

# Kinetics and dynamics of the peripheral neurokinin-1 receptor antagonist SLV317 in healthy individuals

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## Aims

To investigate the pharmacokinetics and the pharmacodynamic effects in dorsal hand veins of the neurokinin-1 receptor antagonist SLV317.

## Methods

In a randomized, double-blind, placebo-controlled cross-over study 19 healthy men received a single oral dose of SLV317 or placebo. Blood samples were collected for analysis of SLV317 plasma concentrations and the inhibition of the venodilator response to substance P was evaluated using the hand vein compliance method.

## Results

Administration of 250 mg SLV317 as an oral solution was well tolerated and resulted in mean peak plasma concentrations ( $\pm$  SEM) of  $77 \pm 9$  ng ml<sup>-1</sup> within  $47 \pm 3$  min; the mean half-life was  $9.9 \pm 1.6$  h. In hand veins precontracted with phenylephrine, local infusion of substance P resulted in a mean venodilation of  $56 \pm 8\%$  and  $49 \pm 6\%$  ( $P = 0.91$ ) before administration of SLV317 or placebo, respectively. SLV317 caused a substantial inhibition of substance P-induced venodilation, whereas placebo had no effect ( $P < 0.001$ ). The maximum antagonizing effect of SLV317 averaged  $95 \pm 8\%$  and was observed after  $1.47 \pm 0.24$  h. Correspondingly, the mean area under the effect curve after administration of SLV317 [ $278 \pm 67\%$  h<sup>-1</sup>; 95% confidence interval (CI) 198, 358] was significantly higher compared with placebo ( $49 \pm 12\%$  h<sup>-1</sup>; 95% CI -24, 122;  $P < 0.001$ ).

## Conclusions

This study demonstrates that the neurokinin-1 receptor antagonist SLV317 is an orally active and highly effective antagonist of substance P-induced effects in humans.

## Introduction

Neurokinin-1 (NK-1) receptors have been identified in the central nervous system as well as in peripheral organs including the gastrointestinal and respiratory system, the genitourinary tract and the vascular endothelium [1]. The undecapeptide substance P, a member of the tachykinin family, is the natural agonist with the

highest affinity to the NK-1 receptor and is a mediator of emesis, pain transmission, neurogenic inflammation and endothelium-dependent vasodilation [1, 2]. Furthermore, substance P mediates the transmission of afferent perceptual signals from the gastrointestinal tract and mediates neuromuscular transmission in the enteric nervous system, resulting in the activation of gastrointesti-

nal motility [1]. Hence, there is considerable potential for neurokinin modulation in the treatment of sensory or motor disorders in inflammatory bowel disease or irritable bowel syndrome [3].

3-[[[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[5-(morpholinomethyl)-2H-1,2,3-triazol-4-yl]methyl]piperazinyl)methyl]-1H-indole dihydrochloride (SLV317) is a potent and highly selective NK-1 receptor antagonist *in vitro* and *in vivo*. Preclinical data have revealed that the compound acts *in vivo* mainly as a peripheral NK-1 receptor antagonist. SLV317 reduced visceral hypersensitivity to colonic distension in rats with a maximal inhibition of visceral hypersensitivity of 70% [4]. SLV317 had weak, but significant effects on gastrointestinal transit. It reduced faecal output in rats and exhibited antidiarrhoeal activity in rats and mice. In a model of inflammatory bowel disease in guinea-pigs, oral doses of SLV317 significantly reduced various parameters of trinitrobenzenesulphonic acid (TNBS)-induced ileitis [5]. Based on these data, SLV317 is a promising compound potentially counteracting visceral pain and inflammation in hypersensitive patients with inflammatory bowel disease or irritable bowel syndrome. However, the presumed mechanism of action (NK-1-antagonism of SLV317) has not been demonstrated in humans so far. Proof of mechanism in humans is of particular importance for the further development of the compound because the primary sequence of the human NK-1 receptor protein differs from the sequence of animal NK-1 receptors. Although these differences do not affect agonist responses, it has been shown that they may markedly reduce the potency of antagonists [6].

