Biomarker Assessments (optional)

Blood sampling for future biomarker research will be performed at selected study sites. Samples will only be collected from patients consenting to participate in this part of the study.

Samples will be collected, biobanked and, if applicable, analyzed at the local laboratory according to local clinical routines. The subset of samples to be collected are listed in table 1 below). The study site will provide reference values for analyzed parameters. If considered necessary, samples may be retained and analyzed for exploratory purpose at a later time-point.

In addition, blood samples will be stored in the local biobank for a future analysis of biomarkers that a specifically targeted analysis not readily available at the participating centers. Blood samples either be used up or destroyed following analyses. If a patient withdraws consent to the biobank storage, it is the responsibility of the site Principal Investigator to withdraw and destroy the stored samples from that specific patient. Withdrawn samples should be destroyed and the action should be documented.

Approximately 20-25 ml of blood will be collected at two occasions.

Results from blood analysis will be stored in separate files and can be added to the final data set at study termination. The data are not essential for the evaluation of primary or secondary end points in the study but may be analyzed in future post-hoc outcome analyses. A pre-specified power analysis for such data has therefore not been performed.

Table 1. Blood samples adressed at Visits 1c and 3b

Inflammation - related	**Metabolic function - related**	**Ventilation - related**	**Cardiovascular function - related**	**Neurocognitive function - related**	**Biobank**
Hs-CRP	Hb1Ac	Hypoxia Induced Factor 1α	proBNP,	NFL	
TNFα	Total cholesterol, LDL, HDL	Carbonic Anhydrase activity	Troponin	pTau	
IL-6			eGFR	GFAP	

	Baseline Evaluation Period			PAP Treatment initiation and training	PAP Treatment Period		Follow-up Evaluation Period		Early termination visit [b]
	Baseline Visit[a]	Sleep Evaluation Baseline	End of diagnostic process				Sleep Evaluation Follow-up	End of study follow-up visit	
Visit	**V1a**	**V1b**	**V1c**	**V2**	**TC1**	**TC2**	**V3a**	**V3b**	**V4**
Week	**-1- -4**	**-1- -4**	**-1- -4**	**0-3**	**4**	**8**	**12**	**12±4**	**Within 2 w**
In- and exclusion criteria	X								
Subject information and informed consent	X								
Anthropometric and basic clinical data									
Demographic data	X								
General medical history & OSA history	X								
Physical examination	X							X	X
Height[c], body weight	X							X	X
Concomitant medication	X		X	X	X	X		X	X
Vital signs[d]	X								
Biomarker sample[f]			**X**					**X**	**X**
Randomization	X								
Objective evaluation of sleep and wake period									
Sleep evaluation: PSG or PG and SAS in random order		X (1 night clinical routine and 3 nights SAS)					X (1 night SAS)		
Sleep rhythm and physical activity (activity watch)	X (start)	X (continued throughout the study)	X	X	X	X	X	X (end of recording and data analysis)	

	Baseline Evaluation Period			PAP Treatment initiation and training	PAP Treatment Period		Follow-up Evaluation Period		Early termination visit [b]
	Baseline Visit[a]	Sleep Evaluation Baseline	End of diagnostic process				Sleep Evaluation Follow-up	End of study follow-up visit	
Visit	**V1a**	**V1b**	**V1c**	**V2**	**TC1**	**TC2**	**V3a**	**V3b**	**V4**
Week	**-1- -4**	**-1- -4**	**-1- -4**	**0-3**	**4**	**8**	**12**	**12±4**	**Within 2 w**
Diagnosis of OSA y/n			X						
PAP treatment start				X					
Follow-Up for PAP treatment					X	X	X	X	X
Patient related symptoms and outcome measures									
CGI-S/PGI-S			X					X	X
CGI-I/PGI-I								X	X
ESS, ISI, ISQ, PSQI, FSS	X							X	X
Sleep Revolution APP cognition, sleep diary	X		X		X	X	X	X	X
DASS21	X								
European Sleep Questionnaire	X							X	X
Cognitive test battery (voluntarily)	X							X	
Adverse events			X	X	X	X		X	X
End of study interview								X	X

f = for selected sites only

Appendix:

- Litiumheparine tube 8 ml plasma, store at benchtop 10 minutes, cold centrifuge for 10 min at 2000 rpm, freeze at -70 °C.

Analyses: Hs-CRP, IL-6, Total cholesterol, LDL, HDL, proBNP,e Troponin, eGFR + creatinne

- EDTA tube 4 ml plasma, turn tube 5-10 times, centrifuge 10 min at 2000 rpm, freeze at -70 °C

Analyses: Hba1c,

- Serum tube 5 ml, store 10 minutes, cold centrifuge within 30 minutes at 2000 rpm, freeze at -70 °C

Analyses: TNFa, HIF_{1a}, Neurofilament Light (NFL), carbonic anhydrase IX (CA IX)

- Litiumheparine tube 4 ml whole blood, Intermediate storage at room temperature, freeze at -70 °C

Analyses: carbonic anhydrase activity