Sponsor

Novartis

Generic Drug Name

Valsartan

Trial Indication(s)

Hypertension

Protocol Number

CVAL489ADE19

Protocol Title

A 2 x 5-weeks open-label, multicenter, randomized cross-over study to compare the reduction of predialysis systolic blood pressure with valsartan (Diovan®) 80 mg compared to irbesartan 150 mg in patients with mild to moderate hypertension on long-term hemodialysis

Clinical Trial Phase

Phase III

Study Start/End Dates

13-May-2004 to 16-Mar-06

Reason for Termination

Not applicable.

Study Design/Methodology

This was a multicenter, open-label, randomized cross-over trial evaluating the efficacy and safety with valsartan 80 mg compared to irbesartan 150 mg in patients with mild to moderate hypertension on long-term hemodialysis.

Centers

15 enrolling centers in Germany and Hungary

Objectives:

Primary objective(s)

To prove non-inferiority of valsartan 80 mg compared to irbesartan 150 mg on predialytic MSSBP after 4 weeks treatment. Non-inferiority is defined as difference between both regimens < 5 mmHg.

Secondary objective(s)

a) To compare changes in predialytic mean supine diastolic blood pressure (MSDBP) and pulse pressure;
b) to compare occurrence of hypotension (SBP < 100 mmHg) with or without symptoms during dialysis;
c) to assess safety and tolerability (adverse events and laboratory abnormalities);
d) to compare changes in different ABPM parameters;
e) to compare changes in quality of life;
f) to compare changes in inflammation-, coagulation- and markers from RAS.

Test Product (s), Dose(s), and Mode(s) of Administration

Valsartan was supplied as 40 and 80 mg capsules in blisters. Ten valsartan 40 mg capsules were dispensed per patient for one week. One capsule was to be taken according to the directive of the physician, starting on the day after the visit. At visit 3 or 6 forty valsartan 80 mg capsules were dispensed for the following 4-week treatment. The patient was advised to take one capsule per day.

Statistical Methods

The primary analysis was performed comparing treatments with respect to the primary efficacy parameter, the predialytic MSSBP in an analysis of variance (ANOVA) model with factors treatment, sequence, period and patient within sequence. Adjusted (=LS-) means were presented for the treatment contrast together with its confidence interval. Non-inferiority was claimed if the confidence interval for the treatment contrast did not exceed the noninferiority margin of 5 mmHg. P-values were computed for the shifted as well as for the non-shifted null hypothesis. In order to obtain a 5% significance level in a non-inferiority setting, two sided 90% confidence intervals were required. P-values were calculated as 5% one-sided.

Secondary Efficacy Parameters: Secondary blood- and pulse pressure measurements were analysed analogously to the primary parameter. Occurrence of symptomatic hypotensive episodes, quality of life as well as lab parameters was presented descriptively. The interpretation of the results was explorative.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients with mild and moderate hypertension defined by a MSSBP ≥ 140 mmHG and < 180 mmHG at Visits 1 and 2 for treated and untreated patients
- Chronic hemodialysis for at least 6 months prior to Visit 1 as substitution therapy.
- If treated with epoetin: patients with a stable hematocrit ≤ 40% (± 5%).

Exclusion Criteria:

- Inability to discontinue angiotensin II receptor blockers (ARBs) safely for a period of 1 week, as required by the protocol.
- Treatment with more than 3 different compounds for the treatment of hypertension at Visit 1.
- Atrial fibrillation

Participant Flow Table

		Total (N=87) n (%)	Valsartan - Irbesartan (N=45) n (%)	Irbesartan - Valsartan (N=42) N (%)
Study completion	treated	87 (100)	45 (100)	42 (100)
	discontinued	24 (27.6)	14 (31.1)	10 (23.8)
	completed	63 (72.4)	31 (68.9)	32 (76.2)
Reason for discontinuation	Adverse event(s)	13 (14.9)	9 (20.0)	4 (9.5)
	Abnormal laboratory value(s)	1 (1.1)	0 (0.0)	1 (2.4)
	Unsatisfactory therapeutic effect	1 (1.1)	0 (0.0)	1 (2.4)
	Protocol violation	5 (5.7)	4 (8.9)	1 (2.4)
	Subject withdrew consent	3 (3.4)	0 (0.0)	3 (7.1)
	Death	1 (1.1)	1 (2.2)	0 (0.0)

