Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Lendormin Tablets 0.25 mg (Delpharm Reims)		EudraCT No.:	
Name of active ingredient: Brotizolam		Page:	Synopsis No.:
Module:		Volume:	
Report date: 21 Dec 2011	Trial No. / U No.: 263.511/ U13-1465-01	Date of trial: 24 Oct 2011–28 Nov 2011	Date of revision (if applicable):

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Title of trial:	A randomized, single-dose, two-way cross-over study to assess the bioequivalence of Lendormin Tablets 0.25 mg (Delpharm Reims) vs. Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.) administered to healthy adult volunteers
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted]
Publication (reference):	1. Jochemsen R, Hermans J, Van Boxtel CJ, Breimer DD. Pharmacokinetics of brotizolam in healthy subjects following intravenous and oral administration. Br J Clin Pharmacol 1983; 16: 285S–90S. 2 Osanai T, Ohkubo T, Yasui N, Kondo T, Kaneko S. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of a single oral dose of brotizolam. Br J Clin Pharmacol 2004; 58: 5:476–481. 3 Bechtel WD. Pharmacokinetics and metabolism of brotizolam in human. Br J Clin Pharmacol 1983; 16: 279S–83S. 4 Danneberg P, Böke-Kuhn K, Bechtel WD, Lehr E. Pharmacological action of some known and possible metabolites of brotizolam. Arzneimittelforschung 1986; 36: 587–91. 5. Jochemsen R, J.G.J., Van Boxtel CJ, Hermans J, Breimer DD. Comparative pharmacokinetics of brotizolam and triazolam in healthy subjects. Br J Clin Pharmacol 1983; 16: 291S–97S.
Clinical phase:	Bioequivalence study
Objectives:	Primary Objective: The objective of the study was to assess the bioequivalence of Lendormin Tablets 0.25 mg (Delpharm Reims) (Test, T) to Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.) (Reference, R) following oral administration. Bioequivalence was assumed if the 90% confidence intervals of the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} ratio were within the range of 80%-125% interval for log-transformed values.

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	Secondary Objective: The other PK-variables were assessed for description purposes. As safety parameters adverse events and vital signs (blood pressure, heart rate and body temperature) were recorded.
Methodology:	Open-label, randomized, two-way crossover design
No. of subjects:	
planned:	Main study: entered: at least 24 subjects
actual:	Enrolled: 24 subjects Treatment of Lendormin Tablets 0.25 mg (Delpharm Reims): entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment of Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.): entered: 24 treated: 24 analysed (for primary endpoint): 24
Diagnosis and main criteria for inclusion:	Healthy volunteers, age between 20 and 40 years, BMI range: between 18.5 and 25 kg/m^2.
Test product:	Lendormin Tablets 0.25 mg (Delpharm Reims)
dose:	0.25 mg
mode of admin.:	Oral
batch no.:	018913
Reference therapy:	Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.)
dose:	0.25 mg
mode of admin.:	Oral
batch no.:	130011
Duration of treatment:	Once single dose for each period (Test plus Reference) with a washout period of at least 7 days.

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Criteria for evaluation:

Inclusion Criteria:

1. Provision of signed written informed consent before enrolment into the study, ability to communicate with the investigators, and to understand and comply with the requirements of the study.
2. Healthy adult, aged between 20 and 40 years old.
3. Body Mass Index (BMI) between 18.5 and 25, inclusive, (BMI will be calculated as weight in kilogram [kg]/height in meters^2 [m^2]).
4. Physically and mentally healthy subjects as confirmed by an interview, medical history, clinical examination, chest x-ray and electrocardiogram.
5. No significant deviation from normal biochemistry examination.
6. No significant deviation from normal haematology examination.
7. No significant deviation from normal urinalysis examination.

Exclusion Criteria:

1. History of drug or alcohol abuse within the past one year.
2. Medical history of drug allergy or sensitivity to analogous drug.
3. Evidence of chronic or acute infectious diseases from 4 weeks before the study.
4. Evidence of any clinical significant renal, cardiovascular, hepatic, hematopoietic, neurological, pulmonary or gastrointestinal pathology.
5. Ongoing peptic ulcer and constipation.
6. Planned vaccination during the time course of the study.
7. Taking any clinical investigation drug from 2 months before the study.
8. Use of any medication, including herb medicine or vitamins from 4 weeks before the study.
9. Donation of greater than 250 ml of blood in the past 3 months prior to dosing or donation of 250 ml of blood in the past 2 months prior to dosing.
10. A positive Hepatitis B surface antigen or positive Hepatitis C antibody result.
11. A positive test for HIV antibody.
12. For female subjects, if they meet the following criteria:
    - Lactating women
    - Positive pregnancy test (urine) at screening, or prior to dosing
    - Do not use adequate contraception during the study
    - Women taking oral contraceptives

