RESULTS

Twenty-five patients were enrolled according to the flowchart in figure 1. One patient was not treated because of a positive drug screening on the first study day and was replaced. Two patients in the opioid subgroup were lost to cross over after the first study day, one female patient due to mild AEs and one male patient after withdrawal of consent. Consequently, 24 patients received a single dose Δ9-THC, and 22 patients received a single dose Diazepam.

Patient demographics and baseline characteristics are described in table 1. The mean age at screening was 52 years, mean BMI was 23.0 kg/m^2, and 9 of 24 patients were female. Patients reported a mean NRS at screening of 6.0, whereas the mean VAS reported in the pain diary was 3.9. The average abdominal pain duration was 8.3 years at screening.

Analgesic efficacy

Primary linear mixed model analysis at time point 2:05H showed no treatment effect of Δ9-THC compared with Diazepam on delta VAS pain at rest (mean diff Δ9-THC - diazepam -.17; 95% CI diff [-.95 to .61]; p=.65). Figure 2 shows the VAS pain at rest and on movement compared to baseline from 0:35H until 5:00H after administration of Δ9-THC as well as diazepam. The AUC VAS pain at rest (mean diff 18.37; 95% CI diff [-60.49 to 97.23]; p=.63) and AUC VAS pain on movement (mean diff -18.14; 95% CI diff [-168.31 to 132.03]; p=.80) after Δ9-THC were both not significantly decreased compared with diazepam. These parameters were similar for opioid vs. non-opioid users.

Pharmacokinetics

Mean plasma concentration-versus-time curves of THC and 11-OH-THC are shown in figure 3 and table 2 summarizes the PK of THC and its active metabolite 11-OH-THC. The PK parameters were similar between opioid and non-opioid users. One patient demonstrated a clearly enhanced C_{max} compared to the rest of the population, which could not be explained by genetic polymorphism.

Pharmacogenetics

Several genetic polymorphisms were observed. Two patients were heterozygote carriers of CYP2C9*2 (C>T) and four patients were heterozygote carriers of CYP2C9*3 (A>C). One patient was found to be AA homozygote and four patients GA heterozygote for CYP2C19*2 (G>A). No CYP2C19*3 (G>A) polymorphisms were observed. Genetic polymorphisms in CYP2C19*17 (C>T) were found for five subjects who were heterozygote CT carriers. Genetic polymorphisms did not evidently effect the pharmacokinetics of Δ9-THC.

Pharmacodynamics

Figure 4 shows the effects of Δ9-THC and diazepam for alertness, mood and calmness obtained by the VAS Bond and Lader questionnaire. No significant differences were found between Δ9-THC vs. diazepam. Feeling anxious obtained by the VAS Bowdle questionnaire was significantly increased after Δ9-THC compared with diazepam (mean diff 166,92; 95% CI diff [10,86 to 322,97]; p=.037).

Overall 10 body sway measurements (4% of all measurements), from which 6 in the eyes closed condition and 8 after Δ9-THC administration, could not be conducted due to adverse events at that particular moment. There were no group differences in balance outcomes in both the eyes open and eyes closed condition between Δ9-THC and diazepam. However, figure 5 shows that balance performance was considerably disturbed in certain individuals after both Δ9-THC and diazepam. These individuals were found in both subgroups. Heart rate was significantly enhanced after Δ9-THC compared to diazepam (at time point 1:40H mean diff -5.5 BPM; 95% CI diff [-9.0 to -1.9]; p=.004). In one patient, heart rate in rest was measured above 100 BPM after Δ9-THC intake. Δ9-THC and diazepam did not affect diastolic or systolic blood pressure. Alterations in heart rate were not associated with PK parameters such as C_{max} and AUC_{inf}.

