2. SYNOPSIS

Name of Sponsor: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: Zegerid®	Volume:	
Name of active ingredient: Omeprazole	Page:	
Title of study:	A Phase III, Multi-centre, Double-blind, Double-dummy, Randomised, Study to Assess the Superiority of Zegerid® 20 mg vs. Losec® 20 mg in the Rapid Relief of Heartburn Associated with GERD as on Demand Therapy	
Investigators:	[redacted]	
Study centre(s):	The study was conducted in six centres in Bulgaria, six centres in the Czech Republic, seven centres in Hungary, 14 centres in Poland, six centres in Romania and two centres in the UK.	
Publication (reference):	None.	
Studied period (years):	Date of first enrolment: 14 April 2011 Date of last completed: 08 September 2011	
Phase of development:	Phase III	
Objectives:		
Primary:	Determine the median time to sustained response, which is defined as a reduction of severity of heartburn associated with gastroesophageal reflux disease (GERD) by 3 points or more on a 9-point Likert severity scale, which was sustained for 45 minutes or more.	
Secondary:	Key secondary: 1. Determine the median time to sustained partial response, defined as a reduction of 2 points or more on the 9-point Likert severity scale, which was sustained for 45 minutes or more. 2. Determine the median time to sustained total relief, defined as zero severity (no heartburn) on the 9-point Likert severity scale, which was sustained for 45 minutes or more. 3. Determine the proportion of patients who have achieved sustained response, sustained partial response or sustained total relief by 45, 60 and 90 minutes. Secondary: 1. Determine the severity of heartburn associated with GERD and change in severity from pre-dose at all time points. 2. Determine the proportion of patients who have achieved sustained response, sustained partial response or sustained total relief at all other time points. 3. Determine the proportion of patients with total relief (defined as zero severity on the 9-point Likert severity scale) of heartburn associated with GERD at all time points. 4. Determine the proportion of patients with response (defined as a reduction in the severity of heartburn from pre-dose of 3 or more points on the 9-point Likert severity scale) at all time points. 5. Determine the proportion of patients with at least partial response (defined as a reduction in the	

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	severity of heartburn from pre-dose of 2 or more points on the 9-point Likert severity scale) at all time points. 6. Determine the area under the severity-time curve (AUC) calculated for the following time periods: 0-60, 0-120 and 0-180 minutes. 7. Determine the usage of Gaviscon® (rescue medication) over the 14 day randomised treatment period. 8. Safety and tolerability.
Methodology:	This study was a phase III, multi-centre, double-blind, double-dummy, randomised study in patients with heartburn associated with GERD
Number of subjects (planned and analysed):	planned: 194 screened: 262 enrolled: 262 drop-outs: 23 randomised: 239 withdrawn: 6 completed: 233 analysed (safety): 236 analysed (efficacy): 228
Diagnosis and main criteria for inclusion:	The trial participants were male or female, between 18 and 75 years old. They had a history of frequent episodes of heartburn associated with GERD for at least 2-3 days per week during 2-4 weeks before screening and had responded to standard PPI therapy in the past 12 months. During the screening period at least 1 evaluable episode of heartburn on 2 separate days at level 4 or higher on the 9-point Likert severity scale (point 3 on a 0-8 point scale) prior to randomisation should have been recorded.
Test products, dose and mode of administration, batch number:	Dosage Form: Zegerid®: 20 mg, powder for oral suspension Batch No.: DHYC Zegerid matching placebo: 20 mg, powder for oral suspension Batch No.: DSKN At Visit 2 (Randomisation Visit), patients were randomised to receive either Zegerid® suspension 20 mg with over-encapsulated placebo capsule or Losec® capsule over encapsulated with placebo suspension in a 1:1 ratio. Each patient received 3 days use of randomised study medication (20 mg Zegerid or 20 mg Losec). Patients were to take 1 pack of randomised study medication (1 dose of each suspension and capsule) each day when they experienced an episode of heartburn for a maximum of 3 days over the 14 day randomised treatment period. Each of the 3 episodes of heartburn for which randomised study medication was taken was to be recorded using the e-diary provided. Study medication was self-administered from Day 1, at maximum once daily when the patient experienced his/her first episode of heartburn (level 4 or higher on the 9-point Likert severity scale [point 3 on a 0-8 point scale]) for that particular day. Further episodes of heartburn on the same day or outside of the 3 days of taking randomised study medication should be treated using study allocated Gaviscon® (rescue medication) as described below.
Duration of treatment:	The duration of the study for each patient was a maximum of 25 days including a one-week screening period, a maximum 14 days treatment period and a follow-up visit on day 17 after randomisation, at latest.
Reference therapy, dose and mode of administration, batch number:	Losec®: 20 mg, over-encapsulated capsule for oral intake Batch Nos.: MD7273 and MC7250 Losec® matching placebo: 20 mg, over-encapsulated capsule for oral intake Batch No.: DHYD The patients received either Zegerid® suspension 20 mg with over-encapsulated placebo capsule or Losec® over encapsulated capsule with placebo suspension. Use of randomised study medication as described for the test product.

