-score was 1.3 (91<sup>th</sup> percentile).

[Figure 6](#) is a chronological summary of Patient (b) (6) height and weight z-scores, with their relationship to initiation and subsequent changes in the patient's uridine replacement therapy regimen.

**Figure 6: Patient (b) (4) - Height & Weight Z-scores over Time**



*Reviewer Comments:*

*Because this patient is post-pubertal and did not have low weight at baseline (b) (6) weight percentiles throughout (b) (6) clinical course corresponded to a weight in the overweight to obese range), treatment with uridine triacetate would not be expected to have an impact on this patient's height and weight. Note that the patient did experience an increase in height velocity after starting uridine replacement therapy at age 11 years (height velocity z-score increased from the 1<sup>st</sup> percentile at age 11 years to the 30<sup>th</sup> percentile at age 12 years).*

*This reviewer notes that height values for this patient were consistently between 157 cm and 157.8 cm from age (b) (6) years, with the exception of a height measurement of 159.5 cm at age (b) (6) years. The applicant stated that the patient's height increased from 157.8 cm at baseline to 160 cm at Month 6. However, this value appears to be due to measurement error or normal variation since this patient would not be expected to have open growth plates at age (b) (6). Rogol et al. note that diurnal variation in standing height measurements of up to (b) (6) cm can occur even when using proper measuring techniques.<sup>28</sup>*

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<sup>28</sup> Rogol AD, Clark PA, Roemmich JN, Growth and pubertal development in children and adolescent: effect of diet and physical activity, *Am J Clin Nutr* 2000; 72(suppl): 521S-528S.

- **Patient** (b) (6)

Patient (b) (6) began treatment with uridine 50mg/kg/day at age 3 years 2 months. (b) (6) uridine dose was increased to 100 mg/kg/day at age 3.2 years and then to 150 mg/kg/day at age 3.7 years.

The medical history for Patient (b) (6) documents failure to thrive at age 9 to 27 months and weight at 5<sup>th</sup> percentile at age 15 to 27 months. Historical height and weight values were available from age 28 months.

Just prior to starting uridine replacement therapy at age 3.2 years, the patient's height z-score was -0.6 and (b) (6) weight z-score was -1. The patient's height z-score decreased to -1 from age 5 years and remained unchanged at the time of study entry (b) (6) weight z-scores improved at ages 4 years (z-score was -0.1) and 5 years (z-score was -0.2) then declined again at age 6 years (z-score was -1.1).

During Study 001, the patient's height z-score decreased slightly from baseline (z-score was -1; 15<sup>th</sup> percentile) to Month 6 (z-score was -1.1; 14<sup>th</sup> percentile), with a corresponding decrease in height velocity z-score (z-score decreased from -0.1[45<sup>th</sup> percentile] to -0.9 [20<sup>th</sup> percentile]).

The patient's weight and weight velocity z-scores increased from baseline to Month 6. At baseline, (b) (6) weight z-score was -1.4 (7<sup>th</sup> percentile) and weight velocity z-score was approximately -0.6 (~25<sup>th</sup> percentile). At Month 6, weight z-score was -1.1 (15<sup>th</sup> percentile) and weight velocity z-score was between 0 and 0.7 (~50<sup>th</sup> to 75<sup>th</sup> percentile).

[Figure 7](#) is a chronological summary of Patient (b) (6) height and weight z-scores, with their relationship to initiation and subsequent changes in the patient's uridine replacement therapy regimen.

(b) (6), (b) (4)

*Reviewer Comments:*

*Although this patient's height and weight measurements were within the normal range for age prior to starting uridine, as observed in the other 2 patients treated with uridine, the patient's weight z-scores improved after starting uridine. Similarly, during Study 001, (b) (4) weight z-score and z-score percentile improved from baseline to Month 6, indicating a treatment response to uridine triacetate.*

• **Patient** (b) (6)

Historical height and weight values were available from age 13 months for Patient (b) (6). The patient's lowest height z-score was -2.3 (< 1<sup>st</sup> percentile) at age 13 months. Between age 13 months and age (b) (6) years (b) (6) age at study entry), (b) (6) height z-score ranged from -1.7 to -1.5 (4<sup>th</sup> -6<sup>th</sup> percentile). The patient's weight z-scores decreased from -1 (15<sup>th</sup> percentile) at age 13 months to -2.2 (1<sup>st</sup> percentile) at age 24 months.

