Clinical Study Report

Title:	Randomized, double blind, active-controlled, parallel study to analyse effects of the combination of aliskiren and valsartan on the vascular structure and function of retinal vessels
Short title:	Aliskiren on Retinal Vasculature Treatment Study (ARTS)
Internal number	CSPP100ADE07T
EudraCT number:	2009-017676-24
ClinicalTrials.gov identifier	NCT01318395
Name of study drug:	Valsartan (Diovan®) and Aliskiren (Rasilez®)
Indication:	Hypertension
Study phase:	Phase 3b
Date first patient enrolled:	14 May 2010
Date last patient completed:	28 June 2012
Principal investigator:	Prof. Dr. med. Roland E. Schmieder
Version and date of report:	Final Version 1.0, 21 November 2013

Sponsor:

Medical Faculty of the University of Erlangen-Nürnberg

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Signature page

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I, the undersigned, have read this report and confirm that to the best of my knowledge it accurately describes the conduct and the results of the study.

Reported by:	Date	Elmar Dunkl	RPS Research GmbH Nürnberg
Reported by:	21 November 2013 Date	Dr. Hans-Joachim Kremer	Medical Writing Service Freiburg
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Reviewed by:	6/12/13 Date	Prof. Dr. med. Roland E. Schmieder	Principal Investigator University of Erlangen
Released by:	6/12/13 Date	Prof. Dr. med. Roland E. Schmieder	On behalf of the Sponsor: University of Erlangen

Synopsis

Referring to Part	Vol:	Page:	
Finished product(s) (incl. active substance(s)):			

Internal ID: CSPP100ADE07T **CT-gov ID: NCT01318395**
Eudra-CT No.: 2009-017676-24 **IND No.: Not applicable**

Title of the study:
Randomized, double blind, active-controlled, parallel study to analyse effects of the combination of aliskiren and valsartan on the vascular structure and function of retinal vessels

Short title (as registered on ClinicalTrials.gov):
Aliskiren on Retinal Vasculature Treatment Study (ARTS)

Sponsor:
University Hospital, University of Erlangen-Nürnberg, Maximiliansplatz 2, 91054 Erlangen, Germany.

Principal investigator:
Prof. Dr. med. Roland E. Schmieder.

Study centre:
University Hospital, University of Erlangen-Nürnberg,

Publication (reference):
Not yet published.

First visit of first patient: 14 May 2010 **Clinical phase:** IIIb (according to protocol)
Last visit of last patient: 28 June 2012 **Type of study:** Therapeutic confirmatory
Database lock: 21 November 2012

Premature discontinuation or interruption(s): Not applicable.

Substantial amendments: There was not any amendment.

Duration of treatment per subject:
Eligible patients received 4 weeks treatment with valsartan (alone) followed by 8 weeks treatment continued treatment with valsartan plus with either aliskiren or placebo, together 12 weeks treatment.

Objectives:
The primary objective was to investigate the combined effect of aliskiren and valsartan compared with valsartan alone on vascular structure, assessed by WLR of retinal arterioles in hypertensive patients.
The secondary objectives were to investigate the combined effects of aliskiren and valsartan compared with valsartan alone:

- On vasodilatory capacity of small retinal arteries in response to Flickerlight.
- On basal nitric oxide (NO) activity of the retinal circulation (N-mono-methyl-l-arginin [L-NMMA]-infusion),
- On pulse wave velocity (PWV) and pulse wave analysis (PWA) [augmentation index (Alx), central systolic and diastolic pressures, central pulse pressure (CPP)],
- On endothelium function of the large and small arteries (change of augmentation index and central pulse pressure in response to L-NMMA infusion), and
- On albuminuria (before and after infusion of L-NMMA).

Methodology:
Randomised, double blind, parallel, mono-centre study comparing the combination of valsartan (VAL) and aliskiren (ALI) with VAL plus placebo (PLA, i.e. in fact valsartan alone) in hypertensive patients.
After a 2-4 week wash-out phase of any previous anti-hypertensive medication (if no previous anti-hypertensive medication, no wash-out phase was necessary), patients were treated in a open label run-in phase with valsartan 160 mg for 1 week and 320 mg valsartan for the next 3 weeks. Thereafter, patients were randomized to additional treatment with aliskiren (150 mg for 1 week and then 300 mg for the following 7 weeks) or placebo (double-blind).

Number of subjects planned:
It was planned to randomised at least 100 and up to 150 patients.

Diagnosis and main selection criteria:
Male or female patients (18-75 years) with mild to moderate uncomplicated essential hypertension with a trough mean sitting DBP $\geq$ 90 mmHg and/or SBP $\geq$ 140 mmHg or pre-treated arterial hypertension could be enrolled. Patient's agreement on performing all study procedures after concise information was sought.
Exclusion criteria comprised, among others, secondary hypertension, severe essential hypertension, history of hypertensive encephalopathy or intracerebral haemorrhage, diabetes mellitus type I or 2, history of myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, or heart failure within the previous six months.

