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APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 208169

Drug Name: XuridenTM (uridine triacetate) oral granules

Indication(s): Uridine replacement therapy in (b) (4) with hereditary
orotic aciduria (HOA)

Applicant: Wellstat Therapeutics Corporation

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1 EXECUTIVE SUMMARY

The sponsor submitted one open-label phase 3 study with four patients to demonstrate the maintenance effect of uridine triacetate as uridine replacement therapy in pediatric patients with hereditary orotic aciduria (HOA). The starting dose of oral uridine triacetate was 60 mg/kg/day, which could be escalated up to a maximum of 300 mg/kg/day and the study duration was 42 days. Among the four patients, one was treatment-naïve and the other three who had been treated with uridine before the study had experienced positive therapeutic responses to uridine. The primary endpoint for the treatment naïve patient was mean corpuscular volume (MCV), and for the three experienced patients, the primary endpoints were MCV, neutrophils, and white blood cell (WBC). Their secondary endpoints were based on urinary orotidine and orotic acid (OA).

According to the sponsor's results, the single treatment-naïve patient did not show significantly improved MCV, but other hematologic parameters exhibited improvement. Treatment with uridine triacetate resulted in stable assessments for the primary endpoints in the three experienced patients. Hematologic parameters for all four patients continued to show stability or improvement during the 6-month treatment extension period. In addition, all four patients' urinary orotidine and OA levels remained stable over the 6 weeks of treatment after the initiation of treatment with uridine triacetate. Three patients' OA levels remained well-controlled in the treatment extension period except for one patient, whose OA level increased by more than twofold. All patients exhibited increase or stability in height and body weight in the 6-week study period and the 6-month extension trial.

The statistical reviewer confirmed the sponsor's efficacy findings. To further assess uridine triacetate's effect on either stabilizing or improving patients' hematologic parameter and levels of OA, the reviewer used patient profiles and bar graphs to illustrate the patients' progress over time including pre-treatment and the extension period. In addition, patients' height and body weight were assessed over time to examine their growth.

2 INTRODUCTION

2.1 OVERVIEW

The sponsor submitted the NDA for the study drug, uridine triacetate, whose proposed indication is uridine replacement therapy (b) (4) with hereditary orotic aciduria (HOA). Uridine triacetate is an acetylated pro-drug of uridine and delivers substantially more bioavailable uridine (4 to 7 times) when administered to animals or humans than oral administration of equimolar doses of uridine itself.

Hereditary orotic aciduria (HOA) is a genetic disorder caused by mutations reducing the activity of uridine monophosphate synthase (UMPS), which converts orotic acid to UMP. Uridine deficiency underlies the symptoms of HOA, including hematologic abnormalities, developmental delays, failure to thrive, and if untreated, early mortality. HOA is a rare congenital autosomal

recessive disorder, and only about 20 cases of this rare disorder have been documented worldwide.

Systemic uridine delivery is the specific compensatory treatment for HOA, providing a good prognosis in most patients. However, uridine is no longer available from the company previously supplying it under compassionate use. At the request of FDA, including the Office of Drug Evaluation III, Division of Gastroenterology and Inborn Errors Products, Office of Orphan Products Development, Office of Drug Shortages and the Office of Rare Disease (refer to March 22 2013 teleconference and August 7 2013 pre-IND meeting), the sponsor developed uridine triacetate as uridine replacement therapy in pediatric patients with HOA. FDA granted Orphan Drug Designation for uridine triacetate in the treatment of HOA on August 9, 2013 and Breakthrough Therapy Designation on April 30, 2014. A priority 8-month review cycle was undertaken in accordance with the Prescription Drug User Fee Act (PDUFA) V Program.

The sponsor’s clinical program for uridine triacetate consists of two Phase II safety studies and one Phase III open-label study 401.13.001. The safety and efficacy studies are listed in the following Table 2.1.

