

# Media Release



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## **SPEEDEL FOCUSES PIPELINE ON SPP301 AND NEXT GENERATION RENIN INHIBITORS**

**- SPP301 to continue development in diabetic kidney disease; SPP200 to be partnered -**

**Basel/Switzerland and Bridgewater NJ/USA, 23 October 2007**

Speedel Holding Ltd (SWX: SPPN) announced today that it will continue development of SPP301 (avosentan) as a potential breakthrough therapy for diabetic kidney disease, which is the leading cause of end-stage renal disease. Based on the analysis of data from the previously halted ASCEND<sup>1</sup> Phase III trial, plus data from a new Speedel study of how SPP301 affects fluid retention in human volunteers, and ongoing preclinical and technical assessments, Speedel plans to start a new Phase IIb dose finding study with SPP301 in 2008. The company has also decided not to continue development on its own of SPP200 (pegmusirudin) for patients undergoing haemodialysis, and is now in active discussions to partner the asset.

**Alice Huxley, CEO of Speedel**, commented: "We have undertaken a thorough review of our pipeline and decided to focus our financial and organisational resources on SPP301 alongside our next generation renin inhibitors. We are very encouraged by the strong reduction in proteinuria from the SPP301 ASCEND Phase III trial, and are confident that we now have a better understanding of how to manage the balance between safety and efficacy. Speedel continues to be an innovator in the development of therapies for cardiovascular and metabolic diseases. Today's announcement demonstrates that we can learn from a setback and move forward stronger with the courage of entrepreneurs and our proven experience and expertise in drug development. "

### **Diabetic kidney disease (diabetic nephropathy)**

According to the WHO in 2000 some 177 million people around the world had some form of diabetes, including undiagnosed cases, and this is projected to double to 366 million in 2030. About 20–40% of patients with type 1 or type 2-diabetes develop nephropathy.<sup>2</sup> Diabetic kidney disease remains a large unmet medical need with a high mortality rate and in 2003 it affected an estimated 7.9 million people<sup>3</sup> diagnosed with diabetes in the US, Europe and Japan.

<sup>1</sup> Avosentan on doubling of Serum Creatinine, ENd stage renal disease and death in Diabetic nephropathy

<sup>2</sup> Diabetes Care, American Diabetes Association 2004

<sup>3</sup> Decision Resources, October 2004

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### SPP301 Phase III ASCEND trial

The pivotal Phase III clinical ASCEND trial was stopped in December 2006 in the interest of patient safety based on a recommendation from the Data Safety Monitoring Board, following a significant imbalance in fluid retention in patients amongst the study arms (placebo, 25mg per day, 50mg per day of SPP301 on top of standard therapy). SPP301 is an endothelin A receptor antagonist (ERA), a class of drug which is well known to have an effect on fluid retention.

Proteinuria has been associated with a high risk of developing end stage renal failure and cardiovascular events in diabetic patients; many studies have demonstrated that a reduction in proteinuria is associated with a reduced incidence of cardiovascular and renal events in this patient population<sup>4</sup>.

The company, the study's various committees, and a panel of key opinion leaders, have completed an extensive analysis of the 1400 patients who were randomised in the trial. The key findings are:

- Strong median reduction of about 50% in proteinuria<sup>5</sup> in patients after 3 and 6 months of treatment with SPP301 on top of standard care including ACE-Is and ARBs<sup>6</sup>; this is a highly clinically relevant decrease and a significant indicator of the potential for a beneficial effect on morbidity and mortality.
- Median treatment duration was too short to detect differences across patient groups in the primary composite morbidity and mortality endpoint (only 3 months duration for SPP301 treated groups)
- For those 590 patients who developed fluid retention, the imbalance across all groups confirmed the recommendation of the DSMB to stop the trial:
  - 211 (46.4%) in 25mg dose group
  - 224 (46.9%) in 50mg dose group
  - 155 (33.8%) on placebo