During Study 001, the patient's height z-scores were -1.6 (5<sup>th</sup> percentile) at baseline and -1.7 (4<sup>th</sup> percentile) at Month 6. (b) (6) weight z-scores were -1.8 (3<sup>rd</sup> percentile) at baseline and -2.3 (1<sup>st</sup> percentile) at Month 6. From age 20 months to 30 months, (b) (6) height and weight velocity z-scores were at approximately the 10<sup>th</sup> to 25<sup>th</sup> percentile.

(b) (6) height velocity z-score decreased from baseline (z-score was approximately 0; 50<sup>th</sup> percentile) to Month 6 (z-score was less than -0.6; < 25<sup>th</sup> percentile). (b) (6) weight velocity

z-score percentile remained from baseline to Month 6 (z-score percentile was approximately -0.6 (25<sup>th</sup> percentile).

[Figure 8](#) is a chronological summary of Patient (b) (6) height and weight z-scores, with their relationship to initiation and subsequent changes in the patient's uridine replacement therapy regimen.



*Reviewer Comments:*

*The negative findings in Patient (b) (6) for a treatment effect on growth may be due to underdosing. As noted earlier, the patient's uridine triacetate dose was doubled at about Month 4 of treatment. Thus, the patient would not have been treated long enough at the higher dose to evaluate for a change in response for growth.*

*5.3.15 Drug Dose Response Relationship*

The main treatment phase of the trial was not designed to evaluate dose response. Three patients received dose increases during the extension phase of the trial. As noted earlier, patients were not on the higher dose regimens long enough to evaluate for a dose response.

*Reviewer Comments:*

*More long-term data are needed in order to better characterize the drug dose response in these patients. In this reviewer's opinion, questions remain regarding the optimal dosing of uridine triacetate needed to achieve and maintain the desired hematologic or growth responses in some of the patients. I recommend that the applicant continue to collect efficacy data for total duration of 2 years as an extension study as a postmarketing commitment. Data collection should include information on any dose adjustment made during the data collection period.*

**5.3.16 Subpopulations**

There were insufficient numbers of patients to perform any subpopulation analyses.

**5.3.17 Analysis of Clinical Information Relevant to Dosing Recommendations**

The trial findings indicate that there is a range of dosing for efficacy. During the extension phase of the trial, two patients were receiving uridine triacetate doses of 120 mg/kg/day, one patient was receiving a dose of 95 mg/kg/day, and one patient remained on the starting dose of 60 mg/kg/day.

*Reviewer Comments:*

*The trial findings are consistent with prior clinical experience with uridine replacement therapy. As discussed in the following section, published case studies indicate that uridine dosing and duration of treatment needed to achieve the desired clinical response is variable (see [Section 5.4](#)). In the case study literature, dosing was titrated based on urine orotic acid levels and clinical response. The applicant has proposed that dosing be titrated based on orotic acid levels, other key laboratory values, and clinical response. This reviewer agrees that dosing titration is appropriate and concurs with the applicant's proposed criteria for increasing dosing. In addition, dosing should be adjusted for weight increases. For further discussion of labeling recommendations for dosing, see [Section 9.2](#).*

**5.3.18 Discussion of Persistence of Efficacy and/or Tolerance Effects**

Based on the patient's prior experience with uridine replacement therapy and the findings of stable hematologic and biomarker findings in the patients transitioned from uridine, the treatment effect of uridine triacetate appears to persist over time. The treatment effect of uridine triacetate on growth also appears to be sustained in the patients who transitioned from uridine; both of the prepubertal patients experienced an increase in weight velocity (rate of weight gain) after 6 months of treatment. The lack of

improvement in hematologic or growth parameters observed in the treatment-naïve patient (Patient (b) (6)) may due to underdosing. Efficacy data for Month 12 of the extension study will provide additional data on the long-term efficacy of uridine triacetate. At the time of this review, these data were pending.

#### 5.4 Published Case Studies

The applicant submitted references for 19 published case studies of patients with HOA (see [Table 10](#)). The largest case series was published by Webster et al in 2001.<sup>29</sup> The majority of cases presented with anemia as well as growth and/or developmental delays. There is one case report of a patient (OAWA2) who had no evidence of megaloblastic changes. The majority of cases included quantitative information on hematologic and biochemical marker responses to treatment that documented normalization or near normalization of hemoglobin and orotic acid levels with treatment. Reductions in orotic acid levels were typically observed within the first week of treatment. The time to treatment response in patients with anemia varied from less than 2 weeks to several months. A similar variability in time to response was observed for white cell abnormalities. Growth delays, most commonly poor weight gain, improved over a span of several months. The majority of patients received the same dose throughout treatment; some patients required a dose increase to achieve their optimal response. Uridine doses listed in the table refer to patient dosing after dose titration was completed.

