Variable		Persistent Frequent Exacerbators	Non_peristent & Infrequent Exacerbators	P-value
N		109	202	
Age (yr)	Mean (SD; N)	51.39(12.35;109)	53.35(13.47;202)	0.208228
Onset or Age at Diagnosis(yr)	Median (IQR; N)	25(27.75;109)	28(33;202)	0.032547
BMI (kg/m2)	Mean (SD; N)	30.27(6.77;109)	28.39(5.30;202)	0.007346
Female	n/N (%)	71/109(65.14%)	115/202(56.93%)	0.159001
Current Smoker	n/N (%)	11/109(10.10)	24/202(11.88)	0.757824
Ex-smoker	n/N (%)	26/109(23.85)	53/202(26.24)	0.757824
Non-smoker	n/N (%)	72/109(66.06)	125/202(61.88)	0.757824
Allergic Rhinitis Diagnosed	n/N (%)	50/109(45.87)	102/202(50.50)	0.714902
Diabetes Diagnosed	n/N (%)	13/109(11.93)	19/202(9.41)	0.734508
Eczema Diagnosed	n/N (%)	41/109(37.61)	57/202(28.22)	0.059194
Non-Allergic Rhinitis Diagnosed	n/N (%)	15/109(13.76)	25/202(12.38)	0.837864
Sinsusitis Diagnosed	n/N (%)	42/109(38.53)	60/202(29.70)	0.312461
Nasal Polyps Diagnosed	n/N (%)	34/109(31.19)	69/202(34.16)	0.864353
Osteoporosis	n/N (%)	35/109(32.11)	45/202(22.28)	0.17558
GERD Diagnosed	n/N (%)	53/109(48.62)	89/202(44.06)	0.48129
Atopy Test Positive	n/N (%)	63/109(57.80)	138/202(68.32)	0.064152
IgE (IU/ml)	Median (IQR; N)	103.5(223.43;104)	131(303.65;196)	0.186982
Exhaled NO (Standard Flow)	Median (IQR; N)	24.5(33;101)	26.5(31;189)	0.484812
Blood Eosinophils (10^3/ul)	Median (IQR; N)	0.20(0.30;105)	0.20(0.32;197)	0.274094
Blood Neutrophils (10^3/ul)	Median (IQR; N)	5(3.3;105)	4.62(2.83;197)	0.13395
Sputum Eosinophils (%)	Median (IQR; N)	2.57(19.81;30)	2.55(12.44;68)	0.875906
Sputum Neutrophils (%)	Median (IQR; N)	57.70(61.39;30)	54.58(41.44;68)	0.433441
FEV1 (% predicted pre-bronchodilator)	Mean (SD; N)	64.76(21.60;107)	66.74(20.47;201)	0.42702
FEV1 (L pre-bronchodilator)	Mean (SD; N)	2.89(0.63;109)	2.90(0.75;202)	0.86326
FVC (% predicted pre-bronchodilator)	Mean (SD; N)	84.90(19.42;107)	88.87(18.70;201)	0.08105
FVC (L pre-bronchodilator)	Mean (SD; N)	3.48(0.80;109)	3.53(0.96;202)	0.623645
Residual Volume	Mean (SD; N)	2.91(1.28;74)	2.68(0.85;143)	0.123412
Sgaw	Mean (SD; N)	0.72(0.59;74)	0.99(0.80;137)	0.012376
TLC	Mean (SD; N)	6.10(1.42;74)	6.32(1.43;143)	0.289286
Regular Xanthine Use	n/N (%)	36/105(34.28)	25/198(12.63)	0.000006
Regular Leukotriene Modifier Use	n/N (%)	46/108(42.59)	85/199(42.71)	0.983739
Regular Tiotropium Use	n/N (%)	29/103(28.16)	50/197(25.38)	0.605823
Regular Xolair Use	n/N (%)	22/104(21.15)	30/198(15.15)	0.190455
Regular OCS Use	n/N (%)	65/108(60.19)	74/197(37.56)	0.000131
Mean ACQ5	Mean (SD; N)	2.72(1.19;104)	2.00(1.13;193)	4.55E-07
Total AQLQ	Mean (SD; N)	4.17(1.09;103)	4.63(1.27;191)	0.001763
Total HADS	Mean (SD; N)	13.97(7.87;79)	12.08(8.23;160)	0.090027
Total SNOT20	Mean (SD; N)	33.89(18.33;105)	31.08(17.16;194)	0.188239
Total ESS	Mean (SD; N)	8.17(4.62;104)	7.68(4.38;191)	0.366648
Total MARS	Mean (SD; N)	22.35(2.42;103)	22.38(2.44;193)	0.909122

Abstract S67 Figure 1

S68 PHASE 1 TRIAL OF AN INTRANASAL RESPIRATORY SYNCYTIAL VIRUS (RSV) SUBUNIT CANDIDATE VACCINE: SAFETY RESULTS FROM THE MUC-SYNGEM STUDY

[1]I Vlachantoni, [1]S Ascough, [2]R Grimaldi, [2]K Leenhouts, [1]C Chiu, [1]P Openshaw. *[1]Imperial College, London, UK; [2]Mucosis Biotechnology, Groningen, Netherlands*

10.1136/thoraxjnl-2017-210983.74

Background RSV is a ubiquitous pathogen causing severe disease in children and the elderly. There is as yet no licensed vaccine. SynGEM, a novel intranasal subunit vaccine based on the RSV F glycoprotein linked to an immunostimulatory bacterium-like-particle carrier, was previously shown in animal models to elicit durable immune responses both locally (nasal secretory IgA) and systemically (serum neutralising antibodies). Induction of mucosal as well as systemic antibodies may enhance protection and reduce transmission. This was the first-in-human phase 1 study of SynGEM in healthy volunteers.

Methods MUC-SynGEM-001 was a randomised, placebo-controlled, phase 1 trial that enrolled healthy adults aged 18–49 years to evaluate the safety and tolerability of SynGEM. Forty-eight participants were randomly assigned to either the low-dose (140 µg F-protein-FP/2 mg BLPs) or high-dose group (350 µg F-protein-FP/5 mg BLPs) and received the vaccine or placebo in a 3:1 ratio. Primary safety outcomes included local or systemic, solicited or unsolicited adverse events (AE) within 28 days and incidence of vaccine-related serious adverse events (SAE) within 57 and 180 days post-vaccination. Antibodies were measured at baseline, day 29 and day 57.

Results Overall incidence of solicited local (83.3% vs 83.3% vs 83.3%) and systemic (88.9% vs 72.2% vs 75.0%) AEs was similar between low-dose, high-dose and placebo groups. Most were of mild severity and only one was severe in a subject subsequently diagnosed with PCR-confirmed influenza A at the time of vaccination. The most common local side effects included nasal discomfort, rhinorrhea and loss of smell whereas fatigue, headache and myalgia were the most frequent systemic effects. Unsolicited AEs were primarily respiratory and reported by 33.3%, 55.6% and 33.3% of participants in the three respective groups. One SAE possibly related to the vaccine was recorded: a high-dose group participant reported persistent pulsatile tinnitus arising after the prime vaccination. Assessment of immunogenicity revealed significant dose-dependent increases in serum and nasal antibodies.

Conclusion SynGEM was generally well tolerated and the data showed that both local and systemic antibodies could be induced by intranasal delivery. However, one SAE was noted and further investigation as to whether intranasal subunit vaccination could be causal is required.

Abstract S68 Table 1 Overview of solicited and unsolicited adverse events

	Group 1: 140 µg F-protein-FP/2 mg BLP		Group 2: 350 µg F-protein-FP/5 mg BLP		Placebo	
	Post prime (n=18)	Post boost (n=17)	Post prime (n=18)	Post boost (n=18)	Post prime (n=12)	Post boost (n=12)
	n (% of subjects with events)					
Local solicited AEs						
Loss of smell	3 (16.7)	4 (23.5)	1 (5.6)	0	2 (16.7)	0
Nasal discomfort	2 (11.1)	3 (17.6)	3 (16.7)	4 (22.2)	3 (25.0)	1 (8.3)
Nasal pain	1 (5.6)	0	1 (5.6)	2 (11.1)	1 (8.3)	0
Rhinorrhea	8 (44.4)	4 (23.5)	6 (33.3)	4 (22.2)	3 (25.0)	2 (16.7)
stuffy nose	8 (44.4)	5 (29.4)	6 (33.3)	4 (22.2)	4 (33.3)	6 (50.0)
Sneezing	6 (33.3)	2 (11.8)	1 (5.6)	3 (16.7)	2 (16.7)	2 (16.7)
Sore throat	2 (11.1)	1 (5.9)	5 (27.8)	3 (16.7)	3 (25.0)	5 (41.7)
Solicited systemic AEs						
Arthralgia	1 (5.6)	2 (11.8)	1 (5.6)	1 (5.6)	0	0
Fatigue	9 (50.0)	7 (41.2)	6 (33.3)	6 (33.3)	7 (58.3)	5 (41.7)
Feeling feverish	2 (11.1)	1 (5.6)	1 (5.6)	1 (5.6)	1 (8.3)	1 (8.3)
Headache	8 (44.4)	4 (23.5)	8 (44.4)	8 (44.4)	4 (33.3)	2 (16.7)
Malaise	2 (11.8)	2 (11.8)	2 (11.1)	0	1 (8.3)	1 (8.3)
Myalgia	5 (27.8)	3 (17.6)	0	2 (11.1)	2 (16.7)	1 (8.3)
All unsolicited AEs						
Oro-pharyngeal pain	0	0	1 (5.6)	5 (27.8)	1 (8.3)	1 (8.3)
Cough	0	1 (5.6)	3 (16.7)	1 (5.6)	0	1 (8.3)

