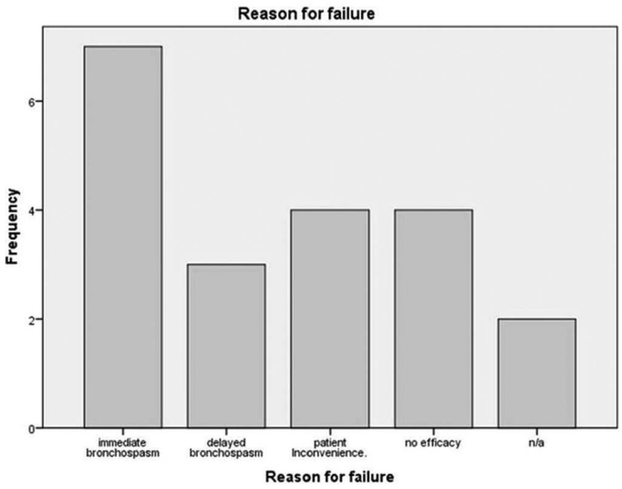
Results There were 20 patients analysed (SAFS, n = 11) and (ABPA n = 9), M: F = 8:12, median age 65.5 yrs (range = 24–78). The median duration of therapy was 30 days (IQR, 0.0–142). Clinical benefit was observed in 2 (10%) in which mean ACQ score improved from 6 to 2, overall mean AQLQ score improved by 0.95 and mean FEV1 improved by 1.2 L (63.1%). Seven (35%) failed the challenge due to bronchospasm. 11 (55%) discontinued within 12 months of therapy due to delayed bronchospasm (n = 3, within 4 weeks), equipment problems (n = 4) and lack of clinical benefit (n = 4) (fig 1). There were no significant changes in immunological and radiological outcomes.

Conclusion Our data suggests that the overall efficacy of nebulised amphotericin in this group of patients may be poor and is associated with high frequency of adverse events. However, the responses were excellent in 2 (10%) patients. It is not clear which patients are likely to respond. Further studies need to be conducted to establish the optimal dose range (dose, frequency), nebulizer type, pressures and identification of patients who may respond.



Abstract S92 Figure 1. Reason for treatment failure in patients treated with non-liposomal, nebulised Amphotericin B (Fungisone). Na = Not applicable (ie no failure observed).

S93 LARYNGEAL OBSTRUCTION DURING EXERCISE IS PREVALENT IN SEVERE ASTHMA

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Introduction Reduced exercise capacity is a common problem for patients with severe asthma, yet the reason for this remains unclear. Exercise induced laryngeal obstruction (EILO) is now recognised to cause dyspnoea on exertion but has never been studied in patients with severe asthma. We therefore undertook this study, utilising a gold standard endoscopic visualisation technique, to evaluate laryngeal function during exercise, in a well-characterised cohort of patients with severe asthma.

Methods Adult patients with severe asthma were recruited following a systematic assessment of their disease. All subjects reported impairment of activities of daily living despite treatment. Subjects underwent a symptom-limited continuous laryngoscopy during exercise (CLE) test. Laryngeal function / EILO was graded against a validated score. Measures of asthma control, perceived dyspnoea, lung function and procedure tolerability were recorded.

Results 32 patients (n = 25; female) completed CLE evaluation (Table 1). All patients were prescribed step 4/5 BTS treatment; 75% were prescribed maintenance oral corticosteroid. Despite this, patients reported poor disease control and high perceived dyspnoea (Table 1). EILO of at least moderate severity (graded ≥2 from max 3) was evident in 14 (44%) patients. The pattern and respiratory phase of EILO varied; inspiratory phase predominant (n = 7; 22%), expiratory phase predominant (n = 5, 16%), present in both phases (n = 2). Subjects with expiratory predominant EILO were more likely to have obstruction at the glottic level (i.e. vocal cord abduction) and poorer lung function. The CLE test was well tolerated; majority of subjects reported no/minimal procedural discomfort.

Conclusion Exercise induced laryngeal obstruction is highly prevalent in patients with severe asthma and is associated with dyspnoea. This abnormal laryngeal function was not evident at rest and may impair physical exercise capacity. Further work is required to explore underlying mechanisms and relationships with dyspnoea during activities of daily living.

Abstract S93 Table 1. Subject characteristics.

