1 TITLE PAGE

SPONSOR:	OxThera IP AB Dragarbrunnsgatan 45 SE-753 20 Uppsala Sweden
CLINICAL STUDY REPORT	
PROTOCOL ID / NUMBER	OC3-DB-02
EUDRACT NUMBER	2009-015817-31
INVESTIGATIONAL PRODUCT	Oxabact™
STUDY TITLE	A Phase 2/3, Double-blind, Randomized, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Oxabact™ to Reduce Urinary Oxalate in Subjects with Primary Hyperoxaluria.
INDICATION(S)	Primary Hyperoxaluria
DEVELOPMENT PHASE	Phase 2/3
COORDINATING CRO	PSR Group Crown Business Center Schiphol Planetenweg 5 2132 HN Hoofddorp The Netherlands
INSTITUTION	
REPORT VERSION & DATE	Version 1.0; 4 July 2011
DATE FIRST PATIENT ENTERED **DATE LAST PATIENT COMPLETED**	18 January 2010 14 January 2011

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THIS STUDY WAS PERFORMED IN COMPLIANCE WITH GOOD CLINICAL PRACTICE, INCLUDING THE ARCHIVING OF ESSENTIAL DOCUMENTS

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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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2 SYNOPSIS

Name of Sponsor:	OxThera IP AB Dragarbrunnsgatan 45 SE-753 20 Uppsala Sweden	
Name of Finished Product:	Oxabact™	
Name of Active Ingredient:	*Oxalobacter formigenes*, strain HC-1	
Title of study:	A Phase 2/3, Double-blind, Randomized, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Oxabact™ to Reduce Urinary Oxalate in Subjects with Primary Hyperoxaluria.	
Investigators and study centers: USA Germany The Netherlands	 Dr. Dawn Milliner, Mayo Clinic, Department of Nephrology, Rochester, USA Dr. Bernd Hoppe, University Children's Hospital, Division of Pediatric Nephrology, Cologne, Germany Dr. Jaap Groothoff, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands	
Publication (reference):	Not applicable	
Study period:	First subject entered: 18 January 2010 Last subject completed: 14 January 2011	
Development Phase:	Phase 2/3	

Objectives:	**Primary objective:** • To evaluate the efficacy of Oxabact™ to reduce urinary oxalate levels from baseline to Week 24 in subjects with Primary Hyperoxaluria (PH). **Secondary objectives:** • To evaluate the safety of Oxabact™ administered for 24 weeks in subjects with PH. • To evaluate the efficacy of Oxabact™ from baseline to Week 24 as regards: - reduction in urinary oxalate levels in various subsets of subjects. - percentage of subjects who have ≥20% reduction in urinary oxalate levels. - reduction in plasma oxalate levels and its correlation to reduction in urinary oxalate levels. - frequency of stone events. • To evaluate the efficacy of Oxabact™ from baseline to Week 8.
Methodology:	This study was a double-blind, randomized, placebo-controlled, multi-center, international study to evaluate the efficacy and safety of Oxabact™ in the reduction of urinary oxalate in subjects with PH. Following screening, eligible subjects were randomized 1:1 to receive Oxabact™ or placebo twice daily for 24 weeks. The randomization was stratified by glomerular filtration rate (GFR) and region (USA or EU). An interim analysis for futility based on the percentage change in urinary oxalate levels (expressed as molar oxalate to creatinine ratio) from baseline to Week 8 was performed in the efficacy population by an independent unblinded statistician on the Data Monitoring Committee (DMC), who had no other involvement with the study. The DMC also evaluated the safety data from the study at the time point for the futility analysis. The DMC provided a recommendation to continue or terminate the trial based on the results of this analysis.
Number of patients:	Total 36: USA: 16 Germany: 15 The Netherlands: 5

Diagnosis and main criteria for inclusion:	Male or female subjects ≥2 years of age with a diagnosis of PH I or PH II and urinary oxalate excretion of >1.0 mmol/1.73 m^2/day at baseline; subjects were on a stable pyridoxine treatment regimen and had an estimated glomerular filtration rate (eGFR) ≥40 mL/min/1.73 m^2. **Inclusion criteria:** 1. Signed informed consent (as applicable for the age of the subject) 2. Male or female subjects ≥2 years of age 3. A diagnosis of PH I or PH II (as determined by standard diagnosis methods) 4. A mean urinary oxalate excretion of >1.0 mmol/1.73 m^2/day at collections performed during screening. 5. Renal function defined as an estimated GFR ≥40 ml/min normalized to 1.73 m^2 body surface area, or a creatinine clearance of ≥40 ml/min normalized to 1.73 m^2 body surface area. 6. Subjects receiving pyridoxine must be receiving a stable dose for at least 3 months prior to entry into the study and must remain on the stable dose during the study. Subjects not receiving pyridoxine at study entry must be willing to refrain from initiating pyridoxine during study participation. **Exclusion criteria:** 7. Inability to collect 2 complete 24-hour urine samples. Each urine collection will be evaluated for completeness based on the urine acceptance criteria 8. Pyridoxine naïve subjects diagnosed as PH I, whose genotype suggests responsiveness to pyridoxine treatment. 9. Subjects that have undergone transplantation (solid organ or bone marrow). 10. The existence of secondary hyperoxaluria, e.g., chronic gastrointestinal diseases such as cystic fibrosis, chronic inflammatory bowel disease and short-bowel syndrome. 11. Current systemic (oral, intramuscular, intravenous) antibiotic use or received systemic antibiotics within 14 days of study enrolment. 12. History of a recurrent infection requiring >2 courses