Safety and Tolerability

All related, probably related and possibly related AEs are presented in table 3. Overall, there was a higher frequency of AEs following Δ9-THC administration compared to diazepam (36 AEs in 22

patients vs. 54 AEs in 24 patients, respectively), although fewer patients reported at least one AE after Δ9-THC administration compared to diazepam (71% vs. 91% respectively). The most frequently reported AEs after Δ9-THC administration were somnolence, dry mouth, dizziness, and euphoric mood. Somnolence, dizziness, and fatigue were most commonly related or possibly related to diazepam administration. All AEs were mild or moderate, and equally divided between opioid and non-opioid users. The number of AEs was not associated with PK parameters such as C_{max} and AUC_{inf}. However, the subject showing the highest C_{max} also had the greatest number of AEs. There were no serious AEs during the study. One patient was withdrawn after the first study day due to somnolence, dizziness, increased heart rate, nausea, paraesthesia, and feelings of tension. There were no clinically relevant changes in vital signs, ECG parameters, or safety laboratory parameters (hematology, biochemistry, and urinalysis).

Table 1: Baseline demographics and disease characteristics

	Sex (M/F)	Age (years)	BMI (kg/m^2)	Etiology CP	Pain screen (NRS)	Pain diary (VAS)	Pain duration (years)	Concomitant medication
Opioid subgroup								
1	M	54	25,7	Post ERCP	6	4,2	5	SOPI, PCM, AC
2	M	48	26,9	Idiopathic	4	4,5	2	SOPI, PCM, AC
3	M	46	26	Idiopathic	7	2,2	21	SOPI, AC, PE
4	F	61	26,6	Idiopathic	5	5,2	15	SOPI, PE
5	M	44	18,8	Neoplasm	3	4,5	0	SOPI, PE
6	M	42	22,5	Alcohol	6	5,1	14	WOPI, PCM, PE
7	M	45	22	Idiopathic	6	7,2	4	SOPI, WOPI, PCM
8	F	42	21,5	Hereditary	6	4,9	13	SOPI, PCM
9	M	52	22,2	Alcohol	5	4,4	1	SOPI, NSAID, PCM
10	M	50	26,2	Idiopathic	8	2,5	2	SOPI, PE
11	F	34	19,5	Idiopathic	4	4,0	11	SOPI, PCM
12	F	52	19,2	Idiopathic	8	4,6	8	SOPI, AC
mean (SD)	**8/4**	**47,5 (7,0)**	**23,1 (3,1)**		**5,7 (1,6)**	**4,4 (1,3)**	**8,0 (6,7)**	
Non-opioid subgroup								
13	F	52	26,2	Idiopathic	8	6,9	11	PCM, AC
14	M	69	26,2	Hereditary	6	5,1	4	-
15	M	56	20,6	Neoplasm	8	4,0	8	AC, PE
16	M	71	23,6	Idiopathic	5	2,1	6	PCM, PE
17	M	51	26,3	Idiopathic	7	4,7	3	NSAID, PCM, PE
18	M	53	24,2	Idiopathic	3	2,5	9	PE
19	M	39	18,4	Idiopathic	7	2,5	6	NSAID, PCM, PE
20	F	54	18,1	Idiopathic	6	3,0	22	PCM, PE
21	F	57	23,8	Idiopathic	6	1,0	6	PE
22	M	44	18,5	Alcohol	9	2,1	6	PCM, PE
23	F	62	23,3	Alcohol	5	3,2	15	PE
24	F	65	26,3	Idiopathic	5	2,7	7	PCM
mean (SD)	**7/5**	**56,1 (9,5)**	**23,0 (3,2)**		**6,3 (1,7)**	**3,3 (1,6)**	**8,6 (5,3)**	
Total mean (SD)	**15/9**	**51.8 (9.3)**	**23.0 (3.1)**		**6.0 (1.6)**	**3.9 (1.5)**	**8.3 (5.9)**	

SOPI Strong opioids including pethidine; WOPI Weak opioids including tramadol en codein; NSAID Non-steroidal anti-inflammatory drugs including diclofenac and ibuprofen; PCM Paracetamol; AC Anticonvulsants including pregabalin and gabapentin; AD Antidepressants; PA Pancreatic enzymes