Table 2.1: Listing of relevant safety and efficacy studies

Study Type	Study ID	Study Design	Indication of Study	Dose of Uridine Triacetate	No. of Subjects	Duration
Efficacy and safety Phase III	401.13.001	Open label, one-arm, two centers	uridine triacetate in pediatric patients with hereditary orotic aciduria	60 mg/kg/day	4 entered 4 completed	May-August 2014 (main study) August 2014-ongoing (treatment extension)
Safety Phase II	401.97.201	open, non-controlled, 2-arm, multi-center	Patients with Type I or II diabetes with diabetic neuropathy	Group 1: 4 g/day (2 g bid) (8 × 500 mg Tabs), Oral; Group 2: 8 g/day (4 g bid) (16 × 500 mg Tabs), oral	Group 1: 20 entered 14 completed Group 12 18 entered 15 completed	April 1997 to June 1999
Safety Phase II	401.97.202	open, non-controlled, 1-arm, single-center;	Patients with Type I or II diabetes with diabetic neuropathy	4 g/day (2 g bid) (8 × 500 mg Tabs), oral	15 entered 10 completed	April 1998 to December 1998

Source: Sponsor’s Table 2.7.6.1–1 of Synopses of Individual Studies of the NDA

The following specific features of Study 401.13.001 were initially agreed to by the FDA (refer to the meeting minutes for December 9 & 11 2013 teleconferences and January 24 2014 information request (IR)):

- The main study was 6 weeks in duration. Patients successfully completing the main study continued to receive the investigational drug under a protocol treatment extension. The proposed starting dose for uridine triacetate was 60 mg/kg/day.

- The primary efficacy endpoints in the trial were hematologic and individualized for each patient. Secondary endpoints were based on urinary orotic acid and uridine exposure (PK).
- Demonstration of a “stable response” as assessed by clinical efficacy endpoints in Protocol 401.13.001 was acceptable to support marketing approval.
- For naïve patients, the change in the primary endpoint was compared after treatment with oral uridine triacetate to that at baseline.

2.2 DATA SOURCES

The sponsor’s NDA submission including the data sets and clinical reports are stored in the following link: <\\CDSESUB1\evsprod\NDA208169\0000>. An IR was sent to the sponsor for extension trial data submission and the link is: <\\Cdsesub1\evsprod\NDA208169\0010\m5>.

3 STATISTICAL EVALUATION

3.1 DATA and ANALYSIS QUALITY

The statistical reviewer confirmed the sponsor’s analysis results for the study 401.13.001 from the raw data submitted in this application. Overall, the data and the analysis quality of this NDA submission are acceptable.

3.2 EVALUATION of EFFICACY

3.2.1 Study Design and Objectives

Study 401.13.001 is an open-label study with 4 patients, entitled “Open-Labe Phase III Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria (HOA).”

During the 42-day trial patients were evaluated for the efficacy variables; pharmacokinetic evaluation of plasma uridine; and age-appropriate safety variables, including height and weight. In addition, the safety and tolerability of uridine triacetate were continued to be monitored approximately every 6 months in a separately-reported Treatment Extension study. The dose of uridine triacetate could be adjusted upwards under pre-specified various conditions starting at 60mg/kg/day.

On Protocol Day 0 (Baseline) patients continued to receive their usual daily dose of oral uridine. The uridine naïve patient received neither uridine (nor uridine triacetate) on Day 0.

On Day 1, oral uridine administration was replaced by administration of oral uridine triacetate which continued daily for 6 consecutive weeks. The starting dose of oral uridine triacetate was 60 mg/kg/day, which could be escalated up to a maximum of 300 mg/kg/day. The dose of uridine triacetate could be given once a day or as equally divided doses twice a day. Signs and symptoms commonly associated with orotic aciduria were assessed at Protocol Day 0 (Baseline), Day 1, Day 28, and Day 42.

The primary objectives of this clinical study were the following:

Main study

- To replace oral administration of uridine with oral administration of uridine triacetate in patients 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 for 6 weeks.

Treatment extension

To provide continued access to uridine triacetate as a source of uridine to patients with HOA who have completed 6 weeks of treatment in the Main Study.

Secondary objectives of this study were:

- 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.

3.2.2 Efficacy Endpoints and Analysis

Primary endpoints

The following table shows the primary efficacy endpoints for each patient along with the rationale for the choice of each variable.