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Efficacy / clinical pharmacology:	Bioavailability is used as a surrogate parameter for efficacy. The plasma concentration-time data for brotizolam were used to determine the following pharmacokinetic parameters: 1. AUC_{0-t} 2. $AUC_{0-\infty}$ 3. C_{max} 4. k_{el} 5. T_{max} 6. $T_{½}$ 7. MRT
Safety:	For both Test drug and Reference drug, no significant changes in vital signs were detected. There was no reported adverse event, significant adverse events, death, or serious adverse events during the study.
Statistical methods:	The main study was a bioequivalence study. At least 24 subjects were performed. The pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, were evaluated statistically by an analysis of variance (ANOVA) appropriate for the experimental design of this study. The statistical model included factors accounting for the following sources of variations: sequence, subjects within sequence, period, and treatment. Analyses for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were performed on difference log-transformed data. For AUC and C_{max}, ratio of difference log-transformed data were compared. Statistical significance of ratio for log-transformed data were assessed using appropriate analysis of variance (ANOVA) for the crossover design using Statistical Analysis System (SAS), version 8.1. or update version. Statistical inferences including 90% confidence interval and Schuirmann's two one-sided test procedures were evaluated. To establish bioequivalence under fasting conditions, the 90% confidence interval for the ratio of the means between the products should fall within the range of 80%-125% interval for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical

Pharmacology results:

Only the data obtained from the subjects who completed the crossover study were analyzed and reported. The pharmacokinetic parameters are summarized as mean ± SD for each treatment in Table S-1. The statistical inferences are summarized in Table S-2.

According to the results of statistical analysis, there is no statistically significant difference between Lendormin Tablets 0.25 mg (Manufactured by Delpharm Reims) and Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.). It indicates that the rate and extent of absorption of Lendormin Tablets 0.25 mg (Manufactured by Delpharm Reims) is equivalent to those of Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.).

Table S-1 Pharmacokinetic parameters of Lendormin Tablets 0.25 mg

Parameter*	Lendormin Tablets 0.25 mg (Delpharm Reims)	Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.)
AUC_{0-t} (hr×ng/mL)	30.954 ± 9.081 (29.34)	30.046 ± 10.211 (33.98)
$AUC_{0-\infty}$ (hr×ng/mL)	36.410 ± 15.279 (41.96)	35.653 ± 17.311 (48.56)
C_{max} (ng/mL)	3.858 ± 1.336 (34.64)	3.422 ± 1.126 (32.90)
MRT (hr)	11.3567 ± 3.5809 (31.53)	11.6530 ± 3.8293 (32.86)
T_{max} (hr)	0.897 ± 0.734 (81.85)	1.451 ± 1.308 (90.18)
$T_{1/2}$ (hr)	8.1361 ± 2.4814 (30.50)	8.2420 ± 2.7587 (33.47)
k_{el}	0.0911 ± 0.0217 (23.84)	0.0912 ± 0.0236 (25.88)

*data were shown as mean ± SD (CV%)

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Table S-2 Statistical analysis of Lendormin Tablets 0.25 mg

Parameter	Confidence interval (%)
$\ln(AUC_{0-t})$	97.17 - 110.36
$\ln(AUC_{0-\infty})$	95.98 - 110.55
$\ln(C_{max})$	103.82 - 121.69

Safety results: For both Test drug and Reference drug, no significant changes in vital signs were detected. No subject was reported any adverse event during the study. There were no reported significant adverse events, death, or serious adverse events during the study.

Conclusions: Based on the results of this study, the confidence interval of $\ln(AUC_{0-t})$, $\ln(AUC_{0-\infty})$ and $\ln(C_{max})$ are 97.17%-110.36%, 95.98%-110.55% and 103.82% - 121.69%, respectively which comply with the acceptable range of bioequivalence interval (80%-125%). Thus, there is no statistically significant difference between Lendormin Tablets 0.25 mg (Delpharm Reims) and Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.). It indicates that the rate and extent of absorption of Lendormin Tablets 0.25 mg (Delpharm Reims) is equivalent to those of Lendormin Tablets 0.25 mg (Synmosa Biopharma Co. Ltd.).