TITLE PAGE

OXABACT™ (OC3-OL-01)

An Open-Label (OL) Extension Study Evaluating the Long-Term Safety of Oxabact™ in Subjects with Primary Hyperoxaluria (PH) who Participated in the Double-Blind (DB) Efficacy Study.

Indication studied:	*Primary Hyperoxaluria*
Developmental phase of study:	*Phase II/III*
Investigational product:	*Oxabact™* *(NLT 10^7 CFU Oxalobacter formigenes), administered for 24 weeks*
First subject enrolled:	*21 April 2008*
Last subject completed:	*02 March 2009*
Release date of report:	*29 October 2009*

Principal Investigators:

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2. SYNOPSIS

Name of Sponsor/Company: OxThera AB **Name of Finished Product:** Oxabact™ (OC3) **Name of Active Ingredient:** *O. formigenes* strain HC-1	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: An Open-Label (OL) Extension Study Evaluating the Long-Term Safety of Oxabact™ in Subjects with Primary Hyperoxaluria (PH) who Participated in the Double-Blind (DB) Efficacy Study.		
Principal Investigator: Bernd Hoppe MD PhD, Jaap W Groothoff MD PhD, Dawn Milliner MD, Pierre Cochat MD, Patrick Niaudet MD, Markus J Kemper MD, PhD, George Deschenes MD, Robert Unwin MD		
Study center(s): University Children's Hospital, Cologne, Germany; Academy Medical Centre, Amsterdam, The Netherlands; Mayo Clinic, Rochester, Minnesota, USA; Edouard Herriott Hospital, Lyon, France; 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): Date first subject enrolled: 21 April 2008 Date last subject completed: 02 March 2009		**Phase of development:** II/III
Objectives: Primary: • To evaluate the Safety of OC3 with continued exposure. Secondary: • To obtain additional efficacy data with up to 48 weeks continuous exposure to OC3.		
Methodology: This was an open-label extension, single-arm, 6-month study evaluating the safety of OC3 with long term exposure in subjects who had completed participation in the double-blind, placebo-controlled efficacy study (OC3-DB-01). Subjects with less than 20% reduction in urinary oxalate levels at week 12 compared to time of screening in the DB study (i.e., at entry into the qualifying study OC3-DB-01) were withdrawn from the study with final safety assessment completed at week 12. All others continued in the study and were monitored for safety throughout the study period.		
Number of subjects (planned and analyzed): Up to 50 subjects planned; 36 subjects entered into the study, 13 subjects were withdrawn at week 12 per protocol, since they had less than 20% reduction in urinary oxalate from time of screening in the DB study. Two additional subjects were withdrawn prior to week 24. In total, 21 subjects completed the study. Safety Population (all analyses): 36 subjects.		

Diagnosis and main criteria for inclusion: Male or female subjects ≥ 5 years of age who had completed the DB study; receiving stable dose of pyridoxine if appropriate.

Test product, dose and mode of administration, batch number:

OC3 (OxThera code for Oxabact™) enteric-coated hydroxypropylmethylcellulose (HPMC) capsules containing not less than (NLT) 10^7 colony forming units (CFU) of lyophilised *O. formigenes* (*strain HC-1*) for oral administration. Subjects received one OC3 capsule twice daily with water after meals, for 12 to 24 weeks.

Batch numbers (active capsules – bulk drug product): 94801-0804-20, 94801-0805-18, 94801-0808-07, 94801-0809-19, 94801-0811-35.

Duration of treatment: 12 to 24 weeks.

Reference therapy, dose and mode of administration, batch number: Not applicable.

Criteria for evaluation:

Efficacy:

- Percentage of subjects who received either placebo or OC3 in the qualifying DB study and have ≥30% reduction in urinary oxalate at 24 weeks from entry into OL study
- Percentage of subjects who received placebo in the qualifying DB study and have ≥20% reduction in urinary oxalate at 24 weeks from entry into OL study
- Percentage of subjects randomized to the treatment arm of DB study that demonstrate continued reduction (≥20%) in urinary oxalate at 48 weeks from screening of DB study
- Reduction in urinary Ca-oxalate super-saturation
- Stabilization or change in glomerular filtration rate (GFR)
- Incidence of renal stones and/or signs and symptoms of renal stones
- Reduction in burden of Ca-oxalate stones

Safety:

- Frequency and severity of adverse events (AEs)
- Abnormal laboratory values
- Clinically relevant changes in physical exams and vital signs

Other endpoints

- Quality of Life assessment was assessed using the Kidney Disease and Quality of Life (KDQOL™ -36) survey at weeks 12 and 24 in adults
- The Quality of Life assessment in children and adolescents was assessed with using the Child Health Questionnaire (CHQ), at weeks 12 and 24

Statistical methods:

All subjects completing the qualifying DB study and willing to participate in the open-label extension were allowed to enter the open-label study. For this reason, the sample size was not based on statistical considerations. It was estimated that the majority of subjects would be enrolled from the qualifying DB study.

