

SUPPLEMENTAL MATERIAL

Supplementary Tables.

Supplementary Table 1. Linear, mixed-effects modelling: Effects of selected variables (disease markers) at baseline, on baseline spirometric and CCP parameters in the sub-cohort of patients who subsequently received biologics.

Dependent Variable: FEV₁ % pred				
Fixed Effects	Est Coefficient	95% CI [Lower, Upper]	dF	p-value
Intercept	89.8	[79.3, 100.4]	64	p<0.001
BD	6.2	[4.6, 7.8]	64	p<0.001
ACQ5	-4.9	[-8.8, -1.0]	62	p=0.019
BEC (x10 ⁹ L ⁻¹)	-9.8	[-21.6, 2.0]	62	p=0.106
Dependent Variable: FVC % pred				
Fixed Effects	Est Coefficient	95% CI [Lower, Upper]	dF	p-value
Intercept	108.0	[98.8, 117.2]	63	p<0.001
BD	5.0	[2.8, 7.2]	63	p<0.001
ACQ5	-7.0	[-10.3, -3.7]	61	p<0.001
FENO	0.1	[0.0-0.2]	61	p=0.056
BEC (x10 ⁹ L ⁻¹)	-7.5	[-17.3, 2.3]	61	p=0.143
Dependent Variable: σlnC_L				
Fixed Effects	Est Coefficient	95% CI [Lower, Upper]	dF	p-value
Intercept	0.76	[0.68, 0.84]	60	p<0.001
BD	-0.08	[-0.12, -0.04]	54	p<0.001
BEC	0.21	[0.09, 0.33]	60	p<0.001
Dependent Variable: σV_D				
Fixed Effects	Est Coefficient	95% CI [Lower, Upper]	dF	p-value
Intercept	0.40	[0.36, 0.44]	60	p<0.001
BD	-0.03	[-0.05, -0.01]	54	p=0.022
BEC (x10 ⁹ L ⁻¹)	0.04	[-0.02, 0.10]	60	p=0.182

CI: Confidence Interval; Df, degrees of freedom; Est, estimated; ACQ-5, asthma control questionnaire-5, FeNO, fractional exhaled nitric oxide, BEC, blood eosinophil count, BD, bronchodilation; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; standard deviation for the standardised deadspace; FRC, functional residual capacity; σ lnC_L, standard deviation for the natural logarithm for the standardised lung compliance. Note non-significant terms were sequentially removed from the model with the least significant first (only include variables with p-value of <0.2).

Supplementary Table 2. Linear, mixed-effects modelling: Effects of biologic therapy on spirometric and computed cardiopulmonography parameters in patients with severe Type-2 high asthma.

Dependent Variable: FEV₁ % pred				
Fixed Effects	Est Value	95% CI [Lower, Upper]	dF	p-value
Intercept	74.2	[69.3, 79.1]	168	p<0.001
BD	6.0	[3.8, 8.2]	168	p<0.001
Visit	5.8	[3.5, 8.2]	168	p<0.001
Dependent Variable: FVC % pred				
Fixed Effects	Est Value	95% CI [Lower, Upper]	dF	p-value
Intercept	93.1	[88.6, 97.6]	167	p<0.001

BD	3.4	[1.2, 5.6]	167	p=0.004
Visit	4.4	[2.0, 6.8]	167	p<0.001

Dependent Variable: $\sigma\ln C_L$

Fixed Effects	Est Value	95% CI [Lower, Upper]	dF	p-value
Intercept	0.85	[0.79, 0.91]	151	p<0.001
BD	-0.07	[-0.11, -0.03]	151	p<0.001
Visit	-0.04	[-0.08, -0.00]	151	p=0.019

Dependent Variable: σVD

Fixed Effects	Est Value	95% CI [Lower, Upper]	dF	p-value
Intercept	0.41	[0.39, 0.43]	151	p<0.001
BD	-0.03	[-0.05, -0.01]	151	p=0.021
Visit	-0.02	[-0.04, -0.00]	151	p=0.081

Note: visit*type of biologic was non-significant and hence removed from the model, as was type of biologic.

Supplementary Table 3. Linear, mixed-effects modelling: Exploring the effects of changes induced by biologic therapy on blood eosinophils, the fraction of exhaled nitric oxide and ACQ-5 symptom score on spirometric and computed cardiopulmonography parameters in the subgroup of patients who had a follow-up visit at 3-4 months after starting biologic therapy.

