Bronchial Rheoplasty For Treatment of Chronic Bronchitis: 12 Month Results from a Multi-Center Study

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Online Data Supplement

Additional Methods

Comprehensive Study Eligibility Criteria

Patients were required to meet all of the following inclusion criteria to enroll in the study:

1. Patient is at least 40 years of age.

2. Patient is diagnosed with chronic bronchitis for a minimum of two years, where chronic bronchitis is defined clinically as chronic productive cough for three months in each of two successive years in a patient in whom other causes of productive cough have been excluded.

3. Patient's responses to the first two questions of the COPD Assessment Test (CAT) must sum to at least 7 points.

4. Patient has a pre-procedure post-bronchodilator FEV_1 of greater than or equal to 30% and less than or equal to 80% of predicted within three months of enrollment. Patients with preserved function ($FEV_1 > 80\%$) are allowed if the patient has a total CAT score ≥ 10 and the sum of the first two questions of the CAT score sum to at least 7 points.

5. Patient has a cigarette smoking history of at least ten pack years.

6. Patient is, in the opinion of the principal investigator, able to adhere to and undergo three bronchoscope procedures inclusive of lung biopsies and Bronchial Rheoplasty procedures.

7. Patient has provided signed informed consent.

Patients were excluded from the study if any of the following conditions applied:

1. Patient has active respiratory infection (e.g., common cold, pneumonia, Mycobacterium avium-intracellulare, tuberculosis) or COPD exacerbation within the last six weeks prior to study treatment bronchoscopy.

2. Patient is treated with >10 mg of prednisolone or prednisone per day.

3. Patient has an implantable cardioverter defibrillator or pacemaker.

4. Patient has a history of arrhythmia within past two years.

5. Patient has abnormal cardiac rhythm at time of procedure.

6. Patient has history of proven lung cancer in last 5 years.

7. Patient has pulmonary nodule or cavity requiring follow-up or intervention unless proven benign and not actively infected (e.g., aspergilloma).

8. Patient has prior lung surgery, such as lung transplant, lung volume reduction surgery, metallic lung implant/prosthesis, metal stent, valves, coils, bullectomy, segmentectomy, or lobectomy. Pneumothorax without lung resection is acceptable. Pleural procedures without surgery are acceptable. Patients who have had a valve removed more than 30 days prior to study screening may be enrolled provided the airway is sufficiently accessible.

9. Patient has Alpha-1-Antitrypsin deficiency.

10. Patient has documented history of asthma diagnosed with onset <30 years of age, clinically significant bronchiectasis or any other significant second lung disease.

11. Patient actively smoked (including tobacco, marijuana, e-cigarettes, vaping, etc.) within the last 6 months.

12. Patient has the inability to walk over 140 meters.

13. Patient has a serious medical condition, such as: uncontrolled congestive heart failure, uncontrolled angina, myocardial infarction in the past year, renal failure, liver disease, cerebrovascular accident within the past 6 months, uncontrolled diabetes, hypertension, autoimmune disease or uncontrolled gastric reflux.

14. Patient has known sensitivity to medication required to perform bronchoscopy (such as lidocaine, atropine, and benzodiazepines).

15. Patient is pregnant, nursing, or planning to get pregnant during study duration.

16. Patient has received chemotherapy within the past 6 months or is expected to receive chemotherapy during participation in this study.

17. Patient is or has been in another clinical investigational study within 6 weeks of baseline.

18. Patient on anticoagulation for cardiovascular indications is unable to have anticoagulants (i.e., Aspirin, Plavix, Coumadin) withheld for at least seven days prior to bronchoscopy in the opinion of the investigator.

Patients were to be maintained on stable pharmacologic treatment regimens for chronic bronchitis per institution and society guidelines throughout the study follow-up. Permitted regimens included inhaled long-acting beta-agonist bronchodilator (LABA), inhaled long-acting antimuscarinic antagonist bronchodilator (LAMA), or both, which could also be combined with inhaled

corticosteroids at the physician's discretion. Patients requiring oral corticosteroids ≤10mg/day were permitted, provided that the dose was not changed in the two months prior to treatment.

