Endothelin Receptor Antagonists in Clinical Research - Lessons Learned

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Endothelin plays a key role in the pathogenesis of renal diseases.

The efforts to approve endothelin receptor antagonists for renal indications failed so far due to renal side effects.

Given the huge prevalence of renal side effects, an understanding of renal „ET pathophysiology“ with a special focus on safety is key for any clinical development program.
Lessons learned from Et-1 transgenic models
Endothelin-1 transgenic Mice

- Kidney Cysts
- Kidney Fibrosis
- Impaired GFR
- No Hypertension

Hocher et al., J Clin Invest (1997)
Chronic Kidney Inflammation in ET-1 tg Mice; an Early Event

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>ET-1 tg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ Lymph. [Lymphocytes/10000 cells]</td>
<td>3.89±0.34</td>
<td>6.12±0.33 #</td>
</tr>
<tr>
<td>CD8+ Lymph. [Lymphocytes/10000 cells]</td>
<td>3.49±0.58</td>
<td>6.00±1.38</td>
</tr>
<tr>
<td>Macrophages [Macrophages/10000 cells]</td>
<td>4.19±0.45</td>
<td>7.89±0.58 #</td>
</tr>
<tr>
<td>B-Lymph. [B-lymphocytes/10000 cells]</td>
<td>3.98±0.79</td>
<td>5.00±0.63</td>
</tr>
</tbody>
</table>

#: p < 0.05 vs WT

Hocher et al., J Hypertens (2004)
L-NAME induced Blood Pressure Increase in ET-1 tg Mice

MAP increase after L-NAME [mm Hg+/−SEM]

WT  ET-1 tg

#: p<0.01

Hocher et al., J Hypertens (2004)
Effects of L-NAME on luminal diameter of afferent glomerular arterioles in ET-1 tg mice

Lack of Endothelial Nitric Oxide Synthase Promotes Endothelin-Induced Hypertension: Lessons from Endothelin-1 Transgenic/Endothelial Nitric Oxide Synthase Knockout Mice

Quaschning et al, JASN 2007
NO-dependent Regulation of the human ET-1 Promoter

ET-1 LacZ tg Mouse + L-NAME

ET-1 LacZ tg Mouse

Dye crystals / cell [mean +/- SEM]

ET-1 LacZ

ET-1 LacZ +L-NAME

#: p<0.05 compared to promotor activity in no-treated ET-1-lacZ transgenic mice

Slowinski et al, J. Physiol 2007
- ET-1 causes kidney damage in a blood pressure independent manner.
- ET-1 is part of a paracrine network. NO is a key player in this network.
- Manipulating pharmacologically the ET system always alters the NO system.
Effects of ET Receptor blockers in animal models and humans with diabetic renal disease.
Effects of endothelin receptor antagonists on the progression of diabetic nephropathy

Hocher et al., Nephron (2001)
Effect of avosentan (5, 10, 25, or 50 mg) and placebo on mean (A) and median (B) relative change in UAER from baseline to week 12 of treatment given in addition to standard renin angiotensin aldosterone system blockade.  

Wenzel R et al. JASN 2009;20:655-664
Atrasentan treatment significantly reduces albuminuria.

Kohan D E et al. JASN 2011;22:763-772
Clinical Safety 1

Water and Salt Retention
Salt-sensitive hypertension in endothelin-B receptor-deficient rats

Systolic blood pressure of ET$_B$ receptor knockout mice and their wildtype littermates on standard or salt enriched (4%) chow, unpublished data.

Gariepy et al., J Clin Invest (2000)
Impaired sodium excretion and elevated blood pressure in endothelin receptor type B deficient rats

Impaired sodium excretion and elevated blood pressure in endothelin receptor type B deficient rats

Ahn et al., JCI  2004
ATPase

\[ 3 \text{Na}^+ \rightarrow 3 \text{Na}^+ \]

\[ 2 \text{K}^+ \rightarrow 2 \text{K}^+ \]

ETB

ET-1

\[ 	ext{eNaC} \]

Blood

Lumen

Blood

ET-1
Combined knockout of collecting duct endothelin A and B receptors causes hypertension and sodium retention