Table 3.1: List of Individual Primary efficacy variables

Patient	Primary efficacy variable	Notes
(b) (6)	Neutrophils	Patient (b) (6) had shown increased neutrophil count following institution of uridine treatment and decreased count during a uridine holiday
(b) (6)	White blood cell count	Patient (b) (6) had a 10-year history of stability with uridine treatment. The Principal Investigator noted that early in (b) (6) history (b) (6) manifested a low white blood cell count.
(b) (6)	Mean corpuscular volume	Patient (b) (6) has had documented macrocytosis since diagnosis in (b) (6). Additionally, the patient had a history of red blood cell counts below current laboratory normal ranges, but with hemoglobin levels within normal range. Treatment with uridine produced stable mean corpuscular volume.
(b) (6)	Mean corpuscular volume	Patient (b) (6), a (b) (6) of (b) (6), was diagnosed with macrocytosis and began treatment with uridine triacetate during the study with no previous exposure to uridine. This patient also had a history of red blood cell counts below current laboratory normal ranges, but with hemoglobin levels within normal range.

Source: Sponsor's Table 9-2 of 401-13-001 body.pdf of the NDA

Secondary endpoints

- Levels of orotic acid and orotidine in urine (Days 0, 1, 28 and 42)
- Plasma levels of uridine in treated patients (Days 0, 1 and 28)

Primary Analysis

Three Experienced patients

The criteria for a stable response in patients previously receiving oral uridine is as follows:

- Assess whether the baseline (Day 0) value is within the laboratory reference range (LRR) expected for that patient.
 - If the value is in the LRR expected for that patient at Day 0 and remains within the LRR expected for that patient at Days 28 and 42, then the response is considered stable.
 - If the value is outside the LRR expected for that patient at Day 0 and improves or the values worsen no more than 15% to 30% when compared to baseline (Day 0) at Day 28 and Day 42, then the responses considered stable.

One Naïve patient

The primary efficacy endpoint is the stability within the LRR or improvement in the patient's principal affected hematologic parameter(s) on Days 28 and 42 compared to baseline (Day 0).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 3.2 displays patients' baseline and demographic characteristics. All 4 patients completed the main study and continued into the Treatment Extension of the protocol.

Table 3.2: Patients Baseline Demographics

Site	Patient	Date of Birth	Date of Informed	Age	Height	Height unit	Weight	Weight unit	Sex	Race
(b) (6)										

3.2.4 Sponsor's Efficacy Results and Conclusions

(1) 42-day Main Study:

1. Table 3.3 shows that replacement of oral uridine with 60 mg/kg oral uridine triacetate in patients with HOA at least maintained the clinical stability of the patients with no

untoward impact on the patients. Furthermore, all patients either continued to benefit from treatment or benefited from initiation of treatment.

2. Urinary orotic acid and orotidine concentrations remained essentially within normal levels.
3. Three patients' heights and weights increased from Baseline to Day 42 except that for Patient (b) (6), whose height remained the same but weight increased from Baseline to Day 42.
4. There was no adverse event attributed to uridine triacetate and no safety concern emerged during the study.

(2) 6-month Treatment Extension:

1. Neutrophil percent and neutrophil counts in Patient (b) (6), have risen into the normal reference range for the first time in this patient's life. In addition, Patient (b) (6) initiated a dose increase from the initial 56 mg/kg/day to 95 mg/kg/day.
2. All four patients appear to have had growth increases over the 5 to 6 months of uridine triacetate treatment.
3. Two of the patients, (b) (6) and (b) (6), initiated a dose increase from the initial 60 mg/kg/day to 120 mg/kg/day, with corresponding increases in plasma uridine exposure assessed by pharmacokinetic measurements. This increased dose has been well tolerated with no safety concerns.

Table 3.3 Summary of Primary Efficacy Results

Patient ID	Age/Sex/Race	Pre-Determined Hematologic Parameters	Normal Range	Visit	Value	% Change from baseline
(b) (6)		Neutrophils PER (%)	26-48	Baseline	21	
				Day 28	26	23.8
				Day 42	23	9.6
				6 months extension	31	48
		WBC (k/mL)	3.9-10.6	Baseline	7.8	
				Day 28	7.8	0.0
				Day 42	7.4	-5.1
				6 months extension	6.7	-14
		MCV (fL)	75-91	Baseline	109.9	
				Day 28	107.4	-2.3
				Day 42	108.5	-1.3
				5 months extension	108	-2
		MCV (fL)	72-90	Baseline	114.6	
				Day 28	113.3	-1.1
				Day 42	113.4	-1.0
				6 months extension	114.7	0

3.2.5 Sponsor's Conclusion

Treatment with uridine triacetate over the 42-day duration of the study resulted in stable assessments for WBC count, lymphocyte count, neutrophil % and count, RBC count, mean corpuscular volume and platelet count for all 4 patients. Thus, the primary variables of mean corpuscular volume, neutrophils, and WBC count were stable during uridine triacetate treatment for the 3 patients with a history of uridine treatment. The single treatment-naïve patient did not

show significantly improved mean corpuscular volume, but other hematologic parameters exhibited improvement.