We aimed to investigate the pharmacokinetics after a single oral dose of SLV317 in healthy male volunteers, confirm the preclinical effects of this compound in humans (proof of mechanism) and investigate the relationship between pharmacodynamic effects and SLV317 plasma concentrations. Pharmacodynamic effects were evaluated by measuring the antagonism of substance P-induced venodilation using the hand vein compliance technique. We have shown previously that NK-1 receptors are present in human hand veins [7] and that substance P produces potent, efficient and reproducible venodilation, provided that the occurrence of tolerance is avoided [8]. Venodilation can therefore be considered as an adequate biomarker for effects mediated through the human NK-1 receptor.

## Methods

### Participants

Nineteen healthy male nonsmokers participated in a randomized, double-blind, placebo-controlled, cross-over

study after each gave written informed consent. After review and approval of the study by the responsible Ethics Committee of the Medical Faculty of the University of Heidelberg, Germany, the study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Only healthy volunteers without concurrent drug use were included in the study. All volunteers had a physical examination, a 12-lead ECG and a laboratory examination to exclude haematological, renal or hepatic dysfunction. Further exclusion criteria were: a history of allergies, known conditions causing endothelial dysfunction such as diabetes, hyperlipidaemia, arterial hypertension, hyperhomocysteinaemia and smoking, regular medication or treatment with drugs within the last 2 weeks, acute or chronic illness, and drug or alcohol abuse.

### Hand vein compliance technique

The participants abstained from alcohol for at least 24 h and from methylxanthine-containing beverages for at least 12 h before the measurements of hand vein compliance were made. Two hours before investigations were started they had a standardized light breakfast. Venodilator responses were investigated in a quiet room maintained at a constant temperature between 23 and 25 °C using the dorsal hand vein compliance technique according to Aellig [9], with modifications as described previously [10]. Hand vein compliance measurements always started in the morning and the participants were asked to remain in a supine position throughout the study.

In brief, the hand under investigation was placed on a vacuum pillow sloping upwards at an angle of 30° from the horizontal. All vasoactive compounds were administered through a butterfly needle at a constant flow rate (0.25 ml min<sup>-1</sup>) into the vein under investigation. In each participant, the same hand vein was used for both study phases. Changes of the diameter of the vein were recorded using a linear variable differential transformer (Schaevitz<sup>®</sup>, Type 100 MHR, Pennsauken, NJ, USA) with a freely movable core (weight 0.5 g) resting over the centre of the vein under investigation. Transformer signals were amplified by a Schaevitz<sup>®</sup> CAS series signal conditioner and the output was recorded on a strip-chart recorder (LKB 2210 recorder, LKB Produkter AB<sup>®</sup>, Bromma, Sweden) at a paper speed of 0.5 cm min<sup>-1</sup>. The difference between the position of the core before and during inflation of a sphygmomanometer cuff on the same upper arm to 40 mmHg gave a measure of the diameter changes under a given congestion pressure. Peak heights on the strip-chart recorder were linearly proportional to the movement of

the core and were measured manually in units according to the Department's standard operating procedures.

#### *Drug administration and assessment of effects*

After having installed the tripod for hand vein compliance technique and having established a stable initial baseline with 4% gelatine solution defined as 100% relaxation, increasing dose rates of the selective  $\alpha_1$ -adrenoceptor agonist phenylephrine (Neo-Synephrine®; Abbott Laboratories, North Chicago, IL, USA; dosages 1.25–8000 ng min<sup>-1</sup>) were locally infused to constrict the vein by about 80%. This precontraction baseline was defined as 0% and the effect of subsequently administered vasodilators was expressed in percentage changes from the difference between the initial baseline diameter during normal saline and the diameter during stable precontraction.

Once precontraction was stable, substance P (Calbiochem/Novabiochem AG, L aufelfingen, Switzerland) was coadministered until the maximal venodilation was reached (approximately 7–10 min). To prevent the peptide from sticking to tubing and syringes, substance P was dissolved in a 4% gelatine solution. Based on the experience of previous experiments in this setting, a substance P dose rate was selected that is at the upper end of the steep part of the dose–response curve [8] (1.5 pmol min<sup>-1</sup>) and thus is already able to detect small antagonistic effects. If a participant reacted with less than 50% venodilation to the dose of 1.5 pmol min<sup>-1</sup>, the dose was doubled to 3 pmol min<sup>-1</sup>.