#### *Reviewer Comments:*

*Webster et al. noted that there are no published follow-up data for these case reports and that published reports were for a treatment period of 2 years or less for most cases. The authors were able to obtain unpublished follow-up information for 10 patients. None were noted as having recurrent anemia or urinary symptoms while maintained on uridine. All but one patient was reported as being well physically; patient PM was reported to have progressive neurologic deterioration, with development of ataxia at age 4 years and loss of ability to walk unaided at age 18 years. The authors noted that some patients had long-term cognitive impairment and that the impact of uridine replacement therapy on neurocognitive development is unclear.<sup>30</sup>*

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<sup>29</sup> Webster DR., Becroft DM et al., Hereditary Orotic Aciduria and Other Disorders of Pyrimidine Metabolism, *Scriver's Online Metabolic & Molecular Bases of Inherited Disease* 2001, Chapter 113: 1-86.

<sup>30</sup> Ibid.

**Table 10: Published Cases of HOA**

	Pt ID	Sex	Age at Onset of Symptoms	Presenting features	Age at Start of Treatment	Treatment/ Dosage	Treatment response	Age at last report	Status at last report	Reference
1	JR	M	3 mon	Pallor, diarrhea	18 mon	Cytidylic acid (115 mg/ml) + Uridylic acid (269 mg/ml)  15 ml/day	Hgb & weight normalized within 2 mon.  Family stopped treatment prior to patient's death.	2 yrs 9 mos	Dead- cause of death was varicella pneumonia & heart failure	(Huguley et al., 1959)
2	DG	M	3mon	Pale, retarded development	19 mon	Uridine 150 mg/kg/day	Hgb normalized, weight normalized within 18 mon.	38 yrs	Well- patient is employed	(Becroft and Phillips, 1965; Becroft et al., 1969)
3	JP	M	10 mon	Weakness, anemia, poor development	20 mon	Uridine 1.5g/day	Hgb increased within 2 weeks; growth improved.	30 yrs	Well	(Haggard and Lockhart, 1967)
4	TH	F	2 mon	Anemia, strabismus	11 mon	Uridine 1.5 gm/day	Hgb normalized within 3 months; growth improved.	26 yrs	Well	(Rogers et al, 1968)
5	FB	F	7 yrs	Fatigue. Hematuria, back & flank pain	7 yrs	Uridine 150 mg/kg/day	Normal baseline growth; Hgb and WBC count normalized	31 yrs	Well	(Tubergen et al., 1969)
6	KP	M	1 day	Multiple malformations	4 mos	Uridine 150 mg/kg/day	Hgb normalized Family stopped treatment after ~1 mon.	6 mos	Dead- cause of death was meningitis & pneumonia	(Fox et al., 1969; Fox et al, 1973)

CHD= congenital heart disease; FTT= failure to thrive; Hgb= hemoglobin; WBC=white blood cell

- Status is as of the last known report for a patient. The most recent published follow-up information for patients 1-14 was 2001.
- "Well" is the status designation used in Webster 2001, from which this table is adapted, to indicate that patients were relatively healthy or stable as a result of sustained uridine replacement therapy.

**Table 10: Published Cases of HOA (cont'd)**

	Pt ID	Sex	Age at Onset of Symptoms	Presenting features	Age at Start of Treatment	Treatment/Dosage	Treatment response	Age at last report	Status at last report	Reference
7	PM	M	6 mon	FTT, anemia	6 mos	Uridine 150 mg/kg/day	Hgb increased; relapsed w/ from about 7 to 11; decreased when treatment was interrupted	24 mos	Well	(Fox et al., 1969; Fox et al., 1973)
8	DM	M	6 mon	Cough, anemia, FTT	2 yrs	Uridine 1.5 gm/day	Report states patient had clinical & hematologic response	18 yrs	Progressive neurological impairment	(Smith and Gilmour, 1975)
9	YS	M	7 yrs	Diarrhea, hematuria, stomatitis, anemia	7 yrs	Uridine 150 mg/kg/day	Hgb improved; no further need for transfusions.  Diarrhea recurred 3 mon into treatment	8 yrs	Dead- cause of death was meningitis	(Girod et al., 1983)
10	RS	F	3 mon	(b) (4) pallor, transient diarrhea	3 mon	Uridine 50 mg/kg/day	Hgb improved; no further need for transfusions	12 yrs	Well	(Girod et al., 1983)
11	XX	F	5 mon	Anemia, FTT, "poor development and progress"	5 mon	Uridine 300 mg/day	Report states that treatment reversed disease symptoms	9 yrs	Well	(McClard et al., 1983)

CHD= congenital heart disease; FTT= failure to thrive; Hgb= hemoglobin; WBC=white blood cell

- Status is as of the last known report for a patient. The most recent published follow-up information for patients 1-14 was 2001.
- "Well" is the status designation used in Webster 2001, from which this table is adapted, to indicate that patients were relatively healthy or stable as a result of sustained uridine replacement therapy.