Comparison of effects of CD-specific KO of ETA/B with CD-specific KO of ET-1, ETA receptor, or ETB receptor on systolic BP. Data are shown as differences in systolic BP on normal and high Na diets between each KO mouse and its own floxed control [CD ET-1 KO vs. floxed ET-1 control (n = 18), CD ETA KO vs. floxed ETA control (n = 12), CD ETB KO vs. floxed ETB control (n = 9), CDETA/B KO vs. floxed ETA/B control (n = 10)]. *P < 0.001 vs. CD ETB KO and P < 0.001 vs. CD ETA KO. **P < 0.001 vs. CD ETA KO and P < 0.001 vs. CD ETA KO and P < 0.025 vs. CD ET-1 KO.

Ge et al., Am J Physiol Renal Physiol. 2008
Diabetic Endothelin B Receptor–Deficient Rats Develop Severe Hypertension and Progressive Renal Failure

Pfab et al, JASN, 2006
The effect of atrasentan on change in UACR from baseline to final visit is independent of edema occurrence during treatment.

Kohan D E et al. JASN 2011;22:763-772
Screen failure was almost exclusively due to an ACR below the inclusion criterion of 35 mg/mmol or a serum creatinine outside the inclusion criteria.

3,523 subjects screened

1,402 subjects randomized

1,392 ITT population

Avosentan 25 mg/d (n=455)
Primary outcome: 37
Death: 21
CV outcome: 68
CHF: 27
Fluid overload: 204

Avosentan 50 mg/d (n=478)
Primary outcome: 41
Death: 17
CV outcome: 71
CHF: 29
Fluid overload: 219

Placebo (n=459)
Primary outcome: 44
Death: 12
CV outcome: 47
CHF: 10
Fluid overload: 141

2,121 not randomized
2,053 screen failure
68 withdrawn

7 never received treatment
3 no follow-up
Urine ACR changed significantly ($P < 0.0001$; see Table 3) in the avosentan (av)-treated groups during the first 6 months of the trial.

Fluid overload occurred in the avosentan-treated groups.
Peripheral Edema

**Risk Ratio (95% CI)**

- **ER Antagonists**
  - Nelson 2008 Atrasentan
  - Carducci 2007 Atrasentan
  - Nelson 2012 Zibotentan
  - James 2010 Zibotentan

- **Immunotherapy**
  - Kantoff 2010 Prostvac VF
  - Small 2006 Sipuleucel T

**Subtotal**

- Overall

**Risk Ratio**

- Kantoff 2010 Prostvac VF
  - Risk ratio (95% CI): 1.34 (0.46, 3.95) 2.4%
  - 0.55 (0.17, 1.79) 2.9%
  - 0.91 (0.42, 1.98) 5.3%
  - 2.55 (2.23, 2.91) 100.0%

**Immunotherapy and endothelin receptor antagonists for treatment of castration resistant prostate cancer**

Ning Shao et al.
But

Furosemide induces mortality in a rat model of chronic heart failure.
Center for Cardiovascular Research, Charité Medical School, Campus Mitte, Berlin, Germany.

Abstract
OBJECTIVES: In an experimental heart failure model, we tested the hypothesis that furosemide causes excess mortality.

BACKGROUND: Post-hoc analysis of large clinical heart failure trials revealed that furosemide treatment might be associated with worsening of morbidity and even mortality in heart failure patients.

METHODS AND RESULTS: Myocardial infarction was induced in 7 ± 1 week old male Wistar rats by ligation of the left coronary artery. In study 1, animals were randomly assigned to treatment with furosemide (10mg/kg/d via drinking water, n=33) or placebo (n=33) starting 18 days after surgery. In study 2, animals received furosemide from day 18 and were then randomized to ongoing treatment with either furosemide only (n=38) or furosemide plus ACE-inhibitor Ramipril (1mg/kg/d, n=38) starting on day 42. In study 1 survival rate in the furosemide group was lower than in the placebo group (hazard ratio {HR} 3.39, 95% confidence interval {CI} 1.14 to 10.09, p=0.028). The furosemide group had a lower body weight (-6%, p=0.028) at the end of the study and a higher sclerosis index of the glomeruli (+9%, p=0.026) than the placebo group. Wet lung weight, infarct size, and cardiac function were similar between the groups. In study 2, the furosemide group had a higher mortality rate than the furosemide+ramipril group (HR 4.55, 95% CI 2.0 to 10.0, p=0.0003).