This fluid retention usually occurred within the first 2 months of dosing with SPP301

- SPP301, like other ERAs, can lead to fluid retention already present in this very sick patient population, many of whom were at Stage 4, the last stage before end-stage renal disease (ESRD)<sup>7</sup>

**Giancarlo Viberti, Chairman of the ASCEND Steering Committee, Professor of diabetes and metabolic medicine at Guy's Hospital London, stated:** "The ASCEND data clearly show the strong potency of SPP301 as a potential therapy for treating diabetic kidney disease. Patients are in urgent need of new therapies and SPP301 could be a significant innovative breakthrough. It may be possible to effectively manage the fluid retention with appropriate intervention and preventive strategies in this fragile patient population. We look forward to learning more about the mechanisms of the fluid retention and to better understanding of the optimal use of this novel therapy."

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<sup>4</sup> NIH Publication No 06-4732, September 2006; De Zeeuw et al, *Circulation* 2004; 110:921-927; Ravera et al, *J Am Soc Nephrol* 16: s48-S52,2005

<sup>5</sup> Measured as albumin to creatinine ratio (ACR)

<sup>6</sup> Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor antagonists (ARBs)

<sup>7</sup> Chronic kidney damage has different stages of disease which progress from stage 1 to stage 5 which is ESRD (National Kidney Foundation K/DOQI guidelines)

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### **SPP301 new study to better understand fluid retention**

The company has undertaken a new study to better understand how SPP301 may cause fluid retention, which is being conducted at the University Hospital of Lausanne, Switzerland, under the direction of Dr Bruno Vogt as lead investigator. First results from this study examining the effect of SPP301 on the kidney function of healthy subjects show:

- There is a significant and clear dose-dependent renal retention of sodium and water in healthy subjects treated with SPP301
- SPP301 did not induce any changes in blood pressure or serum creatinine
- Subjects were able to safely compensate for the sodium/water retention

**Professor Michel Burnier, Head of the Division of Nephrology at the University Hospital of Lausanne, observed:** “These initial results give us a good insight into how treatment with the endothelin receptor antagonist SPP301 may cause fluid retention. Our working hypothesis is that fluid retention of SPP301 is principally due to salt and water retention by the kidney and by implication that SPP301 fluid retention is not cardiac in origin. Our ongoing analysis of this study will be important to show how this potent compound should be best developed in further clinical trials.”

### **SPP301 future development**

Speedel plans to start a new Phase IIb trial in 2008 to further elucidate the appropriate doses of SPP301 in diabetic kidney disease. Further details are planned to be announced at the company's R&D Day on 31 March 2008, and first results are expected in late 2009. Data from the Phase III ASCEND study are planned to be presented at a major medical meeting in 2008.

### **SPP200 decision to partner**

After careful consideration of technical, clinical, regulatory, financial and market factors, Speedel has decided that it will not continue development of SPP200 on its own and has now entered active partnering discussions. The company is keeping all options open and will update the investment community as appropriate in 2008.

SPP200 is a long-acting direct thrombin inhibitor designed to prevent the formation of clots in vascular grafts of patients undergoing haemodialysis. Speedel's Phase II trial was conducted in the US in 127 patients to assess the safety profile of SPP200. The study also provided clinically relevant and significant efficacy data for the compound. Vascular graft occlusion occurs in patients when a clot forms in the graft connecting a patient to the dialysis machine. The study compared the safety profile of SPP200 to that of unfractionated heparin (UFH) which, in the USA, is the gold standard anti-coagulant in haemodialysis.

### **Next generation renin inhibitors**

With three new renin inhibitors in clinical development, Speedel continues to build its mature pipeline by leveraging its expertise and experience in renin inhibition. This novel mode of action has been validated by the 2007 approval of SPP100 (Tekturna/Rasilez)<sup>8</sup> in the US, EU and Switzerland where it is marketed by Novartis in these markets. Both Speedel and Novartis recently won the Wall Street Journal Gold Award for Technology Innovation, which was given to the companies for their work in discovering and developing SPP100 as an innovative therapy for hypertension. Speedel is developing a family of next generation renin inhibitors, and now has three compounds in the clinic: SPP635 in Phase IIa, SPP676 in Phase I and SPP1148 in Phase I.

