Name of Sponsor/Company: OREXO AB Uppsala, Sweden	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: OX17 Capsule	Volume:	
Name of Active Ingredients: Famotidine and omeprazole	Page:	

SYNOPSIS

Title of Study:
An open-label randomized observer-blind study to evaluate 24-hour intragastric pH profile at Day 1 and Day 14 during treatment with a fixed combination of a histamine type 2 receptor antagonist and a proton pump inhibitor

Investigators:
Co-ordinating investigator, Principal investigator, site 1:
Claes Jönson, MD, PhD
Principal Investigator, site 2:
Folke Sjöberg, MD, PhD
Co-Investigators, site 1:
Anders Elfvin, MD
Svein Olav Bratlie, MD
Co-Investigators, site 2:
Zoltan Bak, MD
Jonas Graf, MD
Fredrik Huss, MD, PhD
Anders Samuelsson, MD
Johan Thorfinn, MD, PhD

Study centers:
Site 1: Gastro lab
Sahlgrenska University Hospital
SE-413 45 Gothenburg
Sweden

Site 2: Berzelius Clinical Research Centre
Berzelius Science Park
SE-582 25 Linköping
Sweden

Publication (reference):
This study has not been published.

Studied period (years): 2007 **First patient in:** 26 April 2007 **First patient randomized:** 15 May 2007 **Study completion day:** 27 November 2007	**Phase of development:** II

Objectives:

Primary objective:

- To compare the proportion of time with intragastric pH>4 during the first 12 hours after study drug administration on Day 1, between treatment with a fixed combination of famotidine 10 mg and omeprazole 20 mg (OX17) and with mono-treatment with omeprazole 20 mg.

The primary variable was the proportion of time with intragastric pH>4 during the first 12 hours after study drug administration on Day 1.

Secondary objectives:

- To compare time to pH>4 on Day 1 between treatment with a fixed combination of famotidine 10 mg and omeprazole 20 mg (OX17) and with mono-treatment with omeprazole 20 mg
- To compare the 24-hour intragastric pH profile (acid-suppressive effect) between treatment with a fixed combination of famotidine 10 mg and omeprazole 20 mg (OX17), mono-treatment with famotidine 10 mg and omeprazole 20 mg. The pH profile of the treatments were evaluated, tested and compared using variables derived from the 24-hour pH-metry.
- To assess and compare the efficacy of each study treatment with regard to the need for antacid rescue medication during the treatment periods
- To assess tolerability and safety of treatments
- To assess symptoms during treatment (patient diary 2) and at baseline (patient diary 1)[1].

Methodology:

This study was an observer-blind, randomized open-label parallel-group study in patients with frequent heartburn. The patients were randomized to receive daily administrations of study treatment for a period of 14 days. Twenty-four-hour ambulatory intragastric pH measurements were performed on Day 1 and Day 14 of the treatment period. The study included six visits to the clinic. There was a wash-out period of 28 days for patients using PPIs or H_2-blockers before randomization and treatment. In case of severe heartburn episodes a rescue medication (Novalucol®) was allowed according to instructions. Patients with a history of heartburn for six months or longer, gastresophageal reflux disease confirmed by the Carlsson-Dent questionnaire and two or more episodes of heartburn per week registered in the base-line diary 1 during 2 weeks, were considered eligible if all remaining inclusion criteria and none of the exclusion criteria were met. At Visit 3-4, enrolled patients had to come to the clinic in the morning after having fasted for at least eight hours. A baseline pH measurement was performed prior to the first dose of study medication and the pH measurements did then continue for a total of 24 hours.

During the out-patient period, 11 daily doses of study medication were administrated at home, before breakfast. Any gastro-esophageal reflux symptoms and any intake (time and amount) of antacid rescue medication were noted in the patient diary 2. In the middle of the out-patient period, treatment compliance was checked by a phone call from the study nurse. On the morning of the 14 treatment day (Day 14) the patients returned to the clinic (Visit 5-6) after having fasted for at least eight hours, for a final 24-hour pH measurement, performed in the same way as the first one. On Day 15, a safety follow-up, including physical examination, electrocardiogram (ECG), routine hematology and clinical chemistry was performed. Any ongoing adverse events (AEs) were recorded[2].

[1] This secondary objective was added and included in CSP 10 1266/03 according to Amendment 1, dated 8 June 2007.

[2] Clarifications of the investigational events to be carried out in the study were added to the CSP 10 1266/03 according to Amendment 1.