SLV317 (250 mg and 25 mg quinine sulphate) or placebo (25 mg quinine sulphate), both dissolved in water for injection and mint syrup, were then administered as an oral solution. A SLV317 dose of 250 mg was chosen because this was the highest dose used in preliminary experiments in healthy participants and was well tolerated. For blinding, quinine was added to mimic the bitter taste of SLV317 and mint syrup to disguise the slightly yellowish colour as well as bitter taste of SLV317. The infusion of substance P (same dose as before study drug administration) was repeated at the following time points: 0.5, 1.25, 2, 2.75, 3.5 and 4.25 h after dosing. Each peptide application was separated by a wash-out phase of 45 min to avoid the occurrence of tolerance [8].

Before the end of the experiment, immediately following the last substance P infusion, a single high dose (2  $\mu$ g min<sup>-1</sup>) of the vasodilator sodium nitroprusside (SNP) (Nipruss®; Schwarz Pharma AG, Monheim, Germany) was administered into the hand vein for at least 6 min, to demonstrate that the vein was still fully responsive and that full vasodilation could still be achieved.

Dose rates administered locally into the hand vein were intended not to result in any systemic effects, which were monitored by repeated measurements of heart rate and blood pressure. Blood pressure was taken before and after every infusion of drugs or solvents (sodium chloride, phenylephrine, substance P); a 12-lead ECG was monitored continuously up to the end of the hand vein compliance measurements.

#### *SLV317 pharmacokinetics*

Venous blood samples for SLV317 kinetics were taken 0.25 h before as well as 0.25, 0.5, 0.75, 1, 1.25, 2.0, 2.75, 3.5, 4.25, 6, 8, 12 and 24 h after administration of SLV317. Blood was drawn into vials containing dry heparin, immediately stored on ice (4°C) and plasma was separated within 30 min at 3000 g for 10 min. The samples were stored at –20°C until analysis. When time points of pharmacodynamic (hand vein compliance method) and pharmacokinetic measurements coincided, the pharmacodynamic measurements were first finished before blood samples were taken, accepting a delay in pharmacokinetic sampling of about 5 min.

#### *SLV317 assay*

The plasma samples were analysed using a validated analytical method (Solvay, internal file). This method consists of extraction of SLV317 and its internal standard from plasma with diethylether, concentration and injection into a high-performance liquid chromatography system with MS/MS detection. Accuracy and precision were within specifications; bias was <12%; the interday coefficient of variation was <14%. The lower limit of quantification was set at 0.2 ng ml<sup>-1</sup>.

#### *Safety*

Safety was assessed by measuring ECG, pulse rate, blood pressure, haematology, blood chemistry, urinalysis, and by occurrence of adverse events.

#### *Data analysis and statistics*

Source verification of all data documented in case report forms was performed by an independent clinical monitor. Nineteen individuals were randomized and thus included in the safety analysis. Only the randomized participants who completed both dosing sessions according to protocol were included in the pharmacodynamic analysis ( $n = 17$ ). Two participants had to be withdrawn due to methodological problems during hand vein measurements. One of these two was exposed to SLV317 and complete pharmacokinetic data were obtained, leading to datasets of 18 participants for pharmacokinetic analysis.

The effect of SLV317 was expressed as percentage antagonism of substance P-induced venodilation, calculated as follows:

$$\% \text{ antagonism} = 100\% - \frac{\text{SP} - \text{PC}}{\text{SP}_0 - \text{PC}} \cdot 100$$

where SP = substance P-induced venodilation (units), SP<sub>0</sub> = initial substance P-induced venodilation (predosing) (units) and PC = precontraction baseline (units).