Bronchial Rheoplasty System Description

The RheOx System (Gala Therapeutics Inc., Menlo Park, CA, USA) consists of an electrosurgical generator and a single-use catheter (Figure E1), and is used with standard, off-the-shelf accessories (footswitch, catheter cable, cardiac monitor). The system is designed to deliver pulsed electric fields (high frequency, short duration, non-thermal electrical fields) to the airway epithelium and mucosa. With RheOx, electrical current is delivered between the RheOx Catheter electrode and a commercially available patient-applied dispersive electrode in a series of pulses. The waveform parameters of the current are preset and are not adjustable by the clinician. When activated via a footswitch, the generator delivers current via the catheter to tissue at the point of contact with the electrode located on the distal end of the catheter. This targeted energy delivery, to a depth of approximately 400 micrometers as verified in a preclinical animal model, is intended to cause cell death by disrupting cellular homeostasis leading to processes such as osmotic swelling and apoptosis (E1-E3). This cell death does not destroy the architectural function of the tissue, permitting subsequent regeneration of more normalized epithelium, resulting in a reduction in airway mucus production. The local extracellular matrix is left intact, promoting the regeneration of the epithelium, rather than scarring or a return to metaplasia and mucus hypersecretion. The RheOx System was supplied by Gala Therapeutics Inc. for investigational use and was not for sale in any country at the time the study was conducted.

The RheOx Catheter is a sterile, single-use catheter designed for use by pulmonologists familiar with bronchoscopic techniques. The Catheter electrode, located at the distal end, is contracted from

multiple strands of super-elastic Nitinol wire woven into a braid, which is expanded to contact the airway wall inner surface via the catheter's handle mechanism. This electrode configuration, together with the super-elastic properties of Nitinol, prohibit excessive force from being applied to the airway wall. When the electrode is expanded to contact the airway wall and the Generator is activated, monopolar energy is delivered to the target tissue.

Procedure Description

The bronchoscopist initiates bronchoscopy per standard of care of the treating institution, and completes pre-treatment sample collection (cryo-biopsy, which was performed only for research purposes and is not part of the standard RheOx procedure). The bronchoscope is then navigated to the distal segments of the lower lobe, and the RheOx catheter is inserted into the working channel of the bronchoscope (minimum 2.8mm working channel). The RheOx catheter is extended beyond the distal end of the bronchoscope, and the first target airway is cannulated with the catheter. The electrode at the end of the catheter is expanded, ensuring good contact with the airway walls, and the foot pedal is depressed by the bronchoscopist, delivering pulsed electric field energy to the tissue. The catheter is then moved proximally, ensuring a slight overlap with the previous activation to create a continuous treatment pattern, and the next activation is delivered. This process is repeated until all accessible segments and sub-segments have been treated. The contact length of the electrode is directly dependent on the diameter of the airway, thus the number of total activations (dose) is determined by patient anatomy (i.e. the length and circumference of the airways). Activations distal to the sub-segmental airways can be performed, if feasible, depending on airway dimensions, accessibility, and visibility.

Sampling Technique and Histological Analysis of Airway Cryo-Biopsies

Histological analysis was performed on biopsy samples taken from the airway epithelium prior to each treatment procedure and again at 3 months following treatment of the second (left) lung. The ERBE Cryoprobe system (Erbe USA, Inc., Marietta, GA, USA) was used to obtain endobronchial biopsy samples from the lower and middle lobes, the bronchus intermedius and the mainstem, which correspond to the anatomical locations in each lung where good contact between the airway wall and the catheter electrode can most often be achieved. To avoid taking a follow-up biopsy from the same location as the baseline biopsy, bronchoscopists were instructed to take the biopsies from a specific circumferential zone that differed at each time point. Samples at each prespecified anatomical position were taken from the 6 o'clock location (dorsal) at bronchoscopy 1, from the 10 o'clock location at bronchoscopy 2 and the 2 o'clock location at bronchoscopy 3. Samples were immediately fixed in formalin, labeled, and shipped to the histopathology core laboratory. The formalin-fixed tissue samples were paraffin-embedded, sectioned at 4μm, and slides were stained with hematoxylin and eosin (H&E) and Periodic acid-Schiff (PAS) using standard protocols. The glass slides were reviewed by a board-certified anatomic pathologist with subspecialty training in pulmonary pathology, who was blinded to patient identification, time point, or treatment status for individual samples. Histologic evaluation was performed on samples taken from the right bronchus intermedius (right lung) and left lower lobe (left lung) owing to the predictability of the RheOx catheter electrode contact with the tissue in these locations. However, if these samples were judged to be inadequate, the right lower lobe or lingula endobronchial biopsy samples were substituted for the analysis for the right and left, respectively.