Number of patients (planned and analyzed):

	Total	Treatment group		
		OX17	omeprazole	famotidine
No. planned:	**60**	**20**	**20**	**20**
No. screened:	**106**			
No. randomized:	**61**	**20**	**21**	**20**
No. randomized and treated:	**59**	**20**	**20**	**19**
Males:	**29**	**9**	**11**	**9**
Females:	**24**	**10**	**6**	**8**
Mean age (range):		**53.2 (24-65)**	**51.8 (26-65)**	**44.3 (21-65)**
No. analyzed for efficacy (FAS):	**53**	**19***	**17**	**17**
No. analyzed for efficacy (PPAS):	**50**	**18**	**16**	**16**
No. analyzed for safety:	**59**	**20**	**20**	**19**
No. completed the study:	**53**	**18**	**18**	**17**

* Patient no. 016 did not fill in a diary during the out-patient period and thus**,** 18 patients were included in the FAS for the analyses of symptoms and rescue medication in the OX17 treatment group.
Source: Table 14.1.1, 14.1.3

Diagnosis and main criteria for inclusion:
The study population consisted of male and female patients with frequent heartburn, between 18 and 65 years of age.

Inclusion criteria:
1. Age 18-65 years (inclusive).
2. Signed informed consent.
3. Frequent heartburn (2 or more episodes per week during 14 days prior to Visit 3).[3]
4. A history of episodes of heartburn for six months or longer.
5. Diagnosis of heartburn confirmed by diagnostic questionnaire (Carlsson-Dent).

Exclusion criteria:
1. Ongoing Helicobacter pylori infection.
2. Heartburn induced by stress, alcohol or exercise.
3. Any intake of alcohol within the previous 24 hours before pH measurements and during the pH measurement periods.
4. Any use of nicotine within the previous six months.
5. Any drug abuse.
6. Use of prescription medication within the previous 14 days, or use of prescription medication which based on the terminal half-life may still be present systematically at the screening visit. With the exception of:
   - contraceptives
   - post- menopausal oestrogen treatments
   - allergy medications for treatments of common allergic symptoms as judged by the investigator
   - thyroid substitution hormones
   - low dose anti-depressive treatments
   - treatments of mild hypertension or hyperlipidemia, as judged by the investigator
   - treatment of diabetes mellitus type 1 and type 2
   - medication with a written prescription though available as OTC[4]
7. Any use of proton pump inhibitor or histamine H2-antagonist within the previous 28 days before study drug administration (Visit 3).[4]
8. Use of any antibiotics within 4 weeks before screening visit (Visit 2).[5]
9. History of irritable bowel syndrome.
10. Established or suspected cardiac disease with the exception of well controlled/medicated hypertension or hyperlipidemia.[4]
11. Diabetes mellitus type 1 and type 2 that are not well-controlled/medicated.[5]
12. In the investigators judgement, clinically significant abnormalities at the screening examination or in the laboratory test results.
13. Pregnant or breast feeding woman or woman of childbearing potential not using adequate birth control (e.g. intra-uterine device (IUD), barrier method, oral contraceptive, abstinence).
14. Known hypersensitivity to omeprazole, famotidine or local anaesthesia.
15. Administration of other investigational medication within the previous 30 days of enrolment, or use of investigational medication which based on the terminal half-life may still have been present systematically at the Screening visit.

[3] Inclusion criterion no. 3 was corrected with the proper numbering of the visit in Amendment 1.
[4] Exclusion criteria no. 6, 7, 10 were changed in Amendment 1.
[5] Exclusion criteria no. 8 and 11 were added in Amendment 1.

Test product, dose and mode of administration, batch number:
The test product was the OX17 capsule which consisted of a fixed combination of famotidine 10 mg and omeprazole 20 mg (batches number D07020, D07032, D07039 and D07042[6]).
The patients were randomized into three groups to receive once daily oral administrations of the test product or one of the two reference products.

Reference therapy, dose and mode of administration, batch number:

The reference products were the following:
- omeprazole tablet 20 mg (Prilosec®) (batch. number D07003)
- famotidine tablet 10 mg (Pepcid®AC) (batch number D07004)

The reference products were administrated as once daily oral doses.

Rescue medication
Rescue antacid treatment (Novalucol® tablet for oral administration, batches number D07009, D07012, D07015 and D07018) was available during the pre-study and out-patient periods.

Duration of treatment:
One tablet/capsule per day of one of the three study treatments for a period of 14 days.

Criteria for evaluation:
Efficacy:
Primary endpoint:
- pH registrations/readings every 4 seconds after study drug administration on Day 1 and for the following 12 hours.

