

**Clinical trial results:****The Efficacy and Safety of Valsartan and Combination of Valsartan and Hydrochlorothiazide in the Treatment of Patients with mild to moderate Arterial Hypertension.****Summary**

EudraCT number	2012-005129-57
Trial protocol	SI CZ
Global end of trial date	23 June 2015

**Results information**

Result version number	v1 (current)
This version publication date	07 June 2020
First version publication date	07 June 2020
Summary attachment (see zip file)	VICTORY_Final_Report_Synopsis (Final_report_KCT_02_VICTORY-2015-12-SYNOPSIS.docx)

**Trial information****Trial identification**

Sponsor protocol code	KCT02/2012-VICTORY
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Krka, d.d., Novo mesto
Sponsor organisation address	Dunajska 65, Ljubljana, Slovenia, 1000
Public contact	Tanja Kohek, Krka, d.d., Novo mesto Dunajska 65 1000 Ljubljana, 00386 14751236, tanja.kohek@krka.biz
Scientific contact	Tanja Kohek, Krka, d.d., Novo mesto Dunajska 65 1000 Ljubljana, 00386 14751236, tanja.kohek@krka.biz
Sponsor organisation name	Krka ČR, s.r.o.
Sponsor organisation address	Sokolovská 192/79, Prague, Czech Republic, 180 00
Public contact	Martin Sustr, Krka ČR, s.r.o., Sokolovská 192/79 180 00 Prague, 00420 602 486846, martin.sustr@krka.biz
Scientific contact	Martin Sustr, Krka ČR, s.r.o., Sokolovská 192/79 180 00 Prague, 00420 602 486846, martin.sustr@krka.biz

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric	No
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**investigation plan (PIP)**

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Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
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Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No
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Notes:

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**Results analysis stage**

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Analysis stage	Final
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Date of interim/final analysis	31 August 2015
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Is this the analysis of the primary completion data?	Yes
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Primary completion date	23 June 2015
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Global end of trial reached?	Yes
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Global end of trial date	23 June 2015
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Was the trial ended prematurely?	No
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Notes:

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**General information about the trial**

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Main objective of the trial:

The aim of the study was to establish the efficacy and safety of Valsacor® (valsartan) and Valsacombi® (combination of valsartan and hydrochlorothiazide) in wide populations of patients with mild to moderate arterial hypertension.

Protection of trial subjects:

Previously treated patients had 1 week wash-out period before the active treatment started. All patients who met inclusion criteria of the trial were prescribed 1 tablet of Valsacor® 80 mg daily (only in Russia previously treated patients received Valsacor® 160 mg). The dose was adjusted on V2 (4 weeks), V3 (8 weeks) and V4 (12 weeks) according to achievement of target BP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 2013
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Long term follow-up planned	No
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Independent data monitoring committee (IDMC) involvement?	No
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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Russian Federation: 130
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Country: Number of subjects enrolled	Croatia: 68
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Country: Number of subjects enrolled	Czech Republic: 58
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Country: Number of subjects enrolled	Ukraine: 102
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Country: Number of subjects enrolled	Slovenia: 7
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Worldwide total number of subjects	365
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EEA total number of subjects	133
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Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	291
From 65 to 84 years	74
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

There were 365 patients recruited from 5 countries: Russia, Croatia, Czech Republic, Ukraine and Slovenia.

### Pre-assignment

Screening details:

Patients older than 18 years of both genders with mild to moderate essential hypertension with SBP of 140 – 179 mm Hg and DBP of 90 – 109 mm Hg, who signed informed consent form were eligible for inclusion in the study.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	All Patients
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Arm description:

All patients that were enrolled in the study. The treatment was initiated with 1 tablet of Valsacor® 80 mg daily in all patients (naïve and previously treated patients with 1 week washout period). After four weeks of treatment (V2), the dose was adjusted to 1 tablet of Valsacor® 160 mg daily in patients whose target BP was not achieved. After consequent 4 weeks (V3) in insufficiently treated patients the dose was increased to either Valsacor® 320 mg or Valsacombi® 160/12.5 mg. If target BP levels were not achieved after additional 4 weeks (V4) the dose was increased to Valsacombi® 320/12.5 mg. If the target BP was achieved, the treatment remained the same for another 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Valsacor® 80 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet daily. One tablet contains 80 mg of valsartan.

Investigational medicinal product name	Valsacor® 160 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet daily. One tablet contains 160 mg of valsartan.

Investigational medicinal product name	Valsacor® 320 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet daily. One tablet contains 320 mg of valsartan.

Investigational medicinal product name	Valsacombi® 160/12.5 mg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
1 tablet daily. One tablet contains 160 mg of valsartan and 12.5 mg of hydrochlorothiazide.	
Investigational medicinal product name	Valsacombi® 320/12.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet daily. One tablet contains 320 mg of valsartan and 12.5 mg of hydrochlorothiazide.