Table 2: Pharmacokinetic parameters of THC and 11-OH-THC

		THC		**11-OH-THC**	
		Mean	SD	Mean	SD
Cmax	Group (n=24)	4,01	3,39	4,38	1,50
(ng/mL)	Opioid (n=12)	4,44	4,40	4,51	1,62
	Non-opioid (n=12)	3,58	2,08	4,25	1,44
Tmax	Group (n=24)	122,80	87,99	135,70	77,50
(min)	Opioid (n=12)	126,60	90,49	142,10	86,66
	Non-opioid (n=12)	119,10	89,26	129,30	70,44
$AUC_{0\text{-}Last}$	Group (n=24)	477,50	381,80	764,90	241,30
(ng*min/mL)	Opioid (n=12)	507,90	506,70	777,70	298,10
	Non-opioid (n=12)	447,20	214,70	752,20	180,50
$AUC_{0\text{-}inf}$	Group (n=24)	532,20	442,50	920,70	316,40
(observed)	Opioid (n=11)	577,70	571,10	954,00	400,00
(ng*min/mL)	Non-opioid (n=8)	469,70	173,20	883,70	205,90
$T_{1/2term}$	Group (n=24)	67,12	20,37	110,10	26,57
(min)	Opioid (n=11)	67,89	19,71	111,70	29,51
	Non-opioid (n=8)	66,05	22,57	108,40	24,55

Table 3: Summary of adverse events

Adverse Event	Diazepam (n=22)		Namisol® (n=24)	
	N	%	N	%
General				
Fatigue	8	36%	7	29%
Nervous system symptoms				
Somnolence	11	50%	8	33%
Dizziness	6	27%	4	17%
Headache	3	14%	2	8%
Balance disorder	0	0%	2	8%
Amnesia	0	0%	1	4%
Paraesthesia	1	5%	2	8%
Depressed level of conciousness	1	5%	0	0%
Psychiatric symptoms				
Confusional state	0	0%	2	8%
Indifference	0	0%	1	4%
Euphoric mood	2	9%	4	17%
Derealisation	0	0%	1	4%
Disorientation	0	0%	1	4%
Tension	0	0%	1	4%
Gastro-intestinal system symptoms				
Nausea	1	5%	3	13%
Vomiting	0	0%	1	4%
Steatorrhoea	0	0%	1	4%
Constipation	1	5%	0	0%
Abdominal discomfort	0	0%	1	4%
Dry Mouth	0	0%	5	21%
Throat irritation	0	0%	1	4%
Vision symptoms				
Visual impairment	1	5%	3	13%
Cardiac symptoms				
Heart rate increased	1	5%	1	4%
Eye symptoms				
Dry eye	0	0%	1	4%
Photophobia	0	0%	1	4%
TOTAAL	**36**		**54**	