**Table 10: Published Cases of HOA (cont'd)**

	Pt ID	Sex	Age at Onset of Symptoms	Presenting features	Age at Start of Treatment	Treatment/Dosage	Treatment response	Age at last report	Status at last report	Reference
12	HB	F	4 day	Anemia, CHD, developmental delay, hypogammaglobulinemia	23 mon	Uridine 150 mg/kg/day	Hgb improved after 6 mos; no further need for transfusions	9 yrs	Well	(Alvarado et al., 1988)
13	YF	F	1 mon	CHD, FTT, anemia	3 mon	Uridine 300 mg/kg/day	Hgb increased after 5 months, lymphopenia resolved	18 mon	Well	(Suchi et al., 1997; Yazaki et al, 1987)
14	YY	M	28 yrs	Anemia	--	Untreated	Persistent anemia (Hgb ranges from 28-32); has had 2 episodes of severe anemia	32 yrs	Well- patient is farmer	(Fessas et al., 1992)
15	AM	F	5 mon	FTT, anemia	20 mon	NS		21 mon	Well	Simmonds-personal communication in (Webster et al., 2001)
16	IMAEDA	M	3 yrs	developmental delay, cerebral palsy	13 mon	NS		3 yrs	Well	(Imaeda et al, 1998)
17	OAWA1	M	9 mon	developmental delay, oculomotor dyspraxia		NS		9 mon	Well	(Besley et al., 2000)

CHD= congenital heart disease; FTT= failure to thrive; Hgb= hemoglobin; WBC=white blood cell

- Status is as of the last known report for a patient. The most recent published follow-up information for patients 1-14 was 2001.
- "Well" is the status designation used in Webster 2001, from which this table is adapted, to indicate that patients were relatively healthy or stable as a result of sustained uridine replacement therapy.

**Table 10: Published Cases of HOA (cont'd)**

	Pt ID	Sex	Age at Onset of Symptoms	Presenting features	Age at Start of Treatment	Treatment/Dosage	Treatment response	Age at last report	Status at last report	Reference
18	OAWA2	M	1 yr 6 mon	developmental delay; no evidence of megaloblastic anemia		N/S	No evidence of megaloblastic anemia	10 yrs	Well	(Bailey, 2009)
19	(b) (6)	(b) (6)	(b) (6)	developmental delay, FTT, neutropenia	(b) (6)	Uridine 200 mg/kg/day → Uridine triacetate 60 mg/kg/day		(b) (6)	Well	401.13.001 CSR
20				developmental delay, GI issues, neurological problems	(b) (6)	Uridine 200 mg/kg/day → UA 60 mg/kg/day			Well	401.13.001 CSR
21				FTT, macrocytosis	(b) (6)	Uridine 150 mg/kg/day → Uridine triacetate 120 mg/kg/day			Well	401.13.001 CSR
22				FTT, macrocytosis	(b) (6)	Uridine triacetate 120 mg/kg/day			Well	401.13.001 CSR

CHD= congenital heart disease; FTT= failure to thrive; Hgb= hemoglobin; WBC=white blood cell

- Status is as of the last known report for a patient. The most recent published follow-up information for patients 1-14 was 2001.
- “Well” is the status designation used in Webster 2001, from which this table is adapted, to indicate that patients were relatively healthy or stable as a result of sustained uridine replacement therapy.

## 6 Review of Efficacy

### Efficacy Summary

Efficacy is discussed in [Section 5](#) of this review.

#### 6.1 Indication

The applicant has proposed the following indication:

*“Xuriden is indicated for uridine replacement therapy in pediatric patients with hereditary orotic aciduria.”*

Labeling recommendations are discussed in [Section 9.2](#).

## 7 Review of Safety

### Safety Summary

Chronic treatment with uridine triacetate was well tolerated in patients with hereditary orotic aciduria and other conditions.

There were no treatment-related adverse events reported for Study 001. As of the data cut-off date for the 120 Day Safety Update (May 7, 2015), the four enrolled patients experienced eight mild adverse events that were unrelated to treatment.