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<sup>8</sup> Tekturna/Rasilez<sup>®</sup> are Novartis trademarks

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### Web Cast and Conference Call

At 15.00 CET /14:00 London/ 09:00 EST today 23 October 2007, the company will host a web cast which can be accessed at <http://www.speedel.com/section/6/subsections/8>. In addition participants may join a teleconference facility using the following telephone numbers:

Switzerland: +41 (0) 44 5 804 858  
UK: +44 (0) 845 302 2566  
USA: +1 866 595 6357  
International: +44 (0) 1452 586 157

Passcode for all: 193 453 40

Slides for the web cast will be downloadable and the web cast will be accessible on the company's website until 22 November 2007.

### About SPP301

SPP301 is a once daily oral endothelin-A receptor antagonist (ERA) that Speedel licensed from Roche in October 2000. SPP301, a second generation ERA, was developed out of Roche's endothelin research and drug discovery program, and was specifically optimised for improved liver safety. Speedel took the compound through a number of Phase I and exploratory Phase IIa clinical trials before selecting the novel indication of diabetic nephropathy for a Phase IIb clinical trial, the headline results for which were announced in March 2005. The Phase III ASCEND study began in July 2005 and was stopped in December 2006 in the interest of patient safety. Speedel has exclusive worldwide development and commercialisation rights under the licensing agreement with Roche.

### Phase III pivotal trial - ASCEND<sup>9</sup>

The Phase III pivotal morbidity and mortality ASCEND trial, which began in July 2005, was a randomized, placebo-controlled study designed to assess time to doubling of serum creatinine, end stage renal disease or death in type II diabetic patients with nephropathy. It investigated the effects of therapy with SPP301 (25 mg or 50 mg) or placebo, administered once daily on top of standard treatment which consists of angiotensin converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs). The study, which had been discussed and agreed with the FDA and the EMEA, was conducted in Europe, the Americas and Asia and was expected to be completed by 2009 but was stopped in December 2006 with 1400 patients randomised. The FDA has granted Fast Track status for SPP301 in this indication and had agreed a Special Protocol Assessment defining the design and endpoints for this Phase III trial.

### Phase IIb results demonstrate strong efficacy

Results of the Phase IIb trial were presented in November 2005 at the American Society of Nephrology<sup>10</sup>. A total of 286 patients were enrolled in this randomized, placebo-controlled, double-blind, parallel design trial. It investigated the effects on UAER of 12-week therapy with SPP301 (5 mg, 10 mg, 25 mg or 50 mg) or placebo, administered once daily on top of standard treatment (consisting of angiotensin converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]). Compared to standard care alone, all doses of SPP301 decreased UAER significantly ( $p < 0.001$ ). There was also a significant reduction in total cholesterol at all doses ( $p < 0.001$ ) compared to standard care alone.

SPP301 was shown to reduce proteinuria by at least 30% on top of standard treatment for 55% of all patients across all dose groups. This is a remarkable additive effect in patients already receiving ACE-Is or ARBs, since these drugs are known to have strong antiproteinuric-effects on their own. Importantly, data from the US National Kidney Foundation<sup>11</sup>

<sup>9</sup> Avosentan on doubling of Serum Creatinine, ENd stage renal disease and death in Diabetic nephropathy

<sup>10</sup> The ETA – selective antagonist SPP301 on top of standard treatment reduces urinary albumin excretion rate in patients with diabetic nephropathy. Presented at 38<sup>th</sup> Annual Meeting of the American Society of Nephrology, 11 November 2005, Philadelphia. René Wenzel, Jessica Mann, Christiane Jürgens, Ilknur Yildirim, Heike Bruck, Thomas Philipp, Anna Mitchell.

