OXABACT™ (OC3)

OC3-DB-01

A Phase 2/3, Double-blind, Randomized, Placebo-controlled, Multi-center, International Study to Evaluate the Efficacy and Safety of Oxabact™ to Reduce Urinary Oxalate in Subjects with Primary Hyperoxaluria.

Indication studied:	*Primary Hyperoxaluria*
Developmental phase of study:	*Phase 2/3*
Investigational product:	*Oxabact™ (OC3)* *(NLT 10^7 CFU Oxalobacter formigenes), administered for 24 weeks*
First patient enrolled:	*28 September 2007*
Last patient completed:	*12 September 2008*
Release date of report:	*11 June 2009*

Principal Investigators:

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2. SYNOPSIS

Name of Sponsor/Company: OxThera AB	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Oxabact™ (OC3)		
Name of Active Ingredient: *O. formigenes* strain HC-1		

Title of Study: A Phase 2/3, Double-blind, Randomized, Placebo-controlled, Multi-center, International Study to Evaluate the Efficacy and Safety of Oxabact™ to Reduce Urinary Oxalate in Subjects with Primary Hyperoxaluria.

Principal Investigators: Bernd Hoppe MD PhD, Jaap W Groothoff MD PhD, Dawn Milliner MD, Pierre Cochat MD, Sally-Anne Hulton MD, Patrick Niaudet MD, Markus J Kemper MD, PhD, George Deschenes MD, Robert Unwin MD

Study Center(s): University Children's Hospital, Cologne, Germany; Emma Children's Hospital, Academy Medical Centre, Amsterdam, The Netherlands; Mayo Clinic, Rochester, Minnesota, USA; Edouard Herriott Hospital, Lyon, France; Birmingham Children's Hospital, Birmingham, UK; Hôpital Necker-Enfants Malades, Paris, France; University Children's Hospital, Hamburg, Germany; Hôpital Robert Debré, Paris, France; Royal Free and University College Medical School, London, UK.

Publications (reference):
Not Applicable

Studied period (years):	**Phase of development:**
Date first patient enrolled: 28 September 2007 Date last patient completed: 12 September 2008	2/3

Objectives:
Primary:

- To evaluate the efficacy of OC3 to reduce urinary oxalate levels from Baseline to Week 24 in subjects with Primary Hyperoxaluria (PH).

Secondary:

To evaluate:

- Percentage of subjects who have 20% or greater reduction from Baseline urinary oxalate at Week 24.
- The effect of OC3 on plasma oxalate levels at week 24.
- The effect of OC3 on reduction of calcium oxalate (Ca-oxalate) super saturation.
- The safety of OC3 administered for 24 weeks in subjects with PH.

Methodology: This was a double-blind, placebo-controlled, multi-center, international, clinical study to evaluate the safety and efficacy of OC3 in the reduction of urinary oxalate levels in subjects with PH. Eligible subjects enrolled in the study were randomized (1:1) in each region (EU and US) to receive either study drug or placebo twice daily with meals for 24 weeks. Subjects who completed study treatment were eligible to participate in an extension study where all subjects were planned to receive open label OC3 (Protocol number OC3-OL-01).

Number of patients (planned and analyzed): 50 patients planned; 58 screened; 43 randomized; 41 completed. Analysis groups: safety population: 42, efficacy population: 42, evaluable population: 38. Ad hoc analysis group: 37.

Diagnosis and main criteria for inclusion: Male or female subjects ≥ 5 years of age with a diagnosis of PH I or PH II and urinary oxalate excretion of > 1.0 mmol/1.73m^2/day at Baseline; subjects were either on a stable pyridoxine treatment regimen or pyridoxine- non-responders and have estimated glomerular filtration rate (eGFR) ≥ 50 mL/min normalized to 1.73m^2 body surface area.

Test product, dose and mode of administration, batch number: OC3 (OxThera code for Oxabact^{TM}) gastro-resistant (enteric-coated) HPMC capsules containing not less than (NLT) 10^7 colony forming units (CFU) of lyophilised *O. formigenes* (*strain HC-1*) for oral administration.

Batch numbers (active capsules – bulk drug product): 94801-0705-09, 94801-0706-09, 94801-0708-16, 94801-0709-14, 94801-0803-08.

Duration of treatment: 24 weeks.

Reference therapy, dose and mode of administration, batch number: Placebo in gastro-resistant (enteric-coated) HPMC capsules for oral administration.

Batch numbers (placebo capsules – bulk drug product): 94801-0705-29, 94801-0706-04, 94801-0706-05, 94801-0709-15

Criteria for evaluation:

Efficacy:

Primary endpoint:

Percentage change in urinary oxalate (expressed as mmol/1.73m^2/day) from Baseline to Week 24 (day 168).