The area under the effect–time curve (AUC<sub>e</sub>) was calculated according to the trapezoidal rule. Statistical analysis of AUC<sub>e</sub> was performed using a mixed model analysis of variance (ANOVA) including the factors subject, sequence, period and treatment. Pharmacokinetic calculations were performed using WinNonlin Professional 4.0.1 for Windows (Pharsight Corporation, Mountain View, CA, USA). Differences in vital signs and dose rates were assessed with Wilcoxon signed rank test, unless stated otherwise. Data are expressed as mean ± SEM. A *P*-value of <0.05 was considered significant.

## Results

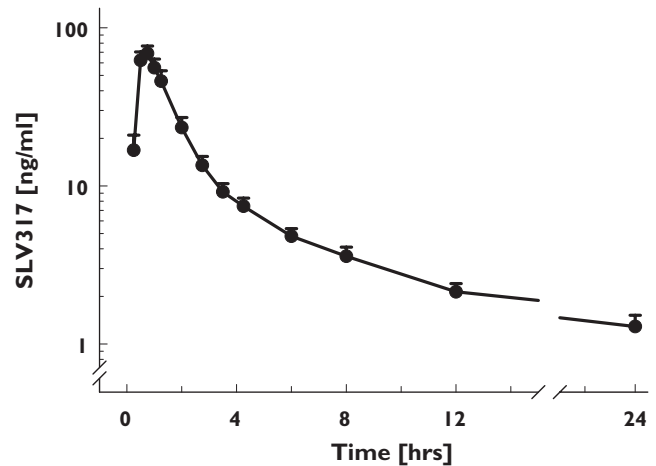
The participants had a mean age of 25 ± 1 years (range 19–32 years), a mean weight of 78.0 ± 1.8 kg (range 68.5–95.8 kg), a mean height of 183 ± 2 cm (range 171–197 cm) and a mean body mass index of 23.4 ± 1.4 kg m<sup>-2</sup> (range 21.1–26.0 kg m<sup>-2</sup>).

### Pharmacokinetics

After oral administration SLV317 was rapidly absorbed and plasma concentrations reached peaks of 77 ± 9 ng ml<sup>-1</sup> within 47 ± 3 min (Figure 1). The mean AUC<sub>0–∞</sub> was 183 ± 22 h ng<sup>-1</sup> ml<sup>-1</sup>; the mean half-life was 9.9 ± 1.6 h. In the terminal phase of concentration–time curves 24 h after dosing, SLV317 was still detectable at low concentrations in all participants. Large interindividual variability was observed for C<sub>max</sub> and AUC, with the ratio between maximal and minimal value being 6.5 for C<sub>max</sub> and 6.3 for AUC.

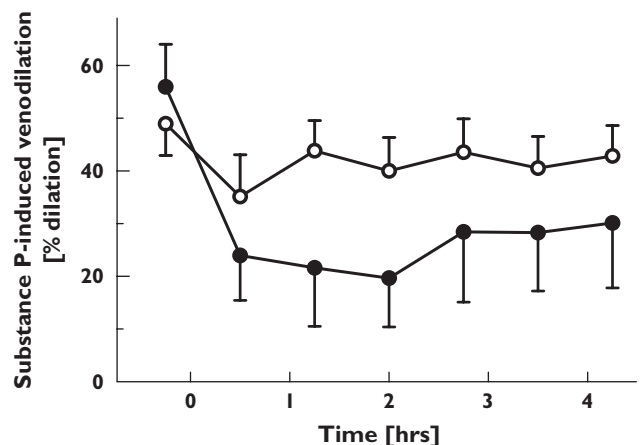
### Pharmacodynamics

Phenylephrine dose rates used to precontract hand veins were similar in both study phases (SLV317 1370 ± 297 ng min<sup>-1</sup>; placebo 1491 ± 286 ng min<sup>-1</sup>; *P* = 0.75), as was the precontraction expressed as a percentage from the initial vein diameter recorded during infusion of solvent (SLV317 21 ± 2%; placebo 25 ± 4%; *P* = 0.81). Substance P dose rates were equal for both study treatments (SLV317 2.0 ± 0.2 ng min<sup>-1</sup>; placebo 2.1 ± 0.2 ng min<sup>-1</sup>; *P* = 1.00 for the sign test) and the mean venodilation induced by substance P was similar immediately before oral administration of SLV317 (56 ± 8%) or placebo (49 ± 6%; *P* = 0.64).