Baseline Characteristics

Demographic characteristics (Safety and ITT population)

Variable		Statistic	Safety Total (N=87)	ITT Total (N=67)	Safety Valsartan - Irbesartan (N=45)	ITT Valsartan - Irbesartan (N=34)	Safety Irbesartan - Valsartan (N=42)	ITT Irbesartan - Valsartan (N=33)
Age [yrs]		N	87	67	45	34	42	33
		NMiss	0	0	0	0	0	0
		Mean	59.6	59.7	61.6	62.4	57.5	57.0
		Std	12.9	13.3	12.4	12.0	13.2	14.1
		Min	28	29	28	34	29	29
		Median	62.0	62.0	63.0	64.0	59.0	60.0
		Max	83	83	83	83	80	80
	< 65 years	n (%)	51 (58.6)	39 (58.2)	24 (53.3)	17 (50.0)	24 (57.1)	17 (51.5)
	>= 65 years	n (%)	36 (41.4)	28 (41.8)	21 (46.7)	17 (50.0)	21 (50.0)	17 (51.5)
Sex	Male	n (%)	52 (59.8)	39 (58.2)	27 (60.0)	18 (52.9)	25 (59.5)	21 (63.6)
	Female	n (%)	35 (40.2)	28 (41.8)	18 (40.0)	16 (47.1)	17 (40.5)	12 (36.4)
Race	Caucasian	n (%)	82 (94.3)	66 (98.5)	44 (97.8)	34 (100)	38 (90.5)	32 (97.0)
	Black	n (%)	2 (2.3)	1 (1.5)	0 (0.0)	0 (0.0)	2 (4.8)	1 (3.0)
	Oriental	n (%)	2 (2.3)		1 (2.2)		1 (2.4)	
	Other	n (%)	1 (1.1)		0 (0.0)		1 (2.4)	

Summary of Efficacy

Primary Outcome Result(s)

Mean supine predialytic systolic blood pressure (ITT-population)

		Unadjusted	Results from ANOVA model *)			
	n	Mean (SD)	LS-Mean	90% CL	p|Diff=0	p|Diff=5
Valsartan	67	150.3 (18.96)	150.3			
Irbesartan	67	151.3 (16.33)	151.4			
Diff. Valsartan - Irbesartan		-1.0	-1.1	[-6.2 , 4.0]	0.7269	0.0253

Secondary Outcome Result(s)

Mean supine predialytic diastolic blood pressure (ITT-population)

Variable: Supine diast. BP (mmHg)

		Unadjusted	Results from ANOVA model *)		
	n	Mean (SD)	LS-Mean	95% CL	p|Diff=0
Valsartan	67	78.7 (12.98)	78.7		
Irbesartan	67	78.0 (14.14)	78.1		
Diff. Valsartan - Irbesartan		0.7	0.7	[-2.9 , 4.2]	0.7126

Quality of Life SF-36 (ITT population)