The primary analysis population was the Safety Population, defined as all subjects who received at least one dose of study drug in the OL study. This population was used in all data summaries.

Of the 41 subjects completing to week 24 of the DB study, 36 subjects entered the OL study and five did not consent to participate in the OL study (all five subjects from one site).

In all summary presentations looking only at data from the OL study, OL baseline was defined as the result at week 24 of the DB study (week 0 of OL study). For summary presentations where data from the DB study was also considered, DB baseline was defined to be the result at screening (or latest assessment prior to initiation of study medication) for the DB study. Endpoints that used data from both the DB and OL studies are percentage reduction in urinary oxalate to creatinine ratio for subjects randomised to OC3 in the DB study and incidence of stone events for all subjects.

For four subjects, who had a urinary oxalate reduction at week 12 of < 20%, but who were not withdrawn from the study due to the timing of the database lock for the double-blind study, any data collected post week 12 was listed only (Subjects 0501, 0502, 0503 and 0504).

Data collected at week 28 at sites in Germany was listed only.

The primary objective of this study was to evaluate the safety of OC3. Because this is a single-arm, open-label study, where the random allocation of treatment is absent and the sample size is not based on statistical considerations, no formal statistical hypotheses was tested.

No interim analyses or early termination of the study were planned or performed.

SAFETY RESULTS:

Overall, OC3 was safe and well tolerated in the OL extension study with no unexpected safety issues raised and the adverse events reported were essentially evenly distributed between subjects who had previously received OC3 treatment compared with those who had received placebo in terms of severity, seriousness and relationship.

A total of 149 adverse events (AEs) were reported in 31 (86%) subjects. The most frequently reported AEs were gastrointestinal symptoms (16 subjects) including abdominal pain, diarrhoea and vomiting. The most commonly reported treatment related adverse events were gastrointestinal symptoms (7 subjects); typically mild abdominal pain. Three serious AEs were reported in two subjects. These were all considered consequences of renal stone obstruction and not related to the study drug.

EFFICACY RESULTS:

Stone events: A greater proportion of subjects who received placebo in the DB study [13 (65.0%)] experienced a stone event (renal stones and/or signs and symptoms of renal stones) compared with those who had received OC3 [5 (31.3%)]. The mean incidence of stone events, adjusted for a 48 week study period, was 0.46 (SD: 0.89) and 0.84 (SD: 1.00) in subjects who had previously received treatment with OC3 or placebo respectively. The validity of these differences should however be considered due to the inherent difficulties in defining a “new” stone event in this subject population, the relatively short follow-up time and varying exposure to study drug.

Renal function: Overall, estimated glomerular filtration rate (eGFR) did not change during the study. Similar results were seen in subjects with Stage II and Stage III chronic kidney disease. Changes in this

parameter were not expected during this relatively short follow-up.

Plasma oxalate: Overall, there were no clinically relevant changes in plasma oxalate during the study.

Urinary oxalate: The majority of subjects [24 (85.7%) subjects] did not show a ≥20% reduction in urinary oxalate to creatinine ratio during this OL study (i.e. did not meet responder criteria).

Among the seven subjects that were given OC3 for 48 weeks (DB and OL study combined) the mean reduction in urinary oxalate per creatinine ratio (Ox:Cr) was 24%. At the end of study, 2 of these subjects were non-responders and 5 remained responders. The corresponding reduction in Oxalate:Creatinine ratio among the seven subjects, who received placebo for 24 weeks during the DB study followed by 24 weeks of OC3 treatment in this OL study, was 23%; however, the reduction during the preceding 24 weeks of placebo treatment was 19% for this subgroup of subjects. Three of these subjects had an additional reduction of ≥20% during the OL study alone.

CONCLUSION:

Investigations following the unexpected results from the DB study revealed that the compliance with urine collection and specimen handling procedures was poor. As reported in the DB study the within-subject variability in urinary oxalate and creatinine complicated the assessment of treatment effect based on urinary oxalate also in this study.

Other factors affecting the study outcome may be due to changes of the investigational product implemented between the earlier phase I/II study and this phase II/III study. The OC3 product used in this study utilized an enteric coated HPMC capsule that differed from the enteric coated gelatin capsule product used in the phase I/II study. The capsule changes were implemented to improve the shelf life of the product and may have affected adequate delivery of bacteria to the lower gastrointestinal tract.

- OC3 is safe and well tolerated after up to 48 weeks of treatment.
- OC3 treatment may reduce urinary oxalate.
- Further investigations are needed to determine efficacy of OC3 treatment.

Date of the report: 29 October 2009