	All (n = 32)	Expiratory EILO (n = 5)	Inspiratory EILO (n = 7)
Age (yr)	43 (12)	47 (11)	39 (15)
BMI (kg/m^2)	29.8 (6.4)	27.1 (4.1)	29.1 (7.8)
FEV_1(% predicted)	68 (18)	47 (18)	74 (17)*
FEV_1/FVC	0.63 (0.14)	0.52 (0.17)	0.70 (0.14)
Asthma Control test (x/25)¶	12 (6–23)	12 (7–20)	9 (6–15)
Nijmegan Score (x/64)¶	23 (6–45)	23 (10–45)	25 (12–45)

Data presented as Mean (SD) or Median (range).
*P<0.05 difference between subgroups

Mechanisms of lung injury

S94 TUMOUR NECROSIS FACTOR RECEPTOR 1 INHIBITION USING A NOVEL INHALED HUMAN ANTIBODY REDUCES INFLAMMATION IN A HUMAN MODEL OF LUNG INJURY INDUCED BY INHALED LIPOPOLYSACCHARIDE; A RANDOMISED PLACEBO-CONTROLLED CLINICAL TRIAL

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Introduction and Objectives Tumour Necrosis Factor receptor 1 (TNFR1) transduces the pro-inflammatory activity of TNF- , whereas signalling through TNFR2 may contribute to tissue repair. Attenuation of TNFR1 signalling, whilst simultaneously preserving the effects of TNFR2 signalling, may be beneficial in management of acute lung injury (ALI). GSK1995057 is a novel, fully human antibody fragment (domain antibody) that selectively binds TNFR1 and antagonises signalling of TNF- via TNFR1.

The aim of this clinical study was to investigate the effect of nebulised GSK1995057 on pulmonary and systemic inflammation and cell injury in an *in vivo* human model of lung injury induced by inhaled lipopolysaccharide (LPS).

Methods Healthy subjects were enrolled in a double-blind, placebo-controlled study and randomised to nebulised GSK1995057 or placebo (1:1) administered 1 hour prior to LPS inhalation. Measurements were performed in bronchoalveolar lavage (BAL) fluid obtained at 6 hours after LPS challenge (7 hours after dosing) and in serum obtained over 24 hours post dosing of GSK1995057. The primary endpoint was BAL neutrophil count at 6 hours post LPS exposure. Data are geometric mean (95% CI).

Results Thirty-seven healthy subjects were enrolled. One subject in the placebo group was excluded from the analysis of BAL markers as the BAL was technically poor. Pre-treatment with inhaled GSK1995057 significantly reduced pulmonary and systemic markers of inflammation. In addition, there was a reduction in pulmonary vWF reflecting reduced endothelial cell injury/activation (Table 1). The prevalence of LPS-induced clinical symptoms (e.g. fever, nausea) was also lower in GSK1995057 treated subjects compared with placebo treated subjects. There were no serious adverse events related to study drug.

Conclusion This is the first report that inhalation of a novel human antibody fragment directed against the TNFR1 receptor attenuates mechanisms implicated in the pathophysiology of ALI. GSK1995057 may be a potential therapy for ALI.

ClinicalTrials.gov identifier: NCT01587807.

This work was funded by GlaxoSmithKline.

Abstract S94 Table 1. Effect of GSK1995057 on markers of pulmonary and systemic inflammation.

BALF	Placebo (n = 18)	GSK1995057 (n = 18)	% reduction	P-value
PMN (10^4 cells/ml)	6.5 (4.5, 9.4)	4.5 (2.89, 6.89) 3.8 (2.8, 5.3)*	31(41)†	0.17(0.03)†
IL-1b(pg/ml)	6.8(4.3, 10.4)	1.4 (1.0, 2.1)	79	<0.0001
IL-6 (pg/ml)	386.1(277.5, 537.4)	169.4 (111.2, 257.9)	56	0.003
IL-8 (pg/ml)	332.1(254.6, 433.2)	117.5 (82.5, 167.54)	65	<0.0001
MIP1alpha (pg/ml)	133.7(87.2, 205.1)	15.6 (8.3, 29.1)	88	<0.0001
MCP-1 (pg/ml)	799.4 (591.6, 1080.2)	159.5(101.9, 249.5)	80	<0.0001
vWF (ng/ml)	12.8(9.2, 17.9)	8.1(6.1, 10.8)	37	0.04
Serum	**Placebo (n = 19)**	**GSK1995057 (n = 18)**	**% reduction**	**P-value**
CRP (g/ml)**	55.2(31.0, 98.4)	12.0 (6.6, 21.8)	78	0.0007
OSM (pg/ml)***	20.7(13.4, 32.0)	7.5(4.8, 11.7)	64	0.002

*PMN data with subject classified as biological outlier (>3 x inter quartile range outside the upper quartile) removed.
†% Reduction and statistical significance for BALPMN data with biological outlier excluded.
** CRP data taken at 24h post GSK1995057 dosing. Data are adjusted means with baseline and time effects considered.
***OSM data taken at 6h post LPS inhalation. Data are adjusted means with baseline and time effects considered.