Secondary endpoints:
- pH registrations/readings every 4 seconds after drug administration on Day 1 and Day 14 and for the following 24 hours.
  - Time to pH>4.
  - Proportion of time with pH>4.
  - Median pH values.
  - pH >4 sustained for >3 and >12 hours.
  - Time to onset of antisecretory action (a rise in pH of $\geq$ one pH unit)
- Need for and consumption of antacid rescue medication during the treatment period
- Symptoms

Safety:
The safety variables assessed in the study were the following:
- Adverse events (AEs) (recorded continuously)
- Withdrawals
- Clinical measurements (physical examination, vital signs, ECG)
- Laboratory measurements (hematology, clinical chemistry, urine analysis)

[6] Batch number D07042 was only used at site 1.

Statistical methods:
Data from the pH-metry were reviewed and approved by a blinded observer, a gastroenterologist otherwise not practically involved in the study, before the statistical analysis was performed. The gastroenterologist did not have access to the randomization list and was thus unaware of the treatment received by each patient.
The treatment groups were compared by analysis of variance. All tests were performed at the 5% level. A supportive analysis for treatment differences was performed using the Extended Mantel-Haenszel test. No adjustment of the significance level due to multiple comparisons was performed. Extended Mantel-Haenszel was also used to test treatment differences regarding the total consumption of rescue medication and the number of symptoms.

SUMMARY – CONCLUSIONS
EFFICACY RESULTS:

Primary objective
The primary objective of the study was to compare the proportion of time with intragastric pH>4 during the first 12 hours after study drug administration on Day 1, between treatment with OX17 and with mono-treatment with omeprazole. This comparison showed a statistically significant difference between OX17 and omeprazole where OX17 had on average 15% more time (or 66% longer time) with intragastric pH>4 during the first 12 hours after IMP administration on Day 1.

Secondary objectives
Time to pH>4 on Day 1 and Day 14
The secondary objective to compare time to pH>4 on Day 1 and Day 14 between treatment with OX17 and with mono-treatment with omeprazole showed that treatment with OX17 on average resulted in a shorter time to reach pH>4 than treatment with omeprazole on both Day 1 and Day 14. This difference was statistically significant for treatment comparison on Day 1, but not on Day 14. Comparison between treatment with OX17 and mono-treatment with famotidine on Day 1 and Day 14 showed that treatment with OX17 on average resulted in a longer time to reach pH>4 on Day 1 and a shorter time to reach pH>4 on Day 14. This difference was statistically significant for comparison on Day 14, but not for comparison on Day 1 (p-value=0.0525).

Summary of time to pH>4 after treatment on Day 1 and Day 14

Population: FAS defined as all randomized patients who received at least one dose of IMP and who had complete data from the pH measurements on Day 1.		**Treatment group**		
		OX17	**omeprazole**	**famotidine**
Time (minutes) to pH>4 after treatment on Day 1	**n (n miss)**	19 (0)	17 (0)	17 (0)
	Mean (SD)	65.5 (33.9)	103.8 (65.9)	40.9 (31.9)
Time (minutes) to pH>4 after treatment on Day 14	**n (n miss)**	18 (1)	17 (0)	17 (0)
	Mean (SD)	27.1 (33.0)	29.4 (42.0)	88.4 (58.4)

Source: Table 8
miss=missing

24-hour intragastric pH profile
The secondary objective of comparing the 24-hour intragastric pH profile (acid-suppressive effect) between treatment with OX17, mono-treatment with famotidine and omeprazole resulted in several secondary variables investigated. The pH profile of the treatments were evaluated, tested and compared using variables derived from the 24-hour pH-metry. The following variables were compared between the different treatments:

Proportion of time spent with intragastric pH>4 for several time periods during Day 1 and Day 14
Treatment with OX17 resulted on average in a higher proportion of time with pH>4 on Day 1 compared to treatment with omeprazole or famotidine for all time periods with the exception of the night-time period where treatment with omeprazole resulted in the highest proportion of time with pH>4. However the only difference that was statistically significant was comparison between OX17 and omeprazole during the first 12 hours after treatment on Day 1. The Extended Mantel-Haenszel test showed that there was a statistically significant difference between the three treatments during the full day-time period, Day 1.