Figure 1: Flowchart

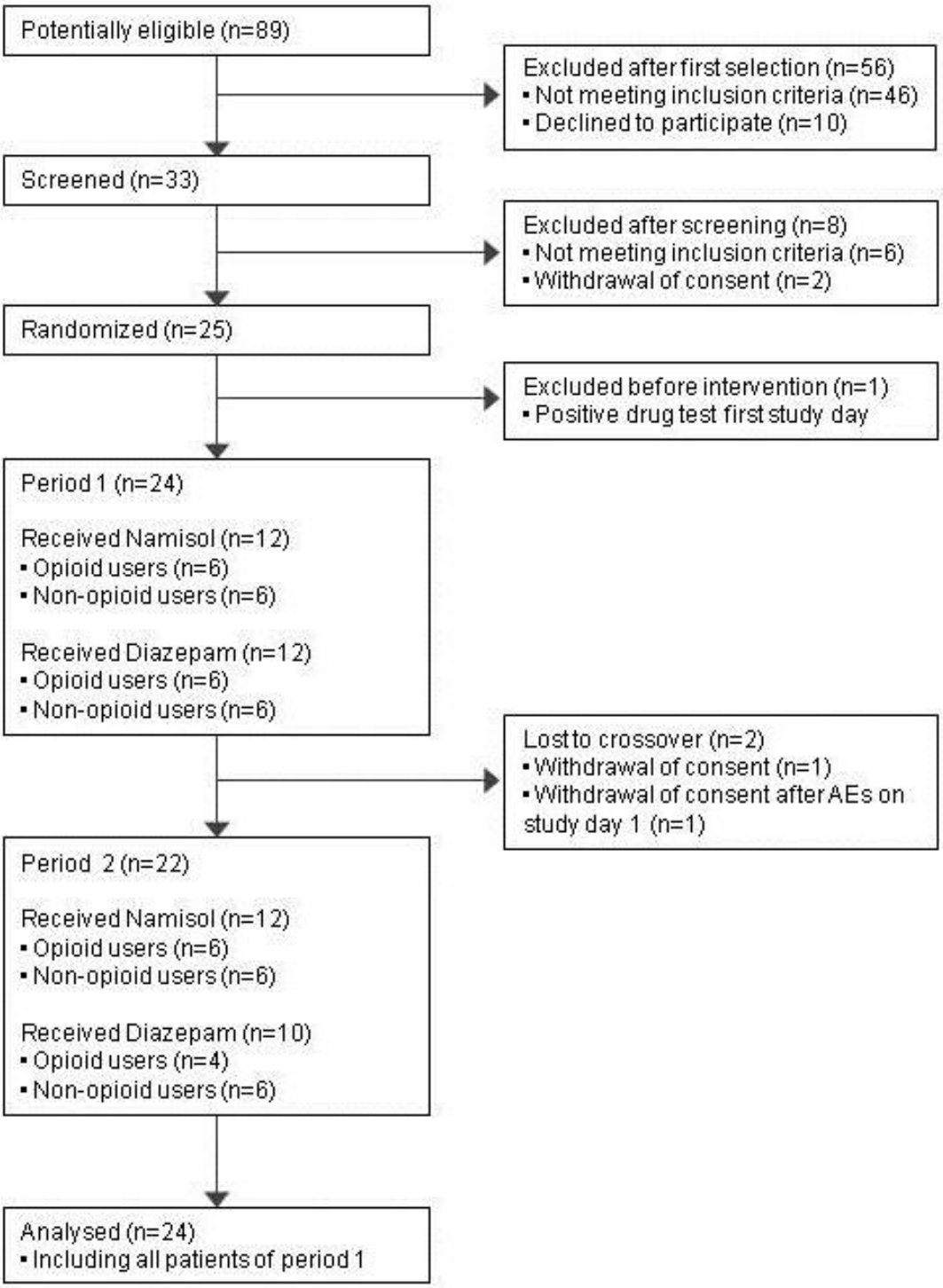


Figure 2: VAS pain. Differences (mean and SEM) in VAS pain compared to baseline were shown for Namisol® and Diazepam measured at rest (A) and on movement (B). Abbreviation: PD= predose (maximal 1 hour prior drug administration)