**Figure 1**

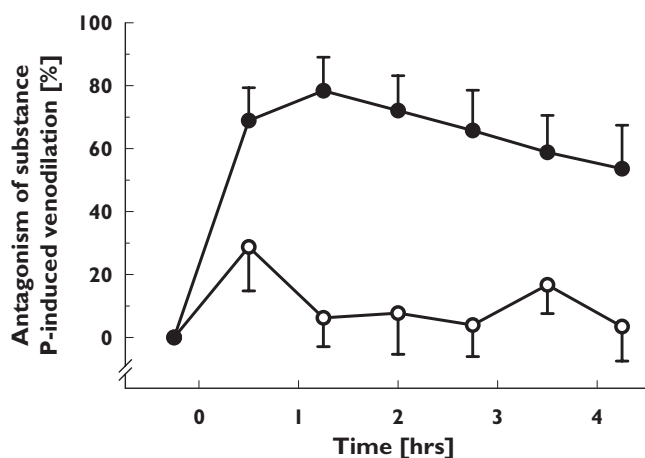
Semilogarithmic plot of plasma concentrations of the NK-1 receptor antagonist SLV317 in 18 healthy participants (mean ± SEM) after administration of 250 mg SLV317 as an oral solution



**Figure 2**

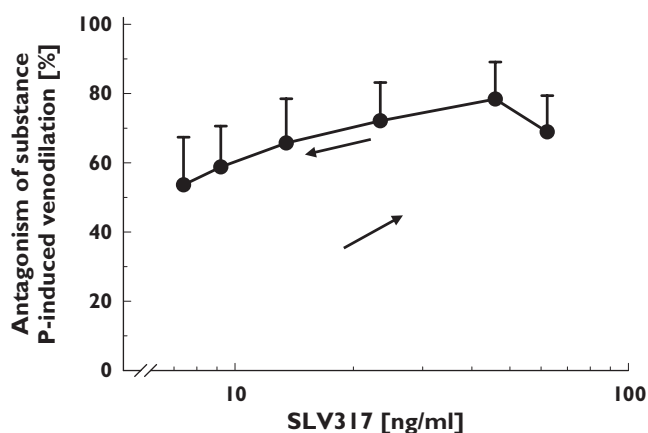
Substance P-induced venodilation expressed as percent reversal of phenylephrine-induced precontraction after oral administration of the NK-1 receptor antagonist SLV317 (●) or placebo (○) in 17 healthy participants (mean ± SEM)

After administration of 250 mg SLV317, substance P-induced venodilation markedly decreased while vasodilation during placebo was unchanged (*P* < 0.001; Figure 2). Correspondingly, the antagonizing effect of SLV317 markedly increased after administration of 250 mg SLV317 compared with placebo (Figure 3). The maximum antagonizing effect of SLV317 (*E*<sub>max</sub>) averaged 95 ± 8% [95% confidence interval (CI) 78, 111] and was observed after 1.47 ± 0.24 h (median 01.25 h; 95% CI 0.96, 1.98). At the time point of *E*<sub>max</sub> under



**Figure 3**

Antagonism of substance P-induced venodilation after oral administration of the NK-1 receptor antagonist SLV317 (●) or placebo (○) in 17 healthy participants over time (mean  $\pm$  SEM). Data are expressed as a percentage of the initial individual response to substance P, which was set to 100%



**Figure 4**

Antagonism of substance P-induced venodilation plotted against the corresponding SLV317 plasma concentrations. Data are from 17 participants; mean  $\pm$  SEM. The arrows indicate the time course of the data points (counter-clockwise hysteresis)

active treatment the antagonism of venodilation under placebo averaged  $19 \pm 14\%$  (95% CI  $-11, 49$ ;  $P < 0.001$ ). Also, the mean  $AUC_c$  after administration of SLV317 ( $278 \pm 67\% \text{ h}^{-1}$ ; 95% CI 198, 358) was significantly higher compared with placebo ( $49 \pm 12\% \text{ h}^{-1}$ ; 95% CI  $-24, 122$ ;  $P < 0.001$ ). There were no carry-over effects ( $P = 0.33$ ) and no period effects ( $P = 0.22$ ) as tested with ANOVA. The response to SNP at the end of the experiment was pronounced and not different for either study treatment (SLV317  $92 \pm 9\%$ ; placebo  $96 \pm 7\%$ ;  $P = 0.69$ ).