Variable		N	N miss.	Mean	SD	Min	Median	Max
GENERAL HEALTH PERCEPTION	Valsartan	55	12	42.5	23.89	0.0	42.0	100.0
	Irbesartan	55	12	41.6	22.44	0.0	40.0	100.0
	Diff. Valsartan - Irbesartan	55	12	0.9	13.27	-27.0	0.0	47.0
MENTAL HEALTH	Valsartan	55	12	67.9	23.31	10.0	76.0	100.0
	Irbesartan	55	12	67.3	25.34	4.0	76.0	100.0
	Diff. Valsartan - Irbesartan	55	12	0.6	18.04	-52.0	0.0	56.0
PAIN ITEMS	Valsartan	56	11	68.3	31.75	0.0	72.0	100.0
	Irbesartan	56	11	68.0	31.86	0.0	74.0	100.0
	Diff. Valsartan - Irbesartan	56	11	0.4	29.97	-100.0	0.0	68.0
PHYSICAL FUNCTIONING	Valsartan	55	12	53.6	31.86	0.0	50.0	100.0
	Irbesartan	55	12	51.2	32.36	0.0	50.0	100.0
	Diff. Valsartan - Irbesartan	55	12	2.4	16.74	-50.0	0.0	45.0
ROLE EMOTIONAL	Valsartan	54	13	70.4	41.80	0.0	100.0	100.0
	Irbesartan	54	13	61.7	44.58	0.0	100.0	100.0
	Diff. Valsartan - Irbesartan	54	13	8.6	43.04	-100.0	0.0	100.0
ROLE PHYSICAL	Valsartan	55	12	56.4	40.89	0.0	75.0	100.0
	Irbesartan	55	12	49.1	42.48	0.0	25.0	100.0
	Diff. Valsartan - Irbesartan	55	12	7.3	32.16	-100.0	0.0	75.0
SOCIAL FUNCTIONING	Valsartan	56	11	78.3	23.78	12.5	87.5	100.0
	Irbesartan	56	11	79.7	22.93	25.0	87.5	100.0
	Diff. Valsartan - Irbesartan	56	11	-1.3	22.70	-62.5	0.0	50.0
VITALITY ITEMS	Valsartan	55	12	48.7	24.27	0.0	45.0	100.0
	Irbesartan	55	12	46.5	27.75	0.0	40.0	100.0
	Diff. Valsartan - Irbesartan	55	12	2.2	18.02	-25.0	0.0	70.0

Mean (ambulatory) systolic blood pressure (ITT population)

Variable: Supine syst. BP (mmHg)

		Unadjusted	Results from ANOVA model *)		
	n	Mean (SD)	LS-Mean	95% CL	p|Diff=0
Valsartan	64	155.9 (13.08)	155.9		
Irbesartan	63	157.2 (13.88)	157.0		
Diff. Valsartan - Irbesartan		-1.4	-1.1	[-5.2 , 3.0]	0.5996

*)ANOVA model: variable = center, patient within center, period, treatment

Mean (ambulatory) diastolic blood pressure (ITT population)

Variable: Supine diast. BP (mmHg)

		Unadjusted	Results from ANOVA model *)		
	n	Mean (SD)	LS-Mean	95% CL	p|Diff=0
Valsartan	64	80.0 (9.38)	79.9		
Irbesartan	63	79.2 (11.77)	79.3		
Diff. Valsartan - Irbesartan		0.8	0.6	[-1.5 , 2.7]	0.5551

*)ANOVA model: variable = center, patient within center, period, treatment

Mean pulse pressure (ITT population)

Variable: Pulse Pressure (mmHg)

		Unadjusted	Results from ANOVA model *)		
	n	Mean (SD)	LS-Mean	95% CL	p|Diff=0
Valsartan	67	71.6 (16.64)	71.6		
Irbesartan	67	73.3 (14.06)	73.3		
Diff. Valsartan - Irbesartan		-1.7	-1.7	[-6.1 , 2.6]	0.4337

*)ANOVA model: variable = center, patient within center, period, treatment

Summary of Safety

Safety Results

Number (%) of patients who died, had other serious or significant AEs

	TOTAL		Valsartan		Irbesartan	
	No. (%) of AEs	No. (%) of patients (n=87)	No. (%) of AEs	No. (%) of patients (n=78)	No. (%) of AEs	No. (%) of patients (n=77)
All AEs	89 (100)	40 (46.0)	39 (100)	27 (34.6)	54 (100)	28 (36.4)
with suspected drug relation	16 (18.0)	10 (11.5)	6 (15.4)	6 (7.7)	11 (20.4)	5 (6.5)
leading to dose adjustment or temp. interruption	1 (1.1)	1 (1.1)	1 (2.6)	1 (1.3)	0 (0.0)	0 (0.0)
leading to permanent discontinuation	18 (20.2)	11 (12.6)	5 (12.8)	4 (5.1)	13 (24.1)	7 (9.1)
requiring concomitant medication/non-drug therapy	37 (41.6)	25 (28.7)	16 (41.0)	14 (17.9)	22 (40.7)	18 (23.4)
Serious AEs	8 (9.0)	7 (8.0)	4 (10.3)	4 (5.1)	4 (7.4)	3 (3.9)
Deaths		1 (1.1)		0 (0.0)		1 (1.3)
SAEs with suspected drug relation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs leading to permanent discontinuation	2 (2.2)	2 (2.3)	1 (2.6)	1 (1.3)	1 (1.9)	1 (1.3)

A patient with multiple AEs is counted only once in the 'TOTAL' column but may appear in more than one treatment column.