<sup>11</sup> Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Am J Kidney Dis. 1999 May; 33 (5): 1004-10

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suggests that such a significant reduction in proteinuria by SPP301 could impact morbidity and mortality in patients with diabetic kidney disease.

In this Phase IIb trial the main adverse events were related to fluid retention. Whereas other ERAs have previously been associated with liver toxicity, SPP301 has not been associated with this side effect so far. In this Phase IIb trial, no significant increases in liver enzymes, aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) were observed with SPP301 compared to placebo.

### **About Diabetic Nephropathy**

**Definition:** Diabetic nephropathy refers to any deleterious effect on kidney structure and/or function caused by diabetes mellitus. More specifically, diabetic nephropathy is thought of in stages, the first being that characterized by microalbuminuria (30-300 mg urinary albumin per 24 hours). This may progress to overt nephropathy or macroalbuminuria (>300 mg urinary albumin per 24 hours). Later still, progressive renal functional decline is characterized by significant decreases in glomerular filtration rate accompanied by rises in serum creatinine, the final result of which is End Stage Renal Disease.

Current therapies include – amongst others - drugs that work on the renin-angiotensin system such as ACE inhibitors and ARBs, which have an antihypertensive effect as well as a renoprotective effect and have been shown to slow disease progression. However, 20-40% of patients with markers of early disease still progress to advanced kidney damage and eventually End Stage Renal Disease and death<sup>12</sup>. Diabetic Nephropathy is a new indication for endothelin receptor antagonists, and the positive Phase II results for SPP301 indicate considerable additional benefit on top of current therapies taken by patients suffering from this chronic disease

**Prevalence:** According to the WHO in 2000, some 177 million people around the world had some form of diabetes, including undiagnosed cases. About 20–40% of patients with type 1 or type 2-diabetes develop nephropathy.<sup>13</sup> Current treatments (primarily antihypertensive treatment and inhibition of the renin angiotensin system) slow progression of DN, but it remains an unmet medical need, with a high mortality rate. DN represents a large and growing unmet medical need with a high mortality rate affecting an estimated 7.9 million people<sup>14</sup> diagnosed with diabetes in the US, Europe and Japan

### **About Endothelin Receptor Antagonists**

Pharmacological blockade of the endothelin system constitutes a relatively new concept for modulating haemodynamic and cellular functions. Substantial evidence from animal testing and clinical studies suggest that endothelin plays a pivotal role in several diseases such as hypertension, chronic heart failure, and chronic nephropathies. Endothelin triggers renal vasoconstriction, decreases glomerular filtration rate and modulates sodium excretion and water balance at the level of the proximal tubule and medullary collecting ducts, by mechanisms that are still unclear. Endothelin also stimulates the renin angiotensin system and atrial natriuretic peptide release and inhibits vasopressin-mediated water re-absorption in the collecting duct. In preclinical testing, chronic administration of Endothelin Receptor Antagonists protected animals, including those with induced diabetes, from developing renal injury.

### **About SPP200**

SPP200 (pegmusirudin), a pegylated recombinant protein, is a long-acting direct thrombin inhibitor. Patients on chronic haemodialysis must generally be connected to a dialysis machine via a graft several times a week. Maintenance of the graft is one of the most challenging problems. Anti-coagulants are given to reduce clotting during dialysis sessions, but despite these precautions the grafts still have a clotting rate of 30-65% per year. According to the US Renal Data System, the cost of graft replacement and maintenance of vascular access is estimated to be more than USD 700 million annually in the US. SPP200 is designed to prevent clot formation in the graft. It has a long duration of action (over 100 hours) and is not removed from the patient's body during dialysis, unlike unfractionated heparin which in the US is the gold standard anti-coagulant in haemodialysis. Speedel believes that these properties of SPP200 are unique and have the potential to protect

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<sup>12</sup> Diabetes Care, American Diabetes Association 2004

<sup>13</sup> Diabetes Care, American Diabetes Association 2004

<sup>14</sup> Decision Resources, October 2004

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these patients from clotting events both during and between dialysis sessions. SPP200 therefore offers potential for reducing the frequency of graft replacements necessitated by these clotting events.