Dependent Variable: FEV₁ % pred

Fixed Effects	Est Value	95% CI [Lower, Upper]	dF	p-value
Intercept	86.9	[81.4, 92.4]	144	p<0.001
BD	5.9	[3.9, 7.9]	144	p<0.001
ACQ5	-3.5	[-5.1, -1.9]	144	p<0.001
BEC (x10 ⁹ L ⁻¹)	-10.8	[-16.1, -5.5]	144	p<0.001

Dependent Variable: FVC % pred

Fixed Effects	Est Value	95% CI [Lower, Upper]	dF	p-value
Intercept	102.1	[97.0, 107.2]	143	p<0.001
BD	3.7	[1.5, 5.9]	143	p=0.001
ACQ5	-2.5	[-4.3, -0.7]	143	p=0.004
BEC (x10 ⁹ L ⁻¹)	-8.2	[-13.7, -2.7]	143	p=0.004

Dependent Variable: $\sigma\ln C_L$

Fixed Effects	Est Value	95% CI [Lower, Upper]	dF	p-value
Intercept	0.75	[0.69, 0.81]	128	p<0.001
BD	-0.07	[-0.09, -0.05]	128	p<0.001
BEC (x10 ⁹ L ⁻¹)	0.19	[0.11, 0.27]	128	p<0.001
ACQ5	0.02	[0.00, 0.04]	128	p=0.178

Dependent Variable: σVD

Fixed Effects	Est Value	95% CI [Lower, Upper]	dF	p-value
Intercept	0.39	[0.37, 0.41]	149	p<0.001
BD	-0.02	[-0.04, 0.00]	149	p=0.025
BEC (x10 ⁹ L ⁻¹)	0.05	[0.01, 0.09]	149	p=0.008

CI: Confidence Interval; Df, degrees of freedom; Est, estimated; ACQ-5, asthma control questionnaire-5; FeNO, fractional exhaled nitric oxide; BEC, blood eosinophil count; BD, bronchodilation; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; standard deviation for the standardised deadspace; FRC, functional residual capacity; $\sigma\ln C_L$, standard deviation for the natural

logarithm for the standardised lung compliance. Note non-significant terms were sequentially removed from the model with the least significant first (only included variables with p-value of <0.2 here).

Supplementary Table 4. Comparison of characteristics between the patients that did and did not show a response in post-bronchodilator $\sigma\ln\text{Cl}$ to therapy with biologics at their 4th injection.

Characteristics	$\sigma\ln\text{Cl}$ non-responders	$\sigma\ln\text{Cl}$ responders
Number of participants (% participants)	24 (53)	21 (47)
OCS (% of patients on maintenance)	11 (46)	8 (38)
Baseline Exacerbation Frequency/year	4.8±2.4	5±3
Exacerbation Frequency after 1 year /year	0.46 ± 0.72	0.29 ± 0.85
Baseline Blood Eosinophil Count / $\times 10^9 \text{ L}^{-1}$	0.35±0.34	0.52±0.55
Follow-up Blood Eosinophil Count / $\times 10^9 \text{ L}^{-1}$	0.05±0.05	0.04±0.04
Δ Blood Eosinophil Count / $\times 10^9 \text{ L}^{-1}$	-0.31±0.32	-0.48±0.54
Baseline FeNO / ppb	46±41	41±28
Follow-up FeNO / ppb	49±35	51±44
Δ FeNO / ppb	3±27	9±36
Baseline ACQ-5 score	2.1±1.2	2.5 ±1.3
Follow up ACQ-5 score	1.4±1.1	0.8±0.9
Δ ACQ-5 score	-0.5±0.9	-1.3±1.3*
Baseline pre-BD FEV ₁ / % predicted	83±24	68±20*
Follow-up pre-BD FEV ₁ % predicted	81±25	82±23
Δ FEV ₁ / % predicted	-2±13	15±15***
Baseline pre-BD FVC / % predicted	100±19	89±19
Follow-up pre-BD FVC / % predicted	101±24	102±15
Δ FVC / % predicted	1.3±13	13±15*
Baseline pre-BD FEV ₁ /FVC	0.66±0.11	0.59±0.11*
Follow-up pre-BD FEV ₁ /FVC	0.65±0.13	0.62±0.11
Baseline pre-BD V _D	0.144±0.044	0.185±0.100
Follow-up pre-BD V _D	0.153±0.051	0.148±0.055
Δ V _D	0.01±0.03	-0.05±0.07
Baseline pre-BD σ V _D	0.38±0.10	0.48±0.11***
Follow-up pre-BD σ V _D	0.42±0.11	0.40±0.12
Δ σ V _D	0.03±0.12	-0.09±0.13*
Baseline pre-BD FRC	2.9±0.70	3.1±0.86
Follow up pre-BD FRC	3.0±0.65	3.2±0.9
Δ FRC	0.08±0.22	-0.07±0.57
Baseline pre-BD $\sigma\ln\text{Cl}$	0.74±0.16	0.98 ±0.24***
Follow-up pre-BD $\sigma\ln\text{Cl}$	0.84±0.21	0.81±0.20

$\sigma\ln\text{Cl}$, standard deviation for the natural logarithm for the standardised lung compliance; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; V_D, deadspace volume (end inspiratory); σ V_D, standard deviation for the standardised deadspace; FRC, functional residual capacity; $\sigma\ln\text{Cl}$, standard deviation for the natural logarithm for the standardised lung compliance. Δ , change in parameter value between baseline and follow up visits. Statistical comparisons are for the $\sigma\ln\text{Cl}$ -Non-Responders with the $\sigma\ln\text{Cl}$ -Responders. Values are means ± SD, *p<0.05, **p<0.01, *** p<0.001.