### Concentration–effect relationship

Figure 4 shows mean substance P-induced venodilation (% antagonism) plotted against the corresponding SLV317 plasma concentrations. High SLV317 plasma concentrations and maximum effects were reached already at the time of the first pharmacodynamic assessment and the antagonistic effect persisted throughout the study while plasma concentrations declined (counter-clockwise hysteresis).

### Safety

Oral administration of 250 mg SLV317 was well tolerated by all participants. Neither SLV317 nor placebo induced significant changes in heart rate, blood pressure or ECG parameters. At baseline and 4.5 h after administration of SLV317 blood pressure values (systolic/diastolic) were  $124 \pm 3/68 \pm 3$  vs.  $127 \pm 2/72 \pm 2$  mmHg ( $P = 0.10/P = 0.12$ ) and heart rate was  $60 \pm 2$  vs.  $63 \pm 2$  beats  $\text{min}^{-1}$  ( $P = 0.14$ ). The respective values after placebo administration were  $125 \pm 3/69 \pm 2$  vs.  $127 \pm 2/71 \pm 2$  mmHg ( $P = 0.14/P = 0.17$ ) and  $62 \pm 3$  vs.  $63 \pm 2$  beats  $\text{min}^{-1}$  ( $P = 0.64$ ).

No serious adverse event occurred. Six adverse events during placebo [mild headache ( $n = 4$ ), cloudy urine, mild orthostatic dysregulation] and three adverse events during SLV317 (mild headache, severe headache, cloudy urine) were reported and classified as possibly related to the study drug. All resolved without any sequelae within the following hours. Cardiovascular, laboratory and physical investigations showed no clinically relevant changes.

### Discussion

This double-blind placebo-controlled study is the first to show that SLV317 is an orally active and highly effective antagonist of substance P-induced effects in humans. SLV317 was rapidly absorbed and well tolerated. It caused a substantial reduction of substance P-induced venodilation, which was already almost fully established at the time of the first measurement (30 min after dosing) and which was still pronounced at the end of the measurements (after 4.25 h).

Because substance P is by definition the natural NK-1 receptor agonist with the highest affinity [11], this peptide is best suited to study NK-1 receptor effects in humans. We have shown previously that NK-1 receptors are present in human hand veins [7] and that substance P produces potent, efficient and reproducible venodilation, provided that the occurrence of tolerance is avoided [8]. Substance P-induced changes in hand vein compliance may therefore constitute a surrogate for effects mediated by the human NK-1 receptor. Thus, this

study shows that SLV317 substantially antagonizes substance P-induced venodilation, suggesting peripheral NK-1-antagonistic activity of SLV317 in humans. We obtained only limited information on the selectivity of SLV317 for the NK-1 receptor in the present study because we administered only one dose of only one additional vasodilator acting through an independent second messenger pathway (sodium nitroprusside). However, SLV317 has been shown to be highly selective for the NK-1 receptor in animal models [4] and the preserved full relaxation of the hand vein through activation of the nitric oxide–cGMP pathway by SNP is in line with these findings. Changes in substance P responses were not caused by counter-regulatory reflex activation or altered vascular smooth muscle reactivity, as indicated by the absence of haemodynamic effects of SLV317 and the similar response to SNP after both SLV317 and placebo treatment.

Rapid onset and the persistence of the antagonistic effect precluded assessment of SLV317 potency by construction of the expected sigmoidal concentration–effect relationship. During the evaluation of hand vein responses SLV317 plasma concentrations declined from a mean maximum of 77 ng ml<sup>-1</sup> (109 nmol l<sup>-1</sup>) to a mean of 7 ng ml<sup>-1</sup> (10 nmol l<sup>-1</sup>), whereas no substantial change in its effect occurred. The sustained antagonizing effect at low concentrations might suggest that SLV317 is a potent NK-1 receptor antagonist and that maximum receptor blockade *in vivo* might already be reached with much lower doses. Information on plasma concentrations required to induce the maximum effect is of interest to define dose ranges for subsequent studies.

