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BRONCHOSCOPIC APPROACHES FOR COPD- CURRENT STATUS

Interventional Bronchoscopy / Thoracoscopy Short Course
30 May 2024 - Preston

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DZL Deutsches Zentrum für Lungenforschung

TLRC Translational Lung Research Center Heidelberg

MF HD

Conflict of Interest disclosure

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Honoraria or consultation fees:

AstraZeneca, Berlin-Chemie, Boston Scientific, CSL Behring, Olympus Medical, COOK Medical

Available bronchoscopic therapies of chronic Bronchitis

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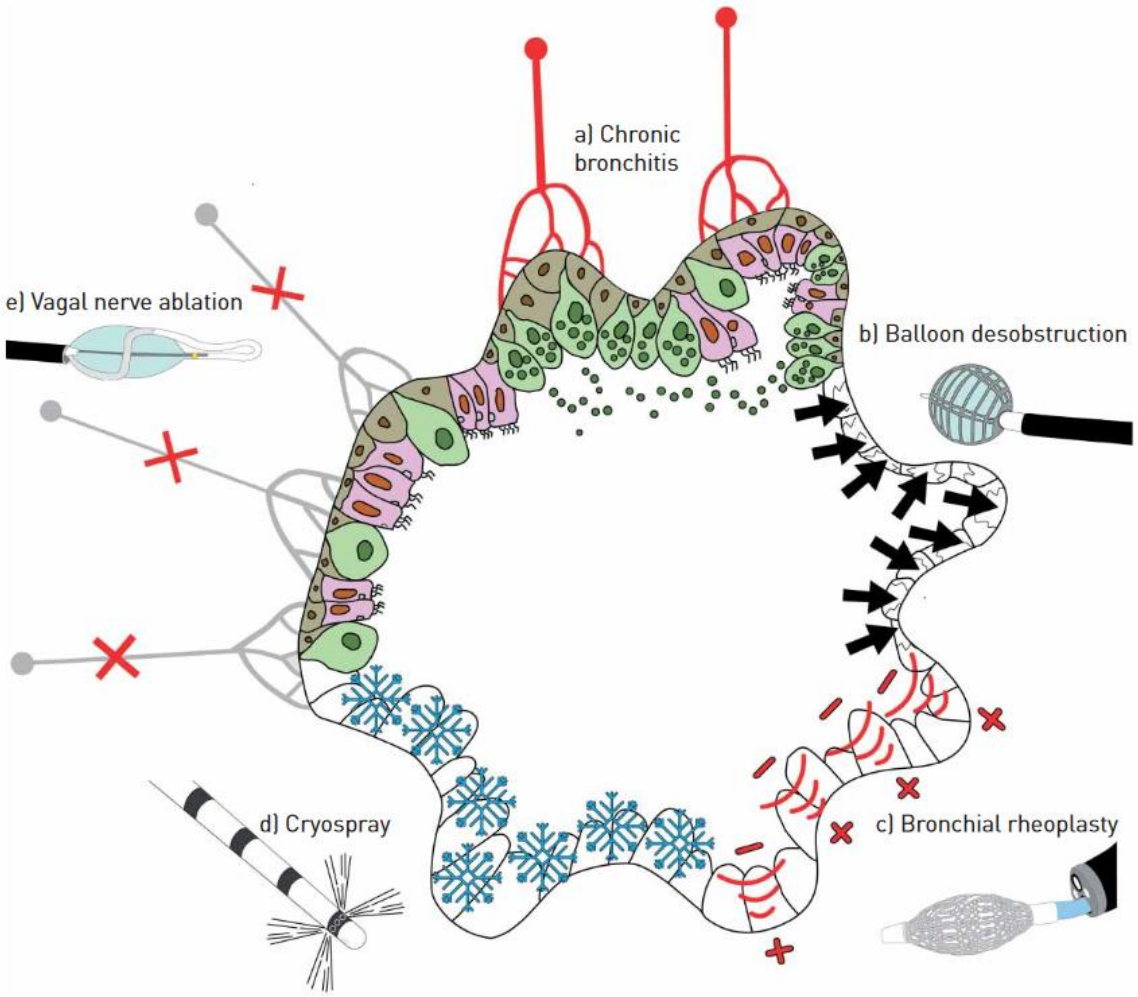

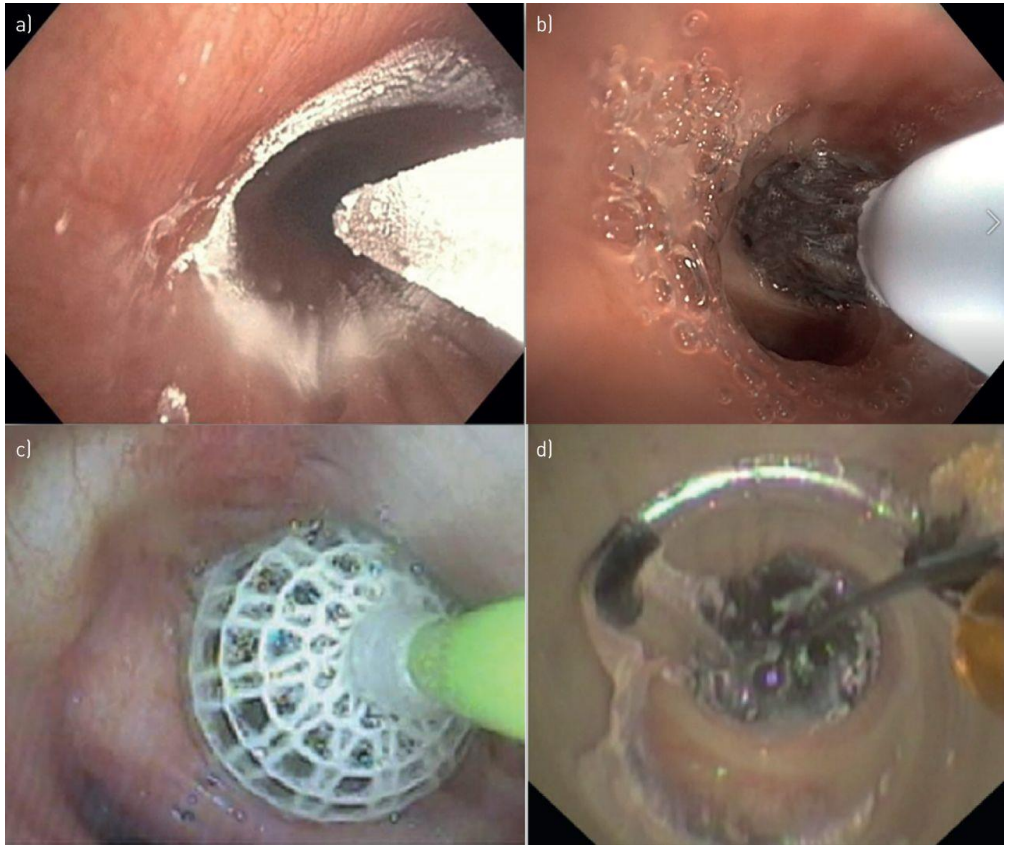

Hartman et al, New bronchoscopic treatment modalities for patients with chronic bronchitis. Eur Respir Rev. 2021 Jan 19; 30(159):200281

Principles of rheoplasty

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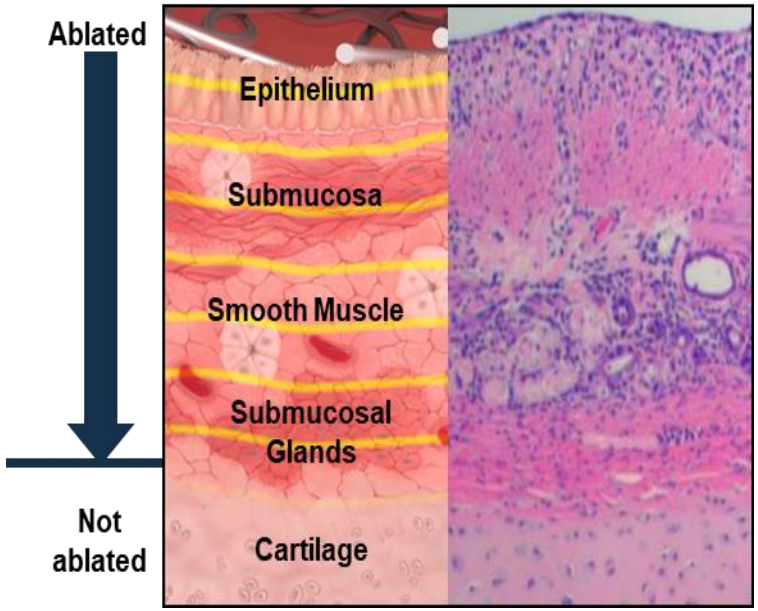
- **RheOx bronchial Rheoplasty** (Gala Therapeutics, San Carlos, CA, USA)

➢ The RheOx catheter delivers pulsed electrical fields (high frequency, short-duration, non thermal electrical fields) to the airway epithelium and submucosal tissue layers

Goal:

➢ to ablate the abnormal mucus-producing cells of the airway causing non-necrotic epithelial and submucosal cell death

➢ thereby allowing normal, healthy epithelial regeneration to occur



➢ Because the treatment uses a monopolar electrode, it is contraindicated for individuals with implantable cardiac devices

➢ CE mark since 2019

Bronchial rheoplasty procedure

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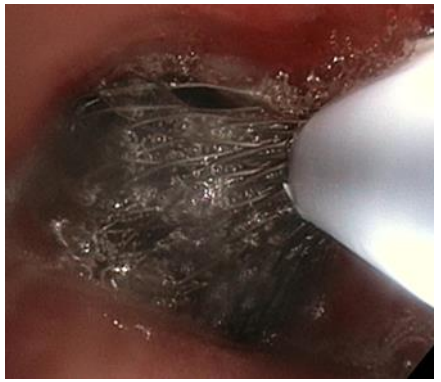
- 2 separate treatments (one lung/treatment), ca 1 month apart

- distal self-expanding basket electrode with shape memory is expanded to circumferentially contact the airway wall and activated via a foot pedal to deliver pulsed electric current over 5 sec

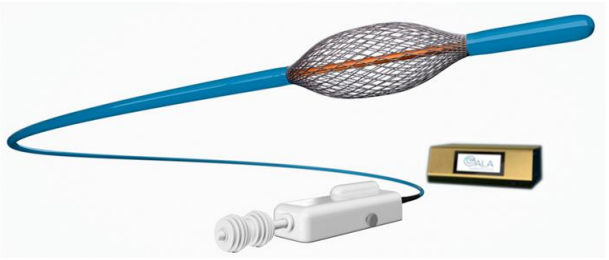


- delivered from the distal to the proximal area of each lung (3mm-18mm)

- repeated in a slightly overlapping manner until all accessible bronchial segments and subsegments are treated, usually 40 - 70 activations per lung

- treatment is performed under general anesthesia with an average procedure time of ~ 30-60 min

Preparation



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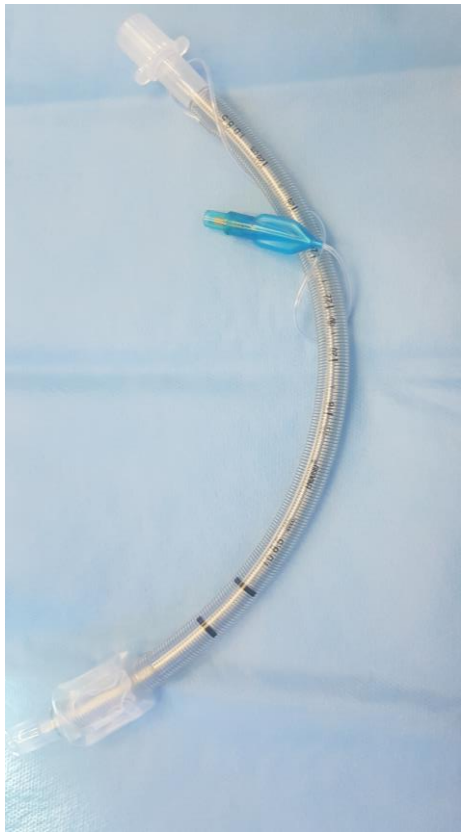
Rigid or flexible intubation?