CONCLUSION: In our rat model of heart failure furosemide, provided at a standard dose, was associated with increased mortality. This increased mortality could be prevented by additional administration of an ACE-inhibitor.

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Clinical Safety 2

Liver Impairment and Water and Salt Handling
Paracrine renal endothelin system in rats with liver cirrhosis

1,†Berthold Hocher, †Rüdiger Zart, *Fritz Diekmann, **Peter Rohmeiss, #Armin Distler, *Hans H. Neumayer, †Christian Bauer & #Peter Gross

Departments of Nephrology, *Universitätsklinikum Charité der Humboldt Universität zu Berlin, **Klinikum Mannheim, University of Heidelberg and #Universitätsklinikum Benjamin Franklin, Free University of Berlin, and 1Institute of Molecular Biology and Biochemistry, Free University of Berlin, Germany

1 Liver cirrhosis was induced in rats by CCl₄ administration. We analysed the expression of endothelin receptor subtypes in the renal cortex and medulla using Scatchard analysis and receptor autoradiography, and measured plasma as well as renal-tissue endothelin-1 concentrations using a specific radioimmunoassay. Furthermore, we analysed the effects of the non-selective (A/B) endothelin receptor antagonist, bosentan (6 and 100 mg kg⁻¹ day⁻¹) on mean arterial blood pressure, water and sodium excretion and glomerular filtration rate.

2 Our study revealed an overexpression of the endothelin B receptor (ET₉) in the renal medulla of rats with liver cirrhosis (Cir: 2775 ± 299 fmol mg⁻¹; Con: 1695 ± 255 fmol mg⁻¹; n = 8; means ± s.d., P < 0.01), whereas the density of ET₉ in the cortex and the endothelin A receptor (ET₆) in the cortex and medulla were similar in both cirrhotic and control rats. Receptor autoradiography showed that the upregulation of medullary ET₉ in cirrhotic rats was due to an upregulation of ET₉ in the inner medullary collecting duct cells.

3 The tissue endothelin-1 concentrations were increased in the renal medulla of cirrhotic rats (Cir: 271 ± 68 pg g⁻¹ wet wt.; Con: 153 ± 36 pg g⁻¹ wet wt., n = 8; means ± s.d., P < 0.01).

4 The glomerular filtration rate was slightly decreased in cirrhotic rats but not altered after bosentan treatment in either cirrhotic or control rats. Bosentan decreased sodium excretion to a similar extent in both cirrhotic and control rats, whereas water excretion was significantly reduced by both dosages of bosentan in cirrhotic rats only (Cir + vehicle: 12.5 ± 0.62 ml day⁻¹, Cir + 6 mg kg⁻¹ day⁻¹ bosentan: 8.6 ± 1.0 ml day⁻¹; Cir + 100 mg kg⁻¹ day⁻¹ bosentan: 7.4 ± 0.6 ml day⁻¹; n = 10; means ± s.e.mean).

5 We therefore suggest that the upregulation of the medullary ET₉ in cirrhotic rats is involved in the regulation of water excretion in rats with CCl₄-induced liver cirrhosis.

Keywords: Endothelin; endothelin receptor antagonist; bosentan; liver cirrhosis; paracrine renal endothelin system; kidney dysfunction in liver cirrhosis
Figure 3  Water excretion was reduced by bosentan in cirrhotic rats only \((n=10; \ P<0.01)\). Bosentan had no influence at all on water excretion in control rats. The rats received bosentan 6 (hatched columns) and 100 (cross-hatched columns) \(\text{mg} \ \text{kg}^{-1} \ \text{day}^{-1}\) respectively or vehicle (open column) by gastric gavage (means±s.e.mean).
Lack of Renal Improvement with Nonselective Endothelin Antagonism with Tezosentan in Type 2 Hepatorenal Syndrome