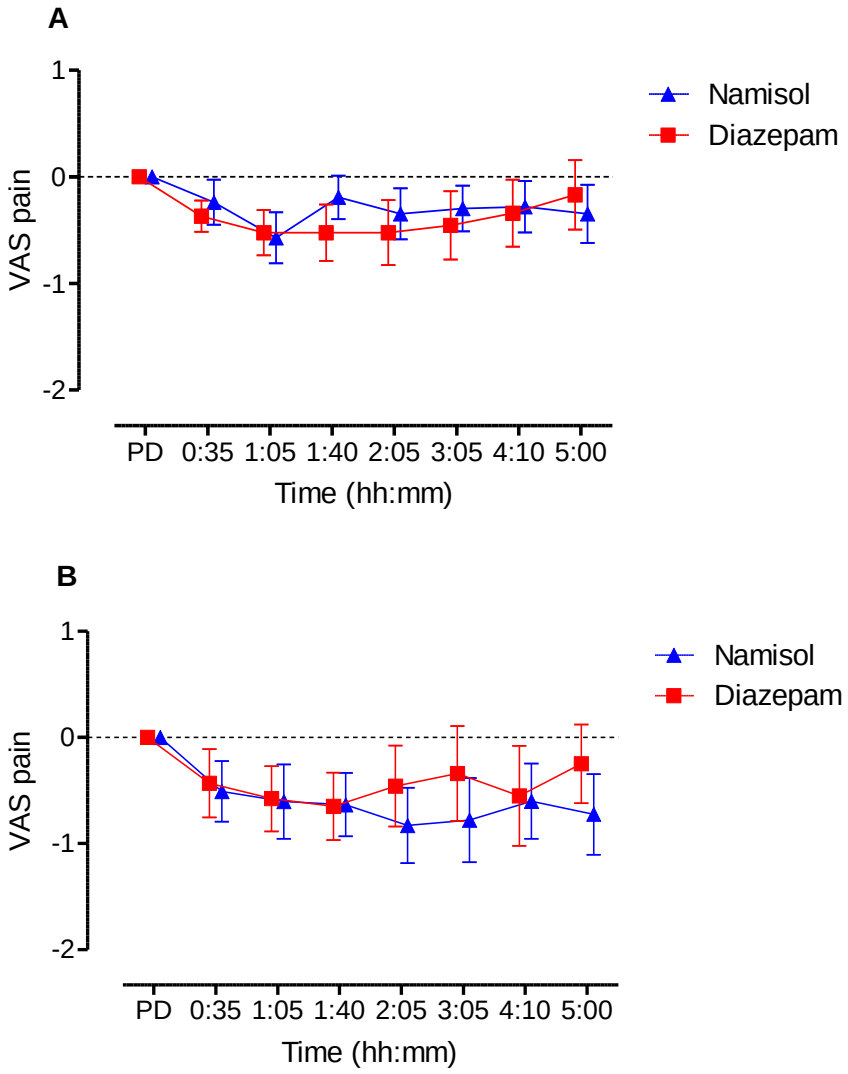
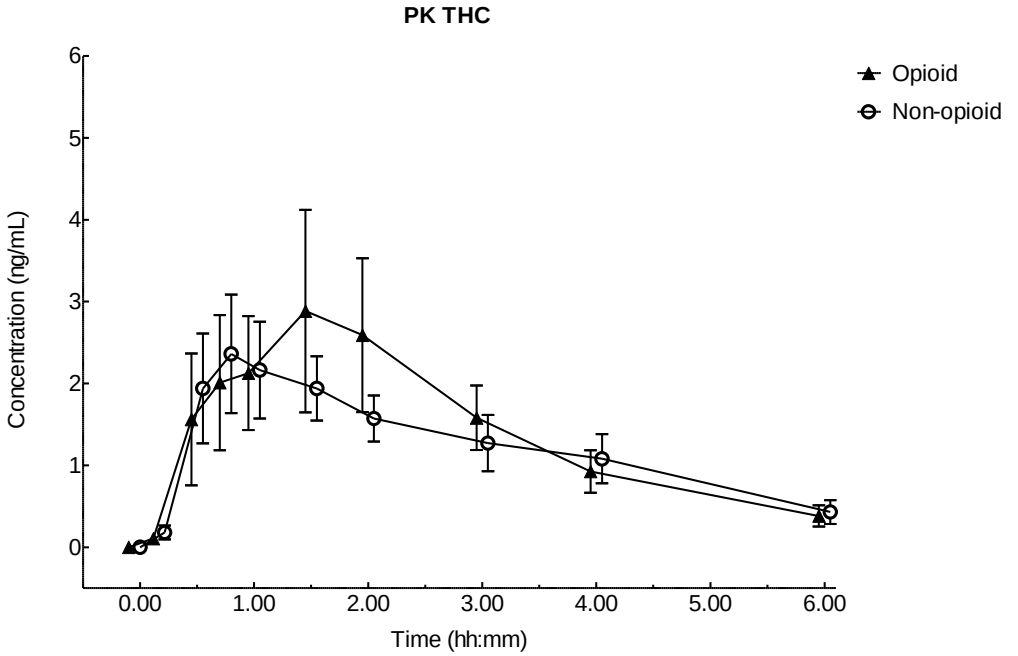


Figure 3: Mean plasma concentration-time curves of THC and 11-OH-THC after a single dose of Namisol®. Error bars represent standard error of the mean (SEM).