Scoring of goblet cell hyperplasia used a semi-quantitative scale reflecting the ratio of normal ciliated bronchial epithelial cells to goblet cells. Scores: 0 = normal ratio of goblet cells to ciliated

bronchial epithelial cells (in general, 1 goblet cell per 10 or more bronchial epithelial cells); 1 = mild goblet cell hyperplasia (1 goblet cell per approximately 3-10 ciliated bronchial epithelial cells); 2 = moderate goblet cell hyperplasia (approaching 1 goblet cell per ciliated bronchial epithelial cell); 3 = severe goblet cell hyperplasia (>1 goblet cell per ciliated bronchial epithelial cell). Example images of scores 0-3 are provided in Figure E2.

References

E1. Valipour A, Ing A, Williamson J, Saghaie T, Steinfort D, Irving L, Snell G, Dabscheck E, Krimsky W, Waldstreicher J, Fernandez-Bussy S. First-in-Human Results of Bronchial Rheoplasty: An Endobronchial Treatment For Chronic Bronchitis (CB) [abstract] *Eur Respir J.* 2018;52:OA2162.

E2. Valipour A, Ing A, Williamson JP, Saghaie T, Irving L, Steinfort D, Snell G, Dabscheck EJ, Martel S, Fortin M, Krimsky WS, Fernandez-Bussy S. First-in-Human Results of Bronchial Rheoplasty: An Endobronchial Treatment for Chronic Bronchitis (CB) [abstract] *Am J Respir Crit Care Med*. 2019;199:A7037.

E3. Valipour A, Ing A, Williamson J, Saghaie T, Steinfort D, Irving L, Fortin M, Martel S, Snell G, Dabscheck E, Waldstreicher J, Krimsky W, Fernandez-Bussy S. Bronchial Rheoplasty For Treatment of Chronic Bronchitis: 6 Month Results from a Prospective Multi-Center Study [abstract] *Eur Respir J.* 2019;54:RCT448.

Table E1. Schedule of Events

	Screening	Visit 2: Bronchoscopy 1 Treatment Session 1 (Tx1)	Visit 3: Follow-up Phone Call 1 week Post-Tx1	Visit 4: Follow-up 1 month Post-Tx1 and Bronchoscopy 2 Treatment Session 2 (Tx2)	Visit 5: Follow-up Phone Call 1 week Post-Tx2	Visit 6: Bronchoscopy #3 Follow up 3 months Post-Tx2	Visit 7: Follow-up 6 months Post-Tx2	Visit 8: Follow-up 12 months Post-Tx2
Informed Consent	X							
Entry Criteria	X							
Medical Hx	X							
Exacerbation Hx*	X	X	X	X	X	X	X	X
Con. Meds*	X	X	X	X	X	X	X	X
Adverse Events†		X	X	X	X	X	X	X
Physical Exam*	X	X		X		X	X	X
CBC & Blood Panel*	X	X		X		X	X	X
AAT Deficiency Test	X							
EKG	X	X‡		X‡		X	X	X
Spirometry*	X			X		X	X	X
Bronchoscopy		X§		X§		X		
Airway Biopsy		X		X		X		

CAT Score*	X		X		X	X	X
SGRQ Score*	X		X		X	X	X

Definition of abbreviations: Tx = treatment; Hx = History; Con = Concomitant; CBC = Complete

Blood Count; AAT = Alpha-1-Antitrypsin deficiency; EKG = Electrocardiogram; CAT = COPD

Assessment Test; SGRQ = St. George's Respiratory Questionnaire

* Noted activities were completed prior to bronchoscopy.

† Adverse events were noted before and after bronchoscopy.

‡ During at least one energy delivery, an EKG was recorded; anesthesia EKG was permitted.

§ Overnight hospital stay was at discretion of the investigator.