As an oral solution, SLV317 kinetics was highly variable with respect to absorption and elimination of the compound. If the potency of the compound were to be defined in this model, future pharmacodynamic studies should be planned with smaller doses or repetitive administration of fractions of the total dose to be able to quantify vascular effects in the steep part of the concentration–effect relationship. Moreover, because of the rapid absorption, pharmacodynamic measurements should start already 15 min after dosing. A solid galenic formulation or even a slow-release formulation might allow the pharmacodynamic evaluation during the absorption process.

In conclusion, this study in healthy participants revealed clear evidence of a profound inhibition of substance P-induced venodilation by a single oral dose of SLV317. This is in complete agreement with the concept that SLV317 acts as a potent inhibitor of human NK-1

receptors *in vivo*. Future studies are required to establish the dose–response relationship in man and to assess a potential therapeutic effect in patients with diseases probably linked to NK-1 receptor stimulation such as visceral pain and inflammation in patients with inflammatory bowel disease or visceral pain in irritable bowel syndrome patients.

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## References

- 1 Leroy V, Mauser P, Gao Z, Peet NP. Neurokinin receptor antagonists. *Exp Opin Invest Drugs* 2000; 9: 735–46.
- 2 Cockcroft JR, Chowienzyk PJ, Brett SE, Ritter JM. Effect of N-monomethyl-L-arginine on kinin-induced vasodilation in the human forearm. *Br J Clin Pharmacol* 1994; 38: 307–10.
- 3 Camilleri M. Treating irritable bowel syndrome: overview, perspective and future therapies. *Br J Pharmacol* 2004; 141: 1237–48.
- 4 Sann H, Jasserand D, Brückner R, Reiche D, Ronken E, van Stuivenberg HH, Eeckhout D, Preuschoff U. Characterisation of the NK1 antagonist SLV317 *in vitro* and *in vivo*. *Gastroenterology* 2004; 126 (4 Suppl 2): W1056 (Abstract).
- 5 Sann H, Ait-Belgnaoui A, Bueno L. Anti-inflammatory influence of the NK1 antagonist SLV317 on trinitrobenzenesulfonic acid (TNBS)-induced ileitis and colitis in guinea-pigs and rabbits. *Gastroenterology* 2005; 128 (4 Suppl 2): A-500 (Abstract).
- 6 Pradier L, Habert-Ortoli E, Emile L, Le Guern J, Loquet I, Bock MD, Clot J, Mercken L, Fardin V, Garret C. Molecular determinants of the species selectivity of the neurokinin type 1 receptor antagonists. *Mol Pharmacol* 1995; 47: 314–21.
- 7 Romero SC, Linder L, Haefeli WE. Neurokinin-1 receptor antagonist R116301 inhibits substance P-induced venodilation. *Clin Pharmacol Ther* 1999; 66: 522–7.
- 8 Strobel WM, Lüscher TF, Simper D, Linder L, Haefeli WE. Substance P in human veins *in vivo*: tolerance, efficacy, potency, and mechanism of venodilator action. *Clin Pharmacol Ther* 1996; 60: 435–43.
- 9 Aellig WH. A new technique for recording compliance of human hand veins 1981. *Br J Clin Pharmacol* 2004; 58: S768–74.
- 10 Fricker R, Hesse C, Weiss J, Tayrouz Y, Hoffmann MM, Unnebrink K, Mansmann U, Haefeli WE. Endothelial venodilator response in carriers of genetic polymorphisms involved in NO synthesis and degradation. *Br J Clin Pharmacol* 2004; 58: 169–77.
- 11 Stout SC, Owens MJ, Nemeroff CB. Neurokinin (1) receptor antagonists as potential antidepressants. *Annu Rev Pharmacol Toxicol* 2001; 41: 877–906.