Annex 1

KWIZDA Pharma GmbH

CLINICAL STUDY REPORT
KWI-NIC-02

Synopsis

Title of Study:	The bioavailability of Nicorandil in humans: A pilot study to investigate the variability of the pharmacokinetic parameters in healthy volunteers.	
Investigator:	Priv. Doz. Dr. Gerhard Garhöfer	
Study centre(s):	AKH Vienna, Dept. of Clinical Pharmacology, Währinger Gürtel 18-20, A-1090 Vienna	
Publication (reference)	-	
Studied period (years): Date of first enrolment/ date of last completed)	Phase of development: Dec-2008/Feb-2009.	Pilot Phase (human pharmacology); Phase I
Objectives:	Investigation of the bioavailability of nicorandil with regard to the inter- and intra-subject variability of AUC0-tz, Cmax, AUC0-(primary objective); Evaluation of the safety and tolerability of nicorandil 20 mg in healthy male and female subjects (secondary objective).	
Methodology:	The study was designed as an open, single dose, replicated treatment, two-period design with a washout period of one week between administrations. The study consisted of a screening day (within 3 weeks before first administration) and two treatment phases. One single oral dose of Dancor® 20 mg tablets was administered at the beginning of each treatment phase.	
Number of patients (planned/analysed):	planned 12; enrolled 13; terminated 12; analysed 12 (13);	
Diagnosis and main criteria for inclusion:	Healthy Caucasian female and male subjects form 18 to 55 years with a Body Mass Index within 18 and 27 kg/m^2.	
Test product, dose and mode of administration, batch number:	Dancor 20 mg Tabletten Merck Vienna, Reg. No.: 1-20770 p.o. administration in fasted state with 200 ml water; Batch no.: 5460230.	
Duration of treatment:	Two treatment phases separated by a minimum of one week washout phase.	

Reference therapy, dose and mode of administration, batch number:	Dancor 20 mg Tabletten Merck Vienna, Reg. No.: 1-20770 p.o. administration in fasted state with 200 ml water; Batch no.: 5460230.
Statistical methods:	Individual data and descriptive statistics ANOVA with fixed factor period and random factor subject after logarithmic transformation CV inter and CV intra (AUC0-tz, Cmax, AUC0-∞).
Efficacy Results:	Due to the goal of this study, the investigation of the bioavailability of nicorandil (with regard to the intra-subject variability of AUC0-tz, Cmax, AUC0-∞) revealed no statistically significant difference ($p<0,05$) between the two repeated measurements. On the other hand, significant ($p<0,05$) inter-subjective effects have been found for these variables. The coefficient of variation (CV) for AUC0-tz, Cmax, tmax is above 30% for some study periods and is an indicator for a high variability drug.
Safety Results:	During the conduct of this bioavailability study, a total of 29 adverse events (AEs) were documented from 13 enrolled subjects. These 29 AEs occurred in 11 subjects; two subjects (subject no. 07 and no. 12) experienced no AE. The main adverse reaction was "headache" which occurred 17-times in 10 subjects within the two treatment periods. Flush, dizziness and vertigo occurred each once in 2 subjects; circulatory problems, common cold*, sore throat**, fever**, cough** and myalgia** were each reported once. In terms of severity, 26/29 adverse events were classified as "mild" and three adverse events (common cold, fever and myalgia) as "moderate". None of the AEs was rated to be of "severe" nature. The outcomes of all 29 adverse events were documented as "recovered" within the entire study period. The relationship of each AE with the administered study medication was classified as "possible" in 22 cases, as "probable" in three and "unlikely" in four of the cases. *Common cold: During the wash-out period (06 to 22-Jan-2009) common cold occurred in subject 08. This AE was rated to be "moderate" in terms of the severity of the event and the following concomitant medication was administered for its treatment: one single oral dose of Aspirin® 500 mg (on 03-Feb-2009) and Mexavit® 500 mg three times daily between 04-Feb-2009 to 06-Feb-2009. **Sore throat**, fever**, cough** and myalgia**: Subject 09 received the following concomitant medication to treat the sore throat, fever, cough and myalgia: two oral doses/day of clarithromycin 250 mg for 8 consecutive days (27-Jan 2009 to 03-Feb-2009) and Parkemed® was administered t.i.d. between 23 to 26-Jan-2009. All the AEs mentioned occurred prior to the start of the 2nd treatment period. For this reason subject 09 discontinued the study following a decision made by the investigators. No severe adverse events occurred during the entire study period or were brought to the attention to the investigators thereafter.

Summary	Due to the primary objective of this study, the investigation of the bioavailability of nicorandil in blood plasma with regard to the intra-subject variability of AUC0-tz, Cmax, AUC0-∞ revealed no statistically significant differences between the two repeated measurements. On the other hand, significant ($p<0,05$) inter-subjective effects have been found for some variables. The coefficient of variation for AUC0-tz, Cmax, tmax is above 30% for 2 treatment periods and these results are therefore an indicator for nicorandil being kinetically a highly variable drug [the variability in AUC and Cmax (at time interval 2) and tmax for both time intervals are indicators that this drug has to be considered as a high variability drug the CV being above 30%.] Concerning the safety of nicorandil (secondary objective), no serious adverse events occurred during the entire study period. A total of 29 transient adverse events were recorded in 13 subjects, whereas 25 events were attributed as being adverse drug reactions (ADRs) resulting from the administration of nicorandil. The outcome of all 29 adverse events was documented as "recovered" within the entire study period. The relationship of each AE with the administered study medication was classified as "possible" in 22 cases, as "probable" in three and "unlikely" in four of the cases. In terms of severity, 26/29 adverse events were classified as "mild" and three adverse events (common cold, fever and myalgia) as "moderate". None of the AEs was rated to be of a "severe" nature. The main adverse reaction was headache, which occurred 17-times in 10 subjects within the two treatment periods. Flush, dizziness and vertigo occurred each once in 2 subjects; circulatory problems were reported in one case. Other AEs (common cold, sore throat, fever, cough and myalgia) were each reported once, occurring in 2 subjects and were not related to the administration of nicorandil.

Conclusion	Based on the kinetic results of nicorandil in blood-plasma of healthy volunteers above, sample size calculations for a cross-over design demonstrating bioequivalence can be performed. The assumed significance level is 5% and the power is 80% and the acceptance range for equivalence for a multiplicative model for the relation of the two means is 0.80 and 1.25. Furthermore, the intra- and inter-subject variability has been estimated from these data. For AUC, the relation between the two means at period I and II is 1.025 and the estimated sample size based on this data to show equivalence is n=19; for Cmax, the relation between the two means is 1.079 and the estimated sample size would be n=14. Regarding tmax, the relation of the two means is 0.811, which is very close to the limits of the usual acceptance range of 0.800. In some guidelines of the CPMP (1991), an acceptance range of (0.70, 1/0.70) has been discussed with regard to a high within-subject coefficient of variation. If limits of the acceptance range between 0.700 and 1/0,700 are assumed a sample size of n=95 has been estimated. Considering the sample size estimation to demonstrate equivalence, the most important factor is the relation between the means and small changes that may lead to a substantial increase of the sample size (e.g., increasing the relation of the means for AUC to from 1.025 to 1.100) the sample size is now n=32 under these assumptions. The second most important factor is intra-subject variation whereas the inter-subject variation has been proven not to have a big influence on the sample size.
Date of report	11th February, 2010