	of systemic antibiotics in the past 6 months, or chronic antimicrobial suppression. 13. Subjects who require immune suppressive therapy (including prednisone of >10 mg daily for more than 2 weeks). 14. Current treatment with a separate ascorbic acid preparation. Ascorbic acid up to 250 mg/day as a component of a multivitamin formulation is not excluded. 15. Known hypersensitivity to esomeprazol (or any of the other ingredients of this medicine), or to any other proton pump inhibitor (PPI) medicine (Nexium contraindication). 16. Concomitant treatment with atazanavir (Nexium contraindication). 17. Pregnancy. 18. Women of child-bearing potential who are not using adequate contraceptive precautions. Sexually active females, unless surgically sterile or at least 2 years post-menopausal, must be using a highly effective contraception (including oral, transdermal, injectable, or implanted contraceptives, intra-uterine device (IUD), abstinence, use of a condom by the sexual partner or sterile sexual partner) for 30 days prior to the first dose of Oxabact™ and must agree to continue using such precautions during the clinical study. 19. Presence of a medical condition that the Principal Investigator considers likely to make the subject susceptible to adverse effect of study treatment or unable to follow study procedures. Note: Subjects from correctional facilities or asylums and subjects who are mentally handicapped are not to be included in the study. 20. Participation in any study of an investigational product, biologic, device, or other agent within 30 days prior to randomization or not willing to forego other forms of investigational treatment during this study.
Test Product:	The study drug consists of Oxabact™ . Due to the pH sensitivity of the *O. formigenes*, the subjects also took a once daily dose of a PPI; Nexium

	(esomeprazol) delayed-release oral suspension, while on study drug. Nexium was given to all subjects, whether on active treatment or placebo.
Dose:	Twice daily dose of lyophilized *O. formigenes* (500 mg, not less than (NLT) 10^7 colony forming units (CFU)/dose) and a buffer powder (1.5 g sodium bicarbonate and 0.5 g citric acid), to be mixed and reconstituted with water prior to administration. Dosing was on fasted stomach 30-60 minutes before breakfast and dinner, i.e., twice daily. Children up to the age of 11 will receive 10 mg Nexium once daily, and from the age of 12 subjects will receive 20 mg Nexium once daily.
Mode of administration	Oral, twice daily
Batch numbers:	94805-1001-27, 94805-1004-63, 94805-1007-06, 94805-1001-16
Duration of treatment:	24 weeks; with 4 weeks post-treatment follow-up. In case repeat urine collection needed to be performed beyond Week 24, the study treatment was continued until the repeat collection was completed, i.e., up to Week 28 at the longest.
Reference therapy:	Placebo for Oxabact™ with the same appearance as the active product.
Criteria for evaluation:	**Efficacy:** Primary endpoint: • Percentage change in urinary oxalate levels (expressed as molar oxalate to creatinine ratio) from baseline to Week 24. Secondary endpoints: • Percentage change in urinary oxalate levels (expressed as molar oxalate to creatinine ratio) from baseline to Week 8 • Percentage change in urinary oxalate levels (expressed as molar oxalate to creatinine ratio) from baseline to Week 24 in subsets of subjects defined by: o baseline urinary oxalate level, above and below median at screening o concomitant vitamin B6 therapy and no vitamin B6 therapy, in PH type I

	o eGFR of ≥90 mL/min/1.73 m^2 (normal renal function) and <90 mL/min/1.73 m^2 (mild to moderate reduction in renal function) o PH Type I and PH Type II o age below 18 and age 18 or above • Percentage of subjects who have ≥20% reduction from baseline urinary oxalate at Week 24. • Percentage change in plasma oxalate levels. • Frequency of stone events (i.e., nephrolithiasis or markers thereof) • Correlation between percentage change in plasma oxalate levels and percentage change in urinary oxalate levels, from baseline to Week 24 **Safety:** • Adverse events (AEs), hematology, clinical chemistry, urinalysis, vital signs and physical examinations
Statistical methods:	**Efficacy:** The primary endpoint, percentage change in urinary oxalate to creatinine ratio, was evaluated using a Wilcoxon-Mann-Whitney test. All secondary endpoints based on percentage changes were also analyzed using a Wilcoxon-Mann-Whitney test. Percentage of subjects having ≥20% reduction in urinary oxalate was analyzed using Fisher's Exact tests. Frequency of stone events was summarized using descriptive statistics and frequency tables. Correlation between percentage change in plasma oxalate levels and percentage change in urinary oxalate levels was analyzed using Spearman rank correlations. **Safety:** The safety data was summarized using descriptive statistics based on frequency, seriousness and severity of AEs. Clinically relevant changes in safety laboratory parameters were also summarized. **Interim futility analysis:** An unblinded interim analysis for futility was performed. The study was not to be stopped prematurely for efficacy benefit. The interim analysis was based on the percentage