General anesthesia



Minimum 2.8 mm working channel

Courtesy of J. Brock

Generator, Monitor, Catheter

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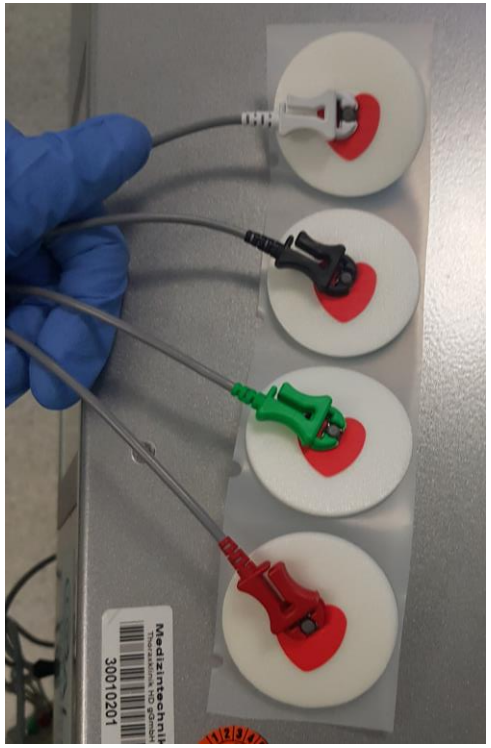

Pulsed electrical fields (high-frequency, short duration, non thermal)

Courtesy of J. Brock

Rheoplasty Procedure – Video

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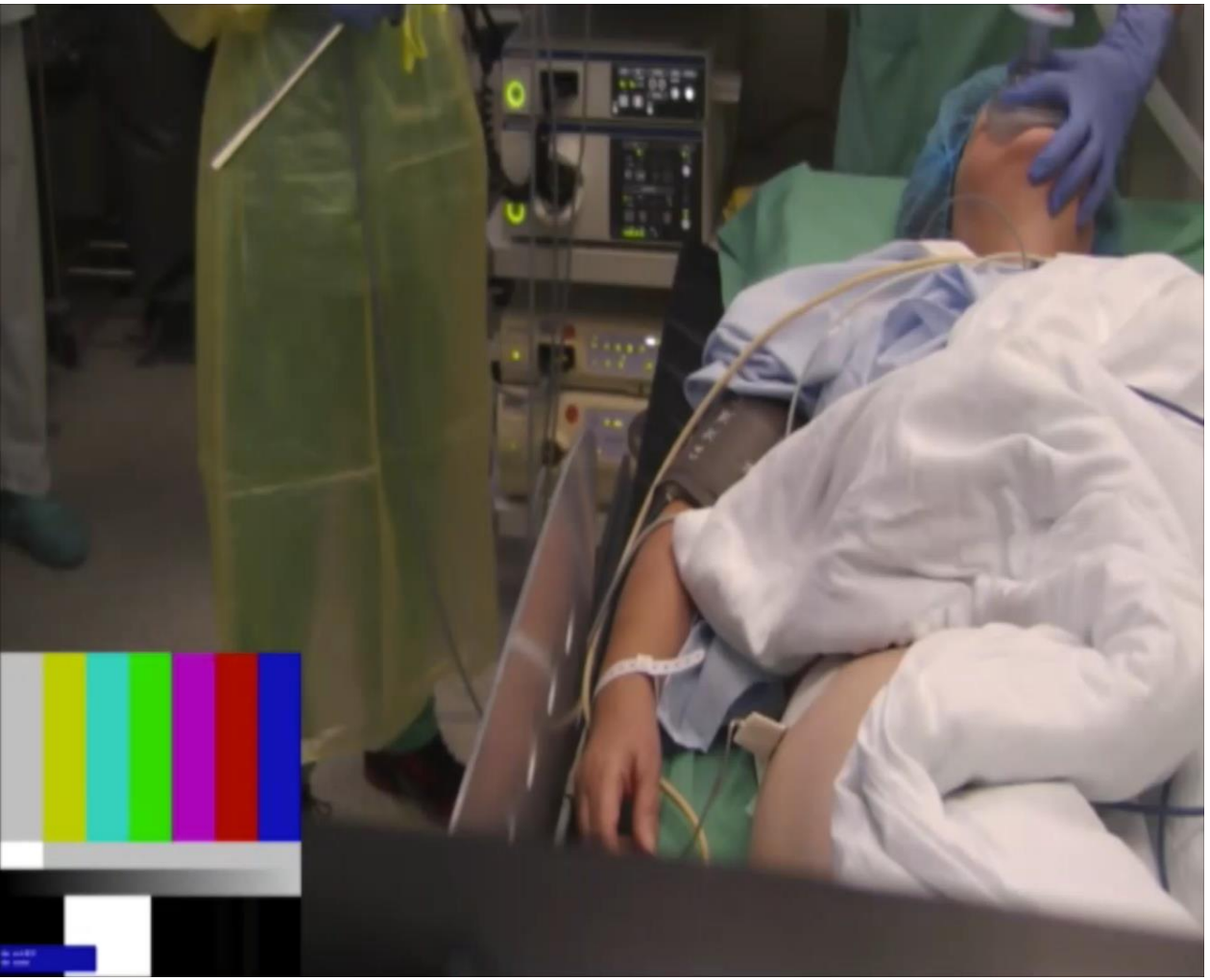

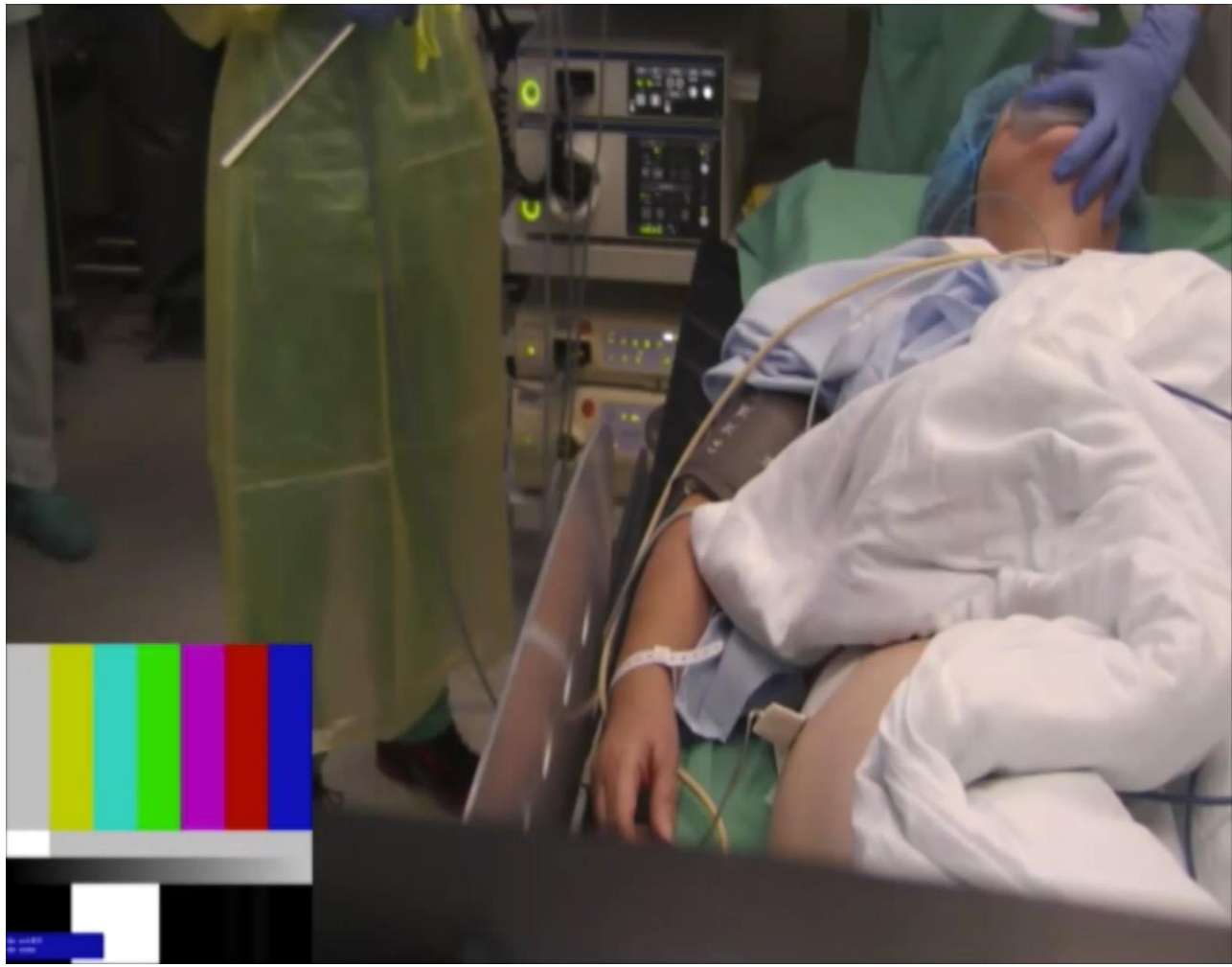

Courtesy of J. Brock

RheOx™ Chronic Bronchitis Clinical Programme

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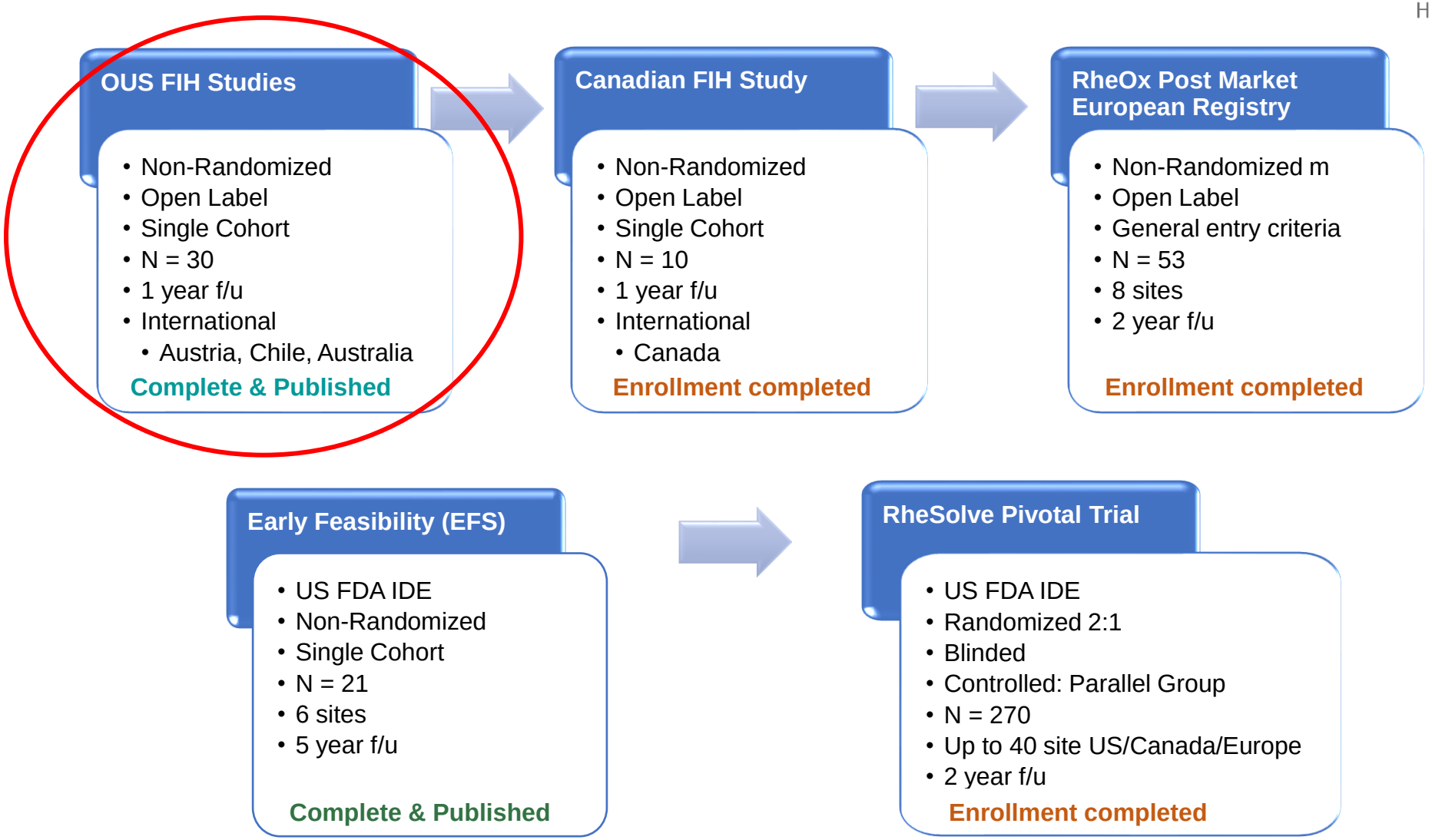

Bronchial Rheoplasty for CB feasibility and safety

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Design: single arm, prospective, multi-center, safety and feasibility study

Endpoints:
primary → safety through 6 months
Secondary → feasibility and clinical utility (quality of life, histopathology) at one year

Enrollment: n=30 at 5 sites

Key Inclusion Criteria

- ✓Chronic bronchitis defined clinically as productive cough for 3 months in 2 successive years
- ✓**Post-BD FEV_1 between 30% and 100% predicted**
- ✓**≥10 py**
- ✓**SGRQ ≥ 25 points and CAT ≥ 10 points (CAT ≥ 7 points in the first 2 questions)**

Quelle Foto: https://images.app.goo.gl/pvChefU9wjh9gN8s8

Valipour et al, Am J Respir Crit Care Med. 2020: 202(5):681-689

Patient Demographics, Baseline Characteristics

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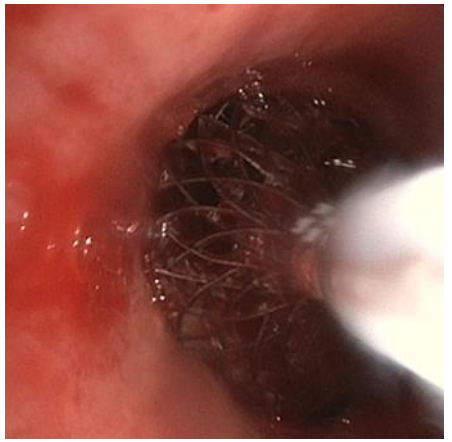
Characteristic	Value (*N = 30 Patients*)
Age, yr	67 (7.4)
Sex, M, *n* (%)	19 (63.3)
BMI, kg/m^2	27.5 (4.7)
Smoking history, pack-years	40.7 (26.5)
FEV_1% predicted[*]	65.0 (21.2)
FEV_1/FVC ratio[*]	0.53 (0.14)
Airflow obstruction, *n* (%)	
CB w/o airflow obstruction	4 (13.3)
GOLD I	4 (13.3)
GOLD II	13 (43.3)
GOLD III	9 (30.0)
TLC% predicted[*]	111.6 (14.2)
RV% predicted[*]	142.2 (39.8)
RV/TLC[*]	48.7 (10.1)
Emphysema, % (−950 HU)	8.0 (9.2)
6MWT, m[†]	443.2 (92.4)



Safety

Event Type	Treatment Recovery Period* (*n Events*)	3 mo† (*n Events*)	6 mo‡ (*n Events*)	12 mo§ (*n Events*)
Device-related‖	0	0	0	0
Procedure-related‖				
COPD exacerbation	1	1	0	0
Mucosal scarring	1	0	0	0
Pneumonia	1	0	0	0
Unrelated to device or procedure				
Atrial fibrillation	1	0	0	0
COPD exacerbation	0	1	1	3
Erysipelas	0	0	1	0
Femoral artery stenosis	0	0	1	1
Lung nodule	0	0	0	1
Musculoskeletal injury	0	0	0	1
Pyelonephritis	0	0	0	1

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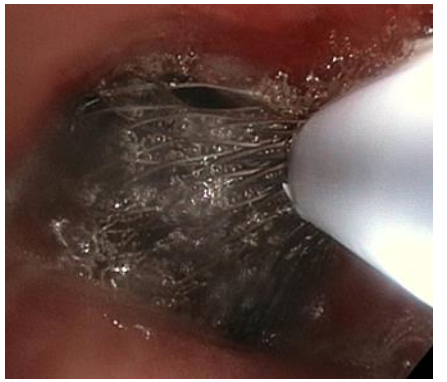

- 4 procedure-related SAEs reported up to 6months
- no additional device or procedure related SAEs between 6-12 months
- all resolved without sequelae

Quality of Life

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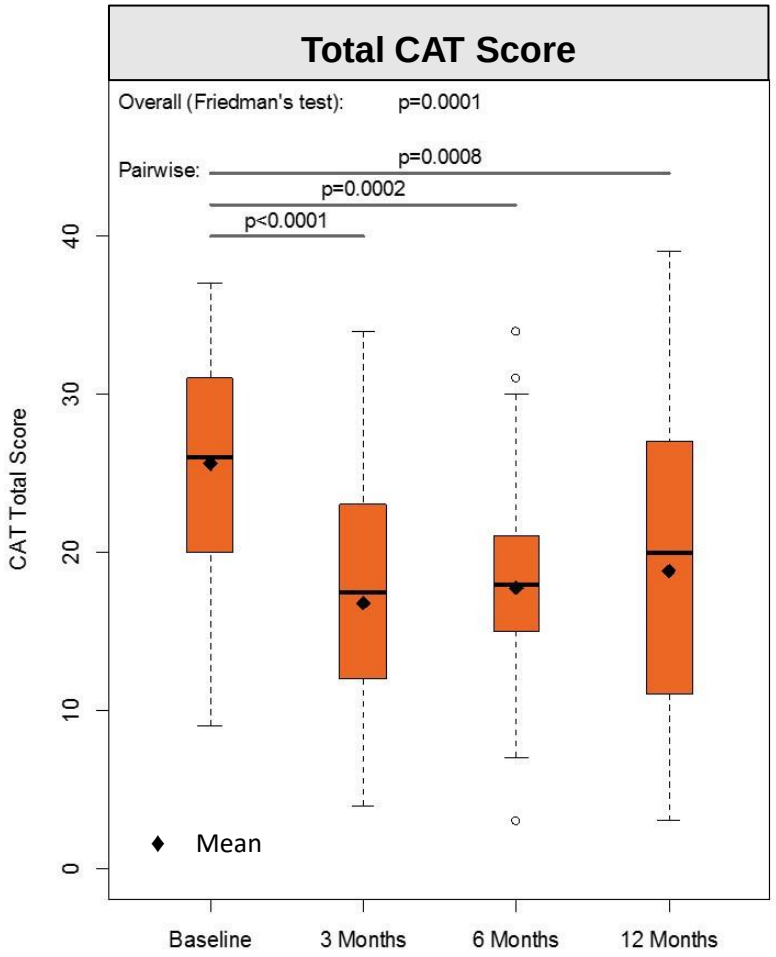

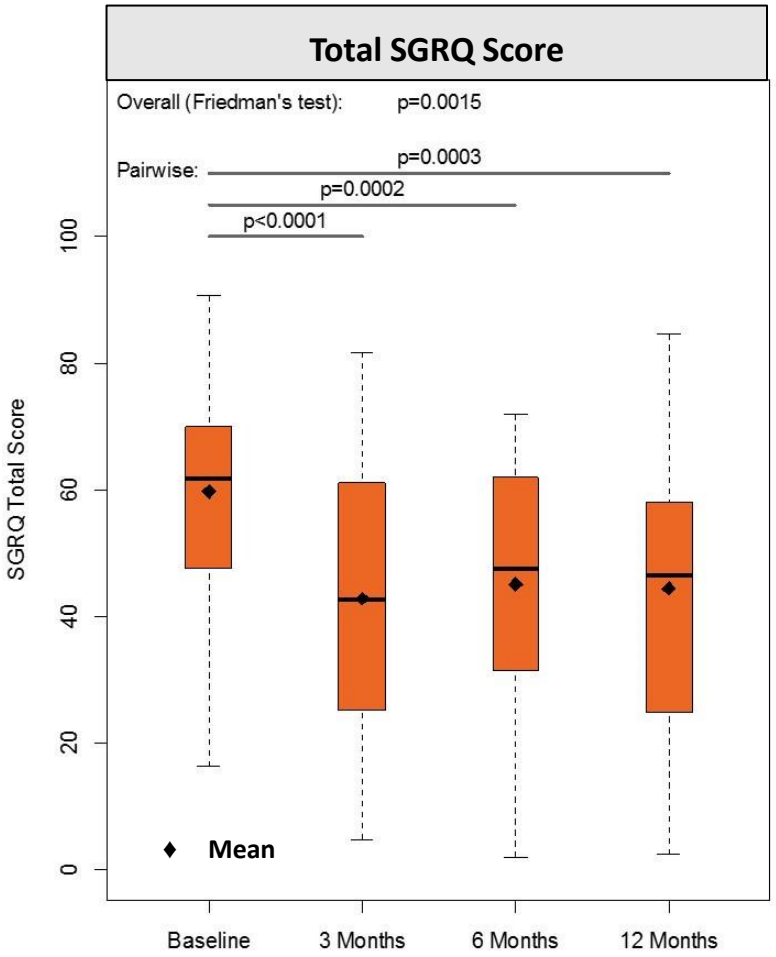

-7.0 points in CAT (MCID is 2.0)
-15.2 in SGRQ (MCID is 4.0)

Histopathology results

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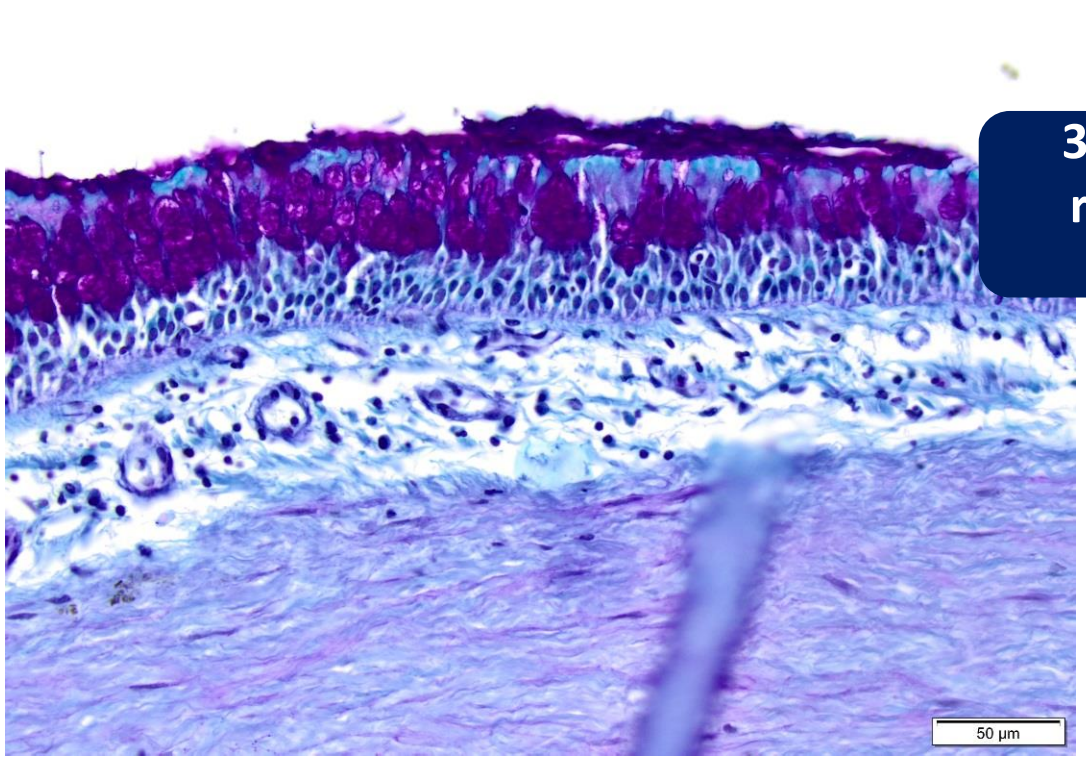
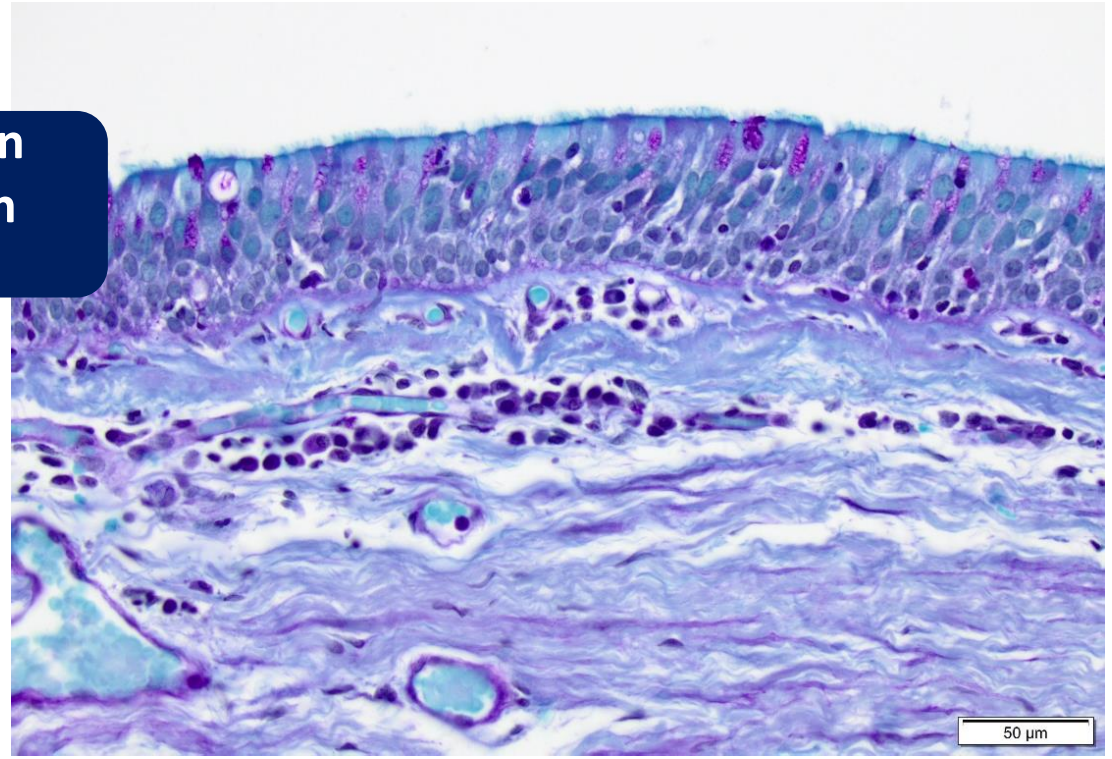
Goblet cell hyperplasia score 3 months after treatment



39% mean reduction p<0.001



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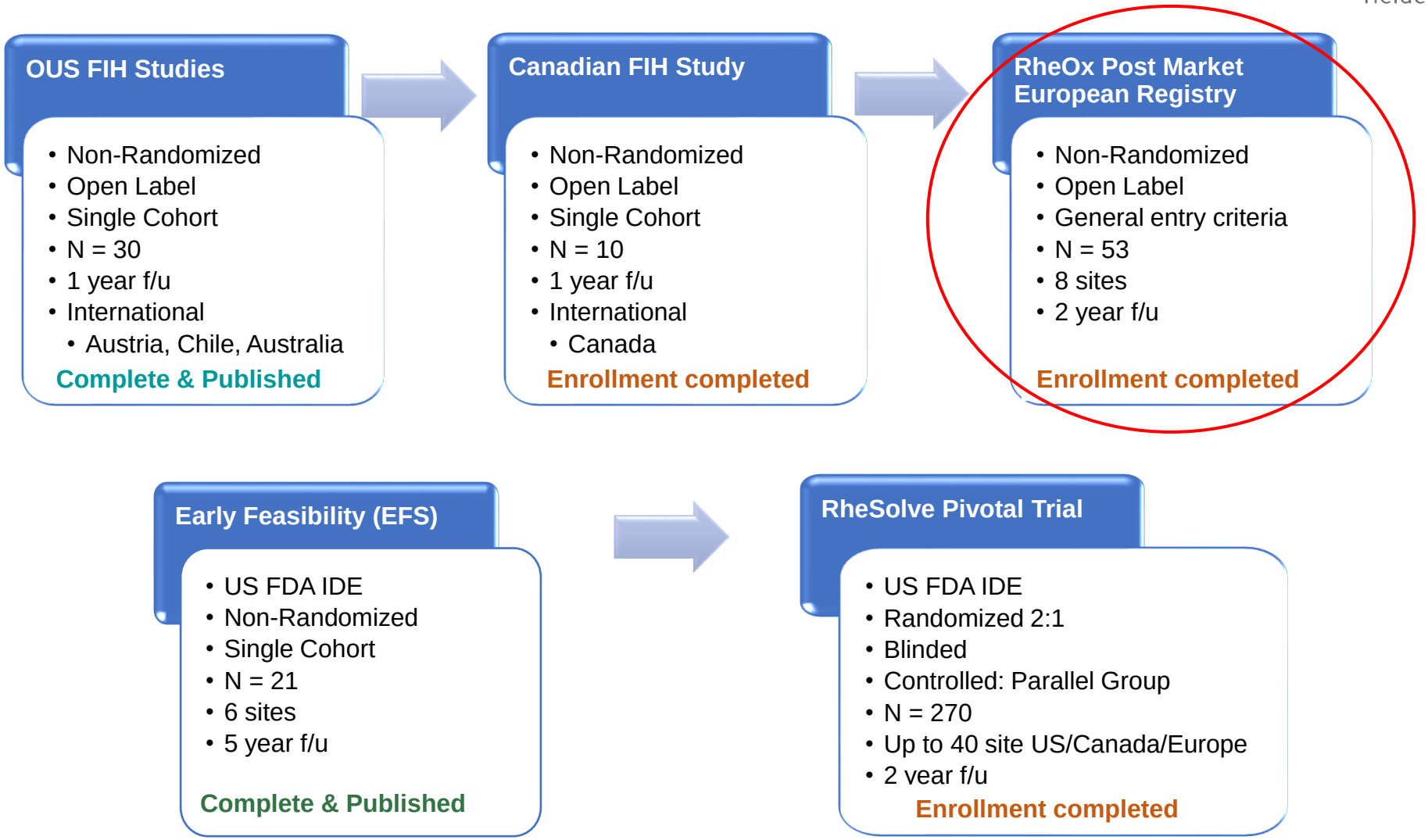

EU Registry:
Methods and Baseline Clinical Characteristics

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Baseline Measure	N=53
Age (years)	67.24 ± 8.7
BMI (kg/m2)	26.4 ± 4.5
Smoking History (Pack Years)	33.4 ± 28.2
Post-BD FEV_1 (% Predicted)	58.1 ± 25.5
FEV_1/FVC (%)	53.3 ±15.8
Residual Volume (% Predicted)	165.2 ± 39.6
Total Lung Capacity (% Predicted)	116.4 ± 14.6
CAT Total Score (points)	24.9 ± 7.0
CAT Phlegm	3.9 ± 0.8
CAT Cough	4.0 ± 0.7
SGRQ Total Score (points)	55.4 ± 18.6
6 Minute Walk Test (meters)	356.3 ± 120.3

Data presented as mean ± SD

- Baseline characteristics indicate a real-world cohort of highly symptomatic COPD patients with CB
- 53 patients, 8 centers in Austria and Germany

➢ Results for FU 6 and 12 months: SAEs, CAT, SGRQ

- Spirometry and symptoms similar to previous studies
- **Residual volume was higher than previous studies**
  - Mean from previous studies ~140%

Safety: Respiratory SAEs

Event Type	Procedure Recovery* (N=53)	Through 6 Months (N=53)	Through 12 Months (N=51)
Bacterial colonization	0	0	1
COPD exacerbation	2	2	1
COVID-19	0	1	0
Lower airway obstruction	0	1	0
Lung infiltration	0	1	0
Mediastinal neoplasm NOS	1	0	0
Pneumonia	0	1	0
Pneumonitis	0	1	0
Pneumothorax	0	2	0
Respiratory infection	1	0	0
Sputum increased	0	1	0
Thoracic pain	2	0	0

**Defined as the 30 days following either Rheoplasty procedure*

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- **Respiratory SAEs: n=16 in 8 patients, 6 in first 30 days, mainly COPD exacerbations (n=4)**

- Mean of 56±15 activations among 104 BR procedures performed in the study

- Adverse event types and frequency similar to diagnostic bronchoscopy

  - 1 device related SAE through 12 months (thoracic pain)
  - 3 procedure related SAEs through 12 months (thoracic pain (2), lung infiltrate)
  - One patient died due to renal failure 193 days following BR, unrelated to the procedure

QoL Outcomes Through 6-Months

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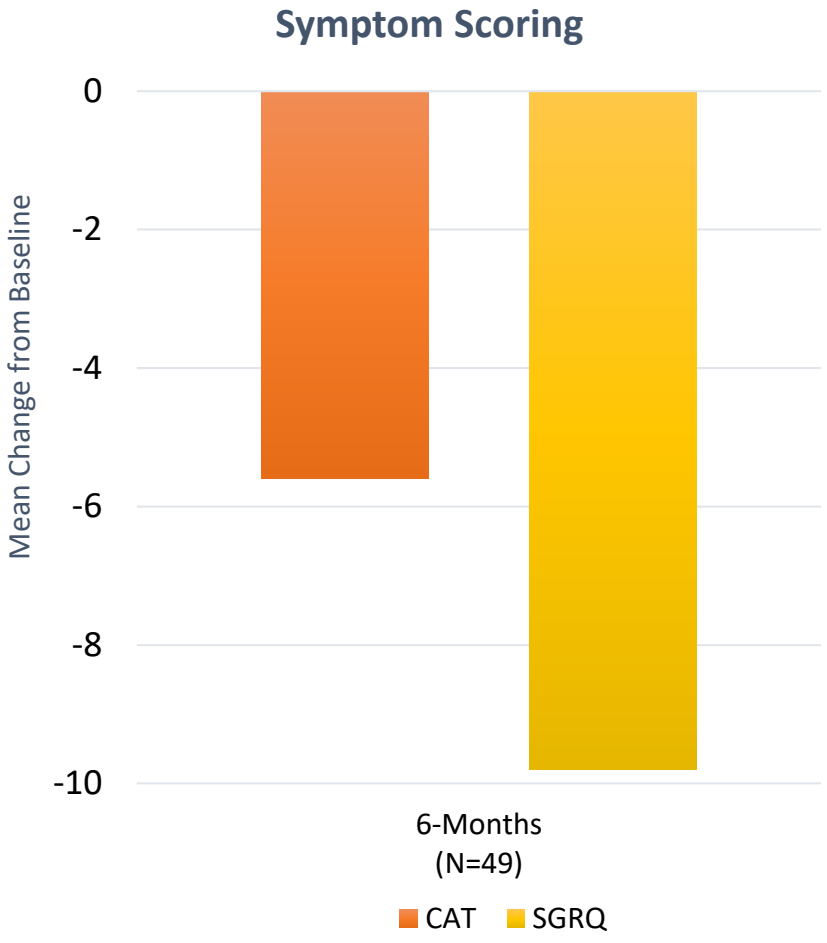

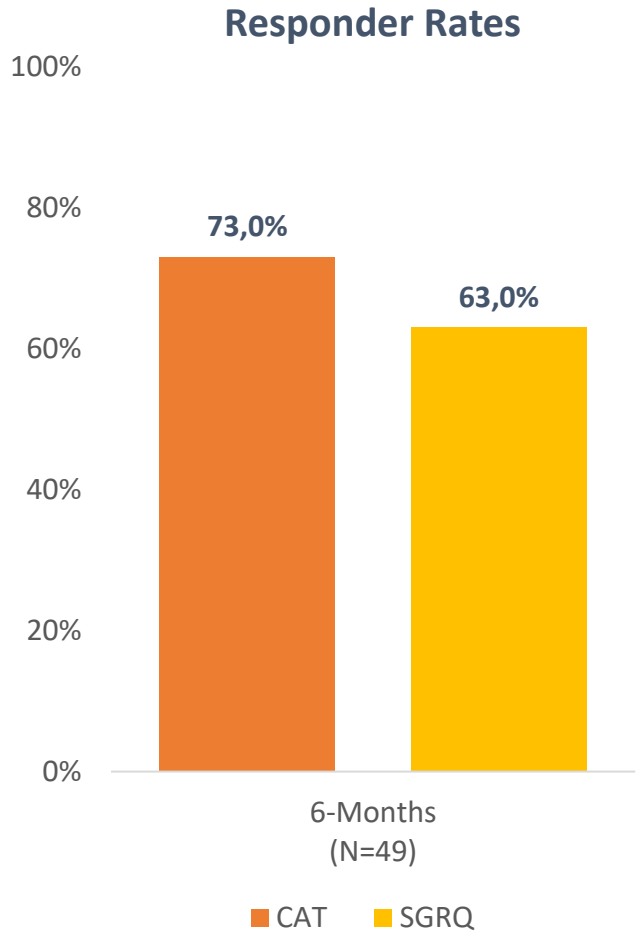

CAT responders (n=35) at study entry compared with non-responders (n=13):

- significantly less residual volume (154.0 vs. 188.2%, p=0.007),
- higher FEV_1 (66.8 vs. 39.6%, p=0.014) and
- 6-minute-walk-distance (393 vs. 289 m, p=0.006).

Responder defined as symptom improvement that met or exceeded the minimally clinically important difference (MCID), -2 points for CAT, -4 points for SGRQ

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OUS FIH Studies

- Non-Randomized
- Open Label
- Single Cohort
- N = 30
- 1 year f/u
- International
  - Austria, Chile, Australia

Complete & Published

Canadian FIH Study

- Non-Randomized
- Open Label
- Single Cohort
- N = 10
- 1 year f/u
- International
  - Canada

Enrollment completed

RheOx Post Market European Registry

- Non-Randomized
- Open Label
- General entry criteria
- N = 53
- 8 sites
- 2 year f/u

Enrollment completed

Early Feasibility (EFS)

- US FDA IDE
- Non-Randomized
- Single Cohort
- N = 21
- 6 sites
- 5 year f/u

Complete & Published

RheSolve Pivotal Trial

- US FDA IDE
- Randomized 2:1
- Blinded
- Controlled: Parallel Group
- N = 270
- Up to 40 site US/Canada/Europe
- 2 vear f/u

Enrollment completed

Chronic obstructive pulmonary disease

BMJ Open Respiratory Research

Bronchial rheoplasty for chronic bronchitis: 2-year results from a US feasibility study with RheOx

Frank C Sciurba ,[1] Mark T Dransfield,[2] Victor Kim ,[3] Nathaniel Marchetti,[4] Alejandro Comellas ,[5] Douglas Kyle Hogarth ,[6] Adnan Majid[7]

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- **Design:** multicentre observational study
- **Enrollment:** n=21 with CB at 6 sites in the USA
- bilateral treatment and 2- year FU

Endpoints:

primary outcome -> safety (incidence of SAEs through 12 months)

secondary outcome -> clinical utility (as determined by the CAT and SGRQ total scores)
Responder rates were calculated by using the established minimally clinically important difference (MCID) thresholds, a reduction of 4 points for the SGRQ and 2 points for CAT

secondary outcome-> frequency of moderate (outpatient treated) **and severe** (hospitalised) **exacerbations** and the Cough and Sputum Questionnaire (**CASA- Q**)

Crawford B, Monz B, Hohlfeld J, et al. Development and validation of a cough and sputum assessment questionnaire. Respir Med. 2008;102 (11):1545–1555.

BMJ Open Respir Res 2023;10:e001710. doi:10.1136/ bmjresp-2023-001710

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Safety:

MedDRA lower-level term (n events)	Treatment recovery period* (n=21)	3 months† (n=21)	6 months‡ (n=21)	12 months§ (n=21)	24 months¶ (n=20)
Worsening dyspnoea	0	0	0	0	1
COPD exacerbation	0	0	0	1	2
Hyponatremia	1	0	0	0	0
Hip fracture	0	0	1	0	0
Pneumonia	0	1	1	0	0
Pulmonary embolism	0	0	0	0	1
Stress cardiomyopathy	0	1	0	0	0
Total	One event in one patient	Two events in two patients	Two events in two patients	One event in one patient	Four events in two patients

- **6 SAEs in 3 pat. through 12 M / 4 SAEs in 2 pat. between 12-24 M**
- **The most frequent non-SAE: COPD exacerbations**
- Pulmonary function remained stable throughout the follow- up period

BMJ Open Respir Res 2023;10:e001710. doi:10.1136/ bmjresp-2023-001710

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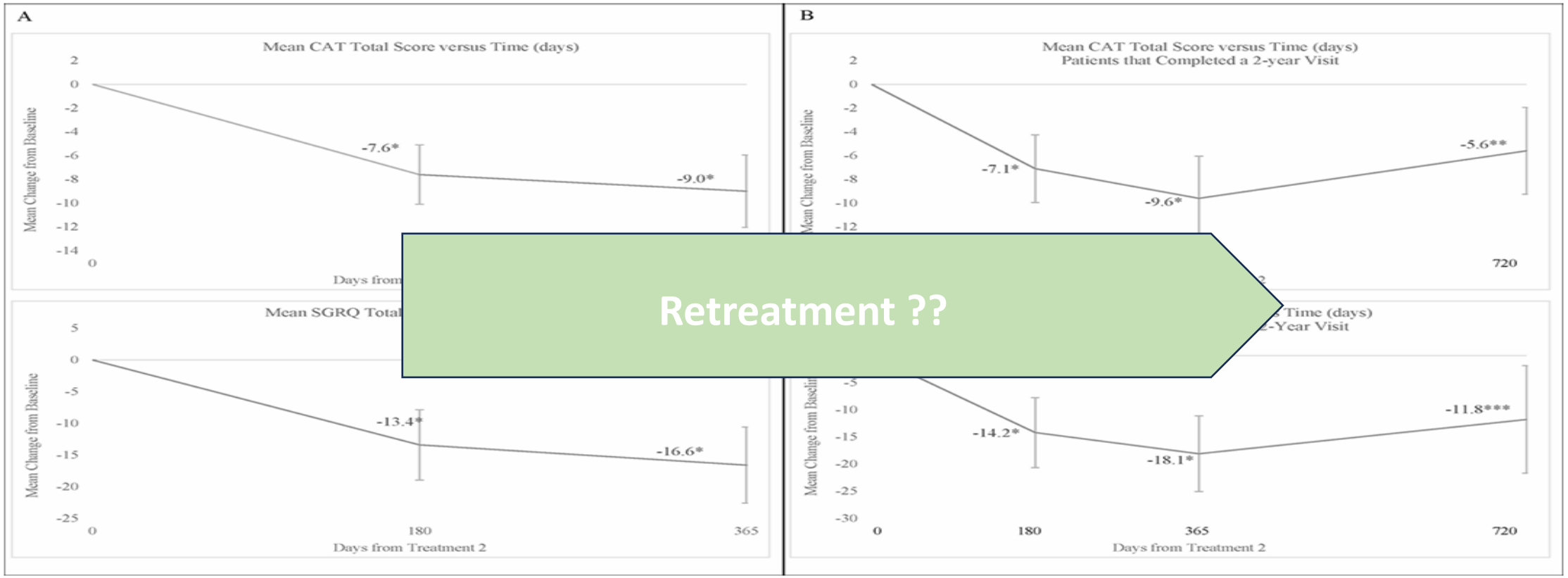

Retreatment ??

- Symptom and QoL improvements both statistically significant and clinically meaningful until the 24- month FU
- Small drop in responder rates between 12 months and 2 years

BMJ Open Respir Res 2023;10:e001710. doi:10.1136/ bmjresp-2023-001710

Chronic obstructive pulmonary disease

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COPD exacerbation rate (events/patient/year)	Baseline* (n=21)	12 months post treatment† (n=21)	12 months post treatment (excluding the treatment recovery period)‡ (n=21)	Post 12 months through 24 months§ (n=20)
All (moderate+severe)	1.19±1.60	0.99±1.46	0.75±1.32	0.88±1.91
Moderate	1.05±1.66	0.94±1.48	0.69±1.33	0.79±1.74
Severe	0.14±0.36	0.05±0.21	0.05±0.25	0.10±0.44

Values are mean±SD (number of events)

- **Reduction of the COPD exacerbations**

BMJ Open Respir Res 2023;10:e001710. doi:10.1136/ bmjresp-2023-001710

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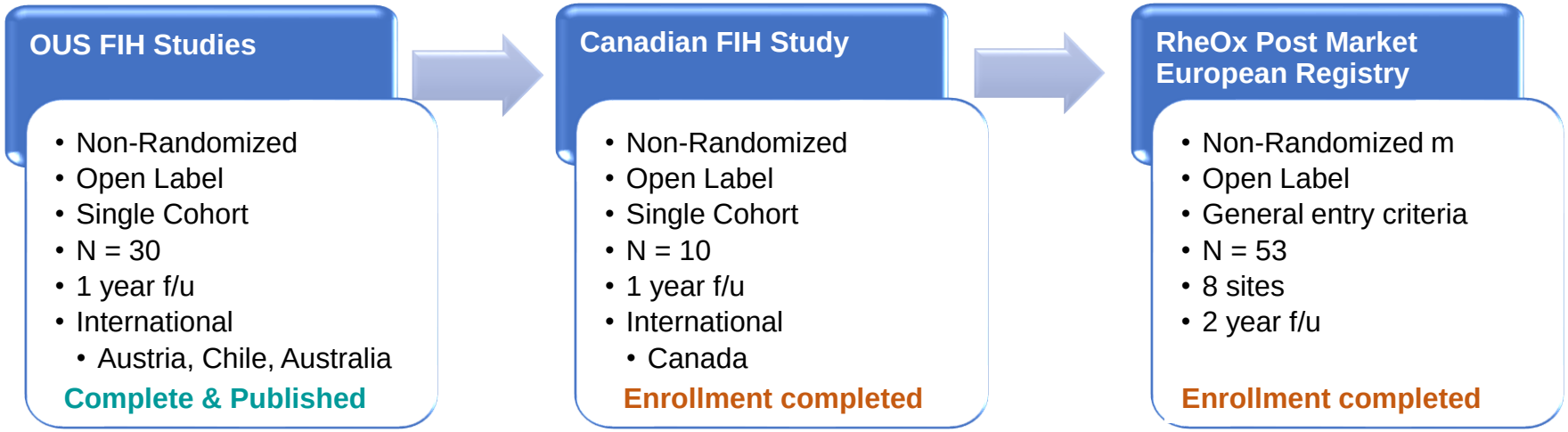

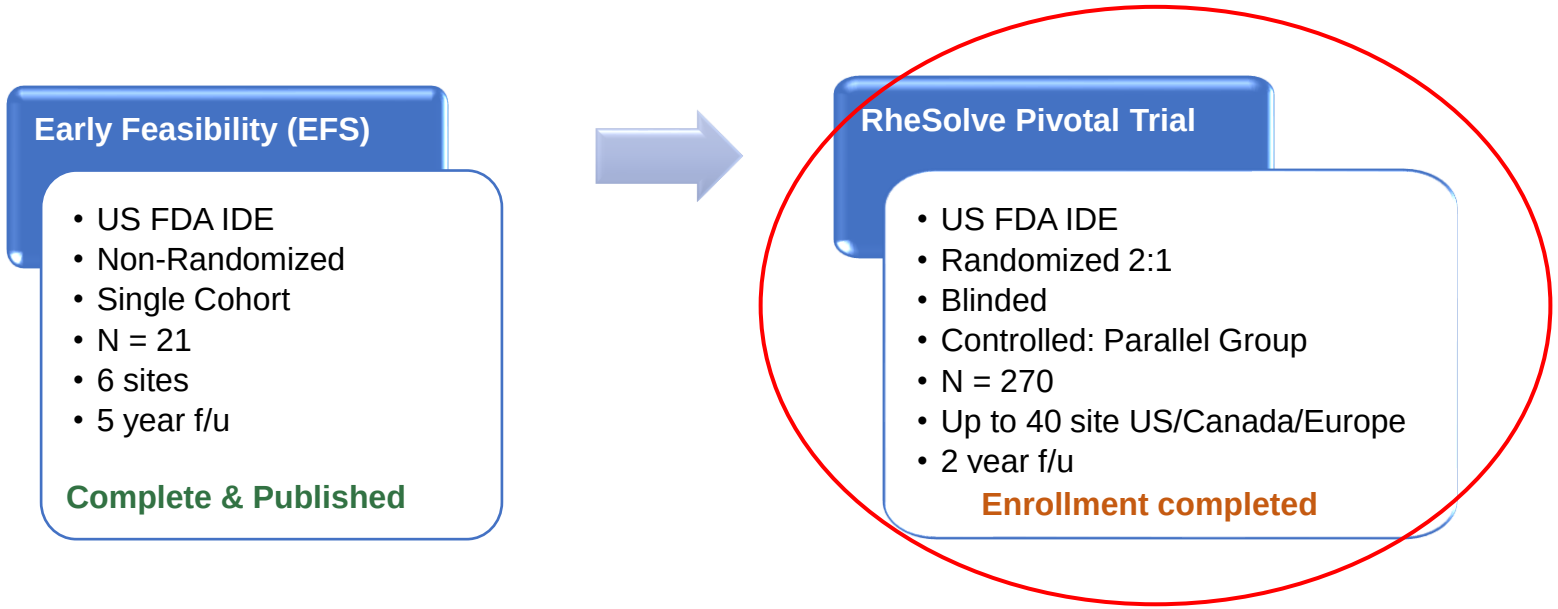

The RheSolve Study

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- ✓ Prospective
- ✓ randomized (2:1)
- ✓ parallel group
- ✓ double-blind
- ✓ multicenter
- ✓ n=270
- ✓ Recruitment complete

➢ **Results pending…**

10 centers in Canada and Europe

40 US centers

Quelle Foto: https://images.app.goo.gl/pvChefU9wjh9gN8s8

Metered Cryo Spray Therapy

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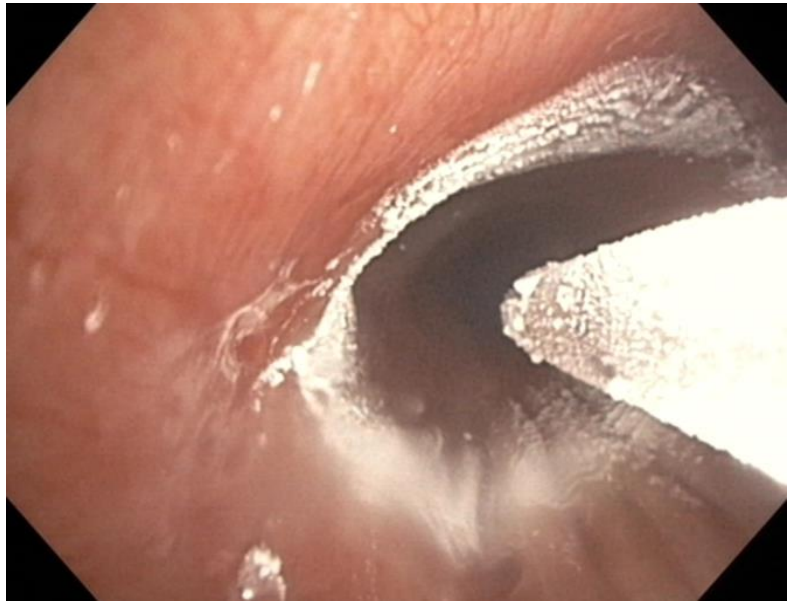

Metered Cryospray (MCS) Therapy

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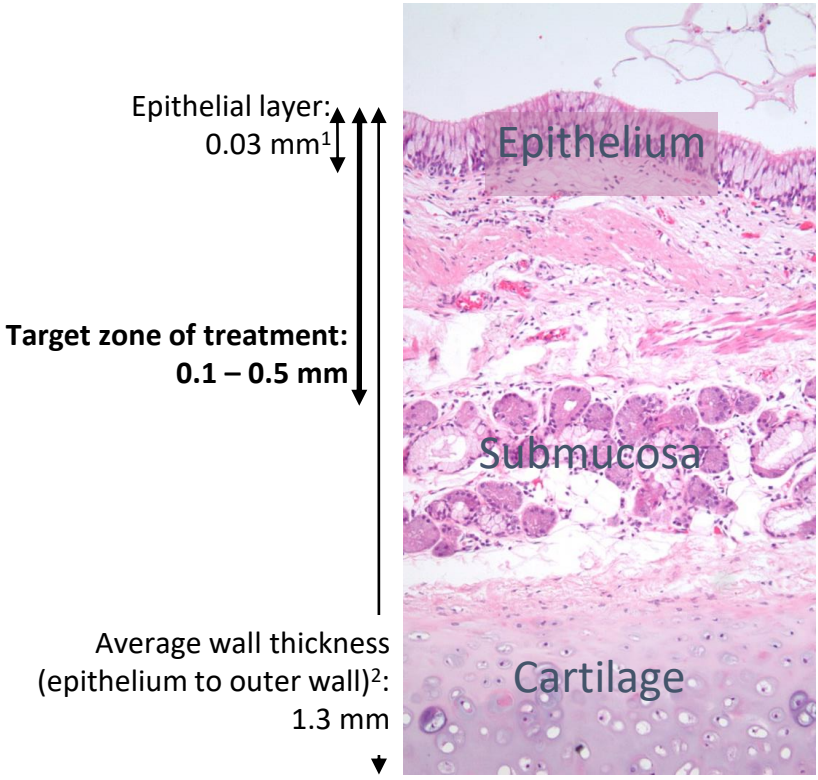
The RejuvenAir system (CSA Medical, Lexington, MA, USA)

Small metered doses cause flash-freezing of the mucosa, at −196˚C, using liquid nitrogen

Goal:

- to cryoablate abnormal epithelium and excessive mucous-producing goblet cells to a depth of 0.1–0.5 mm and a width up to 10 mm
- leaving undamaged the extra-cellular structure that allows for new healthy cells, including cilia and mucus-producing goblet cells, to repopulate
- reduce chronic inflammation and associated airway constriction
- **Re-epithelialisation with healthy mucosa has been demonstrated within 48 h of cryospray treatment**, and so far with durability to 106 days

The RejuvenAir® System is currently under clinical investigation and is not commercially available



[1] Reid, et al, Thorax: 1960: Vol 15; pages 132-141
[2] Montaudon, et al.; J. Anat. (2007) 211, pp 579-88

Pre-procedure planing

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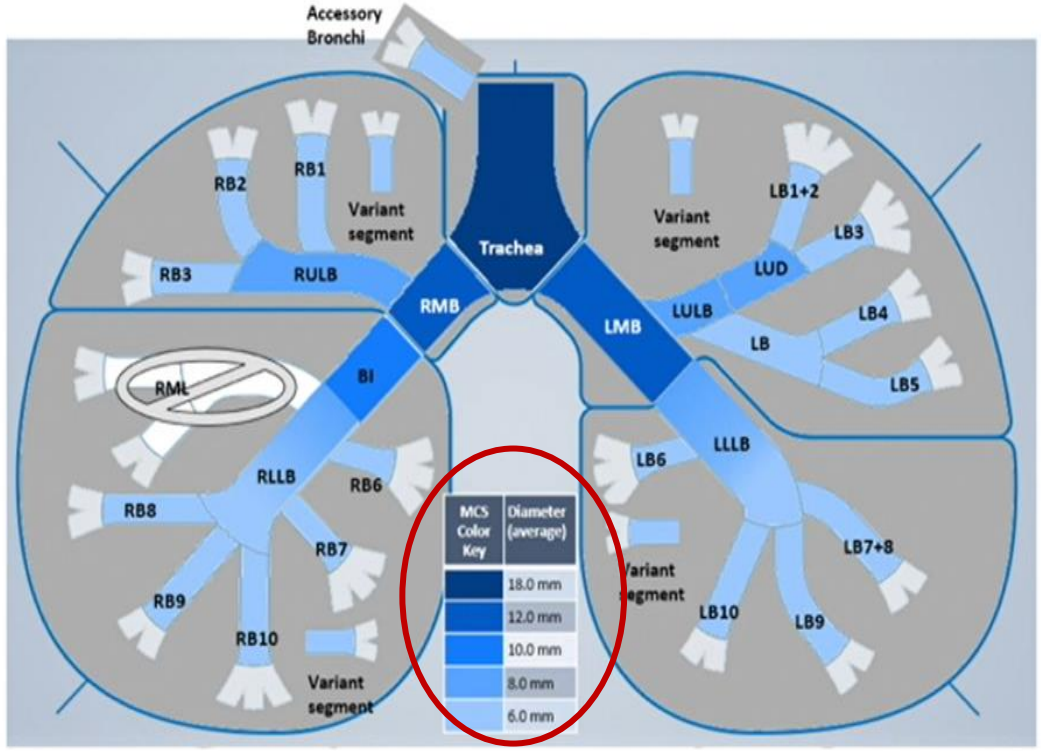

- A unique graphical user interface drives standardized metered cryospray treatment
- specially developed algorithm -> programmed doses of liquid nitrogen are delivered in a radial spray to the bronchial airways

Cryospray procedure

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➢ **3 treatments**

1st right lower lobe and main stem bronchus

2nd left lower lobe and main stem bronchus

3rd both upper lobes, any residual main stem bronchus and the distal end of the trachea

- middle lobe omitted from the procedure on account of the perceived increased risk of barotrauma in a small structure

Cryospray procedure - Video

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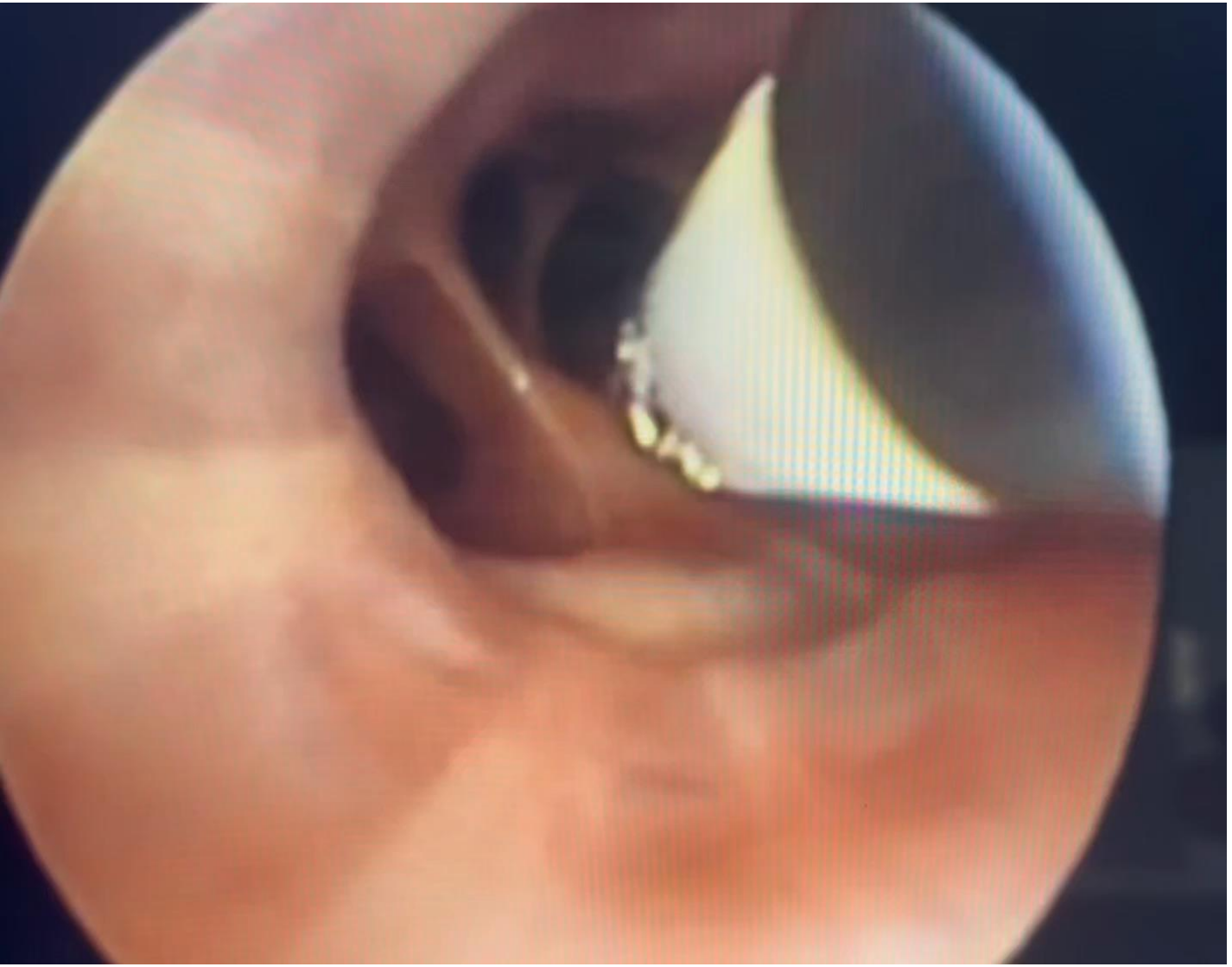

- During delivery of the metered cryospray, a ring of frost can be seen on the tissue towards the end of the catheter

RejuvenAir Studies

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	Lobectomy Safety and Histology Study (EU)	Lobectomy for Safety and Histology (CAN)	Safety and Feasibility Study for Treating Chronic Bronchitis Patients
Design	*Multi-center study with lung cancer patients treated in lobes scheduled for resection within 2 hours of the MCS procedure*	*Single-center study with lung cancer patients treated in lobes scheduled for resection within 2 - 14 days of the MCS procedure*	*Multi-Center study with chronic bronchitis patients treated in trachea through segmentals over three procedure days*
Goals (or objective)	*To study the safety of the RejuvenAir Therapy*		*To evaluate the safety of the RejuvenAir® Cryospray Therapy and to evaluate the feasibility of planned treatment.*
Endpoints	• *AE's and SAE's* • *Histological effect of metered cryospray: Depth of penetration, Tissue characteristics and Healing outcome*		• *AE and SAE's* • *SGRQ* • *Delivery of intended MCS'*
#of Patients	*N = 11 patients*	*N = 6 patients*	*N = 35 patients*
Follow-Up	*30 days*	*30 days*	*3, 6, 9, 12, 24 and 36 months*
Status	*Complete*	*Complete*	*12 months results published*

Initial safety and histology studies

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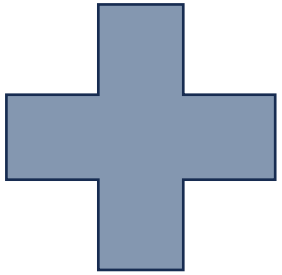
NCT02106143 -> lobectomy or pneumonectomy immediately after MCS



NCT02483052 -> planned lobectomy after MCS

✓ 16 subjects were enrolled and treated at three sites in Europe and Canada

- **Primary end point**

➢ Device related SAEs and post procedure safety

- **Secondary end point**

➢ Potential histologic effects

Results

➢ primary endpoint was met
  - safe delivery of MCS to the segmental and/or lobar bronchi without device-related SAEs

➢ Histology from immediate resection specimens documented **MCS effect** and **nonscarring healed tissue from the delayed resection group**

Slebos, D-J., Breen, D., Coad, J., Klooster, K., Hartman, J., Browning, R., ... Irshad, K. (2017). Safety and Histological Effect of Liquid Nitrogen Metered Spray Cryotherapy in the Lung. American Journal of Respiratory and Critical Care Medicine, 196(10), 1351-1352. DOI: 10.1164/rccm.201611-2220LE

Data Cryospray

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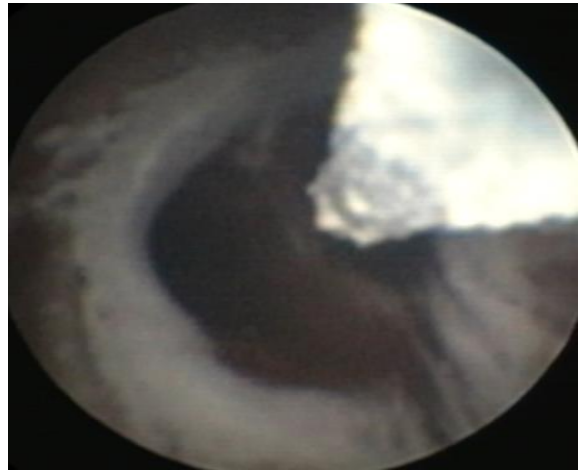
- NCT02483637

- prospective, open-label, single-arm study
- multicentre in UK, Netherlands, Canada
- 35 participants

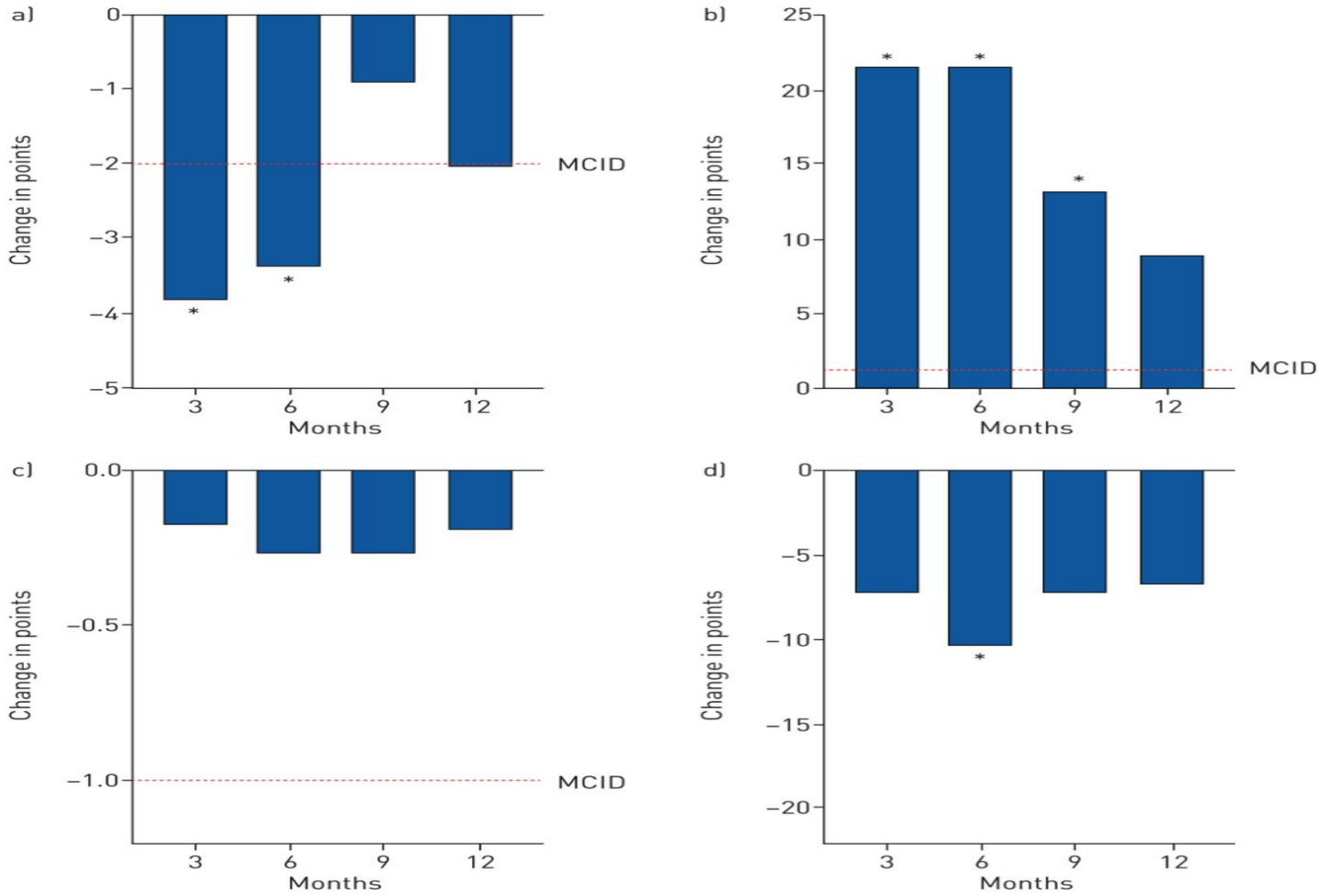


- Objectives:
  - **Feasibility**: completion of treatments
  - **Efficacy**: 3-month change in SGRQ
  - **Safety**: incidence of adverse events (AE)

    at 12 months

Garner JL, Shaipanich T, Hartman JE, et al. A prospective safety and feasibility study of metered cryospray for patients with chronic bronchitis in COPD. Eur Respir J 2020; 56: 2000556

Cryospray efficasy results



Mean changes in patient-reported outcomes over 12 months:

a) COPD Assessment Test score;
b) Leicester Cough Questionnaire score;
c) modified Medical Research Council dyspnoea score;
d) visual analogue scale (activity). MCID: minimal clinically important difference. *: p<0.05 compared to baseline.

Garner JL, Shaipanich T, Hartman JE, et al. Eur Respir J 2020; 56: 2000556

- Persistent clinical improvements in PROs were observed including SGRQ
- CAT score (to 6 months) and Leicester Cough Questionnaire (to 9 months)

Cryospray safety results

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Table S3 (legend): Subject overview of adverse events over 12-months.

Adverse Event (AE) categorisation	N	%
Subjects experiencing any AE	35	100
Subjects experiencing a Serious AE	11	31.4
Subjects experiencing a Device-related AE*	4	11.4
Subjects experiencing a Serious Device Related AE*	0	0
Subjects experiencing a Procedure Related AE*	21	60.0
Subjects experiencing a Serious Procedure Related AE*	0	0
Subjects experiencing a Severe AE**	6	17.1
Subjects experiencing an AE leading to discontinuation***	1	2.9

* = AE is related if: relation to device / procedure is reported 'Possibly', 'Probably' or 'Causal Relationship'.
** = AE is severe if: severity is reported 'Severe'.
*** = AE led to discontinuation if: reason for early withdrawal at End of Study is 'Adverse Event' or 'Death'.

All subjects experienced at least one adverse event (AE)

- 52.6% were classified as respiratory-related
  - of these 36.3% were attributed to the underlying COPD

- **No serious device- or procedure- related adverse events**
- 1/3 experienced an exacerbation in the following year
- No pneumothoraces

- The safety and efficacy of this therapy will require confirmation by prospective randomized, sham-controlled trials

Garner JL, Shaipanich T, Hartman JE, et al. Eur Respir J 2020; 56: 2000556

Targeted Lung Denervation (TLD)

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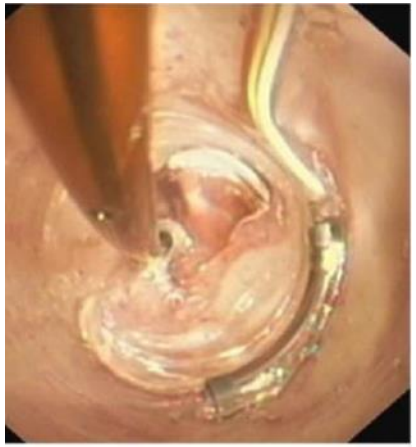
Targeted Lung Denervation (Nuvaira Inc.)

Targeted

- Anatomically only to the lung
- To a depth where the nerves are located

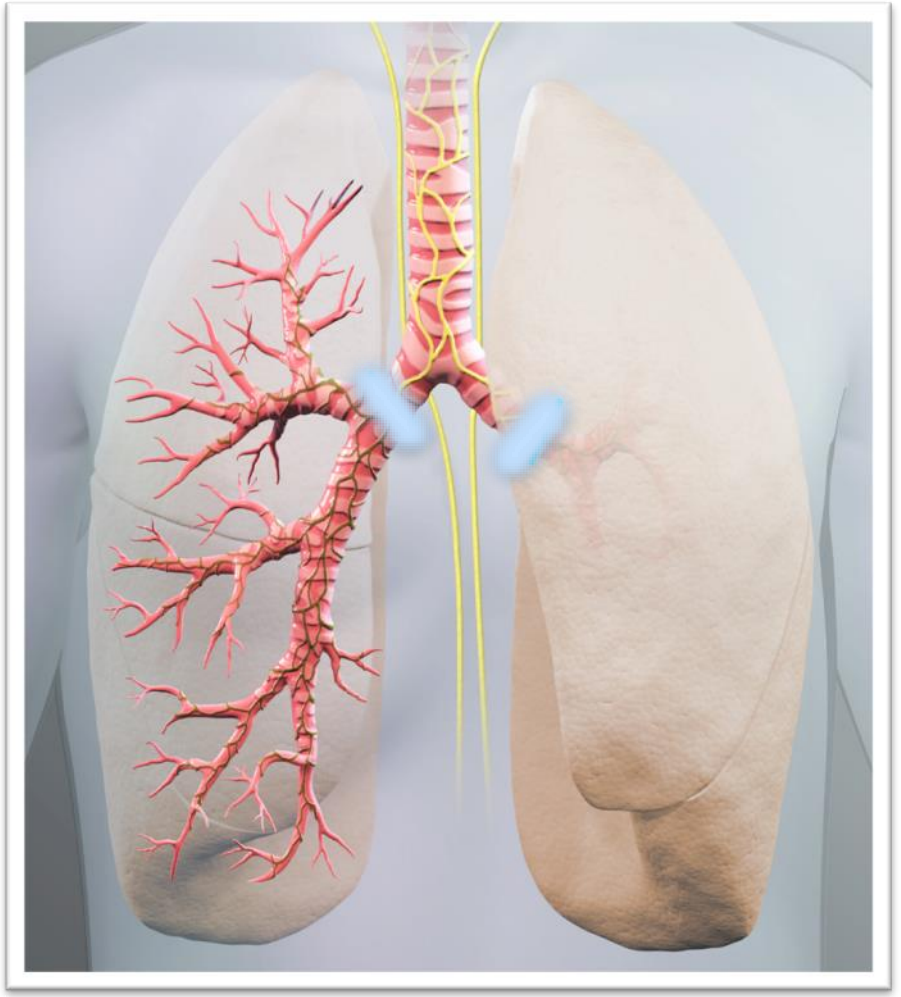
Lung

- Decrease smooth muscle tone
- Decrease mucus production
- Leads to bronchodilation



Denervation

- Disrupt parasympathetic nerves
- Decrease release of acetylcholine



TLD procedure

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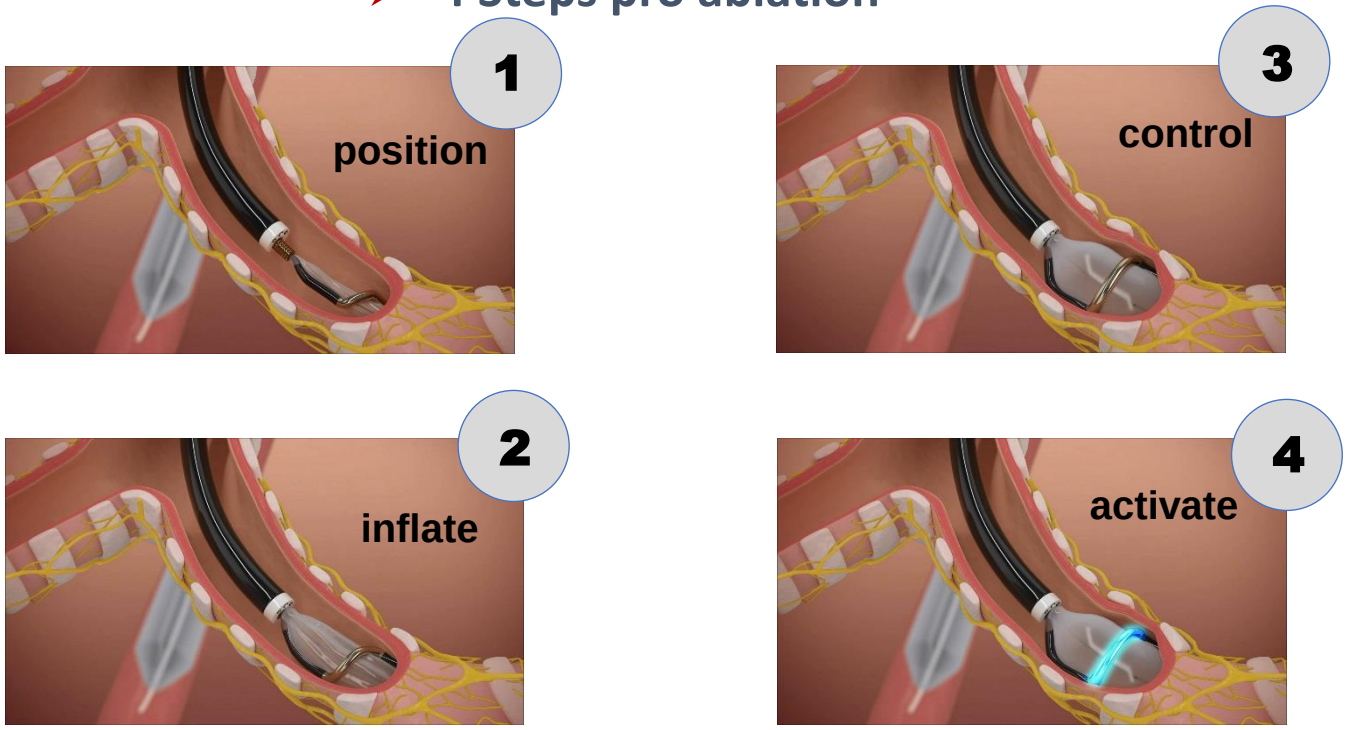
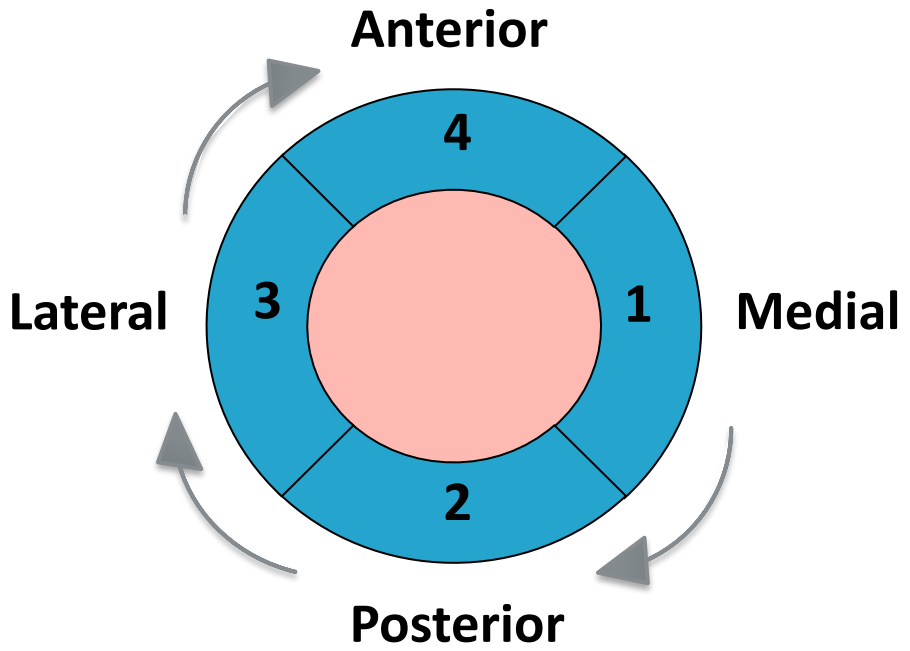
- Radiofrequency (RF) energy
  - Ablation of the bronchial branches of the vagus nerve
    - ➢ permanently decrease parasympathetic stimulation leading to
      - ➢ decreased airway hyperresponsiveness and reduced inflammation