Hematologic parameters for all 4 patients continue to show stability or improvement during the Treatment Extension period, notably in neutrophil counts in Patient (b) (6), who has had life-long neutropenia.

3.2.6 Statistical Reviewer's Findings and Comments

1. The statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints based on the sponsor's pre-specified criteria for a stable response.
2. To further assess uridine triacetate's effect on either stabilizing or improving patients' Neutrophils %, WBC count and MCV, the statistical reviewer produced patient profile graphs (Figures 3.1-3.4) to illustrate the patients' progress over time including pre-treatment, during treatment under main study and extension trial period. The observations are summarized as follows.

Main study

- 1) Patient (b) (6): the baseline measurement of WBC count was within the LRR and both Day 28 and 42 WBC counts remained in the LRR (3.9 to 10.6);
- 2) Patients (b) (6) and (b) (6): their baseline measurements of Neutrophils% and MCV, respectively were outside the LRRs (26% to 48% and 72 to 91), the changes from baseline in Day 28 and 42 were no more than 30%;
- 3) Patient (b) (6) is a naïve patient, the baseline measurement of MCV was outside LRR (72 to 91), the changes from baseline in Day 28 and 42 stayed within 1%. But in Figures 5.1 and 5.2, the baseline measurements for Neutrophils% and WBC count were within the LRR, the changes from baseline in Day 28 and 42 stayed in the LRR.

Extension trial

- 1) For Patient (b) (6), the Neutrophils% increased to 31% which is in the LRR.
 - 2) For Patient (b) (6), the WBC count stayed in the LRR.
 - 3) For Patients (b) (6) and (b) (6), MCV stayed almost the same as those measurements in the main study.
3. For secondary endpoint OA, bar graphs were used to examine patients' stability over time (see Figures 5.4-5.7). For Patient (b) (6), at the end of the extension trial, the OA level jumped by more than twofold compared to that at the baseline (6.9 versus 2.9). All the other patients' OA levels remained within normal levels for both the main study and the extension trial period. Of note, Patient (b) (6) was re-assessed at an unscheduled visit after a high value of OA (6.9) was observed at the end of the extension and the value was then reduced to 3.2, which is near the normal range (≤ 2.8).

4. Figure 5.8-5.9 display patients' height and body weight over time. As seen in the graphs, their weights and heights were increased at the end of the extension trial except for Patient (b) (6) whose height decreased slightly. There are some very small variations for all patients' heights and weights during the treatment under main study and the variations can be counted as measurement errors.



Source: Created by Statistical Reviewer

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4 SUMMARY AND CONCLUSIONS

The sponsor submitted one open-label phase 3 study with 4 patients to demonstrate the maintenance effect of uridine triacetate as uridine replacement therapy in pediatric patients with hereditary orotic aciduria (HOA). The primary endpoints included Neutrophils, WBC count and MCV, and each patient had his/her own primary endpoint. The statistical reviewer confirmed the sponsor's efficacy findings. In summary, based on four patients' measurements of primary endpoints across both main study and extension trial period: 1) Patient (b) (6) baseline measurement of WBC count was within the LRR and after switching to uridine triacetate, the WBC counts remained within the LRR; 2) Patients (b) (6) and (b) (6)'s baseline measures were outside the LRR, the changes from baseline after

switching to uridine triacetate were less than 25% and 1%, respectively in the main study. In the extension trial period, Patient (b) (6)'s Neutrophils% increased to 31% which is in the LRR and Patient (b) (6) MCV remained the same; and 3) Patient (b) (6) baseline measurement of MCV was outside the LRR, the changes from baseline after taking uridine triacetate stayed within 1%, but the patient's other hematologic parameters showed improvement.

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