The applicant submitted safety data from patients treated chronically with uridine triacetate for other indications as supportive safety data. These included safety data for 53 patients with diabetic neuropathy treated with uridine triacetate in Phase 2 clinical trials and 30 patients with a variety of neurometabolic disorders enrolled in compassionate use programs. The most commonly reported adverse reactions (reported in 2 or more patients) in patients with diabetic neuropathy were diarrhea, nausea, abdominal pain, and constipation. Because these gastrointestinal events overlap with symptoms of diabetic gastrointestinal disease (diabetic gastroparesis and diabetic intestinal neuropathy) and due to the open-label trial design, it is difficult to distinguish between disease-related and treatment-related events in this patient population. In addition, patients in the diabetic neuropathy trials received a different formulation of uridine triacetate that contained an excipient known to cause gastrointestinal irritation.

One patient enrolled in a compassionate use program was reported to have hyperactivity after initiation of uridine triacetate that resolved with discontinuation of the drug.

All serious adverse events and deaths reported for the uridine triacetate clinical program were considered to be related to underlying disease.

Based on review of the safety data available for this review cycle, my independent safety analysis did not uncover major discrepancies compared with the applicant's analysis.

## 7.1 *Methods*

### 7.1.1 *Studies/Clinical Trials Used to Evaluate Safety*

In addition to safety data for the 4 patients enrolled in Study 001, information for this clinical review includes data from the following populations:

- 53 patients with diabetic neuropathy enrolled in 2 Phase 2 clinical trials
- 30 patients with neurometabolic conditions enrolled in compassionate use programs

The data cut-off date for the 120-Day Safety Update for the submission was May 7, 2015. The 120-Day Safety Update included additional data for Study 001, including efficacy data up through Month 6 of treatment and adverse events up through the data cut-off date.

### 7.1.2 *Categorization of Adverse Events*

The applicant used the National Cancer Institute Common Terminology Criteria for Adverse Events (CTAE v. 4.03) and the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and AE preferred terms to classify and code AEs. Reporting of adverse events included information such as classification of AE using standard medical terminology (MedDRA Version 17.0), classification of relationship to study medication, classification of severity of AE, and date of onset and resolution of AE. These data appear to be adequate to assess the safety profile of uridine triacetate.

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

Due to differences in exposure and clinical conditions between treatment populations, the applicant did not pool safety data for the patients with HOA with safety data for other populations.

## 7.2 *Adequacy of Safety Assessments*

Safety parameters for clinical trials reviewed included physical examination, vital signs, clinical chemistry, hematology, and urinalysis, concomitant medications, and adverse events. These safety parameters appear to be adequate to assess the safety profile of uridine triacetate.

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

#### Exposure

The safety database includes information on 53 patients with diabetic neuropathy patients enrolled in Study 401.97.201 (Study 201) and Study 401.97.202 (Study 202), and 30 patients with neurometabolic conditions enrolled in compassionate use programs. Patient received uridine triacetate doses ranging from 60 mg/kg/day to 19.8 grams/day.

As of the data cutoff date for the 120-Day Safety Update, all four Study 001 patients had completed more than 6 months of treatment. In Study 201 and 202, duration of exposure ranged from 23 to 467 days and 6 to 201 days, respectively. Drug exposure in patient with metabolic disorders ranged from 1 month to almost 20 years. [Table 11](#) summarizes duration of exposure during uridine triacetate clinical trials and expanded access programs.

**Table 11: Summary of Duration of Exposure to Uridine Triacetate by Treatment Population**

Duration of Exposure	Patients with Diabetic Neuropathy N=53	Patients with Neurometabolic Diseases N=30	Patients with HOA N=4
0-6 mon	15	7	
>6mon to 1 yr	26	1	4
>1 to 2 yrs	12	2	
>2 to 10 yrs		10	
>10 yrs		10	

#### Demographics

Three of four patients were (b) (4) and all patients were (b) (6). Patient ages ranged from (b) (6) years at study entry. Patient age at time of diagnosis ranged from (b) (6) years (see [Table 5](#) for summary demographic information).