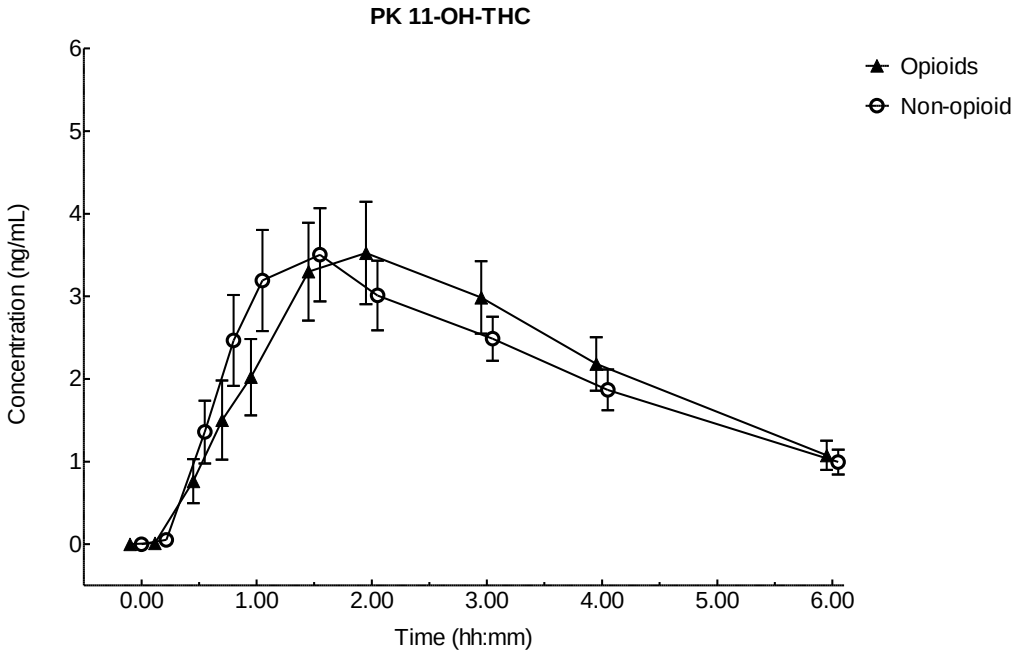
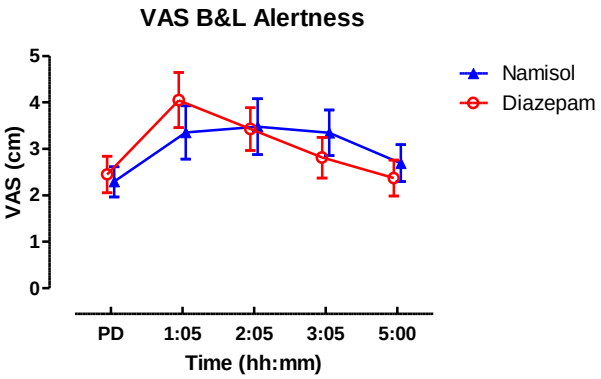
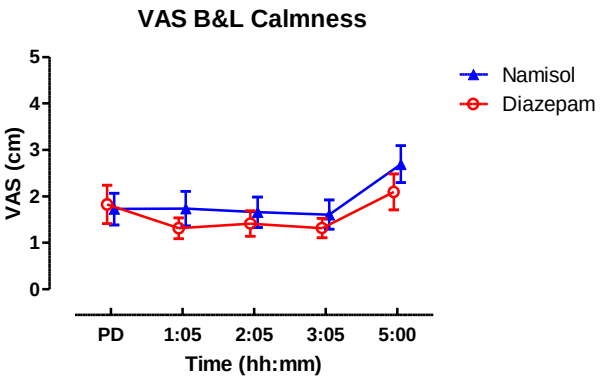


Figure 4: VAS Bond and Lader questionnaire. Mean scores for alertness, calmness and mood were shown for Namisol® and Diazepam. Abbreviation: PD= predose (maximal 1 hour prior drug administration)





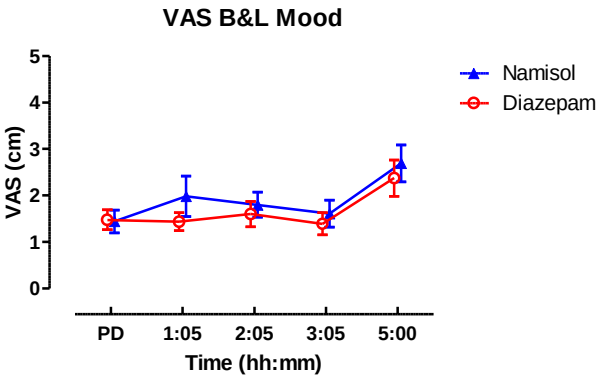


Figure 5: Roll and pitch excursion (90% range) during body sway measurements in eyes closed condition. Each triangle represents one measurement of one subject. Abbreviations: EC= eyes closed; PD= predose (maximal 1 hour prior drug administration)