➢ 4 locations per bronchus

➢ 4 Steps pro ablation





❖ Bilateral treatment

Clinical Development Programme

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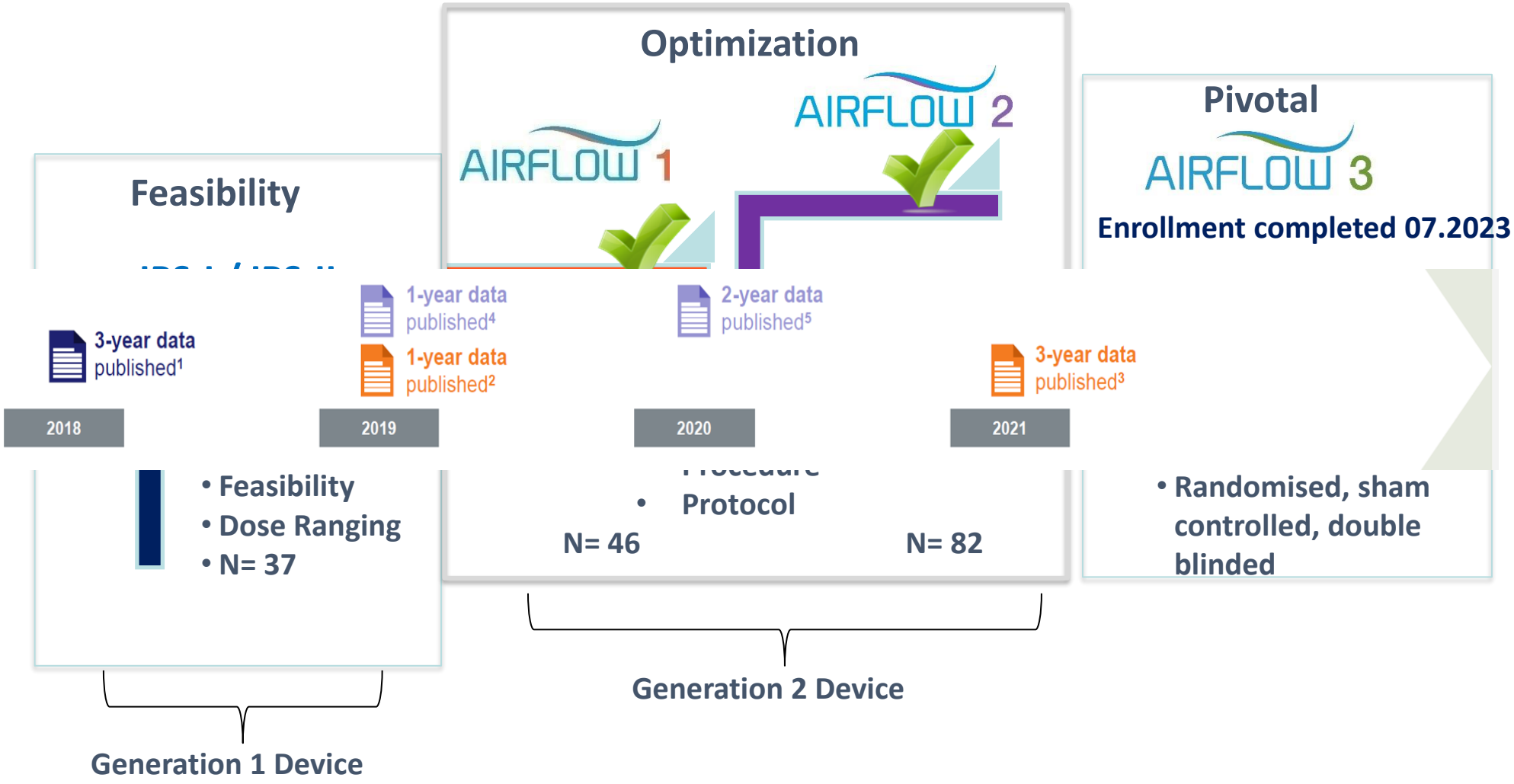

Targeted lung denervation (TLD) – Airflow 2

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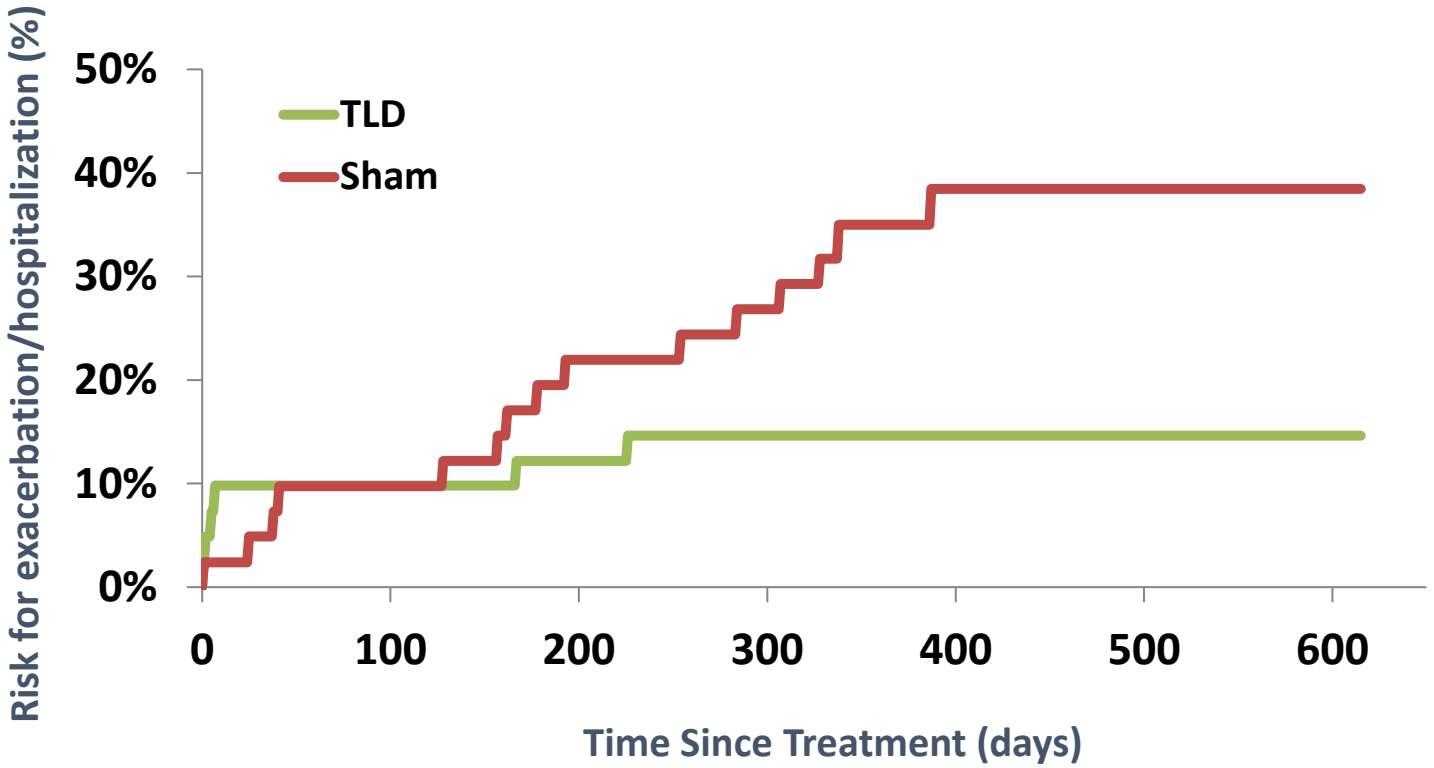
82 patients
COPD III
RCT, 1:1
double-blinded, sham control

TLD vs. SoC

Rate of respiratory related adverse events between 3 and 6.5 months



Valipour A, Int J Chron Obstruct Pulmon Dis. 2020 Nov 5;15:2807-2816.

TLD- safety abstance from esophagus

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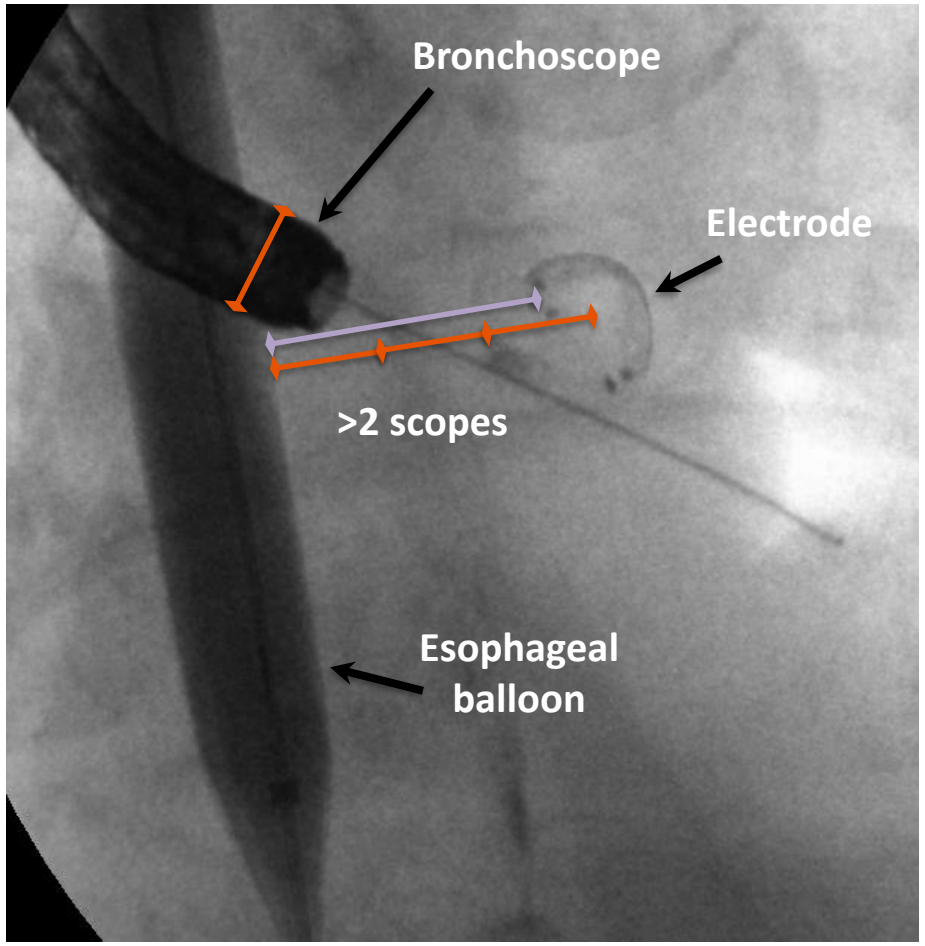

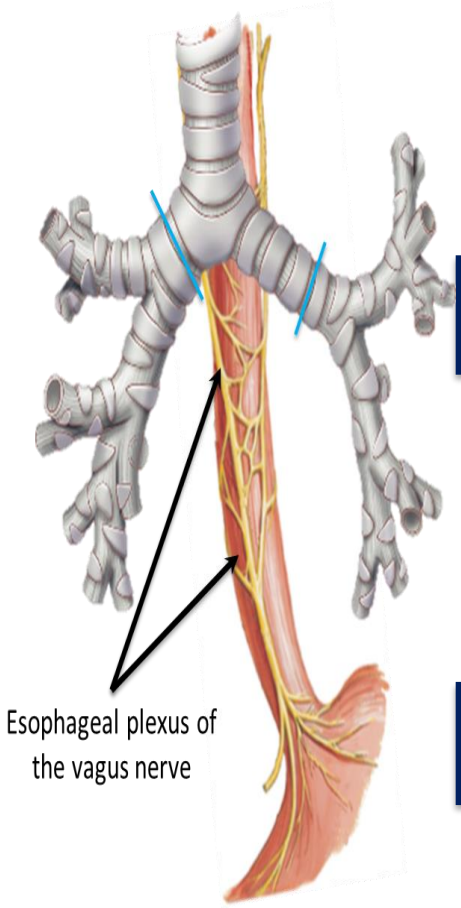

Minimun distance between esophagus and electrode

≥2 Scopes
≥12 mm
→ **High Power**

1.5 - 2 Scopes
9 - 12 mm
→ **Low Power**

<1.5 Scopes
< 9 mm
→ **No Power: do not treat**

Personalised interventional therapies

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- The correct therapy
- For the correct patient
- At the correct time
- For the correct results

- Treatment in specialized centers!

Thank you for your attention!

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