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Rescue medication, dose and mode of administration, batch number:	Gaviscon®: Chewable tablet for oral intake Batch Nos.: 022404, 018305, 015804, 012408 Each patient received 16 days use of Gaviscon®. During the screening period, patients were allowed to take study allocated Gaviscon® (rescue medication) up to 3 tablets per day. During the randomised treatment period, Gaviscon® was to be used for a maximum of 2 tablets per day, if the patient experienced further episodes of heartburn after intake of randomised study medication (but at least 3 hours after the initial intake of study medication) or outside the 3 days of taking randomised study medication.
Criteria for evaluation:	
Efficacy:	The primary efficacy parameter was the time to sustained response, which is defined as a reduction of severity of heartburn associated with GERD by 3 points or more on a 9-point Likert severity scale, which was sustained for 45 minutes or more. Secondary efficacy variables were: Key secondary: 1. The time to sustained partial response, defined as a reduction of 2 or more points on the 9-point Likert severity scale, which was sustained for 45 minutes or more. 2. The time to sustained total response, defined as zero severity (no heartburn) on the 9-point Likert severity scale, which was sustained for 45 minutes or more. 3. The proportion of patients who had achieved sustained response, sustained partial relief or sustained total relief by 45, 60 and 90 minutes. Secondary: 1. The severity of heartburn associated with GERD and change in severity from pre-dose at all time points. 2. The proportion of patients who had achieved sustained response, sustained partial response or sustained total relief at all other time points. 3. The proportion of patients with total relief (defined as zero severity on the 9-point Likert severity scale) of heartburn associated with GERD at all time points. 4. The proportion of patients with response (defined as a reduction in the severity of heartburn from pre-dose of 3 or more points on the 9-point Likert severity scale) at all time points. 5. The proportion of patients with at least partial response (defined as a reduction in the severity of heartburn from pre-dose of 2 or more points on the 9-point Likert severity scale) at all time points. 6. The AUC calculated for the following time periods: 0-60, 0-120 and 0-180 minutes. 7. The usage of Gaviscon® (rescue medication) over the 14 day randomised treatment period.
Safety:	The primary safety parameter was the occurrence of serious adverse events (SAEs) and adverse events (AE)s. Secondary safety parameters were: • physical examination • concomitant medication
Statistical methods:	Descriptive summaries were provided where appropriate for each of the primary and secondary variables. In general, summaries were presented by patient population and by treatment groups and/or overall. Where data had been collected over time, both the observed data and the change from the run-in period were summarised at each time point. Analysis of Efficacy: The primary statistical hypothesis to be tested was that there was no difference in the time to sustained relief in the two treatment groups. It was evaluated in a confirmatory test:

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H_0: Median time in Zegerid group / Median time in Losec group = 1

H_1: Median time in Zegerid group / Median time in Losec group ≠ 1

Differences between the two treatments were tested at a two-sided significance level of 0.05 using a Cox regression model, including a country effect. A 95% confidence interval was presented for the treatment hazards ratio.

All efficacy parameters were defined using the average heartburn severity at each time point with the patient as the unit of analysis. The time to the start of the sustained response was shown in each treatment group using a Kaplan-Meier curve. The median time and the 95% confidence interval were presented for each treatment.

All other secondary endpoints were analysed using the Kaplan-Meier analysis (with a 95% confidence interval for the treatment difference at each time point) and chi-squared tests, descriptive statistics for each treatment at each time point and summaries by treatment in frequency tables (based on the nature of the parameter).

All efficacy analyses have been performed using the modified Intention-to-Treat (mITT), the per Protocol (PP) and the Per Protocol 2 (PP2) set.

In an additional exploratory efficacy analysis, planned and conducted after locking the database and unblinding the data, the episode was the unit of analysis. The primary and the key secondary efficacy parameters as well as the proportion of episodes which had achieved sustained response, sustained partial response or sustained total relief at all other time points were analysed.

Analysis of Safety:

The analysis of safety assessments in this study included summaries of extent of exposure, occurrences of treatment-emergent AEs (including changes in physical examinations) and concomitant medication. They were presented for the safety set.

SUMMARY OF RESULTS

EFFICACY RESULTS:

The results for the primary efficacy parameter, time to sustained response, which is defined as a reduction of 3 points or more on the 9-point Likert severity scale which was sustained for 45 minutes or more were similar in both treatment groups. Result for efficacy parameters are presented for the mITT set if not noted otherwise. In the Losec group 90 patients (81.1%) showed a sustained response after 52.2 minutes (median time) compared to 88 patients (75.2%) after 60 minutes (median time) in the Zegerid group. No significant difference between treatments and no significant country effect was observed.

Regarding the time to sustained partial response more patients showed a sustained partial response in the Zegerid group (109 patients (93.2%)) compared to the Losec group (98 patients (88.3%)) after 37.5 minutes (median time) in both treatment groups. No significant difference between treatments and no significant country effect was observed.