<b>Number of subjects in period 1</b>	All Patients
Started	365
Completed	351
Not completed	14
Consent withdrawn by subject	5
Adverse event, non-fatal	4
Incorrectly included	1
Protocol deviation	3
Noncompliance	1

## Baseline characteristics

### Reporting groups

Reporting group title	All Patients
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Reporting group description:

All patients that were enrolled in the study. The treatment was initiated with 1 tablet of Valsacor® 80 mg daily in all patients (naïve and previously treated patients with 1 week washout period). After four weeks of treatment (V2), the dose was adjusted to 1 tablet of Valsacor® 160 mg daily in patients whose target BP was not achieved. After consequent 4 weeks (V3) in insufficiently treated patients the dose was increased to either Valsacor® 320 mg or Valsacombi® 160/12.5 mg. If target BP levels were not achieved after additional 4 weeks (V4) the dose was increased to Valsacombi® 320/12.5 mg. If the target BP was achieved, the treatment remained the same for another 4 weeks.

Reporting group values	All Patients	Total	
Number of subjects	365	365	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	54.6		
standard deviation	± 12.05	-	
Gender categorical			
Units: Subjects			
Female	196	196	
Male	169	169	

## End points

### End points reporting groups

Reporting group title	All Patients
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Reporting group description:

All patients that were enrolled in the study. The treatment was initiated with 1 tablet of Valsacor® 80 mg daily in all patients (naïve and previously treated patients with 1 week washout period). After four weeks of treatment (V2), the dose was adjusted to 1 tablet of Valsacor® 160 mg daily in patients whose target BP was not achieved. After consequent 4 weeks (V3) in insufficiently treated patients the dose was increased to either Valsacor® 320 mg or Valsacombi® 160/12.5 mg. If target BP levels were not achieved after additional 4 weeks (V4) the dose was increased to Valsacombi® 320/12.5 mg. If the target BP was achieved, the treatment remained the same for another 4 weeks.

### Primary: Antihypertensive efficacy of Valsacor® and Valsacombi®

End point title	Antihypertensive efficacy of Valsacor® and Valsacombi® <sup>[1]</sup>
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End point description:

The primary efficacy endpoint was to evaluate the effect of Valsacor® and Valsacombi® on BP reduction and achievement of target BP. At each control visit, the BP was measured and according to results, the achievement of target BP was obtained.

During the trial, the mean values of SBP and DBP were steadily decreasing. The mean absolute decrease of SBP and DBP were  $26.60 \pm 10.41$  mm Hg and  $14.84 \pm 7.57$  mm Hg, respectively. On the other hand, the mean relative decrease of both SBP and DBP were  $16.8 \pm 6.1\%$  and  $15.2 \pm 7.3\%$ , respectively. The decrease of mean SBP and DBP was statistically significant ( $p < 0.0001$ ) between all of the consecutive visits.

End point type	Primary
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End point timeframe:

16 weeks for one patient - was the same for the whole duration of the study (20.5.2013 - 23.6.2015).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis could not be entered because the interface insisted on selecting at least two arms.

The data was statistically processed: the largest and the smallest data, arithmetic mean of data with standard deviation of data and standard error of mean and the value of t variable in t-test. The unpaired two-tailed Student's t-test and 95% confidence interval was used to compare values between the treatment groups. Differences were considered to be significant at  $p < 0.05$ .

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	365			
Units: mm Hg				
arithmetic mean (standard deviation)				
SBP V1 (Baseline)	156.6 ( $\pm$ 8.98)			
SBP V2	141.3 ( $\pm$ 12.83)			
SBP V3	136.2 ( $\pm$ 10.87)			
SBP V4	133.1 ( $\pm$ 10.37)			
SBP V5	130.0 ( $\pm$ 8.18)			
DBP V1 (Baseline)	95.6 ( $\pm$ 6.01)			
DBP V2	86.9 ( $\pm$ 7.95)			
DBP V3	84.8 ( $\pm$ 7.16)			
DBP V4	82.9 ( $\pm$ 7.26)			

DBP V5	81.0 ( $\pm$ 5.84)			
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## Statistical analyses

No statistical analyses for this end point

### Primary: Effect of treatment on aortic stiffness

End point title	Effect of treatment on aortic stiffness <sup>[2]</sup>
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End point description:

The effect of treatment on aortic stiffness was evaluated indirectly based on the results of PWV (Pulse wave velocity).

The results on the first and the last visit show that mean PWV value at the beginning of the trial was significantly higher than the mean PWV value at the end of the trial. This means that the change of artery diameter at the beginning of the trial was lower than at the end of the trial, proving that aortic stiffness was higher at the beginning of the trial.

