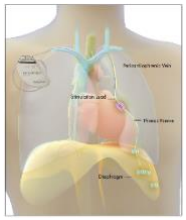
THE remedē ® SYSTEM
TRANSVENOUS PHRENIC NERVE STIMULATION FOR CENTRAL SLEEP APNEA
Clinical Evidence Summary

The **remedē® System** consists of an implantable neurostimulator of the phrenic nerve that is designed to stabilize the breathing pattern and restore sleep throughout the night for adult patients with Central Sleep Apnea (CSA). The system activates automatically at night removing compliance issues and the need for patient interaction. By stimulating the nerve that controls the diaphragm, it utilizes a physiologic mechanism similar to natural breathing. The **remedē® System** meets the unmet clinical need for improving quality of life and a range of sleep metrics in a safe manner for those suffering from CSA.



Central sleep apnea (CSA) is caused by a delay in the brain's response to changes in carbon dioxide (CO_2) levels whereby the brain does not initiate breathing until the CO_2 level has raised significantly above the normal level. This results in rapid deep breathing to expel the excess CO_2 continuing until the CO_2 level is far below normal levels, leading in turn to an extended "pause" of breathing, ranging in duration from roughly 10 to 40 seconds. Each episode results in surges of nor-epinephrine and hypoxia, increasing elapsed time below an oxygen saturation of 90%. CSA differs from Obstructive Sleep Apnea (OSA) which occurs as a result of the muscles in the upper airway relaxing or collapsing during sleep, narrowing the breathing passage and impeding air flow.

Patients with CSA suffer from sleep disruptions and insufficient sleep as evidenced by frequent apneic and hypopneic events, oxygen desaturations, and increased arousals. Sleep disruption results in life altering chronic fatigue, excessive daytime sleepiness, cognitive impairment, and depression which substantially reduces quality of life.

The **remedē® System** is the ***only*** device approved by the FDA (PMA P160039, October 2017) as an implantable phrenic nerve stimulator indicated to treat moderate to severe central sleep apnea (CSA) in adult patients. Phrenic nerve stimulation with the **remedē® System** is a proven therapeutic approach that is supported by the comprehensive positive clinical trial data demonstrating significant improvements in a wide range of sleep metrics as well as patient quality of life.

Author, Year	Title	Study Design	Journal	Sample	Evidence Level	Objective/Outcomes
Costanzo M et al. (2016)	Transvenous Neurostimulation for Central Sleep Apnea: A Randomised Controlled Trial	Prospective, multicenter randomized trial	Lancet 2016; 388: 974–82	151	Level I	Objective was to evaluate the safety and effectiveness of unilateral neurostimulation in patients with central sleep apnea. Eligible patients with an apnea-hypopnea index (AHI) of at least 20 events per h, tested by a polysomnography, underwent device implantation and were randomly assigned (1:1) by a computer-generated method stratified by site to either stimulation (treatment) or no stimulation (control) for 6 months. The primary effectiveness endpoint in the intention-to-treat population was the comparison of the proportions of patients in the treatment versus control groups achieving a 50% or greater AHI reduction from baseline to 6 months, measured by a full-night polysomnography. Significantly more patients in the treatment group (35 [51%] of 68) had an AHI reduction from baseline of 50% or greater at 6 months than had those in the control group (eight [11%] of 73; difference between groups 41%, 95% CI 25–54, p<0·0001). 138 (91%) of 151 patients had no serious-related adverse events at 12 months. Seven (9%) cases of related-serious adverse events occurred in the control group and six (8%) cases were reported in the treatment group. ***Transvenous neurostimulation significantly reduced the severity of central sleep apnea, including improvements in sleep metrics, and was well tolerated.***

Author, Year	Title	Study Design	Journal	Sample	Evidence Level	Objective/Outcomes
Costanzo M et al. (2018)	Sustained 12 Month Benefit of Phrenic Nerve Stimulation for Central Sleep Apnea	Prospective, multicenter, open label RCT (Pivotal Trial)	Am J Cardiol 2018; 121:1400–1408	151	Level I	The objective of this study was to explore the effectiveness of phrenic nerve stimulation in patients with central sleep apnea after 12 months of therapy. Patients with moderate-to-severe CSA were randomized to therapy at 1 month (treatment) or after 6 months (control). Sleep indices were assessed from baseline to 12 months in the treatment group and from 6 months to 12 months in the control group. 60% and 67% of treatment group subjects demonstrated a ≥50% reduction in apnea-hypopnea index (AHI) at 6 months (95% CI 47% to 64%) and at 12 months (95% CI 53% to 78%) respectively. After 6 months of therapy, 55% of the former controls achieved ≥50% reduction in AHI. ***The reduction in AHI documented at 6 months was sustained at 12 months.***
Fox H et al. (2019)	Long-term efficacy and safety of phrenic nerve stimulation for the treatment of central sleep apnea	RCT Pivotal Trial Cohort	SLEEPJ, 2019; 42 (11):1-9	33	Level II	The objective of this study was to evaluate long-term efficacy and safety of phrenic nerve stimulation (PNS) in patients with moderate-to-severe central sleep apnea though 3 years of therapy. Patients were observed every 3 months after implant until FDA approval. At the time of approval and study closure, all patients completed 24 months of follow-up; 33 patients had not reached the 36-month visit. Sleep metrics (apnea–hypopnea index (AHI), central apnea index, arousal index, oxygen desaturation index, rapid eye movement sleep) remained improved through 24 and 36 months with continuous use of PNS therapy. ***The long-term analysis establishes that unilateral TPNS with the remedē System in adult patients with CSA is associated with a high response to therapy and demonstrates a strong safety profile through 36 months.***
Costanzo M et al. (2021)	Transvenous Phrenic Nerve Stimulation for Treatment of Central Sleep Apnea: Five-Year Safety and Efficacy Outcomes	RCT Pivotal Trial Cohort	Nat Sci Sleep 2021: 13 515-526	53	Level II	The objective of this study was to evaluate long-term efficacy and safety of phrenic nerve stimulation (PNS) in patients with moderate-to-severe central sleep apnea though 5 years of therapy. Patients from the Pivotal Trial were invited to enroll in the Post Approval Study (PAS) and 52 completed the 5-year visit. Following TPNS therapy, the defined sleep metrics and sleep architecture showed sustained improvements. There was a statistically significant improvement in the AHI, CAI, and ESS from baseline to 5 years in a per protocol analysis ($p<0.001$). Specifically, the AHI showed a durable improvement from 46 to 17 events and the central apnea index improved from 23 to 1 event. No unanticipated adverse device effects or related deaths occurred through 5 years. ***Results of this prospective long-term 5-year study suggest that TPNS is a safe and effective therapy, resulting in clinically meaningful improvements in sleep and excessive daytime sleepiness for patients with CSA.***
Costanzo M et al. (2018)	Phrenic Nerve Stimulation to Treat Patients with Central Sleep Apnea and Heart Failure	Post-hoc analysis of RCT pivotal trial results	European Journal of Heart Failure 2018 Dec;20(12):1746-1754	96	Level II	The aim of this study was to evaluate if using phrenic nerve stimulation to treat CSA in patients with CSA and HF was associated with changes in HF-Specific metrics. This post-hoc analysis was performed in the subset of patients in the pivotal trial with HF as determined at baseline by the investigator. Of the 96 patients with HF, 81 and 75 completed a 6-month and 12-month post-activation visit. In patients with HF, 53% and 57% had ≥50% reduction in AHI from baseline to 6 -months and 12-months respectively. All observed respiratory and sleep metrics statistically improved from baseline. At 12 months, MLHFQ scores changed by–6.8± 20.0 (P=0.005). The 6-month rate of HF hospitalization was 4.7% in treatment patients (standard error=3.3) and 17.0% in control patients (standard error=5.5) (P=0.065). ***In a subset of HF patients, transvenous phrenic nerve stimulation reduced CSA severity and improved QoL.***
Schwartz AR et al. (2021)	Transvenous phrenic nerve stimulation improves central sleep apnea, sleep quality and quality of life regardless of prior positive airway pressure treatment	Post-hoc analysis of RCT pivotal trial results	Sleep Breathing (2021) doi: 10.1007/s11325-021-02335-x.	56	Level II	The objective of this study was to evaluate TPNS responses among PAP-naïve and prior PAP-treated patients from the remedē® System Pivotal Trial. Of the 151 patients enrolled in the pivotal trial, 56 (37%) used PAP prior to enrollment. In these patients, PAP therapy may have been either poorly tolerated or ineffective. The physiologic and symptomatic responses to TPNS in the PAP-treated group were similar to those in the PAP-naïve group. Polysomnographic and clinical responses to TPNS were comparable in PAP-naïve and prior PAP-treated CSA patients demonstrating that TPNS is a viable therapy across a broad spectrum of CSA patients. ***TPNS can be considered a viable therapeutic option for patients with moderate to severe CSA who are either PAP-naïve or in whom PAP is poorly tolerated, ineffective, or contraindicated.***

Author, Year	Title	Study Design	Journal	Sample	Evidence Level	Objective/Outcomes
Voigt J et al. (2020)	Meta-Analysis Comparing Outcomes of Therapies for Patients with Central Sleep Apnea and Heart Failure with Reduced Ejection Fraction	Meta-Analysis	Am J Cardiol 2020:127:73-83	20 Studies	Level II	This meta-analysis compared outcomes of therapies for CSA including CPAP (7 studies), ASV (9 studies, drugs (3 studies) and Transvenous phrenic Nerve Stimulation (TPNS, 1 study). This analysis reported: CPAP demonstrated statistically significant improvement in AHI, QoL and LVEF but only at 3 months and that long-term usage (>3 months) did not show clinical benefit on any other outcome other than AHI. ASV demonstrated significant and consistent improvements in AHI and daytime sleepiness at 6 months but failed to improve QoL or LVEF and, most importantly, the evidence suggested increased cardiovascular mortality which has led to a black box warning for treatment of CSA with ASV in patients with ejection fraction of <45%. Oxygen therapy has been studied in one RCT compared to ASV and did show an improvement in AHI at 2 months but additional parameters including LVEF and Epworth Sleepiness scale was lacking. TPNS, in contrast to other therapies, demonstrated sustained improvements in AHI, daytime sleepiness and QoL at 6 and 12 months and post-hoc analysis showed statistically significant improvement in LVEF at 12 months. Post-hoc analysis also suggests longer-term (12-18 months) positive cardiovascular and sleep related QoL outcomes with the use of TPNS. ***Based on this analysis, TPNS exhibited positive outcomes on sleep and QoL and is the only therapy for CSA with positive trends in longer term cardiovascular and QoL data.***
Abraham W et al. (2015)	Phrenic Nerve Stimulation for the Treatment of Central Sleep Apnea	Prospective, multicenter, non-randomized	J AM Coll Cardiol HF 2015; 3:360-9	57	Level II	The goal of this Pilot study was to evaluate chronic, transvenous, unilateral phrenic nerve stimulation to treat CSA. The study met its primary endpoint demonstrating a 55% reduction in apnea-hypopnea index from baseline to 3 months. In patients with HF, the MHLWFQ score significantly improved with an average of 10-point improvement (p=0.0009). Device- or procedure-related serious adverse events occurred in 26% of patients through 6 months post therapy initiation, predominantly due to lead repositioning early in the study. Therapy was well tolerated. ***Transvenous, unilateral phrenic nerve stimulation appears safe and effective for treating CSA.***
Jagielski D, et al. (2016)	Transvenous Stimulation of the Phrenic Nerve for the Treatment of Central Sleep Apnea: 12 months' experience with the remede system	Single site, non-randomized	European Journal of Heart Failure 2016 Nov;18(11):1386-1393	47	Level III	This study sought to evaluate the 12-month clinical outcomes of patients with CSA treated with unilateral transvenous phrenic nerve stimulation from a single clinical site. 41 patients completed the follow-up polysomnography at 3, 6 and 12 months. Compared with baseline, at 12-months there was a sustained improved in AHI (49.9 ±15.1 vs 27.5 ± 18.3 events/h, p<0.001) and central apnea index (28.2 ± 15.0 vs 6.0 ±9.2 events/h p<0.001). Statistically significant improvements from baseline to 12 months were documented for oxygen desaturation index, rapid eye movement sleep and sleep efficiency. ***This single site study demonstrates that in patients with CSA transvenous phrenic nerve stimulation is associated with sustained improvement in sleep parameters, symptoms and quality of life.***

Please note that these studies may involve findings that are not contained within the **remedē® System** manual. The intent of providing this data is to disseminate scientific literature currently available about the **remedē® System**. Please read studies described to understand the strengths and limitations of the data.

Indications for Use

The **rem**edē® System is an implantable phrenic nerve stimulator indicated for the treatment of moderate to severe central sleep apnea (CSA) in adult patients.

Contraindications

- The **rem**edē System is contraindicated for the following:
  - Patients with an active infection

Warnings

- The device is MR Conditional. The conditions and precautions can be found in the remedē system manual.
- Diathermy -Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (collectively referred to as diathermy) on patients implanted with the **rem**edē System.
- Electric Shock -When operating under AC power, the **rem**edē System Programmer must be connected to a grounded power source to avoid risk of electric shock.
- Concomitant Active Implantable Devices -Use **rem**edē System with caution in patients with an active implantable device that may be susceptible to unintended interaction with the remedē system.
- Patients with Evidence of Phrenic Nerve Palsy -Therapy with the **rem**edē System may be ineffective in patients who have evidence of phrenic nerve palsy.
- Pediatric Use - The safety and effectiveness of the **rem**edē System has not been established for pediatric use.

Precautions

It is recommended that testing for oversensing of remedē stimulation therapy by the concomitant cardiac device occur at the time of implant and prior to initiating remedē System therapy in patients with a concomitantly implanted cardiac device. Use **rem**edē System therapy with caution in pacemaker-dependent patients without a physiologic escape rhythm. Device interaction may lead to over or undersensing resulting in a loss of pacing. The safety and effectiveness of the remedē System during pregnancy has not been established.

See the Device Manual for detailed information regarding the implant procedure, indications, contraindications, warnings, precautions, and potential complications/adverse events.

Adverse Effects

Possible adverse events which may be associated with the implantation and use of the remedē® system include, but are not limited to, the following: adverse contrast dye reaction such as allergic reaction, pulmonary edema, or worsening renal function, adverse reaction to radiation exposure, thromboembolism, air embolism, bleeding, cardiac perforation including tamponade, hematoma, seroma, local bruising or swelling, hypotension, local wound healing issues at device implant site including wound dehiscence, pocket erosion, extrusion, movement of implanted device, keloid formation, pneumothorax, hemothorax, vascular damage, e.g., venous dissection, perforation, adverse biocompatibility reaction to the implanted system, infection, lead breakage, lead dislodgement, lead not connected or secured appropriately in device header, implantable device malfunction, requirement for more energy to stimulate the nerve or ineffective stimulation, venous occlusion, crosstalk with another implanted device, disrupted sleep, muscle fatigue or discomfort in diaphragm, chest or abdomen from appropriate stimulation, nerve dysfunction, perturbation of blood gases causing hypoxia, hypercapnea and/or hypocapnea, inappropriate sensations, worsening heart failure, respiratory status or overall health, anxiety, arrhythmia, including ventricular fibrillation, death, depression, hypotension, pain, skin irritation or local allergic reaction, thrombus or embolism, potentially leading to pulmonary embolism or stroke.

CAUTION: *Rx only. Prior to use, please see the complete "System Implant and Clinician Use Manual" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions.*

The **rem**edē® System, **rem**edē® EL System, and **rem**edē® EL-X System have received FDA approval. The **rem**edē® System model 1001 has received CE Mark approval.