Florence Wong, Kevin Moore, Jasper Dingemanse, and Rajiv Jalan

Renal vasoconstriction is a key factor in the development of hepatorenal syndrome (HRS) and may be secondary to increased activities of endothelin-1, a potent renal vasoconstrictor. To assess the effects of tezosentan, a nonselective endothelin receptor antagonist, on renal function in patients with type 2 HRS, six male patients, 56.3 ± 2.5 years old, with cirrhosis and type 2 HRS were treated with tezosentan; ascending doses of 0.3, 1.0, and 3.0 mg/hour, each for 24 hours, were used for the initial 2 patients, but a constant dose of 0.3 mg/hour for up to 7 days was used for the remaining 4 patients. The glomerular filtration rate, renal plasma flow, 24-hour urinary volume, mean arterial pressure (MAP), heart rate, tezosentan levels, and vasoactive hormones were measured daily. Albumin was given as required. The study was stopped early because of concerns about the safety of tezosentan in type 2 HRS. Five patients discontinued the study early; one stopped within 4 hours because of systemic hypotension (MAP < 70 mm Hg), and 4 patients stopped at ~4 days because of concerns about worsening renal function (serum creatinine increased from 180 ± 21 to 222 ± 58 μmol/L, P > 0.05) and decreasing urine volume (P = 0.03) but without a significant change in MAP. The plasma tezosentan concentrations were 79 ± 34 ng/mL at a steady state during infusion at 0.3 mg/hour. The plasma endothelin-1 concentrations increased from 2.7 ± 0.3 pg/mL at the baseline to 19.1 ± 7.3 pg/mL (P < 0.05). Conclusion: An endothelin receptor blockade potentially can cause a deterioration in renal function in patients with cirrhosis and type 2 HRS. Caution should be taken in future studies using endothelin receptor antagonists in these patients. (HEPATOLOGY 2008;47:160-168.)
Lack of Renal Improvement with Nonselective Endothelin Antagonism with Tezosentan in Type 2 Hepatorenal Syndrome

Florence Wong et al.

24-Hour Urinary Volume In The 5 Patients Who Received More Than 1 Day Of Tezosentan Infusion

Endothelin Antagonism with Tezosentan in Type 2 Hepatorenal Syndrome
Florence Wong et al.
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Last day</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (mL/minute; n = 130 ± 20)</td>
<td>49 ± 3</td>
<td>43 ± 4</td>
<td>45 ± 3</td>
<td>33 ± 6</td>
<td>38 ± 7</td>
</tr>
<tr>
<td>RPF (mL/minute; n = 700 ± 130)</td>
<td>283 ± 39</td>
<td>259 ± 25</td>
<td>298 ± 20</td>
<td>276 ± 16</td>
<td>273 ± 37</td>
</tr>
<tr>
<td>FF (%; n = 18 ± 3)</td>
<td>18 ± 2</td>
<td>18 ± 2</td>
<td>14 ± 2</td>
<td>14 ± 1</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>24-hour UV (mL)</td>
<td>777 ± 176</td>
<td>608 ± 193</td>
<td>501 ± 136*</td>
<td>432 ± 108*</td>
<td>548 ± 192*</td>
</tr>
<tr>
<td>24-hour UNaV (mmol/day)</td>
<td>11 ± 3</td>
<td>9 ± 3</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>MAP (mm Hg; n = 70-100)</td>
<td>79 ± 4</td>
<td>82 ± 5</td>
<td>81 ± 2</td>
<td>84 ± 6</td>
<td>81 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/minute; n = 60-100)</td>
<td>72 ± 7</td>
<td>69 ± 6*</td>
<td>70 ± 6*</td>
<td>72 ± 6</td>
<td>82 ± 6</td>
</tr>
</tbody>
</table>

FF indicates filtration fraction; GFR, glomerular filtration rate; MAP, mean arterial pressure; RPF, renal plasma flow; UNaV, urinary sodium excretion; and UV, urinary volume.