S95 EXPLOITING THE IMMUNOREGULATORY ROLE OF SIGLEC-E VIA SIALIC ACID-FUNCTIONALISED NANOPARTICLES AS A NOVEL APPROACH FOR THE TREATMENT OF ACUTE LUNG INJURY

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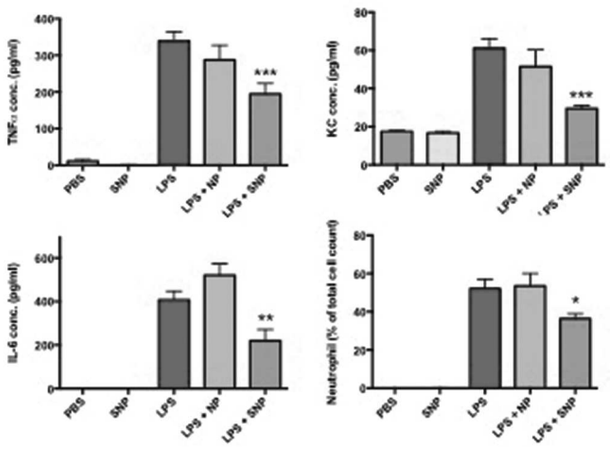
Acute Lung Injury (ALI) is a life-threatening disorder underpinned by dysregulated inflammatory cascades, with resultant injury to lung architecture. Currently, provision of supportive care represents the mainstay of treatment for ALI and novel anti-inflammatory therapeutic strategies are urgently required. We have developed a polymeric nanoconstruct surface-functionalised with sialic acid targeting moieties (SNP), exploiting the anti-inflammatory effects arising from the targeted engagement of Siglec-E receptors on activated macrophages, with potential therapeutic utility in ALI.

Polylactic-co-glycolic acid (PLGA) nanoparticles of uniform size distribution (approximately 150nm in diameter) were synthesised in accordance with a salting-out formulation. Intratracheal instillation of 20µg lipopolysaccharide (LPS) was utilised as a model of ALI in C57BL/6 mice, co-administered with 1µg SNP or non-functionalised nanoparticles (NP). Bronchoalveolar lavage (BALF) samples were collected 24 hours after treatment for analysis by enzyme-linked immunosorbent assay (ELISA).

As exemplified in Figure 1., intratracheal instillation of SNP significantly attenuated BALF levels of pro-inflammatory TNF and IL-6 cytokines, in addition to the neutrophil chemoattractant KC. Moreover, BALF differential cell counts revealed a decrease in neutrophil numbers upon treatment with SNP under LPS-induced pro-inflammatory conditions. Further analyses addressing the therapeutic utility of SNP have been undertaken, including lung wet/dry ratios, histology and toxicological evaluation, with promising outcomes.

This research clearly demonstrates the ability of SNP to diminish the inflammatory response in a murine model of LPS-induced ALI. Considering that chemoattractants and cytokines are key mediators in the pathogenesis of ALI, these results substantiate the credibility of this nanoscaffold as a therapy for ALI. Ultimately, we aim to progress this modality to a human setting, specifically analysing its effects on alveolar macrophages isolated from human volunteers, before advancing to a human *ex vivo* lung perfusion model.



Abstract S95 Figure 1. Therapeutic efficacy of SNP in a murine model of LPS-induced ALI (* $p < 0.05$, ** $p < 0.001$, *** $p < 0.001$ compared to LPS control, as established by one-way ANOVA and Tuley post-hoc test).

S96 SIMVASTATIN AS AN ADJUVANT THERAPY FOR INFECTION AND SEPSIS–IN-VITRO AND IN-VIVO STUDIES SUGGEST PRE-EMPTIVE / EARLY THERAPY IN THE ELDERLY

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