It is estimated that the end-stage renal disease (ESRD) population in the US was approximately 400,000 in 2000 and forecasts indicate that this number will exceed 600,000 in 2010 and 2 million in 2030. More than 300,000 patients with ESRD were on chronic haemodialysis in the US in 2003. Based on Decision Resources Data, Speedel estimates that the number of haemodialysis patients exceeds 250,000 in the five major European markets (Germany, France, United Kingdom, Italy, and Spain) and there are approximately 200,000 haemodialysis patients in Japan. Hypertension and diabetes are the main causes for the growth of this patient population.

### About Speedel

Speedel is a public biopharmaceutical company that seeks to create value for patients, partners and investors by developing innovative therapies for cardiovascular and metabolic diseases. Speedel is a world leader in renin inhibition, a promising new approach with significant potential for treating cardiovascular diseases. Our lead compound SPP100 (Tekturna/Rasilez<sup>1</sup>), the first-in-class direct renin inhibitor, was in-licensed from Novartis in 1999 and licensed-back to Novartis Pharma in 2002 for further development and commercialisation; SPP100 was approved by the FDA in the US in March 2007, and by the EMEA in the EU in August 2007. Our pipeline covers three different modes of action, and in addition to SPP100, includes SPP301 in Phase III (on hold), SPP200 in Phase II, SPP635 in Phase II, SPP1148 and SPP676 in Phase I and several pre-clinical projects.

Speedel develops novel product candidates through focused innovation and smart drug development from lead identification to the end of Phase II. We either partner with big pharma for Phase III and commercialisation in primary-care indications, or we may ourselves complete Phase III development in specialist indications. Candidate compounds for development and the company's intellectual property come from our late-stage research unit Speedel Experimenta and from in-licensing. Our team of approximately 70 employees, including over 30 experienced pharmaceutical scientists, is located at our headquarters and laboratories in Basel, Switzerland and at offices in New Jersey, USA and Tokyo, Japan.

In January 2007 the company raised gross proceeds of CHF 55.5 million (approximately EUR 34.3 million or USD 44.5 million) through a convertible bond issue. In March 2006 the company raised gross proceeds of CHF 83.95 million (approximately EUR 53m or USD 64m) through the public offering of 500,000 treasury shares. Previously, as a private company, we raised gross proceeds of CHF 255 million (approximately EUR 157 million or USD 204 million) from private placements of equity securities and two convertible loans including the conversion premiums. We have had total revenues, principally from milestone payments, of CHF 57.7 million (approximately EUR 37 million or USD 44 million). The company's shares were listed in September 2005 on the SWX Swiss Exchange under the symbol SPPN.

### Forward looking statements

This press release includes forward-looking statements that involve substantial risks and uncertainties. These forward-looking statements are based on our current expectations and projections about future events. All statements, other than statements of historical facts, regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements. The word "may" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations described in these forward-looking statements and you should not place undue reliance on them. There can be no assurance that actual results of our research and development activities and our results of operations will not differ materially from these expectations. Factors that could cause actual results to differ from expectations include, among others: our or our partners' ability to develop safe and efficacious products; our or our partners' ability to achieve positive results in clinical trials; our or our partners' ability to obtain marketing approval and market acceptance for our product candidates; our ability to enter into future collaboration and licensing agreements; the impact of competition and technological change; existing and future regulations affecting our business; changes in governmental oversight of pharmaceutical product development; the future scope of our patent coverage or that of third parties; the effects of any future litigation; general economic and business conditions, both internationally and within our industry, including exchange rate variations; and our future financing plans.

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