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

Key Words: Designer peptide, Hypotension, Renin suppression

O-36
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, three-way 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 640 mg) and placebo or 20 mg 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 160 mg at least equivalent to that of 20 mg 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.

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

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

O-37
EFFECT OF VASOPEPTIDASE INHIBITION BMS189921 ON PI3-KINASE SIGNALING IN VSMCS

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We investigated the effects of new vasopeptidases inhibitor BMS189921 on PI3-kine (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-kine 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-kine protein expression.

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

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

O-38
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:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Delapril</th>
<th>Placebo</th>
<th>Ibesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>154</td>
<td>139</td>
<td>153</td>
<td>140</td>
</tr>
<tr>
<td>DBP</td>
<td>95</td>
<td>83</td>
<td>96</td>
<td>85</td>
</tr>
<tr>
<td>PAI-1 (ng/ml)</td>
<td>39</td>
<td>29</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>Fibrinogen/mg/dl</td>
<td>338</td>
<td>322</td>
<td>311</td>
<td>342</td>
</tr>
</tbody>
</table>

* 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

O-39
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 vasopeptidase, on regression of
HT and CVD in TGR rats. 5 week-old male heterozygous TGR rats were BP and BW matched and randomly allocated to receive a placebo (P), ramipril (RAM, 5 mg/kg BW) or MDL-100,240 (MDL, 40 mg/Kg BW) by gavage. Treatment lasted for 8 weeks, during which BP and BW were measured weekly. After 4 weeks, half of the rats receiving active treatment were randomly allocated to receiving the bradikinin B2 receptor antagonist icatibant (0.5mg/kgBW/day) via osmotic minipumps for 4 weeks. Rats were then euthanized and the heart left (LV) and right ventricle (RV), brain, kidney and adrenals were weighted. The structural changes in the thoracic aorta and in the mesenteric arterioles (100-200 μm i.d.), the in vitro tension responses of endothelium-free segments of the aorta to [5x10-6mmol/L] phenylephrine (Phe), [60 mmol/L] KCl, and ET-1 were determined. Plasma creatinine and aldosterone levels were also measured. To assess the effectiveness of MDL-100,240 in regressing hypertension and related CVD, 3 month-old TGR were also measured. To assess the effectiveness of MDL-100,240 in regressing severe hypertension and CVD, 3 month-old TGR were treated for 4 weeks with MDL-100,240 (3 and 10 mg/Kg/BW/day) via osmotic minipumps.

Compared to P, both MDL and RAM effectively lowered BP throughout the study period (after 8 wks: 202±34 mmHg P, vs 127±4 RAM, vs 144±2 MDL, p<0.001). However Icatibant blunted the BP lowering effect of MDL (24±2 mmHg increase, p<0.001) significantly more than that of RAM (10±5 mmHg increase, NS). Both active treatments hindered cardiac hypertrophy by significantly (p<0.001) decreasing the LV weight (3.66±0.08 mg/g BW P, vs 2.36±0.07 RAM, vs 2.71±0.07 MDL, p<0.001). They also prevented the development of dilatation of the aorta (1.85±0.7 μm P, vs 1.44±0.44 RAM, vs 1.46±0.49 MDL, p=0.005), the hypertrophy of the kidney and mesenteric arterioles (normalized media thickness 25.3±0.5 μm P, vs 20.2±1.5 RAM, vs 21.1±0.9 MDL, p<0.05) and lowered the maximal tension responses to Phe (p<0.01), KCl (p<0.01) and ET-1 (p<0.001). The plasma levels of aldosterone and serum creatinine were also significantly decreased by both active treatments. When infused in older TGR rats both dosages of MDL normalized BP and LV weight. Thus, 1) MDL-100,240 was effective as RAM in regressing severe hypertension and related CVD.

2) Vasopeptidase inhibition seems to contribute to the favorable effects of MDL in this model of Ang II-dependent hypertension.

Key Words: Dual ACE and vasopeptidase inhibitor, Cardiovascular damage, Transgenic Ren2 (TGR) rats

O-40

EFFECT OF DUAL INHIBITION OF ANGIOTENSIN CONVERTING ENZYME AND NEUTRAL ENDOPEPTIDASE ON BLOOD PRESSURE AND RESISTANCE ARTERIES OF DEOXYCORTICOSTERONE ACETATE-SALT HYPERTENSIVE RATS

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Omapatrilat is a new dual inhibitor of neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE). Omapatrilat is an effective anti-hypertensive in low-renin animal models; however its effects on resistance artery structure and function are unknown. To examine this, we studied the effect of omapatrilat in DOCA-salt hypertensive rats and in comparison with the ACE inhibitor enalapril. Uninephrectomized rats were divided into four groups: 1) Normotensive controls; 2) DOCA-salt group: received DOCA+1%NaCl; 3) DOCA-salt+ omapatrilat group: received DOCA+1%NaCl+ omapatrilat (40 mg/kg/d for 3 weeks); 4). DOCA-salt +enalapril group: received DOCA+1%NaCl+ enalapril (10 mg/kg/d for 3 weeks); Systolic blood pressure was significantly reduced in omapatrilat-treated DOCA-salt rats compared to enalapril-treated or untreated DOCA-salt rats (P<0.05). Small artery relaxation responses to acetylcholine were improved by omapatrilat treatment in DOCA-salt rats. Omapatrilat increased lumen diameter and decreased media width and media/lumen ratio (P<0.05) in DOCA-salt rats. Stiffness of resistance artery wall components (slope of the elastic modulus vs stress curve) was unaltered by omapatrilat. Enalapril had no effect on endothelial function and vascular structure in DOCA-salt rats.

In conclusion, dual inhibition of ACE /NEP in DOCA-salt hypertensive rats results in potent anti-hypertensive effects, improved endothelial function and reduction of media/lumen ratio of resistance arteries. NEP inhibition is involved to a large extent in the effect of omapatrilat in this model, since ACE inhibition was ineffective. These actions of omapatrilat may confer protection against the end-organ damage characteristic of severe hypertension.

Key Words: Neutral endopeptidase, Angiotensin converting enzyme, Hypertension