The mean absolute decrease of PWV from the first to the last visit was  $0.95 \pm 1.87$  m/s and mean relative decrease of PWV was  $8.4 \pm 17.6$  %. The decrease of PWV during the trial was statistically significant ( $p < 0.0001$ ).

End point type	Primary
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End point timeframe:

16 weeks for one patient - was the same for the whole duration of the study (20.5.2013 - 23.6.2015).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis could not be entered because the interface insisted on selecting at least two arms.

The data was statistically processed: the largest and the smallest data, arithmetic mean of data with standard deviation of data and standard error of mean and the value of t variable in t-test. The unpaired two-tailed Student's t-test and 95% confidence interval was used to compare values between the treatment groups. Differences were considered to be significant at  $p < 0.05$ .

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: m/s				
arithmetic mean (standard deviation)				
Visit 1	10.086 ( $\pm$ 2.50)			
Visit 5	9.141 ( $\pm$ 2.56)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Effects of treatment on aortic augmentation index (Alx)

End point title	Effects of treatment on aortic augmentation index (Alx) <sup>[3]</sup>
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End point description:

The mean Alx values on the first and the last visit of the trial. The mean absolute decrease of Alx from

the first to the last visit was  $0.23 \pm 10.78$ . The decrease was not statistically significant ( $p = 0.855$ ).

End point type	Primary
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End point timeframe:

16 weeks for one patient - was the same for the whole duration of the study (20.5.2013 - 23.6.2015).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis could not be entered because the interface insisted on selecting at least two arms.

The data was statistically processed: the largest and the smallest data, arithmetic mean of data with standard deviation of data and standard error of mean and the value of t variable in t-test. The unpaired two-tailed Student's t-test and 95% confidence interval was used to compare values between the treatment groups. Differences were considered to be significant at  $p < 0.05$ .

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
arithmetic mean (standard deviation)				
Visit 1	19.865 ( $\pm$ 13.38)			
Visit 5	19.635 ( $\pm$ 12.31)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Central and peripheral BP reduction from V1 to V5

End point title	Central and peripheral BP reduction from V1 to V5 <sup>[4]</sup>
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End point description:

The data on central and peripheral BP were obtained on the first and the last visit of the trial in 74 patients.

The mean absolute decrease of central SBP and DBP were  $19.69 \pm 12.95$  mm Hg (mean relative decrease was  $13.8 \pm 8.6\%$ ) and  $13.99 \pm 8.51$  mm Hg (mean relative decrease was  $14.3 \pm 8.5\%$ ), respectively. On the other hand, the mean absolute decrease of peripheral SBP and DBP were  $20.93 \pm 12.79$  mm Hg (mean relative decrease was  $13.6 \pm 7.7\%$ ) and  $13.84 \pm 8.69$  mm Hg (mean relative decrease was  $14.3 \pm 8.8\%$ ), respectively.

The decrease of both central and peripheral mean SBP and DBP between the first and the last visit of the trial were statistically significant ( $p < 0.0001$ ).

End point type	Primary
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End point timeframe:

16 weeks for one patient - was the same for the whole duration of the study (20.5.2013 - 23.6.2015).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis could not be entered because the interface insisted on selecting at least two arms.

The data was statistically processed: the largest and the smallest data, arithmetic mean of data with standard deviation of data and standard error of mean and the value of t variable in t-test. The unpaired two-tailed Student's t-test and 95% confidence interval was used to compare values between the treatment groups. Differences were considered to be significant at  $p < 0.05$ .

<b>End point values</b>	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: mm Hg				
arithmetic mean (standard deviation)				
Central SBP V1	139.8 (± 11.39)			
Central SBP V5	120.1 (± 12.39)			
Central DBP V1	95.2 (± 7.50)			
Central DBP V5	81.2 (± 6.76)			
Peripheral SBP V1	151.6 (± 10.49)			
Peripheral SBP V5	130.7 (± 11.6)			
Peripheral DBP V1	94.2 (± 7.62)			
Peripheral DBP V5	80.4 (± 6.71)			

### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

16 weeks for one patient - was the same for the whole duration of the study (20.5.2013 - 23.6.2015).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	All Patients
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Reporting group description: -

<b>Serious adverse events</b>	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 365 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 365 (7.12%)		
Cardiac disorders			
Palpitations			
subjects affected / exposed	6 / 365 (1.64%)		
occurrences (all)	10		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 365 (1.92%)		
occurrences (all)	9		
Dizziness			
subjects affected / exposed	6 / 365 (1.64%)		
occurrences (all)	8		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	6 / 365 (1.64%) 6		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 365 (0.55%) 2		

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported