

Neues in der Opioiderhaltungstherapie

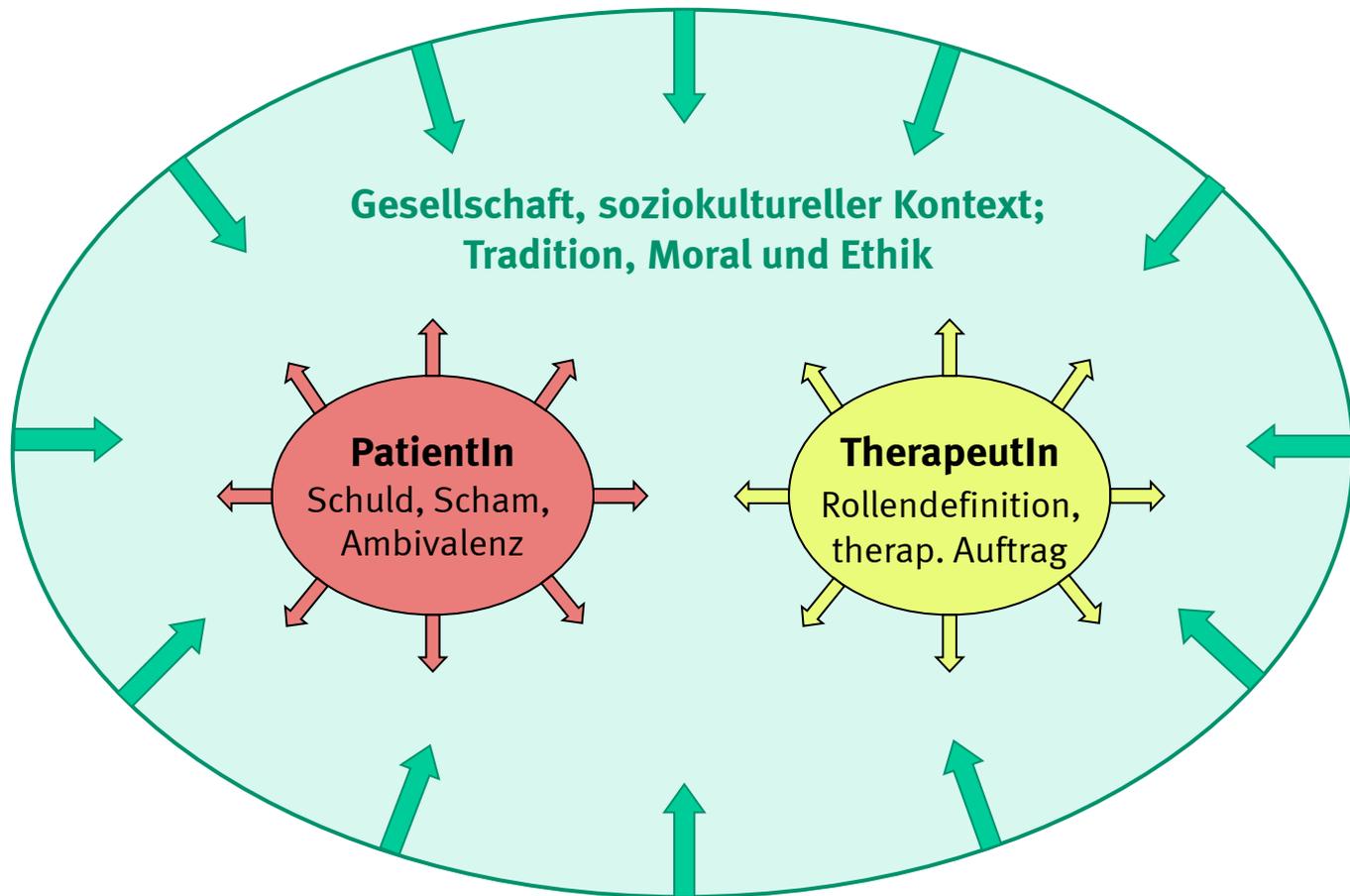
Thilo Beck
Chefarzt Psychiatrie
Arud

Grundlsee, 07.03.2015

Programm

- ↳ Einführung
- ↳ Wahl der Substitutionsmedikation
- ↳ Die Zulassungsstudie SUB9001
- ↳ Diskussion

Spannungsfeld der Überzeugungen



Das richtige Mittel für wen?

- ↳ PatientIn?
- ↳ TherapeutIn?
- ↳ Institution?
- ↳ Versorgungssystem?
- ↳ Gesellschaft?

In der Schweiz zugelassen

- ↳ Methadon (Ketalgin®)
- ↳ Buprenorphin (Subutex®)
- ↳ Retardiertes Morphin (Sevre-Long®)

- ↳ (Diacetylmorphin)

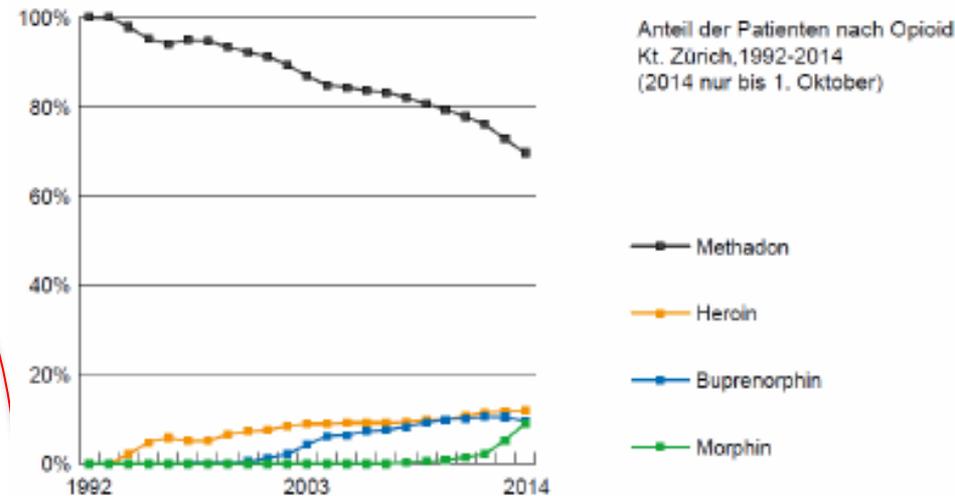
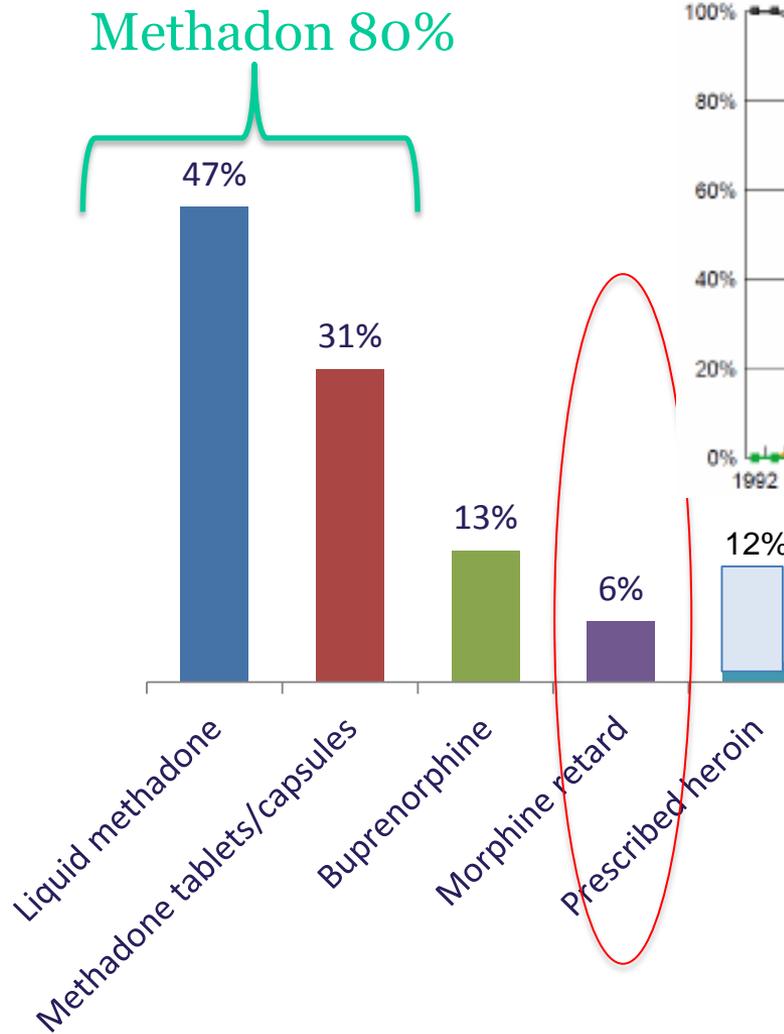
Die Wahl des Substitutionsmittels

Everybody has won and all must have
prizes



Lewis Carrol, 1865
Alice's Adventures in
Wonderland

Aktuelle Behandlung in der Schweiz

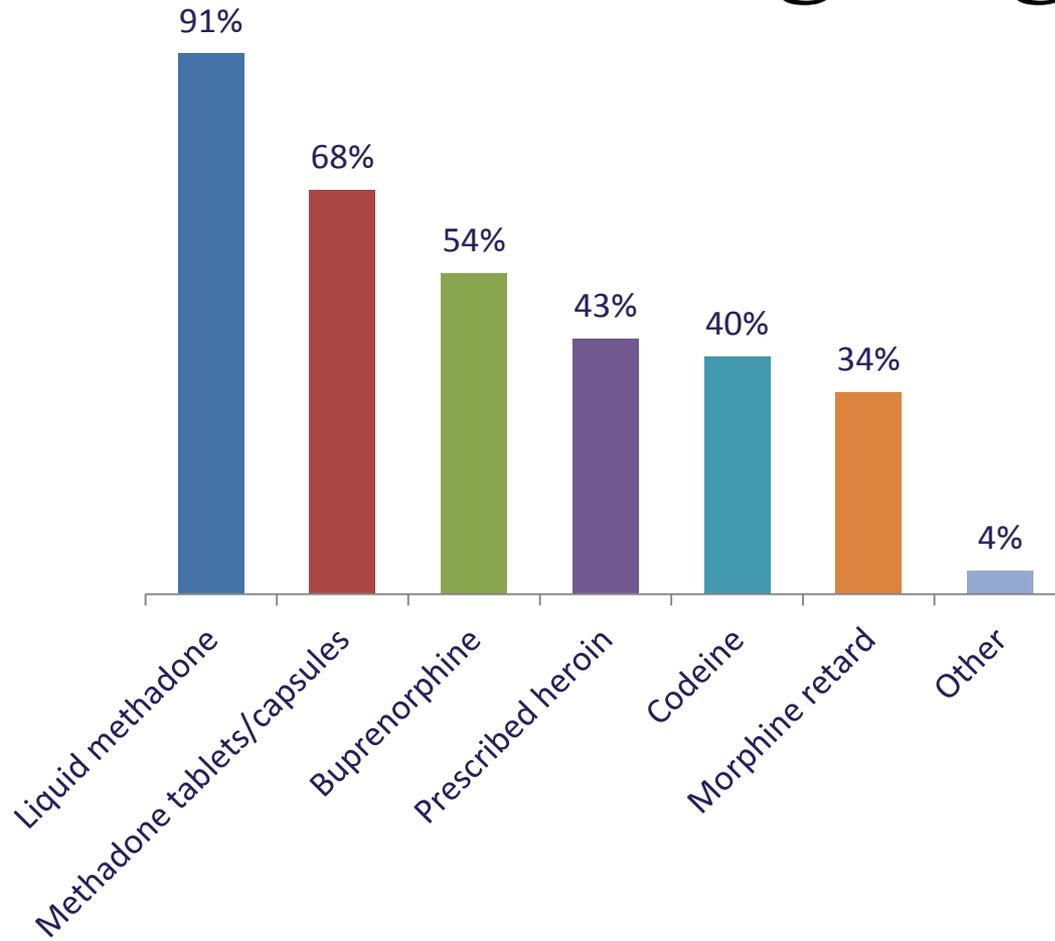


Arud 2014

- Methadon	60%
- SROM	29%
- Buprenorphin	11%

Projekt Access CH 2012: Besson 2014; Nordt 2014 unpublished

Kenntnis der Substitutionsmittel bei Behandlungsbeginn



Indikationsstellung

Informierter Entscheid des
Patienten

Subjektive Verträglichkeit,
passendes Wirkprofil

Ziel(e) der Behandlung

- ↳ Lebensqualität erhalten/verbessern
- ↳ Gesundheit schützen/verbessern
- ↳ Schaden vermindern/verhindern

Verbessern der Lebensqualität und -bewältigung

Kontrolle über Substanzkonsum

Ausbau
von Fähigkeiten

Stabilisieren
der Lebenssituation

Schadensminderung

Sichern des Überlebens

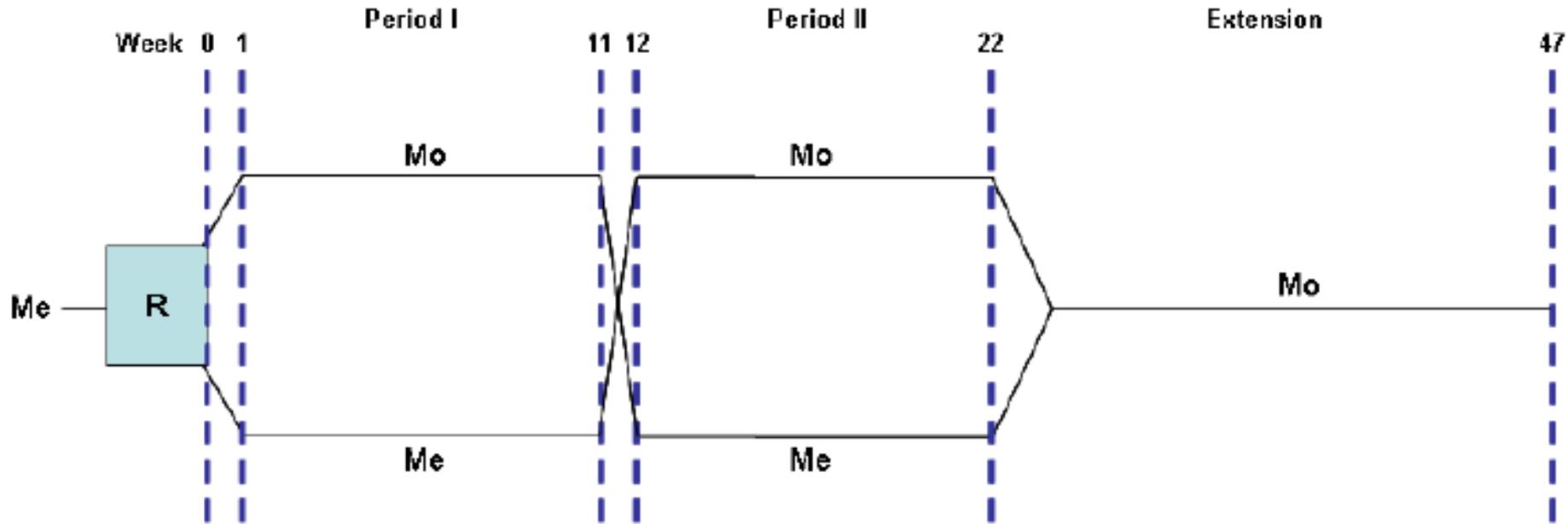
Studie SUB9001: SROM vs GoldstandardMethadon

Randomisiert, Cross-Over, non Inferiority

- ↳ First patient in Juli 2007
- ↳ Last patient out Juni 2011
- ↳ 14 Zentren in der Schweiz (4) und Deutschland (10)
- ↳ 276 Patienten rekrutiert
- ↳ 157 PP-Patienten

SUB9001 Studiendesign

Primary Outcome: Urine samples twice weekly Period I-II



Secondary Outcomes: Weeks 0, 2, 6, 11, 13, 17, 22, 23, 27, 31, 35, 39, 43, 47

SCL-27

Treatment Satisfaction

Drug and Alcohol Use

Craving

ECG: Weeks 0, 11, 13, 22, 35, 47

SUB9001 Outcome-Parameter

- ↳ Heroin-Beikonsum: Urinproben 2x/Woche
- ↳ Adhärenz
- ↳ Craving Heroin, Kokain
- ↳ Zufriedenheit
- ↳ Psychisches Befinden, Nebenwirkungen
- ↳ Beikonsum weiterer psychoaktiver Substanzen
- ↳ QTc-Intervall

SUB9001 PP-Anforderungen

- ↳ Abschluss beider Perioden ≥ 70 und ≤ 84 Tage
- ↳ Urinanalysen ≥ 9 von 11 Wochen/Periode
- ↳ Bezugsunterbrüche ≤ 5 Tage

SUB9001 Einschlusskriterien

- ↳ Opioidabhängigkeit
- ↳ Alter >18 Jahre
- ↳ mindestens 26 Wochen MMT
- ↳ Methadondosis mindestens 50mg
- ↳ keine Absicht, Dosis abzubauen
- ↳ Ausschluss SS, hormonelle Verhütung bei Frauen im gebärfähigen Alter

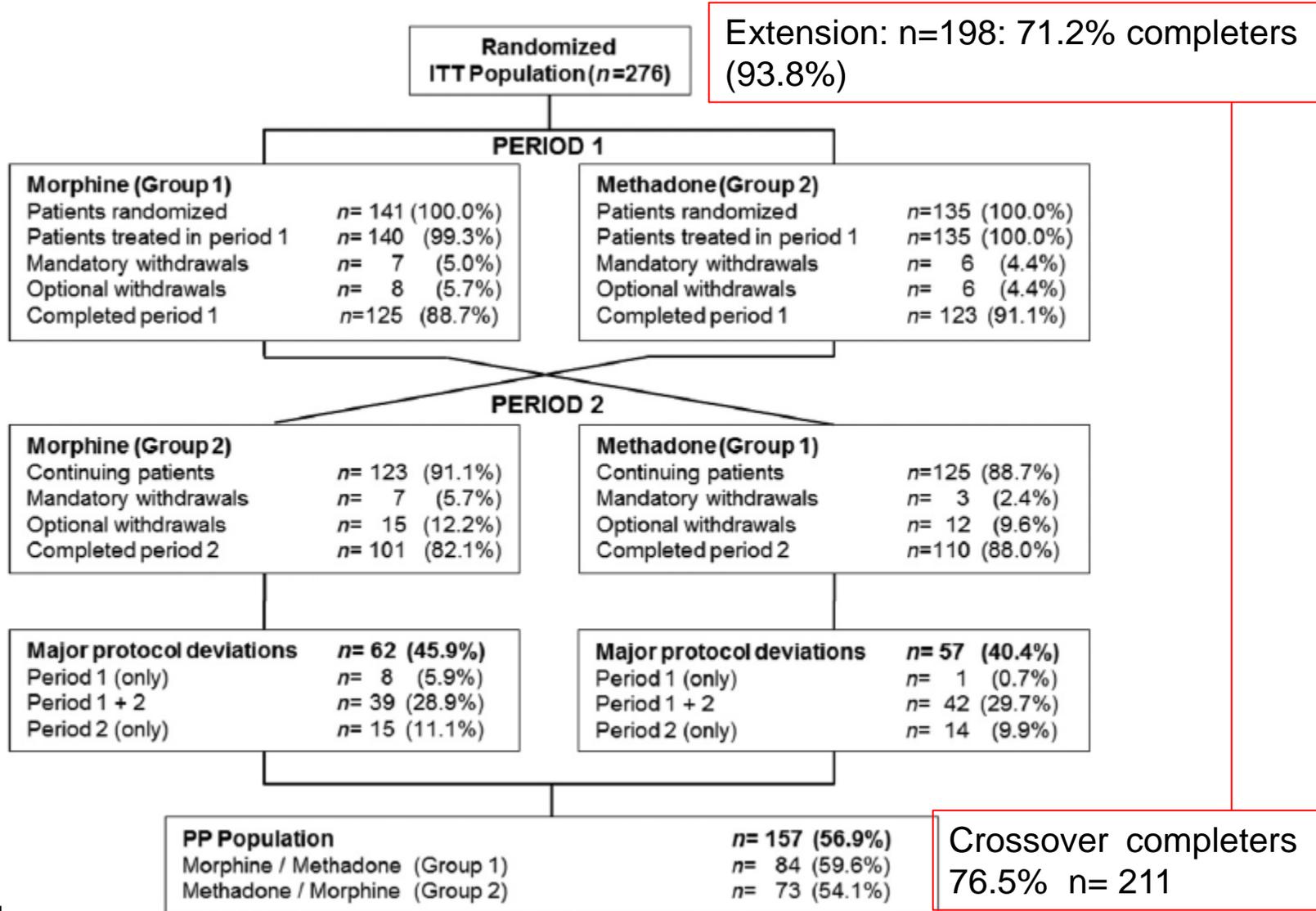
SUB9001 Ausschlusskriterien

- ↳ akute, instabile somatische oder psychische Erkrankung
- ↳ anstehende Haftstrafe
- ↳ $QTc > 450ms$
- ↳ Schwangerschaft, Stillen
- ↳ keine Stabilisierung unter vorhergehender MMT

SUB9001 Sample

	<i>ITT population</i> <i>n = 276</i>	<i>PP population</i> <i>n = 157</i>
Gender		
Male	225 (81.5%)	132 (84.1%)
Female	51 (18.5%)	25 (15.9%)
Age ^a	38.1 ± 7.6 (38.00)	38.9 ± 7.4 (39.00)
Body mass index (calculated) ^a	25.2 ± 4.38 (24.5)	24.77 ± 4.16 (24.3)
Civil status: single	206 (74.6%)	122 (77.7%)
Employment status: full-time job ≥70%	36 (13.0%)	12 (7.6%)
Years of prior maintenance treatment ^a	3.85 ± 4.43 (2.00)	3.58 ± 4.40 (2.00)
Pretreatment: last dose of methadone (mg/day) ^a	98.03 ± 39.95 (90.00)	92.03 ± 30.78 (90.00)
Addiction history		
EuropASI—alcohol ^a	0.12 ± 0.17 (0.03)	0.12 ± 0.18 (0.02)
EuropASI—drugs (modified) ^a	0.31 ± 0.14 (0.31)	0.31 ± 0.15 (0.31)
Age at first heroin consumption ^a	20.26 ± 5.11 (19.00)	20.53 ± 5.08 (19.00)
Patients with ongoing somatic comorbidity	218 (79.0%)	132 (84.1%)
Number of ongoing somatic comorbidities per patient	2.88 ± 1.97	2.84 ± 1.75
HIV—positive	10 (3.6%)	7 (4.5%)
Syphilis—positive	1 (0.4%)	1 (0.6%)
Hepatitis B virus—positive	140 (57.4%)	71 (51.1%)
Hepatitis C virus—positive	158 (57.7%)	105 (67.3%)
Patients with ongoing psychiatric comorbidity	191 (69.2%)	90 (57.3%)
Number of ongoing psychiatric comorbidities per patient	2.19 ± 1.20	1.82 ± 0.98
Number of comedications per patient	3.80 ± 3.52	3.98 ± 3.46

SUB9001 Adhärenz



Heroin-Beikonsum

Non Inferiority erreicht

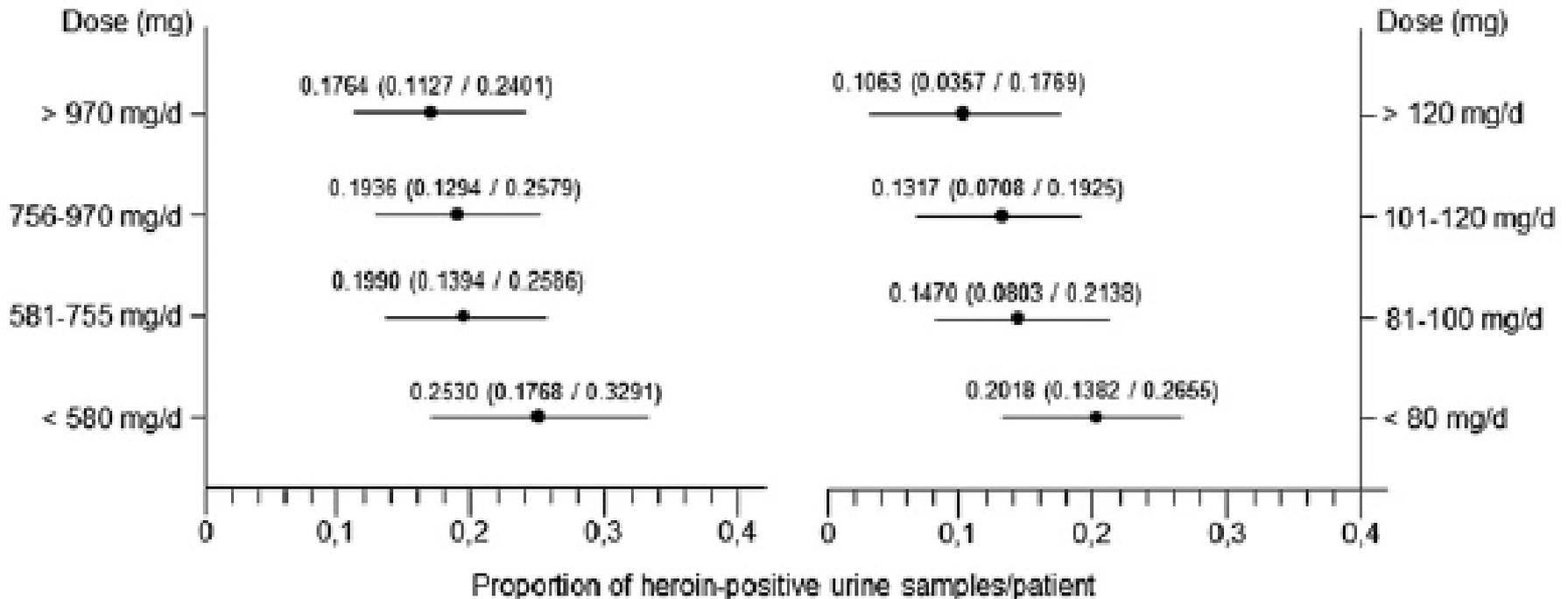
	<i>ITT population (n = 276)</i>	<i>PP population (n = 157)</i>
Use of heroin		
Proportion of heroin-positive urine samples per patient under morphine	0.2564 (95% CI = 0.2330, 0.2799)	0.2020 (95% CI = 0.1811, 0.2229)
Proportion of heroin-positive urine samples per patient under methadone	0.2584 (95% CI = 0.2344, 0.2823)	0.1508 (95% CI = 0.1299, 0.1716)
Difference between morphine and methadone	-0.0019 (95% CI = -0.0355, 0.0316) (<i>P</i> = 0.9104)	0.0513 (95% CI = 0.0217, 0.0808) (<i>P</i> = 0.0008)
Sequence	<i>P</i> = 0.1610	<i>P</i> = 0.0201
Period	<i>P</i> = 0.0293	<i>P</i> = 0.0389
Carry-over effect	<i>P</i> = 0.5152	<i>P</i> = 0.3397

Heroin-Beikonsum

Dosisabhängig für Methadon und SROM

Morphine

Methadone

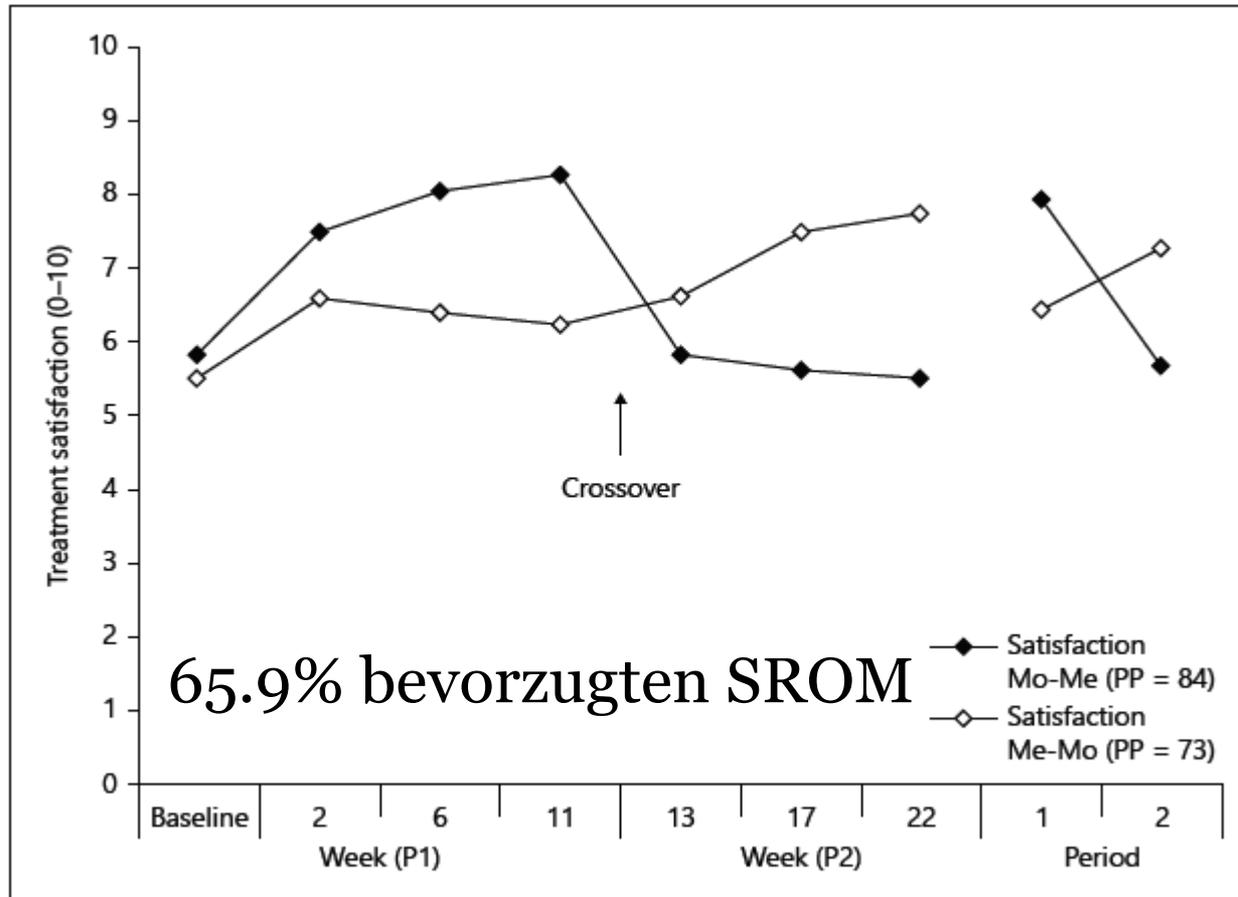


Ø Dosis 791mg

Ø Dosis 103mg

Akzeptanz

Patienten zufriedener mit SROM



Zufriedenheit Extensionsphase

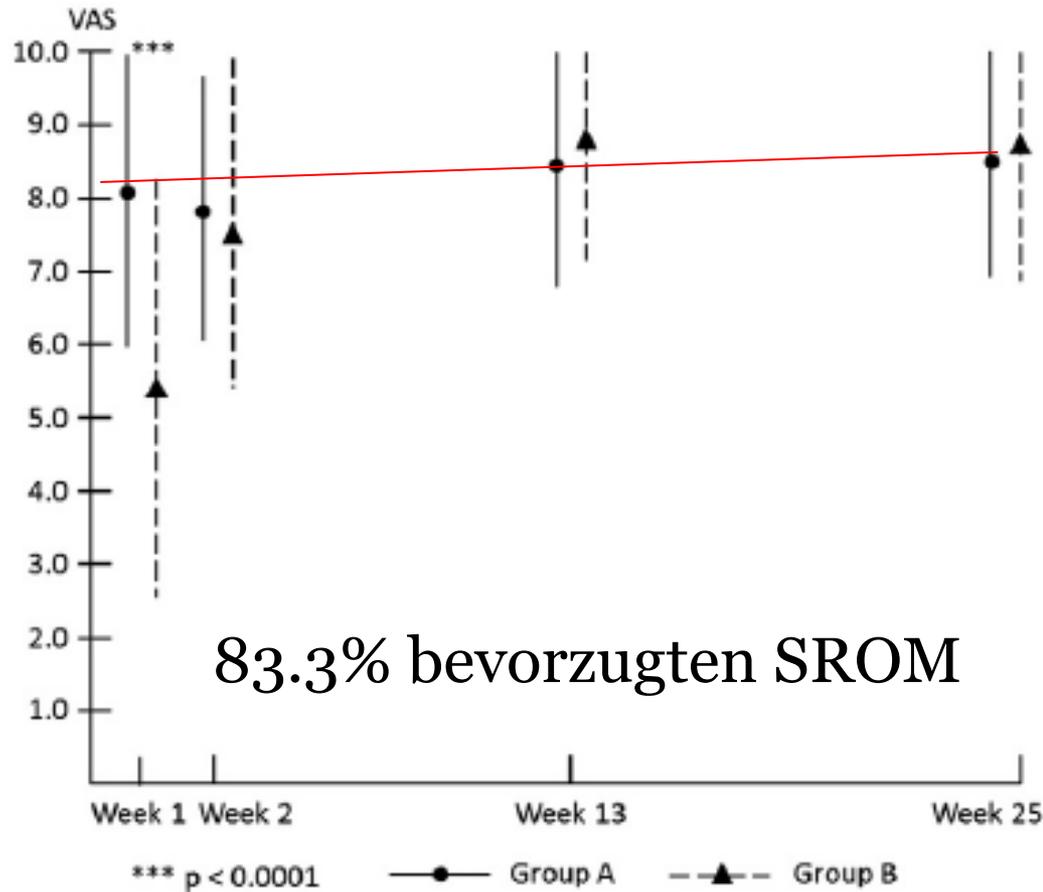
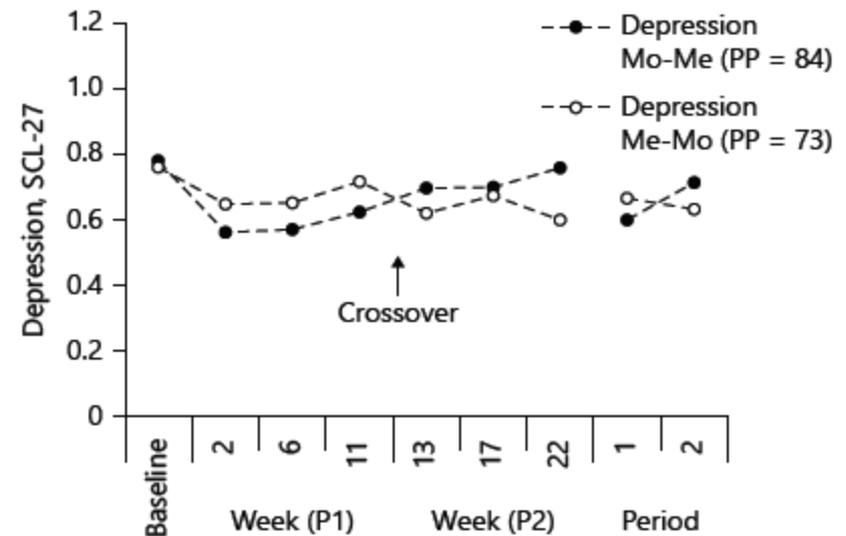
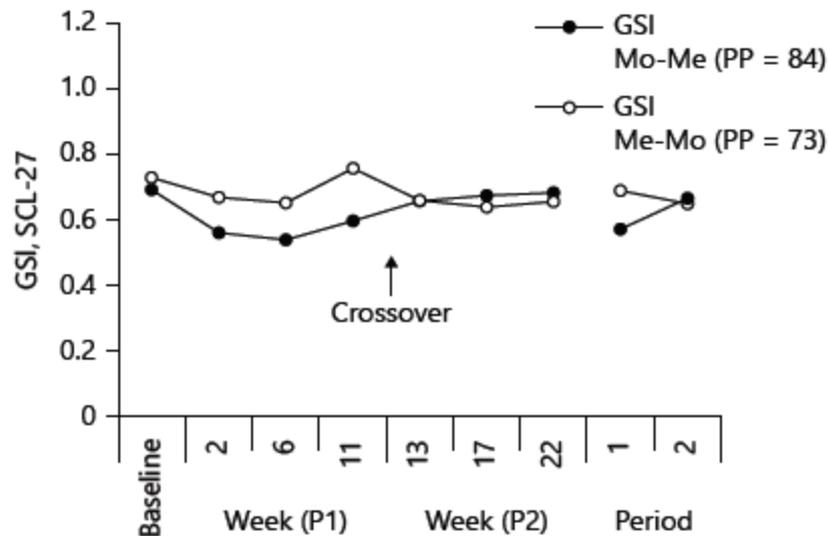