Summary of proportion of time (%) with pH>4 after treatment on Day 1

Population: FAS defined as all randomized patients who received at least one dose of IMP and who had complete data from the pH measurements on Day 1.		**Treatment group**		
		OX17	**omeprazole**	**famotidine**
Baseline period (08.00-08.30)	**n (n miss)**	19 (0)	17 (0)	17 (0)
	Mean (SD)	1.93 (5.59)	5.88 (14.93)	28.82 (43.32)
Post-dose period (08.30-08.00)	**n (n miss)**	19 (0)	17 (0)	17 (0)
	Mean (SD)	26.55 (10.12)	22.98 (20.43)	24.64 (8.95)
Daytime period (08.30-22.30)	**n (n miss)**	19 (0)	17 (0)	17 (0)
	Mean (SD)	34.23(12.67)	23.47 (25.09)	33.59 (11.70)
Night-time period (22.30-06.30)	**n (n miss)**	19 (0)	17 (0)	17 (0)
	Mean (SD)	16.57 (15.79)	23.70 (20.73)	11.63 (12.83)
The first 12 hour period (08.30-20.30)	**n (n miss)**	19 (0)	17 (0)	17 (0)
	Mean (SD)	38.87 (13.94)	23.40 (23.79)	38.42 (13.11)
24 hour period (08.00-08.00)	**n (n miss)**	19 (0)	17 (0)	17 (0)
	Mean (SD)	26.04 (9.93)	22.62 (20.09)	24.73 (9.12)

Source: Table 11
miss=missing

Treatment with omeprazole resulted in the highest proportion of time with pH>4 on Day 14 for all time periods, while treatment with OX17 yielded on average slightly lower proportion of time with pH>4 and patients treated with famotidine had in average the lowest proportion of time with pH>4.There was a statistically significant difference for comparison between OX17 and famotidine for all time
Periods on Day 14, but not for the comparison between OX17 and omeprazole.

Summary of proportion of time (%) with pH>4 after treatment on Day 14

Population: FAS defined as all randomized patients who received at least one dose of IMP and who had complete data from the pH measurements on Day 1.		**Treatment group**		
		OX17	**omeprazole**	**famotidine**
Baseline period (08.00-08.30)	**n (n miss)**	18 (1)	17 (0)	17 (0)
	Mean (SD)	35.37 (41.70)	40.20 (38.61)	6.67 (24.18)
Post-dose period (08.30-08.00)	**n (n miss)**	18 (1)	17 (0)	17 (0)
	Mean (SD)	46.23 (16.10)	55.69 (20.30)	18.70 (14.06)
Daytime period (08.30-22.30)	**n (n miss)**	18 (1)	17 (0)	17 (0)
	Mean (SD)	57.54 (22.24)	65.88 (28.45)	23.17 (12.36)
Night-time period (22.30-06.30)	**n (n miss)**	18 (1)	17 (0)	17 (0)
	Mean (SD)	31.09 (19.51)	41.00 (22.59)	13.85 (23.92)
The first 12 hour period (08.30-20.30)	**n (n miss)**	18 (1)	17 (0)	17 (0)
	Mean (SD)	60.56 (20.90)	67.62 (28.17)	26.08 (12.65)
24 hour period (08.00-08.00)	**n (n miss)**	18 (1)	17 (0)	17 (0)
	Mean (SD)	46.01 (16.35)	55.36 (20.26)	18.45 (14.10)

Source: Table 12
miss=missing

Median pH values for several time periods during Day 1 and Day 14
Regarding the median pH values for the different time periods during Day 1, no major differences between the treatments could be observed. None of the differences between OX17 versus omeprazole and OX17 versus famotidine were statistically significant.
Treatment with OX17 resulted in a higher median pH value for all time periods during Day 14 compared to treatment with famotidine and the differences were statistically significant for all time periods, except for the night time period (p-value of 0.22).

pH>4 sustained for >3 and >12 hours on Day 1 and Day 14
There were only a few patients who fulfilled the criteria of pH sustained for >3 hours on Day 1 and there were no statistically significant differences between the different treatment groups. None of the patients fulfilled the criteria of pH>4 sustained for >12 hours on Day 1.
There were more patients who fulfilled the criteria of pH sustained for >3 hours on Day 14 in the OX17 and omeprazole treatment groups compared to the famotidine group. There was a statistically significant difference between the OX17 treatment group and the famotidine treatment group on Day 14, but not between the OX17 and the omeprazole treatment groups. There were only two patients who fulfilled the criteria of pH>4 sustained for >12 hours on Day 14, both in the omeprazole treatment group.

Time to onset of antisecretory action on Day 1 and Day 14
Treatment with OX17 resulted, on average, in the fastest time to onset of antisecretory action on both Day 1 and Day 14. Patients in the omeprazole treatment group had on average the longest time to onset of antisecretory action on both Day 1 and Day 14. A statistically significant difference between any of the treatments could be observed on Day 1, but not on Day 14. This observed difference on Day 1 shows only that the onset of the antisecretory action could be caused by dissimilarities between any of the treatment groups. However, it is in this context an interesting observation that the most expressed differences were noted between the OX17 and omeprazole groups.