Table E2. Enrollment by Site

Site Number & Name	Location	Patients Enrolled (N=30)
001 – Macquarie University	Sydney, Australia	6
002 – Alfred Health	Melbourne, Australia	1
003 – Royal Melbourne Hospital	Melbourne, Australia	5
004 – Otto Wagner Spital	Vienna, Austria	10
005 – Clínica Alemana	Santiago, Chile	8

Table E3. Device-related* Non-Serious Adverse Events

Event (n events)	Treatment Recovery Period[†]	3 Months[‡]	6 Months[§]	12 Months[ll]
COPD Exacerbation	7	1	0	0
Chest Pain, Non-Cardiac	3	0	0	0
Cough	1	0	0	0
Dyspnea	1	0	0	0
Headache	2	0	0	0
Hemoptysis	2	0	0	0
Increased Sputum	1	0	0	0
Mucosal Granuloma	1	0	0	0
Wheeze	2	0	0	0
TOTAL	**20 events in 10 patients**	**1 event in 1 patient**	**0 events in 0 patients**	**0 events in 0 patients**

* All events judged by the investigator as possibly, probably or definitely related to the device are included.

† 30 days following either treatment.

‡ Follow-up period through 3 months after treatment 2, excluding either treatment recovery period.

§ Follow-up period between 3 months and 6 months after treatment 2.

ll Follow-up period between 6 and 12 months after treatment 2.

Table E4. Procedure-related* Non-Serious Adverse Events

Event (n events)	Treatment Recovery Period[†]	3 Months[‡]	6 Months[§]	12 Months[ll]
Bronchospasm	1	0	0	0
COPD Exacerbation	10	0	0	0
Chest Pain, Non-Cardiac	2	0	0	0
Cough	3	0	0	0
Dyspnea	1	0	1	0
Gastritis, Acute	1	0	0	0
Hemoptysis	18	1	2	0
Hoarseness	1	0	0	0
Increased Sputum	1	0	0	0
Mucosal Granuloma	1	0	0	0
Mucosal Scarring	0	0	1	0
Sore Throat	7	3	1	0
Wheeze	3	0	0	0
TOTAL	**49 events in 17 patients**	**4 events in 3 patients**	**5 events in 3 patients**	**0 events in 0 patients**

* All events judged by the investigator as possibly, probably, or definitely related to the procedure are included.

† 30 days following either treatment.

‡ Follow-up period through 3 months after treatment 2, excluding either treatment recovery period.

§ Follow-up period between 3 months and 6 months after treatment 2.

ll Follow-up period between 6 months and 12 months after treatment 2.

Table E5. Change from Baseline in Component Scores from CAT and SGRQ Questionnaires

Measure	Statistics	Baseline (BL)	3 Months	Change from BL to 3 Mo	6 Months	Change from BL to 6 Mo	12 Months	Change from BL to 12 Mo
CAT Total Score	N*	30	30	30	30	30	29	29
	Mean ± SD	25.6 ± 7.1	16.8 ± 8.0	−8.8 ± 7.6	17.7 ± 7.1	−7.9 ± 8.3	18.8 ± 9.4	−7.0 ± 8.9
	Median (Quartiles†)	26.0 (20.2, 30.8)	17.5 (12.0, 22.2)	−9.5 (−14.8, −3.0)	18.0 (15.0, 20.8)	−8.0 (−14.0, −2.0)	20.0 (11.0, 27.0)	−8.0 (−14.0, 1.0)
CAT Phlegm	N*	30	30	30	30	30	29	29
	Mean ± SD	4.1 ± 0.8	2.3 ± 0.8	−1.8 ± 1.1	2.4 ± 1.2	−1.7 ± 1.5	2.4 ± 1.5	−1.7 ± 1.5
	Median (Quartiles†)	4.0 (4.0, 5.0)	2.0 (2.0, 3.0)	−2.0 (−2.8, −1.0)	2.0 (2.0, 3.0)	−2.0 (−3.0, 0.0)	2.0 (2.0, 3.0)	−2.0 (−3.0, −1.0)
CAT Cough	N*	30	30	30	30	30	29	29
	Mean ± SD	3.6 ± 0.9	2.2 ± 1.0	−1.4 ± 1.3	2.2 ± 1.1	−1.4 ± 1.4	2.6 ± 1.4	−1.1 ± 1.6
	Median (Quartiles†)	4.0 (3.0, 4.0)	2.0 (1.2, 3.0)	−1.0 (−2.0, −0.2)	2.0 (1.0, 3.0)	−1.0 (−2.0, −1.0)	2.0 (1.0, 4.0)	−1.0 (−2.0, 0.0)
SGRQ Total Score	N*	30	30	30	30	30	29	29
	Mean ± SD	59.6 ± 15.3	42.8 ± 22.2	−16.9 ± 20.0	45.0 ± 20.0	−14.6 ± 19.4	44.3 ± 21.9	−15.2 ± 20.4
	Median (Quartiles†)	61.7 (48.0, 69.9)	42.6 (25.6, 60.9)	−13.3 (−25.3, −3.0)	47.6 (31.5, 61.2)	−7.2 (−19.8, −3.1)	46.6 (24.7, 58.0)	−14.7 (−27.8, −2.0)
SGRQ Symptoms	N*	30	30	30	30	30	29	29
	Mean ± SD	76.1 ± 13.4	55.0 ± 20.3	−21.1 ± 21.5	59.8 ± 21.6	−16.3 ± 24.5	56.6 ± 21.2	−19.6 ± 26.2
	Median (Quartiles†)	79.8 (71.1, 83.4)	56.3 (38.9, 71.1)	−17.7 (−38.7, −3.0)	67.0 (49.7, 73.0)	−14.5 (−22.6, −0.6)	61.2 (39.6, 71.8)	−19.9 (−33.9, −0.4)
SGRQ Activities	N*	28	30	28	30	28	29	27
	Mean ± SD	70.0 ± 17.1	56.5 ± 29.9	−12.1 ± 23.0	56.7 ± 27.3	−12.1 ± 21.0	57.7 ± 29.7	−11.3 ± 20.3