Study medication, dose and mode of administration:
During the open label run-in phase patients were treated with valsartan 160 mg for 1 week and then to 320 mg valsartan for the next 3 weeks. After 4 weeks, patients were randomized to valsartan 320 mg and aliskiren (150 mg for 1 week and then 300 mg for the following 7 weeks) or to valsartan 320 mg placebo.
There were certain criteria concerning systolic and diastolic blood pressure (SBP, DBP) that could prohibit uptitration. So it could occur that patients remained on the respective starting dose.

Criteria for evaluation:
Primary variable: Wall to lumen ratio (WLR) measured by scanning laser Doppler flowmetry (SLDF).
Secondary efficacy variables comprised retinal capillary flow, peripheral blood pressures, central blood pressures, pulse wave velocity, heart rate, vital signs (sitting, office), and several deduced variables. In addition the effect study medication on endothelial function was investigated before and after inhibition of the nitric oxide (NO) synthase with L-*N*-monomethylarginine (L-NMMA).
Safety variables comprised adverse events, clinical laboratory, and ECG, and to some extent, again vital signs.

Statistical methods:
An ANCOVA model was used, with treatment group as classification variable and the baseline measurement of WLR as a covariate: WLR (change) = treatment x group WLR (baseline). The adjusted Least Squares Means (LSM) calculated by the ANCOVA was used for further testing, pair-wise comparison (difference of change between groups) was tested and corresponding 95% confidence intervals (CI) were derived. Confirmatory test using ITT with sensitivity test using a per protocol set.
Secondary efficacy variables were analysed for the ITT set. The secondary efficacy criteria were analysed in an explorative manner by use of an analogous ANCOVA model.

Results: Background data:
125 patients were exposed to VAL since Visit 4 (Week 0). From these, 11 were withdrawn and 114 patients were randomised and all these were exposed to study medication. 57 patients were

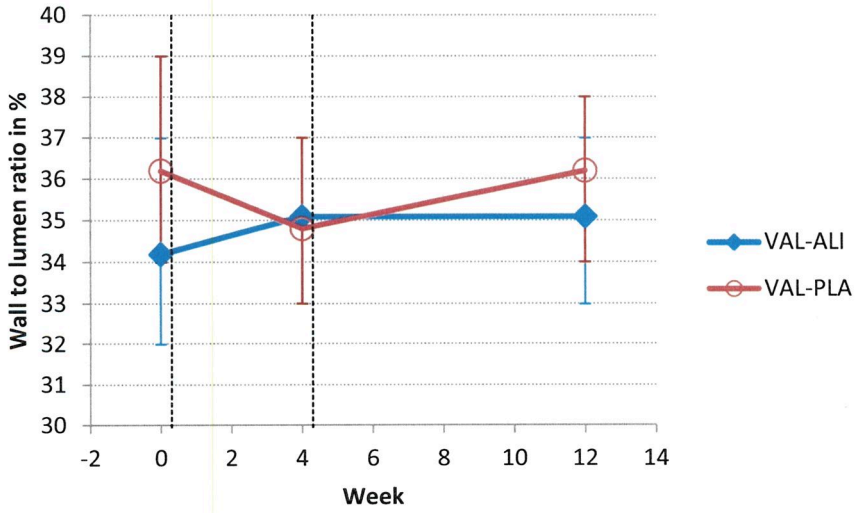
randomised and actually received VAL+ALI, and the same number (57) patients were randomised and actually received VAL+PLA (thus, comprising the safety set). 55 and 54 patients, respectively, were classified as evaluable per ITT, and 51 and52, respectively, as per protocol.

More than ¾ of all patients were male, and all patients were Caucasians.. The study enrolled typical middle-aged hypertensive patients, with a median age of 55 years and some degree of overweight or obesity, evidenced by mean a BMI of about 28 kg/m^2 and a mean waist circumference of 100 cm. Mean sitting SBP at screening (i.e. under previous antihypertensive treatment) ranged between 140 and 143 mm Hg, mean sitting DBP at screening was 88 mm Hg, and mean sitting heart rate was about 70 bpm.

There was no obvious difference between the groups in any analysis set concerning continuous background and baseline data.

Results:-Efficacy:

The change from baseline (V7, Week 4) in WLR variable was to be tested in confirmative manner. At no time and in no group a significant change form baseline (neither Week 0 nor Week 4) was observed in any group (evidenced by the zero-including confidence limits (CL)). The confirmatory estimate for the difference between the groups in changes form Week 4 (i.e. start of combination treatment) yielded an LS mean of -0.02 (95% CI -0.04 to 0.01), p-value 0.2149. Thus, no statistically significant difference between the combination VAL-ALI compared with VAL alone could be detected.