New approaches to characterising paediatric respiratory diseases

S69 GENETIC AND STRUCTURAL CHARACTERISATION OF OUTER DYNEIN ARM VARIANTS CAUSING PRIMARY CILIARY DYSKINESIA

[1]F Daudvohra, [2]MR Fassad, [3]M Dixon, [3]T Burgoyne, [3]AV Rogers, [3]MR Loebinger, [3]C Hogg, [4]HM Mitchison, [5]A Shoemark. *[1]Royal Brompton and Harefield NHS Trust, UCL Great Ormond Street Institute of Child Health and Imperial College London, London, UK; [2]Human Genetics Department, Medical Research Institute, Alexandria University, Egypt and UCL Great Ormond Street Institute of Child Health, London, UK; [3]Royal Brompton and Harefield NHS Trust, London, UK; [4]UCL Great Ormond Street Institute of Child Health, London, UK; [5]School of Medicine, University of Dundee and Royal Brompton and Harefield NHS Trust, London, UK*

10.1136/thoraxjnl-2017-210983.75

Introduction Primary ciliary dyskinesia (PCD) is a heterogeneous, recessive disease, characterised by dysfunction of motile cilia that arises from structural defects. Symptoms include chronic pulmonary disease, rhinosinusitis, otitis media, laterality defects, congenital heart disease and subfertility. The most commonly affected cilia structure is the outer dynein arm (ODA), a complex structure composed of a docking complex and multiple heavy, light and intermediate dynein chains. An understanding of the relationship between the genetic and structural phenotype of ODA variants will allow patient stratification and improve diagnosis through verification of new candidate genes.

Methods 195 PCD patients were genotyped using next generation sequencing. Candidate variants were confirmed by Sanger sequencing and familial segregation analysis. For selected ODA mutations, electron tomography, an extension to transmission electron microscopy, was used to produce high-resolution 3D models of ciliary axonemal microtubular doublets and ODA volume ratios. The data were analysed to determine the impact of eight different gene mutations causing different structural defects of the ODAs.

Results 39% of patients had bi-allelic mutations identified which are associated with ODA structure. These include variants in known PCD genes: DNAH5 (n=39), DNAH11 (n=18), DNAI1 (n=8), DNAI2 (n=5), ARMC4 (n=3), CCDC114 (n=2), DNAL1 (n=1) and mutations in the novel candidate DNAH9. Variants in DNAH9 have been suggested as a cause of PCD previously but disregarded due to lack of phenotypic evidence. 3D models of the ODA complex identified genotype specific changes in the ODA complex in PCD. The ODA structure in PCD was different in the proximal region, in proximity to the microvili, when compared to the distal region, towards the tip of the axoneme. A significant deficiency in the ODA volume was detected at the distal part of the axoneme in the patient with DNAH9 defects, whereas the proximal portion was unaffected, reflecting the protein position of DNAH9.

Conclusion 3D electron tomography can be used to detect subtle changes in the ultrastructure of the ODA in PCD patients with differences detected in the impact of mutations in proximal versus distal regions of the cilia.

S70 CHANGE IN LUNG CLEARANCE INDEX AND EXHALED NITRIC OXIDE AS MARKERS OF SYSTEMIC CORTICOSTEROID RESPONSE IN CHILDREN WITH SEVERE ASTHMA

[1]S Irving, [2]Y Bingham, [3]C Bossley, [2]L Fleming, [2]S Saglani, [2]A Bush. *[1]Royal Brompton and Harefield NHS Foundation Trust, London, UK; [2]Imperial College, London, UK; [3]Kings College Hospital, London, UK*

10.1136/thoraxjnl-2017-210983.76

Introduction Children with severe therapy resistant asthma (STRA) have heterogeneous disease with variable response to steroids. Currently, spirometry (forced expiratory volume in 1 s (FEV_1)) is most widely used to assess treatment response. We hypothesised lung clearance index (LCI) would more sensitively assess steroid response than FEV_1 alone, using our multi-domain approach [JACI 2016;138:413–420] with the addition of LCI to measure response of distal airway disease.

Methods 39 children with STRA were recruited during a clinically-indicated admission for bronchoscopy and intramuscular triamcinolone injection. Prior to triamcinolone, they performed LCI, spirometry, FeNO, and filled in the asthma control test (ACT). They were followed up at 4 weeks and these tests repeated. ACT was considered abnormal if <20, LCI if ≥7.1, FEV_1 percent predicted below 80%, and FeNO if ≥24 parts per billion. Any domain which was abnormal at visit 2 was a non-response.