Summary of time to onset of antisecretory action after treatment on Day 1 and Day 14

Population: FAS defined as all randomized patients who received at least one dose of IMP and who had complete data from the pH measurements on Day 1.		**Treatment group**		
		OX17	**omeprazole**	**famotidine**
Time (minutes) to antisecretory action after treatment on Day 1	**n (n miss)**	19 (0)	17 (0)	17 (0)
	Mean (SD)	73.4 (22.9)	145.6 (69.7)	111.2 (94.1)
Time (minutes) to antisecretory action after treatment on Day 14	**n (n miss)**	18 (1)	17 (0)	17 (0)
	Mean (SD)	84.2 (93.3)	142.1 (131.3)	104.1 (70.6)

Antisecretory action was defined as end time of the first 15 minute interval when an increase of the median pH with more than one pH unit had occurred, compared to baseline (median of 30 minutes pH measurements before dose).
The following patients had not reached an onset of antisecretory action after 5.5 hours after treatment but are reported as 5.5 hours in this table:
Day 1: patients 008 (omeprazole), 110 (famotidine) and 115 (famotidine)
Day 14: patients 004 (omeprazole), 024 (OX17), 025 (omeprazole), 111 (omeprazole), 115 (famotidine), 120 (omeprazole), 126 (omeprazole) and 131 (OX17)
miss=missing
Source: Table 25

Need for antacid rescue medication
The secondary objective of assessing and comparing the efficacy of each study treatment with regard to the need for antacid rescue medication during treatment Day 3 up until Day 13 showed that the patients in the famotidine group had on average used more antacid rescue medication per day (8.2 tablets) compared to patients in the omeprazole group (1.8 tablets) and the OX17 group (0.7 tablets). A statistically significant difference was observed between the OX17 and famotidine treatment groups, but not between the OX17 and omeprazole treatment groups.

Symptoms during treatment
The secondary objective of assessing symptoms during treatment (patient diary 2, Day 3-13)) and baseline (patient diary 1) was performed by studying the recorded symptoms after treatment at Day 1 and Day 14 (during pH-measurement) and from Day 3 up until Day 13 (out-patient period). During the baseline period, the most commonly reported symptom for all treatment groups was “Heartburn” (“En brännande känsla i magen eller bröstet som strålar upp mot halsen”).
The number of patients with symptoms and the number of reported symptoms after treatment were lower at Day 14 compared to Day 1 in all the treatment groups. In the OX17 and omeprazole treatment groups, the most commonly reported symptom was “Other symptom” (“Övriga symptom”) and in the famotidine treatment group the most commonly reported symptom was “”Heartburn” (“Hals/bröstbränna”).
During the out-patient treatment period (Day 3 up until Day 13) there was a statistically significant difference between all of the treatment groups for the symptoms “Heartburn” (“En brännande känsla i magen eller bröstet som strålar upp mot halsen”), “Other symptom” (“Annat symtom”) and “No symptoms at all” (“Inga symtom alls”). Days with no symptoms at all were most commonly reported by patients in the omeprazole treatment (88%) group followed by patients in the OX17 treatment group (84%).

SAFETY RESULTS:

In total, 57 AEs reported by 31 patients, were recorded in the study. The most common AE was headache (in 18 patients), followed by nausea (in 6 patients), flatulence (in 5 patients) and nasopharyngitis (in 3 patients). Most AEs occurred in the patients treated with famotidine (25 AEs), followed by the patients treated with OX17 (19 AEs) and the patients treated with omeprazole (13 AEs). In the omeprazole treatment group, 85% of the reported AEs were considered to be possibly or probably related to the study drug, whereas 63% and 64% of the reported AEs were considered to be study drug related in the OX17 and famotidine treatment groups respectively. All reported AEs were considered to be mild or moderate in intensity, i.e. no severe AEs were reported. Two patients in the famotidine treatment group and one patient in each of the other treatment groups discontinued the study because of AEs. No SAEs or deaths occurred during the study.
No clinically significant abnormal laboratory values were recorded during the study and no relevant abnormal physical findings or relevant changes in vital signs were recorded.
Additionally, no clinically significant abnormal ECGs were found in the study. Based on these safety data it could be concluded that there is no reason for safety concerns for OX17 and the product could be regarded as safe and well tolerated.

CONCLUSIONS:

● The combinational treatment with omeprazole and famotidine increases intragastric pH in GERD patients.

● OX17 combines the advantages of the two individual drugs famotidine and omeprazole, *i e* fast and sustained acid inhibition respectively as assessed by pH measurement parameters.

● OX17 lowers consumption of rescue medication.

● OX17 is safe and well tolerated and no additional AEs than those expected from each individual drug occurred in this study.