

Supplement 3. Secondary outcome parameters. Assessment periods are referenced to the date of spinal cord injury (SCI) diagnosis and include: screening and baseline (S&B; days 5-39), 3-month follow-up (3M; day 91 +/- 10), 6-month follow-up (6M; day 182 +/-10), 12-month follow-up (12M; day 365 +/-10). Additionally, some surveys are administered weekly during the TTNS treatment period (TTNS: weekly), and the bowel and bladder diaries are administered once every two weeks during the treatment period (TTNS: bi-weekly).

Outcome and Measurement Parameter (analysis metric)	Assessment Periods
Occurrence of neurogenic detrusor overactivity (DO) jeopardizing the upper urinary tract over a 1-year time course assessed by: urodynamic investigation and clinical assessment	
DO amplitude ≥ 40 cmH ₂ O, or initiation of DO treatment with antimuscarinics and/or intradetrusor onabotulinumtoxinA injections (time-to-event analysis)	S&B, 3M, 6M, 12M
Differential changes in lower urinary tract (LUT) function, assessed by urodynamic investigation	
Maximum cystometric capacity (mL)	S&B, 3M, 6M, 12M
Compliance (mL/cmH ₂ O)	S&B, 3M, 6M, 12M
DO (present or absent), if present:	S&B, 3M, 6M, 12M
Bladder volume at first DO (mL)	S&B, 3M, 6M, 12M
Maximum DO amplitude (cmH ₂ O)	S&B, 3M, 6M, 12M
Detrusor leak-point pressure (cmH ₂ O)	S&B, 3M, 6M, 12M
Maximum detrusor pressure during storage phase (cmH ₂ O)	S&B, 3M, 6M, 12M
Maximum detrusor pressure during voiding phase (cmH ₂ O)	S&B, 3M, 6M, 12M
Detrusor pressure at maximum flow rate (cmH ₂ O)	S&B, 3M, 6M, 12M
Maximum flow rate (mL/s)	S&B, 3M, 6M, 12M
Voided volume (mL)	S&B, 3M, 6M, 12M
Post void residual (mL)	S&B, 3M, 6M, 12M
Pelvic floor electromyography (EMG) (normal/pathological)	S&B, 3M, 6M, 12M
Videography (vesico-uretero-renal reflux, present/absent)	S&B, 3M, 6M, 12M
Free flow curve pattern	S&B, 3M, 6M, 12M
Differential changes in lower spinal cord function, assessed by neuro-urological physical examination	
Voluntary sphincter contraction (present/absent; if present, weak/strong)	S&B, 3M, 6M, 12M
Resting anal tone (weak/strong/spastic)	S&B, 3M, 6M, 12M
Bulbocavernosus reflex (present/absent)	S&B, 3M, 6M, 12M
Anal reflex (present/absent)	S&B, 3M, 6M, 12M
Sensory testing S2-S5 (algnesia, aesthesia: present/absent, even between sides, type of sensation)	S&B, 3M, 6M, 12M
Differential changes in LUT symptoms, assessed by bladder diary, International Prostate Symptom Score (IPSS), Urinary Symptom Profile (USP)	
Number of voids per 24 hours	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Number of day-time voids	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Number of night-time voids	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Number of intermittent catheterizations	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Number of leakages per 24 hours	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Number of used pads per 24 hours	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Mean post void residual (mL)	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Mean voided volume (mL)	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Pain level (scale, 0-10)	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Level of urgency (scale, 0-4)	S&B, 3M, 6M, 12M, TTNS: bi-weekly
IPSS Symptom Score (sum score, 0-35)	S&B, 3M, 6M, 12M, TTNS: weekly
USP Stress urinary incontinence score (sum score, 0-9)	S&B, 3M, 6M, 12M, TTNS: weekly
USP Overactive bladder score (sum score, 0-21)	S&B, 3M, 6M, 12M, TTNS: weekly
USP Low stream score (sum score, 0-9)	S&B, 3M, 6M, 12M, TTNS: weekly

Differential changes in quality of life, assessed by IPSS, Qualiveen

IPSS Quality of life score (scale, 0-6)	S&B, 3M, 6M, 12M, TTNS: weekly
Qualiveen total score (mean score, 0-4)	S&B, 3M, 6M, 12M, TTNS: weekly
Qualiveen Limitations / Inconvenience subscale (mean score, 0-4)	S&B, 3M, 6M, 12M, TTNS: weekly
Qualiveen Constraints / Restrictions subscale (mean score, 0-4)	S&B, 3M, 6M, 12M, TTNS: weekly
Qualiveen Fears subscale (mean score, 0-4)	S&B, 3M, 6M, 12M, TTNS: weekly
Qualiveen Feelings / Impact on Daily Life subscale (mean score, 0-4)	S&B, 3M, 6M, 12M, TTNS: weekly

Differential changes in sexual function, assessed by clinical assessment, FSFI (females), IIEF (males)