Wall to lumen ratio in percent

ITT, LS means (model V4) with 95% confidence limits, n ranged between 50 and 54. The vertical lines indicate start of treatment with VAL (left) and start of randomised treatment with ALI or PLA (right).

An overview on the effects of the three treatments investigated is presented in the table below.

The data for retinal capillary flow showed changes in different directions in both randomisation groups during the Run-in Phase (although all patients were treated identically), precluding a meaningful interpretation of these data concerning the effect of the combination.

All types of blood pressures measured by various methods in this trial were reduced by VAL alone and these effects were slightly attenuated in the VAL-ALI group, almost always yielding significant differences to the VAL-PLA group.

There was also a small but consistent (across three types of measurements) and statistically significant increasing effect on heart rate observed in the VAL+ALI group.

Overview on outcome of efficacy variables (ITT)

	L-NMMA	Effect of VAL alone	VAL+ALI	Between group difference
Wall to lumen ratio	Not determined	No effect	No effect	Not significant
RCF without flickering	Not determined	Uncertain	Uncertain	Not significant
RCF after flickering	Not determined	Uncertain	Uncertain	Not significant
RCF	Decrease	Uncertain	Increase?	Inconsistent
PWA: SBP	Not determined	(too few data)	(too few data)	(too few data)
PWA: DBP	Not determined	Decrease	Sustained dec.	Significant
PWA: MP	Not determined	Decrease	Uncertain	Not significant
PWA: HR	Not determined	Uncertain	Increase	Significant
PWV	Not determined	Decrease	Sustained dec.	Not significant
PSP	Increase	Decrease	Sustained dec.	Significant
PDP	Increase	Decrease	Sustained dec.	Significant
PMP	Increase	Decrease	Sustained dec	Not significant
CAP	Increase	Decrease	Sustained dec	Significant
HR in this series	Decrease	Uncertain	Increase	Significant
Central aug/PH %	Increase	Decrease	Sustained dec	Significant
HR corr. central aug/PH %	Increase	Decrease	Sustained dec	Trendlike
CSP	Increase	Decrease	Sustained dec	Significant
CDP	Increase	Decrease	Sustained dec	Significant
CPP	Increase	Decrease	Sustained dec	Significant
Urine albumin*	Decrease?	Decrease?	Uncertain	Not significant
Urine creatinine**	Increase	Uncertain	Uncertain	Not significant
Urine sodium*	Increase	Uncertain	Uncertain	Not significant
Urine alb./creat. ratio**	Uncertain	Uncertain	Uncertain	Not significant
Urine sodium/creat. ratio**	Uncertain	Uncertain	Uncertain	Not significant
Mean sitting SBP	Not determined	Decrease	Sustained dec	Significant
Mean sitting DBP	Not determined	Decrease	Sustained dec	Significant
Mean sitting HR	Not determined	Uncertain	Increase	Not significant

Sustained dec(reases): The time courses indicated a slight additional effect compared to V7 or a relevant difference to the pattern in the ALI+PLA group.
Uncertain: There were unclear or even contradicting trends.
* This variable had a rather high variability
** This variable had a very high variability

Results: Safety:

Most frequent adverse events were nasopharyngitis and headache. These terms were only in 1 and 2 cases, respectively, classified as of suspected relationship (to VAL+ALI). Vice versa, their incidence was numerically higher in the VAL+PLA group. Hence, a causal relationship to the combination VAL+ALI appears unlikely.

Most striking among the less frequent AEs was fatigue. It occurred in 6 patients after VAL+ALI, but never after VAL+PLA. Moreover, in 5 of the 6 patients, it was attributed to study medication. Hence, a causal relationship to the combination VAL+ALI appears likely, and it appears that it will occur more frequent than after VAL alone.

Most cases of dizziness were also often attributed to study medication. However, its incidence showed no difference between the groups. Hence, a causal relationship to treatment with VAL appears likely, but the study provides no hint to suspect increased incidence when giving the combination VAL+ALI.

All other terms had only isolated occurrences (when considering the suspected relationship) and did not show different incidences between the groups.

There was no striking outcome in the other safety variables.
The above mentioned terms are already listed as adverse reactions of VAL. The present trial provides no evidence for a higher or lower incidence a already labeled.
Overall, the combination of VAL+ALI appeared to be well tolerated without overt acute risks.

Conclusions:
Combined antihypertensive treatment with valsartan plus aliskiren has no effect on WLR that is different from valsartan plus placebo.
Other efficacy variables indicated a synergistic blood pressure reducing effect of the combination.
The combination of VAL+ALI appeared to be well tolerated without overt acute risks.