Fig. 1. Satisfaction with treatment (self-assessment on Visual Analog Scale).

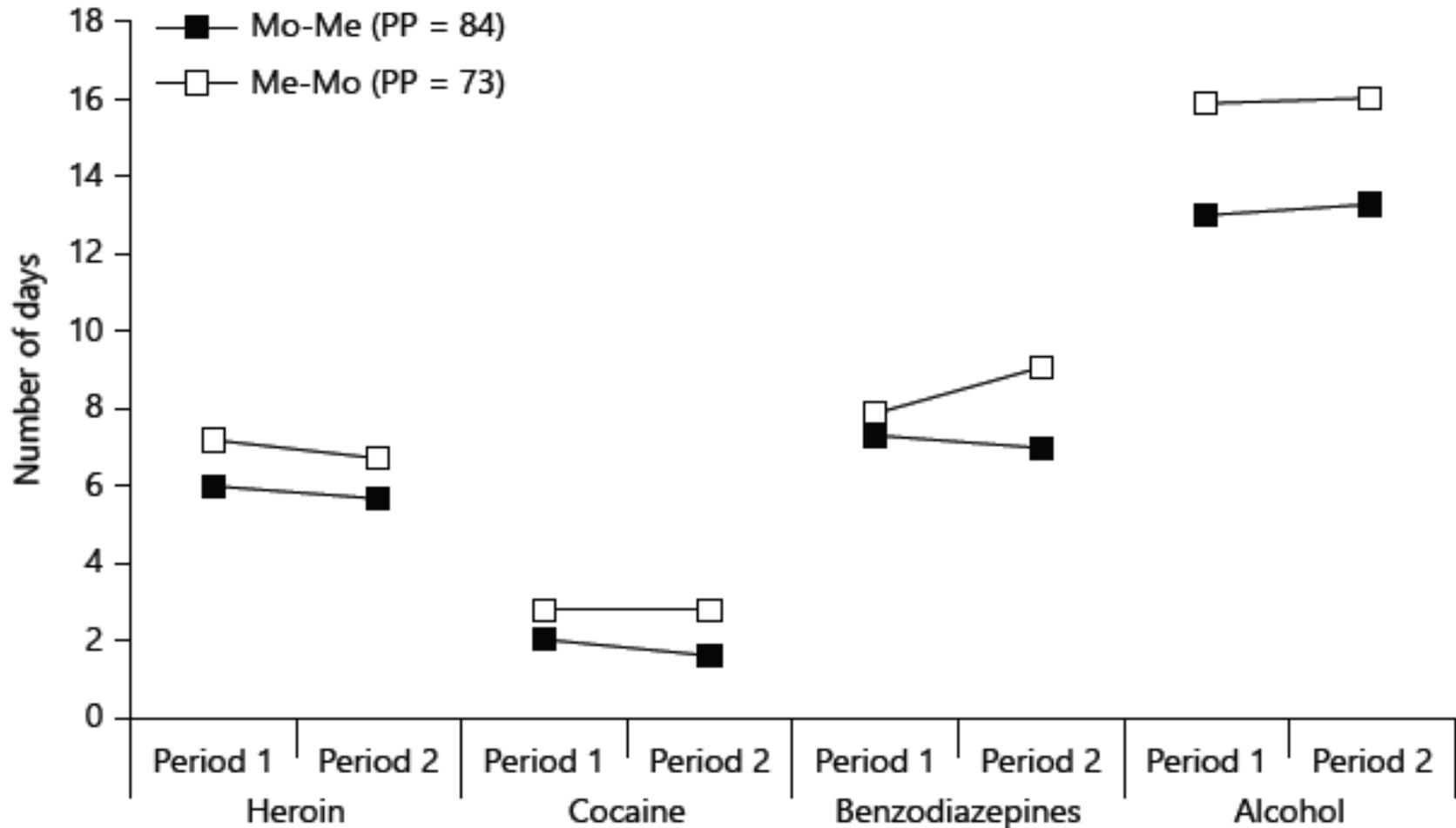
Psychische Verfassung

Symptombelastung geringer unter SRROM



Extension: stabil, Dysthymie weiter rückläufig

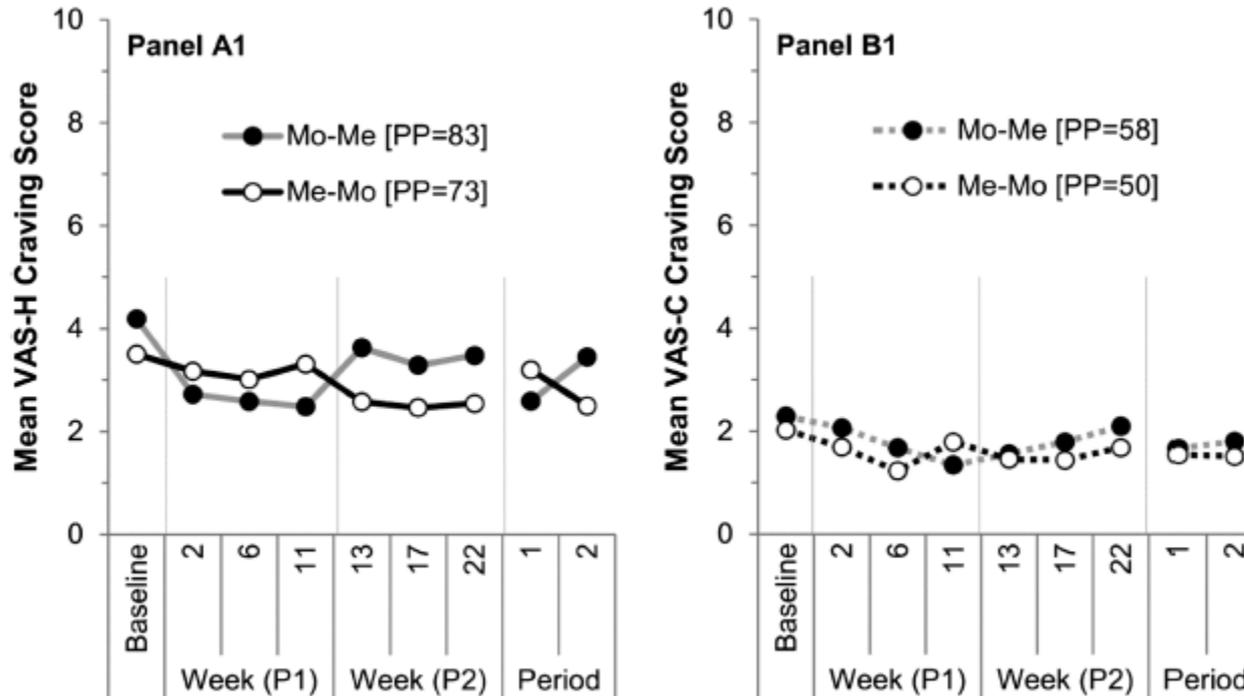
Beikonsum vergleichbar



Craving