Psychogenic erection, M (present / reduced / absent / unknown / not applicable)	S&B, 3M, 6M, 12M
Reflex erection, M (present / reduced / absent / unknown / not applicable)	S&B, 3M, 6M, 12M
Ejaculation, M (present / reduced / absent / unknown / not applicable)	S&B, 3M, 6M, 12M
Orgasmic function, M, F (present / reduced / absent / unknown / not applicable)	S&B, 3M, 6M, 12M
Psychogenic genital arousal, F (present / reduced / absent / unknown / not applicable)	S&B, 3M, 6M, 12M
Reflex genital arousal, F (present / reduced / absent / unknown / not applicable)	S&B, 3M, 6M, 12M
Menstruation, F (present / reduced / absent / unknown / not applicable)	S&B, 3M, 6M, 12M
FSFI, F total score (sum score, 0-36)	S&B, 3M, 6M, 12M
FSFI, F Desire domain (sum score, 0-6)	S&B, 3M, 6M, 12M
FSFI, F Arousal domain (sum score, 0-6)	S&B, 3M, 6M, 12M
FSFI, F Lubrication domain (sum score, 0-6)	S&B, 3M, 6M, 12M
FSFI, F Orgasm domain (sum score, 0-6)	S&B, 3M, 6M, 12M
FSFI, F Satisfaction domain (sum score, 0-6)	S&B, 3M, 6M, 12M
FSFI, F Pain domain (sum score, 0-6)	S&B, 3M, 6M, 12M
IIEF, M total score (sum score, 5-75)	S&B, 3M, 6M, 12M
IIEF, M Erectile Function domain (sum score, 1-30)	S&B, 3M, 6M, 12M
IIEF, M Orgasmic Function domain (sum score, 0-10)	S&B, 3M, 6M, 12M
IIEF, M Sexual Desire domain (sum score, 2-10)	S&B, 3M, 6M, 12M
IIEF, M Intercourse Satisfaction domain (sum score, 0-15)	S&B, 3M, 6M, 12M
IIEF, M Overall Satisfaction domain (sum score, 2-10)	S&B, 3M, 6M, 12M

Differential changes in bowel symptoms, assessed by NBD, bowel diary

NBD Score (version from ISCoS Bowel Function Dataset) (sum score, 0-47)	S&B, 3M, 6M, 12M, TTNS: weekly
Number of defecations per 24h	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Number of urgency episodes per 24h	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Quantity of stool per defecation (Small/Medium/Large)	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Feeling of incomplete evacuation per 24h	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Number of accidental bowel leakages per 24h	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Quantity per bowel leakage (Small/Medium/Large)	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Stool consistency score (Bristol Stool Scale)	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Pain related to defecation (score)	S&B, 3M, 6M, 12M, TTNS: bi-weekly
Medications for bowel	S&B, 3M, 6M, 12M, TTNS: bi-weekly

Differential changes in bowel function and pelvic floor function, assessed by rectal sensitivity examination, anorectal manometry, and barostat assessment

Initial sensation (mL)	S&B, 3M, 6M, 12M
Urgency to defecate (mL)	S&B, 3M, 6M, 12M
Maximum tolerated volume (mL)	S&B, 3M, 6M, 12M
Basal internal anal sphincter pressure (mmHg)	S&B, 3M, 6M, 12M
Squeeze external anal sphincter pressure (mmHg)	S&B, 3M, 6M, 12M
Relaxation internal anal sphincter pressure during defecation (% , mmHg)	S&B, 3M, 6M, 12M
Intraabdominal pressure during defecation (mmHg)	S&B, 3M, 6M, 12M

Defecatory disorder (Rao Classification I-IV)	S&B, 3M, 6M, 12M
Rectal capacity (mL)	S&B, 3M, 6M, 12M
Rectal compliance (mL/mmHg)	S&B, 3M, 6M, 12M
Differential changes in motor and sensory function, assessed by the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) protocol	
American Spinal Injury Association (ASIA) Impairment scale (AIS) Grade (A,B,C,D,E)	S&B, 3M, 6M, 12M
ISNCSCI upper extremity motor score (UEMS) (score, 0-50)	S&B, 3M, 6M, 12M
ISNCSCI lower extremity motor score (LEMS) (score, 0-50)	S&B, 3M, 6M, 12M
ISNCSCI light touch (LT) score (score, 0-112)	S&B, 3M, 6M, 12M
ISNCSCI pin prick (PP) score (score, 0-112)	S&B, 3M, 6M, 12M
Differential changes in functional independence assessed by the Spinal Independence Measure (SCIM) III	
SCIM III Score (sum score, 0-100)	S&B, 3M, 6M, 12M
Differential changes in spasticity, assessed by Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET), Modified Ashworth Scale (MAS)	
SCI-SET Score (sum score, -105 to +105; mean score: -3 to +3, number of positive responses, number of negative responses)	S&B, 3M, 6M, 12M, TTNS: weekly
Muscle tone of knee flexors and extensors (scale, 0-4)	S&B, 3M, 6M, 12M
Muscle tone of elbow flexors and extensors (scale, 0-4)	S&B, 3M, 6M, 12M
Differential changes in brain and spinal cord function as well as cortico-spinal integrity, assessed using neurophysiological and neuroimaging methods: nerve conduction studies (NCS), EMG, electroencephalography (EEG), transcranial magnetic stimulation (TMS)	
Latencies and amplitudes of F-waves to electrical stimulation	S&B, 3M, 6M, 12M
Compound muscle action potentials (cMAP)	S&B, 3M, 6M, 12M
Current perception thresholds (CPTs)	S&B, 3M, 6M, 12M
Sensory evoked potentials (SEPs): latencies and amplitudes in response to electrical nerve stimulation	S&B, 3M, 6M, 12M
Long latency sensory evoked potentials (LL-SEPs): latencies and amplitudes, in response to electrical nerve stimulation	S&B, 3M, 6M, 12M
Sympathetic skin response (SSR): latencies and amplitudes	S&B, 3M, 6M, 12M
Frequency and coherence measures of surface EMG and EEG	S&B, 3M, 6M, 12M
Lower urinary tract sensory evoked potentials (LUTSEPs): latencies and amplitudes in response to electrical LUT stimulation	S&B, 3M, 6M, 12M
Changes in white and grey matter area in the lumbosacral enlargement (LSE) and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in white and grey matter area in upper cervical spinal cord (at C2/C3M) and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in white and grey matter volume of the conus medullaris (CM) and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in grey and white matter volume in the brain and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in fractional anisotropy (FA) in the brain and spinal cord and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in diffusivity in the brain and spinal cord and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in brain and spinal cord tissue microstructure and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in brain function and connectivity during rest and electrical stimulation of the tibial nerve and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Differential changes in biochemical and molecular biomarkers in urine, blood, stool, and bladder tissue, assessed by histomorphology, enzyme-linked immunosorbent assay (ELISA), western blot, reverse transcription polymerase chain reaction (RT-PCR), microbiome analysis	
Biomarkers reflecting oxidative stress (presence/absence and quantities of peptides, proteins, antibodies, and small molecules)	S&B, 3M, 6M, 12M
Expression profile of messenger RNA (mRNA) and microRNA (miRNA) in urine and blood as well as their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in inflammatory markers in bladder tissue, blood, and urine, as well as their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in levels of neurotransmitters (neurotrophins) in blood, and urine, as well as their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in the composition of urinary and stool microbiomes (analysed by sequencing and microbial culturing) and their relation to clinical outcomes	S&B, 3M, 6M, 12M
Changes in the density / quality of afferent / efferent innervation of the bladder tissue and their relation to clinical outcomes	S&B 6M

Safety of TTNS, adverse events and serious adverse events as assessed by clinical record check and patient interview

Urinary tract infection (UTI) (number of occurrences and intensity/severity)	Any time
Infection other than UTI (number of occurrences and intensity/severity)	Any time
Skin irritation at the electrode site (number of occurrences and intensity/severity)	Any time
Irritation-related symptoms (e.g. dysuria, hematuria) with a temporal link to a LUT intervention (i.e. immediately following the intervention) (number of occurrences and intensity/severity)	Any time
Neuro-urological deterioration (number of occurrences and intensity/severity)	Any time
Pressure ulcer (location, number of occurrences and intensity/severity)	Any time
Neurological deterioration (number of occurrences and intensity/severity)*	Any time
Increase in pain (number of occurrences and intensity/severity)*	Any time
Increase in spasticity (number of occurrences and intensity/severity)*	Any time
Deep vein thrombosis / pulmonary embolism (number of occurrences and intensity/severity)	Any time
Autonomic dysreflexia (number of occurrences (suspected and verified) and intensity/severity)	Any time
Transfer/admittance to an acute care facility (number of occurrences and intensity/severity)*	Any time

*only events that qualify as adverse events and serious adverse events are recorded
 cMAP compound muscle action potentials; CPTs, current perception thresholds; DO, detrusor overactivity; ELISA, enzyme-linked immunosorbent assay; EEG, electroencephalography; EMG, electromyography; F, female; FSFI, Female Sexual Function Index; IIEF, International Index of Erectile Dysfunction; IPSS, International Prostate Symptom Score; ISNCSCI, the International Standards for Neurological Classification of Spinal Cord Injury; LL-SEP, long latency sensory evoked potential; LUT, lower urinary tract; LUTSEP lower urinary tract sensory evoked potential; M, male; MAS, Modified Ashworth Scale; miRNA, microRNA; mRNA, messenger RNA; NBD, neurogenic bowel dysfunction; NCS, nerve conduction studies; RT-PCR, Reverse transcription polymerase chain reaction; S&B, screening and baseline; SCI, spinal cord injury; SCI-SET, Spinal Cord Injury Spasticity Evaluation Tool; SCIM, Spinal Cord Independence Measure; SEP, sensory evoked potentials; SSR, Sympathetic skin response; TMS, transcranial magnetic stimulation; TTNS, transcutaneous tibial nerve stimulation; USP Urinary Symptom Profile; UTI, urinary tract infection