#### Reviewer Comments:

*The published literature for HOA indicates that the disease affects equal proportions of males and females. The disease has been reported in multiple racial and ethnic groups. The differences in ages of study patients at the age at time of diagnosis reflect the clinical heterogeneity of the disease, with patients with more severe disease (or a known family history of disease) being diagnosed at a younger age. In published case studies, the age at time of diagnosis ranged from (b) (6)*

### 7.2.2 Explorations for Dose Response

Only one dose of uridine triacetate (60 mg/kg/day) was administered during the main treatment phase of the trial. Two patients experienced doses increases from 60 mg/kg/day to 120 mg/kg/day at Month 4 and one patient experienced a dose increase from 60 mg/kg/day to 95 mg/kg/day at Month 6. Six of the 8 reported adverse events occurred while patients were on the starting dose (concurrent AEs of a viral illness were reported for the (b) (6) that occurred about 2 months after their doses were increased). As noted earlier, none of the AEs were assessed as treatment-related. As discussed in [Section 7.4.1](#) and [Section 7.5.1](#), AEs have been reported in patients in other clinical trials who received uridine triacetate doses of 4 grams/day or greater; however, these AEs appeared to be due to underlying disease and/or use of a formulation of uridine triacetate that contained excipients known to cause gastrointestinal irritation.

### 7.2.3 Special Animal and/or In Vitro Testing

None.

### 7.2.4 Routine Clinical Testing

Routine safety laboratory studies were performed for Study 001. Safety laboratory studies were performed at local laboratory sites. Laboratory results are discussed in [Section 7.4.2](#).

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

Adequate evaluation for potential adverse events for uridine products was performed through a literature search by the applicant.

## 7.3 Major Safety Results

The safety results reviewed in this section are from Study 001. The results include safety data reported in the 120-Day Safety Update.

As of the data cut-off date for the 120-Day Safety Update, there were no serious adverse events, deaths, or discontinuations reported for Study 001. To date, eight adverse events have been reported in four patients (headache [2 patients], flu/viral illness [2 patients], elevated baseline alkaline phosphatase level, sunburn, foot pain, and cherry red spot in eye [1 patient each]). All AEs were assessed as unrelated to treatment. The severity of one event (cherry red spot in eye) was recorded as unknown; the remaining AEs were of mild severity.

## 7.4 Supportive Safety Results

### 7.4.1 Commonly Reported Adverse Reactions

Supportive safety data for uridine triacetate includes data from 53 adult patients with diabetic neuropathy enrolled in two Phase 2 clinical trials and annual report data for 30 patients enrolled in compassionate use programs. Adverse reactions occurring in at least 2 patients in clinical trials in diabetic patients include diarrhea (8 patients), nausea (6 patients), abdominal pain, and constipation (2 patients each). [Table 12](#) summarizes most commonly reported adverse reactions for the clinical trials in patients with diabetic neuropathy (Study 401.97.201 and Study 401.97.202).

**Table 12: Most Commonly Reported Adverse Reactions (2 or more patients) in Uridine Triacetate Trials in Patients with Diabetic Neuropathy**

Preferred Term	401.97.201 N=38		401.97.202 N=15	Total N=53
	4 g/day dose	8 g/day dose	4g/day dose	
Diarrhea	2 (5%)	3 (8%)	3 (20%)	8 (15%)
Nausea	0	1(3%)	5 (33%)	6 (11%)
Abdominal pain	1(3%)	1(3%)	0	2 (4%)
Constipation		0	2 (13%)	2 (4%)

One patient being treated in a compassionate use program was reported to have hyperactivity after starting uridine triacetate; the patient's symptoms resolved when the drug was discontinued. No other adverse events that were assessed as being treatment-related have been reported in patients in compassionate use programs. Six patients with mitochondrial disorders who were treated in compassionate use programs have died from disease complications, including five patients with Leigh syndrome and one patient with an unspecified mitochondrial neurodegenerative disorder.

#### Reviewer Comments:

*This reviewer notes that the gastrointestinal events reported in clinical trials in diabetic patients overlap with symptoms of diabetic gastroparesis and diabetic intestinal neuropathy.<sup>31</sup> The majority of gastrointestinal AEs reported in the clinical trials were assessed as treatment-related. However, because the clinical trials were open-label, it is difficult to distinguish between disease-related and treatment-related events. Patients in the diabetes clinical trials received a different formulation of uridine triacetate that contained (b) (4), a (b) (4) with known gastrointestinal effects. This excipient may also have contributed to the reported gastrointestinal events.*

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<sup>31</sup> Shakil A, Church RJ, Rao SS, Gastrointestinal complications of diabetes, *Am Fam Physician* 2008; 77(12): 1697-1702.