Concerning the time to sustained total relief, more patients showed a sustained total relief in the Losec group (67 patients (60.4%)) compared to the Zegerid group (62 patients (53.0%)) after 105 minutes (median time) in both treatment groups. No significant difference between treatments but a significant country effect in all analysis sets was observed (p=0.0179 mITT, p=0.0174 PP, p=0.0102 PP2).

The proportion of patients who achieved sustained response, sustained partial relief or sustained total relief after 45, 60 and 90 minutes showed no significant difference between treatments in all sets. The evaluation of these parameters over time showed significant differences between treatments after 30 minutes. Concerning sustained response the rate of patients was higher in the Zegerid group and it was significant in the PP2 set (p=0.0351) and regarding sustained total relief the rate of patients was significantly higher after 30 minutes in the Zegerid group compared to the Losec group in all analysis sets (p=0.0199 mITT, p=0.0315 PP, p=0.0267 PP2). No other significant differences at any other time point were observed for these three parameters although there was a trend towards Zegerid in all sets after 15 minutes for patients with sustained total relief.

Regarding the best overall sustained response, the Losec group showed more non-responders (11.7%) as well as more patients with total relief (60.4%) than the Zegerid group (6.8% non-responder and 53% with total relief). In the Zegerid group a higher percentage of patients with partial response (17.9%) and of responders (22.2%) were observed compared to the Losec group

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	(7.2% patients with partial response and 20.7% responder). The best overall response showed similar results with the same tendencies between the different treatment groups. During the first 45 minutes after study medication intake a faster decrease in severity of heartburn was observed in the Zegerid group (- 55.4%) compared to the Losec group (- 51.8%). After 60 minutes the decrease was similar in both treatment groups (~ 63.5%). After 75 to 180 minutes the Losec group showed a faster decrease in severity (up to - 86%) compared to - 83.6% in the Zegerid group. These results were confirmed by the AUC time curves. The usage of Gaviscon® over Screening and the 14 day randomised treatment period and the corresponding change over these periods by treatment was similar in both treatment groups (change of – 0.75 tablets in the Zegerid group compared to a change of – 0.85 tablets in the Losec group). The interval between the intake of study medication and the next intake of medication (study medication or Gaviscon®) was approximately 2 days (48.61 hours) in the Zegerid group compared to more than 2.5 days (64.27 hours) in the Losec group. The additional exploratory analysis failed to show any appreciable differences between the treatment groups.
SAFETY RESULTS:	Overall, the evaluation of AEs (including AEs due to abnormal physical examination results) and concomitant medication revealed that 20 mg Zegerid was safe and as well tolerated as 20 mg Losec. There were no remarkable differences between the different treatment groups for any safety parameters (safety set). The percentage of patients with treatment-emergent AEs in the Zegerid treatment group was similar in both treatment groups (each with four patients, 3.3% in the Zegerid group and 3.5% in the Losec group). One patient dropped out prior to randomisation due to an SAE. No patient withdrew due to a treatment-emergent AE. No severe treatment-emergent AEs were reported. All other treatment-emergent AEs were classified as mild or moderate in severity. One patient (0.8%) suffered from nausea which was judged to be related to Zegerid. One treatment-emergent AE (paronychia) experienced by a patient in the Losec group was reported not to be resolved at the end of the trial. No deaths occurred during the course of this study. No patients of the safety set experienced treatment-emergent SAEs. No treatment-emergent laboratory AEs, AEs leading to withdrawal and AEs requiring an intervention (significant AEs) were observed during the course of the trial. Over the entire trial, the most frequently reported treatment-emergent AEs by MedDRA SOC and Preferred Term were gastrointestinal disorders (including abdominal distension, abdominal upper pain, flatulence and nausea) reported for 5 patients (2.1%). Four of these patients (3.3 %) were in the Zegerid group and one patient (0.9 %) in the Losec group. The number of patients with concomitant medication was similar in each treatment group except for progestogens and estrogens combinations which were used approximately twice as often in the Losec group compared to the Zegerid group.
CONCLUSION:	• No significant differences between Zegerid and Losec were observed regarding the times to sustained response, sustained partial response and sustained total relief • The proportion of patients reaching sustained total relief over time was significantly higher in the Zegerid group after 30 minutes in all analysis sets. No other significant differences over time were observed. • Regarding best overall sustained response, the sustained responder rate was similar in both treatment groups with the Zegerid group showing a higher percentage of patients with sustained partial response and the Losec group showing more non-responders and patients reaching sustained total relief • The severity of heartburn was similar in both treatment groups after 180 minutes after medication intake • As evaluated by AEs and physical examination, 20 mg Zegerid was as safe and well tolerated as 20 mg Losec in patients suffered from heartburn associated with GERD. Zegerid 20 mg is a safe and efficient medication for the treatment of heartburn associated with GERD.
Date of the report:	07 March 2012