| Measure	Statistics	Baseline (BL)	3 Months	Change from BL to 3 Mo	6 Months	Change from BL to 6 Mo	12 Months	Change from BL to 12 Mo
	Median (Quartiles†)	69.9 (58.8, 85.9)	62.3 (35.2, 82.8)	0.00 (−21.4, 5.7)	60.4 (35.5, 73.0)	−6.9 (−26.7, 0.2)	61.1 (35.8, 79.1)	−6.7 (−18.5, 6.7)
SGRQ Impacts	N*	28	29	28	30	28	29	27
	Mean ± SD	51.9 ± 15.9	31.2 ± 22.0	−19.5 ± 22.0	33.6 ± 19.3	−17.8 ± 20.5	32.8 ± 21.2	−19.3 ± 21.3
	Median (Quartiles†)	52.7 (39.8, 61.3)	25.8 (16.4, 43.5)	−19.3 (−31.4, −4.7)	30.2 (19.1, 49.9)	−10.2 (−25.7, −3.3)	35.6 (13.7, 48.7)	−17.5 (−26.2, −7.6)

Definition of abbreviations: BL = baseline; Mo = months; CAT = COPD Assessment Test; SGRQ = St. George's Respiratory Questionnaire; SD = standard deviation
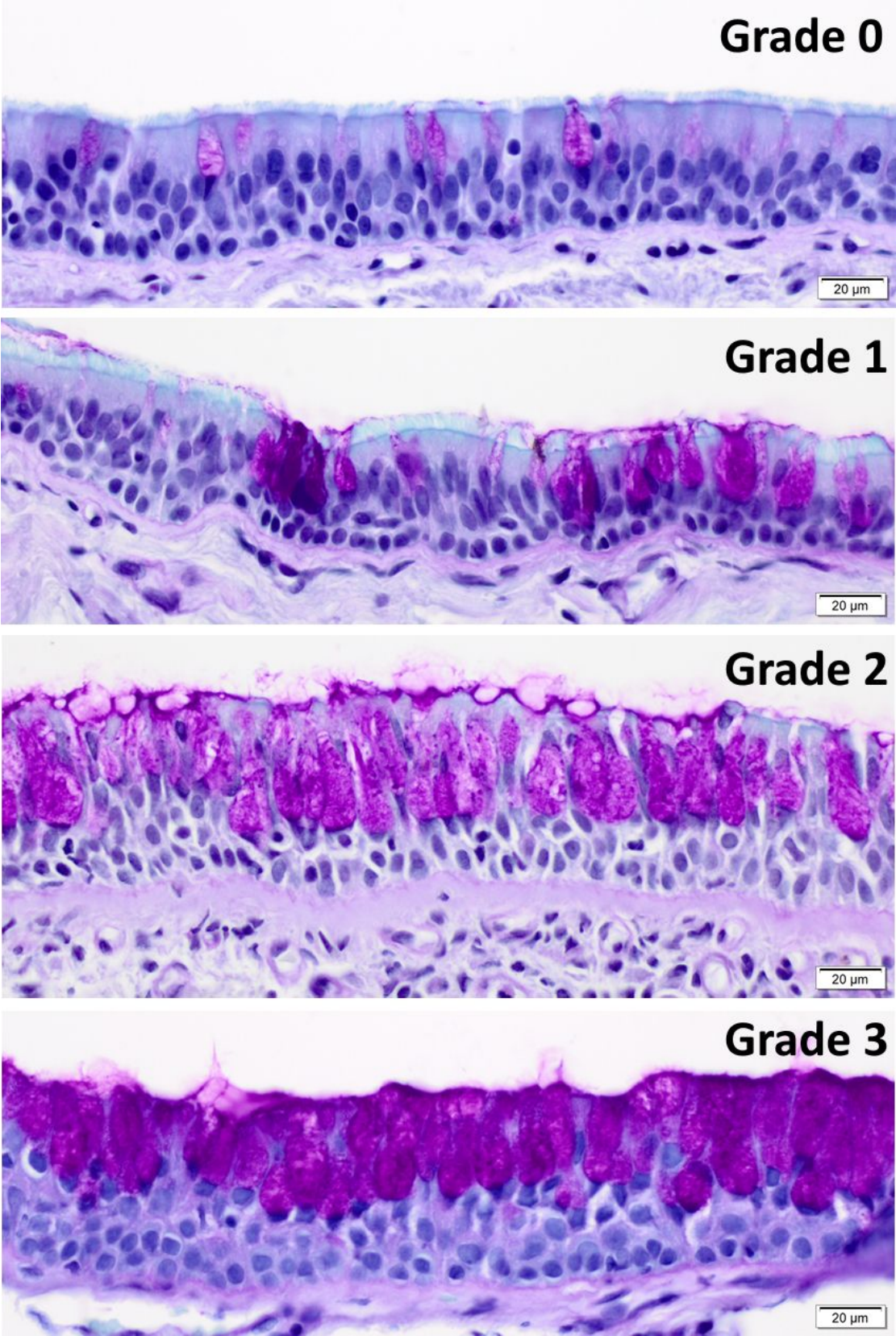
* N varies due to two patients who failed to complete enough baseline SGRQ Activities and Impacts component questions to calculate a score within these domains and one patient with missing SGRQ data at 12 months.