Secondary endpoints:

- Percentage of subjects who are responders (defined as a ≥ 20% reduction in urinary oxalate from Baseline) at Week 24.
- Percentage change in urinary oxalate to Week 12.
- Percentage of subjects who have a ≥ 30% reduction in urinary oxalate from baseline to Week 24.
- Percentage change in urinary oxalate to Week 24.
- Percentage change in urinary oxalate to average of Weeks 12 and 24.
- Change in urinary calcium oxalate supersaturation from Baseline to Week 24.
- Change in urinary oxalate levels to Week 24 in patients with normal renal function and patients with mild to moderate reduction in renal function.
- Change in urinary oxalate levels to Week 24 in patients with PH I or PH II.
- Change in urinary oxalate levels to Week 24 in patients aged ≤ 16 years or ≥ 17 years.
- Change in plasma oxalate levels at Weeks 12 and 24.
- Correlation between change in plasma oxalate levels and in urinary oxalate at Weeks 12 and 24.
- Urinary oxalate and calcium oxalate supersaturation index.
- Creatinine clearance and estimated GFR, summarised by treatment group and time point.

Safety:

Frequency of adverse events (AEs) and serious adverse events (SAEs); laboratory safety data.

Statistical methods: The safety population consists of all randomized subjects who received at least one dose of study drug. Safety analyses were based on the safety population. The efficacy population includes all randomized subjects who received at least one dose of study drug and who provided at least one post-baseline measurement of urinary oxalate. The primary efficacy analyses were based on the efficacy population. The evaluable population includes all randomized subjects who complete the 24-week study period, provide at least one post-Screening measurement of urinary oxalate and receive at least 80% of scheduled doses of study drug per month until the post-Screening measurement time point, with 100% compliance on the days of 24-hour urine collection. Subjects who received antibiotic therapy during or within 14 days prior to a 24-hour urine collection period were excluded from assessment in the evaluable population for that specific urinary oxalate time point. Primary and secondary efficacy endpoint analyses were also performed in the evaluable population.

The primary efficacy analysis compared the percentage changes in urinary oxalate in the Oxabact™ (OC3) and Placebo groups using a two-sided, two-sample non-parametric Wilcoxon rank sum test. This analysis was carried out in the efficacy and evaluable populations.

With the exception of the percentage of subjects who were responders, all secondary efficacy and other endpoints were analyzed using two-sided, two-sample non-parametric Wilcoxon rank sum test to compare the means in the OC3 and Placebo groups. Fisher's exact test was used to compare the percentages of subjects who were responders in the two groups. No analysis other than summaries was performed for the measures of creatinine clearance, estimated GFR and for the quality of life assessments. All statistical analyses were performed using SAS® (Version 8.2).

As a separate ad hoc analysis the primary efficacy endpoint was evaluated for urine collections fulfilling certain eligibility criteria. The ad hoc analyses were also performed for the two largest sites combined in order to minimize the influence of varying procedures for urine collection, handling and shipping. Two-sided, two-sample t-tests were used.

SUMMARY – CONCLUSIONS

Efficacy results: Analysis of the primary efficacy endpoint, percentage change in urinary oxalate (mmol/1.73m^2/day from baseline to Week 24) showed that there was no overall treatment difference between the OC3 and placebo treatment groups in the Efficacy Population. Analysis of each of the secondary efficacy endpoints revealed no notable differences between the OC3 and placebo treatment groups in either the Efficacy or Evaluable Populations. Low numbers of subjects in some groups made meaningful comparisons difficult.

Based on further ad hoc analyses, treatment with OC3 is deemed to be a feasible approach to lowering urinary oxalate in patients with Primary Hyperoxaluria. The effect size seen in this study was however not in line with previous clinical studies.

Safety results: Overall, there were no safety issues raised and the reported adverse events were essentially equally distributed between the OC3 and placebo treatment groups in terms of number, severity, relationship and seriousness.

CONCLUSION:

- OC3 treatment is safe and well tolerated.
- Original analyses did not show any significant difference between OC3 and placebo on reduction of urinary oxalate.
- Ad hoc analyses suggest that treatment with OC3 may lower urinary oxalate in patients with Primary Hyperoxaluria.
- Based on results from the recently completed and earlier clinical studies, OxThera plans to investigate parameters such as product formulation and urine handling. Results of these investigations will be used to modify study design and conduct related to urine collection and processing in future studies.

Date of report: 11 June 2009