*Although some patients treated in compassionate use programs also received high doses of uridine triacetate (21 patients received doses of 6 grams/day or higher), no gastrointestinal events were reported for these programs. These findings are consistent with published studies of clinical investigations of other conditions in which high oral doses of uridine triacetate were administered. In randomized, double-blind, placebo-controlled trials investigating the use of uridine triacetate to treat antiretroviral therapy associated lipoatrophy in patients with HIV, patients were administered a commercial dietary supplement containing uridine triacetate. Dosing ranged from 36 grams to 108 grams a day for 3 months to one year. No statistically significant difference in the incidence of diarrhea was observed in patients in the treatment group compared to the placebo group.<sup>32, 33</sup>*

*In the aggregate, the safety data indicate that treatment with uridine triacetate was associated with minimal toxicity.*

*Diarrhea was reported in two case studies for patients treated with uridine. In one case study, the author attributed the diarrhea to high phosphate and salt content in the uridine formulation used in the patient. In the second case study, the patient had an underlying immunodeficiency and intercurrent infection, which may have contributed to his symptoms. Both patients had a history of recurrent diarrhea prior to starting uridine replacement therapy.<sup>34</sup>*

#### 7.4.2 Laboratory Findings

Any clinically significant laboratory abnormality, as determined by the investigator, could be reported as an AE. One patient (Patient (b) (6)) had an AE of an elevated alkaline phosphate level at baseline; the AE resolved by Day 42.

#### 7.4.3 Vital Signs

Any clinically significant vital sign abnormality, as determined by the investigator, could be reported as an AE. No vital sign AEs were reported for Study 001.

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<sup>32</sup> Sutinen J, Walker UA et al., Uridine supplementation for the treatment of antiretroviral therapy-associated lipoatrophy: a randomized, double-blind, placebo-controlled trial, *Antivir Therapy* 2007; 12: 97-105.

<sup>33</sup> McComsey GA, Walker UA, et al., Uridine supplementation in the treatment of HIV lipoatrophy: results of ACTG 5229; *AIDS* 2010; 24(16): 2507-2515.

<sup>34</sup> Webster DR., Becroft DM et al., Hereditary Orotic Aciduria and Other Disorders of Pyrimidine Metabolism, *Scriver's Online Metabolic & Molecular Bases of Inherited Disease* 2001, Chapter 113: 1-86.

#### *7.4.4 Electrocardiograms (ECGs)*

Electrocardiogram (ECG) assessments were not performed in Study 001.

#### *7.4.5 Special Safety Studies/Clinical Trials*

None.

### *7.5 Other Safety Explorations*

#### *7.5.1 Dose Dependency for Adverse Events*

There were insufficient events from Study 001 to assess for dose dependency for adverse events. As discussed earlier, gastrointestinal events have been reported in clinical trials in other populations in which patients received other formulations of uridine triacetate administered at higher doses (4 grams or greater). However, the reported events appear to have been due to underlying disease and/or excipients contained in the formulation used for the trial.

#### *7.5.2 Time Dependency for Adverse Events*

There were insufficient events from Study 001 to assess for time dependency for adverse events. Based on the almost 20-year clinical experience with uridine triacetate in patients with neurometabolic conditions, there is no apparent time dependency for adverse events.

#### *7.5.3 Drug-Demographic Interactions*

There were insufficient numbers of patients with HOA to perform subgroup analyses for drug demographic interactions. There are no apparent patterns of drug-demographic interactions in patients with diabetic neuropathy or patients with neurometabolic disorders.

#### *7.5.4 Drug-Disease Interactions*

No data are available for drug-disease interactions.

#### *7.5.5 Drug-Drug Interactions*

No drug-drug interactions were examined with regard to safety data.

## 7.6 *Additional Safety Evaluations*

No additional safety evaluations were performed for uridine triacetate.

### 7.6.1 *Human Carcinogenicity*

There was no evidence of human carcinogenicity in the safety evaluation.

### 7.6.2 *Human Reproduction and Pregnancy Data*

There are no adequate and well controlled trials with uridine triacetate in pregnant women. Webster et al. reported pregnancy outcomes for two women with HOA treated with uridine.<sup>35</sup> Both women initiated uridine replacement therapy during childhood and were maintained on doses of 1.5 grams/day prior to pregnancy. One woman had four pregnancies resulting in four normal live births. The second woman had two pregnancies; the first pregnancy resulted in an infant with multiple congenital anomalies (secondary to a familial chromosome abnormality unrelated to HOA) and the second resulted in a normal male. Both women received increased doses of uridine during pregnancy (2.5 grams/day for the first woman and up to 28 grams/day for the second woman). Webster et al. also reported that one male patient with HOA has fathered three children, including two living children and one infant who was stillborn due to Rh isoimmunization.<sup>36</sup>

### 7.6.3 *Pediatrics and Assessment of Effects on Growth*

All four patients enrolled in Study 001 had a medical history of poor growth or failure to thrive at the time of diagnosis. For the three patients who were treated with uridine prior to enrolling in Study 001, historical data demonstrate that height or weight improved in two patients following initiation of uridine replacement therapy, while one patient achieved height and weight measurements within the normal range for age and gender prior to starting uridine replacement therapy.