† 25th percentile, 75th percentile.
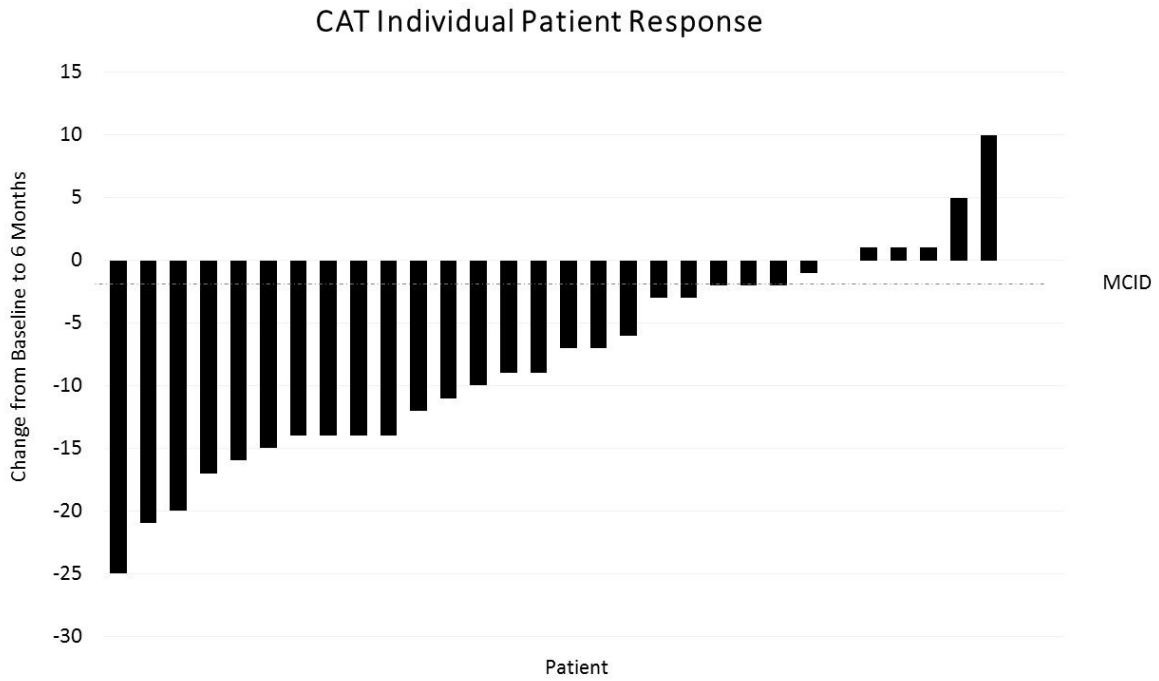
Figure E1. Image of the RheOx System.
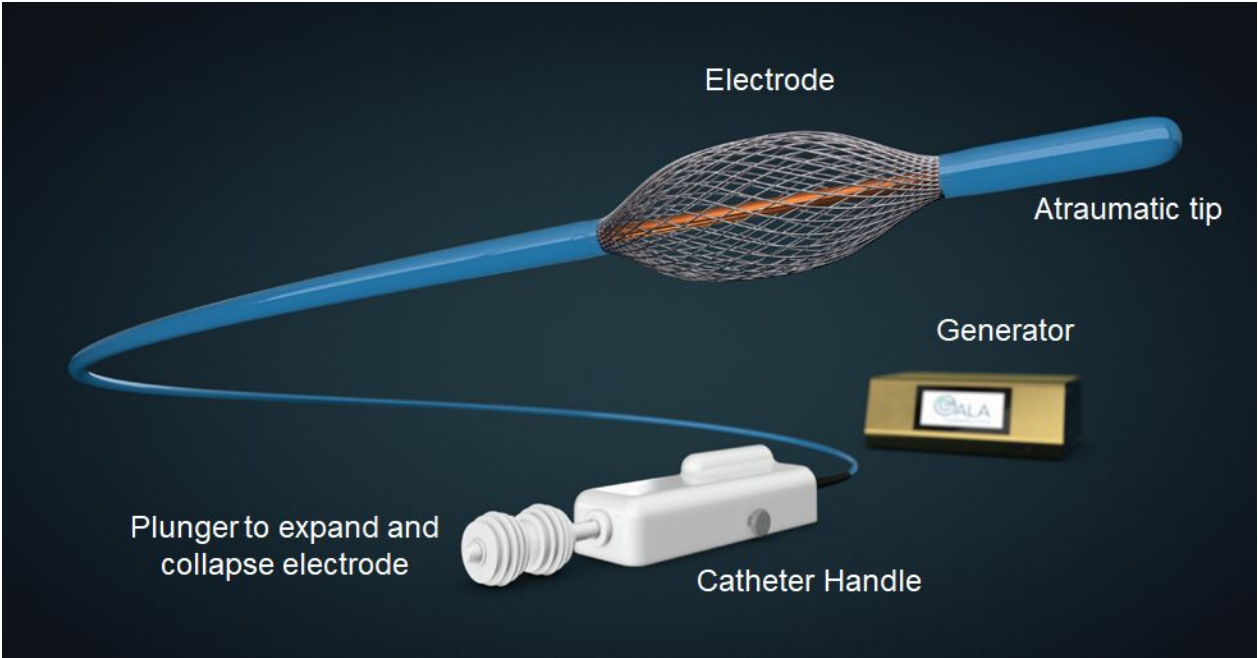
Figure E2. Example Images for Goblet Cell Hyperplasia Grading Scale.

Figure E3. Waterfall Plots Showing Individual Patient Changes from Baseline to Month 6 in CAT and SGRQ Total Scores.

A

CAT Individual Patient Response

B

SGRQ Individual Patient Response