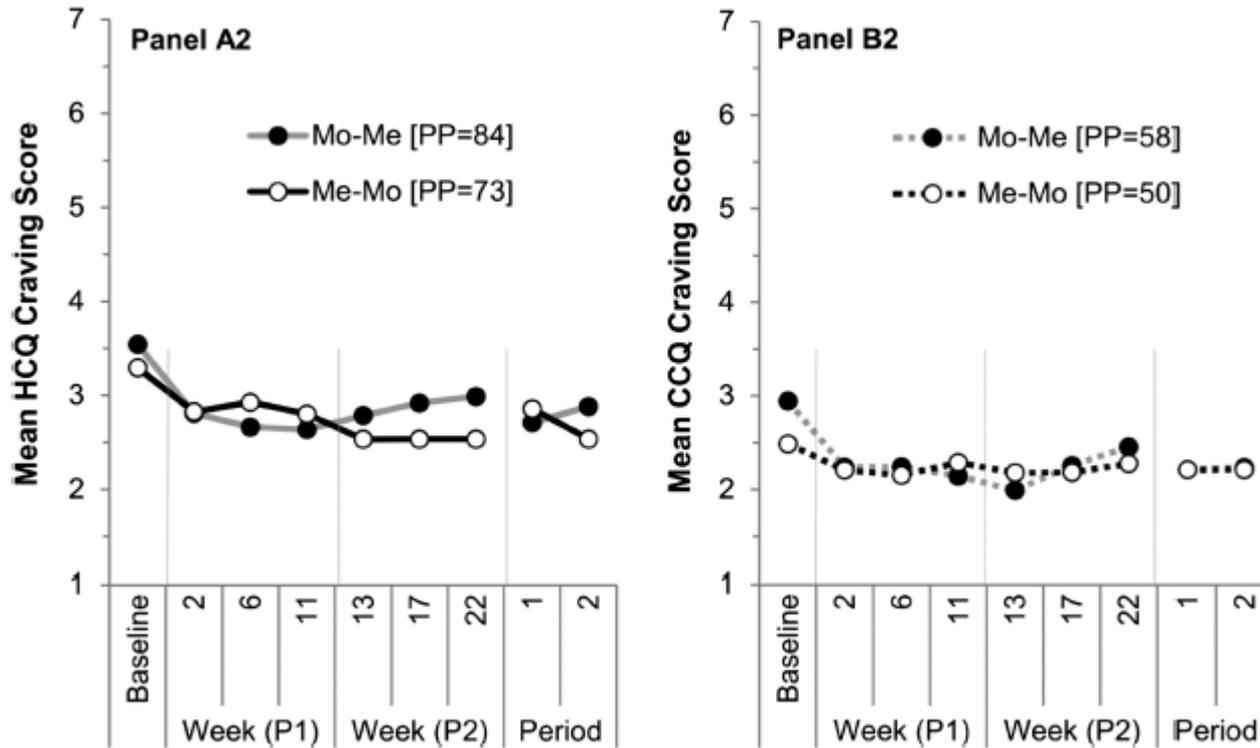
Heroin Craving geringer unter SROM,
Kokain vergleichbar stabil

Extension: Heroin Craving weiter rückläufig

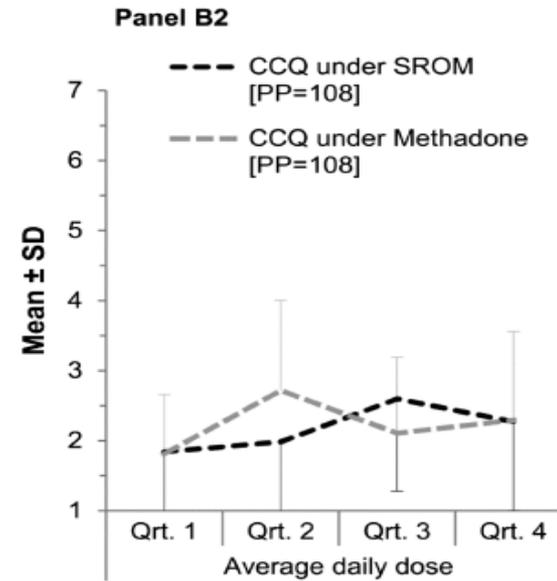
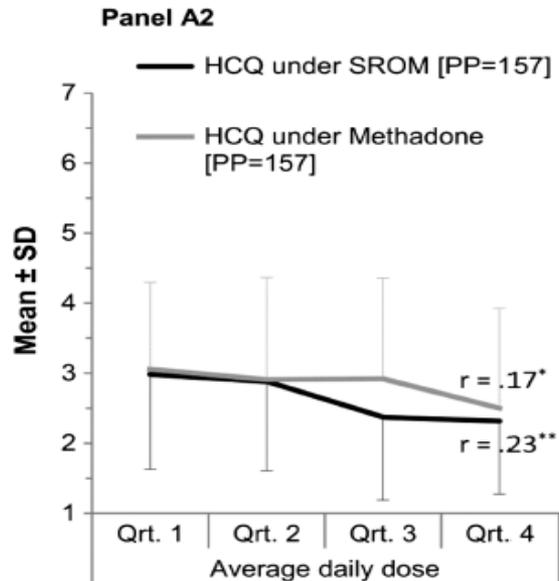
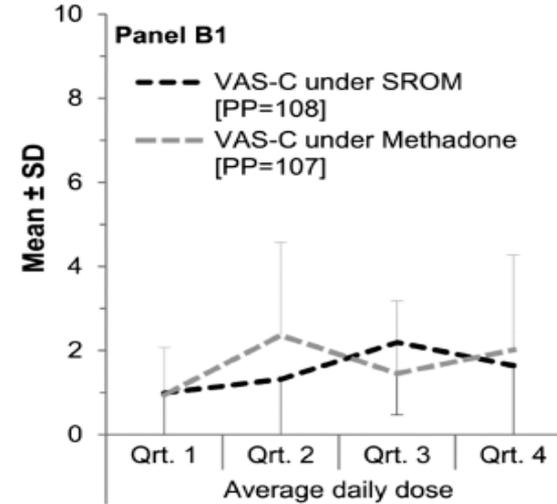
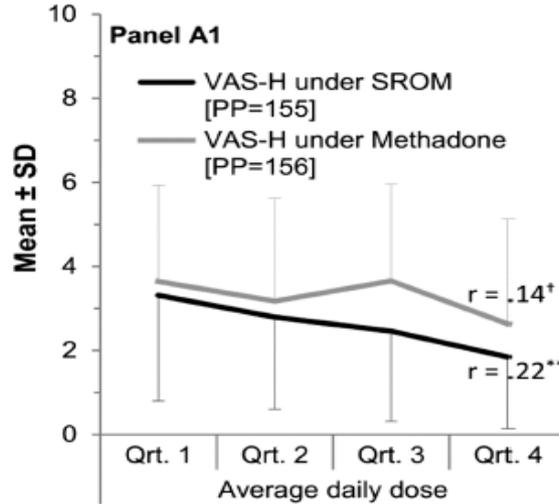