Number (%) of patients with most frequent AEs by preferred term (3% or more for any group)

System organ class	TOTAL (N=87)		Valsartan (N=78)		Irbesartan (N=77)	
Preferred term	n	% of Patients	n	% of Patients	n	% of Patients
VERTIGO	3	(3.4)	1	(1.3)	3	(3.9)
DIARRHOEA	3	(3.4)	1	(1.3)	2	(2.6)
NAUSEA	5	(5.7)	3	(3.8)	2	(2.6)
BRONCHITIS ACUTE	3	(3.4)	3	(3.8)	0	(0.0)
NASOPHARYNGITIS	4	(4.6)	1	(1.3)	3	(3.9)
BACK PAIN	3	(3.4)	1	(1.3)	2	(2.6)
MUSCLE SPASMS	4	(4.6)	2	(2.6)	3	(3.9)
HEADACHE	4	(4.6)	1	(1.3)	3	(3.9)
COUGH	4	(4.6)	3	(3.8)	1	(1.3)

Other Relevant Findings

Treatment emergent hypotension during dialysis (Safety population)

Type	TOTAL (N=87)			Valsartan (N=78)			Irbesartan (N=77)		
Symptoms	n	% of patients	% of all hypotensive episodes	n	% of patients	% of all hypotensive episodes	n	% of patients	% of all hypotensive episodes
All hypotensive episodes									
No. of patients with hypotension	28	(32.2)		23	(29.5)		18	(23.4)	
Total no. of hypotensive episodes	111		(100)	58		(100)	53		(100)
not symptomatic									
No. of patients with hypotension	25	(28.7)		21	(26.9)		16	(20.8)	
Total no. of hypotensive episodes	96		(86.5)	50		(86.2)	46		(86.8)
symptomatic									
No. of patients with hypotension	13	(14.9)		7	(9.0)		7	(9.1)	
Total no. of hypotensive episodes	15		(13.5)	8		(13.8)	7		(13.2)

The row ALL SYSTEM ORGAN CLASSES contains the number of patients with at least one hypotensive episode. A patient with multiple hypotensive episodes was counted only once in the 'All hypotensive episodes' row and in the 'TOTAL' column. Treatment refers to the last treatment received before hypotension started. Percentages based on the no. of patients exposed to that treatment ('N=x').

Treatment emergent hypotension after (within 2 min.) end of dialysis (Safety population)

Type	TOTAL (N=87)			Valsartan (N=78)			Irbesartan (N=77)		
Symptoms	n	% of patients	% of all hypotensive episodes	n	% of patients	% of all hypotensive episodes	n	% of patients	% of all hypotensive episodes
All hypotensive episodes									
No. of patients with hypotension	14	(16.1)		9	(11.5)		11	(14.3)	
Total no. of hypotensive episodes	70		(100)	24		(100)	46		(100)
not symptomatic									
No. of patients with hypotension	14	(16.1)		9	(11.5)		11	(14.3)	
Total no. of hypotensive episodes	68		(97.1)	23		(95.8)	45		(97.8)
symptomatic									
No. of patients with hypotension	2	(2.3)		1	(1.3)		1	(1.3)	
Total no. of hypotensive episodes	2		(2.9)	1		(4.2)	1		(2.2)

The row ALL SYSTEM ORGAN CLASSES contains the number of patients with at least one hypotensive episode. A patient with multiple hypotensive episodes was counted only once in the 'All hypotensive episodes' row and in the 'TOTAL' column. Treatment refers to the last treatment received before hypotension started. Percentages based on the no. of patients exposed to that treatment ('N=x').

Date of Clinical Trial Report

26-Jul-2010