	change in urinary oxalate levels (expressed as molar oxalate to creatinine ratio) from baseline to Week 8 for the efficacy population. This analysis was based on the first 16 subjects randomized into the study who meet the efficacy population definition and have two eligible 24-hour urine collections. The futility analysis was based on a conditional power of current trend approach, where the conditional power cut-off was set at 20%. The unblinded interim analysis was performed by an independent statistician, who was not a member of the study team, and who had no other involvement with the trial.
Results	**Efficacy results:** The primary efficacy analysis showed no reduction of the urinary oxalate following treatment with Oxabact™ for 24 weeks compared to placebo. Both treatments showed a slight decrease in the urinary oxalate compared to baseline. Also after 8 weeks treatment, no difference was observed between Oxabact™ and placebo treatment. The reduction of the urinary oxalate was analyzed in several subsets of subjects, including subject populations based on disease characteristics, age and region. Decreases in urine oxalate were seen in the Oxabact™ group as well as in the placebo group. A significant treatment difference in favor of Oxabact™ treatment was not found. Oxabact™ treatment showed no effect on the overall proportion of responders following 24 weeks of treatment. The percentage responders in the Oxabact™ and placebo group was 25% (5/20) and 42% (5/12), respectively. Oxabact™ treatment did not result in a clinically relevant reduction of the plasma oxalate levels. **Safety results:** Treatment emergent adverse events (TEAEs) were most frequently reported in the placebo group (63 events reported by 14 (93.3%) subjects) compared to the

	Oxabact™ group (37 events reported by 15 (71.4%) subjects). The most frequently reported TEAEs were infections and infestations as well as gastrointestinal disorders. Gastrointestinal disorders were reported for 9 events by 6 subjects (29%) in the Oxabact™ group and for 19 events reported by 8 subjects (53%) in the placebo group. Renal and urinary disorders (i.e., nephrolithiasis and renal colic) were also frequently reported. All of these TEAEs were most frequently reported with placebo. Of all gastrointestinal TEAEs reported, the vast majority were reported within the first 4 weeks after start of study drug administration. The majority of the TEAEs were of mild or moderate intensity and considered by the investigator to be not related to the Oxabact™ treatment. In general, there were more TEAEs with higher severity in the placebo group. Most of the events which were considered related to Oxabact™ treatment were gastrointestinal disorders; 5 possibly related events reported in 4 subjects (19%). In the placebo group, 8 possibly/probably related gastrointestinal events were reported in 3 subjects (20%). One subject was withdrawn from the study due to TEAEs (abdominal pain, flatulence and frequent bowel movements) after three weeks treatment with placebo. Two subjects experienced serious adverse events (SAEs) that were unrelated to study medication; nephrolithiasis/urinary tract infection after 1 week of placebo treatment and nephrolithiasis after 23 weeks of placebo treatment. There were no deaths. Most of the TEAEs were transient and had resolved without sequelae at the time of follow-up. The gastrointestinal problems in one subject who withdrew due to these TEAEs were resolved 4 weeks after discontinued placebo treatment. In one subject, dyspepsia, probably related to Nexium, was reported after 24 weeks of placebo treatment. This TEAE was still not recovered 13 weeks post-treatment. In another

	subject, epistaxis, possibly related to Nexium, was reported after 13 weeks of placebo treatment and this TEAE was still not recovered 7 weeks post-treatment. Overall, treatment with multiple doses of Oxabact™ twice daily was safe and well tolerated.
Conclusions:	- Treatment with Oxabact™ twice daily showed no effect on the reduction of urinary oxalate in subjects with PH after 8 and 24 weeks of treatment. - Treatment with Oxabact™ twice daily showed no statistically significant effect on the reduction of urinary oxalate in subsets of subjects based on disease characteristics, age and region and other subpopulations. - Decreases of the urinary oxalate over time were seen in the Oxabact™ group as well as in the placebo group for subjects with cross-sectional data and subjects with 24 weeks longitudinal data. - No treatment difference in number of responders (≥20% reduction from baseline urinary oxalate at Week 24) was found. - No clinically relevant treatment difference in the percentage change in plasma oxalate levels was found. - No correlation was found between change in urinary oxalate and change in plasma oxalate levels for the Oxabact™ or placebo group. - There was no difference in the percentage of subjects who experienced stone events between Oxabact™ and placebo. - Treatment with multiple doses of Oxabact™ twice daily for 24 weeks was safe and well tolerated in subjects with PH.
Date of the report:	4 July 2011