Craving

Heroin Craving geringer unter SROM,
Kokain vergleichbar stabil



Craving dosis- und substanzabhängig



Cardiale Reizleitung

QTc unter SROM rückläufig

		Pre-treatment, ms (mean \pm SD)	Post-treatment phase, ms (mean \pm SD)	p value
Cross-over 22 weeks	Period I: continuation with methadone	426.98 \pm 18.98 (n = 57)	426.95 \pm 25.52 (n = 57)	0.9917
	Period I: switch from methadone to SROM	420.20 \pm 29.23 (n = 59)	415.29 \pm 25.06 (n = 58)	0.0851
	Period II: switch from methadone to SROM	426.95 \pm 25.52 (n = 57)	416.76 \pm 22.63 (n = 55)	0.0017
	Period II: switch from SROM to methadone	415.29 \pm 25.06 (n = 58)	424.14 \pm 25.09 (n = 57)	0.0045
Extension 25 weeks	Group A: continuation with SROM	416.76 \pm 22.63 (n = 55)	416.67 \pm 24.65 (n = 39)	0.9062
	Group B: switch from methadone to SROM	424.14 \pm 25.09 (n = 57)	416.43 \pm 27.28 (n = 42)	0.0838

424.14 – 416.43

Safety

SROM mit gutem Sicherheitsprofil

	Methadone				SROM							
	Cross-over 22 weeks				Cross-over 22 weeks				Extension 25 weeks			
	AE related ^a		AE not related		AE related ^a		AE not related		AE related ^a		AE not related	
	n	%	n	%	n	%	n	%	n	%	n	%
Number of AEs	466	56	363	44	534	61	345	39	266	43	348	57
Patients with ≥ 1 serious AE	2	1	9	4	1	0	7	3	3	2	10	5
Number of serious AEs	5	24	16	76	1	8	12	92	3	10	27	90
Gastrointestinal disorders	151	18	74	9	183	21	96	11	93	15	65	11
General disorders and administration site conditions	23	3	13	2	32	4	22	2	11	2	21	3
Infections and infestations	3	<1	43	5	2	<1	44	5	5	1	51	8
Musculoskeletal and connective tissue disorders	7	1	22	3	12	1	11	1	11	2	20	3
Nervous system disorders	40	5	40	5	56	6	45	5	24	4	43	7
Psychiatric disorders	117	14	75	9	115	13	43	5	33	5	54	9
Renal and urinary disorders	13	2	8	1	30	3	2	0	13	2	6	1
Respiratory, thoracic and mediastinal disorders	2	<1	21	2	9	1	21	2	15	2	13	2
Skin and subcutaneous tissue disorders	97	12	21	3	70	8	23	3	42	7	24	4
Other	14	1	51	6	25	3	38	4	19	3	51	8

AE = adverse event; SROM = slow release oral morphine.

^a Investigator considered AEs to be 'possibly', 'probably', 'definitely', 'not specified' related to study medication or missing relationship.

Nebenwirkungen

Vermehrtes Schwitzen unter Methadon

	Cross-over phase						Extension phase				
	Methadone			SROM			SROM				
	22 weeks (n = 260)			22 weeks (n = 262)			p value (generalized linear model)		25 weeks (n = 198)		
	n	%	Severity mean ± SD	n	%	Severity mean ± SD.	Frequency	Severity	n	%	Severity mean ± SD
Treatment-related AEs	466	100		534	100				265	100	
Hyperhidrosis	91	19.5	2.5 ± 0.7	55	10.3	2.4 ± 0.8	0.0001	0.0001	28	10.6	2.0 ± 0.8
Constipation	50	10.7	2.5 ± 0.7	55	10.3	2.3 ± 0.7	0.4980	0.5521	45	17.0	1.8 ± 0.7
Nausea	31	6.7	2.1 ± 0.8	34	6.4	2.0 ± 0.6	0.5787	0.5363	7	2.6	1.7 ± 0.5
Mood swings	27	5.8	2.1 ± 0.9	23	4.3	2.2 ± 0.9	0.4285	0.4286	8	3.0	2.1 ± 0.6
Vomiting	22	4.7	2.1 ± 0.5	17	3.2	1.9 ± 0.6	0.2443	0.2416	6	2.3	1.8 ± 0.8
Abdominal pain	21	4.5	1.8 ± 0.5	16	3.0	1.8 ± 0.6	0.2020	0.1999	13	4.9	2.2 ± 0.6
Dizziness	18	3.9	1.5 ± 0.5	14	2.6	1.7 ± 0.8	0.3674	0.3593	8	3.0	1.6 ± 0.8
Headache	18	3.9	1.9 ± 0.8	30	5.6	2.0 ± 0.7	0.1023	0.0960	13	4.9	1.9 ± 0.6
Dry mouth	17	3.6	2.0 ± 0.8	34	6.4	1.8 ± 0.8	0.0096	0.0099	14	5.3	1.6 ± 0.6
Sleep disorder/insomnia	19	4.1	2.1 ± 0.7	17	3.2	2.2 ± 0.7	0.7076	0.7163	8	3.0	2.0 ± 0.0
Pollakisuria	11	2.4	1.7 ± 0.8	23	4.3	2.0 ± 0.8	0.0521	0.0500	13	4.9	1.6 ± 0.5
Agitation	9	1.9	2.1 ± 0.6	4	0.7	2.5 ± 1.0	0.1359	0.1412	4	1.5	2.0 ± 0.8
Restlessness	9	1.9	2.3 ± 0.5	5	0.9	2.2 ± 0.8	0.3978	0.3972	1	0.4	2.0
Fatigue	7	1.5	2.2 ± 0.8	9	1.7	1.6 ± 0.9	0.8026	0.8111	6	2.3	2.0 ± 0.6
Libido disorder	9	1.9	2.6 ± 0.5	6	1.1	2.2 ± 0.4	0.3989	0.3870	3	1.1	1.7 ± 0.6
Others	107	23.0	2.0 ± 0.7	192	36.0	2.0 ± 0.7	<.0001	<.0001	88	33.2	1.8 ± 0.6

SUB9001 Resultate

- ↳ Gleiche Effektivität wie Goldstandard Methadon
- ↳ Patienten zufriedener mit SROM
- ↳ Psychische Symptombelastung geringer
- ↳ Beikonsum weiterer Substanzen unverändert
- ↳ Unterdrückt Heroin-Craving besser (Kokain kein zusätzlicher Effekt)
- ↳ QTc unter SROM rückläufig