*P < 0.05 versus the baseline.
†P < 0.05 versus the last day of treatment.
Clinical Safety 3

Suicidal erythrocyte death
Endothelin B receptor stimulation inhibits suicidal erythrocyte death

Michael Föller,* Hasan Mahmud,* Syed M. Qadri,* Shuchen Gu,* Manuel Braun,* Diwakar Bobbala,* Berthold Hočer,†‡ and Florian Lang*,*†

*Department of Physiology, University of Tübingen, Germany; †Institute of National Sciences, University of Potsdam, Potsdam, Germany; and ‡Center for Cardiovascular Research, Department of Pharmacology and Toxicology, Charité, Campus Mitte, Berlin, Germany

Accelerated erythrocyte clearance of erythrocytes in etb/ mice. Percentage of cleared CFSE-labeled circulating erythrocytes drawn from etb/ (solid bar) and etb/ mice (open bar) 4 d after injection into the same mice. Values are normalized arithmetic means ± se (n=7) of the percentages of CFSE-labeled erythrocytes. *P 0.05 vs. etb/; t test.
Clinical Safety 4

Polycystic kidney disease
Renal endothelin system in polycystic kidney disease

Tissue ET-1

- Sprague-Dawley littermates
- PKD heterozygous
- PKD homozygous

* p < 0.05
** p < 0.005
*** p < 0.000005

Hocher et al., JASN (1998)
ETA Receptor Blockade Induces Tubular Cell Proliferation and Cyst Growth in Rats with Polycystic Kidney Disease.

Hocher et al., JASN (2003)
ETA Receptor Blockade Induces Tubular Cell Proliferation and Cyst Growth in Rats with Polycystic Kidney Disease.

Hocher et al., JASN (2003)

Tubular cell proliferation (BrdU-positive cells/1000 cells)

** p < 0.05
*** p < 0.005

Hocher et al., JASN (2003)
Clinical Safety 5

Radio-contrast media induced acute renal failure
Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism

Andrew Wang, Terry Holcslaw, Thomas M. Bashore, Martin I. Freed, Diane Miller, Michael R. Rudnick, Harold Szerlip, Marc D. Thames, Charles J. Davidson, Neil Shusterman, and Steven J. Schwab

Duke University Medical Center, Durham, North Carolina, USA

BACKGROUND:
Endothelin is a potent vasoconstrictor that has been implicated in the pathogenesis of radiocontrast nephrotoxicity. Endothelin antagonists may reduce the renal hemodynamic abnormalities following radiocontrast administration.

METHODS:
One hundred fifty-eight patients with chronic renal insufficiency [mean serum creatinine +/- SD = 2.7 +/- 1.0 mg/dL (242.3 to +/- 92.8 micromol/L)] and undergoing cardiac angiography were randomized to receive either a mixed endothelin A and B receptor antagonist, SB 290670, or placebo. All patients received intravenous hydration with 0.45% saline before and after radiocontrast administration. Serum creatinine concentrations were measured at baseline, 24 hours, 48 hours, and 3 to 5 days after radiocontrast administration. The primary end point was the mean change in serum creatinine concentration from baseline at 48 hours; the secondary end point was the incidence of radiocontrast nephrotoxicity, defined as an increase in serum creatinine of > or =0.5 mg/dL (44 micromol/L) or > or = 25% from baseline within 48 hours of radiocontrast administration.

RESULTS:
The mean increase in serum creatinine 48 hours after angiography was higher in the SB 209670 group [0.7 +/- 0.7 mg/dL (63.5 +/- 58.6 micromol/L)] than in the placebo group [0.4 +/- 0.6 mg/dL (33.6 +/- 55.1 micromol/L), P = 0.002]. The incidence of radiocontrast nephrotoxicity was also higher in the SB 209670 group (56%) compared with placebo (29%, P = 0.002). This negative effect of SB 209670 was apparent in both diabetic and nondiabetic patients. Adverse effects, especially hypotensi
Clinical Safety 6

ET-1 in early life
ET-1 LacZ tg Mice

Embryo day 16

human prepo-ET-1 promotor (8 kb)

exon 1

P (A)

Slowinski et al, J. Physiol 2007
Clinical Safety 7

Renovascular disease
ETA receptor blockade induces fibrosis of the clipped kidney in two-kidney-one-clip renovascular hypertensive rats.