During Study 001, height and weight measurements in all four patients increased after six weeks of treatment; none of the increases during this period were clinically significant. Both of the prepubertal patients who transitioned from uridine had improved weight gain (weight z-scores and weight velocity z-scores improved) after 6 months of treatment with uridine triacetate; one of the transition patients also had improved height gain (height z-score and height velocity z-score improved). No improvement in height

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<sup>35</sup> Ibid.

<sup>36</sup> Ibid

or weight growth was observed in the treatment-naïve patient. As noted earlier, this patient may not have received an adequate dose of uridine triacetate.

Height and weight parameters remained stable for the adult patient enrolled in the study.

These results are consistent with published case studies that have documented improved growth in pediatric patients following treatment with uridine replacement therapy.

#### *7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound*

No data are available. Base on the drug's mechanism of action, uridine triacetate is unlikely to be of drug abuse potential.

#### *7.7 Additional Submissions / Safety Issues*

None.

## **8 Postmarket Experience**

None

## 9 Appendices

### 9.1 Literature Review/Reference

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## 9.2 Labeling Recommendations

The labeling will be in PLR format. Content and formatting were reviewed to meet the latest best-practices. The final labeling contains all of the labeling revisions negotiated with the applicant.

As noted in [Section 6.1](#), I recommend that Xuriden is indicated for adult and pediatric patients. The published literature for uridine replacement therapy documents the continued benefits of uridine replacement therapy during adulthood. In addition, I recommend the following edits to the applicant's proposed labeling for Xuriden:

- **Section 2 (Dosage and Administration)**

**Recommendation:**

The applicant proposes a dosing range between 60 mg/kg/day up to (b) (4) mg/kg/day. However, a 120 mg/kg/day dose of uridine triacetate provides approximately the same exposure as a 300 mg/kg/day dose of uridine, which corresponds to the upper range of uridine dosing reported in case reports. In addition, the maximum dose of uridine triacetate evaluated in Study 001 to date is 120 mg/kg/day. Therefore, I recommend that the labeled dosing range for uridine triacetate should be 60 mg/kg/day up to 120 mg/kg/day, with a maximum dose of 8 grams/day (which is approximately equivalent to a 120 mg/kg/day dose for a patient of adult weight [70 kg]).

I agree with the applicant's proposed criteria for increasing dosing. In addition, dosing should be adjusted for weight increases and dosing information should be provided in a weight-based table of doses for each dose level (e.g., separate dosing tables for the 60 mg/kg/day dose level and the 120 mg/kg/day dose level,).

The section should also include information on appropriate preparation and administration of Xuriden to infants and young pediatric patients.

- **Section 14 (Clinical Studies)**

**Recommendation:**

I recommend that this section include a summary of information from the published case studies of HOA patients treated with uridine replacement therapy. I also recommend that the section include information on growth in addition to information on hematologic response. At the time of this review, growth data were only available up through 6 months of treatment. I recommend that the label be updated as more long-term growth data (i.e., growth findings after 12 months of treatment) become available.

Clinical Review  
Carla Epps, MD, MPH  
NDA 208169  
Xuriden (uridine triacetate)

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### *9.3 Advisory Committee Meeting*

No advisory committee meeting was held for this application.

### *9.4 Financial Disclosure Review Template*

See form on the following page.

Clinical Review  
 Carla Epps, MD, MPH  
 NDA 208169  
 Xuriden (uridine triacetate)

Clinical Investigator Financial Disclosure  
 Review Template

Application Number: NDA 208169

Submission Date(s): January 8, 2015

Applicant: Wellstat

Product: Xuriden (uridine triacetate)

Reviewer: Carla Epps, MD, MPH

Date of Review: February 19, 2015

Covered Clinical Study (Name and/or Number): 401.13.001

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>2</u> <div style="background-color: #cccccc; width: 100%; height: 15px; margin-top: 5px;">(b) (4)</div> <div style="background-color: #cccccc; width: 100%; height: 15px; margin-top: 5px;">(b) (4)</div>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>37</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

No investigators disclosed financial interests or arrangements and therefore there were no financial interests or arrangement that may have affected the approvability of the application.

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<sup>37</sup> See guidance at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf> .

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CARLA L EPPS  
07/28/2015

ANIL K RAJPAL  
07/28/2015  
I concur with Dr. Epps.