designer peptide in the treatment of cardiovascular diseases such as hypertensive crisis and acute decompensated CHF.

Key Words: Designer peptide, Hypotension, Renin suppression

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THE ORALLY ACTIVE RENIN INHIBITOR SPP100 BLOCKS THE RENIN-ANGIOTENSIN SYSTEM IN HUMANS EQUALLY WELL AS ENALAPRIL

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The activity of the renin-angiotensin system (RAS) is mainly determined by the concentration of active renin. Direct inhibition of renin is therefore a primary goal for blocking the RAS. So far, all specific renin inhibitors lacked potency or were clinically ineffective after oral administration. We tested the new orally active non-peptidic renin inhibitor SPP100 in 18 healthy volunteers on a constant sodium diet (100 mmol/day)using a double-blind, threeway crossover protocol. In 3 periods of 8 days, separated by wash-outs of 1 week, each volunteer received 2 dosage levels of SPP100 once a day (40,80,160 or 640mg) and placebo or 20mg enalapril. SPP100 was well tolerated. Not surprisingly, blood pressure and heart rate remained unchanged in these normal volunteers. SPP100 plasma levels showed that steady state was reached after 8 days of dosing. The table below summarizes median plasma levels at peak (P, 0.5-6h) and trough (T, 24h after dosing)on day 8: In conclusion, the renin inhibitor SPP100 dose-dependently blocks the RAS and decreases angiotensin levels in human subjects following oral administration. The effect is long-lasting and at 160mg at least equivalent to that of 20mg enalapril. SPP100 has the clear potential to become the first renin inhibitor that provides a true alternative to ACE-inhibitors and Ang II receptor antagonists in the therapy of hypertension, cardiovascular and renal disease.

	Placebo	SPP 100 40mg	80mg	160mg	640mg	Enalapril 20mg
Renin pg/ml P	12	34	95	130	670	330
T	11	19	39	64	373	58
PRA ng/ml/h P	1.0	0.28	0.21	0.16	0.08	27
T	1.4	0.89	0.60	0.41	0.39	3.5
Ang I fmol/ml P	3.2	1.6	1.4	0.33	0.70	350
T	7.0	7.1	6.1	4.8	3.1	34
Ang II fmol/ml P	3.0	1.5	1.5	0.61	0.27	0.88
T	4.5	3.7	3.5	3.2	2.5	4.2

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Key Words: renin inhibitor, angiotensin converting enzyme inhibitor, antihypertensive drugs

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EFFECT OF VASOPEPTIDASE INHIBITION BMS189921 ON PI3-KINASE SIGNALING IN VSMCS

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We investigated the effects of new vasopeptides inhibitor BMS189921 on PI3-kinase (PI-K) protein expression in rat male and female vascular smooth muscle cells (VSMCs).

VSMCs were prepared from male and female rats and treated for 15 and 30 min, with 5,10,20 and 100 μM of BMS189921 (Bristol-Mayer Squibb Company). PI3-K protein expression was measured by immunoblot analysis.

BMS induced PI3-K protein expression at all doses and either times in female VSMCS. The maximum effect of BMS in female VSMCs on PI3-kinase protein expression was detected at a dose of 5 μM, 15 min after treatment. This increase was 10.2 - fold compared to control values.

In contrast exposure of male VSMCs to BMS for 15 min and 30 min did not significantly increase PI3-kinase protein expression.

These results indicate that vasopeptide inhibition by BMS189921, in VSMCs activate the PI3-kinase signaling pathway. As PI3-Kinase activation promotes nitric oxide production, this pathway may mediate vasorelaxation of BMS 189921 in female VSMCs.

Key Words: vasopeptidase inhibitor, PI3-kinase, vascular smooth muscle cells

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EFFECT OF DELAPRIL AND IRBESARTAN ON PLASMA PAI-1 AND FIBRINOGEN IN HYPERTENSIVE TYPE 2 DIABETIC PATIENTS

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The aim of this study was to compare the effect of Delapril and Irbesartan on PAI-1 and Fibrinogen in hypertensive type 2 diabetic patients, a population with a known impaired fibrinolysis.

We studied 80 mild to moderate hypertensive patients (DBP>90 and ≤100 mmHg) with well controlled NIDDM, aged 45 to 65 years. Smoker patients were excluded. After a 4 week wash-out placebo period patients were randomly assigned to receive Delapril 30 mg o.d. (n=40) or Irbesartan 150 mg o.d. (n=40) for 12 weeks according to a randomized parallel group design. At the end of the placebo period and of the active treatment period blood pressure was measured and blood samples were taken to evaluate plasma PAI-1, fibrinogen, glucose, HbA1c, cholesterol and triglycerides.

The main results are as follows:

	Placebo	Delapril	Placebo	Irbesartan
SBP	154 ± 12	139 ± 10**	153 ± 13	140 ± 11**
DBP	95 ± 4	83 ± 6**	96 ± 4	85 ± 7**
PAI-1 (ng/ml)	39 ± 19	29 ± 15*	37 ± 18	48 ± 17*°
Fibrinogen(mg/dl)	338 ± 66	322 ± 59	331 ± 67	342 ± 65

* $p < 0,05$; ** $p < 0,01$ vs placebo; ° $p < 0,05$ vs Delapril

No treatment significantly influenced blood glucose, HcA1c and lipid values. These results show that Delapril decreases PAI-1 levels in hypertensive type 2 diabetic patients, while Irbesartan increases it. It suggests that this effect is unrelated with AT-1 receptor blockade: it could be due to the fact that the endothelial receptors that mediate PAI-1 expression in response to Angiotensin II are not type 1 receptor subtypes.

Key Words: PAI-1, Delapril, Irbesartan

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COMPARATIVE EFFECTS OF THE DUAL ACE AND VASOPEPTIDASE INHIBITOR MDL-100,240 AND RAMIPRIL ON HYPERTENSION AND CARDIOVASCULAR DISEASE (CVD) IN ENDOGENOUS ANGIOTENSIN II-DEPENDENT HYPERTENSION

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We investigated the effects of MDL-100,240, a novel inhibitor with a balanced inhibitory activity on ACE and vasopeptidases, on regression of