**Hypothesis:**

Ischemia $\rightarrow$ HIF $\rightarrow$ ET-1 $\rightarrow$ RBF

Hocher et al., J Hypertens (2000)
How can we develop ET Receptor Blockers considering Renal Safety

Consider water and salt retention
patient selection, diuretics, monitoring
there is a prize to pay for diuretics
benefit risk ratio

Kidney function may be worsened by blocking the ET system:

- Chronic Liver Failure
- Any type of cystic kidney disease
- Patients at risk for AKI
- Patients with renovascular hypertension
- Patients at risk for anemia
Is it really a good idea to block the ET system in heart failure?

**Endothelin-1 overexpression restores diastolic function in eNOS knockout mice**

Nicolas Vignon-Zellweger, Katharina Relle, Elodie Kienlen, Markus Alter, Patrick Seider, Juliya Sharkovska, Susi Heiden, Philipp Kalk, Karima Schwab, Barbara Albrecht-Küpper, Franz Theuring, Johannes-Peter Stasch and Berthold Hocher

Endothelin-1 (ET-1) is a potent vasoconstrictor peptide that plays a significant role in cardiovascular physiology. In this study, the authors investigated the effects of ET-1 overexpression in eNOS (endothelial nitric oxide synthase) knockout mice.

- **eNOS/S mice developed diastolic dysfunction; this was rescued by ET-1 transgenic overexpression.**

This study furthermore suggests that cardiac ET-1 overexpression in case of eNOS deficiency causes specifically the regulation of proteins playing a role in oxidative stress, myocytes contractility, and energy metabolism. J Hypertens 2011

(a) Left ventricular end-diastolic pressure and (b) time of relaxation $\tau$ measured by heart catheterization in wild-type, $ET^{+/+}$, $eNOS^{-/-}$, and $ET^{+/+}eNOS^{-/-}$ 9-month-old mice. Results are mean ± SEM ($n = 12$). Mann–Whitney $U$ test: *$P < 0.05$, **$P < 0.01$. 

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(a) Left ventricular end-diastolic pressure and (b) time of relaxation $\tau$ measured by heart catheterization in wild-type, $ET^{+/+}$, $eNOS^{-/-}$, and $ET^{+/+}eNOS^{-/-}$ 9-month-old mice. Results are mean ± SEM ($n = 12$). Mann–Whitney $U$ test: *$P < 0.05$, **$P < 0.01$. 

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Why not ECE/NEP Inhibition?

Novel therapy approach in primary stroke prevention: simultaneous inhibition of endothelin converting enzyme and neutral endopeptidase in spontaneously hypertensive, stroke-prone rats improves survival

Christina Wengenmayer¹, Maxim Krikov¹, Susanne Mueller², Kristin Lucht¹, Arno Villringer³, Berthold Hocher¹, Thomas Unger¹, Christa Thoene-Reineke¹,³

¹Center for Cardiovascular Research, Institut fuer Pharmakologie, Charité - Universitaetsmedizin Berlin, ²Berlin Neuroimaging Center, Berlin School of Mind and Brain, Humboldt Universitaet zu Berlin, ³Forschungseinrichtung fuer Experimentelle Medizin, Charité - Universitaetsmedizin Berlin, Germany

Endothelin-Converting Enzyme/Neutral Endopeptidase Inhibitor SLV338 Prevents Hypertensive Cardiac Remodeling in a Blood Pressure Independent Manner

Philipp Kalk, Yuliya Sharkovska, Elena Kashin, Karoline von Websky, Katharina Relle, Thieno Pfau, Markus Alter, Philippe Guillaume, Daniel Provost, Katrin Hoffmann, Yvan Fischer and Berthold Hocher

Hypertension 2011;57:753-763; originally published online Feb 21, 2011; DOI: 10.1161/HYPERTENSIONAHA.110.163972

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http://hyper.ahajournals.org/cgi/content/full/57/4/755

ORIGINAL ARTICLE

Renoprotective Effects of Combined Endothelin-Converting Enzyme / Neutral Endopeptidase Inhibitor SLV338 in Acute and Chronic Experimental Renal Damage

YULIYA SHARKOVSKA¹,²,⁴,⁸, PHILIPP KALK²,³,⁸, KAROLINE VON WEBSKY¹,², KATHARINA RELLE¹,², THIEMO PFAB²,³, MARKUS ALTER²,³, YVAN FISCHER⁵, BERTHOLD HOCHER¹,²
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